Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for Old World cutaneous leishmaniasis (Review)

Heras-Mosteiro J, Monge-Maillo B, Pinart M, Lopez Pereira P, Garcia-Carrasco E, Campuzano Cuadrado P, Royuela A, Mendez Roman I, López-Vélez R

Heras-Mosteiro J, Monge-Maillo B, Pinart M, Lopez Pereira P, Garcia-Carrasco E, Campuzano Cuadrado P, Royuela A, Mendez Roman I, López-Vélez R.

Interventions for Old World cutaneous leishmaniasis.

Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD005067.

DOI: 10.1002/14651858.CD005067.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for Old World cutaneous leishmaniasis

Julio Heras-Mosteiro[1,2], Begoña Monge-Maillo[3], Mariona Pinart[4], Patricia Lopez Pereira[2], Emely Garcia-Carrasco[5], Pedro Campuzano Cuadrado[1], Ana Royuela[6], Irene Mendez Roman[7], Rogelio López-Vélez[3]

[1]Department of Preventive Medicine and Public Health & Immunology and Microbiology, Rey Juan Carlos University, Madrid, Spain. [2]Department of Preventive Medicine and Public Health, Ramón y Cajal University Hospital, Madrid, Spain. [3]Tropical Medicine & Clinical Parasitology, Infectious Diseases Department, Ramón y Cajal University Hospital, Madrid, Spain. [4]c/o Cochrane Skin Group, The University of Nottingham, Nottingham, UK, Nottingham, UK. [5]Infectious Diseases Department, National Referral Centre for Tropical Diseases, Madrid, Spain. [6]Department of Biostatistics, Biomedical Sciences Research Institute,Hospital Universitario Puerta de Hierro-Majadahonda, Majadahonda, Spain. [7]c/o Cochrane Skin Group, The University of Nottingham, Nottingham, Spain

Contact address: Julio Heras-Mosteiro, Department of Preventive Medicine and Public Health & Immunology and Microbiology, Rey Juan Carlos University, Avda. Atenas s/n, Alcorcón, Madrid, 28922, Spain. juliolhm@gmail.com.

Editorial group: Cochrane Skin Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2017.

Citation: Heras-Mosteiro J, Monge-Maillo B, Pinart M, Lopez Pereira P, Garcia-Carrasco E, Campuzano Cuadrado P, Royuela A, Mendez Roman I, López-Vélez R. Interventions for Old World cutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD005067. DOI: 10.1002/14651858.CD005067.pub4.

ABSTRACT

Background

Cutaneous leishmaniasis, caused by a parasitic infection, is considered one of the most serious skin diseases in many low- and middle-income countries. Old World cutaneous leishmaniasis (OWCL) is caused by species found in Africa, Asia, the Middle East, the Mediterranean, and India. The most commonly prescribed treatments are antimonials, but other drugs have been used with varying success. As OWCL tends to heal spontaneously, it is necessary to justify the use of systemic and topical treatments. This is an update of a Cochrane Review first published in 2008.

Objectives

To assess the effects of therapeutic interventions for the localised form of Old World cutaneous leishmaniasis.

Search methods

We updated our searches of the following databases to November 2016: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We also searched five trials registers and checked the reference lists of included studies for further references to relevant randomised controlled trials (RCTs). We wrote to national programme managers, general co-ordinators, directors, clinicians, WHO-EMRO regional officers of endemic countries, pharmaceutical companies, tropical medicine centres, and authors of relevant papers for further information about relevant unpublished and ongoing trials. We undertook a separate search for adverse effects of interventions for Old World cutaneous leishmaniasis in September 2015 using MEDLINE.

Selection criteria

Randomised controlled trials of either single or combination treatments in immunocompetent people with OWCL confirmed by smear, histology, culture, or polymerase chain reaction. The comparators were either no treatment, placebo/vehicle, and/or another active compound.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias and extracted data. We only synthesised data when we were able to identify at least two studies investigating similar treatments and reporting data amenable to pooling. We also recorded data about adverse effects from the corresponding search.

Main results

We included 89 studies (of which 40 were new to this update) in 10,583 people with OWCL. The studies included were conducted mainly in the Far or Middle East at regional hospitals, local healthcare clinics, and skin disease research centres. Women accounted for 41.5% of the participants (range: 23% to 80%). The overall mean age of participants was 25 years (range 12 to 56). Most studies lasted between two to six months, with the longest lasting two years; average duration was four months. Most studies were at unclear or high risk for most bias domains. A lack of blinding and reporting bias were present in almost 40% of studies. Two trials were at low risk of bias for all domains. Trials reported the causative species poorly.

Here we provide results for the two main comparisons identified: itraconazole (200 mg for six to eight weeks) versus placebo; and paromomycin ointment (15% plus 10% urea, twice daily for 14 days) versus vehicle.

In the comparison of oral itraconazole versus placebo, at 2.5 months' follow up, 85/125 participants in the itraconazole group achieved complete cure compared to 54/119 in the placebo group (RR 3.70, 95% CI 0.35 to 38.99; 3 studies; 244 participants). In one study, microbiological or histopathological cure of skin lesions only occurred in the itraconazole group after a mean follow-up of 2.5 months (RR 17.00, 95% CI 0.47 to 612.21; 20 participants). However, although the analyses favour oral itraconazole for these outcomes, we cannot be confident in the results due to the very low certainty evidence. More side effects of mild abdominal pain and nausea (RR 2.36, 95% CI 0.74 to 7.47; 3 studies; 204 participants) and mild abnormal liver function (RR 3.08, 95% CI 0.53 to 17.98; 3 studies; 84 participants) occurred in the itraconazole group (as well as reports of headaches and dizziness), compared with the placebo group, but again we rated the certainty of evidence as very low so are unsure of the results.

When comparing paromomycin with vehicle, there was no difference in the number of participants who achieved complete cure (RR of 1.00, 95% CI 0.86, 1.17; 383 participants, 2 studies) and microbiological or histopathological cure of skin lesions after a mean follow-up of 2.5 months (RR 1.03, CI 0.88 to 1.20; 383 participants, 2 studies), but the paromomycin group had more skin/local reactions (such as inflammation, vesiculation, pain, redness, or itch) (RR 1.42, 95% CI 0.67 to 3.01; 4 studies; 713 participants). For all of these outcomes, the certainty of evidence was very low, meaning we are unsure about these results.

Trial authors did not report the percentage of lesions cured after the end of treatment or speed of healing for either of these key comparisons.

Authors' conclusions

There was very low-certainty evidence to support the effectiveness of itraconazole and paromomycin ointment for OWCL in terms of cure (i.e. microbiological or histopathological cure and percentage of participants completely cured). Both of these interventions incited more adverse effects, which were mild in nature, than their comparisons, but we could draw no conclusions regarding safety due to the very low certainty of the evidence for this outcome.

We downgraded the key outcomes in these two comparisons due to high risk of bias, inconsistency between the results, and imprecision. There is a need for large, well-designed international studies that evaluate long-term effects of current therapies and enable a reliable conclusion about treatments. Future trials should specify the species of leishmaniasis; trials on types caused by *Leishmania infantum, L aethiopica*, and*L donovani* are lacking. Research into the effects of treating women of childbearing age, children, people with comorbid conditions, and those who are immunocompromised would also be helpful.

It was difficult to evaluate the overall efficacy of any of the numerous treatments due to the variable treatment regimens examined and because RCTs evaluated different *Leishmania* species and took place in different geographical areas. Some outcomes we looked for but did not find were degree of functional and aesthetic impairment, change in ability to detect *Leishmania*, quality of life, and emergence of resistance. There were only limited data on prevention of scarring.

PLAIN LANGUAGE SUMMARY

Treatments for Old World cutaneous leishmaniasis

Background

Old World cutaneus leishmaniasis (OWCL) is an infection caused by the *Leishmania* parasite, which is passed onto humans by the bite of sandflies. It is a serious skin disease associated with a broad range of signs, symptoms, and degrees of severity. We wanted to assess the competence and safety of all available treatments for OWCL.

Review question

We assessed participants with a healthy immune response who had OWCL diagnosed by laboratory methods. Treatments had to be given alone or in combination with another treatment, and they were compared against no treatment, placebo (an inactive substance) only, or another active treatment. Some of the main outcomes we were interested in included the percentage of wounds cured after the end of treatment, the number of participants completely cured after the end of treatment, speed of healing, side-effects of treatment, and clearance of parasites (i.e. infection).

Study characteristics

We reviewed 89 clinical trials, which included 10,583 people, in total, with OWCL. We included participants of both sexes and all ages (mean 24.5 years); most participants were over 18 years of age. Most studies were carried out in single centres in different countries, mainly in the Far or Middle East, and lasted between two to six months. We included a variety of treatments, such as antimonials, antifungals, and antibiotics, which were administered either directly onto the skin or into a wound, taken by mouth, or physically applied (e.g. laser treatment, heat therapy, etc.). Most of the included studies assessed OWCL caused by two species of parasites known as *Leishmania major* (*L. major*) and*Leishmania tropica* (*L. tropica*).

Key results

The evidence is current to November 2016.

Two of the most important treatments that we assessed in this review were itraconazole, an antifungal drug taken by mouth, and paromomycin, an antibiotic applied as an ointment. Trials compared both to a placebo tablet or inactive cream (vehicle).

Participants received 200 mg itraconazole for six to eight weeks or paromomycin ointment at a concentration of 15% plus 10% urea, twice daily for 14 days.

When assessed on average 2.5 months after treatment, more participants were completely cured and cleared of the infection-causing parasites with itraconazole than placebo, but they also had more side effects (mild stomach pain, sickness, and abnormal liver function, as well as headaches and dizziness).

When paromomycin ointment was compared with placebo, there was no difference in the number of completely cured participants or the number who were found to be cleared of parasites when assessed on average 2.5 months after treatment, but those in the paromomycin treatment group had more contained skin reactions (such as swelling, blistering, pain, redness, or itch).

However, as the certainty of the evidence for these outcomes for these particular comparisons was very low, we are not sure of the accuracy of these results.

Neither of our key treatment comparisons assessed the percentage of wounds cured after the end of treatment and speed of healing (i.e. time taken to be cured).

Quality of the evidence

The overall certainty of the evidence for the different outcomes in the two main comparisons was very low. Important reasons for this were that studies were not blinded, or had a small sample size, making the results less precise. Some of the evidence only focused on young people, and the results greatly varied between each study.

We need more research to fill in the following research gaps: 1) trials of OWCL caused by other types of infection such as *L. infantum, L. aethiopica*,*or L. donovani*; 2) involving specific subgroups of people such as children; 3) assessing effectiveness and safety of different anti-*Leishmania* drugs compared with placebo in self-healing forms of leishmaniasis or with traditional first-choice antimonial treatment in complicated form (defined as more than four lesions over 4 cm in size, located close to an opening or small joints, for which previous treatment has failed); and 4) assessing areas such as wound healing and patient-reported outcomes, such as quality of life. In addition, few studies assessed relevant issues such as drug resistance. International collaboration is required to improve the quality and standardisation of future trials in order to develop a better evidence-based approach.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Itraconazole (200 mg for 6-8 weeks) versus placebo for Old World cutaneous leishmaniasis

Patient or population: patients with Old World cutaneous leishmaniasis
Settings: Kuwait, India, and Iran
Intervention: itraconazole (200 mg for 6-8 weeks)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Itraconazole (200 mg for 6-8 weeks)				
Percentage of lesions cured after the end of treatment	Not measured in this comparison					
Percentage of participants with complete cure Follow-up: mean 2.5 months	**Study population**		**RR 3.70** (0.35 to 38.99)	244 (3 studies)	⊕◯◯◯ **Very low**[a]	-
	454 per 1000	**1000 per 1000** (159 to 1000)				
	Moderate					
	100 per 1000	**370 per 1000** (35 to 1000)				
Adverse effects Mild abdominal pain and nausea	**40 per 1000** **0 per 1000**	**95 per 1000** (30 to 302) **0 per 1000** (0 to 0)	**RR 2.36** (0.74 to 7.47) **RR 3.08** (0.53 to 17.98)	204 (3 studies) 84 (3 studies)	⊕◯◯◯ **Very low**[b] ⊕◯◯◯ **Very low**[c]	-
Adverse effects Mild abnormal liver function						

Speed of healing (time taken to be 'cured')	Neither of the studies reported speed of healing (time taken to be 'cured') in this comparison					
Microbiological or histopathological cure of skin lesions Follow-up: mean 2.5 months	Not estimable	Not estimable	**RR 17.00** (0.47 to 612.21)	20 (1 study)	⊕◯◯◯ **Very low**[d]	There were zero events in the placebo group

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio.

GRADE Working Group grades of evidence
High quality/certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality/certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality/certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality/certainty: we are very uncertain about the estimate.

[a]Downgraded by 4 levels due to: risk of bias (2 RCTs have many uncertain items), inconsistency (there is considerable heterogeneity - I^2 = 73%), and imprecision (2 levels due to wide 95% confidence intervals, crossing the line of no effect).
[b]Downgraded by 3 levels due to: risk of bias (many uncertain items in the risk of bias judgment), and imprecision (2 levels due to wide 95% confidence intervals, crossing the line of no effect).
[c]Downgraded by 3 levels due to: risk of bias (many uncertain items in the risk of bias judgment), and imprecision (2 levels due to wide 95% confidence intervals, crossing the line of no effect).
[d]Downgraded by 3 levels due to: risk of bias (many uncertain items in the risk of bias judgment), and imprecision (2 levels due to wide 95% confidence intervals; this outcome is only reported for one study involving 20 participants).

BACKGROUND

Please see Table 1 for a glossary of terms used.

Description of the condition

Definition

Desjeux 1996 describes leishmaniasis as "a group of diseases caused by infection with protozoan parasites of the genus *Leishmania*", transmitted by bites from sandflies infected with the parasite. Leishmaniasis has two main clinical forms of presentation (cutaneous and visceral), which are associated with a broad range of signs, symptoms, and degrees of severity (Herwaldt 1999; Reithinger 2007). Depending on its geographical distribution, cutaneous leishmaniasis (CL) is classified as New World cutaneous leishmaniasis (NWCL) or Old World cutaneous leishmaniasis (OWCL). The latter commonly - though not exclusively - presents as chronic, painless ulcers or nodules. Treatment of cutaneous leishmaniasis is complex and should depend on the *Leishmania* species involved, the area of acquisition of the infection, and the clinical form (Monge-Maillo 2013). Management may vary from local or systemic treatment to no treatment.

Epidemiology and impact

In many tropical and subtropical low- and middle-income countries (LMICs), protozoan parasites are amongst the most common infectious agents and have serious consequences for socioeconomic development (Alvar 2006; WHO 2002). The World Health Organization (WHO) considers leishmaniasis to be one of the most serious parasitic diseases, and the World Health Assembly has advocated for prioritising their control (WHO 2007).

An estimated 700,000 to 1.2 million new CL cases occur each year (Alvar 2012). CL is widely distributed, with 70% to 75% of the global incidence located mainly in 10 countries: Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica, and Peru (Alvar 2012). Global incidence of OWCL is estimated at more than 900,000 cases per year, distributed from the Mediterranean basin across the Near East to Northwest India, with a few foci in Central China as well as a thin band across West Africa and in the Horn of Africa (Alvar 2012; Pigott 2014). OWCL is also increasingly present in immigrants, military personnel, humanitarian aid workers, tourists, and travellers from endemic areas (Reithinger 2007).

Immunosuppression is also a factor that can increase the prevalence of CL, altering its clinical presentation and treatment response (van Griensven 2014). This factor is most closely associated with HIV, but recent years have seen a worldwide increase in other immunosuppressive conditions, mainly because of better medical care for chronic illnesses and the use of immunosuppressive drugs like tumour necrosis factor (TNF) inhibitors (van Griensven 2014). In any case, the reported leishmaniasis case figures seem to be only a fraction of the true burden, and the disease appears to be underestimated and on the rise in several countries (Alvar 2012). Leishmaniasis, as with many other neglected tropical diseases (NTDs), occurs mostly in LMICs, affecting rural and remote locations that may escape official data sources (WHO 2010).

Aetiology and transmission

Five *Leishmania* species cause OWCL: *L major, L tropica, L infantum, L donovani*, and*L aethiopica* (Pace 2014). Most cases are due to *L major*, with around 500,000 cases per year; *L tropica,* with 400,000 cases per year; followed by *L aethiopica,* with 50,000 cases per year (den Boer 2011). Transmission of leishmaniasis is through a complex life cycle involving sandflies belonging to the *Phlebotomus* species (Pace 2014). Non-vector transmission (e.g. by accidental laboratory infection, blood transfusion, or organ transplantation) is possible but rare (Cardo 2006). Transmission of leishmaniasis can be either anthroponotic or zoonotic (Pace 2014).

Zoonotic cutaneous leishmaniasis (ZCL), occurring mostly in rural areas, is where the parasite is transmitted from a range of animals to humans (WHO 2010). It is geographically distributed in the Middle East, North-western China, and North Africa, where it may be caused by *L major*, and in the Mediterranean basin where it is mostly caused by *L infantum* (Pace 2014). The Old World ZCL often heals spontaneously after two to four months, although in some cases it may persist for as long as five years (WHO 2010).

Anthroponotic cutaneous leishmaniasis (ACL) is transmitted from person to person, mainly in urban areas; it is geographically distributed in the Middle East, the Indian subcontinent, and western Asia (WHO 2010). ACL is mostly caused by *L tropica* and also by *L donovani,* which may cause post-kala-azar dermal leishmaniasis (PKDL) in Asia (India, Nepal, and Bangladesh) and in East Africa (Ethiopia, Kenya, and Sudan) (Alvar 2012).

Clinical manifestations

CL can affect the skin and mucous membranes and has been categorised into five different clinical forms: localised, recidivans, diffuse, mucosal, and PKDL.

Localised leishmaniasis

In the localised form, the parasite is confined to the skin (Gonzalez 2008). After an incubation period of 1 to 12 weeks, a papule or bump develops at the site of the insect bite, and the papule grows and turns into an ulcer (González 2009). A typical lesion of the localised form of CL is a painless papule or ulcer covered with an adherent crust of dried exudate and located on exposed parts of the body such as the face, arms, or legs (Gonzalez 2008; González 2009). CL due to *L infantum* usually causes single lesions. By contrast, *L tropic*a frequently causes multiple lesions, as does *L major*, in this case often severely inflamed and ulcerated

lesions that heal slowly and cause large disfiguring or disabling scars. Other variations exist as well: some people may have as many as 200 simple skin lesions, with some growing but not ulcerating (sporotrichoid), while certain *Leishmania* species also infect the lymphatic system, producing lesions along the lymphatic channels (nodular lymphangitis) (Gonzalez 2008). Secondary bacterial infection is common, causing pain and serious disability (Blum 2014). Most lesions heal spontaneously over months or years, leaving permanent scarring with skin thinning. Scarring of leishmaniasis typically displays a depigmented centre and a pigmented border (Reithinger 2007).

Leishmaniasis recidivans

This form appears in around five per cent of people with CL by *L tropica* and is characterised by microsatellite and confluent lesions that relapse and finally ulcerate on the border of previous scars (Sharifi 2010; WHO 2010).

Diffuse leishmaniasis

This form affects only the skin but with generalised skin lesions; it is seen mainly in Africa and transmitted by *L aethiopica* (Alrajhi 2003).

Mucosal leishmaniasis

In mucosal leishmaniasis, the parasite may spread to the mucous membranes, especially those of the nose, mouth, and throat, causing extensive damage and disfiguration. It mainly occurs in South America, but it can also be caused by species from Old World countries including *L tropica*, *L major,* and *L infantum* (WHO 2010).

Post-kala-azar dermal leishmaniasis

PKDL is a form of diffuse cutaneous leishmaniasis and a sequel of visceral leishmaniasis (VL) that may appear in affected individuals up to 20 years after being partially treated or untreated or even in those who supposedly received adequate treatment (Rathi 2005). PKDL is mostly seen in areas where *L donovani* is endemic, such as in Asia (India, Nepal, and Bangladesh) and East Africa (Ethiopia, Kenya, and Sudan) (Alvar 2012).

Diagnosis

Clinically diagnosed OWCL should be confirmed using the traditional diagnostic techniques of smear, parasite culture, and histological analysis of skin by aspiration, scrapings, or biopsies (Saab 2015). Circulating antibodies in the bloodstream are generally low or undetectable in cases of OWCL (Masmoudi 2013). Modern molecular diagnostic techniques, mainly the polymerase chain reaction test (PCR), appear to be the most sensitive single diagnostic test for species identification in skin samples (Faber 2003; Schallig 2002). Identification of the *Leishmania* species involved is essential for selecting the most appropriate treatment.

Description of the intervention

Issues of treatment in CL are difficult to deal with because there are many factors that can influence the efficacy of drugs: the size, the number, and the appearance of the lesions; the duration of the disease prior to treatment; the frequency and time to self-healing; the frequency of relapse and re-infection; the frequency and severity of either mucosal or diffuse involvement; immunosuppression; co-infections; prior anti-*Leishmania* treatment; and the knowledge of resistance to anti-*Leishmania* drugs (Gonzalez 2008). Laboratory studies have described acquired resistance to anti-*Leishmania* drugs for decades, but only recently has clinical resistance been described. Monitoring resistance is currently controversial due to an inadequate correlation between clinical and in vitro resistance and a need for knowledge about the biochemical and molecular mechanisms of resistance (Croft 2006).

The location of the lesion (e.g. face or joints) and the patient's sex and age often determine the choice of treatment (González 2009). Other factors are intrinsic and related to the different *Leishmania* species (Safi 2012). An effective treatment in one geographical area for a given organism may not work in a different geographical area or for a different organism in the same location. In these cases, efficacy depends not only on the *Leishmania* species but also on the response of the person to the parasite and factors such as immunity, variable clinical response to treatments, drug toxicity, drug resistance, HIV co-infection and adherence (Blum 2014).

Different authors have described many treatments for OWCL (Modabber 2007; WHO 2008; WHO 2010), of which we summarise the most relevant in Table 2. Nonetheless, several authors have pointed out the lack of properly controlled clinical trials (Hepburn 2001, Herwaldt 1999; Moskowitz 1999; Monge-Maillo 2013). Another disadvantage and paradox is the lack of availability of most of these drugs in rural and poorer areas where leishmanias appears most frequently (Gonzalez 2008). Systemic treatments are generally given to those with CL who present with big ($\geq$ 5 cm), multiple (> 5), or disseminated lesions; in those who have simple lesions involving cosmetically sensitive areas or joints, with mucosal reaction, or with the presence of nodular lymphangitis or lymphadenopathies; or for whom local therapy has failed (Blum 2014). For people with immunosuppression, there is controversy. Some experts consider that acquired or induced immunosuppression is a risk factor for developing mucosal leishmaniasis, so they recommend systemic treatment. Meanwhile, other experts have considered different treatment for the same type of people (Blum 2012).

Systemic and intralesional antimonials

Meglumine antimoniate and sodium stibogluconate

The current mainstays of systemic treatment for OWCL are the pentavalent antimony (Sb^{v+}) compounds sodium stibogluconate (SSG) (Pentostam, Stibanate) and meglumine antimoniate (MA) (Glucantime) (Asilian 2004a; WHO 2010); they often constitute the control condition in trials of new treatments. The recommended dosage is 20 mgSb^{v+}/kg/d intramuscularly (IM) or intravenously (IV) for 20 to 30 days (WHO 2010); oral administration is not an option. SSG and MA can also be administered intralesionally (IL) with the recommended dosage of 1 mL to 5 mL per session every 3 to 7 days. Up to 10 sessions are needed depending on the clinical response, but most people require less than five sessions.

Despite the widespread use of SSG and MA, there are concerns about their cost, toxicity, and the development of drug resistance. Parenteral antimonial drugs are associated with severe adverse and often dose-dependent effects, including nausea, vomiting, diarrhoea, skin eruptions, dizziness, cardiac arrhythmia, hypotension, arthralgia, myalgia, abdominal discomfort, headache, reversible elevation of hepatocellular enzymes, occasional anaemia, and thrombocytopaenia (Aronson 2010; Ejaz 2014; Esfandiarpour 2002; Farajzadeh 2015; Mohebali 2007; Momeni 2002). Pain at the site of the injection is greater in intralesional administration than in the intravenous/intramuscular route (Iraji 2005; Momeni 2002; Salmanpour 2006). Whilst there is no general consensus on optimum treatment, there are active lines of research to identify alternatives to systemic antimonials (Jowkar 2012). Momeni 2002 has investigated combination therapies with allopurinol, and Sadeghian 2006a with pentoxifylline, as treatments that may help to reduce drug resistance by increasing the efficacy of the antimonials, reducing their doses, or both.

Infiltration of skin lesions (injecting a substance directly into the infected lesion) can be very painful. Adverse effects of IL treatments are burning at the site of injection, itching, inflammation, and vasovagal shock due to severe pain (Layegh 2009; Mapar 2010). A safe and efficient therapeutic method for IL injection is the use of a Dermojet device (Bogenrieder 2003). Preventing bloodborne transmission of other infectious diseases in LMICs entails reducing the use of injections, implementing blood safety practices, and providing sterile injection equipment in healthcare centres (Kermode 2004; Simonsen 1999). Several studies provide evidence for the efficacy of intralesional pentavalent antimonials for OWCL, mainly in Asia and the Mediterranean basin (Alkhawajah 1997; Uzun 2004). Moreover, local administration reduces the systemic toxicity of antimonials; people may receive anywhere from a few injections or - for those with multiple or complicated lesions - daily injections for up to 40 days (Mujtaba 1999). (Complicated CL is defined as more than 4 lesions over 4 cm in size, which are periorificial or located close to small joints, for which previous treatment has failed. Clinically important lymphatic dissemination is present, as well as underlying immunosuppressive conditions, and "there is significant comorbidity for which systemic treatments could be contraindicated in a benefit-risk assessment (e.g. unbalanced diabetes, malnutrition)" (Gradoni 2017).)

Self-limiting lesions are normally amenable to weekly or alternate day IL injections of SSG or MA (Alkhawajah 1997; Mujtaba 1999). According to some authors, deficient infiltration of the lesions is one of the most common and important causes of treatment failure with IL antimonials (Faghihi 2003). There are also other studies that have evaluated the association of intralesional pentavalent antimonials as a way to increase the efficacy (Asilian 2003; Munir 2008).

Non-antimonial systemic treatments

Oral antifungal

Oral azole antifungal drugs (fluconazole, ketoconazole, itraconazole) are potential therapeutic agents in CL. The first reports of oral ketoconazole for the treatment of CL in both the New and the Old World came out in the early 1980s (Urcayo 1982; Weinrauch 1983a; Weinrauch 1983b). However, reports of liver toxicity and low cure rates for certain species led to ketoconazole being withdrawn from the market, making it necessary to search for other azoles (Alrajhi 2002). In the mid- to late 1980s, another azole called itraconazole was touted as a treatment for CL (Borelli 1987; Cauwenberg 1986), with different cure rates depending on the species involved (Momeni 1996; Nassiri-Kashani 2005). Fluconazole, another antifungal azole, has also been used as an alternative therapy for CL, with good cure rates at different doses (Alrajhi 2002; Emad 2011).

Oral dapsone

Some studies have proposed the antibiotic/antileprotic drug dapsone as an inexpensive oral alternative to the treatment currently used for CL (Dogra 1986; Dogra 1991), although the main side effect of dapsone is blood cell destruction and anaemia (Dogra 1991).

Oral allopurinol

Allopurinol (a medicine used to treat gout) alters protein synthesis and inhibits the growth of *Leishmania* in vitro (Momeni 2002); different authors have assessed its use as a potential therapeutic agent for the treatment of both CL and VL, mainly in combination with pentavalent antimonials (Chunge 1985; Jha 1983; Kager 1981; Momeni 2002).

Oral antibiotics

Researchers have also reported several other oral antibiotics like metronidazole and cotrimoxazole as possibly promising anti-*Leishmania* agents in the treatment of VL (Rodriguez-Cuartero 1990), while others have looked into the efficacy of a short-term course of

antibiotic rifampicin for CL (Bygbjerg 1980). Oral azithromycin is another antibiotic that is effective in vitro and in mice (Minodier 2007), but research has not established it as superior to antimonials for OWCL in humans (Layegh 2007), even when combined with allopurinol (Dastgheib 2012). Thus, azithromycin needs further investigation for human leishmaniasis.

Oral pentoxifylline

Oral pentoxifylline, used in people with vascular diseases, also has anti-*Leishmania* effects (Lessa 2001), decreasing the inflammatory reaction and the resulting tissue damage (Sadeghian 2006a). Pentoxifylline has a good safety profile, although nausea, arthralgias, dizziness, abdominal pain, and diarrhoea can occur (Lessa 2001).

Oral miltefosine

Oral miltefosine, which was originally developed as an anticancer drug, is active against the *Leishmania* membrane (Croft 2006). Miltefosine was included in the WHO essential medicines list as an anti-leishmaniasis medicine in March 2011 (WHO 2011), and in March 2014, the US Food and Drug Administration (FDA) approved oral miltefosine for visceral, cutaneous, and mucosal leishmaniasis (FDA 2014). Miltefosine seems active against most *Leishmania* species, but with variable efficacy depending on geographical regions, even for the same species (Monge-Maillo 2015; Soto 2004; Stojkovic 2007). Limited experience with miltefosine for OWCL shows efficacy, mostly against *L major* (Dorlo 2011; Mohebali 2007; Stojkovic 2007). The most commonly reported adverse drug reactions associated with miltefosine are transient gastrointestinal discomfort, nausea, vomiting, abdominal pain, and mild elevation of liver enzymes and serum creatinine (Mohebali 2007). Women of childbearing age require contraception beyond the end of treatment because this drug is contraindicated during pregnancy (Sindermann 2006).

Oral zinc sulphate

Early studies on oral zinc sulphate reported promising results for the treatment of CL (Sharquie 1996; Sharquie 1997; Sharquie 2001), although more recent studies have not reported good cure rates (Yazdanpanah 2011).

Oral artesunate

Artemisinin is effective against promastigotes in vitro, and artemisinin and artemether are leishmanicidal for amastigotes in infected murine macrophages (Adam 2008; Keiser J 2007). However, an RCT performed in Sudan did not show that artesunate combined with sulphamethoxypyrazine/pyrimethamine was better than placebo for OWCL (Adam 2009).

Other oral drugs

Jiang 2002 was the first to describe using omeprazole, a common treatment for peptic ulcer diseases, as a potential antiparasitic drug for the growth of *L donovani* in a laboratory setting, and Nilforoushzadeh 2008 concluded it was a good alternative to antimonials when these have to be given in a lower dose.

Parenteral liposomal amphotericin B

Amphotericin B, an antifungal drug used since 1960 (Sampaio 1960), is commonly used for treating American mucocutaneous leishmaniasis, HIV co-infection, and visceral leishmaniasis (VL) in areas where *Leishmania* is resistant to antimonial and pentamidine drugs (Karamian 2007; Laguna 1999; Musa 2005; Sampaio 1997; Sundar 2007a; Thakur 1996). There has been little experience with this drug for OWCL due to pentavalent antimonials' dominance as the most commonly systemic regimens until now. However, the toxicity of pentavalent antimonials has prompted an increase in the administration of amphotericin B (mostly the lipid formulations), with promising results mainly with *L major* and *L tropica* (Solomon 2011; Wortmann 2010). Zanger 2011 also reported a case of OWCL due to *L aethiopica* in a immunosuppressed person with response to liposomal amphotericin B.

Non-antimonial topical or intralesional therapies

Mild disease caused by *L major* is often self-healing (Alkhawajah 1997; Nilforoushzadeh 2006). OWCL can be managed with local care alone and may not require other specific therapies when it is a simple CL (Shazad 2005), defined as CL: not caused by *Leishmania* species with common mucosal dissemination; not a diffuse, recurrent or post-kala-azar CL; with no lymphatic nodes affected; with small lesions; with fewer than five lesions; with lesions that are not localised in joints or aesthetic areas; or in people who are not immunocompromised (Nilforoushzadeh 2006). Topical and local therapies are attractive options that are appropriate for early self-limiting lesions, offering reduced systemic toxicity and possibilities for outpatient treatment (Iraji 2004).

Topical antifungals

Early research on topical antifungals was based on clotrimazole, miconazole, and ketoconazole. The only RCT performed was in Saudi Arabia; investigators compared clotrimazole and miconazole and concluded that clotrimazole was more effective (Larbi 1995). Topical ketoconazole was tested in Afghanistan, but it did not significantly change the course of the lesions (Storer 2005).

Topical paromomycin (aminosidine)

Topical formulations often offer easier administration, fewer adverse effects, and sometimes cost-effectiveness, although there

may be difficulties in getting enough of the active drug absorbed through the skin (Jowkar 2012). Paromomycin is an antibiotic in the aminoglycoside family, originally identified as an anti-*Leishmania* drug in the 1960s. Parenteral formulations have been used for VL (Sundar 2007b), and topical preparations for CL since 1987 (Asilian 1995). The literature uses the names paromomycin, aminosidine, monomycin, and neomycin E interchangeably, although the active principle is the same (Bryceson 1994). Two main topical preparations are available for CL: 15% paromomycin sulphate dissolved in a soft white paraffin base, either with 12% methyl benzethonium chloride (MBCL) or with 10% urea (Faghihi 2003; Shazad 2005). Paromomycin ointment combined with MBCL has been shown to be more efficacious than with urea (Iraji 2005). The original paromomycin formulation is no longer used because of its toxicity, and newer penetration-enhancing formulations have been subjected to clinical evaluation (Davis 2003). More recently, studies have also evaluated new combinations of paromomycin plus gentamycin (Ben Salah 2009). Of the topical preparations, paromomycin ointment is commonly the first-line treatment in uncomplicated CL (Asilian 2006). Adverse effects encountered were redness, pruritus, burning, oedema, local pain, inflammation, contact dermatitis, urticaria, or lymphadenitis with pain (Ben Salah 2013).

Intralesional zinc sulphate

Intralesional zinc sulphate had a direct anti-*Leishmania* effect against *L major* and *L tropica* species in both an in vitro and in vivo study (Firooz 2005; Najim 1998).

Topical imiquimod

Topical imiquimod is an immune response modifier used for treating genital warts and premalignant skin cancer conditions, first used in combination with antimony for American CL (Arevalo 2007).

Intralesional hypertonic sodium chloride

Intralesional hypertonic sodium chloride solution (HSCS) can act by its osmotic effect to destroy the parasite as well as the surrounding tissue of the granuloma (Sharquie 1995; Sharquie 1997). It appears to be a cheap, safe, and effective local method for treating CL.

Intralesional interferon-gamma (IFN-γ)

Intralesional interferon (IFN-γ) is a lymphokine originally used for the treatment of leprosy, cancer, HIV, and chronic granulomatous disease, and it has been shown to enhance the leishmanicidal capacity of human monocytes in vitro (Badaro 1990; Passwell 1986).

Topical aminoglycoside ointment (WR279,396)

The topical aminoglycoside ointment (WR279,396) is a hydrophilic formulation of paromomycin 15% plus a second aminoglycoside (gentamicin 0.5%) that was developed for topical administration, avoiding the potential skin irritation of other combinations performed with MBCL. Researchers in Tunisia have studied this combination of ointment (WR279,396) for *L major*, with better results than vehicle (Ben Salah 2009).

Intralesional metronidazole

Metronidazole was initially the first line treatment for trichomoniasis and later for amoebiasis and giardiasis. Its effectiveness for cutaneous leishmaniasis is controversial. Several case reports and a clinical trial performed in Iraq showed good cure rates for OWCL with intralesional metronidazole (Al-Waiz 2004). However, a more recent clinical trial performed in Iran showed that metronidazole is ineffective (Mapar 2010). Moreover intralesional metronidazole injection was very painful.

Topical miltefosine

Pre-clinical animal studies initially evaluated topical miltefosine, showing a potential benefit for NWCL and OWCL (Schmidt-Ott 1999). A trial in Syria did not demonstrate efficacy of topical miltefosine for OWCL (Garnier 2002). However, a recent RCT in Iran showed that topical miltefosine was significantly more efficacious than meglumine antimoniate (Asilian 2014).

Topical dapsone

Dapsone is a synthetic sulfone employed orally for infectious diseases such as leprosy and for certain cutaneous disorders such as nodulocystic acne. However, the potential for systemic toxicity has limited its use in many cases. Topical formulations have also been developed especially for acne, thus reducing the possible systemic secondary effects (Stotland 2009). For OWCL an RCT in Iran compared dapsone 5% gel mask plus intralesional meglumine antimoniate (ILMA) versus cryotherapy plus ILMA, but investigators did not find any statistically significant difference in cure rates (Fekri 2015).

Topical 0.045% pharmaceutical chlorite (DAC N-055)

DAC N-055 seems to promote tissue regeneration, which may be of benefit for cutaneous lesions due to OWCL (Migdal 2011). A clinical trial in Afghanistan compared this treatment, both alone and in combination with bipolar high frequency electrocauterisation, versus intralesional antimonials (Stahl 2014). Use of electrocauterisation is based on the fact that physical wound debridement practised with bipolar high frequency electrosurgical cauterisation (HF-EC) seems to speed up wound healing (Jebran 2014). The results of the RCT showed that DAC N-055 alone was significantly more efficacious than ILMA (Stahl 2014).

Topical Thio-Ben

An Iranian study reported promising results in OWCL using topical thioxolone plus benzoxonium chloride, or Thio-Ben (Daie Parizi 1992; Daie Parizi 1996). Thioxolone, which has long been topically administered for the treatment of acne and psoriasis, is recognised as a safe drug. A later RCT from Iran compared topical Thio-Ben plus cryotherapy versus meglumine antimoniate (Glucantime) plus cryotherapy (Daie Parizi 2015), showing that topical Thio-Ben plus cryotherapy had good efficacy for OWCL, with fewer side affects than ILMA.

Physical therapies

People with OWCL may receive a range of physical treatments, including vaporisation, cauterisation, freezing, surgical excision, and the application of local heat.

Laser

Carbon dioxide (CO^2) lasers have been used to vaporise CL lesions, thereby destroying affected tissue without significant side effects in normal tissue (Asilian 2004b). Studies have shown that a single session is enough, with lesions healing within three to four weeks, with quite admissible cosmetic results, although the procedure is painful and requires local anaesthetic (Shamsi Meymandi 2011).

Trichloroacetic acid (TCA)

The efficacy of TCA for treating CL could be due to the destruction of infected tissue and skin regeneration (Nilforoushzadeh 2006).

Cryotherapy

Cryotherapy with liquid nitrogen has been used to treat individual lesions, destroying infected tissue, but it is labour intensive (Layegh 2009). As an effective, painless, low-cost technique with few side effects, it is an especially good option for children (Layegh 2009; Salmanpour 2006). However, it is not suitable for multiple or complicated lesions (Alrajhi 2003; Bassiouny 1982; Layegh 2009; Leibovici 1986; Minodier 2007; Mosleh 2008; Ranawaka 2011).

Thermotherapy

Laboratory studies have reported that *Leishmania* parasites cannot multiply in macrophages when temperatures are greater than 39°C (Berman 1981; Sacks 1983). These findings have stimulated investigations into the efficacy of thermotherapy for CL with direct-current electrical stimulation (Sharquie 1998), ultrasound (Aram 1987), infrared light (Junaid 1986), hot-water baths (Neva 1984), laser (Asilian 2004b; Babajev 1991; Meawad 1997; Rodriguez 1990), radiofrequency waves, and ThermoMed device (Reithinger 2005; Sadeghian 2007; Aronson 2010). The procedure is painful and may require local anaesthetic (Sadeghian 2007).

Topical photodynamic therapy

Photodynamic therapy is a light-mediated technique that causes cytolysis of *Leishmania* parasites, resulting in an effective and safe therapeutic option for OWCL (Asilian 2006).

Mesotherapy

Mesotherapy is based on the use of a specific amount of variable substance (hormones, nutrients, enzymes, pharmaceuticals, and detergents, among others) and is not an invasive technique. People have received it for treating cellulite and acne scars, reducing aging skin, and rejuvenating the hands and neck (Amin 2006; Rohrich 2003). One RCT performed in Iran compared mesotherapy with ILMA, finding no difference in cure rates between the two therapeutic options (Kashani 2010).

Methods for promoting healing

Methods used in wound healing, including dressing and antiseptics, are often employed in ulcerative lesions of CL to accelerate cure, normalise epithelialisation, and reduce scarring, especially at cosmetic sites (Stahl 2014). Compromised wound healing due to repetitive trauma, contamination, and infection are major problems encountered in people with OWCL, and it is important to improve scar formation or at least not interfere with the natural healing process (Gonzalez 2008). A recent consensus panel on recommendations for chronic and acute wound dressings reported that "hydrocolloid (polymer dressings with medium absorption properties and containing carboxymethylcellulose) and low-adherent dressings seem to be the most suitable dressings for the epithelialisation stage of chronic and acute wounds" (Vaneau 2007). The highest impact of scarring and ulcerative lesions is on the faces of young women, which exposes them to stigma and which may affect their marriage prospects (Weigel 2001; Reithinger 2005b). To assess the cosmetic impact, clinicians often use the Burn Scar Index (also known as the Vancouver Scar Scale) to document change in scar appearance (Baryza 1995), which should be ideally measured six months after completion of treatment (Modabber 2007).

Alternative therapies

Increasing treatment failure with antimonial drugs has accelerated the search for alternative therapies (Nilforoushzadeh 2007). Up to 80% of the world's population may depend on medicinal plants as the only source of remedies for this disease; modern drugs may be either too expensive or wholly inaccessible (Fatima 2005). Practitioners of both traditional and modern medicine in Iran have long used herbal remedies and honey (Nilforoushzadeh 2007; Zerehsaz 1999). Different plants with medicinal value (*Azadirachta indica*, *Acacia nilotica*, and *Allium sativa*), traditionally used in the west and central parts of Sudan, have proven to have active anti-*Leishmania* activity on *L major* promastigotes in vitro (Fatima 2005;

Khalid 2005). Honey is effective for wound healing through enhancement of granulation and epithelialisation stages, enhancement of debridement, and downsizing of wound malodour (Moore 2001; Pieper 2003). Studies have described that honey from flowers in Australia and New Zealand has antibacterial effects (Pieper 2003).

How the intervention might work

OWCL is a heterogeneous group of diseases that differ in their clinical presentation, prognosis, and response to different the therapeutic interventions. There are two main factors affecting response to treatment: the species of *Leishmania* and the clinical form of the disease.

The mechanisms of action of the different therapeutic options for OWCL are diverse and may act over different targets, which can result in a complementary effect when working in combination (González 2009). There are two main types of therapeutic options: local physical therapies and local or systemic pharmacological therapies (Gonzalez 2008). Physical therapies such as HSCS, CO_2 lasers, TCA, cryotherapy, thermotherapy, and photodynamic therapy can destroy the parasite, the infected tissues, and the locally formed granulomas (González 2009). Pharmacological therapies, such as pentavalent antimonials, amphotericin B and its lipid formulations, miltefosine, paromomycin, and pentamidine, seem to enter the host cells and act against amastigotes, compromising the parasite metabolism, altering the parasite membrane fluidity or damaging the parasite mitochondria, among other mechanisms of action (Gonzalez 2008).

Therapeutic interventions could work in several ways: healing the forms of disease that would run a chronic course without treatment (*L aethiopica*); avoiding the progression of the disease to more complex clinical forms (mucocutaneous leishmaniasis, diffuse cutaneous leishmaniasis, leishmaniasis recidivans, etc.); speeding the healing of those forms that would naturally cure (*L major*); avoiding sequelae and disfiguring residual lesions (*L major, L tropica, L infantum*); and decreasing the human reservoir in anthroponotic forms (*L tropica*).

As a wide range of interventions are available, from physical or pharmacological local therapy to parenteral treatment, and response to treatment varies depending on the *Leishmania* species, knowing the optimal therapeutic approach in each situation is of great interest. This review aims to analyse the different interventions in order to provide the best treatment options for OWCL.

Why it is important to do this review

Controlling CL currently depends on early detection and rapid treatment (González 2009). The mainstays of treatment have been pentavalent antimonials, but other oral and topical treatment alternatives have become available in recent years (Gonzalez 2008). Global health development policies have mainly focused on innovative research to develop effective and affordable tools to tackle neglected tropical diseases (NTDs) and provide necessary new knowledge (WHO 2010). WHO is now prioritising the delivery of drugs that are currently available and using existing resources to reduce mortality, morbidity, and disability as a result of NTDs in low-income countries (Savioli 2006). However, evidence for the comparative effectiveness, cost-effectiveness, and safety of different treatment strategies is needed to improve disease control.

This systematic review focused on addressing the effects of treatments for the localised form of CL due to *L tropica* and *L major*, which account for more than 90% of CL in the Old World (WHO 2010). Since the overwhelming majority of OWCL cases heal spontaneously within 3 to 18 months (Blum 2014), the rationale for using systemic and topical treatments needs to be well established and preferably stratified for different geographic regions and *Leishmania* species. Separate Cochrane Reviews have addressed treatments for American CL and prevention measures for all types of cutaneous and mucosal leishmaniasis (González 2009; González 2015).

The protocol of this review was first entitled 'Interventions for solitary or limited cutaneous leishmaniasis'. However, we split the clinical subject into two reviews. We amended the title of the present review, first published in 2008 (Gonzalez 2008), to 'Interventions for Old World cutaneous leishmaniasis', and we also published a separate Cochrane Review, entitled 'Interventions for American cutaneous and mucocutaneous leishmaniasis' (González 2009). Thus, some parts of the Background and Methods sections are common to both reviews.

OBJECTIVES

To assess the effects of therapeutic interventions for the localised form of Old World cutaneous leishmaniasis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

All immunocompetent people who had localised OWCL confirmed by parasitological diagnostic methods (i.e. tissue smears, histology, culture or PCR).

Types of interventions

The interventions were either single therapy or combination therapy. The comparators were either no treatment, placebo/vehicle only, or another active compound.

1. Systemic and intralesional antimonials

1.1 Meglumine antimoniate (Glucantime)
1.2 Sodium stibogluconate (Pentostam)

2. Non-antimonial systemic treatments

2.1 Oral antifungals
2.2 Oral dapsone
2.3 Oral allopurinol
2.4 Oral antibiotics
2.5 Oral pentoxifylline
2.6 Oral miltefosine
2.7 Oral zinc sulphate
2.8 Oral artesunate

3. Non-antimonial topical or intralesional therapies

3.1 Topical antifungals
3.2 Topical paromomycin (aminosidine)
3.3 Intralesional zinc sulphate
3.4 Topical imiquimod
3.5 Intralesional hypertonic sodium chloride (HSCS)
3.6 Intralesional interferon-gamma (IFN-γ)
3.7 Topical aminoglycoside ointment (WR279,396)
3.8 Intralesional metronidazole
3.9 Topical miltefosine
3.10 Topical dapsone
3.11 Topical 0.045% pharmaceutical chlorite (DAC N-055)
3.12 Topical Thio-Ben

4. Physical therapies

4.1 Laser
4.2 Trichloroacetic acid
4.3 Cryotherapy
4.4 Thermotherapy
4.5. Topical photodynamic therapy
4.6. Mesotherapy

5. Measures for promoting healing

6. Alternative therapies

Types of outcome measures

We did not limit the measurement of any outcomes based on length of follow-up.

Primary outcomes

1. Percentage of lesions cured after the end of treatment
2. Percentage of participants with a complete cure after the end of treatment

By cured, we meant that all inflammatory signs disappeared (either skin oedema, hardening, or both) and that complete scarring or healthy repair occurred in ulcerative lesions. We did not consider lesions to be healed if there was no re-epithelialised skin, or if inflammatory signs remained after follow-up.

Secondary outcomes

1. Speed of healing (time taken to be 'cured')
2. Duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years
3. Degree of functional and aesthetic impairment
4. Prevention of scarring
5. Quality of life
6. Adverse effects

Tertiary outcomes

1. Change in ability to detect *Leishmania* by parasitological diagnostic methods (e.g. smear, PCR, or culture)
2. "Emergence of treatment failures (defined as a decline in the efficacy of a drug against a population of parasites previously susceptible to that compound. The definition assumes that the original susceptibility of the population is known, which is not always the case for *Leishmania*)" (Ponte-Sucre 2003)
3. Microbiological or histopathological cure of skin lesions
4. Development of cell-mediated immunity (i.e. positive leishmanin skin test)

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

For this update, we revised all our search strategies in line with current Cochrane Skin practices. Details of the previous search strategies are available in Gonzalez 2008.

We searched the following databases up to 17 November 2016:

- Cochrane Skin Specialised Register, using the search strategy in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 10) in the Cochrane Library, using the strategy in Appendix 2.
- MEDLINE via Ovid (from 1946), using the strategy in Appendix 3

- Embase via Ovid (from 1974) using the strategy in Appendix 4.
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 5.

Trials registers

We searched the following trials registers in October 2015 using the term 'cutaneous leishmaniasis'.

- ISRCTN registry (www.isrctn.com).
- ClinicalTrials.gov (www.clinicaltrials.gov).
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

Searching other resources

References from unpublished studies

We checked the bibliographies of included studies and key papers identified by our searches for further references to relevant trials.

Unpublished literature

We wrote to national programme managers, general coordinators, directors, clinicians, regional officers from endemic countries in the WHO Eastern Mediterranean Region, pharmaceutical companies, and relevant authors for further information about unpublished and ongoing trials. We also contacted the following tropical medicine centres.

- Department of Infectious Diseases and Tropical Medicine at the University of Munich, Germany.
- Swiss Tropical Institute, Switzerland; Prince Leopold Institute of Tropical Medicine, Belgium.
- McGill Centre for Tropical Disease, Canada.
- Tulane University School of Public Health & Tropical Medicine, USA.
- London School of Hygiene & Tropical Medicine, UK.
- Tropical Medicine at the Liverpool School of Tropical Medicine, UK.
- Department of Public Health and Tropical Medicine James Cook, University of North Queensland, Australia.
- Institut Pasteur, France.
- Bernhard Nocht Institute, Germany.
- TropEdEurop, Spain.

Adverse effects

We searched MEDLINE (Ovid) from 1946 to 30 September 2015 for adverse or side effects of interventions for Old World cutaneous leishmaniasis using the search strategy in Appendix 6.

Data collection and analysis

Some parts of this review use text that was originally published in other Cochrane Reviews (predominantly van Zuuren 2015, Ingram 2015, and Delamere 2008; the latter was an exemplar Cochrane Review at the time the original review was written).

Selection of studies

We checked the titles and abstracts identified from the searches by at least two authors (JHM, PC, PLP, BMM, EGM). If it was unclear, then two authors obtained the full text study for independent assessment (BMM, EGM). The authors decided which trials met the inclusion criteria. The authors resolved any disagreements by discussion, with referral to a third author (AR) if necessary. We describe excluded studies and reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

At least two independent authors (MP, LR, JHM, PLP) carried out data extraction using a pre-designed data extraction form. We extracted data for all outcomes for all relevant drugs, paying attention particularly to the doses and therapy frequencies. We resolved disagreements by discussion. We obtained the missing data from trial authors when possible.

Assessment of risk of bias in included studies

The quality assessment included an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Higgins 2011).

- The method for generating the randomisation sequence.
- The method for concealing allocation - it was considered 'adequate' if personnel and participants could not have foreseen assignment.
- Blinding (participants, clinicians, outcome assessors).
- Loss to follow-up in each arm (split into postrandomisation exclusions and later losses if possible), and whether participants were analysed in the groups to which they were originally randomised (intention-to-treat).

In addition, the quality assessment also included the following.

- Declaration of sample size calculation.
- Definition of inclusion and exclusion criteria.
- Reporting of *Leishmania* species involved.
- Time of follow-up.

- Baseline comparability of severity of infection, age, sex, and duration of complaint.
- Conflict of interest.

We assessed these other risks of bias. When trials reported two or more incorrectly, we judged them to be at high risk. When trials reported only one incorrectly, we judged them to be at unclear risk. We recorded the information in 'Risk of bias' tables (Characteristics of included studies) and described the quality of each study based on these components.

Measures of treatment effect

We reported all outcome data with their associated 95% confidence interval (CI). We expressed results as risk ratios (RR) and 95% CIs for dichotomous outcomes. We presented continuous outcomes with the same scale as reported in each trial, with a mean change from baseline with its associated standard deviation (SD), or as weighted mean difference (MD) or standardised mean difference (SMD) if more than one study was available.
If enough information was available in the study reports, we decided to describe hazard ratios (HR) for time-to-event outcome data.

Unit of analysis issues

We found that most RCTs included in this review assessed participants instead of lesions as the unit of analysis. When lesions were used as unit of analysis, comparisons were performed with lesions cured over lesions at start, not taking into account the correlation of multiple lesions per participant. We only pooled together studies which reported number of participants cured (not number of lesions), due to unit of analysis issues.
The approach followed to 3-arm trials, was comparing the arms in pairs (A vs B, B vs C, and A vs C).
We only considered parallel group designs for all clinical trials. We did not consider cross-over trials in this review because they are an inappropriate design for treatments that can potentially cure an infectious disease. We did not find any particular additional important information in the specific search for adverse effects for every particular treatment. Authors described these qualitatively in the Results and Discussion sections.

Dealing with missing data

For all missing data from trials that were less than 10 years old, we tried to contact the authors. Only six of the trials explicitly stated intention-to-treat (ITT) analysis. Where an ITT was not stated, we used the numbers originally randomised to the groups in order to calculate effect estimates.
For each study, we took all participants that were randomised into account when introducing the data in our tables. We sent emails to study authors asking for more information, and we recorded these emails and their responses. When we had no response, we assumed that missing data were treatment failures. Concerning the losses to follow-up, it was not always possible to determine the arm in which the losses occurred, making ITT analyses impossible. In that case, we introduced only available data into the tables for analysis.

Assessment of heterogeneity

To assess the consistency of the study results, we obtained the I^2 statistic, which measures the proportion of total variation across studies that is due to heterogeneity rather than chance. I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. We analysed statistical heterogeneity using a Chi^2 test (on 1 degree of freedom, with a significance level of 0.05) (Higgins 2003).

Assessment of reporting biases

In this review, the low number of studies evaluating similar interventions and comparisons did not permit an assessment of publication bias. In future updates, if a sufficient number of trials assessing similar effects are identified for inclusion in this review, publication bias will be assessed according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in section 10.4.3.1 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If asymmetry is identified we will try to assess other possible causes and these will be explored in the discussion if appropriate

Data synthesis

We performed data synthesis only when we were able to identify at least two studies investigating similar treatments and reporting data amenable to pooling. Although there is inevitably a degree of heterogeneity between the studies included in a review, we entered these into a meta-analysis if clinical reasoning could explain the heterogeneity and if there was a coherent argument for combining the studies. We used the random-effects model, as this is more conservative in the presence of heterogeneity.
The percentage of lesions cured after the end of treatment was the primary outcome measure if available. If this were not available, we used secondary and tertiary outcomes. To estimate differences between treatments, we pooled trials that evaluated similar interventions and controls and calculated a weighted treatment effect across trials, using a random-effects model. Where it was not possible to perform a meta-analysis, we summarised the data for each trial.

Subgroup analysis and investigation of heterogeneity

In view of the limited number of included studies covering any one specific intervention, we did not conduct any of the subgroup analyses that we originally planned: *Leishmania* species, location

and severity of infection, geographical setting, diagnostic techniques, type of treatment (topical, systemic, or combination), and relapse or re-infection.

We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, the comparisons, and the outcomes as specified in the criteria for included studies.

Sensitivity analysis

We plan to carry out a sensitivity analysis by excluding studies at high risk of bias.

Summary of findings tables

We used the GRADE approach to rate certainty of the evidence (for each outcomes) and strength of recommendations (Guyatt 2008). For better understanding of the review, we highlighted the GRADE assessments in 'Summary of findings' tables of key comparisons and outcomes.

Depending on the study design, risk of bias, consistency of the results across studies, and precision of the overall estimated across studies, certainty of evidence can be high, moderate, low, or very low.

RESULTS

Description of studies

Results of the search

The previous version of this review identified 49 trials with 5559 randomised participants (Gonzalez 2008).

The update searches of the five databases (see Electronic searches) retrieved 517 records. Our searches of other resources identified six ongoing studies. We obtained no response from the institutions we contacted to try to identify further trials.

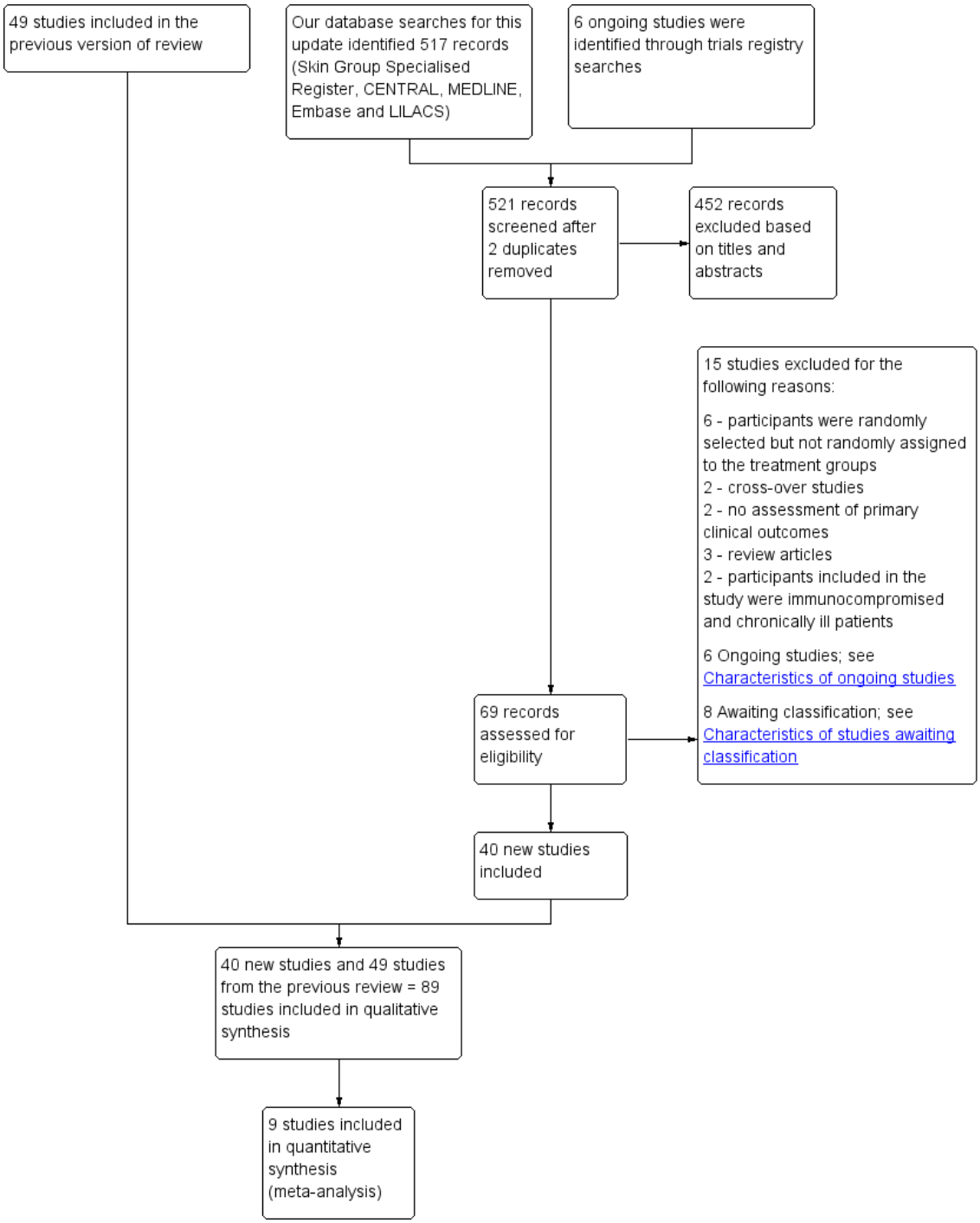
Once we removed duplicates, we had a total of 521 records. We excluded 452 records based on titles and abstracts and obtained the full text of the remaining 69 records. We excluded 15 studies (see Characteristics of excluded studies) and included 40, taking the total number of included studies to 89 (see Characteristics of included studies).

There are eight studies awaiting assessment: (Farajzadeh 2016a; Farajzadeh 2016b; Hanif 2016; Jaffary 2016; Na-Bangchang 2016; Rajabi 2016; Refai 2016; Sattar 2012) (see Characteristics of studies awaiting classification). We found six ongoing trials (see Characteristics of ongoing studies).

Two studies were reported in two references: Nilforoushzadeh 2006 and Shanehsaz 2015.

For a further description of our screening process, see the study flow diagram Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 89 studies (including 40 new to this update) involving 10,583 randomised participants with Old World cutaneous leishmaniasis (see Characteristics of included studies table).

Design

All of the studies were RCTs: 30 were placebo-controlled, and 59 had an active treatment comparator. Seventy-two took place after the year 2000; 85 were single-centre studies, and the other 4 were multicentre studies (Asilian 1995; Asilian 2003; Ben Salah 2009; Ejaz 2014).

Sample sizes

The number of participants included in the individual studies ranged from 18 to 444; the most common sample size was 50 to 120 participants (interquartile range).

Setting

The studies included in this review took place in different countries, mainly in the Far or Middle East. Fifty-three took place in Iran; seven in India; five in Africa (Sudan and Tunisia), four each in Saudi Arabia and Afghanistan; three each in Pakistan, Iraq, and Syria; two each in Kuwait and Sri Lanka; and one each in Yemen, Turkey, and the USA (recruiting Department of Defense healthcare beneficiaries who were likely to have been infected in Iraq or in Kuwait). Most studies took place in regional hospitals, teaching hospitals, local healthcare clinics, and skin disease research centres. A few studies were in military hospitals or army medical centres.

Participants

The studies had a mean of 41.5% of women participants, but this ranged from 23% to 80%. Four RCTs conducted by military institutions only included men (Aronson 2010; Ejaz 2014; Mashood 2001; Shazad 2005). Mean age in the individual studies ranged from 12 years to 56 years, with an overall mean age of 24.5 years. There were three RCTs including participants exclusively under 14 years (Asilian 1995; Asilian 2003; Lynen 1992). This review focused on *L major* and*L tropica* infections because of the paucity of studies involving *L infantum*,*L aethiopica*, or*L donovani*.

Interventions

Trials evaluated a wide range of interventions, which we categorised into six types.

1. Systemic and intralesional antimonials (8 studies).
2. Non-antimonial systemic treatments (28 studies).
3. Non-antimonial topical or intralesional therapies (28 studies).
4. Physical therapies (28 studies).
5. Measures for promoting healing (1 study).
6. Alternative therapies (5 studies).

The 89 studies covered 68 comparisons, and 59 included an active control arm. Duration of the intervention in most studies ranged between two and eight weeks (mean six weeks).

We describe examples of the first four categories in the Methods section under Types of interventions. The study on promotion of healing compared two topical interventions: diminazene aceturate (Berenil) versus cetrimide plus chlorhexidine (Savlon). Examples of alternative therapies were topical interventions based on substances like garlic, herbal extracts, or honey.

Systemic and intralesional antimonials included meglumine antimoniate (MA) and sodium stibogluconate (SSG) administered intramuscularly (IM) or intralesionally (IL). The standard dosage was 20 mg/kg/d, though some studies used higher doses such as 30 mg/kg/d or 60 mg/kg/d. The standard schedule frequency was 20 days (three weeks), but in some studies the treatment was extended until achieving cure.

Non-antimonial systemic treatments included oral antifungals such as ketoconazole, itraconazole, and fluconazole. Trials compared itraconazole only against placebo or no treatment, whereas the trials on ketoconazole and fluconazole compared increasing dosages. Some trials compared ketoconazole versus intramuscular or intralesional SSG and intralesional meglumine antimoniate (ILMA). This treatment category also included oral dapsone versus placebo, oral allopurinol versus intramuscular meglumine antimoniate (IMMA) or intravenous sodium stibogluconate (IVSSG), oral antibiotics alone or combined versus placebo or IMMA, oral pentoxifylline alone or combined versus IMMA, oral zinc sulphate versus IMMA and oral artesunate versus placebo.

Non-antimonial topical or intralesional therapies comprised topical antifungals like miconazole, ketoconazole, amphotericin B, and clotrimazole as well as topical paromomycin alone or in combination with oral ketoconazole, photodynamic therapy, intralesional zinc sulphate, hypertonic sodium chloride (HSCS), INF-ɣ , metronidazole, topical imiquimod, miltefosine, dapsone, 0.045% pharmaceutical chlorite (DAC N-055), and Thio-Ben. The vast majority were tested against ILMA or ILSSG, with some therapies also compared to placebo/vehicle (topical paromomycin) or different regimens of paromomycin (photodynamic therapy).

Physical therapies included ablative or fractional CO_2 laser, compared against each other, IMMA, or cryotherapy. Trichloroacetic acid (TCA), alone or combined with non-ablative CO_2 laser, was

compared with ILMA. Cryotherapy, alone or combined with 15% paromomycin and/or ILMA, was compared with ILMA alone or combined. Cryotherapy was also combined with topical treatments such as 3% salicylic acid cream and 3% sodium nitrite cream and compared against cryotherapy plus 3% salicylic acid cream plus a vehicle. Thermotherapy using radiofrequency waves was compared with ILMA, ILSSG, and IMSSG. Another type of thermotherapy included electrocauterisation, tested with or without DAC N-055.

Measures for promoting healing included topical diminazene aceturate (Berenil) versus topical cetrimide and chlorhexidine (Savlon), and trials of alternative therapies included topical interventions alone or combined compared with ILMA (topical honey plus ILMA; topical *Cassia fistula* alone or with fruit gel plus ILMA; and topical *Achilles millefolium* cream plus ILMA) or IMMA (topical herbal extract).

Heterogeneity in study design, medium to high levels of data bias, missing standard deviations, and a mix of different comparators, dosing regimens, and scheduled frequency did not, in general, permit pooling of the data or allow us to make accurate and direct comparisons of a substantial number of the interventions.

Outcomes

Three RCTs did not clearly report the time points when the primary outcome was assessed (Dandashli 2005; Mapar 2010; Salmanpour 2006), and the remaining studies reported a time ranging from the end of treatment to six months after treatment.

1. **Percentage of lesions cured after the end of treatment**. Only 18 RCTs reported the primary outcome as percentage of lesions cured at three months after the end of treatment (Al Hamdi 2010; Alkhawajah 1997; Aronson 2010; Asilian 2004a; Asilian 2006; Dandashli 2005; El-Sayed 2010; Firooz 2005; Harms 1991; Jowkar 2012; Khatami 2013; Larbi 1995; Maleki 2012; Mujtaba 1999; Ranawaka 2015; Shamsi Meymandi 2011; Shanehsaz 2015; Sharquie 2001).
2. **Percentage of participants with a complete cure after the end of treatment**. The rest of the studies reported the percentages in terms of participants cured.

Varying numbers of studies reported the following secondary outcome measures.

1. **Speed of healing** (time taken to be 'cured') in 16 studies (Alrajhi 2002; Aronson 2010; Asilian 2004b; Ben Salah 2009; Farajzadeh 2015; Jaffary 2014b; Jebran 2014; Layegh 2009; Mujtaba 1999; Nilforoushzadeh 2007; Nilforoushzadeh 2013; Ranawaka 2015; Reithinger 2005; Sharquie 1997; Sharquie 2001; Stahl 2014).
2. **Duration of remission and percentage of people with treated lesions that recur within more than 6 months** in nine studies (Al-Fouzan 1991; Bumb 2013; Ejaz 2014; Faghihi 2003; Fekri 2015; Mujtaba 1999; Ranawaka 2010; Ranawaka 2015; Sadeghian 2006b).
3. **Degree of functional or aesthetic impairment** (no studies measured this outcome).
4. **Prevention of scarring** in eight studies (Alkhawajah 1997; Asilian 2004b; Asilian 2006; Faghihi 2003; Mujtaba 1999; Sadeghian 2007; Sharquie 1997; Sharquie 2001).
5. **Quality of life** (no studies measured this outcome).
6. **Adverse effects** in all but eight studies (Al Hamdi 2010; Asilian 2014; Farajzadeh 2015; Kochar 2006; Nilforoushzadeh 2004; Nilforoushzadeh 2008; Nilforoushzadeh 2012; Nilforoushzadeh 2013).

Three studies did not report secondary outcomes (Jaffar 2006; Kochar 2006; Nilforoushzadeh 2004).

A number of studies also reported tertiary outcome measures.

1. **Change in ability to detect *Leishmania* by *parasitological diagnostic methods*** (e.g. smear, polymerase chain reaction (PCR), or culture). Two RCTs reported results where *Leishmania* was detected by parasitological diagnostic methods (e.g. PCR or culture, positive smears) (Jaffary 2014A; Jebran 2014). No studies reported emergence of resistance.
2. **Emergence of treatment failures** (defined as a decline in the efficacy of a drug against a population of parasites previously susceptible to that compound (Ponte-Sucre 2003). The definition assumes that the original susceptibility of the population is known, which is not always the case for *Leishmania*). No studies reported this outcome.
3. **Microbiological or histopathological cure of skin lesions**, reported in 15 studies (Aronson 2010; Asilian 1995; Asilian 2003; Asilian 2004a; Ben Salah 1995; Dogra 1990; Dogra 1991; Dogra 1996; Harms 1991; Jebran 2014; Kashani 2010; Kochar 2000; Momeni 2002; Nilforoushzadeh 2006; Shamsi Meymandi 2011).
4. **Development of cell-mediated immunity** (i.e. positive leishmanin skin test). One study reported the percentage of participants who developed Leishman bodies three months after treatment (Kashani 2010).

Excluded studies

We excluded 15 RCTs for the reasons described in the Characteristics of excluded studies tables and below.

- Participants were randomly selected but not randomly assigned to the treatment groups.
- Cross-over studies.
- No assessment of clinical primary outcomes.
- Review and meta-analysis.
- Participants included in the study were immunocompromised and chronically ill patients.

Studies awaiting assessment

We identified seven studies from full-text screening (Farajzadeh 2016a; Farajzadeh 2016b; Hanif 2016; Jaffary 2016; Na-

Bangchang 2016; Rajabi 2016; Refai 2016), and one by assessing an abstract (Sattar 2012). These studies evaluated the following.

- Intralesional injection of zinc sulphate versus ILMA (Glucantime)e.
- IMMA plus vehicle versus IMMA plus topical terbinafine.
- Intralesional versus oral chloroquine administration.
- ILMA (Glucantime) plus topical trichloroacetic acid (TCA) 50% versus ILMA alone versus fractional carbon dioxide laser.
- Shiunko ointment versus vehicle.
- Topical liposomal form of azithromycin versus ILMA (Glucantime).
- Radiofrequency-induced heat therapy versus ILMA (Glucantime).
- Topical ointment prepared from the stem extract of *Morinda citrifolia*.

We will evaluate them in a future update of this review.

Ongoing studies

We identified six ongoing studies (Characteristics of ongoing studies).

Risk of bias in included studies

Please see Figure 2 for the 'Risk of bias' summary: review authors' judgments about each risk of bias item for each included study, and see Figure 3 for the 'Risk of bias' graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

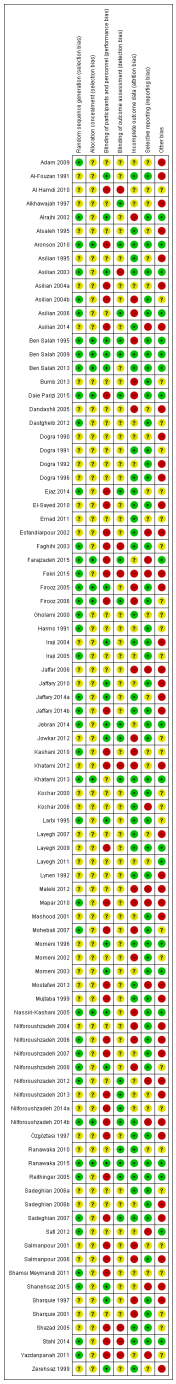
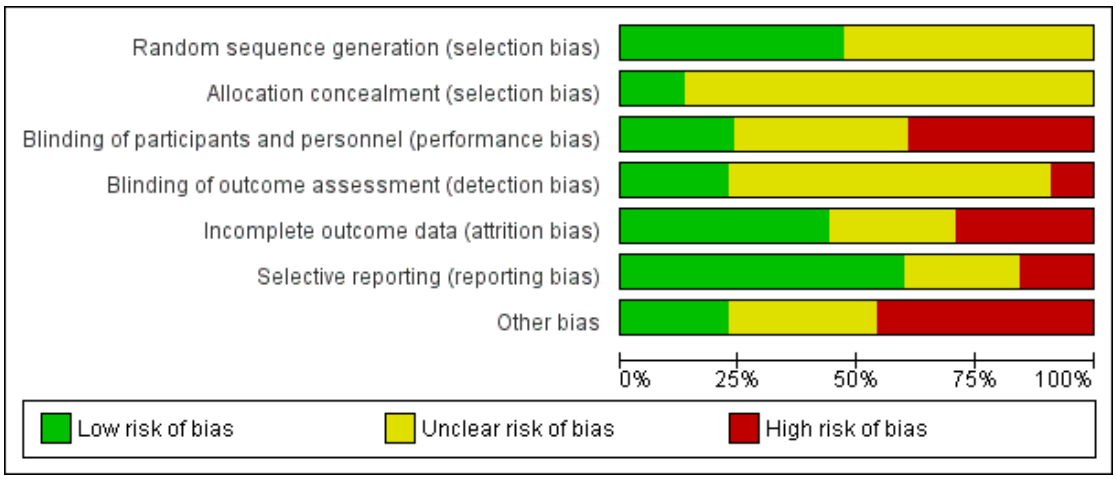


Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Our assessment of the risk of bias in the included studies has broadly followed the criteria set in the protocol. We thought the quality of the RCTs was generally poor for the following reasons.

Allocation

Forty-two (47.2%) studies clearly described an adequate method of random sequence generation, meriting a judgment of low risk of bias, whereas the risk of bias in the rest of the studies (47/89, 52.8%) was unclear (Characteristics of included studies; Figure 2; Figure 3).

Of the 42 studies that were at low risk for sequence generation, only 12 (13.5%) also used an adequate method of allocation concealment (Aronson 2010; Ben Salah 1995; Ben Salah 2009; Ben Salah 2013; Farajzadeh 2015; Firooz 2005; Firooz 2006; Khatami 2013; Nassiri-Kashani 2005; Nilforoushzadeh 2014b; Daie Parizi 2015; Ranawaka 2015; see Characteristics of included studies for details). However, in most studies (77, 86.5%), the method used to conceal the allocation prior to assignment was unclear.

Blinding

Only 21 studies were at low risk of performance bias because they clearly reported blinding participants or used other methods that we judged as unlikely to add risk of bias. Thirty-three studies did not provide enough information about the blinding of the participants. Among the 35 studies that did not blind the intervention and were at high risk of bias, there were some interventions that were impossible to blind due to the different administration routes (Esfandiarpour 2002; Farajzadeh 2015; Jaffary 2014b; Nilforoushzadeh 2013; Daie Parizi 2015; Sadeghian 2007; Salmanpour 2001; Salmanpour 2006).

With regard to the blinding of the outcome assessment, most studies 62/89 (69.7%) did not provide enough information about the blinding. Authors described 20 studies as blinded, and we therefore judged them to be at low risk of bias, whereas we judged 7 studies to be at high risk. See Characteristics of included studies for further details on who was blinded.

Incomplete outcome data

Of the 89 included studies, we considered the risk of bias for 39 (43.8%) to be low; for 24 (27.0%), unclear; and for 26 (29.2%), high.

Dropouts

The overall number of participants lost to follow-up was 1439, or 13.6% of the total number of study participants included in the review. We have categorised the dropouts into groups according to the percentage of evaluable participants (Characteristics of included studies).

Intention-to-treat analyses

Sixty-four studies accounted for losses to follow-up, while the other 25 did not report dropouts. However, 55 out of the 64 studies did not carry out intention-to-treat (ITT) analyses, or rather they just assessed participants who completed treatment. For each study, we took all randomised participants into account when introducing the data in our tables. We assumed that missing data were treatment failures. Concerning the loss to follow-up, it was not always possible to determine the arm in which the losses occurred, complicating ITT analyses. In that case, we introduced only available data into the tables for analysis.

Selective reporting

Of the 89 included studies, 53 (59.55%) reported all expected outcomes, meriting a judgment of low risk of bias. We considered 22 studies (25.72%) to be at unclear risk of bias. Fourteen studies (15.73%) failed to report, or reported only incompletely (making it impossible to enter the data into meta-analysis), results for a key outcome that would be expected to have been reported, and we therefore considered these studies to be at high risk of bias.

Other potential sources of bias

We assessed other potential sources of bias such as sample size calculation, the reporting of *Leishmania* species and baseline comparability among intervention groups. If a study reported all three items correctly, we classified it as being at low risk of bias. If at least one of the items were not reported correctly, we classified it as being at high risk of bias, and if the study did not report enough information to assess if there were other biases present, we classified it as being at unclear risk of bias. Of the 89 included studies, we considered the risk of bias to be high in 41 (46.07%), unclear in 28 (31.46%), and low in 20 (22.47%).

Effects of interventions

See: **Summary of findings for the main comparison** Itraconazole (200 mg for 6 to 8 weeks) versus placebo for Old World cutaneous leishmaniasis; **Summary of findings 2** Paromomycin ointment versus vehicle for Old World cutaneous leishmaniasis

Please see the 'Summary of findings' tables, where we have summarised the certainty of the body of evidence for two of the most clinically important comparisons (Summary of findings for the main comparison; Summary of findings 2). We have produced two forest plots for our primary outcome, with subgroups for each comparison (see Figure 4; Figure 5), and we have summarised adverse effects in seven tables (see Table 3; Table 4; Table 5; Table 6; Table 7; Table 8; Table 9).

Figure 4. Forest Plot of Primary Outcome: Lesions Cured (Various comparisons)

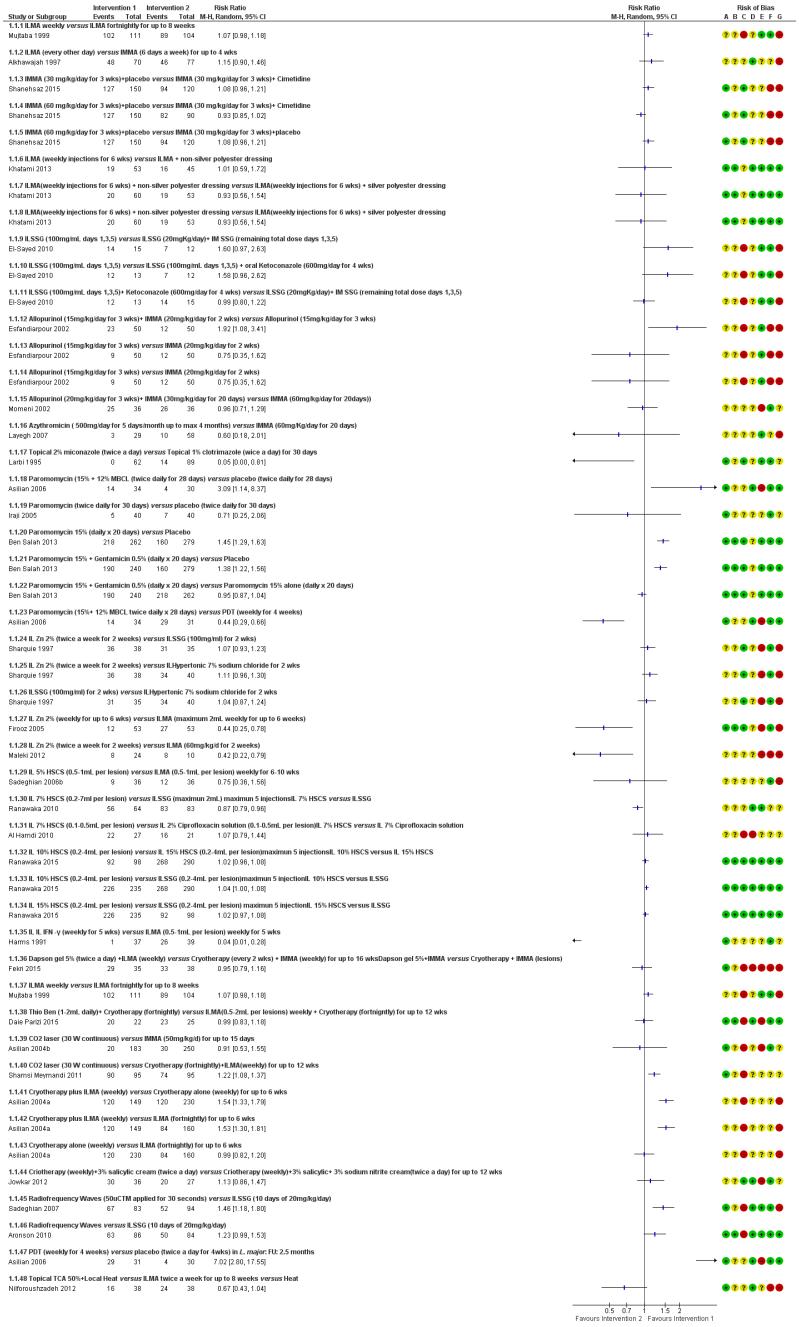
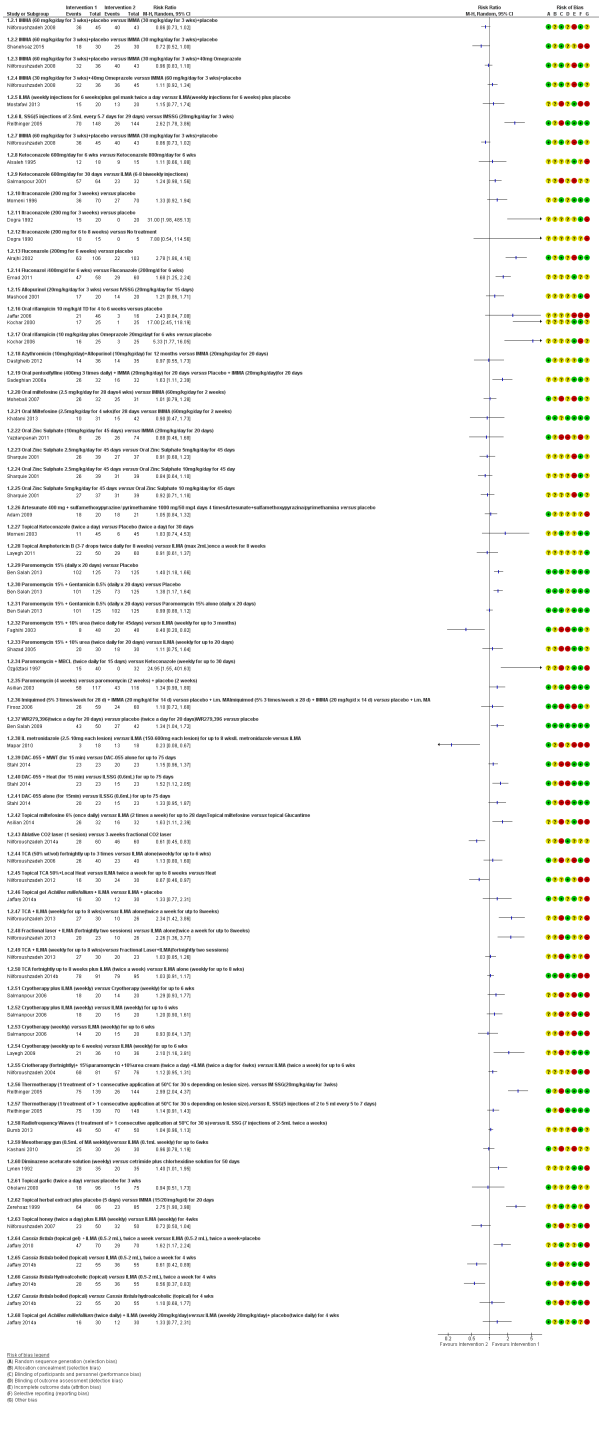


Figure 5. Forest plot of primary outcome: 1.2 Participants cured (Various comparisons)



We describe only those outcomes with data below. If a particular primary, secondary, or tertiary outcome is missing, then this is because we did not find suitable data. Pooling of outcome data across studies to provide a summary estimate of effect was only possible for five interventions and comparisons; these investigated the effects of topical paromomycin, itraconazole, radiofrequency waves, oral dapsone, and intramuscular meglumine antimoniate (IMMA). We categorised a substantial number of the studies included in this review as being at unclear or high risk of bias (see Figure 2 and Figure 3), so readers should interpret the results with caution.

We have addressed our pre-specified outcomes under the following intervention headings.

1. Systemic and intralesional antimonials.
2. Non-antimonial systemic treatments.
3. Non-antimonial topical or intralesional therapies.
4. Physical therapies.
5. Measures for promoting healing.
6. Alternative therapies.

We have also referred in the text to tables where we have summarised reports of adverse effects of the different interventions.

1. Systemic and intralesional antimonials

1.1 Meglumine antimoniate

1.1.1 Different doses of intralesional meglumine antimoniate

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Pakistan compared intralesional meglumine antimoniate (ILMA) weekly versus fortnightly, until complete cure or up to eight weeks (Mujtaba 1999). Two months after treatment, 92% (102/111) of the lesions were cured in the weekly, and 85.6% (89/104) in the fortnightly group. There was no statistical difference between weekly and fortnightly administration (risk ratio (RR) 1.07, 95% confidence interval (CI) 0.98 to 1.18; N = 215; 1 study, Analysis 1.1).

Secondary outcome: speed of healing (time taken to be 'cured')

Most lesions had healed at six weeks in both groups with minimal or absent scarring.

Secondary outcome: adverse effects

Authors did not report adverse effects in any of the participants, except transient pain at the site of the injections in both groups.

1.1.2 Intralesional versus intramuscular meglumine antimoniate

Primary outcome: percentage of lesions cured after the end of treatment

One RCT from Saudi Arabia compared ILMA every other day versus IMMA 6 days a week, over a 30-day period until the lesions had blanched (Alkhawajah 1997). The authors reported a comparable cure rate: 68.6% (48/70) and 59.7% (46/77) of the of lesions in the respective groups at the end of the treatment period (RR 1.15, 95% CI 0.90 to 1.46; N = 147; 1 study, Analysis 2.1).

Secondary outcome: adverse effects

Regarding adverse effects, both groups reported pain at the site of injection, but it was greater in the ILMA group.

1.1.3 Different doses of IMMA

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Syria compared IMMA 60 mg/kg/d plus placebo versus IMMA 30 mg/kg/d plus placebo or cimetidine for three weeks (Shanehsaz 2015). Three months after treatment, 91.1% (82/90) of the lesions were cured in the IMMA 60 mg plus placebo group, 84.6% (127/150) in the IMMA 30 mg plus cimetidine group, and 78.3% (94/120) in IMMA 30 mg plus placebo group. We did not find any significant differences in cure rates between the IMMA 30 mg plus cimetidine group versus the IMMA 30 mg plus placebo group (RR 1.08, 95% CI 0.96 to 1.21; N = 270; 1 study, Analysis 3.1) or between the IMMA 30 mg plus cimetidine group versus the IMMA 60 mg group (RR 0.93, 95% CI 0.85 to 1.02; N = 240; 1 study, Analysis 4.1). Cure rates were significantly higher in the IMMA 60 mg group compared with the IMMA 30 mg plus placebo group (RR 1.16 95% CI 1.04 to 1.30; N = 210; 1 study, Analysis 5.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

A pooled analysis of two trials showed that cure rates in the IMMA 60 mg group were better than in the IMMA 30 mg plus placebo group (RR 0.83, 95% CI 0.71 to 0.96; N = 148; Nilforoushzadeh 2008; Shanehsaz 2015, Analysis 6.1). We assessed the certainty of evidence as low, which means we are uncertain whether there is much difference in cure rate between these two concentrations of IMMA.

An RCT from Iran compared IMMA 60 mg/kg/d plus placebo versus IMMA 30 mg/kg/d plus placebo or omeprazole for three weeks (Nilforoushzadeh 2008). Three months after treatment, there was complete cure in 93% (40/43) of participants in the IMMA 60 mg plus placebo group, 89% (32/36) in the IMMA 30 mg plus omeprazole group, and 80% (36/45) in the IMMA 30 mg plus placebo group. There were no significant differences in cure rates in any comparisons: IMMA 30 mg plus omeprazole versus IMMA 60 mg (RR 0.96, 95% CI 0.83 to 1.10; N = 79; 1 study, Analysis 7.1), IMMA 30 mg plus placebo versus IMMA 60 mg plus placebo (RR 0.86, 95% CI 0.73 to 1.02; N = 88; 1 study, Analysis 8.1), or IMMA 30 mg plus omeprazole versus IMMA 30 mg plus placebo (RR 1.11, 95% CI 0.92 to 1.34; N = 81; 1 study, Analysis 9.1).

Secondary outcome: adverse effects

Regarding adverse effects, Shanehsaz 2015 reported serious adverse effects in 83.3% (n = 25) participants in the IMMA 60 mg dose group and 60% (n = 18) participants in the IMMA 30 mg group; 40% (n = 12) of participants in the IMMA 60 mg dose group and 23.3% (n = 7) in the 30 mg group experienced skin hypersensitivity, while there were five and three cases, respectively, of cardiac toxicity (QT prolongation) (Analysis 6.2). Hence, there were fewer serious adverse effects (RR 0.72, 95% CI 0.52 to 1.00; N = 60, 1 study), fewer skin reactions (RR 0.58, 95% CI 0.27 to 1.28; N = 60, 1 study), and less QT prolongation (RR 0.60, 95% CI 0.16 to 2.29; N = 60, 1 study) in the IMMA 30 mg plus placebo group, but none of the results were significant.
In Nilforoushzadeh 2008, the authors reported one case of anaphylactic shock to meglumine antimoniate (not described).

1.1.4 ILMA alone versus ILMA plus silver or non-silver dressing

Primary outcome: percentage of lesions cured after the end of treatment

One RCT from Iran compared weekly injections of ILMA for 6 weeks alone versus ILMA at the same dose plus silver or non-silver dressing (Khatami 2013). We performed an ITT analysis considering the lesions allocated in each arm at the beginning of the study: 26 participants with 45 lesions in the ILMA-alone group, 31 participants with 60 lesions in the ILMA plus silver dressing group, and 26 participants with 53 lesions in the ILMA plus non-silver dressing group. At one month after treatment, 35.5% (16/45) of lesions were cured in the ILMA-alone group, 33.3% (20/60) in the ILMA plus silver dressing group, and 35.8% (19/53) in the ILMA plus non-silver dressing group. There were no significant differences in cure rates between groups: ILMA plus non-silver dressing versus ILMA alone (RR 1.01, 95% CI 0.59 to 1.72; N = 98, Analysis 10.1); ILMA plus silver dressing versus ILMA alone (RR 0.94, 95% CI 0.55 to 1.60; N = 105, Analysis 11.1); or ILMA plus silver dressing versus ILMA plus non-silver dressing (RR 0.93, 95% CI 0.56 to 1.54; N = 113, Analysis 12.1).

Secondary outcome: adverse effects

Regarding adverse effects, participants reported itching and burning in 7.5% (n = 3) of lesions in ILMA alone group, 10.9% (n = 6) of lesions in the ILMA plus silver group, and 17.7% (n = 8) lesions in the ILMA plus non-silver group; there was also oedema in 12.5% (n = 5), 7.2% (n = 4), and 6.6% (n = 3) of the lesions, respectively. One lesion in each group showed exudation, and another lesion was accompanied by dermatitis in the ILMA plus non-silver group. There were no significant differences in any adverse effects rates in any comparison (Analysis 10.2; Analysis 10.3; Analysis 11.2; Analysis 11.3; Analysis 12.2; Analysis 12.3).

1.1.5 ILMA plus gel mask versus ILMA plus vehicle

Primary outcome: percentage of participants with a complete cure after the end of treatment

One RCT from Iran compared ILMA (weekly injections for six weeks) plus gel mask twice a day with ILMA (weekly injections for six weeks) plus placebo (Mostafavi 2013). At the end of treatment, 75% (15/20) and 65% (13/20) of participants, respectively, had complete cure. There were no significant differences in cure rates between groups (RR 1.15, 95% CI 0.77 to 1.74; N = 40; 1 study, Analysis 13.1).

Secondary outcome: adverse effects

Regarding adverse effects, none of the participants from either group suffered severe adverse effects such as local irritation or pruritus.

1.2 Sodium stibogluconate

1.2.1 Intralesional versus intramuscular sodium stibogluconate (SSG)

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared ketoconazole 200 mg three times daily for four weeks plus intralesional sodium stibogluconate (ILSSG) (100 mg/mL on days 1, 3, and 5) versus intralesional

plus intramuscular sodium stibogluconate (20 mg/kg/d intralesionally on days 1, 3, and 5, and 80 mg/kg/d intramuscularly simultaneously) versus ILSSG alone (100 mg/mL on days 1, 3, and 5) (El-Sayed 2010). The authors reported that two months after treatment, 92.3% (12/13), 93.3% (14/15), and 58.3% (7/12) of lesions were cured in the respective groups. There were no significant differences between intralesional plus intramuscular SSG versus ILSSG alone (RR 1.60, 95% CI 0.97 to 2.63; N = 27; 1 study, Analysis 14.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Afghanistan compared ILSSG (five injections of 2 mL to 5 mL every 5 to 7 days, depending on lesion size) for up to 29 days versus intramuscular sodium stibogluconate (IMSSG) (20 mg/kg/d for 21 days) (Reithinger 2005). Two months after treatment, 47.3% (70/148) and 18% (26/144) of participants had complete cure in the ILSSG and IMSSG groups, respectively (RR 2.62, 95% CI 1.78 to 3.86; N = 292; 1 study, Analysis 15.1).

Secondary outcome: speed of healing (time taken to be 'cured')

In Reithinger 2005, the speed of healing took a median of 75 days in the ILSSG group and 100 days or more for the IMSSG group (the original paper reported that the time to cure was significantly shorter for participants treated with thermotherapy; P = 0.003, by the log-rank test).

Secondary outcome: adverse effects

Regarding adverse effects, Reithinger 2005 reported that one participant experienced bradycardia and one an undefined local reaction in the ILSSG group. In the IMSSG group, one participant reported bradycardia, one tachycardia, and one palpitation. There were no significant differences in adverse effects rates between groups (RR 0.32, 95% CI 0.03 to 3.08; N = 292; 1 study, Analysis 15.2). In El-Sayed 2010, all participants from ILSSG group suffered pain and swelling at the intralesional site, which calmed on its own within two days. IMSSG was associated with pain at the injection site.

2. Non-antimonial systemic treatments

2.1 Oral antifungals

2.1.1 Different doses of ketoconazole

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Kuwait compared oral ketoconazole at 600 mg/d versus 800 mg/d for six weeks or until the participant was cured, whichever occurred earlier (Alsaleh 1995). The authors reported that at the end of treatment, 66.7% (12/18) and 60% (9/15) of participants in the respective groups had a complete cure (RR 1.11, 95% CI 0.66 to 1.88; N = 33; 1 study Analysis 16.1). Thereafter, investigators followed up participants every one to two months for a period of six months, with no change.

Secondary outcome: adverse effects

None of the participants from either group relapsed during a six-month follow-up. With regard to adverse effects, one participant had nausea and vomiting in the ketoconazole 800 mg/d group. There were no significant differences in adverse effects rates between groups (RR 0.28, 95% CI 0.01 to 6.43; N = 33; 1 study, Analysis 16.2).

2.1.2 Ketoconazole versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared oral ketoconazole 600 mg/d for 30 days versus six to eight injections of ILMA, biweekly (Salmanpour 2001). The authors reported that six weeks after treatment, 89% (57/64) and 72% (23/32) of participants in the respective groups had a complete cure. There were no significant differences between groups (RR 1.24, 95% CI 0.98 to 1.56; N = 96; 1 study, Analysis 17.1).

Secondary outcome: adverse effects

In the ketoconazole group the most common side effect cited was nausea and abdominal pain, and liver enzymes doubled in two participants, returning to normal two weeks after the end of treatment. There were no significant differences in adverse effects rates between groups (RR 2.54, 95% CI 0.13 to 51.36; N = 96; 1 study, Analysis 17.2). In the ILMA group, the most common side effect was redness and swelling after the injection. None of the side effects were significant enough to discontinue treatment.

2.1.3 Ketoconazole plus ILSSG versus ILSSG alone versus ILSSG plus IMSSG

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared oral ketoconazole plus ILSSG for four weeks versus ILSSG plus IMSSG versus ILSSG alone (El-Sayed 2010). The authors reported that two months after treatment, 92.3% (12/13), 93.3% (14/15), and 58.3% (7/12) of the lesions were cured in the respective groups. There were no significant differences between comparisons of either ketoconazole plus ILSSG versus ILSSG alone (RR 1.58, 95% CI 0.96 to 2.62; N = 25; 1 study, Analysis 18.1) nor between ketoconazole plus ILSSG versus ILSSG plus IMSSG (RR 0.99, 95% CI 0.80 to 1.22; N = 28; 1 study, Analysis 19.1).

Secondary outcome: adverse effects

Regarding adverse effects, in one trial all participants complained of pain and swelling at the intralesional injection site that subsided on its own within days; no participants in the oral ketoconazole group reported adverse effects (El-Sayed 2010).

We also found one trial comparing oral ketoconazole with topical paromomycin/MBCL (Özgöztasi 1997); we assess this comparison in the topical paromomycin section (section 3.2 below).

2.1.4 Itraconazole versus placebo

Primary outcome: percentage of participants with a complete cure after the end of treatment

Three RCTs compared itraconazole versus placebo and reported complete cure three months after the end of treatment as a primary outcome (Al-Fouzan 1991; Dogra 1996; Nassiri-Kashani 2005). Although heterogeneity was high (P = 0.02; I^2 = 73%), the three studies obtained results favouring itraconazole, so we decided to maintain the pool of results and the meta-analysis (RR 3.70, 95% CI 0.35 to 38.99; N = 244; 3 studies, Analysis 22.1).

Please see Summary of findings for the main comparison, where we assessed the certainty of evidence as very low, which means we are very uncertain about the difference in cure with itraconazole compared to placebo.

Two RCTs evaluated complete cure of participants at other time points. An RCT from Iran compared oral itraconazole for three weeks versus placebo (Momeni 1996). Fifty-one days after treatment, results showed complete cure of participants in 51.4% (36/70) and 38.6% (27/70) of the participants, respectively. There were no significant differences in cure rates between groups (RR 1.33, 99% CI 0.82 to 2.18; N = 140; 1 study, Analysis 21.1). An RCT from India compared oral itraconazole for six weeks with placebo (Dogra 1992). At the end of the treatment period, 75% (15/20) of participants in the oral itraconazole group and 0% (0/20) of the participants in the placebo groups achieved a complete cure. There were no statistically significant differences in cure rates between groups (RR 31.00, 99% CI 0.83 to 1151.33; N = 40; 1 study, Analysis 20.1).

Secondary outcome: adverse effects

In Al-Fouzan 1991, two participants from the itraconazole group reported nausea and headache during the course of treatment, and one participant had elevated liver enzymes that returned back to normal upon discontinuation of the drug. Dogra 1992 reported nausea in 12 cases (30%) between the itraconazole and dapsone groups. In the itraconazole group, two participants (10%) also had mildly abnormal liver function that reverted after completion of therapy. In Momeni 1996, six participants in the itraconazole group and four participants in the placebo group complained of mild abdominal pain and nausea. None of the laboratory values were outside normal limits. In Dogra 1996, one participant showed abnormal liver function and one nausea in the itraconazole group. Participants in the placebo group did not report adverse effects. In Nassiri-Kashani 2005, the most common adverse effects were gastrointestinal complaints and headache - reported only in the itraconazole group during the follow-up period. Participants in the placebo group reported adverse effects only during the treatment period.

Participants of itraconazole group had more side effects, including mild abdominal pain and nausea (RR 2.36, 95% CI 0.74 to 7.47; 3 studies, N = 204, Analysis 22.2) as well as mild abnormal liver function (RR 3.08, 95% CI 0.53 to 17.98; N = 84, 3 studies, Analysis 22.2). However, the very low certainty of the evidence means we are uncertain about these results (Summary of findings for the main comparison).

Tertiary outcomes: microbiological or histopathological cure of skin lesions

In Dogra 1996, parasitological cure was significantly higher (Fisher's exact test P = 0.048) in participants receiving itraconazole compared to placebo. Parasitological cure occurred in 80% (8/10) of itraconazole-treated participants but in none of the participants in the placebo group at six weeks follow-up (RR 17.0, 95% CI 0.47 to 612.21; N = 20; 1 study, Analysis 22.3).

Please see Summary of findings for the main comparison where we assessed the certainty of evidence.

2.1.5 Itraconazole versus no treatment

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from India compared oral itraconazole 200 mg/d for six weeks versus no treatment (Dogra 1990). The authors reported complete cure of participants in 66.7% (10/15) of the treatment group but in none of the no treatment group. Low statistical power meant that these differences could have been due to chance (RR 7.88, 99% CI 0.23 to 265.70; N = 20; 1 study, Analysis 23.1).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

Participants responding to therapy had no relapses at three-month follow-up.

Secondary outcome: adverse effects

Regarding adverse effects, the drug was generally well tolerated, although 20% (3/15) of participants in the itraconazole group reported mild headache and dizziness. There were no significant differences in adverse effects rates between groups (RR 2.63, 95% CI 0.16 to 43.63; N = 20; 1 study, Analysis 23.2).

Tertiary outcomes: microbiological or histopathological cure of skin lesions

At six weeks, 66.7% (10/15) of the participants in the itraconazole group were free of parasites. Untreated participants were still parasitologically active. Low statistical power meant that these differences could have been due to chance (RR 7.88, 95% CI 0.54 to 114.56; N = 20; 1 study, Analysis 23.3).

2.1.6 Fluconazole versus placebo

Primary outcome: percentage of lesions cured after the end of treatment

One RCT from Aleppo, Syria compared fluconazole 200 mg/d for six weeks versus placebo (Dandashli 2005). The authors reported that at the end of treatment, 28.4% (75/264) of the lesions in the fluconazole group and 9.8% (10/102) in the placebo group had completely resolved. Cure rates were higher in the oral fluconazole group compared with placebo (RR 2.90, 95% CI 1.56 to 5.38, Analysis 24.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

One RCT from Saudi Arabia compared oral fluconazole 200 mg/d versus placebo for six weeks (Alrajhi 2002). Three months after treatment, 59% (63/106) participants in the oral fluconazole and 21% (22/103) in the placebo group had achieved complete cure (RR 2.78, 95% CI 1.86 to 4.16; N = 209; 1 study, Analysis 24.2).

Secondary outcome: speed of healing (time taken to be 'cured')

Only Alrajhi 2002 reported the speed of healing, finding that this took a median of 8.5 weeks in the fluconazole group and 11.2 weeks in the placebo group (the original paper reported that the time to cure was significantly shorter for participants treated with thermotherapy; $P < 0.001$, by the log-rank test). Also, none of the participants with complete healing had a relapse during a mean follow-up of seven months.

Secondary outcome: adverse effects

In both studies participants from reported mild and similar side effects, although the authors did not describe them (Alrajhi 2002; Dandashli 2005).

2.1.7 Different doses of fluconazole

Primary outcome: percentage of participants with a complete cure after the end of treatment

One RCT from Iran compared oral fluconazole 400 mg/d versus 200 mg/d for six weeks (Emad 2011). The authors reported that at the end of treatment, 48.3% (29/60) of participants in the 200 mg group and 81% (47/58) in the 400 mg group achieved complete cure (RR 1.68, 95% CI 1.25 to 2.24; N = 118; 1 study, Analysis 25.1).

Secondary outcome: adverse effects

Regarding adverse effects, two participants in the 400 mg group discontinued treatment because of a rise of serum creatinine and liver enzymes. Participants in the 400 mg group reported 45 (75%) cases of cheilitis and 10 (16.6%) cases of nausea, compared to none in the 200 mg group (cheilitis: RR 94.08, 95% CI 5.93 to 1492.36; nausea: RR 21.71, 95% CI 1.30 to 362.21; N = 118; 1 study, Analysis 25.2).

2.2 Oral dapsone

2.2.1 Dapsone versus placebo

Primary outcome: percentage of participants with a complete cure after the end of treatment

Two RCTs comparing oral dapsone versus placebo reported complete cure after the end of treatment as a primary outcome (Dogra 1991; Dogra 1992). Although heterogeneity was high ($P = 0.02$; $I^2 = 73\%$), both studies obtained results favouring dapsone, so

we decided to maintain the pool of results and meta-analysis (RR 24.08, 95% CI 1.44 to 403.43; N = 160; 2 studies; I^2 = 71%, Analysis 26.1).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

In Dogra 1992, participants initially responding to therapy did not relapse at follow-up, while two cases with single lesions (10%) demonstrated spontaneous healing in the placebo group at three months' follow-up.

Secondary outcome: adverse effects

Regarding adverse effects, 30% (n = 12) of participants in the dapsone group experienced nausea. In Dogra 1991, 5% (3/60) of participants in the dapsone group developed anaemia and 15% (9/60), nausea. Nausea rates were higher in the dapsone group compared with placebo (RR 21.86, 95% CI 3.04 to 157.29; N = 160; 2 studies; I^2 = 0%, Analysis 26.2).

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Regarding the parasitological cure, 5% (3/60) of participants in the placebo group showed healing with negative smears one month after treatment (Dogra 1991).

2.3 Oral allopurinol

2.3.1 Allopurinol versus IMMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared oral allopurinol 15 mg/kg/d for three weeks versus IMMA 30 mg/kg/d for two weeks versus oral allopurinol 15 mg/kg/d plus IMMA 30 mg/kg/d simultaneously, using the same dosage schedule (Esfandiarpour 2002). The authors reported that 18% (9/50) of participants receiving allopurinol alone achieved complete cure, compared to 24% (12/50) in the IMMA group and 46% (23/50) in the allopurinol plus IMMA group at the end of the treatment period. The group receiving allopurinol plus IMMA had better cure rates than those receiving allopurinol alone (RR 3.83, 95% CI 1.71 to 8.60; N = 100; 1 study, Analysis 27.1) or IMMA alone (RR 1.92, 95% CI 1.08 to 3.41; N = 100; 1 study, Analysis 28.1). There was no difference regarding cure rates between the groups receiving allopurinol alone versus IMMA alone (RR 0.75, 95% CI 0.35 to 1.62; N = 100; 1 study, Analysis 29.1).

An RCT from Iran compared oral allopurinol 20 mg/kg/d plus IMMA 10 mg/kg/d versus IMMA 20 mg/kg/d alone for up to 28 days (Ejaz 2014). There was no data to address the primary outcome of percentage of participants with a complete cure.

Another RCT in an Iranian army camp compared oral allopurinol 20 mg/kg/d plus low-dose IMMA 30 mg/kg/d for 20 days versus IMMA 60 mg/kg/d for 20 days (Momeni 2002). In this trial the authors reported that 51 days after treatment, 69% (25/36) and 72% (26/36) of participants, respectively, achieved a complete cure (RR 0.96, 95% CI 0.71 to 1.29; N = 72; 1 study, Analysis 30.1).

Secondary outcome: adverse effects

Esfandiarpour 2002 observed a few adverse effects in the allopurinol group: three participants experienced nausea and heartburn, and two saw a mild increase in serum glutamic-oxaloacetic transaminase and serum glutamic pyruvic transaminase levels. In Momeni 2002 participants tolerated the drugs well, and only 17% (6/36) in the combined treatment group complained of mild abdominal pain and nausea; however, 3% (1/36) of participants in the IMMA group developed skin eruption, and 11% (4/36) suffered generalised muscle pain and weakness. There was no significant difference between groups in total adverse effects (Analysis 30.2). Ejaz 2014 reported secondary infection in 12.1% (n = 21) of participants in the allopurinol plus IMMA group and in 12.5% (n = 19) of participants in the IMMA group, myalgia in 5.7% (n = 10) and 7.9% (n = 12), anorexia in 7.5% (n = 13) and 5.9% (n = 9), and ECG changes in 0.6% (n = 1) and 1.98% (n = 3), respectively. In the IMMA alone group one participant suffered chest pain; two, pain at the injection site; and five, abscess. There was no significant difference regarding adverse effects rates between the two groups (Analysis 31.1).

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Only one study reported that 83.3% (30/36) of participants in the allopurinol plus IMMA group and 75% (27/36) in the IMMA alone group had parasitologically free lesions one month after the end of treatment (Momeni 2002). There was no difference regarding cure rates between groups ((RR 1.11, 95% CI 0.88 to 1.41; participants = 72; studies = 1) Analysis 30.3).

2.3.2 Oral allopurinol versus intravenous sodium stibogluconate

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT with participants from the Pakistani army compared oral allopurinol 20 mg/kg/d versus intravenous sodium stibogluconate (IVSSG) for 15 days (Mashood 2001). The authors reported at the end of the treatment period, 85% (17/20) of participants in the allopurinol group and 70% (14/20) in the IVSSG group achieved a complete cure. There was no significant difference regarding cure rates between groups (RR 1.21, 95% CI 0.86 to 1.71; N = 40; 1 study, Analysis 32.1).

Secondary outcome: adverse effects

Mashood 2001 observed adverse effects that included nausea, vomiting, anorexia, and diarrhoea in 5% (1/20) of participants in the allopurinol group and 20% (4/20) of participants in the IVSSG group. In the SSG group, 10% (2/20) of participants experienced liver abnormalities and 15% (3/20), myalgia and body aches. In the allopurinol group, 5% (1/20) had elevated liver enzymes, and 10% (2/20), macular rash, but there was no myalgia or body aches. There was no significant difference in adverse effects rates between the allopurinol group and IVSSG alone group (Analysis 32.2).

2.4 Oral antibiotics

For a summary of adverse effects of oral antibiotics please see Table 3.

2.4.1 Oral rifampicin versus placebo

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Saudi Arabia compared oral rifampicin 10 mg/kg/d for four to six weeks versus placebo (Jaffar 2006). Three months after treatment, 45.7% (21/46) of participants in the oral rifampicin group and 18.8% (3/16) of the placebo group achieved complete cure. There was no difference in cure rates between oral rifampicin and placebo (RR 2.43, 95% CI 0.84 to 7.08; N = 62; 1 study, Analysis 33.1).

Two RCTs from India address the primary outcome of percentage of participants with a complete cure at the end of treatment. Kochar 2000 compared 10 mg/kg/d oral rifampicin for four weeks versus placebo, reporting that 68% (17/25) and 4% (1/25) of participants, respectively, achieved complete cure by the end of the treatment period (RR 17.00, 95% CI 2.45 to 118.19; N = 50; 1 study, Analysis 33.1). Kochar 2006 compared 10 mg/kg/d oral rifampicin plus 20 mg/d omeprazole for six weeks versus placebo, reporting that 64% (16/25) participants in the rifampicin group and 12% (3/25) in the placebo group had achieved a complete cure at the end of the treatment period (RR 5.33, 95% CI 1.77 to 16.05; N = 50; 1 study, Analysis 34.1).

Secondary outcome: adverse effects

Jaffar 2006 reported that one participant had elevated liver enzymes that returned back to normal upon discontinuation of the drug. Kochar 2000 reported that the drug was very well tolerated, and there were no adverse effects during therapy.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Kochar 2000 reported an absence of parasites in 8% (2/25) and 32% (8/25) of partially healed lesions in the rifampicin and placebo groups, respectively, at the end of treatment (RR 0.25, 95% CI 0.06 to 1.06; N = 50; 1 study, Analysis 33.2).

2.4.2 Oral terbinafine plus cryotherapy versus IMMA plus cryotherapy

Secondary outcome: speed of healing (time taken to be 'cured')

An RCT from Iran compared cryotherapy (liquid nitrogen via a cotton swab for 10 s to 25 s every two weeks for four weeks) plus either oral terbinafine 500 mg/d for four weeks or plus IMMA 15 mg/kg/d (Farajzadeh 2015). After three months' follow-up, the crude hazard ratio was 0.53 (95% CI 0.30 to 0.98) and after adjustment for sex, it was 0.35 (95% CI 0.19 to 0.69). A Kaplan-Meier analysis indicated that the difference in complete treatment between the groups was not significant.

2.4.3 Azithromycin with or without allopurinol versus IMMA

Primary outcome: percentage of lesions with a complete cure after the end of treatment

An RCT from Iran compared azithromycin 500 mg for five days/month up to a maximum of four months with IMMA 60 mg/kg/d for 20 days (Layegh 2007). After 16 weeks of follow-up, 10.3% (13/29) and 34.4% (20/58) of the lesions were cured in the respective groups (RR 0.60, 95% CI 0.18 to 2.01; N = 87; 1 study, Analysis 35.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared azithromycin 10 mg/kg/d (maximum 500 mg/d) plus allopurinol 10 mg/kg for one month versus IMMA 20 mg/kg/d for 20 days (Dastgheib 2012); 38.9% (14/36) and 40% (14/35) of participants, respectively, had achieved complete cure at two months after treatment (RR 0.97, 95% CI 0.55

to 1.73; N = 71, Analysis 36.1). There was no statistical difference in cure rates between azithromycin plus allopurinol versus IMMA in ulcerated (P = 0.40) and non-ulcerated (P = 0.37) lesions or with regard to the site of lesions (P = 0.30).

Secondary outcome: adverse effects

Regarding adverse effects, Dastgheib 2012 reported that one (2.7%) participant in the azithromycin plus allopurinol group had gastrointestinal complaints and severe headache, and three (8.3%) experienced slight gastrointestinal complications (nausea, heartburn, and epigastric pain). Layegh 2007 described only nausea and vomiting in two participants (9%) in the azithromycin alone group. Only Dastgheib 2012 reported myalgia in two (5.7%) participants in the IMMA group. There were no significant differences in adverse effects rates between groups (Analysis 35.2; Analysis 36.2).

2.5 Oral pentoxifylline

2.5.1 Oral pentoxifylline plus IMMA versus placebo plus IMMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared oral pentoxifylline 400 mg three times daily plus IMMA 20 mg/kg/d versus IMMA 20 mg/kg/d plus placebo, for 20 days (Sadeghian 2006a). Three months after treatment, 81.3% (26/32) and 50% (16/32) of the participants in the respective groups had achieved complete cure (RR 1.63; 95% CI 1.11, 2.39, Analysis 37.1).

Secondary outcome: adverse effects

Regarding adverse effects, one participant in the IMMA plus placebo group had an allergic macule-papular itchy rash. There were no significant differences in adverse effects rates between groups (RR 0.33, 95% CI 0.01 to 7.89; N = 64; 1 study, Analysis 37.2).

2.6 Oral miltefosine

2.6.1 Oral miltefosine versus IMMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT in Iran compared oral miltefosine 2.5 mg/kg/d for four weeks versus IMMA 20 mg/kg/d for two weeks (Mohebali 2007). Three months after treatment, 81.3% (26/32) and 80.6% (25/31) of participants in the respective groups had achieved complete cure (RR 1.01; 95% CI 0.79, 1.28, Analysis 38.1).

An RCT from Iran compared oral miltefosine 2.5 mg/kg/d for four weeks versus IMMA 60 mg/kg/d for two weeks (Khatami 2012). At one month after treatment, 32% (10/31) and 35.7% (15/42) of the participants in the respective groups had achieved complete cure (RR 0.90, 95% CI 0.47 to 1.73; N = 73; 1 study, Analysis 39.1).

Secondary outcome: adverse effects

Mohebali 2007 did not report any relapse at six months post-treatment. With regard to adverse effects, during the first week participants from the miltefosine group suffered from nausea, vomiting, diarrhoea, abdominal pain, and cough. Participants from the IMMA group had only diarrhoea and local pain. During the second week, participants receiving miltefosine suffered from nausea, vomiting, abdominal pain, headache, itch, and fever. Participants receiving IMMA developed those adverse effects as well as local pain, chest pain, and cough. Khatami 2012 only reported that adverse effects were higher in the miltefosine arm (nine cases versus one case).

2.7 Oral zinc sulphate

2.7.1 Different doses of oral zinc sulphate

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iraq compared oral zinc sulphate at different doses: 2.5 mg/kg/d, 5 mg/kg/d, or 10 mg/kg/d, versus no treatment (Sharquie 2001). The authors reported that 45 days after treatment, 66.7% (26/39) in the 2.5 mg/kg/d group, 73% (27/37) in the 5 mg/kg/d group, and 79% (31/39) in the 10 mg/kg/d group had achieved complete cure. In the control group, all lesions were still active at day 45. There were no significant differences in cure rates between oral zinc sulphate 2.5 mg/kg/d versus 5 mg/kg/d (RR 0.91, 95% CI 0.68 to 1.23; N = 76; 1 study, Analysis 40.1); 2.5 mg/kg/d versus 10 mg/kg/d (RR 0.84, 95% CI 0.64 to 1.10; N = 78; 1 study, Analysis 41.1); or 5 mg/kg/d versus 10 mg/kg/d (RR 0.92, 95% CI 0.71 to 1.18; N = 76; 1 study, Analysis 42.1).

Secondary outcome: speed of healing (time taken to be 'cured')

In the zinc sulphate 2.5 mg/kg/d group, the mean time taken to cure was 30.8 days (range 21 to 45): 29.96 days (range 15 to 45) in

the 10 mg/kg/d group and 28.32 days (range 15 to 45) in the 10 mg/kg/d (the original paper reported that the time to cure was not statistically significant between the different treatment groups). None of the participants recovered in the control group.

Secondary outcome: prevention of scarring

In all treatment groups there was minimal or no scarring at the site of lesions.

Secondary outcome: adverse effects

Regarding adverse effects, one participant each in the 2.5 mg/kg/d, 5 mg/kg/d, and 10 mg/kg/d group had nausea and vomiting. Only one participant from the 5 mg/kg/d group had a leishmanid reaction, while two participants in the 2.5 mg/kg/d group and two from the 5 mg/kg/d group, plus one participant in the 10 mg/kg/d group, had oedema. There were no significant differences in adverse effects rates between groups (Analysis 40.2; Analysis 41.2; Analysis 42.2).

2.7.2 Oral zinc sulphate versus IMMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared oral zinc sulphate (ZS) in a dose of 10 mg/kg/d for 45 days versus IMMA 20 mg/kg/d for up to 20 days (Yazdanpanah 2011). The authors reported that 45 days after treatment, 30.2% (8/26) and 35.5% (26/74) of the respective groups achieved complete cure (RR 0.88, 95% CI 0.46 to 1.68; N = 100; 1 study, Analysis 43.1).

Secondary outcome: adverse effects

Regarding adverse effects, the authors did not report any adverse effects in the oral zinc sulphate group, but six participants in the IMMA group dropped out because of adverse effects, including severe erythema and pruritus at inoculation site and severe muscular pain.

2.8 Oral artesunate

2.8.1 Oral artesunate plus sulphamethoxypyridazine/pyrimethamine versus placebo

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Sudan compared oral artesunate plus sulphamethoxypyrazine/pyrimethamine (400 mg artesunate plus 1000 mg/50 mg sulphamethoxypyrazine/pyrimethamine for four days, four times each two weeks) versus placebo (Adam 2009). The authors reported that 72 days after treatment, 90% (18/20) and 85.7% (18/21) of the respective groups had a complete cure (RR 1.05, 95% CI 0.84 to 1.32; N = 41; 1 study, Analysis 44.1).

Secondary outcome: adverse effects

One participant in the placebo arm developed a mild skin rash with itching. There was no significant difference in biological tests (liver and renal function tests) in any of the participants before or after treatment.

3. Non-antimonial topical or intralesional therapies

3.1 Topical antifungals

3.1.1 Topical 2% miconazole versus topical 1% clotrimazole

Primary outcome: percentage of lesions with a complete cure after the end of treatment

An RCT from Saudi Arabia compared 2% miconazole cream twice a day with 1% clotrimazole cream twice a day for 30 days (Larbi 1995). The authors reported there was no lesions healed in the miconazole group and 15% (14/89) of the lesions healed completely in the clotrimazole group at the end of treatment (RR 0.05, 95% CI 0.00 to 0.81; N = 151; 1 study, Analysis 45.1).

Secondary outcome: adverse effects

In both treatment groups, the medication was well tolerated, with no reported adverse effects.

3.1.2 Ketoconazole cream versus vehicle

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical ketoconazole versus vehicle, twice daily for 21 days (Momeni 2003). The authors reported that 51 days after treatment, 24% (11/45) and 13% (6/45) of the participants in the respective groups achieved complete cure. There were no significant differences in cure rates between topical ketoconazole and vehicle (RR 1.83, 95% CI 0.74 to 4.53; N = 90; 1 study, Analysis 46.1).

Secondary outcome: adverse effects

Regarding adverse effects, the drugs were well tolerated, and only two participants (group unknown) complained of mild pruritus at the site of the lesions.

3.1.3 Amphotericin B versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical liposomal amphotericin B (3 to 7 drops twice daily) versus ILMA (maximum 2 mL) for eight weeks (Layegh 2011). We performed an ITT analysis considering the participants allocated in each arm at the beginning of the study. After six months of follow-up, 44% (22/50) and 48.3% (29/60) of the participants in the amphotericin B and ILMA groups, respectively, achieved complete cure (RR: 0.91, 95% CI 0.61 to 1.37; N = 110; 1 study, Analysis 47.1).

Secondary outcome: adverse effects

One (1.7%) participant in amphotericin B group presented hypersensitivity, and five (10%) mild pruritus around the lesions. Seven (11.7%) participants in the ILMA group suffered erythema and oedema at the injection site. There were no significant differences in any hypersensitivity rates (RR 3.59, 95% CI 0.15 to 86.19), mild pruritus rates (RR 13.16, 95% CI 0.75 to 232.30), or erythema and oedema rates (RR 0.08, 95% CI 0.00 to 1.36) between groups (N = 110; 1 study, Analysis 47.2).

3.2 Topical paromomycin (aminosidine)

For a summary of adverse effects of topical paromomycin please see Table 4.

3.2.1 Paromomycin versus vehicle

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared topical 15% paromomycin sulphate in 12% MBCL (PR-MBCL) versus vehicle, twice daily for 30 days (Asilian 2006). Two months after treatment, 41.2% (14/34) and 13.3% (4/30) of the lesions in the PR-MBCL and placebo groups, respectively, had completely healed (RR 3.09, 95% CI 1.14 to 8.37; N = 64; 1 study Analysis 48.1).

An RCT from Iran compared topical 15% paromomycin in 10% urea (PR-U) versus vehicle, twice daily for 30 days (Iraji 2005); 12.5% (5/40) and 17.5% (7/40) of the lesions in the respective groups had healed completely one month after treatment (RR 0.71, 95% CI 0.25 to 2.06; N = 80; 1 study, Analysis 49.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

A pooled analysis of two trials showed no significant differences in cure rates between topical PR-U and vehicle (RR 1.00; 95% CI 0.86, 1.17; Asilian 1995; Ben Salah 1995; Analysis 50.1). Please see Summary of findings 2 where we assessed the certainty of evidence as very low, meaning that we are uncertain whether there is much difference in cure rate between paromomycin and vehicle.

An RCT from Iran compared PR-U versus vehicle, twice daily for 14 days (Asilian 1995). Two and a half months after treatment, 63.5% (80/126) and 63.2% (79/125) of those receiving PR-U and vehicle, respectively, achieved a complete cure.

An RCT from Tunisia compared PR-U in soft white paraffin versus vehicle, twice daily for 14 days (Ben Salah 1995). Two and a half months after treatment (day 105), 60.6% (40/66) in each group achieved complete cure.

An RCT from Tunisia compared topical 15% paromomycin plus gentamicin 0.5% versus 15% paromomycin alone versus vehicle, daily for 20 days (Ben Salah 2013). Five and a half months after treatment (day 168), 80% (101/125), 82% (102/125) and 58% (73/125) of participants, respectively, had achieved a complete cure. Paromomycin alone (RR 1.40, 95% CI 1.18 to 1.66, Analysis 51.1) and paromomycin plus gentamicin (RR 1.38, 95% CI 1.17 to 1.64, Analysis 52.1) were more efficacious than vehicle. There was no significant difference between topical 15% paromomycin plus gentamicin 0.5% and 15% paromomycin alone (RR 0.99, 95% CI 0.88 to 1.12; N = 250; 1 study, Analysis 53.1).

Secondary outcome: prevention of scarring

Only Asilian 2006 reported that at the end of the study there was no significant difference in number of deep or disfiguring scars between the PR-MBCL group (8/34 lesions; 23.5%) and vehicle group (3/10; 10%) (RR 2.35; 95% CI 0.69 to 8.07; N = 64; 1 study, Analysis 48.2). However, we have used the number of lesions originally randomised in presenting the data in this analysis, whereas in the original paper the authors assessed scarring only in lesions that were completely healed at the end of the study (which perhaps makes more sense as a denominator). Both methods of calculating the degree of scarring failed to show any significant differences.

Secondary outcome: adverse effects

Twelve participants between the PR-U and vehicle groups in Ben Salah 1995 reported a local reaction (inflammation, vesiculation, pain and/or redness); 8 participants from the PR-U group and

11 from the vehicle group in Asilian 1995 complained about redness, local pain, vesiculation, and inflammation; 3 participants in the PR-U group in Iraji 2005 reported mild contact dermatitis; and participants in all three groups in Asilian 2006 reported mild and tolerable itch, burning, redness, discharge, oedema, and pain. In Ben Salah 2013, all adverse effects deemed by the investigators to be at least possibly related to a study treatment were reactions of mild or moderate severity at the application site. The paromomycin group reported a little more skin/local reaction (RR 1.42, 95% CI 0.67 to 3.01; N = 713, Analysis 50.2); however, the very low certainty of the evidence means we are not confident about these results (Summary of findings 2).

Tertiary outcomes: microbiological or histopathological cure of skin lesions

In a pooled analysis of two studies comparing PR-U versus placebo, there was no significant difference in the number of negative parasitologic smears at a mean follow-up of 2.5 months (RR 1.03; 95% CI 0.88 to 1.20; Asilian 1995; Ben Salah 1995; Analysis 50.3). The certainty of evidence was very low, meaning we are uncertain whether there was any difference in parasitological cure between the two groups. In another study (Asilian 2006), 64.7% (22/34) in the PR-MBCL group and 20% (6/30) in the vehicle group were parasitologically free two months after the end of treatment (RR 3.24, 95% CI 1.52 to 6.90; N = 64; 1 study, Analysis 48.3).

3.2.2 PR-U versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared PR-U ointment, twice per day for a mean duration of 45 days and a maximum duration of 3 months versus ILMA weekly (Faghihi 2003). At less than two months after treatment, the authors reported complete cure of participants in 16.6% (8/48) and 41.7% (20/48) of the PR-U and ILMA groups, respectively (RR 0.40, 95% CI 0.20 to 0.82; N = 96; 1 study, Analysis 54.1).

Another RCT from Iran compared PR-U ointment twice a day for 20 days versus ILMA (dose unspecified) every other day for 20 days (Shazad 2005). One week after the end of treatment, 66.7% (20/30) and 60% (18/30) participants of the respective groups achieved complete cure (RR 1.11, 95% CI 0.75 to 1.64; N = 60; 1 study, Analysis 55.1).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

Faghihi 2003 reported a reactivation in 6.3% (3/48) of the participants in both groups at one year after complete recovery, due to lymphatic spread in the PR-U group and non-lymphatic spread in the ILMA group (RR 1.00, 95% CI 0.21 to 4.71; N = 96; 1 study, Analysis 54.2). Scarring occurred in 4.2% (2/48) of participants in the PR-U group and for 8.3% (4/48) in the ILMA group (RR 0.50, 95% CI 0.10 to 2.60; N = 96; 1 study, Analysis 54.3).

Secondary outcome: adverse effects

Regarding adverse effects, Shazad 2005 reported that 1/30 in the PR-U group and 3/30 participants in the ILMA treatment group withdrew from the study because of cutaneous reactions like erythematosus, urticaria, or lymphadenitis with pain. They were all put on systemic MA and cured thereafter. They did not observe any systemic toxic reaction attributable to the drug. There were no significant differences in adverse effects rates between groups (RR 0.33, 95% CI 0.04 to 3.03; N = 60; 1 study Analysis 55.2).

3.2.3 PR-MBCL versus oral ketoconazole

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Turkey compared topical PR-MBCL twice per day for 15 days versus oral ketoconazole 600 mg/d for 30 days (Özgöztasi 1997). One month after the end of treatment the authors reported complete cure of participants in 37.5% (15/40) of the paromomycin group and none in the ketoconazole group (RR 24.95, 95% CI 1.55 to 401.63; N = 72; 1 study, Analysis 56.1).

Secondary outcome: adverse effects

Irritant contact dermatitis was the most common adverse effect described in the PR-MBCL group. In contrast, the ketoconazole-treated participants reported no adverse effects.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

The PR-MBCL and the ketoconazole groups showed incomplete improvement (absence of parasites on culture or smear): just 20% (8/40) and 21.9% (7/32) of participants, respectively, had achieved a microbiological cure at four weeks post-treatment (RR 0.91, 95% CI 0.37 to 2.25; N = 72; 1 study, Analysis 56.2).

3.2.4 PR-MBCL versus topical photodynamic therapy (PDT)

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared topical PR-MBCL twice daily for 28 days versus topical PDT every week for four weeks (Asilian 2006). Two months after treatment, results showed complete cure of lesions in 41.2% (14/34) and 93.5% (29/31) of the PR-MBCL and PDT groups, respectively (RR 0.44, 95% CI 0.29 to 0.66; N = 65; 1 study, Analysis 57.1).

Secondary outcome: prevention of scarring

At the end of the study, there was no statistical difference (Fisher's exact test P = 0.0558) in the number of deep or disfiguring scars between paromomycin (8/24) and PDT groups (0/31) (RR 15.54, 95% CI 0.39 to 625.57; N = 65; 1 study, Analysis 57.2).

Secondary outcome: adverse effects

Both groups experienced mild and tolerable itch, burning, redness, discharge, oedema, and pain.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Two months after the end of treatment, 64.7% (22/34) of the lesions in the PR-MBCL group were parasitologically free, as were all 31 lesions in the PDT group (RR 0.65, 95% CI 0.51 to 0.84; N = 65; 1 study, Analysis 57.3).

3.2.5 Different regimens of topical paromomycin

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared two tubes of 15 g of paromomycin ointment (each tube was enough for two applications per day for 14 days) for a four-week treatment versus one tube of 15 g of paromomycin ointment for two weeks plus vehicle for two additional weeks (Asilian 2003). Two and a half months after treatment, results showed complete cure of participants in 50% (58/117) and 37% (43/116) of the four-week and two-week regimens, respectively. There was no significant difference in cure rates between the four-week and the two-week treatment (RR 1.34, 95% CI 0.99 to 1.80; N = 233; 1 study, Analysis 58.1).

Secondary outcome: adverse effects

Participants tolerated the treatment well, and investigators did not observe any adverse effect or adverse reactions to the ointment in either group.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Three months (105 days) after treatment initiation, there was a small difference in parasitological cure in favour of the four-week regimen 49/117 (41%) versus 33/116 (28.4%) respectively (RR 1.47, 95% CI 1.03 to 2.11; N = 233; 1 study, Analysis 58.2).

3.3 Intralesional zinc sulphate

For a summary of adverse effects of intralesional zinc sulphate please see Table 5.

3.3.1 Intralesional (IL) zinc sulphate versus ILSSG versus IL hypertonic sodium chloride solution (HSCS)

Primary outcome: percentage of lesions with a complete cure after the end of treatment

An RCT from Iraq compared mono doses of IL 2% zinc sulphate solution versus ILSSG 100 mg/mL versus IL 7% HSCS (Sharquie 1997). Investigators left a few lesions on unimportant and unexposed parts of the body as controls. At six weeks after treatment, 94.8% (36/38), 88.5% (31/35), and 85% (34/40) of the lesions, respectively, had healed completely. There were no statistical differences between any comparison: 2% zinc sulphate solution versus ILSSG (RR 1.07, 95% CI 0.93 to 1.23; N = 73; 1 study, Analysis 59.1); 2% zinc sulphate solution versus IL 7% HSCS (RR 1.11, 95% CI 0.96 to 1.30; N = 78; 1 study, Analysis 60.1), or ILSSG versus IL 7% HSCS (RR 1.04, 95% CI 0.87 to 1.24; N = 75; 1 study, Analysis 61.1). In the untreated group, nine participants with 38 lesions were followed up for six weeks, showing no decrease in the size of the lesions and no disappearance of parasites.

Secondary outcome: speed of healing (time taken to be 'cured')

Sharquie 1997 reported that in the zinc sulphate group most lesions were cured by 30 days. In the HSCS and in the ILSSG group, lesions were cured after 30 days.

Secondary outcome: prevention of scarring

In all three groups the scar was minimal or absent after healing, but all participants developed postinflammatory hyperpigmentation.

In the control group, some lesions (mainly on the lower limbs) showed signs of infection.

Secondary outcome: adverse effects

Regarding adverse effects, all participants from both groups in the Sharquie 1997 study had pain at the time of the injection.

3.3.2 IL zinc sulphate versus ILMA

Primary outcome: percentage of lesions with a complete cure after the end of treatment

An RCT from Iran compared IL zinc sulphate up to six times weekly versus ILMA up to six times weekly (maximum 2 mL) (Firooz 2005). At five weeks after treatment, 22.6% (12/53) and 50.9% (27/53) of the lesions in the respective groups had healed completely (RR 0.44, 95% CI 0.25 to 0.78; N = 106; 1 study, Analysis 62.1). However, baseline characteristics were unbalanced: both mean diameter induration and mean diameter ulceration were higher in the zinc sulphate group (induration: 10.0 mm (standard deviation (SD) 11.4)), and ulceration: 2.7 mm (SD 4.6)) than in the MA group (induration: 2.4 mm (SD 8.7) and ulceration 0.6 mm (SD 3.6)). However, the authors claimed that there was no significant difference between the two groups (P > 0.05; exact p value not reported).

An RCT from Iran compared two double bouts of IL zinc sulphate, delivered at a two-week interval, versus six weekly bouts of ILMA 60 mg/kg/d (Maleki 2012). At eight weeks after starting treatment, 33.3% (8/24) and 80% (8/10) of participants achieved complete cure in the respective groups (RR 0.42, 95% CI 0.22 to 0.79; N = 34; 1 study, Analysis 63.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

One RCT from Iran compared IL zinc sulphate with ILMA at a maximum dose of 2 mL (Iraji 2004). In cases with slight to mild improvement, the authors gave another injection after two weeks. The authors reported complete cure in 53% (26/49) and 38% (21/55) of participants in the respective groups at the end of the treatment period. There were no significant differences in cure rates between groups (RR 1.39, 95% CI 0.91 to 2.13; N = 104; 1 study, Analysis 62.2).

Secondary outcome: adverse effects

In Firooz 2005, the most commonly observed adverse effect was pain, found in 25% (18/72) of participants: in 36.1% (13/36) of participants in the zinc sulphate group and 13.9% (5/36) in the ILMA group (RR 2.60, 95% CI 1.03 to 6.54, Analysis 62.3). In the zinc sulphate group, 8.4% (3/36) of participants complained about burning at the injection site. Itching occurred in 8.4% (3/36) and in 25% (9/36), and inflammation in 19.4% (7/36) and 22.2% (8/36) of the cases in the zinc sulphate and ILMA group, respectively. There were no significant differences in other adverse effects rates between groups (Analysis 62.3). Iraji 2004 reported pruritus, erythema, and scaling in the periphery of the injection site in three cases in the ILMA group; IL zinc sulphate was painful, and the severity caused vasovagal shock in two cases. There were no significant differences in skin reactions (RR 7.84, 95% CI 0.42 to 148.08; N = 104; 1 study, Analysis 62.3) or severe pain rates (RR 5.60, 95% CI 0.28 to 113.87; N = 104; 1 study, Analysis 62.3) between groups. In another study the side effects seen in both groups were pain after injection and hyperpigmentation (Maleki 2012). All participants in the zinc sulphate group experienced burning after injection and necrosis of the lesions, and three of these participants also had inflammation and swelling. There were no significant differences in inflammation and swelling rates between groups (RR 3.08, 95% CI 0.17 to 54.71; N = 34; 1 study, Analysis 63.2).

3.4 Topical imiquimod

3.4.1 Imiquimod cream versus IMMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared 5% imiquimod cream three times per week for 28 days plus IMMA 20 mg/kg/d for 14 days versus vehicle plus IMMA at the same dose (Firooz 2006). At 3.5 months after treatment, 44.1% (26/59) and 40% (24/60) of participants in the treatment and control groups, respectively, achieved complete cure (RR 1.10, 95% CI 0.72 to 1.68; N = 119; 1 study, Analysis 64.1).

Secondary outcome: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

At four months after treatment, relapse occurred in 1/32 participants available for assessment and treated with imiquimod plus IMMA, and in 3/37 control participants (RR 0.39, 95% CI 0.04 to 3.52; N = 69; 1 study, Analysis 64.2).

Secondary outcome: adverse effects

The only adverse effects related to topical treatment were moderate itch and a burning sensation in three imiquimod-treated participants. There were no significant differences between groups (RR 7.12, 95% CI 0.38 to 134.84; N = 119; 1 study, Analysis 64.3).

3.5 Intralesional hypertonic sodium chloride solution

For details about the adverse effects of intralesional hypertonic sodium chloride solution (HSCS) please see Table 6.

3.5.1 IL 7% HSCS versus ILSSG

Primary outcome: percentage of lesions with a complete cure after the end of treatment

An RCT from Sri Lanka compared IL HSCS (0.2 mL to 4 mL per lesion and maximum 5 injections) versus ILSSG (maximum 2 mL and 5 injections) (Ranawaka 2010). Average duration of treatment was 8.78 weeks and 5.11 weeks, respectively. At 18 months of follow-up, 92.2% (86/96) and 100% (136/136) lesions had healed completely in the respective groups (RR 0.87, 95% CI 0.79 to 0.96; N = 147; 1 study, Analysis 65.1). There was no difference in treatment response between therapies with regard to the size, duration, or location (head, trunk, upper, and lower extremities) of the lesions.

Secondary outcome: prevention of scarring

In both groups the scar was minimal or absent after healing, but all participants developed postinflammatory hyperpigmentation.

Secondary outcome: adverse effects

There were no systemic adverse effects with ILSSG or HSCS in Ranawaka 2010. Pain during injection was the only local side effect noted with both therapies. After healing, scarring was minimal, but all participants receiving both treatments had postinflammatory hyperpigmentation, which faded over six to eight months.

3.5.2 IL 5% HSCS versus ILMA

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared IL HSCS (0.5 mL to 1 mL) with ILMA (0.5 mL to 1 mL) weekly for 6 to 10 weeks (Sadeghian 2006b). At the end of treatment, 25% (9/36) and 33.3% (12/36) lesions had healed in the respective groups (RR 0.75, 95% CI 0.36 to 1.56; N = 72; 1 study, Analysis 66.1).

Secondary outcome: adverse effects

In the HSCS group, there were three cases of sporotrichotic dissemination but with no allergic reactions. In the ILMA group, there were three cases of sporotrichotic dissemination, two satellite lesions, and two allergic reactions including redness, oedema, and severe itch around the lesions. There were no significant differences in sporotrichotic dissemination rates (RR 1.00, 95% CI 0.22 to 4.63; N = 72; 1 study) or allergic reactions rates (RR 0.20, 95% CI 0.01 to 4.03; N = 72; 1 study) between groups (Analysis 66.2).

3.5.3 IL 7% HSCS versus IL ciprofloxacin solution

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iraq compared IL 7% HSCS (0.1 mL to 0.5 mL per lesion) with IL ciprofloxacin solution 2 mg/mL (0.1 mL to 0.5 mL per lesion) (Al Hamdi 2010). At two months after treatment, 76.2% (16/21) and 81.5% (22/27) of the lesions had healed in the respective groups. There was no difference in cure rates between IL HSCS and IL ciprofloxacin (RR 1.07, 95% CI 0.79 to 1.44; N = 48; 1 study, Analysis 67.1).

3.5.4 IL 10% HSCS versus IL 15% HSCS versus ILSSG

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Sri Lanka compared IL 10% HSCS versus IL 15% HSCS versus ILSSG (0.2 mL to 4 mL per lesion and maximum five injections) (Ranawaka 2015). The authors reported that three months after treatment, 93% (268/290), 93.6% (92/98), and 96.3% (226/235) of the lesions in the respective groups had completely healed. There was no difference in cure rates between any comparison: IL 15% HSCS versus IL 10 % HSCS (RR 1.02, 95% CI 0.96 to 1.08; N = 388, Analysis 68.1); ILSSG versus IL 10% HSCS (RR 1.04, 95% CI 1.00 to 1.08; N = 525, Analysis 69.1); and ILSSG versus IL 15% HSCS (RR 1.02, 95% CI 0.97 to 1.08; N = 333; 1 study, Analysis 70.1).

Secondary outcome: speed of healing (time taken to be 'cured')

There was no difference in speed of healing between IL 15% HSCS versus IL 10% HSCS (MD −1.45, 95% CI −4.34 to 1.44 weeks; N = 388; 1 study, Analysis 68.3). Lesions in ILSSG group cured significantly faster than in 10% HSCS group (MD −5.20, 95% CI −6.31 to −4.09 weeks; N = 525, Analysis 69.3) and in IL 15%

HSCS group (MD −6.65, 95% CI −9.41 to −3.89 weeks; N = 333, Analysis 70.3).

Secondary outcome: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

After six months of follow-up, the authors described four cases of relapse in 10% HSCS group, four cases in 15% HSCS group and three in the ILSSG group (Ranawaka 2015). There was no significant difference in this outcome in any comparisons: 15% HSCS versus 10% HSCS (RR 2.93, 95% CI 0.75 to 11.50; N = 362; 1 study, Analysis 68.2), ILSSG versus 10% HSCS (RR 0.90 95% CI 0.20 to 3.96, Analysis 69.2), and ILSSG versus 15% HSCS (RR 1.02, 95% CI 0.97 to 1.08, Analysis 70.2).

Secondary outcome: adverse effects

All participants experienced pain during injections, particularly in the 15% HSCS group. All lesions presented postinflammatory hyperpigmentation, which faded over six to eight months. Ulceration and necrosis occurred in 30% (30/98) of the lesions treated with 15% HSCS and in 3.1% (9/290) of the lesions in the 10% HSCS group. There were statistically significant differences in ulceration and necrosis rates between the IL 15% HCS group and the 10% HSCS group (RR 9.86, 95% CI 4.86 to 20.04; N = 388; 1 study, Analysis 68.4) and between the IL 15% HCS group and ILSSG group (RR 145.41, 95% CI 8.98 to 2354.65; N = 333; 1 study, Analysis 70.4), with more events in the IL 15% HCS group.

3.6 IL interferon-gamma (IFN-γ)

3.6.1 IL IFN- γ versus ILMA

Primary outcome: percentage of lesions with a complete cure after the end of treatment

An RCT from Syria compared IL IFN-γ versus ILMA once weekly for five weeks (Harms 1991). At one month after treatment, 3% (1/37) and 76% (29/38) of the lesions had healed completely in the respective groups. The cure rates in the IL IFN-γ group were significantly lower than in the ILMA group (RR 0.04, 95% CI 0.01 to 0.28; N = 76; 1 study, Analysis 71.1).

Secondary outcome: adverse effects

In the IFN-γ arm, pain at the injection site of was mild on 68 occasions, moderate on 47, and severe on 38. In the ILMA group it was mild on 55 occasions, moderate on 51, and severe on 40. Other adverse effects included local maculopapular erythema in the ILMA group and headache in the IFN-γ group.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Parasitological assessment one month after the end of treatment showed 65% (24/37) and 100% (38/38) of the lesions were parasite-free in the IFN-γ and ILMA groups, respectively (RR 0.65, 95% CI 0.51 to 0.83; N = 75; 1 study, Analysis 71.2).

3.7 Topical aminoglycoside ointment (WR279,396)

3.7.1 WR279,396 ointment versus placebo

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Tunisia compared WR279,396 (a third generation aminoglycoside ointment) versus vehicle twice daily for 20 days (Ben Salah 2009). After a six-month follow-up, 86% (43/50) and 64% (27/42) of the participants in the respective groups achieved complete cure (RR 1.34, 95% CI 1.04 to 1.72; N = 92, Analysis 72.1).

Secondary outcome: adverse effects

Regarding adverse effects, 30% (n = 15) of participants from the WR279,396 and 24% (n = 10) from the vehicle groups suffered from erythema at the site of application (RR 1.26, 95% CI 0.63 to 2.50; N = 92; 1 study); 14% from both groups (n = 7 and n = 6, respectively) had mild pain within 30 minutes of application (RR 0.98, 95% CI 0.36 to 2.69; N = 92; 1 study); 28% (n = 14) and 21% (n = 9) presented mild increases and decreases in hearing acuity from baseline; 28% (n = 14) and 21% (n = 9) had changed hearing acuity (RR 1.31, 95% CI 0.63 to 2.71; N = 92; 1 study), and there were no deaths reported in either group. See Analysis 72.2.

3.8 Intralesional metronidazole

3.8.1 IL metronidazole versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT compared weekly intralesional metronidazole (2.5 mg to 10 mg = 0.5 mL to 2 mL for each lesion) with weekly ILMA (150

mg to 600 mg = 0.5 mL to 2 mL for each lesion) for up to eight weeks (Mapar 2010). At the end of treatment, 16.6% (3/18) and 72.2% (13/18) of participants in the respective groups achieved complete cure (RR 0.23, 95% CI 0.08 to 0.67; N = 36, Analysis 73.1).

Secondary outcome: adverse effects

Authors did not describe any systemic or local adverse effects with metronidazole, but two participants in the ILMA group suffered local inflammatory reactions with oedema and induration that diminished in about 10 days. There were no significant differences in local inflammatory reactions rates between groups (RR 0.20, 95% CI 0.01 to 3.89; N = 36; 1 study, Analysis 73.2). In both groups the participants reported severe pain at the site of injections, but in the ILMA group it was intolerable.

3.9 Topical miltefosine

3.9.1 Topical miltefosine versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical miltefosine ointment 6% once daily versus ILMA twice a week for up to 28 days (Asilian 2014). At one month after treatment, 81.3% (26/32) and 50.0% (16/32) of the participants in the respective groups achieved complete cure (RR 1.63, 95% CI 1.11 to 2.39; N = 64; 1 study, Analysis 74.1).

3.10 Topical dapsone

3.10.1 Niosomal dapsone 5% gel mask plus ILMA versus cryotherapy plus ILMA

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared niosomal dapsone 5% gel mask (twice a day) plus ILMA (weekly) versus cryotherapy (every two weeks) plus ILMA (weekly) for up to 16 weeks (Fekri 2015). At 16-week follow-up, 82% (29/35) and 86% (33/38) of the lesions had healed in the respective groups (RR 0.95, 95% CI 0.79 to 1.16; N = 73; 1 study, Analysis 75.1).

3.11 Topical 0.045% pharmaceutical chlorite (DAC N-055)

3.11.1 Topical 0.045% pharmaceutical chlorite (DAC N-055) with and without bipolar high frequency electrocauterisation versus ILSSG

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Afghanistan compared 0.045% pharmaceutical chlorite (DAC N-055) plus bipolar high frequency electrocauterisation for 15 minutes versus 0.045% DAC N-055 for 15 minutes alone versus ILSSG 0.6 mL for up to 75 days (Stahl 2014). After a 75-day follow-up, the authors reported a complete cure in 100% (23/23), 87% (20/23), and 65% (15/23) of the participants in the respective groups. There was no difference between DAC N-055 plus electrocauterisation versus DAC N-055 alone (RR 1.15, 95% CI 0.96 to 1.37; N = 46; 1 study, Analysis 76.1). DAC N-055 plus electrocauterisation was more efficacious than ILSSG (RR 1.52, 95% CI 1.12 to 2.05; N = 46; 1 study, Analysis 77.1), and DAC N-055 alone was not more efficacious than ILSSG (RR 1.33, 95% CI 0.95 to 1.87; N = 46; 1 study, Analysis 78.1).

Secondary outcome: speed of healing (time taken to be 'cured')

The hazard ratio for DAC N-055 versus ILSSG was 4.4 (95% CI 2.2 to 8.7) in the per protocol analysis (P < 0.001) and 3.2 (95% CI 1.6 to 6.3) in the intention-to-treat analysis (P < 0.001). The lesion closed three to four times faster in the DAC N-055 group than in the ILSSG group.

Secondary outcome: adverse effects

Regarding adverse effects, four participants developed reulceration of lesions in the DAC N-055 plus electrocauterisation group, three in the DAC N-055 alone group, and seven in the ILSSG group. There were no significant differences in reulceration rates between DAC N-055 plus electrocauterisation versus DAC N-055 alone (RR 1.33, 95% CI 0.34 to 5.30; N = 46; 1 study, Analysis 76.2). Two participants (8.7%) developed keloids and keloid scars in the DAC N-055 plus electrocauterisation group.

3.12 Topical Thio-Ben

3.12.1 Topical Thio-Ben plus cryotherapy versus ILMA plus cryotherapy

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared 1 mL to 2 mL of Thio-Ben tincture daily plus cryotherapy (liquid nitrogen (−195°C) fortnightly versus ILMA weekly (dose of 0.5 mL to 2 mL per lesion) plus cryotherapy (Daie Parizi 2015). After three months' follow-up 91% (20/22) and 92% (23/25) of the lesions had healed completely in the respective groups. There was no difference between Thio-Ben plus cryotherapy and ILMA plus cryotherapy (RR 0.99, 95% CI 0.83 to 1.18; N = 47; 1 study, Analysis 79.1).

Secondary outcome: speed of healing (time taken to be 'cured')

On average, lesions required the same amount of time to achieve a complete cure: 2.45 months in the Thio-Ben plus cryotherapy group and 2.41 months in the ILMA plus cryotherapy group (Daie Parizi 2015).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

The rate of relapse was slightly, but not significantly, higher in the Thio-Ben group 20% (4/22) than in the ILMA group 13% (3/25) (RR 1.52, 95% CI 0.38 to 6.04; N = 47; 1 study, Analysis 79.2).

Secondary outcome: adverse effects

Regarding adverse effects, investigators observed itching and mild erythema in almost all cases with different degrees of severity, and oedema especially after cryotherapy in almost all lesions. Participants from the ILMA plus cryotherapy group experienced pain at the injection site in almost all cases, while three participants reported dizziness and nausea (RR 0.16, 95% CI 0.01 to 2.96; N = 47; 1 study), and one had a hypersensitive reaction (RR 0.38, 95% CI 0.02 to 8.80; N = 47; 1 study, Analysis 79.3). There was poor adherence to treatment particularly among children.

4. Physical therapies

4.1 Laser

See Table 7 for a summary of adverse effects of lasers and Table 8 for a summary of adverse effects of cryotherapy.

4.1.1 CO_2 laser versus IMMA

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared CO_2 laser applied to the lesion (30 W, continuous) versus IMMA (50 mg/kg/d) for 15 days (this treatment was repeated after 15 days of rest) (Asilian 2004b). At six weeks after treatment, 11% (20/183) and 12% (30/250) of the lesions had healed completely in the respective groups (RR 0.91, 95% CI 0.53 to 1.55; N = 433; 1 study, Analysis 80.1).

Secondary outcomes: speed of healing

The time taken to be cured was one month for the CO_2 laser group and three months for the IMMA group.

Secondary outcome: prevention of scarring

In the laser group, study authors considered most scars to be 'acceptable', except in five cases (4%) in which the lesions were located on the joints or neck, and the resulting scars were raised and hypertrophic.

Secondary outcome: adverse effects

In the laser group, 3% (4/123) of participants experienced hyperpigmentation and persistent redness (RR 12.28, 95% CI 0.67 to 226.62; N = 433; 1 study, Analysis 80.2), and five participants had hypertrophic scarring (RR 0.16, 95% CI 0.01 to 2.96; N = 47; 1 study, Analysis 80.2). In the IMMA group, 9% (22/250) of participants reported myalgia, sensitivity, headache, urticaria, and nausea; these were higher in the IMMA group than in the laser group (RR 0.03, 95% CI 0.00 to 0.50; N = 433; 1 study, Analysis 80.2).

4.1.2 CO_2 laser versus cryotherapy plus ILMA

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared CO_2 laser (30 W, continuous) applied to the lesion (repeated maximum 3 to 5 times) versus combined cryotherapy (liquid nitrogen 10 s to 25 s) biweekly plus ILMA (0.5 mL to 2 mL per lesion) weekly until complete cure or up to 12 weeks (Shamsi Meymandi 2011). At 12 weeks, 94.7% (90/95) and 77.9% (74/95) of the lesions had healed in the respective groups. CO_2 laser was more efficacious than cryotherapy plus ILMA (RR 1.22, 95% CI 1.08 to 1.37; N = 190; 1 study, Analysis 81.1).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

There was no worsening (increase in size of the lesions) or relapse after the two types of treatment.

Secondary outcome: adverse effects

The authors reported adverse effects to participants (80 participants per group). In the laser group, 25% (n = 20) of participants had hyperpigmentation and trivial scarring, compared to 18.7% (n = 15) in the cryotherapy plus ILMA group (RR 1.33, 95% CI 0.73 to 2.44; N = 190; 1 study); 8.75% (n = 7) and 18.8% (n = 15), respectively, had atrophic scars (RR 0.47, 95% CI 0.20 to 1.09; N = 190; 1 study), and 5% (n = 4) in the laser group only had hypopigmentation plus trivial scarring (RR 9.00, 95% CI 0.49 to 164.88; N = 190; 1 study; Analysis 81.2).

4.1.3 Ablative CO

- **laser versus fractional CO**
- **laser**

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared ablative CO_2 laser (10 ns, frequency: use of 20 kHz, and power: 25 Kw for one session) versus fractional CO_2 laser (energy: 25, one pulse, pass: 1, dot cycle: 6) until complete cure or up to 12 weeks (Nilforoushzadeh 2014a). At six months' follow-up, 46.7% (28/60) and 76.7% (46/60) of participants in the respective groups achieved a complete cure (RR 0.61, 95% CI 0.45 to 0.83; N = 120; 1 study, Analysis 82.1).

Secondary outcome: adverse effects

Nilforoushzadeh 2014a reported erythema in two participants (3.3%) in the ablative CO_2 laser group and four (6.7%) in the fractional CO_2 laser group (RR 0.50, 95% CI 0.10 to 2.63; N = 120; 1 study, Analysis 82.2).

4.2 Trichloroacetic acid

4.2.1 Trichloroacetic acid versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared trichloroacetic acid (TCA) 50% (wt/vol) applied fortnightly until complete re-epithelialisation or up to three times versus ILMA (0.5 mL to 2 mL per lesion) weekly until complete re-epithelialisation of the lesions or up to six weeks (Nilforoushzadeh 2006). At the end of the treatment period, 65% (26/40) and 57.5% (23/40) of participants in the respective groups achieved a complete cure (RR 1.13, 95% CI 0.80 to 1.60; N = 80; 1 study, Analysis 83.1).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

Recurrence occurred in 12.5% (5/40) of the cases in the TCA group and 10% (4/40) in the ILMA group after three months' follow-up (RR 1.25, 95% CI 0.36 to 4.32; N = 80; 1 study, Analysis 83.2).

Secondary outcome: adverse effects

The observed adverse effects included mild erythema and itch (two cases in the ILMA group), with no significant differences between groups (RR 0.20, 95% CI 0.01 to 4.04; N = 80; 1 study, Analysis 83.3).

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Parasitological assessment at week 6 showed 72.5% (29/40) and 75% (30/40) of the lesions were parasite-free in the TCA and ILMA groups, respectively. Parasitologic tests were positive at week 6 in 27.5% (11/40) and 25% (10/40) of the cases in the TCA and ILMA groups, respectively. There were no significant differences in parasitologic test rates between groups ((RR 0.97, 95% CI 0.74 to 1.26; participants = 80; studies = 1 Analysis 83.4).

4.2.2 Non-ablative laser plus TCA versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared non-ablative laser (weekly for four consecutive weeks) plus TCA (applied weekly for up to two weeks) versus ILMA (twice a week up to eight weeks) alone (Nilforoushzadeh 2012). At six months' follow-up, 42.1% (16/30) and 63.2% (24/30) of the participants in the respective groups achieved a complete cure (RR 0.67, 95% CI 0.46 to 0.97; N = 60, Analysis 84.1).

Primary outcome: percentage of lesions cured after the end of treatment

The authors performed a subgroup analysis according to sex. In the male group, 36.3% (8/22) of the lesions treated with laser plus TCA, and 53.3% (8/15) receiving ILMA, had healed completely at six months (RR 0.68, 99% CI 0.26 to 1.77; N = 37). In females, cure rates in the respective groups were 50% (8/16) and 69.6% (16/23) (RR 0.72, 99% CI 0.34 to 1.50; N = 39; Analysis 84.2).

4.2.3 TCA plus ILMA versus factional laser plus ILMA versus ILMA alone

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared TCA (applied weekly for up to eight consecutive weeks until the lesion was frosted) plus ILMA versus fractional laser (fortnightly two sessions) plus ILMA versus ILMA alone twice a week until complete re-epithelialisation of the lesions or up to eight weeks (Nilforoushzadeh 2013). At six months' follow-up, 90% (27/30) of the participants in the TCA plus ILMA group, 87% (20/23) in the fractional laser plus ILMA group, and 38.5% (10/26) in the ILMA alone group achieved complete cure. Cure rates were significantly higher in the TCA plus ILMA group compared with ILMA alone (RR 2.34, 95% CI 1.42 to 3.86; N = 56; 1 study, Analysis 85.1). ILMA alone was less efficacious than fractional laser and ILMA (RR 2.26, 95% CI 1.36 to 3.77; N = 49; 1 study, Analysis 86.1). There was no difference in complete cure rates between TCA plus ILMA versus fractional laser plus ILMA (RR 1.03, 95% CI 0.85 to 1.26; N = 53; 1 study, Analysis 87.1).

Secondary outcome: speed of healing (time taken to be 'cured')

Analysis of time to heal data in the Nilforoushzadeh 2013 study only showed significant differences in mean time to heal between TCA plus ILMA versus ILMA alone groups (MD −1.60, 95% CI −2.35 to −0.85 weeks, Analysis 85.2).

Secondary outcome: adverse effects

Nilforoushzadeh 2013 reported adverse effects in 80% (n = 72) of participants. There were five (6.9%) cases of local irritation, two (2.8%) cases of infection, one (1.4%) case of enlargement of lesion, and three (4.2%) cases of satellite lesions. The study did not describe the adverse effects by intervention.

4.2.4 TCA plus ILMA versus ILMA alone

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared TCA 50% (applied fortnightly up to frosting the lesion) plus ILMA (twice a week until complete resolution of the lesions or up to eight weeks) versus ILMA alone (twice a week until complete resolution of the lesions or up to eight weeks) (Nilforoushzadeh 2014b). At the end of the treatment period, 85.7% (78/91) and 80% (76/95) of the participants in the respective groups achieved a complete cure (RR 1.07, 95% CI 0.94 to 1.22; N = 186; 1 study Analysis 88.1). The authors also performed an analysis by the type of lesions (papule, nodule, plaque or ulcerative nodule), but they did not observe any difference between groups.

4.3 Cryotherapy

4.3.1 Cryotherapy alone versus ILMA plus cryotherapy versus ILMA monotherapy

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared a combination of cryotherapy (freezing time was 10 s to 30 s with a thawing interval of 20 s) plus ILMA (after 5 to 10 min of cryotherapy) versus cryotherapy alone versus ILMA monotherapy (0.2 mL to 1.5 mL per session per week) (Salmanpour 2006). Ninety per cent (18/20), 70% (14/20), and 75% (15/20) of the participants in the respective groups had achieved a complete cure; however, authors did not report the time of this assessment. There were no statistical difference in cure rates between any comparisons: cryotherapy plus ILMA versus cryotherapy alone (RR 1.29, 95% CI 0.93 to 1.77; N = 40; 1 study, Analysis 89.1); cryotherapy plus ILMA versus ILMA alone (RR 1.20, 95% CI 0.90 to 1.61; N = 40; 1 study, Analysis 90.1), or cryotherapy alone versus ILMA alone (RR 0.93, 95% CI 0.64 to 1.37; N = 40; 1 study, Analysis 91.1).

An RCT from Iran compared cryotherapy (liquid nitrogen (−195°C) twice to the lesion for 10 s to 15 s, with a thawing interval of 20 s) versus ILMA monotherapy (0.2 mL to 1.5 mL per lesion) weekly for up to six weeks (Layegh 2009). At six months' follow-up, 58.3% (21/36) and 27.8% (10/36) of the cryotherapy and ILMA group, respectively, achieved a complete cure (RR 2.10, 95% CI 1.16 to 3.81; N = 72; 1 study, Analysis 92.1).

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared cryotherapy (liquid nitrogen (−195°C) 10 s to 25 s with a thawing interval of 20 s) plus ILMA (after thawing, 0.5 mL to 2 mL per lesion) versus cryotherapy alone versus ILMA alone (0.5 mL to 2 mL per lesion) fortnightly until complete cure or for up to six weeks (Asilian 2004a). At the end of the treatment period, 80.5% (120/149), 52.2% (120/230) and 52.5% (84/160) of the lesions in the respective groups had healed completely. Cure rates were significantly higher in the cryotherapy plus ILMA group compared with cryotherapy alone (RR 1.54, 95% CI 1.33 to 1.79; N = 379; 1 study, Analysis 93.1) and ILMA alone (RR 1.53, 95% CI 1.30 to 1.81; N = 309; 1 study Analysis 94.1). There were no significant differences in cure rates between ILMA alone and cryotherapy alone groups (RR 0.99, 95% CI 0.82 to 1.20; N = 390; 1 study, Analysis 95.1).

Secondary outcome: speed of healing (time taken to be 'cured')

Only one study reported that none of the cured lesions recurred during the six-month follow-up period (Asilian 2004a).

Secondary outcome: adverse effects

Asilian 2004a reported mild adverse side effects, such as postinflammatory hypopigmentation: 5/100 of cases in the combined cryotherapy and ILMA group and 10/230 in the cryotherapy group. There were no significant differences in adverse effects rates between groups (Analysis 93.2; Analysis 94.2; Analysis 95.2). In Salmanpour 2006 there were no serious side effects in any of the treatment groups. However, 35% of the cases in the cryotherapy plus ILMA group, 60% in the cryotherapy alone group, and 20% in the ILMA alone group showed erythema and oedema of the lesions and perilesional area, but these adverse effects rates were not statistically different (Analysis 89.2; Analysis 90.2; Analysis 91.2). The most common adverse effects reported by Layegh 2009 were erythema and oedema at the treated site; these adverse reactions appeared during the initial hours after treatment. Layegh 2009 also described blistering at the treatment site, which became evident one or two days after treatment with a good response to local treatment. Other minor adverse effects are shown in Table 8.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Only Asilian 2004a reported that all cured lesions showed negative direct smears at the end of treatment and six weeks after treatment.

4.3.2 Triple combination of cryotherapy plus 15% paromomycin plus ILMA versus ILMA monotherapy

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared a combined triple therapy of cryotherapy (fortnightly for up to 3 sessions) plus 15% paromomycin plus 10% urea cream applied twice a day for 4 weeks plus ILMA (twice a day for four weeks after cryotherapy) versus ILMA monotherapy twice every week until complete healing or for a maximum of six weeks (Nilforoushzadeh 2004). At six weeks after treatment, 84% (68/81) and 75% (57/76) of the participants in the respective groups had achieved complete cure. There were no significant differences in cure rates between groups (RR 1.12, 95% CI 0.95 to 1.31; N = 157; 1 study, Analysis 96.1).

4.3.3 Triple combination cryotherapy plus 3% salicylic acid cream plus 3% sodium nitrite cream versus cryotherapy plus 3% salicylic acid cream plus vehicle

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared cryotherapy (once a week) plus 3% salicylic acid cream (twice a day) plus 3% sodium nitrite cream (twice a day) versus cryotherapy plus 3% salicylic acid cream for up to 12 weeks (Jowkar 2012). At the end of the treatment period, 83.3% (30/36) and 74.1% (20/27) of the lesions in the respective groups had healed completely (RR 1.13, 95% CI 0.86 to 1.47; N = 63; 1 study, Analysis 97.1).

Secondary outcome: adverse effects

Jowkar 2012 reported erythema, a burning sensation, and skin irritation in seven participants (19.4%) in the cryotherapy plus salicylic acid plus sodium nitrate group, and in one participant (3.7%) in the cryotherapy plus salicylic acid plus vehicle group. Statistically, this was not a significant difference (RR 5.25, 95% CI 0.69 to 40.17; N = 63; 1 study, Analysis 97.2). See Table 8.

4.4 Thermotherapy

For a summary of adverse effects of thermotherapy please see Table 9.

4.4.1 Thermotherapy using radiofrequency waves versus ILMA

Primary outcome: percentage of lesions cured after the end of treatment

One RCT from Iran compared controlled localised heating using a radiofrequency heat generator (4 MHz, maximum output 90 W weekly) versus ILMA (0.1 mL to 4 mL per lesion) for four consecutive weeks (Sadeghian 2007). Six months after treatment, 80.7% (67/83) and 55.3% (52/94) of the lesions in the respective groups had healed completely. Cure rates were significantly higher in the thermotherapy group compared with ILMA (RR 1.46, 95% CI 1.18 to 1.80; N = 177; 1 study, Analysis 98.1).
We assessed the certainty of evidence as very low.

Primary outcome: percentage of participants with a complete cure after the end of treatment

There were two studies assessing complete cure after the end of treatment (Sadeghian 2007; Safi 2012). Heterogeneity was substantial (P = 0.08; I^2 = 68%), although both effects are in the same direction. The pooled analysis showed no significant difference in cure rates between thermotherapy and ILMA groups (RR 1.23, 95% CI 0.97 to 1.55; N = 499; 2 studies, Analysis 98.2).
We assessed the certainty of evidence as very low.

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

Only the study from Iran reported not finding relapse from lesions with complete response in either group after six months of follow-up (Sadeghian 2007).

Secondary outcome: prevention of scarring

Sadeghian 2007 reported that although all participants with complete response in both groups had scars, the size of the scars was smaller in the heat-treated group (15.9 mm before and 11.2 mm after treatment) than in the ILMA-treated group (15.0 mm before and 14.8 mm after treatment).

Secondary outcome: adverse effects

In Sadeghian 2007, allergic reactions such as erythema, oedema, and pruritus occurred in the ILMA group in four participants with 10 lesions, and there were also four cases of post-treatment sporotrichotic lesions and three cases of satellite lesions. There was only one case with satellite lesions after treatment in the ILMA group. Safi 2012 reported mild and minimal adverse effects only in the ILMA group.
Participants treated with controlled localised heating reported fewer allergic reactions (RR 0.05, 95% CI 0.00 to 0.76; N = 117, 1 study, Analysis 98.3) but with very low-certainty evidence.

4.4.2 Thermotherapy using radiofrequency waves versus intralesional or intravenous sodium stibogluconate (SSG)

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iraq and Kuwait compared IVSSG (20 mg/kg/d) for 10 doses versus one session of thermotherapy using radiofrequency waves (50 uCTM applied for 30 s) (Aronson 2010). Two months after treatment, 73.3% (63/86) and 59.5% (50/84) of lesions had healed completely in the respective groups. There was no difference in cure rates between groups ((RR 1.23, 95% CI 0.99 to 1.53; participants = 170; studies = 1); Analysis 99.1).

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Afghanistan compared ILSSG (five injections every five to seven days depending on the lesion size) for up to 29 days versus IMSSG (20 mg/kg/d) daily for 21 days versus thermotherapy using radiofrequency waves (one session of > 1 consecutive application at 50°C for 30 s depending on lesion size) (Reithinger 2005). Two months after treatment, 47.3% (70/148), 18% (26/144) and 54% (75/139) of the participants in the respective group had achieved a complete cure. Cure rates were significantly higher in the thermotherapy group compared with IMSSG (RR 2.99, 95% CI 2.04 to 4.37; N = 283; 1 study, Analysis 100.1), but there was no difference compared with ILSSG (RR 1.14, 95% CI 0.91 to 1.43; N = 287; 1 study, Analysis 101.1).
An RCT from India compared ILSSG (2 mL to 5 mL per lesion twice a week, for seven injections over 29 days versus thermotherapy using radiofrequency waves (one treatment of two or more consecutive applications at 50°C for 30 s depending on lesion size) (Bumb 2013). Six months after treatment, 98% and 94% of participants in the respective groups had achieved a complete cure (RR 1.04, 95% CI 0.96 to 1.13; N = 100; 1 study, Analysis 102.1).

Secondary outcome: speed of healing (time taken to be 'cured')

In the Reithinger 2005 study, the speed of healing took a median of 75 days for the ILSSG group, 100 days or more for the IMSSG group, and 53 days for the thermotherapy group (the original

paper reported that the time to cure was significantly shorter for participants treated with thermotherapy; P = 0.003, by the log-rank test). Bumb 2013 described a median time to heal of 11 weeks (95% CI 8 to 12) in the thermotherapy group and 10 weeks (95% CI 8 to 12) in the ILSSG group. In Aronson 2010, time to heal was similar (P = 0.24) in both groups in the analysis using blinded reading of photographs.

Secondary outcome: adverse effects

Reithinger 2005 described secondary infection in 3.7% (5/148) of participants in the ILSSG group, 1.4% (2/144) in the IMSSG group, and 5.7% (8/139) in the thermotherapy group, and there were no statistical differences in either comparison: thermotherapy versus ILSSG (RR 4.14, 99% CI 0.55 to 31.03; N = 283; 1 study, Analysis 100.2) or thermotherapy versus IMSSG (RR 1.70, 99% CI 0.41 to 7.17; N = 287; 1 study, Analysis 101.2). The authors also reported one participant with bradycardia and one an undefined local reaction in the ILSSG group. In the IMSSG group, one participant reported bradycardia, one tachycardia, and one palpitation. In the thermotherapy group, some participants experienced superficial second degree burns. In Bumb 2013, radiofrequency heat treatment (RFHT) was associated with less scarring and hyperpigmentation compared with ILSSG. Aronson 2010 reported four participants (15%) in the thermotherapy group and three (11%) in the ILSSG group suffered serious adverse effects (RR 1.30, 95% CI 0.30 to 5.64; N = 170; 1 study, Analysis 99.2). See Table 9.

4.4.3 Electrocauterisation plus DAC n-055 or electrocauterisation

Secondary outcome: speed of healing (time taken to be 'cured')

An RCT from Afghanistan compared bipolar high-frequency electrocauterisation plus daily moist-wound-treatment (MWT) with polyacrylate hydrogel including 0.045% DAC N-055 versus electrocauterisation plus vehicle (Jebran 2014). The speed of healing took a median of 43.15 days for the electrocauterisation plus DAC N-055 group and 42 days for the electrocauterisation group.

Secondary outcome: adverse effects

Six participants in each group had bacterial and fungal superinfections (8% in the electrocauterisation plus DAC n-055 group and 9% in the electrocauterisation group; RR 0.85, 95% CI 0.29 to 2.50; N = 135; 1 study, Analysis 103.1), and two participants in electrocauterisation plus DAC n-055 group and four participants in the electrocauterisation group reported Keloïd formation (5% and 6%, respectively; RR 0.42, 95% CI 0.08 to 2.24; N = 135; 1 study, Analysis 103.1). Other minor adverse effects are shown in Table 9.

4.5 Topical photodynamic therapy (PDT)

4.5.1 Topical PDT versus vehicle

Primary outcome: percentage of lesions cured after the end of treatment

An RCT from Iran compared topical PDT every week for four weeks (0% 5-aminolevulinic acid (5-ALA) hydrochloride in a water-in-oil cream) (Asilian 2006). Lesions irradiated using visible red light at 100 J/cm² per treatment session) with vehicle twice daily also for 28 days. Two months after treatment, 93.5% (29/31) of the lesions in the PDT group and 13.3% (4/30) in the vehicle groups healed completely. Cure rates were significantly higher in the PDT group compared with vehicle (RR 7.02, 95% CI 2.80 to 17.55; N = 61; 1 study, Analysis 104.1).

Secondary outcome: prevention of scarring

At the end of the study, none of the lesions had deep or disfiguring scars in the PDT group. However, 20% (3/30) of the lesions in the vehicle group had deep or disfiguring scars (RR 0.14, 95% CI 0.01 to 2.57; N = 61; 1 study, Analysis 104.2). Both groups had mild and tolerable itch, burning, redness, discharge, oedema, and pain as adverse effects.

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Two months after treatment, parasitological cure rates were significantly higher in the PDT group (100%, 31/31 lesions) compared to placebo (20%, 6/30) (RR 4.69, 95% CI 2.37 to 9.31; N = 61; 1 study, Analysis 104.3).

The same author also compared PDT with topical paromomycin plus methyl benzethonium chloride, which we analyse in section 3.2, 'Topical paromomycin (aminosidine)'.

4.6 Mesotherapy

4.6.1 Mesotherapy versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

One RCT from Iran compared mesotherapy (0.05 mL injection of MA in each shot in the depth of 2 mm) versus ILMA (0.1 mL of MA) for up six weeks (Kashani 2010). Three months after treatment, 83.3% (25/30) and 86.7% (26/30) of participants in the respective groups had achieved complete cure (RR 0.96, 95% CI 0.78 to 1.19; N = 60; 1 study, Analysis 105.1).

Secondary outcome: speed of healing (time taken to be 'cured')

The authors did not report significant improvement in ulcer, induration, erythema, or scar size between the two groups. However, the study described faster improvement in participants who received mesotherapy compared to ILMA: ulcerated lesions improved at the rate of 0.27 cm per week (SD 0.14) and 0.15 cm per week (SD 0.72), respectively, with an improvement for erythema of 0.31 cm per week (SD 0.15) and 0.22 cm per week (SD 0.07).

Secondary outcome: adverse effects

Pain severity evaluated by VAS was significantly higher in the ILMA group than in the mesotherapy group (7.67 cm versus 6.06 cm; P = 0.005). Two participants in the mesotherapy group and one in the ILMA group suffered an allergic reaction. There were no significant differences in allergic reaction rates between groups (RR 2.00, 95% CI 0.19 to 20.90; N = 60; 1 study; Analysis 105.2).

Tertiary outcomes: development of cell-mediated immunity (i.e. positive leishmanin skin test)

Three months after treatment, there were positive *Leishmania* antibodies in three participants in the mesotherapy group and two participants in the ILMA group. There were no significant differences in adverse effects rates between groups (RR 1.50, 95% CI 0.27 to 8.34; N = 60; 1 study) (Analysis 105.3).

5. Measures for promoting healing

5.1 Topical diminazene aceturate (Berenil) versus topical cetrimide plus chlorhexidine (Savlon)

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Sudan compared diminazene aceturate solution versus cetrimide plus chlorhexidine solution for 50 days (Lynen 1992). At the end of the treatment period, 80% (28/35) and 57% (20/35) of participants of in the respective groups achieved a complete cure, with a statistically significant difference in between groups and in favour of the diminazene aceturate solution (RR 1.40, 95% CI 1.01 to 1.95; N = 70; 1 study, Analysis 106.1).

Secondary outcomes: duration of remission and percentage of people with treated lesions that recur within six months, one year, two years, and three years

In the diminazene aceturate group, three re-ulcerations occurred (two after 20 days and one after 25 days of cure). In the chlorhexidine group, two re-ulcerations occurred after 35 days of cure.

Secondary outcome: adverse effects

Extreme drying of ulcers and surrounding skin occurred in participants in the diminazene aceturate solution (Berenil) group. Participants from the cetrimide plus chlorhexidine solution (Savlon) group experienced a slight burning sensation and drying of the skin at the site of treatment.

6. Alternative therapies

6.1 Garlic cream

6.1 Topical garlic cream versus vehicle

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared 5% garlic cream treatment versus vehicle twice a day under occlusion with sterile gauze for three hours, for three weeks (Gholami 2000). At 40 days after treatment, 18.75% (18/96) and 20% (15/75) of the participants in the respective groups had achieved a complete cure. There were no significant differences in cure rates between groups (RR 0.94, 95% CI 0.51 to 1.73; N = 171; 1 study, Analysis 107.1).

6.2 Herbal extract

6.2.1 Topical herbal extract versus IMMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical herbal extract Z-HE, covered with a dressing for five consecutive days plus placebo injection (0.5 mL saline) versus IMMA (15 mg/kg/d to 20 mg/kg/d) plus vehicle (petrolatum and charcoal powder) for 20 consecutive

days (Zerehsaz 1999). Six weeks after treatment, 74.4% (64/86) and 27.1% (23/85) of participants in the respective groups had achieved complete cure. There was a statistically significant difference in cure rates between topical herbal extract Z-HE compared with IMMA (RR 2.75, 95% CI 1.90 to 3.98; N = 171; 1 study, Analysis 108.1).

Secondary outcome: adverse effects

Participants in the IMMA reported urticaria and generalised itch.

6.3 Honey

6.3.1 Topical honey plus ILMA versus ILMA monotherapy

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical honey soaked gauze twice a day plus ILMA (weekly) versus ILMA (weekly) for four weeks (Nilforoushzadeh 2007). Results showed that two and a half to three months after treatment, 46% (23/50) and 64% (32/50) of the participants in the respective groups had achieved a complete cure, but with no significant difference between them (RR 0.72, 95% CI 0.50 to 1.04; N = 100; 1 study, Analysis 109.1).

Secondary outcome: speed of healing (time taken to be 'cured')

The mean time taken to be cured after omitting dropouts was 7.04 weeks and 6.3 weeks in the honey plus ILMA and the ILMA groups, respectively.

6.4 *Cassia fistula*

6.4.1 Topical *Cassia fistula* fruit gel plus ILMA versus ILMA plus vehicle

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical *Cassia fistula* fruit gel plus ILMA (0.5 mL to 2 mL) twice a week versus ILMA (0.5 mL to 2 mL) twice a week plus vehicle (Jaffary 2010). Results showed that three months after treatment, compete healing occurred in 67.1% and 41.4% of the participants in the respective groups. There was a statistically significant difference in cure rates in favour of *Cassia fistula* fruit gel as an adjuvant to ILMA compared with ILMA monotherapy (RR 1.62, 95% CI 1.17 to 2.24; N = 140; 1 study, Analysis 110.1).

Secondary outcome: adverse effects

Nine (12.9%) participants in each group suffered from adverse effects such as itching and erythema (RR 1.00, 95% CI 0.42 to 2.37; N = 140; 1 study, Analysis 110.2).

6.4.2 Topical concentrated boiled *Cassia fistula* versus topical *Cassia fistula* hydroalcoholic versus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical concentrated boiled *Cassia fistula* versus topical *Cassia fistula* hydroalcoholic versus ILMA (0.5 mL to 2 mL), twice a week for four weeks (Jaffary 2014b). Results showed that four months after treatment, 40% (22/55), 36% (20/55), and 65% (36/55) of the participants in the respective groups had achieved complete cure. Efficacy of ILMA was higher than concentrated boiled extract (RR 0.61, 95% CI 0.42 to 0.89; N = 110; 1 study, Analysis 111.1) and hydroalcoholic extract of *Cassia fistula* (RR 0.56, 95% CI 0.37 to 0.83; N = 110; 1 study, Analysis 112.1), but there was no significant difference between application of concentrated boiled extract and hydroalcoholic extract of *Cassia fistula* (RR 1.10, 95% CI 0.68 to 1.77; N = 110; 1 study, Analysis 113.1).

Secondary outcome: speed of healing (time taken to be 'cured')

Participants receiving ILMA healed more quickly than those treated with concentrated boiled extract of *Cassia fistula* (MD −1.80 weeks, 95% CI −3.49 to −0.11; N = 110; 1 study, Analysis 111.2), but there was no difference between concentrated boiled extract of *Cassia fistula* and hydroalcoholic extract (MD −0.30 weeks, 95% CI −1.70 to 1.10; N = 110; 1 study, Analysis 113.2). There was also no difference between hydroalcoholic extract of *Cassia fistula* and ILMA (MD −1.50 weeks, 95% CI −3.20 to 0.20; N = 110; 1 study, Analysis 112.2).

Secondary outcome: adverse effects

Three (5.5%) participants in the concentrated boiled extract group and two (3.6%) in the other groups withdrew from the study due to an allergic reaction to the medications. There was no significant difference among these three groups in this regard: boiled extract of *Cassia fistula* versus ILMA (RR 1.50, 95% CI 0.26 to 8.63; N = 110; 1 study, Analysis 111.3), hydroalcoholic extract of *Cassia*

fistula versus ILMA (RR 1.00, 95% CI 0.15 to 6.85; N = 110; 1 study, Analysis 112.3), or boiled extract of *Cassia fistula* versus hydroalcoholic extract of *Cassia fistula* (RR 1.50, 95% CI 0.26 to 8.63; N = 110; 1 study, Analysis 113.3).

6.5*Achilles millefolium*

6.5.1 Topical*Achilles millefolium* cream plus ILMA versus vehicle plus ILMA

Primary outcome: percentage of participants with a complete cure after the end of treatment

An RCT from Iran compared topical gel of 5% *Achilles millefolium* (twice daily) plus ILMA (weekly injections at 20 mg/kg/d) versus ILMA (weekly injections of 20 mg/kg/d) plus vehicle (twice daily) for four weeks (Jaffary 2014a). Two months after treatment, 53% (16/30) and 40% (12/30) of the participants in the respective groups had achieved a complete cure. There was no difference in cure rates between *Achilles millefolium* as an adjuvant to ILMA compared with ILMA monotherapy (RR 1.33, 95% CI 0.77 to 2.31; N = 60; 1 study, Analysis 114.1).

Secondary outcome: adverse effects

Eight (26.6%) participants in the *Achilles millefolium* group reported mild or moderate severe itching and redness, and one experienced severe itching and increasing wound discharge. In the control group, two participants reported mild itching (6.6%) and one, severe itching (3.3%). There were no significant differences in itching rates between groups (RR 3.00, 95% CI 0.90 to 10.01; N = 60; 1 study, Analysis 114.2)

Tertiary outcomes: microbiological or histopathological cure of skin lesions

Six weeks after treatment, 33% of the participants in the *Achilles millefolium* group and 40% in the control group had parasitological cure (RR 0.83, 95% CI 0.43 to 1.63; N = 60; 1 study, Analysis 114.3).

Results from the MEDLINE search for adverse effects

We performed a MEDLINE search for adverse or side effects combined with therapeutic terms. However, we could only find general papers reporting known adverse effects derived from the evaluated drugs that are already mentioned in the Background under the Description of the intervention section.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Paromomycin ointment versus matched vehicle for Old World cutaneous leishmaniasis

Patient or population: patients with Old World cutaneous leishmaniasis
Settings: primary health centres, Iran and Tunisia
Intervention: paromomycin ointment (15% + 10% urea) twice daily for 14 days
Comparison: vehicle

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Vehicle	Paromomycin ointment (15% + 10% urea) twice daily for 14 days			
Percentage of lesions cured after the end of treatment	Not measured in this comparison				
Percentage of participants with complete cure Follow-up: mean 2.5 months	**Study population**		**RR 1.00** (0.86 to 1.17)	383 (2 studies)	⊕◯◯◯ **Very low**[a]
	623 per 1000	**623 per 1000** (536 to 729)			
	Moderate				
	619 per 1000	**619 per 1000** (532 to 724)			
Adverse effects Skin/local reactions	**Study population**		**RR 1.42** (0.67 to 3.01)	713 (4 studies)	⊕◯◯◯ **Very low**[b]
	96 per 1000	**136 per 1000** (64 to 287)			
	Moderate				

	90 per 1000	**128 per 1000** (60 to 271)			
Speed of healing (time taken to be 'cured')	Not measured in this comparison				
Microbiological or histopathological cure of skin lesions Follow-up: mean 2.5 months	**Study population**		**RR 1.03** (0.88 to 1.2)	383 (2 studies)	⊕◯◯◯ **Very low**[c]
	859 per 1000	**884 per 1000** (756 to 1000)			
	Moderate				
	792 per 1000	**816 per 1000** (697 to 950)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR**: risk ratio; **N/A**: not applicable.

GRADE Working Group grades of evidence
High quality/certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality/certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality/certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality/certainty: we are very uncertain about the estimate.

[a]Downgraded by 4 levels due to risk of bias (1 RCT has many uncertain risks), indirectness (2 levels because one of the studies focused on young people), and imprecision (the confidence interval around the estimate risk ratio ranges from a 14% reduction to a 17% increase in the risk ratio for healing with paromomycin).
[b]Downgraded by 4 levels due to risk of bias (2 RCTs have many uncertain risks), indirectness (2 levels because one of the studies focused on young people), and imprecision (the confidence interval crosses the line of no effect).
[c]Downgraded by 5 levels due to risk of bias (1 RCT has many uncertain risks), inconsistency (there is considerable heterogeneity - I^2 = 84%), indirectness (2 levels because one of the studies focused on young people), and imprecision (the confidence interval around the estimate risk ratio ranges from a 12% reduction to a 20% increase in the risk ratio for healing with paromomycin).

DISCUSSION

Summary of main results

The randomised controlled trials (RCTs) included in this review assessed a broad range of treatments and many different clinical questions. Yet together, there were few opportunities to describe and pool useful data. We have some concerns regarding the precision of data reported in several studies. Furthermore, because most RCTs were at high risk of bias, it was difficult to conclude whether one treatment was more beneficial than the comparator much of the time. Many interventions ruled ineffective in an essentially inconclusive study could still prove to have some benefit if evaluated with greater statistical power. Nonetheless, this review accurately documents the existing RCT evidence on the usefulness of treatments, and that relevant information can be extracted for practice and future research.

We found 89 RCTs that covered more than 20 different interventions, broadly categorised into six main groups: antimonial drugs, non-antimonial systemic treatments, non-antimonial topical and intralesional treatments, physical therapies, methods for promoting healing, and alternative therapies. Given that sample size per se is not a source of potential bias but a source of potential imprecision that may lead to bias, care has to be exercised in not concluding that the evaluation of the efficacy of interventions of small-sized RCTs was untrustworthy.

It was difficult to evaluate the efficacy of any of the multiple treatments due to the variable treatment regimens examined and because the studies evaluated different *Leishmania* species and took place in different geographical areas. Moreover, most of the studies compared different regimens, and only a few RCTs compared treatments with sham therapies.

We created 'Summary of findings' tables for two comparisons (Summary of findings for the main comparison; Summary of findings 2); however, where measured, we rated all of the key outcomes included as very low-certainty evidence, so we are not confident that the results found are conclusive.

- A pooled analysis of three RCTs comparing itraconazole versus placebo favoured itraconazole with very low certainty of evidence, in terms of the following outcomes.
    - Percentage of participants with complete cure (N = 244).
    - Adverse effects (mild abdominal pain and nausea (N = 204) and mild abnormal liver function (N = 84).
    - Microbiological or histopathological cure of skin lesions (N = 20, only in one RCT).
- A pooled analysis of two RCTs comparing paromomycin ointment plus 10% urea versus vehicle showed no difference in cure rate between interventions with a very low certainty of evidence, in terms the following outcomes.
    - Percentage of participants with complete cure (N = 383).
    - Microbiological or histopathological cure of skin lesions (N = 383).
- However, the paromomycin group had more skin/local reactions, as assessed in four studies (N = 713).

Neither of the key comparisons offer data on the percentage of lesions cured after the end of treatment and speed of healing (i.e. time taken to be cured).

Overall completeness and applicability of evidence

Not all of the trials assessed the primary, secondary, and tertiary outcomes that we hoped to evaluate in this review. Our two main comparisons did not report our primary outcome of the percentage of lesions cured, and the comparisons that did measure this outcome (along with percentage of participants cured) lacked data on long-term effects. Assessing the two primary outcomes, we established that dealing with participants rather than with numbers of lesions proved to be a better cure criteria: lesions cured did not provide a realistic reflection of the number of participants that achieved complete cure or rather, whether all their lesions had healed. In addition, from a clinical perspective, it may be more relevant to know whether a person is completely or partially cured irrespective of the number of lesions fully healed by the tested drug. In fact, only 18 RCTs reported the primary outcome as percentage of lesions cured; the rest reported the percentages in terms of participants cured.

The main secondary outcome reported in our studies was the description of adverse effects, which is key when deciding a specific therapeutic option. Several RCTs also reported other secondary outcomes, but none reported the degree of functional and aesthetic impairment or quality of life. Only two tertiary outcomes were reported ('Microbiological or histopathological cure of skin lesions' in 15 trials and 'Development of cell-mediated immunity (i.e. positive leishmanin skin test)' in just one trial.

Many of the included studies did not specify the infecting species of leishmaniasis or made assumptions regarding the disease-causing species. We did not find any RCTs related to *L aethiopica* infections. There is also a lack of evidence for *L infantum* and*L donovani*: of the 41 new studies included in this updated systematic review, only two studies assessed *L donovani*-infected participants, and another one assessed the efficacy of a treatment in one *L infantum*-infected participant together with 66*L major*- and one*L tropica*-infected participants. Twenty studies reported *L major, L tropica,* or both.

Most included participants were adults, and all were immunocompetent; thus, our findings are not necessarily applicable to subsets of people such as women of childbearing age, children, people with co-morbid conditions, and immunocompromised individuals with no drug interactions.

The difficulty in determining the actual time point for cure in clinically significant terms in these studies is due to a lack of any universal measure for successful cure in OWCL. In fact, we found that most of the included RCTs did not explore cure rates past three months after treatment cessation. On the contrary, in most cases they assessed the primary outcome at the end of treatment or before three months.

The applicability of the results of this review to clinical practice is limited. The most important limitation in order to determine a specific conclusion for clinical practice is the short follow-up period reported in most studies. This impedes finding the real cure rate for OWCL because it is not possible to clearly confirm healing without long-term assessment (e.g. until at least six months after treatment has finished). There are no studies evaluating liposomal amphotericin B as a systemic treatment. Currently, because of the toxicity of pentavalent antimonials in most developed countries when systemic treatment is needed for OWCL, liposomal amphotericin B could be a good option, but at the time of writing there was no published information regarding its effectiveness.

Quality of the evidence

Most included trials were poorly designed and reported. Poor reporting is a major issue, and most studies were at unclear risk for one or more important bias domains in the 'Risk of bias' assessment. Risk of bias was generally moderate due to performance, attrition, or reporting bias. Most studies did not guard properly against performance bias (by blinding participants and healthcare professionals). Blinded outcome assessment was unclear. Adequate randomisation was reported in 47.2% (42/89) of the included studies. Only 13.5% (12/89) reported adequate allocation concealment. Double-blinding was found in 44.9% (40/89) of the studies. There was inadequate description of baseline characteristics in 10.1% (9/89) of the studies. Thirty point three per cent (27/89) of the studies reported sample size calculation. Only two studies assessed compliance (Firooz 2006; Lynen 1992). The causative parasite was not mentioned in 32.6% (29/89) of the studies, and 34.8% (31/89) of the trials mentioned the endemic nature of the parasite in the area, assuming that was the species causing the disease. The timing for outcome assessment was not reported in 2.2% (2/89) of the trials.

Because resources for clinical research into neglected diseases are limited, there is a need to prioritise and carry out properly designed clinical trials. We found many mistakes in the write-up of published manuscripts. Thus, it is essential that submitted journal manuscripts undergo rigorous peer review.

For the two main comparisons, we created 'Summary of findings' tables and conducted GRADE assessments on the certainty of evidence for the key outcomes, which we found to be very low. Risk of bias, as highlighted above, was one of the reasons for downgrading the evidence. We also downgraded evidence for imprecision, as many of the confidence intervals were very wide, likely due to the small sample size and low number of events in many of the studies assessed. Furthermore, in two cases (for 'participants complete cure' in the comparison itraconazole versus placebo, and 'microbiological/histopathological cure of skin lesions' in the comparison paromomycin ointment versus vehicle), we downgraded evidence for inconsistency due to the high I^2 values and the inconsistent direction or size of effect. In addition, we also observed indirectness in the outcomes measured in the comparison paromomycin ointment versus vehicle, as the evidence assessed only focused on young people.

Overall, considerable numbers of participants withdrew or were lost to follow-up. Most trial authors stated that they performed an adherence assessment, but results were seldom shown in the assessed studies.

Potential biases in the review process

Studies with more positive effects are more likely to be published than those with less conclusive results (Chalmers 2009), or those written in languages other than English (Bigby 2003). To tackle the problem of publication bias, we wrote to authors from endemic countries and the WHO asking for information. Besides, we searched databases of ongoing trials and others as well. However, the fact that eight studies have not yet been incorporated and are awaiting classification may be a source of potential bias.

Agreements and disagreements with other studies or reviews

Khatami 2007 performed a non-Cochrane systematic review on acute Old World cutaneous leishmaniasis. They included 50 studies with a total of 5515 participants. However, we detected quite a few inconsistent results. Firstly, review authors cited 51 RCTs instead of the 50 reported in the abstract and the Materials and methods, and we excluded three of these in our review for several reasons (Dogra 1986; El On 1992; Trau 1987): one was a cross-over trial, which is an inappropriate design for evaluating potential curative treatments in an infection (El On 1992), and we considered the generation of the randomisation sequence to be inadequate in the other two. We considered another four trials to be non-randomised in our review (Crawford 2005; el-Safi 1990; Mapar 2001; Vardy 2001). One RCT that Khatami 2007 included dealt with two case reports (el-On 1985). Secondly, if clinical trials reported in the paper's tables III to VII are included, review authors mentioned only 47 studies, while omitting 4. However, we do agree with Khatami 2007 in terms of the variable quality and methods of RCTs, providing weak evidence for treatment of OWCL, and regarding the importance of properly designing RCTs to improve their quality and to provide better evidence for the treatment of OWCL.

Two non-systematic reviews gathered evidence on Old World cutaneous leishmaniasis treatments (Blum 2014; Monge-Maillo 2013). The fact that these reviews did not use a systematic approach confers many biases and does not assure inclusion of all published studies. One study was more restrictive on selecting the studies and included only controlled clinical trials (Blum 2014), whereas the other was more permissive and also included other published data based on retrospective studies and large case series. However, review authors analysed the methodology of each of the studies, considering that only clinical trials were able to give a high quality of evidence (Monge-Maillo 2013). Moreover, these studies were not so restrictive regarding the period of follow-up needed and considered all the end points reported (percentages of lesions and of participants cured). In this way review authors considered certain therapeutic regimens such as dapsone for *L tropica* or itraconazole for *L major* to have a a higher quality of evidence than in the Cochrane Review. Even though these reviews (Blum 2014, Monge-Maillo 2013) do not have the methodological rigour of a Cochrane Review, they are relevant in clinical practice because they give therapeutic recommendations stratified according to their level of evidence and *Leishmania* species implicated.

AUTHORS' CONCLUSIONS

Implications for practice

We have updated information from randomised controlled trials (RCTs) of treatments for Old World cutaneous leishmaniasis (OWCL) and summarised the best available evidence using quantitative and qualitative methods. We have endeavoured to provide information to help clinicians choose the most appropriate treatment. We have been careful not to be too prescriptive because the purpose of this systematic review is to present information rather than offer advice.

There are few treatments for CL with robust evidence from multiple randomised trials. This may be because OWCL can heal spontaneously - in many cases within a couple of months - without any need for therapeutic intervention. *L major*-caused CL can heal spontaneously in 40% to 70% of cases at 3 months and close to 100% at 12 months. Spontaneous cure rates for *L tropica*-caused CL are 1% at 3 months, 68% at 12 months, and usually close to 100% in three years (Asilian 1995; Ben Salah 1995; Zakraoui 1995). Therefore, in many cases people with CL do not receive any drug. When clinicians do prescribe treatment, they usually prefer less toxic local treatments, reserving systemic treatments (azole drugs, miltefosine, antimonials, amphotericin B formulations) for complex cases.

We cannot make firm recommendations about the use of our two key comparisons.

- Itraconazole versus placebo.
- Paromomycin ointment (15% plus 10% urea) versus vehicle.

Due to the very low certainty of the evidence, and even though our analyses favoured itraconazole in terms of complete cure and lesions cured, we cannot be sure our results are conclusive. Similarly, although we found no difference between paromomycin ointment and vehicle in terms of these same outcomes, the very low certainty of the evidence casts doubt on our results, as it also does we do when we report more mild adverse effects with itraconazole and paromomycin ointment.

Our other key outcomes of microbiological or histopathological cure of skin lesions and speed of healing (i.e. time taken to be cured) were not measured for these key comparisons. None of the included studies assessed participant-focused measures of success, such as quality of life and degree of functional and aesthetic impairment.

We have identified gaps in knowledge that imply difficulties and limits in terms of clinical practice. RCTs that compare local versus systemic treatment are scarce, and the results discordant.

Also, there is in many cases a lack of knowledge on when treatment is really needed, since OWCL can also heal spontaneously.

Although we included 89 studies in this review, most of them explore different therapeutic regimens: not only different drugs, but even the same drug administered locally or systemically or with different doses or regimens. This means that only one RCT evaluated most regimens with a specific *Leishmania* species and with a different clinical presentation, which may reduce the strength of the recommendation and limit the possibility to extrapolate the results to other *Leishmania* species.

Twenty-nine studies did not isolate the *Leishmania* species. This can make it difficult to apply the result to clinical practice because a particular therapeutic regimen may have good results among a specific *Leishmania* species but not with another OWCL species. In addition, the same *Leishmania* species may vary its response to a certain treatment when the only difference is the geographical area where the infection was acquired (Monge-Maillo 2013). Therefore, it may be difficult for physicians to extrapolate the published results to their daily clinical practice.

Before starting treatment for localised CL, and especially in the zoonotic form, people with OWCL need to be informed of the possibility of spontaneous healing and the lack of evidence for some treatments. Healthcare practitioners can still play an important role in providing information and wound healing management even if there is no good evidence for any special regimen of healing support.

The eight studies in Studies awaiting classification may alter the conclusions of the review once assessed.

Implications for research

This updated systematic review has identified the need for large, well-conducted RCTs to assess the benefits and harms of interventions for OWCL.

Design

We considered only one RCT to be at low risk of bias in all domains (Ranawaka 2015). To encourage the implementation of well-designed clinical trials specifically aimed at developing effective treatments (both primary and adjuvant), González 2010 developed guidelines for clinical trials of cutaneous leishmaniasis. However, it is evident from the newly included RCTs that improvement of study quality and standardisation of outcomes is still needed. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative (www.cometinitiative.org) is working to improve the standardisation of study outcomes by raising awareness of the need for systematised methodologies that acknowledge the complexity of CL and define reproducible, measurable, and clinically meaningful outcomes (Olliaro 2013). Future trials need to ensure they follow this guidance and also adhere to the CONSORT Statement (Schulz 2010), especially to improve the reporting of important bias domains, the causative parasite, and timing of outcome assessment. Future studies should also be sufficiently powered.

Resources are particularly limited for research into neglected diseases in LMICs, even those that present major public health problems. Cost and licensing entanglements (freedom to operate) need to be considered before investing money in conducting new trials. Prioritisation for clinical research in OWCL is a necessity.

Participants

A number of interventions are currently used in women of childbearing age and children, in those with comorbidities, and in immunocompromised individuals with no drug interactions. Future trials should assess safety and efficacy in those subgroups.

Leishmania species

The current evidence for different types of clinical management of OWCL and particularly for species such as *L infantum*,*L aethiopica*,*L major*,*L tropica*, and*L donovani* is either lacking or of very low quality. Eighteen studies did not even report the species of leishmaniasis, which can theoretically be easily determined with the use of new DNA techniques. However, these techniques require an investment in infrastructures that is unaffordable for the resource-restricted laboratories located in disease-endemic countries. Of the 23 studies that reported the *Leishmania* species, only 11 (48%) confirmed which caused the development of the disease, and the other 12 mentioned the endemic nature of a specific parasite strain and assumed it was the disease-causing species. Since treatment sensitivity is species-dependent, species identification is critical in future trials, for the choice of the best treatment outcome, with the fewest side effects and late complications (de Vries 2015).

Outcomes

None of the studies addressed measurements of quality of life, degree of functional and aesthetic impairment, or relevant issues such as drug resistance or change in ability to detect *Leishmania*. Outcomes evaluating participants' values and preferences are needed to ensure greater responsiveness of practice guidelines and support shared decision-making.

With only limited data on prevention of scarring, the development of successful approaches to enhance wound healing or diminish scar formation within targeted areas, or both, will lead to a lower risk of developing scars in these sites. These issues are also possible future trial priorities.

Reducing adverse effects derived from treatment should also be a priority in research. Intramuscular or intravenous drugs are associated with more severe adverse effects. There is a need for less painful and better-tolerated novel treatment modalities, particularly for children. Alternatives to intramuscular or intravenous treatments should be a research priority, as well as efficacious, well-tolerated and inexpensive oral agents with enough sensitivity to treat all target species, with few serious adverse effects.

Future studies should assess the long-term effects of treatment, as healing cannot be clearly confirmed without a long-term assessment (e.g. at least six months after treatment has finished). For this, it is important to make an a priori decision about the postintervention time frame, based on the maximum length of time after the event during which improvement is attributed to the intervention (Goodman 2007).

Interventions

Future trials should aim at assessing the efficacy of treatments, ideally administered with a single dose of drug or with a short regimen, as this improves adherence. Other lines of research on interventions are for oral or self-administered treatments requiring minimal supervision (the route of administration can be topical but oral is preferred).

Although frequently used and recommended for the treatment of localised OWCL, we found limited evidence on the use of wound healing to treat OWCL, so this is an important area to test.

Furthermore, as highlighted in the previous review, there is a need for more evidence of the effectiveness and safety of different anti-*Leishmania* drugs compared with placebo in self-healing forms of leishmaniasis or with traditional first-line antimonials in complicated form, as the basis to recommend alternative safe, efficacious, and affordable treatments. The number of new studies using an

active drug as a comparator has doubled, contrasting with fewer placebo-controlled studies.

ACKNOWLEDGEMENTS

The authors wish to acknowledge Alireza Firooz for translating and extracting data from Iranian papers, Nieves Plana for her help in developing this review, and Ludovic Reveiz for his help in data extracting for the review.

The Cochrane Skin editorial base wishes to thank Sam Gibbs, Cochrane Dermatology Editor for this review; Matthew Grainge, Statistical Editor; Ching-Chi Chi, Methods Editor; the clinical referees, Sabha Mushtaq and Iraj Sharifi; and Meggan Harris, who copy-edited the review.

REFERENCES

References to studies included in this review

Adam 2009 ***{published data only}***
Adam I, Hagelnur A. Artesunate plus sulfamethoxypyrazine/pyrimethamine for the treatment of cutaneous leishmaniasis: a double-blind, placebo-controlled clinical trial. *International Journal of Antimicrobial Agents* 2009;**34**(4):380–1. PUBMED: 19409761]

Al-Fouzan 1991 ***{published data only}***
al-Fouzan AS, al-Saleh QA, Najem NM, Rostom AI. Cutaneous leishmaniasis in Kuwait. Clinical experience with itraconazole. *International Journal of Dermatology* 1991;**30**(7):519–21. PUBMED: 1663089]

Al Hamdi 2010 ***{published data only}***
Al Hamdi K, Awad AH, Moker HM. Evaluation of intralesional 0.2% ciprofloxacin as a treatment for cutaneous leishmaniasis. *Eastern Mediterranean Health Journal* 2010;**16**(1):89–93. PUBMED: 20214164]

Alkhawajah 1997 ***{published data only}***
Alkhawajah AM, Larbi E, al-Gindan Y, Abahussein A, Jain S. Treatment of cutaneous leishmaniasis with antimony: intramuscular versus intralesional administration. *Annals of Tropical Medicine and Parasitology* 1997;**91**(8):899–905. PUBMED: 9579209]

Alrajhi 2002 ***{published data only}***
Alrajhi AA, Ibrahim EA, De Vol EB, Khairat M, Faris RM, Maguire JH. Fluconazole for the treatment of cutaneous leishmaniasis caused by leishmania major. *New England Journal of Medicine* 2002;**346**(12):891–5. PUBMED: 11907288]

Alsaleh 1995 ***{published data only}***
Alsaleh QA, Dvorak R, Nanda A. Ketoconazole in the treatment of cutaneous leishmaniasis in Kuwait. *International Journal of Dermatology* 1995;**34**(7):495–7. PUBMED: 7591417]

Aronson 2010 ***{published data only}***
Aronson NE, Wortmann GW, Byrne WR, Howard RS, Bernstein WB, Marovich MA, et al. A randomized controlled trial of local heat therapy versus intravenous sodium stibogluconate for the treatment of cutaneous Leishmania major infection. *PLoS Neglected Tropical Diseases* 2010;**4**(3):e628. PUBMED: 20231896]

Asilian 1995 ***{published data only}***
Asilian A, Jalayer T, Whitworth JA, Ghasemi RL, Nilforooshzadeh M, Olliaro P. A randomized, placebo-controlled trial of a two-week regimen of aminosidine (paramomycin) ointment for treatment of cutaneous leishmaniasis in Iran. *American Journal of Tropical Medicine and Hygiene* 1995;**53**(6):648–51. PUBMED: 8561269]

Asilian 2003 ***{published data only}***
Asilian A, Jalayer T, Nilforoosshzadeh M, Ghassemi RL, Peto R, Wayling S, et al. Treatment of cutaneous leishmaniasis with aminosidine (paromomycin) ointment: double-blind, randomized trial in the Islamic Republic of Iran. *Bulletin of the World Health Organization* 2003;**81**(5):353–9. PUBMED: 12856053]

Asilian 2004a ***{published data only}***
Asilian A, Sadeghinia A, Faghihi G, Momeni A. Comparative study of the efficacy of combined cryotherapy and intralesional meglumine antimoniate (Glucantime) vs. cryothrapy and intralesional meglumine antimoniate (Glucantime) alone for the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2004;**43**(4):281–3. PUBMED: 15090013]

Asilian 2004b ***{published data only}***
Asilian A, Sharif A, Faghihi G, Enshaeieh Sh, Shariati F, Siadat AH. Evaluation of CO laser efficacy in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2004;**43**(10):736–8. PUBMED: 15485530]

Asilian 2006 ***{published data only}***
Asilian A, Davami M. Comparison between the efficacy of photodynamic therapy and topical paromomycin in the treatment of Old World cutaneous leishmaniasis: a placebo-controlled, randomized clinical trial. *Clinical & Experimental Dermatology* 2006;**31**(5):634–7. PUBMED: 16780497]

Asilian 2014 ***{published data only}***
Asilian A, Omrani Sh, Nilforoushzadeh MA. Comparing the effects of topical miltefosine and glucantime in treatment of cutaneous leishmaniasis. *Journal of Isfahan Medical School* 2014;**31**(269):2257–63.

Ben Salah 1995 ***{published data only}***
Ben Salah A, Zakraoui H, Zaatour A, Ftaiti A, Zaafouri B, Garraoui A, et al. A randomized, placebo-controlled trial in

Tunisia treating cutaneous leishmaniasis with paromomycin ointment. *American Journal of Tropical Medicine and Hygiene* 1995;**53**(2):162–6. PUBMED: 7677218]

Ben Salah 2009 ***{published data only}***
Ben Salah A, Buffet PA, Morizot G, Ben Massoud N, Zâatour A, Ben Alaya N, et al. WR279,396, a third generation aminoglycoside ointment for the treatment of Leishmania major cutaneous leishmaniasis: a phase 2, randomized, double blind, placebo controlled study. *PLoS Neglected Tropical Diseases* 2009;**3**(5):e432. PUBMED: 19415122]

Ben Salah 2013 ***{published data only}***
Ben Salah A, Ben Messaoud N, Guedri E, Zaatour A, Ben Alaya N, Bettaieb J, et al. Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. *New England Journal of Medicine* 2013;**368**(6):524–32. PUBMED: 23388004]

Bumb 2013 ***{published data only}***
Bumb RA, Prasad N, Khandelwal K, Aara N, Mehta RD, Ghiya BC, et al. Long-term efficacy of single-dose radiofrequency-induced heat therapy vs. intralesional antimonials for cutaneous leishmaniasis in India. *British Journal of Dermatology* 2013;**168**(5):1114–9. PUBMED: 23298394]

Daie Parizi 2015 ***{published data only}***
Daie Parizi MH, Karvar M, Sharifi I, Bahrampour A, Heshmat Khah A, Rahnama Z, et al. The topical treatment of anthroponotic cutaneous leishmaniasis with the tincture of thioxolone plus benzoxonium chloride (Thio-Ben) along with cryotherapy: A single-blind randomized clinical trial. *Dermatologic Therapy* 2015;**28**(3):140–6. PUBMED: 25847678]

Dandashli 2005 ***{published data only}***
Dandashi A. Treatment of cutaneous leishmaniasis with fluconazole: a randomized double-blind, placebo-controlled trial. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2005;**19**(Suppl 2):43.

Dastgheib 2012 ***{published data only}***
Dastgheib L, Naseri M, Mirashe Z. Both combined oral azithromycin plus allopurinol and intramuscular Glucantime yield low efficacy in the treatment of Old World cutaneous leishmaniasis: a randomized controlled clinical trial. *International Journal of Dermatology* 2012;**51**(12):1508–11. PUBMED: 23171020]

Dogra 1990 ***{published data only}***
Dogra J, Aneja N, Lal BB, Mishra SN. Cutaneous leishmaniasis in India: Clinical experience with itraconazole (R51 211 Janssen). *International Journal of Dermatology* 1990;**29**(9):661–2. PUBMED: 2177041]

Dogra 1991 ***{published data only}***
Dogra J. A double-blind study on the efficacy of oral dapsone in cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991;**85**(2):212–3. PUBMED: 1887473]

Dogra 1992 ***{published data only}***
Dogra J. Cutaneous leishmaniasis in India: evaluation of oral drugs (dapsone versus itraconazole). *European Journal of Dermatology* 1992;**2**:568–9.

Dogra 1996 ***{published data only}***
Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *International Journal for Parasitology* 1996;**26**(12):1413–5. PUBMED: 9024895]

Ejaz 2014 ***{published data only}***
Ejaz A, Qadir SNUR, Malik N, Bari AU. Comparison of low-dose meglumine antimoniate/ allopurinol combination therapy with full dose meglumine antimoniate alone in the treatment of cutaneous leishmaniasis - A randomized controlled trial. *Journal of Pakistan Association of Dermatologists* 2014;**24**(2):108–114. EMBASE: 373774478]

El-Sayed 2010 ***{published data only}***
El-Sayed M, Anwar AE. Intralesional sodium stibogluconate alone or its combination with either intramuscular sodium stibogluconate or oral ketoconazole in the treatment of localized cutaneous leishmaniasis: a comparative study. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2010;**24**(3):335–40. PUBMED: 19744259]

Emad 2011 ***{published data only}***
Emad M, Hayati F, Fallahzadeh MK, Namazi MR. Superior efficacy of oral fluconazole 400 mg daily versus oral fluconazole 200 mg daily in the treatment of cutaneous leishmania major infection: a randomized clinical trial. *Journal of the American Academy of Dermatology* 2011;**64**(3):606–8. PUBMED: 21315963]

Esfandiarpour 2002 ***{published data only}***
Esfandiarpour I, Alavi A. Evaluating the efficacy of allopurinol and meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2002;**41**(8):521–4. PUBMED: 12207774]

Faghihi 2003 ***{published data only}***
Faghihi G, Tavakoli-kia R. Topical paromomycin vs intralesional meglumine antimoniate in cutaneous leishmaniasis. *Clinical and Experimental Dermatology* 2003;**28**(1):13–6. PUBMED: 12558620]

Farajzadeh 2015 ***{published data only}***
Farajzadeh S, Esfandiarpour I, Haghdoost AA, Mohammadi S, Mohebbi A, Mohebbi E, Mostafavi M. Comparison between combination therapy of oral terbinafine and cryotherapy versus systemic meglumine antimoniate and cryotherapy in cutaneous leishmaniasis: a randomized clinical trial. *Iranian Journal of Parasitology* 2015;**10**(1):1–8. PUBMED: 25904940]

Fekri 2015 ***{published data only}***
Fekri A, Rahnama Z, Khalili M, Dookhani AP, Khazaeli P, Beigi KB. The efficacy of co-administration of topical niosomal dapsone gel and intralesional injection of glucantime in cutaneous leishmaniasis in comparison with

cryotherapy plus intralesional injection of glucantime. *Journal of Kerman University of Medical Sciences* 2015;**22**(2): 117–32. PUBMED: 603502875]

Firooz 2005 ***{published data only}***

Firooz A, Khatami A, Khamesipour A, Nassiri-Kashani M, Behnia F, Nilforoushzadeh M, et al. Intralesional injection of 2% zinc sulphate solution in the treatment of acute Old World cutaneous leishmaniasis: a randomized, double-blind, controlled clinical trial. *Journal of Drugs in Dermatology* 2005;**4**(1):73–9. PUBMED: 15696988]

Firooz 2006 ***{published data only}***

Firooz A, Khamesipour A, Ghoorchi MH, Nassiri-Kashani M, Eskandari SE, Khatami A, et al. Imiquimod in combination with meglumine antimoniate for cutaneous leishmaniasis: a randomized assessor-blind controlled trial. *Archives of Dermatology* 2006;**142**(12):1575–9. PUBMED: 17178983]

Gholami 2000 ***{published data only}***

* Gholami A, Khamesipour A, Momeni A, Ghazanfari T, Nilforoushzadeh MA, Darajeh Z, et al. Treatment of cutaneous leishmaniasis with 5% garlic cream: a randomized, double-blind study. *Iranian Journal of Dermatology* 2000;**3**(3):2–6. CENTRAL: CN–00454251]

Harms 1991 ***{published data only}***

Harms G, Chehade AK, Douba M, Roepke M, Mouakeh A, Rosenkaimer F, et al. A randomized trial comparing a pentavalent antimonial drug and recombinant interferon-gamma in the local treatment of cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991;**85**(2):214–6. PUBMED: 1909469]

Iraji 2004 ***{published data only}***

Iraji F, Vali A, Asilian A, Shahtalebi M, Momeni AZ. Comparison of intralesionally injected zinc sulphate with meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. *Dermatology* 2004;**209**(1):46–9. PUBMED: 15237267]

Iraji 2005 ***{published data only}***

Iraji F, Sadeghinia A. Efficacy of paromomycin ointment in the treatment of cutaneous leishmaniasis: results of a double-blind, randomized trial in Isfahan, Iran. *Annals of Tropical Medicine and Parasitology* 2005;**99**(1):3–9. PUBMED: 15701249]

Jaffar 2006 ***{published data only}***

Jaffar H. Rifampicin in cutaneous leishmaniasis - a therapeutic trial in Saudi Arabia. *Journal of Pakistan Association of Dermatologists* 2006;**16**(1):4–9. EMBASE: 44265597]

Jaffary 2010 ***{published data only}***

Jaffary F, Nilforoushzadeh MA, Ansari N, Rahimi M. Treatment of cutaneous leishmaniasis: cassia fistula fruit gel-intralesional glucantime Vs. placebo gel- intralesional glucantime combination. *Tehran University Medical Journal* 2010;**67**(10):705–11.

Jaffary 2014a ***{published data only}***

Jaffary F, Nilforoushzadeh MA, Tavakoli N, Zolfaghari B, Shahbazi F. The efficacy of Achilles millefolium topical gel along with intralesional injection of glucantime in the treatment of acute cutaneous leishmaniasis major. *Advanced Biomedical Research* 2014;**3**:111. PUBMED: 24804185]

Jaffary 2014b ***{published data only}***

Jaffary F, Nilforoushzadeh MA, Moradi S, Derakhshan R, Ansari N. Concentrated extracts of Cassia fistula versus intralesional injection of meglumine antimoniate in treatment of acute cutaneous leishmaniasis. *Journal of Skin and Stem Cell* 2014;**1**(1):e16631. EMBASE: 604236618]

Jebran 2014 ***{published data only}***

Jebran AF, Schleicher U, Steiner R, Wentker P, Mahfuz F, Stahl HC, et al. Rapid healing of cutaneous leishmaniasis by high-frequency electrocauterization and hydrogel wound care with or without DAC N-055: a randomized controlled phase IIa trial in Kabul. *PLoS Neglected Tropical Diseases* 2014;**8**(2):e2694. PUBMED: 24551257]

Jowkar 2012 ***{published data only}***

Jowkar F, Dehghani F, Jamshidzadeh A. Is topical nitric oxide and cryotherapy more effective than cryotherapy in the treatment of old world cutaneous leishmaniasis?. *Journal of Dermatological Treatment* 2012;**23**(2):131–5. PUBMED: 20964568]

Kashani 2010 ***{published data only}***

Kashani MN, Sadr B, Nilforoushzadeh MA, Arasteh M, Babakoohi S, Firooz A. Treatment of acute cutaneous leishmaniasis with intralesional injection of meglumine antimoniate: comparison of conventional technique with mesotherapy gun. *International Journal of Dermatology* 2010;**49**(9):1034–7. PUBMED: 20883265]

Khatami 2012 ***{published data only}***

Khatami A, Rahshenas M, Bahrami M, Ghoorchi MH, Eskandari SE, Sharifi I, et al. Miltefosine in treatment of cutaneous leishmaniasis: a randomized controlled trial (Poster P-31). 6th International Dermato-Epidemiology Association Congress, Malmo, Sweden, 26-28 August 2012. *British Journal of Dermatology* 2012;**167**(2):e23. EMBASE: 71050777]

Khatami 2013 ***{published data only}***

Khatami A, Talaee R, Rahshenas M, Khamesipour A, Mehryan P, Tehrani S, et al. Dressings combined with injection of meglumine antimoniate in the treatment of cutaneous leishmaniasis: a randomized controlled clinical trial. *PloS One* 2013;**8**(6):e66123. PUBMED: 23826087]

Kochar 2000 ***{published data only}***

Kochar DK, Aseri S, Sharma BV, Bumb RA, Mehta RD, Purohit SK. The role of rifampicin in the management of cutaneous leishmaniasis. *QJM : Monthly Journal of the Association of Physicians* 2000;**93**(11):733–7. PUBMED: 11077029]

Kochar 2006 ***{published data only}***

Kochar DK, Saini G, Kochar SK, Sirohi P, Bumb RA, Mehta RD, et al. A double blind, randomised placebo controlled trial of rifampicin with omeprazole in the treatment of human cutaneous leishmaniasis. *Journal of Vector Borne Diseases* 2006;**43**(4):161–7. PUBMED: 17175700]

Larbi 1995 *{published data only}*
Larbi EB, al-Khawajah A, al-gindan Y, Jain S, Abahusain A, al-Zayer A. A randomized, double-blind, clinical trial of topical clotrimazole versus mizonazole for treatment of cutaneous leishmaniasis in the eastern province of Saudi Arabia. *American Journal of Tropical Medicine and Hygiene* 1995;**52**(2):166–8. PUBMED: 7872446]

Layegh 2007 *{published data only}*
Layegh P, Yazdanpanah MJ, Vosugh EM, Pezeshkpoor F, Shakeri MT, Moghiman T. Efficacy of azitromycin versus systemic meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2007;**77**(1):99–101. PUBMED: 17620637]

Layegh 2009 *{published data only}*
Layegh P, Pezeshkpoor F, Soruri AH, Naviafar P, Moghiman T. Efficacy of cryotherapy versus intralesional meglumine antimoniate (Glucantime) for treatment of cutaneous leishmaniasis in children. *American Journal of Tropical Medicine and Hygiene* 2010;**80**(2):172–5. PUBMED: 19190206]

Layegh 2011 *{published data only}*
Layegh P, Rajabi O, Jafari MR, Emamgholi Tabar Malekshah P, Moghiman T, Ashraf H, et al. Efficacy of topical liposomal amphotericin B versus intralesional meglumine antimoniate (Glucantime) in the treatment of cutaneous leishmaniasis. *Journal of Parasitology Research* 2011;**2011**:656523. [DOI: 10.1155/2011/656523; PUBMED: 22174993

Lynen 1992 *{published data only}*
Lynen L, Van Damme W. Local application of diminazene aceturate: an effective treatment for cutaneous leishmaniasis? . *Annales de la Société Belge de Médecine Tropicale* 1992;**72**(1):13–9. PUBMED: 1567264]

Maleki 2012 *{published data only}*
Maleki M, Karimi G, Tafaghodi M, Raftari S, Nahidi Y. Comparison of intralesional two percent zinc sulfate and glucantime injection in treatment of acute cutaneous leishmaniasis. *Indian Journal of Dermatology* 2012;**57**(2):118–22. PUBMED: 22615508]

Mapar 2010 *{published data only}*
Mapar MA, Omidian M. Intralesional injections of metronidazole versus meglumine antimoniate for the treatment of cutaneous leishmaniasis. *Jundishapur Journal of Microbiology* 2010;**3**(2):79–83. EMBASE: 2010406291]

Mashood 2001 *{published data only}*
Mashhood AA, Hussain K. Efficacy of allopurinol compared with pentostam in the treatment of old world cutaneous leishmaniasis. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP* 2001;**11**(6):367–70. EMBASE: 2001264054]

Mohebali 2007 *{published data only}*
Mohebali M, Fotouhi A, Hooshmand B, Zarei Z, Akhoundi B, Rahnema A, et al. Comparison of miltefosine and meglumine antimoniate for the treatment of zoonotic cutaneous leishmaniasis (ZCL) by a randomized clinical trial in Iran. *Acta Tropica* 2007;**103**(1):33–40. PUBMED: 17586452]

Momeni 1996 *{published data only}*
Momeni AZ, Jalayer T, Emamjomeh M, Bashardost N, Ghassemi RL, Meghdadi M, et al. Treatment of cutaneous leishmaniasis with itraconazole. Randomized doubl-blind study. *Archives of Dermatology* 1996;**132**(7):784–6. PUBMED: 8678570]

Momeni 2002 *{published data only}*
Momeni AZ, Reiszadae MR, Aminjavaheri M. Treatment of cutaneous leishmaniasis with a combination of allopurinol and low-dose meglumine antimoniate. *International Journal of Dermatology* 2002;**41**(7):441–3. PUBMED: 12121563]

Momeni 2003 *{published data only}*
* Momeni AZ, Aminjavaheri M, Omidghaemi MR. Treatment of cutaneous leishmaniasis with ketoconazole cream. *Journal of Dermatological Treatment* 2003;**14**(1):26–9. PUBMED: 12745852]

Mostafavi 2013 *{published data only}*
Mostafavi SA, Shatalebi MA, Attar AM, Hejazi H, Mottaghinejad A, Fadaei R, et al. Preparation and evaluation of clinical effects of glucantime gel mask. *Journal of Isfahan Medical School* 2013;**31**(231):389–99. EMBASE: 2014593999]

Mujtaba 1999 *{published data only}*
* Mujtaba G, Khalid M. Weekly vs. fortnightly intralesional meglumine antimoniate in cutaneous leishmaniasis. *International Journal of Dermatology* 1999;**38**(8):607–9. PUBMED: 10487452]

Nassiri-Kashani 2005 *{published data only}*
Nassiri-Kashani M, Firooz A, Khamesipour A, Mojtahed F, Nilforoushzadeh M, Hejazi H, et al. A randomized, double-blind, placebo-controlled clinical trial of itraconazole in the treatment of cutaneous leishmaniasis. *Journal of the European Academy of Dermatology and Venereology: JEADV* 2005;**19**(1):80–3. PUBMED: 15649196]

Nilforoushzadeh 2004 *{published data only}*
Nilforoushzadeh MA. Efficacy of combined triple therapy (paromomycin ointment, cryotherapy and intralesional Glucantime) in comparison with intralesional Glucantime for treatment of acute cutaneous leishmaniasis. *Iranian Journal of Dermatology* 2004;**3**(7):136–9.

Nilforoushzadeh 2006 *{published data only}*
* Nilforoushzadeh MA, Jaffary F, Reiszadeh MR. Comparative effect of topical trichloroacetic acid and intralesional meglumine antimoniate in the treatment of acute cutaneous leishmaniasis. *International Journal of Pharmacology* 2006;**2**(6):633–6. EMBASE: 2007084731]
Nilforoushzadeh MA, Reiszadeh MR, Jafari F. Topical trichloroacetic acid compared with intralesional glucantime injection in the treatment of acute wet cutaneous leishmaniasis: An open clinical trial. *Iranian Journal of Dermatology* 2003;**2**(6):34–9.

Nilforoushzadeh 2007 *{published data only}*
Nilforoushzadeh MA, Jaffary F, Moradi S, Derakhshan R, Haftbaradaran E. Effect of topical honey application along

with intralesional injection of glucantime in the treatment of cutanneous leishmaniasis. *BMC Complementary and Alternative Medicine* 2007;**7**:13. PUBMED: 17466071]

Nilforoushzadeh 2008 ***{published data only}***
Nilforoushzadeh MA, Jaffary F, Ansari N, Siadat AH, Nilforoushan Z, Firouz A. A comparative study between the efficacy of systemic meglumine antimoniate therapy with standard or low dose plus oral omeprazole in the treatment of cutaneous leishmaniasis. *Journal of Vector Borne Diseases* 2008;**45**(4):287–91. PUBMED: 19248655]

Nilforoushzadeh 2012 ***{published data only}***
Nilforoushzadeh MA, Naeeni FF, Sattar N, Haftbaradaran E, Jaffary F, Askari G. The effect of intralesional meglumine antimoniate (Glucantime) versus a combination of topical trichloroacetic acid 50% and local heat therapy by non-ablative radiofrequency on cutaneous leishmaniasis lesions. *Journal of Research in Medical Sciences* 2012;**17**(1 Suppl 1): S97–S102. EMBASE: 2013471627]

Nilforoushzadeh 2013 ***{published data only}***
Nilforoushzadeh MA, Siadat AH, Ansari N, Haftbaradaran E, Ahmadi E. A comparison between the effects of glucantime, topical trichloroacetic acid 50% plus glucantime, and fractional laser plus glucantime on cutaneous leishmaniasis lesions. *Journal of Isfahan Medical School* 2013;**30**(221):2450–9. EMBASE: 2013245548]

Nilforoushzadeh 2014a ***{published data only}***
Nilforoushzadeh MA, Siadat AH, Haftbaradaran E, Minaravesh M. Comparative study of the efficacy of CO2 and fraxel lasers in treatment of cutaneous leishmaniasis scars. *Journal of Isfahan Medical School* 2014;**31**(269 SPEC.ISSUE):2277–84. EMBASE: 2014574591]

Nilforoushzadeh 2014b ***{published data only}***
Nilforoushzadeh MA, Jaffary F, Derakhsahan R, Haftbaradaran E. Comparison between intralesional meglumine antimoniate and combination of trichloroacetic acid 50% and intralesional meglumine antimoniate in the treatment of acute cutaneous leishmaniasis: a randomized clinical trial. *Journal of Stem Cells* 2014;**1**(1):e16633. [DOI: 10.5812/jssc.16633; EMBASE: 2015013267

Özgöztasi 1997 ***{published data only}***
Özgöztasi O, Baydar I. A randomized clinical trial of topical paromomycin versus oral ketoconazole for treating cutaneous leishmaniasis in Turkey. *International Journal of Dermatology* 1997;**36**(1):61–3. EMBASE: 1997097334]

Ranawaka 2010 ***{published data only}***
Ranawaka RR, Weerakoon HS. Randomized, double-blind, comparative clinical trial on the efficacy and safety of intralesional sodium stibogluconate and intralesional 7% hypertonic sodium chloride against cutaneous leishmaniasis caused by L. donovani. *Journal of Dermatological Treatment* 2010;**21**(5):286–93. PUBMED: 20438389]

Ranawaka 2015 ***{published data only}***
Ranawaka RR, Weerakoon HS, Silva SH. Randomized, double-blind, controlled, comparative study on intralesional 10% and 15% hypertonic saline versus intralesional sodium stibogluconate in Leishmania donovani cutaneous leishmaniasis. *International Journal of Dermatology* 2015;**54**(5):555–63. PUBMED: 25600472]

Reithinger 2005 ***{published data only}***
Reithinger R, Mohsen M, Wahid M, Bismullah M, Quinnell RJ, Davies CR, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by Leishmania tropica in Kabul, Afghanistan: a randomized, controlled trial. *Clinical Infectious Diseases* 2005;**40**(8):1148–55. PUBMED: 15791515]

Sadeghian 2006a ***{published data only}***
Sadeghian G, Nilforoushzadeh MA. Effect of combination therapy with systemic glucantime and pentoxifylline in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2006;**45**(7):819–21. PUBMED: 16863518]

Sadeghian 2006b ***{published data only}***
Sadeghian G, Nilfroushzadeh MA, Siadat AH. A comparison between intralesional hypertonic sodium chloride solution and meglumine antimoniate in the treatment of cutaneous leishmaniasis. *Egyptian Dermatology Online Journal* 2;**1**:8.

Sadeghian 2007 ***{published data only}***
Sadeghian G, Nilfroushzadeh MA, Iraji F. Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. *Clinical and Experimental Dermatology* 2007;**32**(4):371–4. PUBMED: 17376205]

Safi 2012 ***{published data only}***
Safi N, Davis GD, Nadir M, Hamid H, Robert LL, Case AJ. Evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Kabul, Afghanistan: a randomized controlled trial. *Military Medicine* 2012;**177**(3):345–351. PUBMED: 22479925]

Salmanpour 2001 ***{published data only}***
Salmanpour R, Handjani F, Nouhpisheh MK. Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimoniate (Glucantime) for the treatment of cutaneous leishmaniasis. *Journal of Dermatological Treatment* 2001;**12**:159–62. PUBMED: 12243707]

Salmanpour 2006 ***{published data only}***
Salmanpour R, Razmavar MR, Abtahi N. Comparison of intralesional meglumine antimoniate, cryotherapy and their combination in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 2006;**45**(9):1115–6. PUBMED: 16961529]

Shamsi Meymandi 2011 ***{published data only}***
Shamsi Meymandi S, Zandi S, Aghaie H, Heshmatkhah A. Efficacy of CO(2) laser for treatment of anthroponotic cutaneous leishmaniasis, compared with combination of cryotherapy and intralesional meglumine antimoniate. *Journal of the European Academy of Dermatology and Venereology : JEADV* 2011;**25**(5):587–91. PUBMED: 20666876]

Shanehsaz 2015 ***{published data only}***
* Shanehsaz SM, Ishkhanian S. A comparative study between the efficacy of oral cimetidine and low-dose systemic meglumine antimoniate (MA) with a standard dose

of systemic MA in the treatment of cutaneous leishmaniasis. *International Jornal of Dermatology* 2015;**54**(7):834–8. PUBMED: 26108265]

Shanehsaz SM, Ishkhanian S. Therapeutic and adverse effects of standarddose and low-dose meglumine antimoniate during systemic treatment of Syrian cutaneous leishmaniasis patients. *Journal of Pakistan Association of Dermatologists* 2014;**24**(2):115–121. EMBASE: 2014549292]

Sharquie 1997 ***{published data only}***

Sharquie KE, Najim RA, Farjou IB. A compararive controlled trial of intralesionally- administered zinc sulphate, hypertonic sodium chloride and pentavalent antimony compound against cutaneous leishmaniasis. *Clinical and Experimental Dermatology* 1997;**22**(4):169–73. PUBMED: 9499605]

Sharquie 2001 ***{published data only}***

Sharquie KE, Najim RA, Farjou IB, Al-timimit DJ. Oral zinc sulphate in the treatment of acute cutaneous leishmaniasis. *Clinical and Experimental Dermatology* 2001; **26**(1):21–6. PUBMED: 11260171]

Shazad 2005 ***{published data only}***

Shazad B, Abbaszadeh B, Khamesipour A. Comparison of topical paromomycin sulfate (twice/day) with intralesional meglumine antimoniate for the treatment of cutaneous leishmaniasis caused by L. major. *European Journal of Dermatology* 2005;**15**(2):85–7. PUBMED: 15757817]

Stahl 2014 ***{published data only}***

Stahl HC, Ahmadi F, Schleicher U, Sauerborn R, Bermejo JL, Amirih ML, et al. A randomized controlled phase IIb wound healing trial of cutaneous leishmaniasis ulcers with 0.045% pharmaceutical chlorite (DAC N-055) with and without bipolar high frequency electro-cauterization versus intralesional antimony in Afghanistan. *BMC Infectious Diseases* 2014;**14**:619. PUBMED: 25420793]

Yazdanpanah 2011 ***{published data only}***

Yazdanpanah MJ, Banihashemi M, Pezeshkpoor F, Khajedaluee M, Famili S, Tavakoli Rodi I, et al. Comparison of oral zinc sulfate with systemic meglumine antimoniate in the treatment of cutaneous leishmaniasis. *Dermatology Research & Practice* 2011;**269515**:1–4. [DOI: 10.1155/ 2011/269515; PUBMED: 21747837

Zerehsaz 1999 ***{published data only}***

Zerehsaz F, Salmanpour R, Farhad H, Ardehali S, Panjehshahin MR, Tabei SZ, et al. A double-blind randomized clinical trial of a topical herbal extract (Z-HE) vs. systemic meglumine antimoniate for the treatment of cutaneous leishmaniasis in Iran. *International Journal of Dermatology* 1999;**38**(8):610–2. PUBMED: 10487453]

References to studies excluded from this review

Alavi-Naini 2012 ***{published data only}***

Alavi-Naini R, Fazaeli A, O'Dempsey T. Topical treatment modalities for old world cutaneous leishmaniasis: a review. *Prague Medical Report* 2012;**113**(2):105–18. PUBMED: 22691282]

Banihashemi 2015 ***{published data only}***

Banihashemi M, Yazdanpanah MJ, Amirsolymani H, Yousefzadeh H. Comparison of lesion improvement in lupoid leishmaniasis patients with two treatment approaches: trichloroacetic Acid and intralesional meglumine antimoniate. *Journal of Cutaneous Medicine and Surgery* 2015;**19**(1):35–9. PUBMED: 25775661]

Bumb 2010 ***{published data only}***

Bumb RA, Mehta RD, Ghiya BC, Jakhar R, Prasad N, Soni P, et al. Efficacy of short-duration (twice weekly) intralesional sodium stibogluconate in treatment of cutaneous Leishmaniasis in India. *British Journal of Dermatology* 2010;**163**(4):854–8. PUBMED: 20500797]

Dogra 1986 ***{published data only}***

Dogra J, Lal BB, Misra SN. Dapsone in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 1986;**25**(6):398–400. PUBMED: 3531044]

Dogra 1994 ***{published data only}***

Dogra J, Aneja N. Leishmaniasis and itraconazole: a controlled clinical trial on cutaneous subtypes. *International Journal of Antimicrobial Agents* 1994;**4**(4):309–11. PUBMED: 18611622]

Dorlo 2012 ***{published data only}***

Dorlo TP, Balasegaram M, Beijnen JH, de Vries PJ. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *Journal of Antimicrobial Chemotherapy* 2012;**67**(11):2576–97. PUBMED: 22833634]

El On 1992 ***{published data only}***

el-On J, Halevy S, Grunwald MH, Weinrauch L. Topical treatment of Old World cutaneous leishmaniasis caused by Leishmania major: a double blind control study. *Journal of the American Academy of Dermatology* 1992;**27**(2 Pt 1): 227–31. PUBMED: 1430361]

Frankenburg 1993 ***{published data only}***

Frankenburg S, Gross A, Jonas F, Klaus S. Effect of topical paromomycin on cell-mediated immunity during cutaneous leishmaniasis. *International Journal of Dermatology* 1993;**32** (1):68–70. PUBMED: 8425810]

Kim 2009 ***{published data only}***

Kim DH, Chung HJ, Bleys J, Ghohestani RF. Is paromomycin an effective and safe treatment against cutaneous leishmaniasis? A meta-analysis of 14 randomized controlled trials. *PLoS Neglected Tropical Diseases* 2009;**3** (2):e381. PUBMED: 19221595]

Moosavi 2005 ***{published data only}***

Moosavi Z, Nakhli A, Rassaii S. Comparing the efficiency of topical paromomycin with intralesional meglumine antimoniate for cutaneous leishmaniasis. *International Journal of Dermatology* 2005;**44**(12):1064–5. PUBMED: 16409282]

Nilforoushzadeh 2010 ***{published data only}***

Ali NM, Fariba J, Elaheh H, Ali N. The efficacy of 5% trichoroacetic acid cream in the treatment of cutaneous leishmaniasis lesions. *Journal of Dermatological Treatment* 2012;**23**(2):136–9. PUBMED: 21034291]

Nilforoushzadeh 2011 *{published data only}*
Nilforoushzadeh MA, Jaffary F, Ansari N, Moradi S, Siadat AH. The comparison between trichloroacetic acid 50% and CO2 laser in the treatment of cutaneous leishmaniasis scar. *Indian Journal of Dermatology* 2011;**56**(2):171–3. PUBMED: 21716542]

Siavash 2013 *{published data only}*
Shanehsaz SM, Ishkhanian S. Electrocardiographic and biochemical adverse effects of meglumine antimoniate during the treatment of Syrian cutaneous leishmaniasis. *Egyptian Dermatology Journal* 2013;**9**(1):5.

Singh 1995 *{published data only}*
Singh S, Singh R, Sundar S. Failure of ketaconazole in oriental sore in India. *Journal of Chemotherapy* 1995;**7**(4): 202–3. PUBMED: 8904156]

Trau 1987 *{published data only}*
Trau H, Schewach-Millet M, Shoham J, Doerner T, Shor R, Passwell JH. Topical application of human fibroblast interferon (IFN) in cutaneous leishmaniasis. *Israel Journal of Medical Sciences* 1987;**23**(11):1125–7. PUBMED: 3325468]

References to studies awaiting assessment

Farajzadeh 2016a *{published data only}*
Farajzadeh S, Hakimi Parizi M, Haghdoost AA, Mohebbi A, Mohammadi S, Pardakhty A, et al. Comparison between intralesional injection of zinc sulfate 2 % solution and intralesional meglumine antimoniate in the treatment of acute old world dry type cutaneous leishmaniasis: a randomized double-blind clinical trial. *Journal of Parasitic Diseases* 2016;**40**(3):935–9. PUBMED: 27605813]

Farajzadeh 2016b *{published data only}*
Farajzadeh S, Heshmatkhah A, Vares B, Mohebbi E, Mohebbi A, Aflatoonian M, et al. Topical terbinafine in the treatment of cutaneous leishmaniasis: triple blind randomized clinical trial. *Journal of Parasitic Diseases* 2016; **40**(4):1159–64. [DOI: 10.1007/s12639-014-0641-1; PUBMED: 27876906

Hanif 2016 *{published data only}*
Hanif MM, Akram K, Mustafa G. Intralesional versus oral chloroquine in cutaneous leishmaniasis: comparison of outcome, duration of treatment and total dose of drug. *Journal of the College of Physicians and Surgeons Pakistan* 2016;**26**(4):260–2. PUBMED: 27097693]

Jaffary 2016 *{published data only}*
Jaffary F, Nilforoushzadeh MA, Siadat A, Haftbaradaran E, Ansari N, Ahmadi E. A comparison between the effects of Glucantime, topical trichloroacetic acid 50% plus Glucantime, and fractional carbon dioxide laser plus Glucantime on cutaneous leishmaniasis lesions. *Dermatology Research and Practice* 2016;**2016**:6462804. PUBMED: 27148363]

Na-Bangchang 2016 *{published data only}*
Na-Bangchang K, Ahmed O, Hussein J, Hirayama K, Kongjam P, Aseffa A, et al. Exploratory, phase II controlled trial of shiunko ointment local application twice a day for 4 weeks in Ethiopian patients with localized cutaneous leishmaniasis. *Evidence-Based Complementary and Alternative Medicine* 2016;**2016**:5984709. PUBMED: 27195014]

Rajabi 2016 *{published data only}*
Rajabi O, Layegh P, Hashemzadeh S, Khoddami M. Topical liposomal azithromycin in the treatment of acute cutaneous leishmaniasis. *Dermatologic Therapy* 2016;**29**(5):358–63. [DOI: 10.1111/dth.12357; PUBMED: 27073044

Refai 2016 *{published and unpublished data}*
Refai W, Madarasingha N, Weerasingha S, Senarath U, De Silva A, Fernandopulle R, et al. Efficacy, safety and cost-effectiveness of thermotherapy for L. donovani-induced cutaneous leishmaniasis: a randomized controlled clinical trial. *International Journal of Infectious Diseases* 2016;**45**:74. CENTRAL: CN–01142616]

Sattar 2012 *{published data only}*
Sattar FA, Ahmed F, Ahmed N, Sattar SA, Malghani MA, Choudhary MI. A double-blind, randomized, clinical trial on the antileishmanial activity of a Morinda citrifolia (Noni) stem extract and its major constituents. *Natural Product Communications* 2012;**7**(2):195–6. PUBMED: 22474954]

References to ongoing studies

ACTRN12614001288617 *{unpublished data only}*
ACTRN12614001288617. A clinical trial to assess the safety and effect of heat therapy in comparison to standard intra-lesional sodium stibogluconate for cutaneous leishmaniasis [In patients with cutaneous leishmaniasis, thermotherapy was compared with standard intra–lesional therapy with regard to efficacy and safety]. anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12614001288617 Date first received: 10 December 2014.

IRCT138904091159N7 *{unpublished data only}*
IRCT138904091159N7. Comparison between two groups in the treatment of cutaneous leishmaniasis [Comparison between the efficacy of intralesional placebo and nitric oxide releasing patch versus placebo patch and glucantime in the treatment of cutaneous leishmaniasis]. www.irct.ir/searchresult.php?id=1159&number=7 Date first received: 2 September 2013.

IRCT2013092414746N1 *{unpublished data only}*
IRCT2013092414746N1. Treatment of patients with ZCL [The effect of MJ1 (Topical dairy extract) versus routine care for treatment of cutaneous leishmaniasis (rural) in Isfahan Iran :a randomized controled clinical trial (RCTs) –]. apps.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2013092414746N1 Date first received: 20 February 2014.

NCT00840359 *{unpublished data only}*
NCT00840359. Study of the Efficacy of Daylight Activated Photodynamic Therapy in the Treatment of Cutaneous Leishmaniasis [Phase 2 Study of the Efficacy of Daylight Activated Photodynamic Therapy in the Treatment of Cutaneous Leishmaniasis]. clinicaltrials.gov/ct2/show/NCT00840359 Date first received: 8 February 2009.

NCT01050777 ***{unpublished data only}***

NCT01050777. Efficacy of Topical Liposomal Form of Drugs in Cutaneous Leishmaniasis [Pilot Study of Efficacy of Topical Nano–liposomal Meglumine Antimoniate (Glucantime) or Paromomycin in Combination With Systemic Glucantime for the Treatment of Anthroponotic Cutaneous Leishmaniasis (ACL) Caused by Leishmania Tropica]. clinicaltrials.gov/ct2/show/NCT01050777 Date first received: 13 January 2010.

SLCTR/2014/028 ***{unpublished data only}***

SLCTR/2014/028. Treatment for leishmaniasis [Randomized, double blind, controlled study on efficacy and safety of intralesional metronidazole vs intralesional sodium stibogluconate in L. donovani cutaneous leishmaniasis]. slctr.lk/trials/276 Date first received: 18 October 2014.

Additional references

Adam 2008

Adam I, Elhardello OA, Elhadi MO, Abdalla E, Elmardi KA, Jansen FH. The antischistosomal efficacies of artesunate-sulfamethoxypyrazine-pyrimethamine and artemether-lumefantrine administered as treatment for uncomplicated *Plasmodium falciparum* malaria. *Annals of Tropical Medicine and Parasitology* 2008;**102**(1):39–44. [PUBMED: 18186976]

Al-Waiz 2004

Al-Waiz M, Sharquie KE, Al-Assir M. Treatment of cutaneous leishmaniasis by intralesional metronidazole. *Saudi Medical Journal* 2004;**25**(10):1512–3. [PUBMED: 15494841]

Alrajhi 2003

Alrajhi AA. Cutaneous leishmaniasis of the Old World. *Skin Therapy Letter* 2003;**8**(2):1–4. [PUBMED: 12728282]

Alvar 2006

Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. *Trends in Parasitology* 2006;**22**(12):552–7. [PUBMED: 17023215]

Alvar 2012

Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLoS One* 2012;**7**(5):e35671. [PUBMED: 22693548]

Amin 2006

Amin SP, Phelps RG, Goldberg DJ. Mesotherapy for facial skin rejuvenation: a clinical, histologic, and electron microscopic evaluation. *Dermatologic Surgery* 2006;**32**(12): 1467–1472. [PUBMED: 17199654]

Aram 1987

Aram H, Leibovici V. Ultrasound-induced hyperthermia in the treatment of cutaneous leishmaniasis. *Cutis* 1987;**40**(4): 350–3. [PUBMED: 3677796]

Arevalo 2007

Arevalo I, Tulliano G, Quispe A, Spaeth G, Mathlashewski, Llanos-cuantas A, et al. Role of imiquimod and parenteral meglumine antimoniate in the intitial treatment of cutaneous lesihmaniasis. *Clinical Infectious Diseases* 2007; **44**(12):1549–54. [PUBMED: 17516397]

Babajev 1991

Babajev KB, Babajev OG, Korepanov VI. Treatment of cutaneous leishmaniasis using a carbon dioxide laser. *Bulletin of the World Health Organization* 1991;**69**(1): 103–6. [PUBMED: 1905204]

Badaro 1990

Badaro R, Falcoff E, Badaro FS, Carvalho EM, Pedral-Sampaio D, Barral A, et al. Treatment of visceral leishmaniasis with pentavalent antimony and interferon gamma. *New England Journal of Medicine* 1990;**322**(1): 16–21. [PUBMED: 2104665]

Baryza 1995

Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. *Journal of Burn Care Rehabilitation* 1995;**16**(5):535–8. [PUBMED: 8537427]

Bassiouny 1982

Bassiouny A, El Meshad M, Talaat M, Kutty K, Metawaa B. Cryosurgery in cutaneous leishmaniasis. *British Journal of Dermatology* 1982;**107**(4):467–74. [PUBMED: 7126453]

Berman 1981

Berman JD, Neva FA. Effect of temperature on multiplication of Leishmania amastigotes within monocyte-derived macrophages in vitro. *American Journal of Tropical Medicine and Hygiene* 1981;**30**(2):318–21. [PUBMED: 7235124]

Bigby 2003

Bigby M, Williams H. Appraising Systematic Reviews and Meta-analyses. *Archives of Dermatology* 2003;**139**(6): 795–798. [PUBMED: 12810513]

Blum 2012

Blum J, Lockwood DN, Visser L, Harms G, Bailey MS, Caumes E, et al. Local or systemic treatment for New World cutaneous leishmaniasis? Re-evaluating the evidence for the risk of mucosal leishmaniasis. *International Health* 2012;**4**(3):153–63. [PUBMED: 24029394]

Blum 2014

Blum J, Buffet P, Visser L, Harms G, Bailey MS, Caumes E, et al. LeishMan recommendations for treatment of cutaneous and mucosal leishmaniasis in travelers, 2014. *Journal of Travel Medicine* 2014;**21**(2):116–29. [PUBMED: 24745041]

Bogenrieder 2003

Bogenrieder T, Lehn N, Landthaler M, Stolz W. Treatment of Old World cutaneous leishmaniasis with intralesionally injected meglumine antimoniate using a Dermojet device. *Dermatology* 2003;**206**(3):269–72. [PUBMED: 12673089]

Borelli 1987

Borelli D. A clinical trial of itraconazole in the treatment of deep mycoses and leishmaniasis. *Reviews of Infectious Diseases* 1987;**9**(Suppl 1):S57–63. [PUBMED: 3027848]

Bryceson 1994

Bryceson AD, Murphy A, Moody AH. Treatment of 'Old World' cutaneous leishmaniasis with aminosidine ointment:

results of an open study in London. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994;**88**(2):226–8. [PUBMED: 8036683]

Bygbjerg 1980
Bygbjerg IC, Knudsen L, Kieffer M. Failure of rifampicin therapy to cure cutaneous leishmaniasis. *Archives of Dermatology* 1980;**116**(9):988. [PUBMED: 7416770]

Cardo 2006
Cardo LJ. Leishmania: risk to the blood supply. *Transfusion* 2006;**46**(9):1641–45. [PUBMED: 16965594]

Cauwenberg 1986
Cauwenberg G, De Doncker P. Itraconazole (R 51 211): a clinical review of its anti mycotic activity in dermatology, gynecology, and internal medicine. *Drug Development Research* 1986;**8**:317–23. [DOI: 10.1002/ddr.430080136

Chalmers 2009
Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;**374**(9683): 86–9. [PUBMED: 19525005]

Chunge 1985
Chunge CN, Gachihi G, Muigai R, Wasunna K, Rashid JR, Chulay JD, et al. Visceral leishmaniasis unresponsive to antimonial drugs. III. Successful treatment using a combination of sodium stibogluconate plus allopurinol. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1985;**79**(5):715–8. [PUBMED: 3006296]

Crawford 2005
Crawford R, Holmes D, Meymandi S. Comparative study of the efficacy of combined imiquimod 5% cream and intralesional meglumine antimoniate versus imiquimod 5% cream and intralesional meglumine antimoniate alone for the treatment of cutaneous leishmaniasis. *Journal of the American Academy of Dermatology* 2005;**52**:S118.

Croft 2006
Croft SL, Seifert K, Yardley V. Current scenario of drug development for Leishmaniasis. *Indian Journal of Medical Research* 2006;**123**(3):399–410. [PUBMED: 16778319]

Daie Parizi 1992
Daie Parizi MH. Treatment of cutaneous leishmaniasis with local application of the tincture of Thioxolone and benzoxonium chloride (first research in the world) at annual congress of Iranian society of pediatrics, Tehran, Iran, Oct 1992. *The Annual Book of Congress* 1992;**1**:121–5.

Daie Parizi 1996
Daie Parizi MH, Shamsaddini S. Comparison between topical treatment with Thioxolone, Benzoxonium Chloride tincture and intralesional injection of Meglumine Antimoniate on cutaneous Leishmaniasis. *Journal of Kerman University of Medical Sciences* 1996;**3**(1):7–14.

Davis 2003
Davies CR, Kaye P, Croft SL, Sundar S. Leishmaniasis: new approaches to disease control. *BMJ* 2003;**326**(7385): 377–82. [PUBMED: 12586674]

de Vries 2015
de Vries HJ, Reedijk SH, Schallig HD. Cutaneous leishmaniasis: recent developments in diagnosis and management. *American Journal of Clinical Dermatology* 2015;**16**(2):99–109. [PUBMED: 25687688]

Delamere 2008
Delamere FM, Sladden MJ, Dobbins HM, Leonardi-Bee J. Interventions for alopecia areata. *Cochrane Database of Systematic Reviews* 2008;**2**:CD004413. [DOI: 10.1002/14651858.CD004413.pub2

den Boer 2011
den Boer M, Argaw D, Jannin J, Alvar J. Leishmaniasis impact and treatment access. *Clinical Microbiology and Infection* 2011;**17**(10):1471-7. [PUBMED: 21933305]

Desjeux 1996
Desjeux P. Leishmaniasis. Public health aspects and control. *Clinical Dermatology* 1996;**14**(5):417–23. [PUBMED: 8889319]

Dorlo 2011
Dorlo TP, van Thiel PP, Schoone GJ, Stienstra Y, van Vugt M, Beijnen JH, et al. Dynamics of parasite clearance in cutaneous leishmaniasis patients treated with miltefosine. *PLoS Neglected Tropical Diseases* 2011;**5**(12):e1436. [PUBMED: 22180803]

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Biasin meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34. [PUBMED: 9310563]

el-On 1985
el-On J, Weinrauch L, Livshin R, Even-Paz Z, Jacobs GP. Topical treatment of recurrent cutaneous leishmaniasis with ointment containing paromomycin and methylbenzethonium chloride. *British Medical Journal (Clinical Research Ed.)* 1985;**291**(6497):704–5. [PUBMED: 3929905]

el-Safi 1990
el-Safi SH, Murphy AG, Bryceson AD, Neal RA. A double-blind clinical trial of the treatment of cutaneous leishmaniasis with paromomycin ointment. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990;**84** (5):690–1. [PUBMED: 2278070]

Faber 2003
Faber WR, Oskam L, van Gool T, Kroon NC, Knegt-Junk KJ, Hofwegen H, et al. Value of diagnostic techniques for cutaneous leishmaniasis. *Journal of the American Academy of Dermatology* 2003;**49**(1):70–4. [PUBMED: 12833011]

Fatima 2005
Fatima F, Khalid A, Nazar N, Abdalla M, Mohomed H, Toum AM, et al. In vitro assessment of anti - cutaneous leishmaniasis activity of some Sudanese plants. *Turkiye Parazitoloji Dergisi* 2005;**29**(1):3–6. [PUBMED: 17167733]

FDA 2014
US Food, Drugs Administration. News and Events - FDA News Release 2014. www.fda.gov/NewsEvents/Newsroom/

PressAnnouncements/ucm389671.htm (acessed prior to 10 October 2016).

Garnier 2002
Garnier T, Croft SL. Topical treatment for cutaneous leishmaniasis. *Current Opinion in Investigational Drugs (London, England : 2000)* 2002;**3**(4):538–44. [PUBMED: 12090720]

González 2009
González U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004834.pub2

González 2010
González U, Pinart M, Reveiz L, Rengifo-Pardo M, Tweed J, Macaya A, et al. Designing and reporting clinical trials on treatments for cutaneous leishmaniasis. *Clinical Infectious Diseases* 2010;**51**(4):409–19. [PUBMED: 20624067]

González 2015
González U, Pinart M, Sinclair D, Firooz A, Enk C, Vélez ID, et al. Vector and reservoir control for preventing leishmaniasis. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: 10.1002/14651858.CD008736.pub2

Goodman 2007
Goodman AC. Beware the "Texas sharp shooter" in rate ratios of progression. *BMJ* 2007;**334**(7591):440. [PUBMED: 17332546]

Gradoni 2017
Gradoni L, López-Vélez R, Mokni M. World Health Organization. Manual on case management and surveillance of the leishmaniasis in the WHO European Region. www.who.int/leishmaniasis/resources/EURO˙WHO˙Leish˙manual˙on˙case˙management˙and˙surveillance˙9789289052511˙2017.pdf?ua=1 (accessed prior to 15 November 2017).

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6. [PUBMED: 18436948]

Hepburn 2001
Hepburn NC. Management of cutaneous leishmaniasis. *Current Opinion in Infectious Diseases* 2001;**14**(2):151–4. [PUBMED: 11979125]

Herwaldt 1999
Herwaldt BL. Leishmaniasis. *Lancet* 1999;**354**(9185):1191–9. [PUBMED: 10513726]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60. [PUBMED: 12958120]

Higgins 2011
Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. [PUBMED: 22008217]

Ingram 2015
Ingram JR, Woo PN, Chua SL, Ormerod AD, Desai N, Kai AC, et al. Interventions for hidradenitis suppurativa. *Cochrane Database of Systematic Reviews* 2015, Issue 10. [DOI: 10.1002/14651858.CD010081.pub2

Jha 1983
Jha TK. Evaluation of allopurinol in the treatment of kala-azar occurring in North Bihar, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1983;**77**(2):204–7. [PUBMED: 6868102]

Jiang 2002
Jiang S, Meadows J, Anderson SA, Mukkada AJ. Antileishmanial activity of the antiulcer agent omeprazole. *Antimicrobial agents and chemotherapy* 2002;**46**(8):2569–74. [PUBMED: 12121934]

Junaid 1986
Junaid AJ. Treatment of cutaneous leishmaniasis with infrared heat. *International Journal of Dermatology* 1986;**25**(7):470–2. [PUBMED: 3771049]

Kager 1981
Kager PA, Rees PH, Wellde BT, Hockmeyer WT, Lyerly WH. Allopurinol in the treatment of visceral leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1981;**75**(4):556–9. [PUBMED: 6275579]

Karamian 2007
Karamian M, Motazedian MH, Mehrabani D, Gholami K. Leishmania major infection in a patient with visceral leishmaniasis: treatment with Amphotericin B. *Parasitology Research* 2007;**101**(5):1431–4. [PUBMED: 17659388]

Keiser J 2007
Keiser J, Utzinger J. Artemisinins and synthetic trioxolanes in the treatment of helminth infections. *Current Opinion in Infectious Diseases* 2007;**20**(6):605-12. [PUBMED: 17975411]

Kermode 2004
Kermode M. Unsafe injections in low-income country health settings: need for injection safety promotion to prevent the spread of blood-borne viruses. *Health Promotion International* 2004;**19**(1):95–103. [PUBMED: 14976177]

Khalid 2005
Fatima F, Khalid A, Nazar N, Abdalla M, Mohomed H, Toum AM, et al. In vitro assessment of anti - cutaneous leishmaniasis activity of some Sudanese plants. *Türkiye Parazitoloji Dergisi* 2005;**29**(1):3–6. [PUBMED: 17167733]

Khatami 2007
Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: a systematic review of the randomized controlled trials. *Journal of the American Academy of Dermatology* 2007;**57**(2):335.e1–29. [PUBMED: 17337090]

Laguna 1999
Laguna F, López-Vélez R, Pulido F, Salas A, Torre-Cisneros J, Torres E, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing

meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. *AIDS* 1999;**13**(9):1063–9. [PUBMED: 10397536]

Leibovici 1986
Leibovici V, Aram H. Cryotherapy in acute cutaneous leishmaniasis. *International Journal of Dermatology* 1986;**25**(7):473–5. [PUBMED: 3533799]

Lessa 2001
Lessa HA, Machado P, Lima F, Cruz AA, Bacellar O, Guerreiro J, et al. Successful treatment of refractory mucosal leishmaniasis with pentoxifylline plus antimony. *American Journal of Tropical Medicine and Hygiene* 2001;**65**(2):87–9. [PUBMED: 11508396]

Mapar 2001
Mapar MA, Kavoosi H, Dabbagh MA. Assessment of the effect of topical opium in treatment of cutaneous leishmaniasis. *Iranian Journal of Dermatology* 2001;**4**(16):23–8.

Masmoudi 2013
Masmoudi A, Hariz W, Marrekchi S, Amouri M, Turki H. Old World cutaneous leishmaniasis: diagnosis and treatment. *Journal of Dermatological Case Reports* 2013;**7**(2):31–41. [PUBMED: 23858338]

Meawad 1997
Meawad OB. Selective heat therapy in cutaneous leishmaniasis: a preliminary experience using the 585 nm pulsed dye laser. *Journal of the European Academy of Dermatology and Venereology: JEADV* 1997;**8**(3):241–4. [EMBASE: 27286057]

Migdal 2011
Migdal C, Serres M. Reactive oxygen species and oxidative stress. *Medical Science* 2011;**27**(4):405–412. [PUBMED: 21524406]

Minodier 2007
Minodier P, Parola P. Cutaneous leishmaniasis treatment. *Travel Medicine and Infectious Disease* 2007;**5**(3):150–8. [PUBMED: 17448941]

Modabber 2007
Modabber F, Buffet PA, Torreele E, Milon G, Croft SL. Consultative meeting to develop a strategy for treatment of cutaneous leishmaniasis. Institute Pasteur, Paris. 13-15 June, 2006. *Kinetoplastid Biology and Disease* 2007;**6**:3. [PUBMED: 17456237]

Monge-Maillo 2013
Monge-Maillo B, López-Vélez R. Therapeutic options for old world cutaneous leishmaniasis and new world cutaneous and mucocutaneous leishmaniasis. *Drugs* 2013;**73**(17):1889–920. [PUBMED: 24170665]

Monge-Maillo 2015
Monge-Maillo B, López-Vélez R. Miltefosine for visceral and cutaneous leishmaniasis: drug characteristics and evidence-based treatment recommendations. *Clinical Infectious Diseases* 2015;**60**(9):1398–404. [PUBMED: 25601455]

Moore 2001
Moore OA, Smith LA, Campbell F, Seers K, McQuay KJ, Moore RA. Systematic review of the use of honey as a wound dressing. *BMC Complementary and Alternative Medicine* 2001;**1**:2. [PUBMED: 11405898]

Moskowitz 1999
Moskowitz PF, Kurban AK. Treatment of cutaneous leishmaniasis: Retrospective and advances for the 21st century. *Clinical Dermatology* 1999;**17**(3):305–15. [PUBMED: 10384870]

Mosleh 2008
Mosleh IM, Geith E, Natsheh L, Schönian G, Abotteen N, Kharabsheh S. Efficacy of a weekly cryotherapy regimen to treat Leishmania major cutaneous leishmaniasis. *Journal of the American Academy of Dermatology* 2008;**58**(4):617–24. [PUBMED: 18249466]

Munir 2008
Munir A, Janjua SA, Hussain I. Clinical efficacy of intramuscular meglumine antimoniate alone and in combination with intralesional meglumine antimoniate in the treatment of old world cutaneous leishmaniasis. *Acta Dermatovenerologica Croatica: ADC* 2008;**16**(2):60–4. [PUBMED: 18541100]

Musa 2005
Musa AM, Khalil EA, Mahgoub FA, Hamad S, Elkadaru AM, El Hassan AM. Efficacy of liposomal amphotericin B (AmBisome) in the treatment of persistent post-kala-azar dermal leishmaniasis (PKDL). *Annals of Tropical Medicine and Parasitology* 2005;**99**(6):563–9. [PUBMED: 16156969]

Najim 1998
Najim RA, Sharquie KE, Farjou IB. Zinc sulphate in the treatment of cutaneous leishmaniasis: an in vitro and animal study. *Memórias do Instituto Oswaldo Cruz* 1998;**93**(6):831–7. [PUBMED: 9921312]

Neva 1984
Neva FA, Petersen EA, Corsey R, Bogaert H, Martinez D. Observations on local heat treatment for cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 1984;**33**(5):800–4. [PUBMED: 6091468]

Olliaro 2013
Olliaro P, Vaillant M, Arana B, Grogl M, Modabber F, Magill A, et al. Methodology of clinical trials aimed at assessing interventions for cutaneous leishmaniasis. *PLoS Neglected Tropical Diseases* 2013;**7**(3):e2130. [PUBMED: 23556016]

Pace 2014
Pace D. Leishmaniasis. *Journal of Infection* 2014;**69**(Suppl 1):S10–S18. [PUBMED: 25238669]

Passwell 1986
Passwell JH, Shor R, Shoham J. The enhancing effect of interferon-beta and -gamma on the killing of Leishmania tropica major in human mononuclear phagocytes in vitro. *Journal of Immunology* 1986;**136**(8):3062–6. [PUBMED: 3082979]

Pieper 2003
Pieper B, Caliri MH. Nontraditional wound care: A review of the evidence for the use of sugar, papaya/papain, and fatty acids. *Journal of Wound, Ostomy, and Continence Nursing* 2003;**30**(4):175-83. [PUBMED: 12851592]

Pigott 2014
Pigott DM, Golding N, Messina JP, Battle KE, Duda KA, Balard Y, et al. Global database of leishmaniasis occurrence locations, 1960-2012. *Scientific Data* 2014;**30**(1):140036. [PUBMED: 25984344]

Ponte-Sucre 2003
Ponte-Sucre A. Physiological consequences of drug resistance in Leishmania and their relevance for chemotherapy. *Kinetoplastid Biology and Disease* 2003;**2**(1):14. [PUBMED: 14613496]

Ranawaka 2011
Ranawaka RR, Weerakoon HS, Opathella N. Liquid nitrogen cryotherapy on Leishmania donovani cutaneous leishmaniasis. *Journal of Dermatological Treatment* 2011;**22**(4):241–5. [PUBMED: 20818996]

Rathi 2005
Rathi SK, Pandhi RK, Chopra P, Khanna N. Post-kala-azar dermal leishmaniasis: a histopathological study. *Indian Journal of Dermatology, Venereology and Leprology* 2005;**71**(4):250–53. [PUBMED: 16394433]

Reithinger 2005b
Reithinger R, Aadil K, Kolaczinski J, Mohsen M, Hami S. Social impact of leishmaniasis, Afghanistan. *Emerging Infectious Diseases* 2005;**11**(4):634–6. [PUBMED: 15834984]

Reithinger 2007
Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infectious Diseases* 2007;**7**(9):581–96. [PUBMED: 17714672]

Rodriguez 1990
Rodriguez ME, Inguanzo P, Ramos A, Perez J. Treatment of cutaneous leishmaniasis with CO2 laser radiation. *Revista Cubana de Medicina Tropical* 1990;**42**(2):197–202. [PUBMED: 2128547]

Rodriguez-Cuartero 1990
Rodriguez-Cuartero A, Pérez-Blanco FJ, López-Fernández A. Co-trimoxazole for visceral leishmaniasis. *Infection* 1990;**18**(1):40. [PUBMED: 2312176]

Rohrich 2003
Rohrich RJ, Janis EJ, Reisman NR. Use of off-label and non-approved drugs and devices in plastic surgery. *Plastic and Reconstructive Surgery* 2003;**112**(1):241–243. [PUBMED: 12832901]

Saab 2015
Saab M, El Hage H, Charafeddine K, Habib RH, Khalifeh I. Diagnosis of cutaneous leishmaniasis: why punch when you can scrape?. *American Journal of Tropical Medicine and Hygiene* 2015;**92**(3):518–22. [PUBMED: 25561563]

Sacks 1983
Sacks DL, Barral A, Neva F. Thermosensitivity patterns of Old vs. New World cutaneous strains of Leishmania growing within mouse peritoneal macrophages in vitro. *American Journal of Tropical Medicine and Hygiene* 1983;**32**(2):300–4. [PUBMED: 6837841]

Sampaio 1960
Sampaio SA, Godoy JT, Paiva L, Dillon NL, da Lacaz CS. The treatment of American (mucocutaneous) leishmaniasis with amphotericin B. *Archives of Dermatology* 1960;**82**:627–35. [PUBMED: 13745957]

Sampaio 1997
Sampaio RN, Marsden PD. Treatment of the mucosal form of leishmaniasis without response to glucantime, with liposomal amphotericin B. *Revista da Sociedade Brasileira de Medicina Tropical* 1997;**30**(2):125–8. [PUBMED: 9148335]

Savioli 2006
Savioli L, Engels D, Daumerie D, Jannin J, Alvar J, Asiedu K, et al. Response from Savioli and colleagues from the Department of Neglected Tropical Diseases, World Health Organization. *PLoS medicine* 2006;**3**(6):e283. [PUBMED: 16789805]

Schallig 2002
Schallig HD, Oskam L. Molecular biological applications in the diagnosis and control of leishmaniasis and parasite identification. *Tropical Medicine and International Health* 2002;**7**(8):641–51. [PUBMED: 12167091]

Schmidt-Ott 1999
Schmidt-Ott R, Klenner T, Overath P, Aebischer T. Topical treatment with hexadecylphosphocholine (Miltex) efficiently reduces parasite burden in experimental cutaneous leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(1):85–90. [PUBMED: 10492799]

Schork 1967
Schork MA, Ramington RD. The determination of sample size in disease studies in which drop out or non-adherence is a problem. *Journal of Chronic Diseases* 1967;**20**(4):233–9. [PUBMED: 6023231]

Schulz 2010
Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine* 2010;**152**(11):726–32. [DOI: 10.7326/0003-4819-152-11-201006010-00232

Sharifi 2010
Sharifi I, Fekri AR, Aflatoonian MR, Khamesipour A, Mahboudi F, Dowlati Y, et al. Leishmaniasis recidivans among school children in Bam, South-east Iran, 1994-2006. *International Journal of Dermatology* 2010;**49**(5):557–561. [PUBMED: 20534092]

Sharquie 1988
Sharquie KE, Al-Talib K, Chu AC. Intralesional therapy of cutaneous leishmaniasis with sodium stibogluconate antimony. *British Journal of Dermatology* 1988;**119**(1):53–7. [PUBMED: 2841964]

Sharquie 1995
Sharquie KE. A new intralesional therapy for cutaneousd leishmaniasis with hypertonic sodium chloride solution. *Journal of Dermatology* 1995;**22**(10):732–7. [PUBMED: 8586751]

Sharquie 1996
Sharquie KE, Al-Azzawi KE. Intralesional therapy for cutaneous leishmaniasis with 2% zinc sulfate solution. *Journal of Pan-Arab League of Dermatologists* 1996;**7**:41–6.

Sharquie 1998
Sharquie KE, Al-Hamamy H, El-Yassin D. Treatment of cutaneous leishmaniasis by direct current electrotherapy: the Baghdadin device. *Journal of Dermatology* 1998;**25**(4): 234–7. [PUBMED: 9609980]

Simonsen 1999
Simonsen L, Kane A, Lloyd J, Zaffran M, Kane M. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. *Bulletin of the World Health Organization* 1999;**77**(10):789–800. [PUBMED: 10593026]

Sindermann 2006
Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2006;**100**(Suppl 1): S17–20. [PUBMED: 16730362]

Solomon 2011
Solomon M, Pavlotsky F, Leshem E, Ephros M, Trau H, Schwartz E. Liposomal amphotericin B treatment of cutaneous leishmaniasis due to Leishmania tropica. *Journal of the European Academy of Dermatology and Venereology* 2011;**25**(8):973–7. [PUBMED: 21129042]

Soto 2004
Soto J, Arana BA, Toledo J, Rizzo N, Vega JC, Diaz A, et al. Miltefosine for new world cutaneous leishmaniasis. *Clinical Infectious Diseases* 2004;**38**(9):1266–72. [PUBMED: 15127339]

Stojkovic 2007
Stojkovic M, Junghanss T, Krause E, Davidson RN. First case of typical Old World cutaneous leishmaniasis treated with miltefosine. *International Journal of Dermatology* 2007; **46**(4):385–7. [PUBMED: 17442078]

Storer 2005
Storer E, Wayte J. Cutaneous leishmaniasis in Afghani refugees. *Australasian Journal of Dermatology* 2005;**46**(2): 80-3. [PUBMED: 15842398]

Stotland 2009
Stotland M, Shalita AR, Kissling RF. Dapsone 5% gel: a review of its efficacy and safety in the treatment of acne vulgaris. *American Journal of Clinical Dermatology* 2009;**10** (4):221–7. [PUBMED: 19489655]

Sundar 2007a
Sundar S, Chakravarty J, Rai VK, Agrawal N, Singh SP, Chauhan V, et al. Amphotericin B treatment for Indian visceral leishmaniasis: response to 15 daily versus alternate-day infusions. *Clinical infectious Diseases* 2007;**45**(5): 556–61. [PUBMED: 17682988]

Sundar 2007b
Sundar S, Jha TK, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for Visceral leishmaniasis in India. *New England Journal of Medicine* 2007;**356**(25):2571–81. [PUBMED: 17582067]

Thakur 1996
Thakur CP, Pandey AK, Sinha GP, Roy S, Behbehani K, Olliaro P. Comparison of three treatment regimens with liposomal amphotericin B (AmBisome) for visceral leishmaniasis in India: a randomized dose-finding study. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996;**90**(3):319–22. [PUBMED: 8758093]

Urcayo 1982
Urcayo FG, Zaias N. Oral ketoconazole in the treatment of cutaneous leishmaniasis. *International Journal of Dermatology* 1982;**21**(7):414–6. [PUBMED: 6290403]

Uzun 2004
Uzun S, Durdu M, Culha G, Allahverdiyev AM, Memisoglu HR. Clinical features, epidemiology, and efficacy and safety of intralesional antimony treatment of cutaneous leishmaniasis: recent experience in Turkey. *Journal of Parasitology* 2004;**90**(4):853–9. [PUBMED: 15357081]

van Griensven 2014
van Griensven J, Carrillo E, López-Vélez R, Lynen L, Moreno J. Leishmaniasis in immunosuppressed individuals. *Clinical Microbiology and Infection* 2014;**20**(4):286–299. [PUBMED: 24450618]

van Zuuren 2015
van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MMD, Charland L. Interventions for rosacea. *Cochrane Database of Systematic Reviews* 2015, Issue 4. [DOI: 10.1002/14651858.CD003262.pub5

Vaneau 2007
Vaneau M, Chaby G, Guillot B, Martel P, Senet P, Téot L, et al. Consensus panel recommendations for chronic and acute wound dressings. *Archives of Dermatology* 2007;**143** (10):1291–4. [PUBMED: 17938343]

Vardy 2001
Vardy D, Barenholz Y, Naftoliev N, Klaus S, Gilead L, Frankenburg S. Efficacious topical treatment for human cutaneous leishmaniasis with ethanolic lipid amphotericin B. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2001;**95**(2):184–6. [PUBMED: 11355557]

Weigel 2001
Weigel MM, Armijos RX. The traditional and conventional medical treatment of cutaneous leishmaniasis in rural Ecuador. *Revista Panamericana de Salud Publica [Pan American Journal of Public Health]* 2001;**10**(6):395–404. [PUBMED: 11820108]

Weinrauch 1983a
Weinrauch L, Livshin R, El-On J. Cutaneous leishmaniasis treatment with ketoconazole. *Cutis* 1983;**32**(3):288-90, 294. [PUBMED: 6313298]

Weinrauch 1983b
Weinrauch L, Livshin R, Even-Paz Z, El-On J. Efficacy of ketoconazole in cutaneous leishmaniasis. *Archives of Dermatology* 1983;**275**(5):353–4. [PUBMED: 6318670]

WHO 2002
World Health Organization (WHO). Leishmaniasis. World Health Report 2002. www.who.int/whr/2002/annex/en/ (accessed 2 April 2004).

WHO 2007
World Health Organization (WHO). Control of leishmaniasis. Report by the Secretariat 22 March 2007. apps.who.int/gb/archive/pdf˙files/WHA60/A60˙10-en.pdf (accessed before 11 October 2016).

WHO 2008
World Health Organization (WHO). Report of the Fifth Consultative Meeting on Leishmania/HIV Co-infection. Addis Ababa, Ethiopia, 20-22 March 2007. www.who.int/leishmaniasis/resources/Leishmaniasis˙hiv˙coinfection5.pdf (accessed before 11 October 2016). [WHO/CDS/NTD/IDM/2007.5]

WHO 2010
World Health Organization (WHO). Control of the leishmaniases: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva 22-26 March 2010. WHO technical report series 949. apps.who.int/iris/bitstream/10665/44412/1/WHO˙TRS˙949˙eng.pdf (accessed before 11 October 2016). [ISBN 9789241209496]

WHO 2011
World Health Organization (WHO). Application for Inclusion of Miltefosina on WHO Model List of Essential Medicines. Submitted to the EML Secretariat for consideration. November 2010. www.who.int/selection˙medicines/committees/expert/18/applications/Miltefosine˙application.pdf (accessed 11 October 2016).

Wortmann 2010
Wortmann G, Zapor M, Ressner R, Fraser S, Hartzell J, Pierson J, et al. Lipsosomal amphotericin B for treatment of cutaneous leishmaniasis. *American Journal of Tropical Medicine and Hygiene* 2010;**83**(5):1028–33. [PUBMED: 21036832]

Zakraoui 1995
Zakraoui H, Ben Salah A, Ftaiti A, Marrakchi H, Zaatour A, Zaafouri B, et al. Spontaneous course of lesions of Leishmania major cutaneous leishmaniasis in Tunisia. *Annales de Dermatologie et Venereogie* 1995;**122**(6-7):405–7. [PUBMED: 8526421]

Zanger 2011
Zanger P, Kotter I, Raible A, Gelanew T, Schonian G, Kremsner PG. Case report: Successful treatment of cutaneous leishmaniasis caused by Leishmania aethiopica with liposomal amphothericin B in an immunocompromised traveler returning from Eritrea. *American Journal of Tropical Medicine and Hygiene* 2011;**84**(5):692–4. [PUBMED: 21540377]

Zeglin 2009
Zeglin O. Infectiology and Tropical Dermatology Part 17: cutaneous leishmaniasis - a casuistry with after assessment [Infektiologie und Tropendermatologie – Teil 17: kutaneleishmaniasis – eine kasuistik mit nachbegutachtung]. *Dermatology* 2009;**15**(4):246ff.

References to other published versions of this review

Gonzalez 2008
González U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD005067.pub3

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adam 2009

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Omdurman Hospital for Tropical Diseases, Sudan *Study period*: August 2007 to March 2008 (7 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: people with cutaneous leishmaniasis, confirmed microscopically by finding amastigotes in slit skin smears, if they had not received any previous treatment (Antimonial) *Exclusion criteria*: pregnant women, people weighing < 10 kg, malnourished people and those with a history of allergy to sulphonamides or artemisinins *N randomised*: 41 (group 1: n = 20, group 2: n = 21) *Withdrawals*: 0 *N assessed*: 41 (100%) (group 1: n = 20, group 2: n = 21) *Mean age (SD)*: group 1: 30.6 years (18.0), group 2: 28.5 years (15.3) *Baseline data*: • N lesions (mean, SD): group 1: 2.1 (1.4); group 2: 2.2 (1.3) • Size of lesion (median, IQR): group 1: 3.4 cm (1.5); group 2: 3.2 cm (1.3) • Creatinine (mean, SD): group 1: 0.9 mg/dL (0.3), group 2: 0.9 mg/dL (0.2) • Alanine aminotransferase (mean, SD): group 1: 36.7 IU (9.5), group 2: 37.3 IU (4.5)
Interventions	*Type of interventions*: • *Group 1*: AS + SMP (100 mg artesunate + 250 mg/12.5 mg sulphamethoxypyrazine/pyrimethamine) (Co-Arinate®; Dafra Pharma NV, Turnhout, Belgium). 4 tablets on 4 consecutive days were administered and repeated 4 times with 2-week intervals without treatment • *Group 2*: matched placebo *Duration of intervention*: 8 weeks *Co-interventions*: pentosan was administered to participants who failed treatment with the study drug as well as to participants who had received placebo tablets
Outcomes	*Healing rates*: disappearance and/or shrinkage of the lesions. Lesions were identified, measured and numbered by their specific location on the participant's body before treatment and after 36 days and 72 days. Reported at the end of treatment *Adverse effects*: participants were questioned about expected adverse effects for 3 days (days 5-7) following administration of the doses. These were considered drug-related if they were not reported at presentation
Notes	*Study funding sources*: Dafra Pharma NV/SA, Turnhout, Belgium *Possible conflicts of interest*: none declared
Risk of bias	

Adam 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated block-randomisation, blinded to the treating physician, was used to allocate patients to the two treatment arms"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a double-blind, placebo controlled clinical trial"; "blinded to the treating physician…" Comment: not fully reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts are unclear
Selective reporting (reporting bias)	Unclear risk	Protocol not available; not registered in a prospective clinical trial registry
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Al Hamdi 2010

Methods	*Study design*: randomised, prospective clinical trial *Setting/location*: outpatient clinic of Basra teaching hospital, south Iraq *Study period*: April 2004 to March 2005 (11 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania major* and *L tropica* *Inclusion criteria*: all patients with cutaneous leishmaniasis who were diagnosed clinically by the same dermatologist *Exclusion criteria*: ≥ 20 lesions; pregnancy, lactation; hypersensitivity to pentavalent antimonials or local anaesthetic; serious medical illness, lesion in proximity to mucous membranes, face, or cartilage; implanted metallic devices; unwillingness to avoid procreation for at least 2 months *N randomised*: 38 participants, 70 lesions: group 1 = 35, group 2 = 35 *Withdrawals*: group 1: 14 lesions; group 2: 8 lesions *N assessed*: lesions assessed: group 1: 21 (60%); group 2: 27 (77%) *Age range*: 1.5 to 64 years (1.5-45 years in group 1 and 3-64 years in group 2) with a mean of 21.1 years *Sex*: 52.5% males, 47.5% females

	Baseline data: • N lesions treated at start of study: group 1, 35; group 2, 35 • N lesions per participant: group 1 - 1:7, 2:5, 3:1, > 3:7; group 2 - 1:7, 2:8, 3:2, > 3:5 • N lesions by site - face and neck: group 1: 8, group 2: 3; upper limbs: group 1: 19, group : 10; lower limbs: group 1: 7, group 2: 18; trunk group 1: 1, group 2: 4 • Mean lesion size before study: group 1, 1.74 cm, group 2, 1.70 cm • Range of lesion duration before study: group 1: 1 month-1 year; group 2: 1 month-5 years
Interventions	*Type of interventions*: • *Group 1*: hypertonic sodium chloride solution (HSCS) (7%) (7 g dissolved in 100 mL distilled water and autoclaved) • *Group 2*: ciprofloxacin solution (2 mg/mL) Both drugs were injected into the lesions in amounts of 0.1-0.5 mL according to the size of the lesion *Duration of intervention*: 8 weeks
Outcomes	*Clinical cure*: resolution of active lesion with or without scarring. A scoring system was specially designed as follows. The diameter of lesions was recorded in mm using a ruler and scored as: 0 (total healing); 1 (0 cm to < 0.5 cm); 2 (0.5 cm to < 1 cm); 3 (1 cm to < 1.5 cm); 4 (1.5 cm to < 2 cm); 5 (2 cm to < 2.5 cm); or 6 (≥ 2.5 cm). The degree of induration was assessed by palpation in comparison with the participant's normal skin and given the following scores: 0, 0.5, 1, 1.5, 2, or 3. The degree of erythema was assessed visually and scored as: 0, 0.5, 1, 1.5, 2, or 3. Ulceration was scored as: 1 (present) or 0 (absent). The scores of these 4 parameters were added to give a total score for each lesion Time points reported: the changes in total score between weeks: lesions were assessed at the start and again at 2-week intervals after treatment for 8 weeks: 0, 2, 4, 6, and 8 weeks of treatment. Follow-up continued for 8 weeks until complete healing took place
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported; probably an open trial

Al Hamdi 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported; probably an open trial. No information on how lesions were assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	After excluding participants who defaulted on treatment, 21/35 lesions were analysed in group 1 (HSCS) and 27/35 in group 2 (ciprofloxacin)
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Not registered in a clinical trial registry. Pre-specified outcomes of the review were reported Tables were not available in the links of the journal, and .pdf does not work. No adverse effects reported in the text
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Al-Fouzan 1991

Methods	*Study design*: randomised controlled trial *Setting/location*: Kuwait *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* or *L major* in the area *Inclusion criteria*: positive for leishmanial parasites (amastigotes) on microscopic examination. Women of childbearing age were instructed to use potent and adequate contraceptive measures before the initiation of treatment *Exclusion criteria*: not described *N randomised*: 24. Oral itraconazole: 15; placebo: 9 *Withdrawals*: 0 *N assessed*: N = 24. Oral itraconazole: 15; placebo: 9 *Age range*: 12-52 years *Sex*: male/female: 13/11 *Baseline data*: single or multiple lesions, active being nodule, nodule-ulcerative, or ulcerative. The site of lesions including both groups was 75% on upper limbs; 46% on lower limbs; 25% on the face, and 4% on the trunk. The duration of the lesion varied between 1 and 14 months
Interventions	*Type of interventions*: • *Group 1*: oral itraconazole 200 mg twice daily. There was a 12-year-old boy who was given a dose of 100 mg once daily (3 mg/kg per day) • *Group 2*: placebo capsules twice daily during meals. *Duration of intervention*: 6-8 weeks *Duration of follow-up*: 12 weeks post-treatment

Al-Fouzan 1991 (*Continued*)

Outcomes	*Primary outcome*: percentage of participants 'cured' 2 months after treatment. The response to treatment was graded as excellent (reduction in size of lesion by 80% up to complete clearance); good (reduction in size of lesion by 50%) and poor when there is minimal or no change of lesion *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur within 6 months and 1, 2, and 3 years (for a period up to 3 months after suspension of the drug) *Adverse effects* Time points reported: 8 weeks and 12 weeks post-treatment
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The participants were randomly divided into two groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups" No further information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The drug and the placebo were supplied in capsules with the same shape No information about blinding of personnel was provided but it is not likely to add risk of bias being oral administration
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment was described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Alkhawajah 1997

Methods	*Study design*: randomised controlled trial *Setting/location*: Al-Ahssa, Saudi Arabia *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* in the area *Inclusion criteria*: only a few (1-3) simple lesions, on a non-facial site; clinically confirmed CL by direct slit smears and/or in skin-punch biopsies of the active, infiltrated edge of a representative lesion *Exclusion criteria*: multiple or disseminated lesions, lesions aged > 6 months, pregnancy, chronic illness, immunologically compromised condition, hyperallergic reaction to the trial drugs, treatment with regular medications which may affect specific therapy, treatment with antileishmanial drugs within the previous 6 months, the presence of scars of previously healed lesions *N participants (lesions) randomised*: 80. IMMA group: 40 (77); ILMA group: 40 (70) *Withdrawals*: 13 (13). IMMA group: 9 (9); ILMA group: 4 (4) *N assessed*: 67. IMMA group: 31 (68); ILMA group: 36 (66) *Mean age (range)*: range 13-42 years. IMMA group: 29.8 years (15-41); ILMA group: 31.5 years (13-42) *Sex*: male: 48, female: 19 *Baseline data*: • Lesion type in the IMMA group were: nodular 20%; nodular-ulcerative 24%; flat-ulcerative 19%; and plaque-like 5% • Lesion type in the ILMA group were: nodular 24%; nodular-ulcerative 18%; flat-ulcerative 15%; and plaque-like 9% • Lesion site (% of lesions) in the IMMA group: shoulder 7; upper arm 11; lower arm 14; elbow 1; hand 10; thigh 5; knee 4; leg 12; and foot 4 • Lesion site (% of lesions) in the ILMA group: shoulder 5; upper arm 9; lower arm 11; elbow 2; hand 8; thigh 7; knee 3; leg 12; and foot 9 • IMMA group: median size of lesion (MSL) 1.8 cm^2; median duration of lesions before therapy (MDLBT): 72.7 days • ILMA group: MSL: 1.2 cm^2. MDLBT: 67.9 days
Interventions	*Type of interventions*: • *Group 1*: IMMA 15 mg/kg/d daily on 6 days/week up to 12 injections • *Group 2*: ILMA 0.2 to 0.8 mL/lesion every other day over a 30 day period or until lesion had blanched *Duration of intervention*: • *Group 1*: 15 days • *Group 2*: 30 days *Duration of follow-up*: 1 month post-treatment
Outcomes	*Primary outcome*: percentage of lesions 'cured' at the end of treatment *Secondary outcomes*: prevention of scarring *Adverse effects* Time points reported: days 15, 30
Notes	*Study funding sources*: none described *Possible conflicts of interest*: none declared

Alkhawajah 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "enrolled patients were randomly assigned to one of two treatment groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "enrolled patients were randomly assigned to one of two treatment groups" Comment: no further information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding of participants and personnel was provided but the different administration via of the drug is impossible to blind, although it is unlikely to add risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Lesions were assessed, whenever a patient came for his or her injection (s) , by an observer who was unaware of the treatment the patient was receiving."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information about dropouts
Selective reporting (reporting bias)	Unclear risk	No information about adverse effects was provided
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Alrajhi 2002

Methods	*Study design*: randomised controlled trial *Setting/location*: Al-Ahsaa and Ryyadh, Saudi Arabia *Study period*: 15 months *Sample size calculation*: to detect a difference of 22% in the rate of healing between the placebo group and the treatment group, assuming a healing rate of 45% in the placebo group, with a power of 90% and a two-sided type I error of 5%, 101 subjects were needed in each group. To compensate for loss to follow-up, 25% more participants were to be enrolled in each group
Participants	*Type of Leishmania*:*L major* 56 participants (27%) *Inclusion criteria*: age > 12 years, presence of lesions parasitologically confirmed leishmaniasis, non-use of antileishmanial therapy during previous 2 months *Exclusion criteria*: pregnancy, potential for pregnancy, breastfeeding; presence of lesions on the face or ears; presence of more than 10 lesions; history of liver disease; elevated serum, creatinine concentration, abnormal results on liver-function tests; allergy to fluconazole *N randomised*: 209. 106 were assigned to the fluconazole group, and 103 were assigned to the placebo group *Withdrawals*: 63 received the container of capsules at the first visit and never returned for follow-up: 37 participants assigned to receive placebo and 26 participants of fluconazole group One participant in the placebo group, who was therefore excluded from the analyses *N assessed*: 145. Fluconazole group: 80, placebo group: 65 *Age and sex*: not described *Baseline data*: • Intervention group: MNL: 3.1, MSL: 17 mm, MDLBT: 9.2 weeks • Control group: MNL: 3.7, MSL: 19 mm, MDLBT: 7.7 weeks
Interventions	*Type of interventions*: • *Group 1*: fluconazole orally 200 mg • *Group 2*: placebo 200 mg *Duration of intervention*: 6 weeks *Co-interventions*: SSG was offered during follow-up if oral therapy was considered to have failed (14 participants in the fluconazole group and 33 in the placebo group) *Duration of follow-up*: 1 year post-treatment
Outcomes	*Healing rates*: • Percentage of participants 'cured' 3 months after treatment • Speed of healing (time taken to be 'cured') *Adverse effects* Time points reported: 6 weeks, 3 months of follow-up, 1 year post-treatment
Notes	*Baseline imbalances*: because of the criteria for inclusion and the limited number of women at risk for *Leishmania* in the study areas, there was only one female participant. Most of the participants were foreign construction workers or farmers originally from countries where CL is not endemic. One of 5 participants was a local national *Study funding sources*: supported in part by a grant (no. 146-1414) from Pfizer and the Ministry of Health of Saudi Arabia *Possible conflicts of interest*: none declared

Alrajhi 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the randomisation sequence was generated from a random-number table"
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation sequence was generated from a random-number table" Comment: no further information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "assigned to receive either fluconazole (Diflucan, Pfizer, New York) in the form of a 200-mg capsule once daily for six weeks or a matching placebo" "An independent observer evaluated the rates of compliance and side effects by interviewing patients and counting their remaining capsules."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No further information about blinding of outcome assessment was provided
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of drops out: 63/209 (30.14%). Missing outcome data imbalanced in numbers across groups. Fluconazole orally 200 mg: 26. Placebo group: 37. An ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Low risk	Other items assessed correctly reported

Alsaleh 1995

Methods	*Study design*: randomised controlled trial *Setting/location*: Kuwait *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp not specified *Inclusion criteria*: only the smear-positive cases included in the study *Exclusion criteria*: participants younger than 14 years and pregnant nursing women *N randomised*: 33. Group 1, ketoconazole 600 mg: 18; Group 2, ketoconazole 800 mg: 15

	Withdrawals: 7. Group 1: 3, Group 2: 4 *N assessed*: 26. Group 1: 15, Group 2: 11 *Age range*: 14-66 years *Sex (male/female)*: 26/7 *Severity of illness*: 1-8 lesions. Site of the lesions in the ketoconazole 600 mg group: 46% on the upper extremities and 24/% on the lower extremities. In the ketoconazole 800 mg: 58% on the upper extremities; 21% on the lower extremities and 21% on head and neck Ketoconazole 600 mg: MNL: 3.56 (range 2-8). MDLBT: 3.4 months (range 1.5-7) Ketoconazole 800 mg: MNL: 3.27 (range 1-6). MDLBT: 4.5 months (range 1-12)
Interventions	*Type of interventions*: • *Group 1*: ketoconazole 600 mg daily • *Group 2*: ketoconazole 800 mg daily *Duration of intervention*: 6 weeks or until the participant was cured (whatever occurred early) *Duration of follow-up*: 6 months
Outcomes	*Healing rates*: percentage of participants 'cured' at the end of treatment (If there was more than 90% improvement of these parameters: re-epithelisation and decrease in the size and inflammation of the lesions, with a negative smear for *Leishmania* parasites) *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur within 6 months *Adverse effects* Time points reported: 1, 2, 4, 6, 8 weeks post-treatment
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding was provided

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge.
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Aronson 2010

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Walter Reed Army Medical Center (WRAMC) in Washington *Study period*: 24 months (2004-6) *Sample size calculation*: a sample size of 27 participants per treatment group was planned, assuming a 73% cure rate for ThermoMed (TM), 99% for SSG, controlling for a probability of a type I error at alpha = 0.05 and was predicted to have 80% power to determine a 26% difference in outcome
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: eligible participants were Department of Defense healthcare beneficiaries with parasitologically confirmed cutaneous leishmaniasis. At Walter Reed Army Medical Center (WRAMC) in Washington. All participants were likely infected in Iraq or Kuwait. All were treatment naive *Exclusion criteria*: 20 lesions; pregnancy, lactation; hypersensitivity to pentavalent antimonials or local anaesthetic; serious medical illness; lesion in proximity to mucous membranes, face, or cartilage; implanted metallic devices; unwillingness to avoid procreation for at least 2 months *N randomised*: 56, IVSSG: 28. Localised TM device heat treatment: 28 Participants with clinical failure at 2 months were offered cross-over treatment. Afer 2 months: SSG: 29 (−1, +3), TM: 25 (−3, +1) *Withdrawals*: 2. TM: 1 (lesion not amenable to heat), SSG: 1 (not confirmed *L major*) *N assessed*: 54 (96.43%) completed treatment: TM: 27 (96.43%), SSG: 27 (96.43%). 53 (94.64%) completed 12 months follow-up: TM: 27 (96.43%), SSG: 26 (92.86%) *Median age (range)*: TM: 25 years (20-53); SSG: 24 years (18-57) *Sex*: TM: males: 28 (100%), SSG: males: 27 (96%), females: 1 (4%) *Baseline data*: • Mean number of lesions (range): TM: 2 (1-14), SSG: 3 (1-17) • Mean duration of lesions (range): TM: 126 days (45-231), SSG: 138 days (50-270) • Amastigotes present (%): TM: 22 (79), SSG: 18 (64) • Culture isoenzyme *L major** (%): TM: 12/23 (52), SSG: 12/24 (50) • *L major* spp PCR positive: TM: 28 (100), SSG: 27 (96) • Complicated leishmaniasis, presence of significant regional adenopathy or subcutaneous nodules (%): TM: 5 (18), SSG: 8 (29) • Location of the target lesion: TM: head and neck 11 (12%), arms 40 (43%), legs 27 (29%), back 11 (12%), chest 5 (5%). SSG: head and neck 6 (6%), arms 65 (67%), legs 14 (14%), back 3 (3%), chest 9 (9%)

	• MSL (range): TM: 155 mm² (9-1014), SSG: 110 mm² (9-1720)
Interventions	*Type of interventions*: • *Group 1*: quote: "Localized ThermoMed (TM) device heat treatment: one treatment session using the ThermoMed Model 1.8 device (TM). Prior to thermotherapy, each lesion was cleansed, anaesthestized, moistened, and overlying eschar was removed. 2 trained physicians performed TM treatments. TheTM probe was placed on the skin, covering the lesion with 50uCTM treatments applied for 30 s in a grid fashion extending 4 mm into border skin. The lesion size determined the number of applications. Each lesion was then covered with a dressing (Coverlet, Beiersdorf-Jobst, Wilton CT) that was changed daily." • *Group 2*: IVSSG 20 mg/kg/d for 10 doses (GlaxoSmithKline, UK) *Duration of intervention*: TM: 1 session. SSG: 10 days. *Co-interventions*: participants randomised to thermotherapy received oral antibiotics for secondary bacterial infections of the leishmaniasis lesion(s) prior to treatment. SSG arm participants were treated concurrently with antibiotics **Follow-up**: 2, 6, and 12-24 months post-treatment.
Outcomes	*Clinical cure of the lesions*: clinical cure was defined as complete epithelialisation or visually healed at 2 ± 1 month after completion of therapy and no reactivation in 12 months after the start of treatment. Clinical failure was less than complete epithelialisation or visually not healed at 2 ± 1 month after treatment completion. Relapse failure was defined as skin lesion persistence at the treatment site or elsewhere in the period up to 12 months after start of therapy, regardless of appearance at 2 ± 1 month after treatment completion *Laboratory cure of the lesions*: microbiological cure: they looked for an eradication of the infection *Time to healing*: survival analysis of time to healing for the 2 treatment arms *Adverse effects*: toxicity profile Time points reported: 2, 6, 12 months. Toxicity profile: daily physician evaluations
Notes	*Study funding sources*: this trial was supported by Walter Reed Army Medical Center, The North Atlantic Regional Medical Command, and the US Army Medical and Materiel Development Agency *Possible conflicts of interest*: the authors have declared that no competing interests exist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The statistician (RH) generated the randomisation plan in blocks of 4 subjects using www.randomization.com. The research pharmacist made assignments using the randomisation plan in sequential order
Allocation concealment (selection bias)	Low risk	The allocation sequence was unavailable to investigators until completion of the trial

Aronson 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sequential photographs were independently assessed by blinded leishmaniasis experts, who were clinicians experienced in the treatment of CL, with a tiebreaker assessment when needed
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/56 withdrawals. An ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Clinical Trial Registration: ClinicalTrials.gov NCT 00884377; all prespecified outcomes were reported
Other bias	Low risk	Other items assessed correctly reported

Asilian 1995

Methods	*Study design*: randomised controlled trial *Setting/location*: 8 primary health centres around Borkhar, north of Isfahan, Iran *Study period*: 14 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: infections here were thought to be caused entirely by *L major* parasites, although there is probably some *L tropica* infection within the city of Isfahan *Inclusion criteria*: 2 years or older, single lesion that was parasitologically positive, < 5 cm in diameter, at least 3 cm from the eyes, lesion present < 4 months *Exclusion criteria*: pregnant or nursing mothers, previously treated for leishmaniasis, intercurrent illness or a history of allergy to aminoglycoside *N randomised*: 251, aminosidine group: 126 (134 lesions); placebo group: 125 (134 lesions) *Withdrawals*: not described *N assessed*: aminosidine group: 123 lesions; placebo group: 123 lesions *Age (years)*: aminosidine group: < 15 years: 114, >15 years: 12; placebo group: < 15 years: 105, > 15 years: 20 *Sex* (male/female): aminosidine group: 64/62; placebo group: 67/58 *Baseline data*: • 12 to 17 participants had papular lesions; 12 to 16 nodular; 76 to 79 nodule-ulcerative; 11 to 12 flat-ulcerative, and 13 to 20 plaque-like lesions. • *Site of lesion*: aminosidine group: limb: 82, head: 35, trunk: 9; placebo group: limb: 90, head: 28, trunk: 7 • PR (15% aminosidine and 10% urea): MNL: 1, MDLBT: 1.5 weeks • Vehicle: MNL: 1, MDLBT: < 4 weeks

Asilian 1995 (*Continued*)

Interventions	*Type of interventions*: • *Group 1*: paromomycin (PR) (15% aminosidine and 10% urea) in petroleum ointment twice a day • *Group 2*: vehicle *Duration of intervention*: 14 days *Co-interventions*: additional treatment, usually parenteral antimony, was given if lesions were judged to have worsened (25 participants in the PR-treated group and 28 in the placebo group) *Duration of follow-up*: 105 days after starting treatment
Outcomes	*Healing rates*: percentage of participants 'cured' 2.5 months after treatment. Definite cure was defined as complete epithelialisation on days 45 or 105 *Adverse effects* *Tertiary outcomes*: microbiological or histopathological cure of skin lesion Time points reported: 15, 45, 105 days
Notes	*Study funding sources*: this work was supported in part by he UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR) and Isfahan University of Medical Sciences *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation of treatment was carried out in Geneva (Switzerland) but did not state how that was done
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Identical ointment tubes were numbered and allocated to consecutive eligible participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups (16 drops out of 251, 10%)
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified

Asilian 1995 (*Continued*)

Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Asilian 2003

Methods	*Study design*: randomised controlled trial *Setting/location*: 3 primary health centres around Borkhar district north of Isfahan, Iran *Study period*: not described *Sample size calculation*: determined on the basis of a 2-week cure rate of 50% at day 45 and unexpected 4-week cure rate of 70%
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: participants with a single parasitologically confirmed lesion, < 5 cm in diameter *Exclusion criteria*: lesions duration > 4 months and < 2 years, pregnant or nursing mothers, treated previously, any intercurrent illness or history of allergy to aminoglycoside *N randomised*: 233. 117 were allocated to receive 4 weeks of active treatment and 116 to receive 2 weeks of active treatment *Withdrawals*: 17, 9 in 4 weeks of active treatment and 8 in 2 weeks of active treatment *N assessed*: 216, 108 in each group. *Mean age (SD)*: 4 weeks of active treatment: 9.2 years (8.9); 2 weeks of active treatment: 9.0 years (8.8) *Sex ratio (male/female)*: 4 weeks of active treatment: 47/53; 2 weeks of active treatment: 44/56 *Baseline data*: ulcerated lesion (SD): 4 weeks of active treatment 85 (79); 2 weeks of active treatment 95 (88)
Interventions	*Type of interventions*: • *Group 1*: PR (aminosidine) ointment for 4 weeks n = 117. Mean number of lesions: 1. • *Group 2*: PR (aminosidine) ointment for 2 weeks followed by 2 weeks of paraffin = 116. Mean number of lesions: 1 *Co-interventions*: if lesions were bad enough, they were treated with antimonate *Duration of follow-up*: 105 days after starting treatment
Outcomes	*Healing rates*: 'Clinical cure' was defined as > 50% re-epithelialisation of the original lesion, and 'clinical and parasitological cure' as either complete re-epithelialisation or clinical cure plus a parasitologically negative smear. The primary study endpoints were clinical cure and clinical and parasitological cure at day 29, when the 4 weeks of active treatment ended *Adverse effects* *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: days 29, 45, 105
Notes	*Study funding sources*: this investigation was supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases *Possible conflicts of interest*: none declared

Asilian 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list after participants returned their first used tube after 2 weeks
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The vehicle and active ointments looked and smelled identical Outcome is not likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	The clinical and parasitological evaluators were blinded to each other's assessment All efforts were made to reduce the introduction of bias into this study; however, duration of the lesion, which was self-reported by the participants or their guardians, could introduce bias if the durations were significantly different in the 2 arms by chance
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	Other items assessed correctly reported

Asilian 2004a

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Diseases and Leishmania Research Center of Isfahan (Iran) *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* but spp not declared *Inclusion criteria*: confirmed diagnosis parasitologically and clinically, lesions with duration of < 8 weeks *Exclusion criteria*: participants with a history of > 8 weeks, those with allergy to antimonials, lactating or pregnant women

	N randomised participants (lesions): 400 (539). Combined cryotherapy and ILMA: 100 (149), cryotherapy alone: 200 (230), ILMA alone: 100 (160) *Withdrawals*: 30 participants (46 lesions) *N assessed (lesions)*: 370 (493). Group 1: 93 (132); group 2: 185 (210); group 3: 92 (151) *Age*: range 2-65 years. Mean: group 1, 32 years; group 2, 27 years; group 3, 25 years *Sex (male/female)*: 186/184. Group 1, 46/47; group 2, 95/90; group 3, 45/47 *Baseline data*: not described
Interventions	*Type of interventions*: • *Group 1*: combined cryotherapy + ILMA: cryotherapy involved the application of liquid nitrogen via a cotton swab for 10-25 s until the lesion and 1-2 mm of surrounding normal tissue appeared frozen. Then, after thawing, ILMA was administered, enough to blanch the lesion and a 1 mm rim of surrounding normal skin (only participants in groups 1 and 3 received ILMA). Generally, 0.5-2 cm^3 of the solution (Glucantime) was required for individual lesions, depending on their size. • *Group 2*: cryotherapy alone • *Group 3*: ILMA alone Different modalities of treatment were not given to the same participant in different lesions (i.e. each participant received ILMA alone, cryotherapy alone, or combined cryotherapy and ILMA) *Duration of intervention*: fortnightly until complete cure or for up to 6 weeks *Duration of follow-up*: 6 months
Outcomes	*Healing rates*: percentage of participants 'cured' 2.5 months after treatment *Adverse effects*: mild adverse side effects, such as postinflammatory hypopigmentation and hyperpigmentation *Tertiary outcomes*: microbiological or histopathological cure of skin lesions
Notes	*Baseline imbalances*: in number of participants and lesions among the groups *Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 400 patients were randomly divided into three groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "The 400 patients were randomly divided into three groups" Comment: no further information was provided.

Asilian 2004a (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment doesn't appear as blinded and the different treatments are difficult to blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No good information about adverse effects.
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Asilian 2004b

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin and Leishmaniasis Research Center of Isfahan (Iran) *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: not reported *Inclusion criteria*: age 7-70 years, disease confirmed clinically and by laboratory methods, lesions present, surface area of lesions $\leq$ 5 cm² *Exclusion criteria*: disease duration > 4 months; pregnant or breastfeeding; chronic disease; immune suppression; and sporotrichoid forms *N participants randomised (lesions)*: 233 (433). 123 (183) were included in the CO_2 laser group and 110 (250) in the IMMA group *Withdrawals*: 59 (112). CO_2 laser group: 40 (72), IMMA group: 19 (40) *N assessed (lesions)*: 174 (321). CO_2 laser group: 83 (111), IMMA group: 91 (210) *Age*: range 12-60 years *Sex (male/female)*: 55/68 included in the CO_2 laser group; 40/70 in the IMMA group (control group) *Baseline imbalances*: no *Severity Illness*: in 47% of cases, participants had one lesion and in 53% of cases they had 2-5 lesions. There were more lesions on the upper limbs (43%), and lesions were < 5 cm². In the remaining, the lesion duration was 2-4 months Mean number of lesions: CO_2 laser group: 1.49; IMMA group: 2.27
Interventions	*Type of interventions*: • *Group 1*: CO $_2$ laser (30 W, continuous) was applied to the lesion and an area 2-3 mm around it.

Asilian 2004b (*Continued*)

	This procedure was repeated until the ulcer bed turned brown. After completion of the procedure, the ulcer was covered with 2% erythromycin ointment. • *Group 2*: IMMA 50 mg/kg/d for 15 days and after 15 days of rest, this treatment was repeated. *Co-interventions*: in the first group, lesions were locally anaesthetised by injection of 1%-2% lidocaine *Duration of follow-up*: 24 weeks
Outcomes	*Healing rates*: • Percentage of lesions 'cured' 1.5 months after treatment • Speed of healing (time taken to be 'cured') • Prevention of scarring *Adverse effects*
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: none described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: the author was contacted. The randomisation was through coin flip method
Allocation concealment (selection bias)	Unclear risk	Comment: the author was contacted. The randomisation was through coin flip method, but the method to conceal the allocation was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No data provided, but the treatment is unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided about blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in the missing data between the groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Unclear risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Asilian 2006

Methods	*Study design*: randomised controlled trial *Setting/location*: Department of Dermatology, Isfahan University of Medical Sciences (Iran) *Study period*: September 2004 to May 2005 (8 months) *Sample size calculation*: after following a formula, sample size and number of lesions would be a maximum of 20 participants and 40 lesions, respectively, for each group
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: confirmation of typical CL by positive Giemsa-stained direct smear for Leishman-Donovan bodies *Exclusion criteria*: > 2 lesions, lesions with > 20 mm induration diameter, duration of the disease > 2 months, previous use of any anti-leishmanial treatments, pregnant or nursing women, children < 5 years of age, serious concomitant medical problems, history of seizure, photosensitivity *N participants randomised (lesions)*: 60 (99). Photodynamic therapy (PDT): 20 (31); topical paromomycin: 20 (35); vehicle: 20 (33) *Withdrawals* (n = 3): 1 participant with one lesion in topical paromomycin group and 2 participants with 3 lesions (one participant had 2 lesions and the other had one) in vehicle group did not complete the study because they used the ointment irregularly *N assessed (lesions)*: 57 (95). Photodynamic therapy (PDT): 20 (31); topical paromomycin: 19 (34); placebo: 18 (30) *Age*: range 5-59 years. Mean (SD): PDT 22.2 years (15); topical paromomycin: 24.2 years (17); vehicle 22.3 years (15) *Sex (n, (%))*: PDT: female: 12 (60)/male: 8 (40); topical paromomycin: female: 8 (42.1)/male: 11 (57.9); vehicle: female: 11 (61.1)/male: 7 (38.9) *Severity of illness*: the most common sites of lesions (< 10) were on the extremities *Total number of lesions*: PDT 31; topical paromomycin 34; vehicle 30 MNL: PDT 1.55; topical paromomycin 1.75, vehicle 1.65 Mean duration of lesions (SD): PDT 38 days (11); topical paromomycin 35 days (11); vehicle 36 days (11.6)
Interventions	*Type of interventions*: • *Group 1*: PDT (10% 5-aminolevulinic acid (5-ALA) hydrochloride in a water-in-oil cream, applied topically). Lesions irradiated using visible red light at 100 J/cm² per treatment session, repeated weekly for 4 weeks • *Group 2*: PR (15% PR sulphate + 12% MBCL) in a soft white paraffin-based ointment applied topically twice daily at 1 mm thickness over the total surface of the lesion(s) for 28 days. • *Group 3*: vehicle applied twice daily at 1 mm thickness over the total surface of the lesion(s) for 28 days. *Duration of intervention*: 4 weeks *Duration of follow-up*: these groups were followed for 2 months after the end of treatment
Outcomes	*Healing rates*: percentage of lesions 'cured' 2 months after treatment; prevention of scarring *Scale*: 'complete improvement' was defined as loss of induration and other signs of inflammation, complete re-epithelialisation and return to normal skin texture as well as 'parasitological cure', i.e. a negative Giemsa-stained direct smear. 'Partial improvement' was considered as flattening, reduction in size and induration without complete re-

	epithelialisation. All lesions showing no decrease in size or induration were regarded as 'treatment failures' *Adverse effects* *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: days 7, 14, 21, 28, 90
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The participants were randomly divided into three groups of 20 subjects each, using computer-based randomisation."
Allocation concealment (selection bias)	Unclear risk	No information about allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Subjects in both the paromomycin and placebo groups and the clinician treating them were blinded with respect to the topical treatment received. However, it was not possible to blind subjects in the PDT group."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The dermatologist was not aware of the type of the treatment that the patient was receiving."
Incomplete outcome data (attrition bias) All outcomes	High risk	No defaults were included in the analyses. No good information about adverse effects
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	Low risk	Other items assessed correctly reported

Asilian 2014

Methods	*Study design*: randomised, prospective, clinical trial *Setting/location*: Skin and Leishmaniasis Research Center of Isfahan, Barkhar Health Center and Department of Dermatology, Isfahan University of Medical Sciences (Iran) *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: fewer than 4 lesions of < 1 month old and < 3 cm, lesions not located on the face, > 15 years of age, lesions located neither on muscles nor were sporotrichoid lesions; receiving no medication for leishmaniasis *Exclusion criteria*: history of susceptibility to MA or miltefosine; pregnant or breastfeeding; immunosuppressed; had taken systemic medication interfering with p-450 enzyme; or history of kidney, liver, and heart failure *N randomised*: 64. Topical miltefosine: 32, ILMA: 32 *Withdrawals*: 0 *N assessed*: 64 (100%). Topical miltefosine: 32, ILMA: 32 *Mean age (SD)*: 23.12 years (13.30) *Sex*: topical miltefosine: 17 males (53%) and 15 females (47%). ILMA: 16 males (50%) and 16 females (50%) *Baseline data*: mean (SD) size of the lesions before treatment in the group treated with miltefosine and ILMA was 4.4 cm (3.1) and 2.3 cm (2.2), respectively
Interventions	*Type of interventions*: • *Group 1*: topical miltefosine (ointment 6%), once daily (28 days) in a way that the lesion was completely smeared with the ointment • *Group 2*: ILMA, twice a week (up to 28 days) *Duration of intervention*: 28 days
Outcomes	*Clinical cure*: cure of cutaneous leishmaniasis was defined as follows: • Complete cure: the lesion was flat, no induration observed, epidermal crease observed. • Partial cure: reduction in size of the lesions, but no epidermal creases observed. • Uncured: clinically no reduction observed in the lesion size or even an increase in the lesion size observed. *Adverse effects*: participants were questioned about expected adverse effects for 3 days (days 5-7) following administration of the doses. These were considered drug-related if they were not reported at presentation Time points reported: at the end of treatment, 1 month after treatment
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups" Comment: insufficient detail was reported

Asilian 2014 (*Continued*)

		about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open trials. Photography was done from all the lesions both at the first visit and all the follow-up visits
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Protocol not available; not registered; in clinical trial registry; adverse effects not reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Ben Salah 1995

Methods	*Study design*: randomised controlled trial *Setting/location*: Sidi- Bouzid. Tunisia *Study period*: 9 months *Sample size calculation*: the ideal sample size was estimated to be 120 based on a rate of success of treatment of 80%, 30%-45% self-healing in the vehicle group (type I error = 0.01and type II error = 0.10), and 10%-20% loss to follow-up
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: aged 2-60 years, single lesion diagnosed by the presence of parasite in stained dermal smears, no previous anti-leishmanial treatment *Exclusion criteria*: known allergy, adverse reactions to aminoglycoside antibiotics, multiple lesions, an active lesion measuring > 5 cm in diameter, if their ulcerated lesion had already persisted for more than 4 months, lesions < 3 cm from the eye, who by the physician's judgment required systemic antimonial treatment: participants with serious concomitant diseases, under medication for other illnesses likely to interfere with this study; pregnant women or nursing mothers *N randomised*: 132. Paromomycin group: 66; vehicle: 66 *Withdrawals*: 17. Paromomycin group: 9; vehicle: 8 *N assessed*: 115. Paromomycin group: 57; vehicle: 58 *Mean age (SD)*: paromomycin group: 19.2 years (2.31); vehicle: 18.2 years (1.65) *Sex (ratio M:F)*: paromomycin group: 1.04; vehicle: 1.07 *Baseline data*:

	• Location of the lesions: paromomycin group: upper limbs: 47.4%, lower limbs: 38.6% trunk: 5.3%, face: 8.8%. Vehicle: upper limbs: 41.4%, lower limbs: 51.7%, trunk: 3.5%, face: 3.5% • Description of the lesions: paromomycin group: papular: 21.0%, nodular: 21.0%, nodo-ulcerative: 73.7%, flat and ulcerative: 5.2%. Vehicle: papular: 19.0%, nodular: 17.2% nodo-ulcerative: 74.1%, flat and ulcerative 7.0% • Days from appearance of lesion to onset of treatment (mean (SD)): paromomycin group: 39.7 (2.95). Vehicle: 33.5 (2.75)
Interventions	*Type of interventions*: • *Group 1*: 15% PR and 10% urea in soft white paraffin ointment • *Group 2*: vehicle (10% urea in soft white paraffin) *Duration of intervention*: twice daily for 14 days *Duration of follow-up*: 105 days
Outcomes	*Healing rates*: percentage of participants with complete re-epithelisation of the lesion, 2. 5 months after treatment initiation (105 days) *Parasitological cure*: percentage of lesions with negative smear and culture, 2.5 months after treatment initiation (105 days) *Adverse effects* Time points reported: days 15, 45, 105
Notes	*Study funding sources*: this investigation received funding from the United Nations Development Program/World Bank/World Health Organization Special Program for Research and TraininginTropical Diseases(grant ID:TDK910677) *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The tubes containing drug or placebo were supplied by the WHO/TDR, randomly numbered, and were given in numerical order to patients as they were admitted into the study."
Allocation concealment (selection bias)	Low risk	Quote: "The tubes containing drug or placebo were supplied by the WHO/TDR, randomly numbered, and were given in numerical order to patients as they were admitted into the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The code remained unknown to patients and investigators until the study had been completed"

Ben Salah 1995 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The code remained unknown to patients and investigators until the study had been completed"
Incomplete outcome data (attrition bias) All outcomes	High risk	No defaults were included in the analysis
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Low risk	Other items assessed correctly reported

Ben Salah 2009

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Sidi Bouzid,Tunisia, and Paris, France *Study period*: 22 months *Sample size calculation*: the protocol calculated a sample size of 50 participants per group with 80 percent power and a Type I error rate of 5 percent to detect a 30% difference in the proportion of participants achieving CCR, assuming a CCR proportion of 35% in the vehicle group and 65 percent in WR279, 396 participants, with a 5% expected rate of loss to follow-up
Participants	*Type of Leishmania*: *L major*, *L tropica*, *L infantum* *Inclusion criteria*: aged 5-75 years, presence of parasitologically confirmed CL, lesions that were primarily ulcerative (i.e. not purely verrucous or nodular) and measured $\geq$ 1 cm² and $\leq$ 5 cm² *Exclusion criteria*: history of known or suspected hypersensitivity or idiosyncratic reactions to aminoglycoside; previous use of antileishmanial drugs (within 3 months) or nephrotoxic or ototoxic drugs; prior diagnosis of leishmaniasis; more than 5 lesions, or a lesion in the face that in the opinion of the attending dermatologist could potentially cause significant disfigurement; significant medical problems as determined by history or laboratory studies; breastfeeding and pregnancy *N randomised*: 92. WR279,396: 50; vehicle: 42 *Withdrawals* (n = 2): WR279,396: 1; vehicle: 1 *N assessed (%)*: 90 (95.7). WR279,396: 49 (94.2), vehicle: 41 (97.6) *Age < 18 years - n (%)*: WR278,396: 47 (94), vehicle: 33 (79) *Sex*: male: 54, female: 38 *Severity of illness*: *N lesions*: 1: 54, 2: 16, 3: 13, 4 or 5: 9 *Total lesion area (median, IQR)*: WR279,396: 128 (85 to 223), vehicle: 154 (70 to 264) *Index lesion area (median, IQR)*: WR279,396: 92 (55 to 141), vehicle: 115 (50 to 172) *Leishmania spp - n (%)*: *L major*: WR279,396: 32 (64), vehicle: 24 (57). *L Infantum*: WR279,396: 1 (2), placebo: 0 (0). *L tropica*: WR279,396: 1 (2), vehicle: 0 (0). Unidentified: WR279,396: 16 (32), placebo: 18 (43)
Interventions	*Type of interventions*: • *Group 1*: WR279,396 is an off-white to yellowish, thick cream containing 15% (w/w) paromomycin-sulphate (Farmitalia) and 0.5% (w/w) gentamicin-sulphate (Schering) as active components.

	• *Group 2*: the vehicle consisted of a cream without the active components and trace amounts of colorings agents to match the appearance and maintain the blind. *Duration of intervention*: 20 days
Outcomes	*Clinical cure*: defined as complete re-epithelialisation (i.e. length 6 width of ulceration = 060) of the index lesion by day 50 or a 50% re-epithelialisation by day 50 followed by complete re-epithelialisation on or before day 100 with no relapse ever having occurred from day 50 through day 180. Relapse was defined as an increase in the area of ulceration relative to the previous measurement. Participants who did not complete the 180-day period of observation were considered to have failed to achieve complete clinical response (CCR) because relapse could not be fully assessed *Complete clinical response at the index lesion according to baseline characteristics*: influence of baseline factors on effect of treatment. *Time to healing*: time course of complete re-epithelialisation measured at 20, 50, 100, 180 days since start of treatment *Adverse effects*: immediate: observed within 30 min of application. Delayed: observed just prior to next application
Notes	*Study funding sources*: the Office of the Surgeon General (OTSG), Chief, Human Subjects Protection Division, U.S. Army MRMC, Fort Detrick, MD 21702-5012. IND50,098 HSRRB Protocol#1791. Co-sponsor: Institute Pasteur, Rue du Dr. Roux, Paris, France *Possible conflicts of interest*: MG has no financial competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A sequence of genuine random numbers for the randomisation procedure was obtained from the 'fourmilab.ch/hotbits' website by a member of the Department of Chemical Information, Walter Reed Army Institute of Research, Silver Spring, Maryland and purged of duplicates The random numbers are generated by a process which takes advantage of the inherent uncertainty in the quantum mechanical laws of nature. Specifically, they are generated by timing successive pairs of radioactive decays detected by a Geiger-Muëller tube interfaced to a computer. This process is better than the pseudo-random number algorithms typically used in computer programs. The randomisation of the study drugs was done by an independent group, Fischer BioServices, Rockville, Maryland a contractor to The U.S. Army Medical Research Acquisition Activity (USAMRAA), Ft. Detrick, Maryland."

Ben Salah 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	The randomisation of the study drugs was done by an independent group; however, allocation concealment is not fully described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The vehicle lacked the active components and trace amounts of colorings agents to match the appearance and maintain the blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Investigators, who were blinded to whether participants received WR279,396 or placebo-vehicle, evaluated lesions for clinical response on D20 (i.e. the end of the treatment period), D50 (i.e., 30 days after the conclusion of treatment), D100, and D180". Investigators measured all lesions in 2 perpendicular directions and took photographs at the following time points: prior to therapy, at the end of therapy
Incomplete outcome data (attrition bias) All outcomes	Low risk	49 of 50 participants randomised to WR279,396 and 41 of 42 participants randomised to placebo-vehicle completed the study. With one exception, applications of study drugs were conducted according to the protocol
Selective reporting (reporting bias)	Low risk	ClinicalTrials.gov NCT00703924. Prespecified outcomes were reported
Other bias	Low risk	Other items assessed correctly reported

Ben Salah 2013

Methods	*Study design*: randomised controlled trial *Setting/location*: Sidi Bouzid, Tunisia *Study period*: January 2008 to July 2011 (42 months) *Sample size calculation*: the sample size of 375 participants was based on estimated rates of final clinical cure of 94% in the paromomycin - gentamicin group and 71% in the vehicle-control group, as shown in a previous study. On the basis of these rates, a sample size of 125 participants in each of these 2 groups provided a statistical power of 99% to detect a significant difference in the rates of final clinical cure rates (94% vs 71%)
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: aged 5-65 years; good health besides cutaneous leishmaniasis if female; absence of pregnancy and lactation; the presence of $\leq$ 5 lesions, with an index lesion that was ulcerative; lesions measured 1-5 cm in diameter; lesions confirmed to contain

	Leishmania by means of culture or microscopical examination of lesion material *Exclusion criteria*: included clinically significant lymphadenopathy or mucosal involvement, against which a topical agent would not be expected to be effective *N randomised*: 383 (129 were assigned to paromomycin-gentamicin; 128 were assigned to paromomycin; 126 were assigned to vehicle control) *Withdrawals*: 8 participants (4, paromomycin-gentamicin; 3, paromomycin; 1, vehicle control) *N assessed*: 375 participants (125 in each of the 3 groups) *Mean age (SD)*: 24 years (16) (paromomycin-gentamicin, 23 years (16); paromomycin, 25 years (16); vehicle 23 years (15) *Sex*: male 193 (51%) (paromomycin-gentamicin, 56 (45%); paromomycin, 68 (54%); vehicle control, 69 (55%)) *Baseline data*: • Paromomycin-gentamicin: total N of lesion in group: 243. Mean (SD) area of all lesion ulcers per participants: 126 mm² (121) • Paromomycin: total N of lesion in group: 272. Mean (SD) area of all lesion ulcers per participants: 90 mm² (75) • Vehicle control: total N of lesion in group: 282. Mean (SD) area of all lesion ulcers per participants: 98 mm² (112)
Interventions	*Type of interventions*: • *Group 1*: paromomycin-gentamicin topical cream were manufactured by Teva Pharmaceuticals in accordance with Good Manufacturing Practices • *Group 2*: paromomycin alone topical cream were manufactured by Teva Pharmaceuticals in accordance with Good Manufacturing Practices • *Group 3*: vehicle control manufactured by Teva Pharmaceuticals in accordance with Good Manufacturing Practices *Duration of intervention*: 20 days
Outcomes	*Final cure of index lesion* *Total re-epithelialisation of ulcerated lesions at 42 days* *Adverse effects* Time points reported: 168 days
Notes	*Study funding sources*: the study was sponsored by the Office of the Surgeon General, Department of the Army *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A permuted block randomisation schema was generated using nQuery, employing random block sizes, for the first 330 randomisation numbers. As 7 subjects were randomised that did not receive treatment at the time when the new randomisation list was generated, the plan in generat-

Ben Salah 2013 (*Continued*)

		ing the new list was to balance the assignments in the new list for these 7 subjects to achieve the 1:1:1 allocation balance overall. The second randomisation was performed using SAS Version 9.2."
Allocation concealment (selection bias)	Low risk	The randomisation of the study drugs was done by an independent group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The placebo consisted of the vehicle without the active components and trace amounts of colorings agents to match the appearance and maintain the blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The modified intention-to-treat population consisted of patients who received at least one dose of study treatment. We tested two hypotheses using a fixed testing-sequence procedure with an overall two-sided alpha level of 0.05 or less."
Selective reporting (reporting bias)	Low risk	ClinicalTrials.gov number, NCT00606580. Pre-specified outcomes were reported
Other bias	Low risk	Other items assessed correctly reported

Bumb 2013

Methods	*Study design*: randomised, phase I, open-label, clinical trial *Setting/location*: Department of Dermatology at SP Medical College and PBM Hospital, Bikaner, India *Study period*: June 2009 to December 2010 (19 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: aged ≥ 4 years, 4 or fewer lesions, a parasitologically confirmed diagnosis of CL by demonstration of organisms (*L tropica* bodies) in the lesion smear or biopsy *Exclusion criteria*: included lesion size > 5 cm diameter, prior treatment failure with SSG, treatment for CL within 2 months of enrolment into the study, any chronic condition that might prevent the patient from completing the study therapy and subsequent follow-up *N randomised*: 100; radiofrequency-induced heat therapy (RFHT): 50; ILSSG: 50

	Withdrawals: not described *N assessed*: 100 *Median (range) age*: RFHT: 20 years (4-70); ILSSG: 20.5 years (4-85) *Sex*: RFHT: male 27, female 23; ILSSG: male 20, female 30 *Baseline data*: • Number of lesions: median (range); RFHT: 1 (1-7); ILSSG: 1 (1-4) • Number of lesions per participant (%): 1 lesion: RFHT, 30 (60); ILSSG: 32 (64). 2 lesions: RFHT, 14 (28); ILSSG: 13 (26). > 2 lesions: RFHT, 6 (12); ILSSG, 5 (10) • Median size of lesions (range): RFHT, 2 cm (0.5-5); ILSSG, 2 cm (0.5-14) • Median duration of illness (range): RFHT, 3 months (1-9); ILSSG, 3 months (1-18)
Interventions	*Type of interventions*: • *Group 1*: the RFHT group received a single application of a controlled and localised delivery of radiofrequencies into lesions for 30-60 s depending on the thickness of the lesion. The application was performed under local anaesthesia (1% lidocaine) using a current field radiofrequency generator (ThermoMed 1.8) • *Group 2*: ILSSG group, the participants were treated with an intralesional injection of SSG (50 mg/cm² of lesion), twice a week for 7 injections *Duration of intervention*: RFHT, 5 days; ILSSG, 4 weeks *Co-interventions*: all participants were prescribed oral nonsteroidal anti-inflammatory drugs and topical antibacterial cream (fusidic acid cream) for 5 days
Outcomes	*Cure rate*, assessed as follows: • Complete cure: the total re-epithelialisation of the lesions • Partial cure: decreased induration and erythema Time points reported: 6, 8, 10, 12, 16, and 20 weeks after the initiation of treatment, and at 5, 6, 9, 12 and 18 months post-treatment
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were N randomised in a 1:1 ratio" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated

Bumb 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The clinician who recorded healing was blinded to the modality of treatment." Comment: not clear how the assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No information about numbers or reasons for withdrawals during treatment. It seems that there was withdrawals only in the follow-up: 44% at 18 months in RFHT group and 16% at 18 months in the SSG group. Losses to follow-up were heterogeneous between groups and no ITT analyses were performed
Selective reporting (reporting bias)	Low risk	Outcomes of interest were reported in results
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Daie Parizi 2015

Methods	*Study design*: randomised single blind parallel clinical trial *Setting/location*: Leishmaniasis Center in Dadbin Health Care Clinic in Kerman, Iran *Study period*: 15 months. Participants recruitment: 8 months (December 2012 to August 2013) *Sample size calculation*: based on the data from previous study, and by considering the confidence interval of 95%, sample size was determined as 23 lesions per group. Regarding to a possible loss in follow-up period, finally 32 lesions were allocated in each group
Participants	*Type of Leishmania*: *L amastigote* (Leishman-Donovan bodies) *Inclusion criteria*: positive direct smear or documented skin biopsy for *L amastigote* (Leishman-Donovan bodies), > 2 years of age, no previous therapy for leishmaniasis, ulcerated lesions for those lesions that were included in Thio-Ben + cryotherapy (TC) group *Exclusion criteria*: pregnancy, lesions on the eyelids and lips, having more than 5 lesions, positive history of confirmed immunodeficiency disorders or immunosuppression, disease duration for more than a year, positive history of allergy or hypersensitivity to thioxolone, benzoxonium chloride, or pentavalent antimony compounds *N randomised*: 64 lesions of 47 participants, Thio-Ben + cryotherapy (TC) group (32 lesions, 22 participants), ILMA (32 lesions, 25 participants) *Withdrawals*: 16 lesions of 9 participants (10 lesions from TC and 6 from ILMA group) were removed from the study arms because of their poor adherence to the trial protocol and lost to follow-up. Additionally, one participant (with one lesion) was excluded because of developing a hypersensitive reaction to MA in the course of the treatment *Lesions assessed*: 48 lesions in 47 participants. TC: 22, ILMA: 25 *Mean age (SD)*: TC 23.5 years (16.4), ILMA 25.4 years (19.4)

	Sex (n (%)): TC: male 6 (27.2%), female: 16 (72.7%); ILMA: male 19 (76%), female: 6 (24%) *Baseline data*: • Location of lesion: TC: face 5 (22.7%), elbow 1 (4.5%), hand 13 (59.1%), foot 1 (4.5%), ear 1 (4.5%), arm 1 (4.5%), neck 0. ILMA: face 6 (24%), elbow 3 (12%), hand 10 (40%), foot 2 (8%), ear 1 (4%), arm 2 (8%), neck 1 (4%) • Mean (SD) duration of disease: TC, 4.1 months (2.9); ILMA, 3.1 months (2.4)
Interventions	*Type of interventions*: • *Group 1*: 1-2 mL of tincture of Thio-Ben (depending on the size of the lesion) topically by a cotton swab that was held with a mild pressure on the lesion for about 3-4 min, every other day • *Group 2*: ILMA containing 8.1% Sb5+ (81 mg/mL), once a week with the dose of 0.5-2 mL per lesion *Co-intervention*: in addition, at the beginning, and then every 2 weeks, cryotherapy with liquid nitrogen (−195°C) was performed for all lesions in both groups *Duration of intervention*: 3 months or until the lesion was cured, whichever came first *Duration of follow-up*: 6 months after the termination of the treatment to evaluate the incidence of relapse (reported at 1 month, 2 months, 5 months)
Outcomes	*Clinical cure of the lesions*: • Complete cure: complete subsidence of induration and re-epithelialisation of the lesion • Partial cure: reduction of the size of lesion by 50% and more • Improvement: reduction of the size of lesion by less than 50% • No response: no significant reduction of the size of lesion • Deterioration: any increase in the size of the lesion *Adverse effects* *Relapse*: participants that developed with relapse of the lesions at the previously involved area Time points reported: clinical cure was reported when it occurs or for a maximum of 3 months *Adverse effects* were assessed at follow-up during therapy; they were the safety endpoints of the treatments, and 6 months after the termination of the treatment
Notes	*Study funding sources*: this study was supported and funded by the Vice Chancellor for Research, Kerman University of Medical Sciences. The founder had no financial or proprietary interest in any material or method used in this study and had no role in study design, data collection and analysis, or preparation of the manuscript *Possible conflicts of interest*: no conflict of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised allocation was performed by blocked randomisation method with block size of 2

Daie Parizi 2015 (*Continued*)

Allocation concealment (selection bias)	Low risk	Randomised allocation was performed by blocked randomisation method and was prepared by the analyst of the research team who had no clinical involvement in the trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was impossible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessing the outcomes and data analyst were blinded to group assignment. The photographs were reviewed by the dermatologist of the research team who was blinded to study groups. The photographs did not contain any indicator that could help differentiate the group of the lesion
Incomplete outcome data (attrition bias) All outcomes	High risk	The numbers of withdrawals were high in both groups: 31.25% (10/32) in TC group and 18.75 % (6/32) in the ILMA group. Participants were removed from the study arms because of their poor adherence to the trial protocol and lost to follow-up. No intention-to-treat analysis was done
Selective reporting (reporting bias)	Low risk	The study published reported our outcomes
Other bias	Low risk	Other items assessed correctly reported

Dandashli 2005

Methods	*Study design*: randomised controlled trial *Setting/location*: Aleppo, Syria *Study period*: June 2009 to December 2010 (19 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: not described *Exclusion criteria*: not described *N randomised*: 79 *Withdrawals*: 14 *N assessed*: 65. 46 participants (264 lesions) in the fluconazole group and 19 participants (102 lesions) in the placebo group *Age (years)*: not described *Sex*: not described *Baseline data*: not described

Dandashli 2005 (*Continued*)

Interventions	*Type of interventions*: • *Group 1*: fluconazole orally 200 mg/d for 6 weeks • *Group 2*: placebo orally for 6 weeks *Duration of follow-up*: not reported
Outcomes	*Healing rates*: percentage of lesions 'cured' (follow-up not reported) *Adverse effects* Time points reported: not described
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared This is an abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned to treatment" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly assigned to treatment" Comment: no further information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information about blinding was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information about blinding was provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Side effects were mild and similar in both groups" Comment: no further information on adverse effects was provided. Withdrawals: 14/79 (17.7%) and no ITT analyses were performed
Selective reporting (reporting bias)	Unclear risk	No protocol available. Not possible to allocate to high or low risk
Other bias	High risk	Sample size calculation and baseline comparability were not correctly reported

Dastgheib 2012

Methods	*Study design*: prospective randomised controlled trial *Setting/location*: dermatology clinic in Saadi Hospital, an academic center in Fars Province, Iran *Study period*: December 2008 to March 2010 (15 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: participants that presented with skin lesions suspicious of CL, not receiving any previous treatment, positive for leishmaniasis with direct smears *Exclusion criteria*: pregnant and nursing women; children < 12 years old; lesions on the face; disease for more than 3 months; more than 5 active lesions; participants with any serious systemic disease or previous history of sensitivity to MA, allopurinol, or azithromycin; any difficulty in laboratory results before initial treatment (CBC diff, LFT, BUN, Cr); those who refused to sign the written informed consent form *N randomised*: 86 participants *Withdrawals*: 14 participants (6 in azithromycin + allopurinol group and 8 IMMA group) one lost follow-up because of adverse effect *N assessed*: 71 participants (36 azithromycin + allopurinol group and 35 IMMA group) *Mean age (SD; range)*: 38.2 years (12.6); range 16-64. Azithromycin + allopurinol group: 39.7 years (12.6); IMMA: 36.8 years (12.8) *Sex*: 28 females and 53 males (azithromycin + allopurinol group: 13 females and 23 males; IMMA group: 15 females and 20 males *Baseline data*: most participants in azithromycin + allopurinol group had more than 3 lesions (72.3%) and in the IMMA group most participants also had more than 3 lesions (65.8%)
Interventions	*Type of interventions*: • *Group 1*: azithromycin capsules (Tehran Chemie Pharmaceutical Company, Tehran, Iran) at a daily dose of 10 mg/kg (maximum dose of 500 mg) + allopurinol tablets (Hakim Pharmaceutical Company, Tehran, Iran) at a daily dose of 10 mg/kg (maximum doses 800 mg) • *Group 2*: IMMA (Aventis Laboratories, France) at a dose of 20 mg/kg of antimony *Duration of intervention*: group 1, 2 months; group 2, 20 days. *Co-interventions*: in case of any secondary bacterial infection, participants were with oral cephalexin for 10 days after which the antileishmanial was administered
Outcomes	*Cure rate*, assessed as follows: • Complete response: complete re-epithelialisation and relief of induration • Partial response: more than 50% re-epithelialisation and decrease of induration and size of lesion • No response: < 50% decrease of induration and size of lesion or worsening of lesion was considered as no response *Adverse effects* Time points reported: 2 months after completing treatment
Notes	*Study funding sources*: funded by deputy of research, Shiraz University of Medical Sciences *Possible conflicts of interest*: none declared
Risk of bias	

Dastgheib 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A total of 71 participants who met the inclusion criteria in the trial were randomly divided into two treatment groups according to simple even and odd number allocation"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Fourteen of 86 patients dropped out due to poor compliance (six patients in the combination therapy and eight in the Glucantime group). The number and reason for their withdrawal were almost the same in both treatment groups. One patient also developed GI complications and headache while taking the combination therapy of azithromycin and allopurinol; therefore, overall 71 subjects completed the study." Comment: no ITT analyses were performed. However, withdrawals accounted for <20% and were homogeneous among the treatment groups
Selective reporting (reporting bias)	Low risk	Our primary outcomes (cure and adverse effects) were described in Methods and reported in Results
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Dogra 1990

Methods	*Study design*: randomised controlled trial *Setting/location*: India *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropic*a in the area *Inclusion criteria*: participants with cutaneous *Leishmania* confirmed by the presence of *L tropic*a bodies in the slit skin smear stained with Leishman stain. *Exclusion criteria*: women of child-bearing age *N randomised*: 20 *Withdrawals*: 0 *N assessed*: 20 (100%). Intervention group: 15, control group: 5 *Age*: range 14-56 years. *Baseline data*: single or multiple lesions, the duration of the lesions varied from 4 to 16 weeks
Interventions	*Type of interventions*: • *Group 1*: itraconazole orally 4 mg/kg per day for 6 weeks (max 200 mg). MNL: 2. MDLBT: 9 weeks • *Group 2*: control group (no treatment) *Duration of follow-up*: 6 weeks, but 3 months for relapses assessment
Outcomes	*Primary outcome*: percentage of participants 'cured' at the end of treatment. The essential criteria for declaring the participant was cured was complete disappearance of the induration or redness in the nodular form and complete healing in the ulcerative form, accompanied by smear positivity conversion *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur within 3 months *Adverse effects* *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: clinical cure: 4 weeks, clinical and parasitological cure: 6 weeks
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Proportion of 2 to 4:1 Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment

Dogra 1990 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Selective reporting (reporting bias)	Unclear risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Dogra 1991

Methods	*Study design*: randomised controlled trial *Setting/location*: India *Study period*: not described *Sample size calculation*: the number of subjects was determined by the standard method of Schork 1967
Participants	*Type of Leishmania*: *L tropic*a in the area *Inclusion criteria*: demonstration of *Leishmania* from skin lesion by the slit smear technique. *Exclusion criteria*: pregnant women and children < 12 years old, suffering from any chronic illness, immunocompromised, allergic to sulphones, prior therapy for cutaneous *Leishmania* in any form, patients with scars of healed leishmanial lesions, lesions of > 4 months duration *N randomised*: 120. 60 in each group *Withdrawals*: 0 *N assessed*: 120 (100%), 60 in each group *Age*: range 15-56 years *Sex*: 52 males/68 females *Baseline data*: the duration of the lesions ranged from 3 weeks to 3 months. Lesions were situated mainly on the exposed parts of the body (face, arms and feet). 46 participants (24 in dapsone group and 22 in placebo group) had a single lesion while 74 participants had multiple lesions (maximum 13)
Interventions	*Type of interventions*: • *Group 1*: dapsone tablets (100 mg) • *Group 2*: placebo tablets *Duration of intervention*: every 12 h for 6 weeks

Dogra 1991 (*Continued*)

	Duration of follow-up: 6 weeks
Outcomes	*Primary outcome*: percentage of participants 'cured' at the end of treatment *Secondary outcome*: adverse effects *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: clinical response: days 15 and 45. Clinical and parasitological response: 6 weeks
Notes	*Informed consent obtained*: yes *Study funding sources*: - *Possible conflicts of interest*: -

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "... and was randomly allocated to receive either tablets of dapsone (100 mg) or placebo tablets which were identical in appearance" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "... and was randomly allocated to receive either tablets of dapsone (100 mg) or placebo tablets which were identical in appearance" Comment: no further information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind therapeutic trial" Comment: participants looks like blinded but no description about personnel blinding were provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind therapeutic trial" Comment: no further information about blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All relevant outcome data were provided
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Dogra 1992

Methods	*Study design*: randomised controlled trial *Setting/location*: India *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* in the area *Inclusion criteria*: participants with localised CL and only smear positive cases *Exclusion criteria*: not being smear positive *N randomised*: 60, 20 in each group *Withdrawals*: 0 *N assessed*: 60 (100%), 20 in each group *Age (years)*: ≥ 15 years *Sex*: not described *Severity of illness*: 8, 11, and 12 participants had multiple lesions in the itraconazole, dapsone and placebo groups respectively
Interventions	*Type of interventions*: • *Group 1*: itraconazole 4 mg/kg/d (max. 200 mg) • *Group 2*: dapsone 4 mg/kg in 2 doses/d • *Group 3*: placebo control group *Duration of intervention*: 6 weeks *Duration of follow-up*: 6 weeks, but 3 months for assessment of relapses
Outcomes	*Healing rates*: percentage of participants 'cured' at the end of treatment. Strict clinical and parasitological criteria were followed to asses cure *Adverse effects* Time points reported: healing rates at the end of treatment
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Dogra 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Dogra 1996

Methods	*Study design*: randomised controlled trial *Setting/location*: India *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*:*L major and tropica* in the area *Inclusion criteria*: participants with localised CL. Demonstration of parasites from skin lesions by slit smear examination *Exclusion criteria*: women of child-bearing age, children < 18 years old, participants suffering from any chronic illness, immunocompromised, prior therapy for CLs in any form, scars of healed leishmanial lesions, lesions of 4 months or more duration, participants showing abnormality in liver function tests *N randomised*: 20 *Withdrawals*: 0 *N assessed*: 20 (100%) *Age*: range 19-62 years *Sex*: 15 males/5 females *Baseline data*: the duration of the lesions ranged from 2 weeks to 16 weeks, they were mainly seen on exposed parts of the body. 9 had a single lesion and 11 participants had a multiple lesion
Interventions	*Type of interventions*: • *Group 1*: itraconazole orally (2 100 mg capsules) for 6 weeks n = 10. 4/10 participants had single lesions. • *Group 2*: placebo orally (2 capsules) for 6 weeks n = 10. 5/10 participants had single lesions. *Duration of intervention*: 6 weeks *Duration of follow-up*: 3 months
Outcomes	*Primary outcome*: percentage of participants 'cured' 3 months after treatment *Secondary outcome*: adverse effects *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: clinical response: day 15. Clinical and parasitological response: 6 weeks
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Dogra 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated randomly to receive capsules of itraconazole 100 mg or identical placebo" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were allocated randomly to receive capsules of itraconazole 100 mg or identical placebo" Comment: no further information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind therapeutic trial" Comment: participants looks like blinded but no description about personnel blinding was provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind therapeutic trial" Comment: participants looks like blinded but no description about assessment blinding was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability was not correctly reported

Ejaz 2014

Methods	*Study design*: randomised controlled trial *Setting/location*: Pakistan at dermatology departments of Combined Military Hospital, Kharian Camtonment, Combines Military Hospital, Quetta and Combined Military Hospital, Muzaffarabad *Study period*: January 2008 to December 2010 (35 months) *Sample size calculation*: assuming equal-sized groups, keeping the equivalence trial design, standardised difference of 0.05 and power at 90%, sample size was calculated as 150 participants in each arm using Altman nomogram. A total of 300 participants were needed for the study and 24 extra participants were recruited to cater for dropouts
Participants	*Type of Leishmania*: not described *Inclusion criteria*: men and women over 18 years of age having parasitologically proven CL requiring systemic therapy, willing for admission to hospital for the study and regular follow-up visits, and consenting not to use any other treatment for CL during trial *Exclusion criteria*: pregnant, compromised immune system (i.e. diabetics or cancer patients), diffuse cutaneous or visceral leishmaniasis, complete or incomplete treatment with antimony compounds in the last 3 months, history of hepatic, renal, or cardiovascular disease *N randomised*: 324. Group 1: 151; group 2: 173 *Withdrawals*: not described *N assessed*: 324 (100%) *Age*: mean 27.9 years (SD 6.5), range 17-48 years *Sex*: all were male soldiers *Baseline data*: most participants (39.2%) had a single lesion, but one participant had 15 lesions. Maximum lesions were found on exposed parts of body, arms and legs accounted for 42.3% and 47.2% of lesions respectively. Plaques were the most common morphological pattern seen (82.7%) Mean (SD) size of lesions at baseline was 28.8 mm (16.1). Group 1: 29.7 mm (16.4); group 2: 28 mm (15.8). Mean induration at baseline was 17.5 mm (11.6). Group 1: 17.7 mm (11.5); group 2: 18 mm (12.8)
Interventions	*Type of interventions*: • *Group 1*: IMMA (Glucantime, Lot No. 888, Aventis Laboratories, France) 20 mg/kg/d until clinical resolution or for 28 days maximum • *Group 2*: IMMA 10 mg/kg/d + oral allopurinol (Zyloric - 300, Batch No. 2ZMAF, GlaxoSmithKline Pakistan Limited) 20 mg/kg/d *Duration of intervention*: 28 days maximum
Outcomes	*Successful treatment*: was defined as complete re-epithelialisation of the ulcer and disappearance of the induration, or reduction of more than 50% of the ulcer and the indurations areas in relation to the last clinical evaluation *Adverse effects*: serious adverse event was defined as life-threatening, or prolongation of existing hospitalisation, or causing persistent or significant disability. Non-serious adverse effects, not qualifying the above criteria were clinically judged by the investigator to be definitely related, probably related, possibly related, or not related to the trial medication Time points reported: follow-up phase lasted 6 months
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Ejaz 2014 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Simple randomisation through a random number table and allocation ratio being 1: 1
Allocation concealment (selection bias)	Unclear risk	"Randomisation sequence generation and allocation of medicine was done by lead investigators at the three research set ups" Comment: no information on the method of allocation concealment was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded from the treatment groups; however, it is not clear how this was done. No placebo was provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were 18 dropouts due to various complications, 9 belonging to each group" Comment: ITT analyses were performed.
Selective reporting (reporting bias)	Unclear risk	Protocol not available. The trial was registered with www.anzctr.org.au and the registration number is ACTRN12607000295448. Some outcomes registered in the protocol were not reported: successful treatment; therapeutic failure; reactivation
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

El-Sayed 2010

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: the Saudi Hospital in Sanaa, Yemen *Study period*: 21 months; participants recruited from June 2006 to June 2007 *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp *Inclusion criteria*: all had the clinical signs of cutaneous leishmaniasis and a majority of their cutaneous lesions were found smear positive for mastigotes. 4 participants with a negative smear preparation were diagnosed by tissue culture using NNN (Novey, McNeal and Nicolle) medium *Exclusion criteria*: skin lesions of more than 8 weeks duration, allergic to antimonial drugs, lactating or pregnant *N participants randomised (lesions)*: N = 30: ILSSG, n = 10 participants (12 lesions), ILSSG + IMSSG, n = 10 (15), ILSSG + oral ketoconazole: n = 10 (13) *Withdrawals*: no *N assessed*: 30 (100%) *Age*: range 12-50 years (mean 23.5, SD 14). Group 1: 12-50 (24.3, SD 15); group 2: 13-48 years (22.5, SD 14); group 3: 12-49 years (25.1, SD 12) *Sex (male/female)*: group 1, 5/5; group 2, 7/3; group 3, 4/6 *Baseline data*: • Group 1: duration of disease (weeks) 2-5. Site: face 10, upper extremities: 2. Type of ulceration: nodules 5, plaques 7 • Group 2: duration of disease (weeks) 3-7. Site: face 14, upper extremities: 1. Type of ulceration: nodules 8, plaques 7 • Group 3: duration of disease (weeks) 2-8. Site: face 12, upper extremities: 1. Type of ulceration: nodules 6, plaques 7
Interventions	*Type of interventions*: • *Group 1*: ILSSG (100 mg/mL) alone, following a treatment schedule on alternate day's injection • *Group 2*: ILSSG + IMSSG injections. A part of the dose (calculated as 20 mg/kg/d) was injected intralesionally on days 1, 3, 5 as in group 1. The remaining amount of the total dose was given intramuscularly simultaneously on the same day. • *Group 3*: ILSSG as in group 1 + oral ketoconazole (200 mg 3 times daily) for 4 weeks *Duration of intervention*: in all groups, treatment was continued until clearance or for a maximum of 3 treatment cycles at 4 week intervals (12 weeks) *Follow-up*: performed monthly for 6 months after the last treatment
Outcomes	*Clinical cure*: the cure was indicated by complete re-epithelialisation, the disappearance of oedema, induration and other signs of inflammation and a negative Giemsa-stained direct smear of a scraping of the skin at the lesion site. In the 4 participants diagnosed only by a positive culture before enrolment, the cure was indicated by a negative culture at the end of the 12 weeks *Adverse effects* Time points reported: 4, 8, 13 weeks. Adverse effects: at the end of treatment
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

El-Sayed 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "A follow-up assessment was performed by the treating clinician, the patient and by comparing the serial photographs" Comment: open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Emad 2011

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: PCR-proven *L major* cutaneous infection, age > 12 years, not using anti-*Leishmania* therapies during the past 2 months, duration of lesions < 4 moths *Exclusion criteria*: pregnancy, breastfeeding, presence of lesions on ears and/or face, number of lesions >10, history of liver or kidney disease *N randomised*: 120 participants (fluconazole 200 mg: 60; fluconazole 400 mg: 60) *Withdrawals*: 2 in the 400 mg group *N assessed*: 118 participants *Mean (SD) age*: fluconazole 200 mg, 36.45 years (15.34); fluconazole 400 mg, 35.38 years (13.81) *Sex (male/female)*: 65/55 (fluconazole 200 mg, 30/30; fluconazole 400 mg, 35/25) *Baseline data*: • Mean number of lesions (SD): fluconazole 200 mg, 3.10 (2.08); fluconazole 400

	mg, 3.21 (2.09) • Mean duration of lesions (SD): fluconazole 200 mg, 7.12 weeks (2.51); fluconazole 400 mg, 7.43 weeks (2.6) • Size of lesions (SD): fluconazole 200 mg, 19.84 mm (8.97); fluconazole 400 mg, 21.87 mm (8.93)
Interventions	*Type of interventions*: • *Group 1*: high dose fluconazole 200 mg twice daily • *Group 2*: low dose fluconazole100 mg twice daily *Duration of intervention*: 6 weeks
Outcomes	*Complete healing*: defined as complete re-epithelialisation of the lesions at intervals of 2, 4 and 6 weeks *Adverse effects* Time points reported: 6 weeks
Notes	*Study funding sources*: grant from Shiraz University of Medical Sciences, Shiraz, Iran *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were then randomized into two equal groups to receive either fluconazole 100 mg or 200 mg twice daily. " Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts were reported in the fluconazole 400 mg group. ITT analysis were performed
Selective reporting (reporting bias)	Unclear risk	Our primary outcomes (Complete healing and adverse effects) were described in Methods and reported in Results

Emad 2011 (*Continued*)

Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Esfandiarpour 2002

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* in the area *Inclusion criteria*: positive direct smear or documented skin biopsy, not pregnant or nursing at the time of therapy, no serious systemic illness, no sensitivity to antimonial drugs or AL *Exclusion criteria*: not having received treatment for at least 2 months before entry into the study *N randomised*: 150. 50 in each group *Withdrawals*: 0 *N assessed*: 150 (100%). 50 in each group *Age*: mean age 14 years. Group 1 (AL): 14, group 2 (IMMA): 14.5, group 3 (AL + IMMA): 14 *Sex*: male/female: 69/81. 23/27 in each group *Baseline data*: the common sites of involvement were the face and extremities. By groups were as follows: oral AL: face: 62%; upper limbs: 34%; lower limbs: 4%, and trunk: nil. IMMA: face: 48%; upper limbs: 38%; lower limbs: 14%, and trunk: nil. AL + IMMA: face: 78%; upper limbs: 15%; lower limbs: 6%, and trunk: 2%. Most participants had plaque-type, papular, and nodular lesions. By groups: AL: plaque: 64%, papule: 29%, and nodule: 7%. IMMA: plaque: 71%, papule: 18%, and nodule: 11%. AL + IMMA: plaque: 77%, papule: 19%, and nodule: 4% Mean number of lesions: group 1, 1.5; group 2, 1.8; group 3, 1.4. Most had multiple lesions ($\leq$ 7 lesions) Mean duration of lesions: group 1, 8 months; group 2, 7.4 months; group 3, 8 months
Interventions	*Type of interventions*: • *Group 1*: AL orally 15 mg/kg/d for 3 weeks • *Group 2*: IMMA 30 mg/kg/d for 2 weeks • *Group 3*: AL + IMMA simultaneously *Duration of follow-up*: one month
Outcomes	*Primary outcome*: percentage of participants 'cured' at the end of treatment. The response to treatment was graded as excellent (reduction in the size of the lesion by at least 80% or complete clearance), good (reduction in the size of the lesion by 50%), and poor (minimal or no change in the lesion) *Secondary outcome*: adverse effects Time points reported: end of treatment and 2 and 4 weeks later

Esfandiarpour 2002 (*Continued*)

Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomly divided into three groups." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "the patients were randomly divided into three groups." Comment: no further information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: the treatment it is not possible to blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no reference to the outcome assessment blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing outcome data
Selective reporting (reporting bias)	High risk	Comment: no reference to adverse effects
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Faghihi 2003

Methods	*Study design*: randomised controlled trial *Setting/location*: Isfahan, Iran *Study period*: 15 months *Sample size calculation*: yes
Participants	*Type of Leishmania*: *L major* is endemic in Isfahan *Inclusion criteria*: clinical and parasitological diagnosis of CL *Exclusion criteria*: pregnant or had > 3 lesions, ulcerative lesions, lesions with cartilage or lymphatic involvement or hypersensitivity to the drug *N randomised*: 96 participants, 48 in each group *Withdrawals*: 0

Faghihi 2003 (*Continued*)

	N assessed (lesions): 96 (190). 48 (95) in each group *Age (years)*: age range 1-48 years (mean age of 16 years old and a median of 14.5 years) *Sex*: male/female: 40/56 *Baseline data*: all lesions treated were papules or early nodules with mean diameter of about 4 mm. Mean number of lesions per person in each group: 1
Interventions	*Type of interventions*: • *Group 1*: 15% PR sulphate and 10% urea in Eucerin ointment, applied twice daily at 1 mm thickness over the total surface of the lesion(s) • *Group 2*: ILMA injections of 1.5 g/5 mL (maximum 12), weekly. The mean amount of solution required for each lesion was 0.2 mL to 0.8 mL. *Duration of intervention*: treatment was continued in both groups for 3 months or until complete recovery (return to the normal tissue texture without any atrophic changes or scar formation) *Duration of follow-up*: one year
Outcomes	*Primary outcome*: percentage of participants 'cured' within 2 months after treatment. Complete recovery or cure was defined as re-epithelialisation and return to normal tissue texture in less than 2 months, with no residual scar or relapse after follow-up of up to 1 year *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur within one year; prevention of scarring Time points reported: completely recovered (cured) (< 2 months). Healed (in 2-3 months)
Notes	*Study funding sources*: Isfahan University of Medical Sciences (Pharmacy College and its Research Laboratory) and the Amin Leishmaniasis Research Group in Isfahan City *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "In the period of recruitment, […] they were randomised by fixed block random allocation"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment description do not appear as blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	In statistical methods section, quote "There was no blinding method used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Faghihi 2003 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Farajzadeh 2015

Methods	*Study design*: randomised controlled trial *Setting/location*: Afzalipour Hospital, Kerman University of Medical Sciences, Iran *Study period*: 1 year (2011-12) *Sample size calculation*: a sample size of 40 participants per treatment group was planned, a probability of a type I error at alpha = 0.05 and beta = 0.1 to determine a 20% difference between topical terbinafine compared with control group
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: participants between 2-60 years and without serious medical illness were included, not have received any other leishmanicidal treatment during last 3 months, duration of their lesions should be less than 6 months *Exclusion criteria*: cardiac, hepatic, renal and other systemic diseases; pregnant and nursing women; hypersensitivity to trial drugs *N randomised*: 80, 40 in each group *Withdrawals*: 0 *N assessed*: 80, 40 in each group *Mean (SD) age*: terbinafine: 16.3 years (14.8), IMMA: 20.74 years (19.4) *Sex (n, %)*: terbinafine: male 18 (45); female 18 (45); the sex of 4 (10) participants was unknown. IMMA: male: 16 (40); female: 18 (45); the sex of 6 (15) participants was unknown *Baseline data*: • Mean duration of lesions (SD): terbinafine: 3.97 months (0.3). IMMA: 3.81 months (0.3) • Mean number of lesions (SD): terbinafine: 1.85 (1.3). IMMA: 1.93 (1.16) • Mean size of lesions (SD): terbinafine: 4.15 mm^2 (5.97). IMMA: 5.21 mm^2 (10.65) • The most frequent location of the lesions was on participants' face (terbinafine: n = 99, 45.8% vs IMMA: n = 93, 50%)
Interventions	*Type of interventions*: • *Group 1:* oral terbinafine, 125 mg/d (for less than 20 kg body weight), 250 mg/d (20-40 kg body weight), 500 mg/d (for more than 40 kg body weight) • *Group 2*: 15 mg/kg/d IMMA (Glucantime; Haupt Pharma in France) *Co-interventions:* Both groups received cryotherapy every 2 weeks for 4 weeks *Duration of intervention*: group 1: 4 weeks, group 2: 3 weeks *Duration of follow up:* patients were followed monthly for 3 months after the treatment
Outcomes	*Clinical cure*: clinical response was determined based on the following criteria: • Complete improvement (decrease in induration size > 75%) • Partial improvement (decrease in induration size between 25% and 75%)

	• No improvement (decrease in induration size < 25%) *Time to clinical cure*: development of oartial and complete response to treatment in IMMA and terbinafine groups Time points reported: the improving rate determined by measuring indurations at baseline, in the middle (day 10 for IMMA group and day14th for terbinafine group), and at the end of the study (day 21 for IMMA group and day 28 for terbinafine group)
Notes	*Study funding sources*: Kerman University of Medical Sciences accepted the financial support of this study *Possible conflicts of interest*: the authors declare that there is no conflict of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation sequence was obtained by the use of a randomisation table
Allocation concealment (selection bias)	Low risk	A simple block randomisation list with a block size of 4 was accumulated by a team member who was not involved in the enlistment and follow-up of the participants. The randomisation allocation concealment was carried out by sending the randomisation numbers in envelopes to a dermatologist who was responsible for giving the assigned treatment after each participant was en-rolled.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different administration of treatments: oral terbinafine and IMMA
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was an assessor blind trial in which the outcome assessor was unaware of the drugs used by the participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	The study published does not report 2 primary outcomes: adverse effects and recurrence
Other bias	Low risk	Other items assessed correctly reported

Fekri 2015

Methods	*Study design*: randomised controlled trial *Setting/location*: Afzalipour hospital affiliated to Kerman University of Medical Sciences and Dadbin Health Center, Kerman/Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: - *Inclusion criteria*: age over 7 years, positive smear or biopsy, providing informed consent *Exclusion criteria*: pregnant or lactating, lesions on face, more than 5 lesions, duration longer than one year, size larger than 3 cm, any treatment in past month, history of allergy to MA or dapsone, systemic diseases, taking immunosuppressive drugs in past 6 months, lupoid or sporotrichoid forms *N randomised*: 73 *Withdrawals*: 5 *N assessed (lesions)*: 68 (73). Group 1: 33 (35); group 2: 35 (38) *Mean (SD) age*: 29.6 years (15.4) in group 1, 31.6 years (20.4) in group 2 *Sex (male/female)*: intervention group: 17/16, group 2: 14/17 *Baseline data*: • Number of lesions: 38 lesions in group 1 and 35 in group 2 • Mean±SD of duration of lesions (months): 4.6 ± 9.3 in group 1 and 3.7 ± 1.9 in group 2 • Mean±IQR of the initial lesion size (mm2): 2 (1.4-2.9) in group 1 and 1.5 (1.1-3) in group 2
Interventions	*Type of interventions*: • *Group 1*: weekly ILMA + niosomal dapsone gel twice a day • *Group 2*: weekly ILMA + cryotherapy every 2 weeks *Duration of intervention*: until complete healing or max 16 weeks
Outcomes	*Healing response*: complete healing (100% epithelialisation and loss of induration), moderate healing (50-99% epithelialisation and loss of induration), no response (less than 50% epithelialisation and loss of induration) Time points reported: 16 weeks after beginning intervention, 1 year later for recurrence
Notes	*Study funding sources*: Kerman University of Medical Sciences *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment

Fekri 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	High risk	No reasons for missing outcome data
Selective reporting (reporting bias)	High risk	One outcome of interest in the review is not reported: adverse effects, so that it cannot be entered in a meta-analysis
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Firooz 2005

Methods	*Study design*: randomised controlled trial *Setting/location*: Isfahan, Iran *Study period*: 6 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* endemic in the area *Inclusion criteria*: the presence of parasitologically confirmed lesion(s) of CL, aged 12-60 years, and otherwise healthy on the basis of medical history and physical examination *Exclusion criteria*: women of childbearing age without adequate effective contraception; pregnant or breastfeeding; duration of lesions > 8 weeks; the presence of lesions on face, joints or near the mucous membranes; the presence of > 5 lesions or any lesion with a diameter > 5 cm; history of any antileishmanial therapy in the past 4 weeks *N participants randomised (lesions)*: 72 (106). 36 (53) treated with zinc sulphate (ZS) and 36 (53) treated with ILMA *Withdrawals participants (lesions)*: 37 (56). ZS group 23 (34): unresponsive: 12, lost to follow-up: 5, non-medical events: 2, protocol deviation: 2, complications: 1, patient request: 1. ILMA 14 (22): unresponsive: 2, lost to follow-up: 10, non-medical events: 1, patient request: 1 *N assessed (lesions)*: 35 (50). 13 (19) treated with ZS and 22 (31) treated with ILMA *Mean (SD) age*: 20.2. years (9.6). ZS group: 18.1 years (6.1); ILMA: 22.3 years (11.2) *Sex (male/female)*: 33/39. ZS group: 19/17; ILMA group: 14/22. *Baseline data*: • Location of the lesions (n (%)): head and neck: ZS group: 7 (13.2); ILMA group: 1 (1.9); trunk: ZS group: 3 (5.7); ILMA group: 1 (1.9); upper extremity: ZS group: 28 (52.8); ILMA group: 32 (60.4); lower extremity: ZS group: 15 (28.3); ILMA group: 19 (35.8) • ZS group: MNL (SD): 1.4 (0.8). MSL (SD): 7.6 mm (5.5). MDLBT: 5.8 weeks

	(2.0) • ILMA group: MNL (SD): 1.5 (0.8). MSL (SD): 7.9 mm (7.5). MDLBT: 5.5 weeks (2.3)
Interventions	*Type of interventions*: • *Group 1*: IL 2% zinc sulphate • *Group 2*: ILMA *Duration of intervention*: up to 6 weeks *Duration of follow-up*: 5 weeks
Outcomes	*Healing rates*: percentage of lesions 'cured' 5 weeks after treatment. Complete re-epithelialisation of each ulcer with marked reduction in induration with or without scarring was considered as the main efficacy parameter *Amount of injection into each lesion* *Adverse effects*: the pain experienced by the participant (using a verbal analogue scale on a 0-10 scale) was recorded Time points reported: 6 weeks
Notes	*Study funding sources*: this study was supported by a grant from Chancellery of Research, Tehran University of Medical Sciences *Possible conflicts of interest*: none declared The plot and the figures were not matched accordingly

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	The randomisation sequence was concealed from the investigators until the data entry was completed and the data bank was locked
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double-blind" Comment: the preparation and coding of drugs were done by a pharmacist outside of the research team and investigators were blinded to them
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of dropouts (37/72, 54%). Missing outcome data imbalanced in numbers and reasons across intervention groups. ZS group: 23. ILMA group: 14. 'As-treated'

Firooz 2005 (*Continued*)

		analysis done with substantial departure of the intervention received from that assigned at randomisation
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Firooz 2006

Methods	*Study design*: randomised controlled trial *Setting/location*: Mashad, Iran *Study period*: 18 months *Sample size calculation*: 45 participants per treatment group were needed to have 80% power to detect a significant difference in the expected cure rate of 50% in the vehicle group and the desired cure rate of 80% in the imiquimod-treated group at week 8 with a type Ierror level of 0.05. To compensate for 20% estimated dropout, 54 participants would be required in each group
Participants	*Type of Leishmania*: *L tropica* endemic in the area *Inclusion criteria*: parasitologically proven cases of CL based on positive smear or culture, otherwise healthy participants *Exclusion criteria*: pregnant or lactating women, duration of the lesions > 6 months, number of lesions > 5, any lesions > 5 cm, history of any standard course of treatment with antimonials, history of allergy to antimonials, serious systemic illnesses, participation in any drug trials in the last 60 days *N participants randomised (lesions)*: 119 (252). 59 (128) participants in the imiquimod group and 60 (124) in the vehicle group *Withdrawals*: 30 participants. Imiquimod group (n = 17): 9 lost to follow-up, 4 inadequate efficacy, 3 protocol deviation, 1 consent withdrawal. Vehicle group (n = 13): 9 lost to follow-up, 2 inadequate efficacy, 2 protocol deviation *N assessed*: 89. 42 participants in the imiquimod group and 47 in the vehicle group *Mean (SD) age*: 27.0 years (SD 1, range 12-60). Imiquimod group: 7.4 years (13); vehicle group: 6.5 years (12) *Sex*: approximately 50%-55% of the participants were female (35/59 in the imiquimod group, and 31/60 in the vehicle group) *Baseline data*: • Lesions were mainly located on the upper extremities (66.3%) and around 15% to 17% on the face and lower extremities • Location of lesions (n (%)): face: imiquimod group: 20 (15.6), vehicle group: 19 (15.3); trunk: imiquimod group: 1 (0.8); vehicle group: 1 (0.8); upper extremity: imiquimod group: 85 (66.4); vehicle group: 82 (66.1); lower extremity: imiquimod group: 22 (17.2); vehicle group: 22 (17.7) • Imiquimod group: MNL: 2.2. MDLBT: 13 weeks. MSL: 174 mm^2 • Vehicle group: MNL: 2.0. MDLBT: 13.2 weeks. MSL: 237 mm^2

Firooz 2006 (*Continued*)

Interventions	*Type of interventions*: • *Group 1*: imiquimod cream 5% + IMMA • *Group 2*: vehicle + IMMA *Duration of intervention*: imiquimod and vehicle 3 times per week for 28 days, IMMA 20 mg/kg/d for 14 days *Duration of follow-up*: 20 weeks after initiation of treatment
Outcomes	*Primary outcome*: percentage of participants 'cured' 3.5 months after treatment. Clinical cure of the participants, defined as more than 75% reduction in the size of lesions compared with baseline *Secondary outcomes*: the relapse rate (defined as a reappearance of lesions at the site or periphery of previously healed lesions or an increase in the size of lesions after initial improvement) was assessed 16 weeks after the end of treatment *Adverse effects* Time points reported: at the end of the treatment period (week 4) and 4 weeks later Intention-to-treat analysis of rates of complete re-epithelialisation, clinical cure, and clinical improvement at weeks 4, 8,and 20 after initiation of treatment
Notes	*Study funding sources*: this study was supported by the Small Grants Scheme for Operational Research in Tropical and Other Communicable Diseases from the Joint World Health Organization Eastern Mediterranean Region Division of Communicable Diseases and the Special Program for Research and Training in Tropical Diseases *Possible conflicts of interest*: the funding source was involved in the study design, in the writing of the manuscript, and in the decision to submit the manuscript for publication, but not in the collection, analysis, or interpretation of data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomly divided into 2 groups according to a list made by a simple randomisation block design"
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation allocation concealment was performed by sending the randomisation numbers in envelopes to a pharmacist who was responsible for giving the assigned treatment after each eligible patient was enrolled."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment unlikely to be blinded. This study was a single-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To keep the trial blinded, the physicians who were responsible for evaluation of patients were uninvolved in the

Firooz 2006 (*Continued*)

		process of allocation and drug dispensing and were unaware of the drug used by the patients."
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals: 30/119 (25.2%); no ITT analyses performed
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Gholami 2000

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: 24 months *Sample size calculation*: yes
Participants	*Type of Leishmania*:*L major* *Inclusion criteria*: CL confirmed with direct smear, age 5-50 years, maximum number of lesions 3, duration of disease < 100 days *Exclusion criteria*: previous treatment for leishmaniasis, use of immunosuppressives, history of chronic systemic disease, lesions on face, pregnancy or lactating, age < 5 years, duration of disease > 100 days *N randomised*: 197 *Withdrawals*: 26 *N assessed*: 171. 96 were treated with garlic 5% cream and 75 with vehicle *Mean age*: garlic, 18.5 years; vehicle, 23.7 years *Sex (male/female)*: garlic, 51/45; placebo, 38/37 *Baseline data*: not reported
Interventions	*Type of interventions*: • *Group 1*: garlic cream 5% • *Group 2*: vehicle *Duration of intervention*: both applied twice daily under occlusion with sterile gauze for 3 hours, for 20 days *Duration of follow-up*: 60 days (after the 3 week treatment, participants were followed for another period of 40 days)
Outcomes	*Healing rates*: percentage of participants 'cured' one month (40 days) after treatment Time points reported: yes
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared We only have the abstract. The author (A Khamesipour) was contacted and kindly agreed to extract the data from the original paper written in Persian

Gholami 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	List generated by a computer
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of dropouts (26/197; < 25%)
Selective reporting (reporting bias)	Unclear risk	All relevant outcomes reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Harms 1991

Methods	*Study design*: randomised controlled trial *Setting/location*: Aleppo, Syria *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: up to 3 lesions diagnosed clinically and parasitologically as CL; absence of chronic or intercurrent systemic disease *Exclusion criteria*: pregnancy and no prior antimonial medication *N randomised and withdrawals*: not reported *N participants assessed (lesions)*: 40 (75) ILMA: 20 (38); IFN-γ: 20 (37) *Mean age (range)*: ILMA: 21 years (6-60); IFN-γ: 27 years (12-57) *Sex (male/female)*: 17/23. ILMA: 9/11; IFN-γ: 2/12 *Baseline data*: • Type of lesions (%). ILMA group: papular: 13; papular-nodular: 21; nodular-ulcerative: 61; plaque-form: 5. IFN-γ group: papular: 19; papular-nodular: 19; nodular-ulcerative: 62; plaque-form: none • Lesion site (%). ILMA group: upper extremity: 63; lower extremity: 18; face: 18; trunk: none. IFN-γ group: upper extremity: 59; lower extremity: 30; face: 8; trunk: 3 • Median size (range) (mm) : ILMA group:15 x 14(4 x 4- 49 x 42);IFN-γ group:

Harms 1991 (*Continued*)

	13 x 11(7 x 7- 45 x 40) • Mean duration of lesions before treatment (range) (months): ILMA group: 2.5(1-6); IFN-γ group:2.5(2-8)
Interventions	*Type of interventions*: • *Group 1*: ILMA (1-3 mL) • *Group 2*: IL Lyophilised recombinant IFN-γ (25 mg) *Duration of intervention*: once weekly for 5 weeks *Duration of follow-up*: 10 weeks
Outcomes	*Primary outcome*: percentage of lesions 'cured' one month after treatment Secondary outcome: adverse effects *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: weeks 3, 6, 10
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table method used
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information about blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information about blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up were reported.
Selective reporting (reporting bias)	Low risk	Comment: all relevant outcomes provided
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Iraji 2004

Methods	*Study design*: randomised controlled trial *Setting/location*: Department of Dermatology, Isfahan Medical University, Iran *Study period*: 10 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp: due to a previous study in the area, it was likely that participants were infected with *L major* *Inclusion criteria*: proven leishmaniasis based on typical lesions of ACL and a positive direct smear. Number of lesions < 4 and duration of lesion < 12 weeks *Exclusion criteria*: cases of reinfection, pregnant or nursing women, those who had lesion on the face or joints and participants with sporotrichoid or erysipeloid lesions *N randomised*: 104. ILMA: 55, zinc sulphate (ZS): 49 *Withdrawals*: 38. ILMA: 20, ZS: 18. 13 due to occurrence of new lesions: 7 from ILMA group and 6 from ZS group; 6 participants with sporotrichoid spread: 4 from the ILMA group and 2 from the ZS group; 19 participants lost to follow-up: 9 from the ILMA group and 10 from the ZS group *N assessed*: 66. ILMA: 35, ZS: 31 *Mean age (range)*: ILMA: 11 years (2-67); ZS: 12 years (3-64) *Sex (male/female)*: 50/54. ILMA: 14/21; ZS: 17/14 *Baseline imbalances*: sex distribution in each group *Severity of illness*: Mean duration of lesions (SD) (weeks): ILMA: 6.73 ±0.53 ;ZS: 7.64±0.12
Interventions	*Type of interventions*: • *Group 1*: ILMA injection of 50 mL • *Group 2*: IL ZS injection of 50 mL In cases where there was a slight to mild improvement, another injection was given after 2 weeks *Duration of intervention*: 2-6 weeks *Duration of follow-up*: 6 weeks
Outcomes	*Healing rates*: percentage of participants 'cured' at the end of treatment. The results of treatment were graded according to the system of Sharquie 1997 slight = 1, mild = 2, moderate = 3, marked = 4, 5 = total clearance of the lesion and parasite not detected in the affected area by smear *Adverse effects* Time points reported: 2, 4, 6 weeks
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence

Iraji 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were treated randomly with intralesional injection of any of 2 similar 50-mL vials marked A (MA) or B (ZS) by an independent physician. ZS solution was prepared by dissolving 2 g ZS ($ZNSO_4W$ $7H_2O$) per 100 mL of bidistilled deionised water. The blinding was unlikely to have been broken.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	The study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability was not correctly reported

Iraji 2005

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: not described *Sample size calculation*: the required sample size, 40 in each treatment group, was estimated, assuming one in every 4 cases would not provide full data, using the formula n = [Z1 − (a/2) + Z1 − b] 2 × [P1(1 − P1) + P2(1 − P2)]/(P1 − P2)2, and setting P1 (the paromomycin efficacy) to 0.7, P2 (the vehicle efficacy) to 0.3, a to 0.05, b to 0.1, Z1 − (a/2) to 1.96, and Z(1 − b) to 1.64
Participants	*Type of Leishmania*: *L tropica* and *L major* are responsible for hyperendemic CL in rural areas and endemic CL in parts of many cities in Iran *Inclusion criteria*: had the clinical signs of CL and all of their cutaneous lesions were found smear-positive for amastigotes *Exclusion criteria*: cases who had first noticed a skin lesion > 3 months previously, had lesions on their face, had lesions with diameter of > 3 cm, had received previous treatment, or who were lactating or pregnant *N randomised*: 80, 40 in each group

	Withdrawals: 15. Intervention group: 10; control group: 5 *N assessed*: 65. Intervention group: 30; control group: 35 *Age*: range 8-55 years. Mean intervention group: 21.4 years; control group: 21.5 years *Sex (male/female)*: 33/32. Intervention group: 19/11; control group: 14/21 *Baseline data*: mean duration of lesions (years): intervention group: 1.65; control group: 1.75
Interventions	*Type of interventions*: • *Group 1*: PR sulphate 15% + 10% urea applied to a 1 mm-thick layer twice daily • *Group 2*: vehicle control group (Eucerin containing 10% urea) applied topically twice daily *Duration of intervention*: 30 days *Duration of follow-up*: for clinical and parasitological follow-up on day 30 and for only parasitological follow-up on day 60
Outcomes	*Healing rates*: percentage of participants 'cured' one month after treatment, clinical and parasitological cure • Complete healing was defined as a reduction in the size and induration of the lesion(s) by at least 75% and lesion smears that appeared amastigote-free • Partial cure was defined as a reduction in the size and induration of the lesion(s) by > 25% but < 75%, and lesion smears that appeared amastigote-free. • Failure was defined as a reduction in the size and induration of the lesion(s) by < 25% and/or an amastigote-positive smear *Adverse effects* Time points reported: days 30 (clinical and parasitological follow-up) and 60 (parasitological follow-up)
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The cases enrolled were assigned to two treatment groups, placebo or paromomycin, using computer-based randomisation."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as "double blind" but no description about allocation method was given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment described

Iraji 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data about dropouts were given
Selective reporting (reporting bias)	Low risk	Relevant outcomes were reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Jaffar 2006

Methods	*Study design*: randomised controlled trial *Setting/location*: Saudi Arabia (Bahrain) *Study period*: 12 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: proved positive for *Leishmania* parasites (amastigotes) on microscopic examination or biopsy *Exclusion criteria*: not described *N randomised*: 62. Rifampicin: 46; placebo: 16. Rifampicin: 2 groups were analysed; group 1a (children aged 3-11 years - mean age, 7. 5 years), and group 1b (adults aged 12-65 years - mean age, 33 years). 32 participants enrolled in group 1a and 30 in group 1b. Out of these, 8 participants in each group (16 in total) served as control to receive the placebo *Withdrawals*: 21 participants lost to follow-up. Rifampicin: 12; placebo: 9 *N assessed*: 41. Rifampicin: 34; placebo: 7. Number participants imbalanced between groups *Age*: range 3-65 years; mean 20 years *Sex (male/female)*: 43/19 *Baseline data*: the duration of the lesions varied between 1 and 12 months (mean 2.6 months). The lesions of CL were single or multiple and were mostly over the extremities (upper limbs 51% and lower limbs 38%) and to a lesser extent on the face 30%. Most of the lesions were active being nodular, nodule-ulcerative, or ulcerative. 2 of the participants were members of the same family. However, the rest of the participants had a negative family history
Interventions	*Type of interventions*: • *Group 1*: rifampicin orally in a dose of 10 mg/kg/d • *Group 2*: placebo *Duration of intervention*: 2 equally divided doses during meals for 4-6 weeks *Duration of follow-up*: 3 months
Outcomes	*Primary outcome*: percentage of participants 'cured' 3 months after treatment *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur up to 3 months of follow-up *Adverse effects*

Jaffar 2006 (*Continued*)

Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Comment: "Randomized" but no further information was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Each subject in the control group was given placebo, which was supplied, in capsules/suspension identical in shape and colour to that given in the rifampicin group." Participants look blinded but no information about personnel were provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: "Double-blinded" but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	There is a 38.87% of follow-up, the percentage is very different between the groups, and it isn't explained
Selective reporting (reporting bias)	High risk	No adverse effects data available
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Jaffary 2010

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Disease and Leishmaniasis Research Center of Isfahan (SDLRC), Iran *Study period*: not described *Sample size calculation*: not described

Jaffary 2010 (*Continued*)

Participants	*Type of Leishmania*: not described *Inclusion criteria*: not described *Exclusion criteria*: not described *N randomised*: 140 participants *Withdrawals*: 64 *N assessed*: 76 participants (47 with ILMA and topical *Cassia fistula* fruit gel and 29 participants in vehicle group) *Age*: not described *Sex*: not described *Baseline data*: not described
Interventions	*Type of interventions*: • *Group 1*: *Cassia fistula* fruit gel + ILMA • *Group 2*: vehicle gel + ILMA *Duration of intervention*: not described
Outcomes	*Cure*: complete cure, partial cure and treatment failure *Adverse effects* (itching and erythema) Time points reported: 12 weeks
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared We only have the abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "140 patients with cutaneous leishmaniasis referring to Skin Diseases and Leishmaniasis Research Center of Isfahan (SDLRC) were randomly allocated in two groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: the vehicle came exactly in the same colour and shape as the drug and the application procedure was also the same. We think the outcome is unlikely to be influenced by lack of blinding of personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Jaffary 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is no information about withdrawals.
Selective reporting (reporting bias)	Low risk	Our primary outcomes (cured and adverse effects) were described in the Methods and reported in the text
Other bias	High risk	Sample size calculation, inclusion criteria, reporting of *Leishmania* spp involved and baseline comparability was not correctly reported

Jaffary 2014a

Methods	*Study design*: double-blind, randomised controlled study *Setting/location*: Isfahan, Iran *Study period*: January 2009 to February 2010 (13 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: met the histological criteria for presence of parasite, age > 5 years, acute leishmanial lesions smaller than 5 cm^2, fewer than 5 lesions, more than 3 months of disease duration *Exclusion criteria*: pregnancy, women of childbearing age, history of administration of immune suppressive drugs in the last 6 months or anti-leishmanial drugs in the last month *N randomised*: 60 participants, 30 in each group *Withdrawals*: 0 *N assessed*: 60, 30 in each group *Mean (SD) age*: 25.29 years (4.01). *Achillea millefolium* 5%: 25.8 years (3.7); vehicle: 24.6 years (4.2). *Sex*: 15 (25%) female; 45 (75%) male. *A millefolium*: 7 (23.3%) female, 23 (76.6%) male; vehicle: 8 (26.6%) female, 22 (73.3%) male) *Baseline data*: • Mean number of lesions (SD): *A millefolium*: 1.56 (0.8); vehicle: 1.52 (0) • Type of lesions (%): *A millefolium*: papule 8/44 (18.1), ulcer 16/44 (36.3), plaque 10/44 (22.7), nodule 10/44 (22.7). vehicle: papule: 9/38 (23.6), ulcer: 16/38 (42.1), plaque: 11/38 (28.9), nodule: 12/38 (31.5) • Mean duration of lesions (SD): *A millefolium*: 3 months (0.5); vehicle: 2.7 months (0.7)
Interventions	*Type of interventions*: • *Group 1*: topical gel of 5% *A millefolium* (yarrow (containing 5% polyphenol) • *Group 2*: vehicle gel. The vehicle gel was prepared using the same material except for the plant extract and chlorophyll was used as colorings agent. Both gels were identical in terms of the colour and consistency *Duration of intervention*: 4 weeks *Co-interventions*: all participants received 4 weekly an injections of MA (Glucantime,

Jaffary 2014a (*Continued*)

	Paris, France) at a dose of 20 mg/kg
Outcomes	*Definition*: complete or partial cure of lesions Time points reported: week 12 (visits months - 3)
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "During this double-blind randomised study, 60 patients were randomised into two treatment groups by using random allocation computer software. "
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "During this double-blind randomised study ..." Quote: "Both gels were identical in terms of the colour and consistency."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported, therefore ITT analyses performed
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Jaffary 2014b

Methods	*Study design*: randomised parallel clinical trial *Setting/location*: Skin Diseases and Leishmaniasis Research Center (SDLRC), Isfahan, Iran *Study period*: not described *Sample size calculation*: not described

Participants	*Type of Leishmania*: not described *Inclusion criteria*: 6-60 years old, with positive results of leishmaniasis smear test *Exclusion criteria*: size of lesion > 3 cm, > 5 lesions, lesion duration > 12 weeks, lesion located on the eyelid or < 2 cm away from the eye, pregnant or lactating *N randomised*: 165, 55 in each of 3 treatment groups *Withdrawals*: 7; 3 (5.5%), participants were in the concentrated boiled extract group and 2 (3.6%) participants in the other groups withdrew from the study due to the allergic reaction to the medications *N assessed*: 158. Concentrated boiled extract of *Cassia fistula*: 52; hydroalcoholic extract of *C fistula*: 53; ILMA: 53 *Mean (SD) age*: boiled extract of *C fistula*: 20.6 years (12.4); hydroalcoholic extract of *C fistula*: 19.8 years (11.5); ILMA: 22.9 years (13.6) *Sex (n,(%))*: boiled extract of *C fistula*: male: 35 (63.6), female: 20 (36.4); hydroalcoholic extract of *C fistula*: male: 29 (52.7), female: 26 (47.3); ILMA: male: 25 (45.5), female: 30 (54.5) *Baseline data*: • Location of lesions (n(%)): ○ Concentrated boiled extract of *C fistula*: foot 9 (16.4), hand 25 (45.5), trunk 5 (9.1), head and neck 8 (14.5), hand and foot 8 (14.5). ○ Hydroalcoholic extract of *C fistula*: foot 11 (20), hand 23 (41.8), trunk 6 (11), head and neck 10 (18.2), hand and foot 5 (9.1). ○ ILMA: foot 8 (14.5), hand 24 (43.6), trunk 5 (9.1), head and neck 11 (20), hand and foot 7 (12.7) • Mean number of lesions (SD): ○ Concentrated boiled extract of *C fistula*: 1.8 (1.13) ○ Hydroalcoholic extract of Cassia fistula: 1.72 (0.98) ○ ILMA: 2.03 (1.07) • Kind of lesions (n(%)): ○ Concentrated boiled extract of *C fistula*: nodule 23 (41.8), papule 17 (30.9), papule and nodule 15 (27.3) ○ Hydroalcoholic extract of *C fistula*: nodule 30 (54.5), papule 11 (20), papule and nodule 14 (25.5) ○ ILMA: nodule 39 (70.9), papule 5 (9.1), papule and nodule 11 (20)
Interventions	*Type of interventions*: • *Group 1*: concentrated boiled extract of C fistula. 500 g of *C fistula* was powdered and then mixed with water with ratio of 1:3, then boiled for 30 minutes and concentrated by distillation in vacuum condition. • *Group 2*: hydroalcoholic extract of Cassia fistula on the lesions. 500 g of *C fistula* was powdered and mixed with 70% ethanol with ratio of 1:3, then placed in a percolator. After 48 hours, extraction was performed. The extract was then concentrated using distillation in vacuum condition. • *Group 3*: ILMA. 0.5-2 mL twice a week *Duration of intervention*: until complete resolution of the lesion (complete epithelialisation) or for a maximum duration of 4 weeks *Follow-up*: 3 months after completing the project, they were examined every month to assess the recurrence of the lesions

Outcomes	*Clinical and parasitological cure*: lesions were considered completely cured (improvement) , if the participants achieved both clinical and parasitological resolutions (negative results of direct smear). Participants were considered resistant to the treatment, if no clinical changes were observed in the lesion or it was worsened *Time to healing*: comparison of complete cure time of the cutaneous Leishmaniasis lesions between 3 groups *Adverse effects*: allergic reaction to the medications Time points reported: week 1, 2, 3, 4, 16, complete cure
Notes	*Study funding sources*: the study was self-funded *Possible conflicts of interest*: there was no conflict of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The participants were randomly allocated to 3 groups using table of random numbers
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different administration of treatments: 2 groups: apply the extract-soaked gauze; third group: ILMA
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons (allergic reaction to the medications) of withdrawals were similar and small in 2 of the groups 3.5% (3/28) in concentrated boiled group vs 3. 6% (2/28) in the other groups
Selective reporting (reporting bias)	Low risk	The study published reports our primary outcomes: cured and adverse effects
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Jebran 2014

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Leishmania Clinic of the German Medical Service (GMS), Darwaze-e-Lahory, 1st district, Kabul, Afghanistan *Study period*: 36 months (2004-7) *Sample size calculation*: sample size was calculated based on the primary outcome (i. e. complete wound healing). A number of 40 participants each was calculated to be necessary to obtain a power of 80% (significance level 5%). A presumed dropout rate of 20% led to a minimum total enrolment of 100 participants
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: male or female participants of the GMS Clinic; 5 years of age or older; with non-ulcerated (papule/nodule) or ulcerated lesions (ulcer with or without crust); presence of at least one parasitologically confirmed CL lesion and no prior history of leishmaniasis and/or anti-parasitic treatment *Exclusion criteria*: participants below age 5; with the presence of CL lesion(s) on or immediately adjacent to the nose, lips or eyes; pregnancy, or serious co morbidities *N randomised*: 135. Group 1: 73; group 2: 62 *Withdrawals*: due to protocol breach: group 1, n = 14; group 2, n = 8. Lost to follow-up: group 1, n = 21; group 2, n = 22 *N assessed*: 113 (83.7%): group 1: 59 (80.82%); group 2: 54 (87.09%). *Mean age (range)*: group 1: 18.62 years (5-66); group 2: 18.16 years (6-63) *Sex (male/female)*: 93/42; group 1: n = 51/22; group 2: n = 42/20. *Baseline data*: • Lesion type: group 1: papule or nodule: 24, ulcer: 49; group 2: papule or nodule: 17, ulcer: 45 • Location of the target lesion: group 1: 22 face, 2 shoulder/neck, 42 upper extremity, 7 lower extremity; group 2: 14 face, 0 shoulder/neck, 44 upper extremity, 4 lower extremity • MLDBT (range): group 1: 2.92 months (1-12); group 2: 2.61 months (1-9) • Giemsa smear: group 1: G0 (no amastigotes (AM)): 2, G 1 (1-10 AM): 49, G2 (11-100 AM): 7, G3 (> 100 AM): 15; group 2: G0 (no AM): 0, G 1 (1-10 AM): 40, G2 (11-100 AM): 11, G3 (> 100 AM): 11 • Parasite load in the 1st biopsy (*Leishmania* per gram tissue): mean (SEM): group 2: 9.14 (2.85) × 107; group 2: 1.54 (0.83) × 108. • Wound surface after EC treatment: mean (SEM): group I: 347.9 mm^3 (23.39); group 2: 391.9 mm^3 (27.80)
Interventions	*Type of interventions*: • *Group 1*: superficial coagulation and removal of lesion tissue was performed using bipolar high-frequency electrocauterisation (EC; also termed high-frequency electrocoagulation) with the help of the electrosurgical Mini Cutter HMC 80 HF. After EC, a polyacrylate hydrogel with freshly prepared 0.045% (w/w) pharmaceutical sodium chlorite (sodium chlorosum, DAC N-055) gel was applied to the lesions, daily • *Group 2*: superficial coagulation and removal of lesion tissue was performed using bipolar high-frequency electrocauterisation (EC; also termed high-frequency electrocoagulation) with the help of the electrosurgical Mini Cutter HMC 80 HF. After EC, a polyacrylate hydrogel without DAC N-055 *Duration of intervention*: time to wound closure *Co-interventions*: systemic antibiotics were only given if bacteria were detected and the

	wound infection was severe. Neither local nor systemic antifungal therapy was allowed to exclude anti-protozoal effects on the *Leishmania* infection
Outcomes	*Primary outcome - time to wound closure (days)*: the time needed for complete epithelialisation of the lesion wound was defined and photodocumented *Secondary outcome - microbiological cure*: the parasite load (*Leishmania*/g) of the lesions was taken prior to electrocauterisation (1st time), after wound closure (2nd) and after 6 months (3rd) *Adverse effects*: such as bacterial or fungal superinfections of the wounds, the formation or scars and the rate of re-ulcerations were monitored during the treatment and follow-up period
Notes	*Possible conflicts of interest*: not described *Study funding sources*: this study was supported by the German-Academic Exchange Service (travel grants to KWS, AFJ and FM), the Senior Expert Service (travel grants to KWS) and the Interdisciplinary Center of Clinical Research at the Universitätsklinikum Erlangen (IZKF, project A49 to US and CB). The founders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomly assigned with the help of a GMS computer at a ratio of 1:1"
Allocation concealment (selection bias)	Unclear risk	Quote: "RS and KWS were responsible for the enrolment of the patients and their assignment to the treatment groups." Comment: not further information was provided regarding the method for allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The participants, the medical personnel treating and evaluating the patients, the investigators analysing the clinical course of treated lesions, as well as the lab members performing the parasitological analyses were blinded. The preparation of the two different gels (marked as jelly A and B), which could not be visually distinguished, was performed by a technician who was not involved in the treatment of patients"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The participants, the medical personnel treating and evaluating the patients, the investigators analysing the clin-

Jebran 2014 (*Continued*)

		ical course of treated lesions, as well as the lab members performing the parasitological analyses were blinded. The preparation of the two different gels (marked as jelly A and B), which could not be visually distinguished, was performed by a technician who was not involved in the treatment of patients"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14 participants of group 1 and 8 participants of group 2 were retrospectively excluded due to deviations from the study protocol For the follow-up analysis, 6 months after wound healing, only 70 participants could be included, as 21 participants of group I and 22 participants of group II did not observe their appointments
Selective reporting (reporting bias)	Low risk	Main outcomes were included. Trial was registered at clinicaltrial.gov: NCT00947362
Other bias	Low risk	Other items assessed correctly reported

Jowkar 2012

Methods	*Study design*: double-blind, randomised placebo-controlled clinical trial *Setting/location*: south of Iran *Study period*: October 2007 to January 2009 (15 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* and *L tropica* *Inclusion criteria*: men and women aged at least 12 years old, positive smear and/or polymerase chain reaction (PCR) for CL, cutaneous lesions of less than 4 months' duration *Exclusion criteria*: pregnancy and lactation, facial lesions, lesions of more than 4 months' duration, complete or incomplete treatment with a systemic or topical medication within the previous month, drug sensitivity *N randomised*: 100 participants *Withdrawals*: 37 participants *N assessed*: 63 participants (36 in treatment and 27 in control group) *Age*: range 12-62 years (mean 32.6 (SD 12) in the treatment group and 33.1 (14) in the vehicle group) *Sex (male/female)*: 35/28 *Baseline data*: • Location of lesion(s): treatment: arm 12, hand 5, wrist 5, leg 7, foot 5, trunk 1, neck 1; control: arm 5, hand 7, wrist 4, leg 5, foot 2, trunk 2, neck 2 • Type of lesion: treatment: plaque 19 and nodule 17; control: plaque 14 and

	nodule 13 • Origin of the lesion: treatment: rural 24 and urban 12; control: rural 17 and urban 10
Interventions	*Type of interventions*: • *Group 1*: 3% sodium nitrite in aqueous cream • *Group 2*: aqueous cream alone (vehicle) *Duration of intervention*: 12 weeks *Co-interventions*: simultaneously, cryotherapy once a week and aqueous cream containing 3% salicylic acid (emulsifying ointment 30 g, phenoxyethanol 1 g and freshly boiled and cooled water 69 g)
Outcomes	*Clinical response*: • Complete clinical response: complete re-epithelialisation of the ulcer and disappearance of induration • Partial clinical response: reduction of more than 50% of the ulcer and induration in relation to the last clinical evaluation • Absence of clinical response: increase or reduction of less than 50% of the ulcer and the indurated area in relation to the last clinical evaluation *Adverse effects* Time points reported: 12 weeks
Notes	*Study funding sources*: not described *Possible conflicts of interest*: no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This investigation was designed as a 12-week, double blind, N randomised, placebo-controlled study and its protocol was approved by the ethics committee of the vice chancellor of research affairs of Shiraz University." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The identically coded and packaged creams were applied two times daily." Quote: "The study was blinded to both the patients and the assessing physician."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The study was blinded to both the patients and the assessing physician."

Jowkar 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	100 participants were enrolled but only 63 completed the study. Reasons for withdrawal were not reported
Selective reporting (reporting bias)	Low risk	Our primary outcomes (cure and adverse effects) were described in Methods and reported in Results
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Kashani 2010

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences, Tehran, Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* and *L major* *Inclusion criteria*: the participants with CL who attended to Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences, Tehran, Iran. The diagnosis was based on clinical findings and physical examination and confirmed by Giemsa-stained direct smear of the lesion *Exclusion criteria*: ore than 5 lesions; lesions greater than 5 cm in diameter; received anti-CL treatment during the previous month; lesions on the face and around vital organs; diabetic individuals; pregnant, lactating female participants; subjects with active infectious diseases *N randomised*: 85. Group 1: mesotherapy administration of meglumine antimonate: 41. Group 2: ILMA injection: 44 *Withdrawals*: 25. Group 1: 11 (7 lost to follow-up, 3 inadequate efficacy, 1 allergic reaction). Group 2: 14 (10 lost to follow-up, 2 inadequate efficacy, 2 allergic reaction) *N assessed*: 60 (70.59%). Group 1: 30 (73.17%), group 2: 30 (68.18%) *Mean (SD) age*: Group 1: 25.24 years (16), group 2: 24.32 years (15.26) *Sex (male/female)*: Group 1: 19/11, group 2: 17/13 *Baseline data*: • Group 1: type of lesions (n (%)): papule 2 (6.66), nodule 6 (20), plaque 22 (73.33). Location of lesions (n (%)): upper extremities 15 (50), lower extremities 9 (30), other 9 (20).Ulcer (mean(SD), cm) (mean(SD), cm) 1.80 (0.64). Erythema (mean (SD), cm) 2.25 (0.66). Induration 0.91 cm (0.41) • Group 2: type of lesions (n (%)): papule 3 (10), nodule 7 (23.33), plaque 20 (66.66). Location of lesions (n (%)): upper extremities 13 (43.33), lower extremities 10 (33.33), other 7 (23.33). Ulcer(mean(SD), cm) 1.86 (0.55). Erythema (mean(SD), cm) 2.34 (0.69). Induration (mean (SD)) 1.12 cm (0.682)

Interventions	*Type of interventions*: • *Group 1*: "Inderm Mesotherapy Gun (Innovative Med. Inc., Irvine, CA, USA) was set to inject 0.05 mL of MA in each shot in the depth of 2 mm using a 30 G needle. The shots were repeated in each 5 mm of the lesion." • *Group 2*: 0.1 mL of MA (Glucantime, Rhone-Poulenc, France) was injected intradermally in the periphery of the lesions using a 30-G needle. The shots were repeated in each 1 cm of lesion until the whole lesion was blanched. *Duration of intervention*: 6 weeks or until complete cure
Outcomes	*Clinical cure*: 3 categories were defined for ulcer healing: complete cure: complete re-epithelialisation of the ulcer with loss of induration; partial cure: 25 to 99% re-epithelialisation of lesions; failure: less than 25% re-epithelialisation of lesions. Improvement of the lesions: ulcer improvement (cm), induration improvement (cm), induration improvement (cm), speed of improvement (cm/week), speed of erythema improvement (cm/week), scare size (cm) *Microbiological cure*: Leismanian body: negative, positive. *Pain severity during injection*: visual analogue scale (VAS; 0 to 10). *Amount of drug used (mL/cm²) and number of treatment sessions* *Adverse effects* Time points reported: 3 months after treatment. Adverse effects: after the each treatment session
Notes	*Study funding sources*: this study was supported by a research grant from Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences, Tehran, Iran *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomised according to a computer generated simple randomisation list to be treated with intralesional injection of MA using either the classic method or mesotherapy gun."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment

Kashani 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	14/44 participants with the conventional technique and 11/41 with mesotherapy gun withdrawn the study (29.4%)
Selective reporting (reporting bias)	Unclear risk	Protocol not available; not registered in a trial registry; SD not provided for pain severity (VAS) Insufficient information to permit judgment
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Khatami 2012

Methods	*Study design*: randomised controlled trial *Setting/location*: Bam and Mashhad in Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: parasitologically proven cases of CL; otherwise healthy subjects on the basis of medical history, physical examination and results of blood tests; age 12-50 years; body weight >40 kg; willingness to participate in the trial and signing the informed consent *Exclusion criteria*: not described *N randomised*: 138 participants (75 in IMMA and 63 in miltefosine) *Withdrawals*: 33 in IMMA and 32 in miltefosine *N assessed*: 42 in IMMA arm and 31 in miltefosine *Age (years)*: not described *Sex*: not described *Baseline data*: not described
Interventions	*Type of interventions*: *Group 1*: oral miltefosine 2.5/kg/d for 28 days *Group 2*: IMMA 60 mg/kg/d for 14 days *Duration of intervention*: not described *Co-interventions*: not described
Outcomes	*Healing of their lesions and occurrence* *Adverse effects* Time points reported: participants were evaluated weekly for 28 days and then 1 month later
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Khatami 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote:"This open N randomised controlled trial was carried out in Bam and Mashhad in Iran …" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:"This open N randomised controlled trial was carried out in Bam and Mashhad in Iran …"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote:"This open N randomised controlled trial was carried out in Bam and Mashhad in Iran…"
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up quite high (around 50%) Intervention group: 32/63= 50.8% Control group: 33/75= 44%
Selective reporting (reporting bias)	Unclear risk	It is an abstract. At least they reported complete cure of cases and adverse effects
Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability was not correctly reported

Khatami 2013

Methods	*Study design*: randomised, assessor-blind, controlled clinical trial *Setting/location*: Kashan, Tehran, Iran *Study period*: September 2008 to April 2010 (19 months) *Sample size calculation*: 56 lesions per treatment group were needed to have 80% power to detect a significant difference in the expected cure rate of 60% in the ILMA alone group and the desired cure rate of 85% in the ILMA and either silver or non-silver dressing-treated group at week 10 with a type I error level of 0.05. Compensating for a 20% loss-to-follow-up, recruiting 68 (round up to 70) lesions per treatment group looked reasonable
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: parasitologically confirmed cases of CL based on positive smear and/or culture; otherwise healthy subjects on the basis of medical history; age of 12-60 years;

	willingness to participate in the study and signing the informed consent form (by the participant or his/her parent/guardian in cases younger than 18 years) *Exclusion criteria*: pregnant or lactating women; duration of lesion more than 3 months; number of lesions more than 5; ulcer size greater than 5 cm in largest diameter; history of receiving full course standard treatment (antimonials); history of allergy to MA or silver; serious systemic illnesses (as judged by the physician); participation in any drug trials in the last 60 days; indication for systemic treatment with MA; presence of secondary bacterial infection of the lesion according to clinical appearance *N randomised*: 83 participants (158 lesions) ILMA: 26 participants (45 lesions); ILMA + non-silver dressing: 26 participants (53 lesions); ILMA + silver dressing: 31 participants (60 lesions) *Withdrawals*: 10 participants (18 lesions) *N assessed*: 73 (140 lesions) *Mean (SD) age*: 28.81 years (14.45). ILMA: 32.88 years (12.92); ILMA + non-silver dressing: 30.31 years (15.41); ILMA + silver dressing: 24.13 years (13.97) *Sex*: male 39; ILMA: male 8; ILMA + non-silver dressing: male 11; ILMA + silver dressing: male 20 *Baseline data*: • Mean duration of lesions (SD): 7.951 weeks (2.67); ILMA: 8.31 weeks (2.86); ILMA + non-silver dressing: 8.46 weeks (2.15); ILMA + silver dressing: 7.23 weeks (2.82) • Mean number of lesions (SD): 1.90 (1.21); ILMA: 1.77 (1.34); ILMA + non-silver dressing: 2.00 (1.47); ILMA + silver dressing: 1.94 (1.12) • Induration area median (IQR): 169 mm² (79-433); ILMA: 270 mm² (120-557); ILMA + non-silver dressing: 156 mm² (67-490); ILMA + silver dressing: 141 mm² (48-346). • Ulceration area median (IQR): 6 mm² (1-25); ILMA: 8 mm² (2-37); ILMA + non-silver dressing: 6 mm² (0-15); ILMA + silver dressing: 6 mm² (0-24)
Interventions	*Type of interventions*: • *Group 1*: eligible participants were randomly allocated into 2 groups and treated for 6 weeks with either: ○ Weekly injections of ILMA combined with application of a non-silver dressing (AtraumanH, Hartmann, CMC Consumer Medical Care GmbH, Germany) on the lesions, or ○ Weekly injections of ILMA combined with application of a silver containing dressing (AtraumanH Ag, Hartmann, CMC Consumer Medical Care GmbH, Germany) on the lesions. • *Group 2*: weekly injections of ILMA (GlucantimeH; Rhodia Laboratories, Rhone-Poulenc, France) alone *Duration of intervention*: 6 weeks
Outcomes	*Clinical cure* (complete healing defined as more than 75% reduction, clinical improvement defined as 50%-75% reduction, and no response to treatment defined as less than 50% reduction in the size of the lesion compared with baseline) *Relapse*: defined as a reappearance of lesions at the site or periphery of previously healed lesions or an increase in the size of lesions after initial improvement was assessed 5 months after the termination of treatment *Adverse effects*: itching and burning, exudation, oedema, and dermatitis

	Time points reported: oucomes were assessed at the end of the treatment period (end of week 6), then at 4 weeks and 5 months after the last treatment session
Notes	*Study funding sources*: the budget of the research project has been provided by the Vice-Chancellery of Research of Tehran University of Medical Sciences *Possible conflicts of interest*: the authors have declared that no competing interests exist

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A random sequence generated by using the online software Random Sequence Generator, which is available at URL: www.random.org [22]. It was done by an investigator with no clinical involvement in the trial. R. Talaee was responsible for enrolment of the patients."
Allocation concealment (selection bias)	Low risk	Quote: "The method for randomisation concealment was to use sequentially numbered, opaque, sealed envelopes (SNOSE) . The envelopes were kept in a safe box, which was only accessible to A. Khatami who was responsible for assigning the patients to the interventions."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An assessor who was blinded to the type of treatment visited the patients at weekly intervals during the treatment period and 1- month and 5 months after the last treatment session"
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intent-to-treat analysis was performed at 2 time points (end of the treatment period (day 42) and one month later (day 72)). The numbers of and the reasons for withdrawals were not significantly different between the 3 groups: 11% ILMA group; 19% ILMA + non-silver and 6.45% ILMA + silver
Selective reporting (reporting bias)	Low risk	Comment: all relevant outcomes were reported

Other bias	Low risk	Other items assessed correctly reported

Kochar 2000

Methods	*Study design*: randomised controlled trial *Setting/location*: India *Study period*: 5 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: participants with a confirmed diagnosis of *L tropica*. The diagnosis was confirmed by demonstrations of *L tropica* bodies (amastigote stage of *L tropica* under oil immersion). *Exclusion criteria*: no mention about inclusion or exclusion criteria *N randomised*: 50. Rifampicin 1200 mg/d orally: 25; placebo: 25 *Withdrawals*: 4. Rifampicin 1: 2 (lost to follow-up); placebo: 2 (withdrew due to exacerbation of lesions) *N assessed*: 46. Rifampicin: 23; placebo: 23 *Mean (SD) age*: rifampicin 29.54 years (17.34); placebo: 26.96 years (10.96) *Sex (male/female)*: rifampicin: 10/13; placebo: 9/14 *Baseline data*: • Type of lesions (% rifampicin versus placebo): ulcerative: 21.7 versus 17.4, nodular: 30.4 versus 30.4; nodule-ulcerative: 17.4 versus 30.4, and erythematous plaques: 30.4 versus 21.7. • Regarding the distribution (%): face: 17.5 versus 20.9; neck; 3.5 versus 0; shoulder: 1.75 versus 0; arms: 17.5 versus 20.9; hand: 19.2 versus 18.6; legs: 28 versus 16.2; feet: 8.77 versus 20.9, and abdomen: 3.5 versus 2.32 • Mean number of lesions (SD): rifampicin 2.92 (4.61); placebo 2.08 (0.78) • Mean duration of lesions (SD): rifampicin 3.58 months (6.14); placebo: 3.23 months (2.93) • Mean size of lesions (SD): rifampicin 31.91 mm² (15.99); placebo: 37.04 mm² (12.37)
Interventions	*Type of interventions*: • *Group 1*: rifampicin 1200 mg/d orally • *Group 2*: placebo capsules orally *Duration of intervention*: 2 divided doses for 4 weeks *Duration of follow-up*: 4 weeks *Co-interventions*: the 2 withdrew due to exacerbation of lesions in placebo group and were treated by another therapeutic regimen
Outcomes	*Healing rates*: percentage of participants 'cured' at the end of treatment: a cure was defined as complete healing and disappearance of the lesion or reversible hypopigmentation at the site of lesion. Incomplete or partial healing was defined as a reduction in the size of a lesion and the absence of parasites on smear. A treatment failure or non-healing was defined as the absence of any change in the lesion and persistence of parasites on smear *Adverse effects* *Tertiary outcomes*: microbiological or histopathological cure of skin lesions

Kochar 2000 (*Continued*)

	Time points reported: at the end of the treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Comment: "Randomized" but no further information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: "Double-blinded" but no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: "Double-blinded" but no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all relevant outcomes were reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Kochar 2006

Methods	*Study design*: randomised controlled trial *Setting/location*: hospital, Bikaner, India *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: participants with a confirmed diagnosis of anthroponotic CL *Exclusion criteria*: - *N randomised*: 50. Intervention group: 25, placebo group: 25 *Withdrawals*: 6 lost to follow-up. Intervention group: 2, placebo group: 4 *N assessed*: 44. Intervention group: 23, placebo group: 21

	Age: intervention group: n = 12, 16-20 years; n = 5, 21-30 years; n = 3, 31-40 years; n = 2, 41-50 years; n = 2, 51-60 years; n = 0, 61-70 years. Placebo group: n = 10, 16-20 years; n = 4, 21-30 years; n = 5, 31-40 years; n = 3, 41-50 years; n = 2, 51-60 years; n = 1, 61-70 years *Sex (male/female)*: 34/16. Intervention group: 17/8; placebo group: 17/8 Male predominance was probably due to the habit of sleeping in open spaces outside the house without mosquito nets and improper clothing during night when the sandflies are active *Baseline data*: • Type of lesion: ○ Intervention group: erythematous nodular: 11; erythematous plaque: 3; ulcerative: 3; erythematous ulcerative: 2; nodular: 4; nodular ulcerative: 2 ○ Placebo group: erythematous nodular: 9; erythematous plaque: 5; ulcerative: 2; erythematous ulcerative: 5; nodular: 2; nodular ulcerative: 2 • Ratio lesions:participant ○ Intervention group: 1:14; 2:5; 3:5; > 3:1 ○ Placebo group: 1:14; 2:7; 3:4; > 3:0 • Distribution of lesions: ○ Intervention group: face: 4; neck: 3; arms: 6; hand: 9; back: 2; abdomen: 1; buttock: 1; legs: 4; foot: 3 ○ Placebo group: face: 11; neck: 2; arms: 6; hand: 9; back: 2; abdomen: 3; buttock: 1; legs: 3; foot: 4 • Most cases were presented with 1 to 3 months of duration of the disease.
Interventions	*Type of interventions*: • *Group 1*: rifampicin (1200 mg/d) in 2 divided doses + omeprazole 20 mg • *Group 2*: placebo *Duration of intervention*: 6 weeks *Duration of follow-up*: 6 weeks
Outcomes	*Healing rates*: percentage of participants 'cured' at the end of treatment: complete healing; partial response; no response Time points reported: at the end of treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Comment: "Randomized" but no further information provided

Kochar 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: "Double-blinded" but no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: "Double-blinded" but no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across group
Selective reporting (reporting bias)	High risk	Comment: no adverse effects information reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Larbi 1995

Methods	*Study design*: randomised controlled trial *Setting/location*: Saudi Arabia *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*:*L major* *Inclusion criteria*: only participants in whom parasites (amastigotes) were demonstrated were enrolled *Exclusion criteria*: pregnancy, chronic illness, immunocompromised or hyper allergic reaction to the trial drugs, treatment with regular medications such as antituberculous agents and steroids, which might have affected specific therapy, treatment with anti-leishmanial drugs within the previous months, the presence of scars of previously treated lesions *N randomised*: 58. 2% miconazole cream: 27; 1% clotrimazole cream: 31 *Withdrawals*: 4: 2% miconazole cream: 4 (lost to follow-up); 1% clotrimazole cream: 0 *N participants assessed (lesions)*: 54 (151). 2% miconazole cream:n23 (62); 1% clotrimazole cream: 31 (89) *Mean (SD) age*: 2% miconazole cream: 19.5 years (15.4); 1% clotrimazole cream: 21.5 years (12.8) *Sex (male/female)*: 42/12. 2% miconazole cream: 17/6; 1% clotrimazole cream: 25/6 *Baseline data*: • Lesion type (%): 2% miconazole group: nodular: 21 (34%), nodule-ulcerative: 37 (59%) and papular: 4 (7%). 1% clotrimazole group: nodular: 36 (41%), nodule-ulcerative: 50 (56%) and papular: 4 (3%) • Location of lesions: 2% miconazole group(percentage): the lower limbs: 56%; upper limbs 39%; head, neck, upper chest: 5%. 1% clotrimazole group: lower limbs: 34%; upper limbs: 46%; head, neck, upper chest: 19%, abdomen and groin: 1%.

	• 2% miconazole group: MNL: Saudi: 2.2 and non-Saudi 3.4. MSL (range): 1.02 cm (0.06-5). Mean duration of lesions before treatment (SD): 2.1 weeks (1.3) • 1% clotrimazole group: MNL: Saudi: 2.3 and non-Saudi 3.5. MSL (range): 1.38 cm (0.05-6). Mean duration of lesions before treatment (SD): 2.3 weeks (1.2)
Interventions	*Type of interventions*: • *Group 1*: 2% miconazole cream • *Group 2*: 1% clotrimazole cream *Duration of intervention*: twice daily for 30 consecutive days *Duration of follow-up*: 30 days
Outcomes	*Healing rates*: percentage of lesions 'cured' at the end of treatment. Response to treatment was based on results of repeated parasitologic evaluation and/or clinical changes using the same parameters as in the follow-up. On this basis, response to treatment was graded into 4 categories: • Lesion fully healed (lesions were completely healed and parasitologically negative • Size reduced (lesions showed a reduction in infiltration, erythema, and size with positive or negative parasitology • No change (lesions did not show any change in infiltration, erythema, size, and parasitology • Lesions worsened or size increased (there was an increase in the size of the lesion and a worsening of infiltration and erythema and positive parasitology) *Adverse effects* Time points reported: at the end of treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out by using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients admitted into the trial were given unlabeled tubes containing either 1% clotrimazole cream or 2% miconazole" Comment: we think that the outcome is unlikely to be influenced
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Larbi 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 27 participants treated with 2% miconazole, 4 defaulted and were lost to follow-up; they were excluded from analysis" (4/27 = 14.28%)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but he published reports probably include all expected outcomes
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Layegh 2007

Methods	*Study design*: randomised, prospective *Setting/location*: dermatology department of Qaem University Hospital, Mashhad, Iran *Study period*: from October 2004 through November 2005 (13 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not reported (although they reported that CLL is endemic and *L tropica* and, less commonly, *L major* are the most prevalent species) *Inclusion criteria*: aged > 2 years with CL of < 6-months' duration; no treatment of the current infection during the last 3 months; and no history of a renal or liver disease *Exclusion criteria*: pregnant women; history of intolerance or allergy to Glucantime or macrolides; simultaneous use of antacids containing Al and Mg, theophyline, phenytoin, barbiturates, carbamazepine, and cyclosporin *N randomised*: 49: azithromycin: 22 (35 lesions), IMMA: 27 (58 lesions). *Withdrawals*: 2 (azithromycin group) *N assessed*: 47 participants; 20 (29 lesions) in the azithomicin group and 27 (58 lesions) in the IMMA group *Mean (SD) age*: range 4-70 years; azithromycin: 21.77 years (17.13) and IMMA: 22.78 years (13.17) *Sex (male/female)*: 24/25; azithromycin: 8/14; IMMA: 16/11 *Baseline data*: • Mean number of lesions (SD): azithromycin: 1.86 (1.52) and IMMA: 2.15 (1.38) • Mean duration of lesions (SD): azithromycin: 4.28 months (1.39) and IMMA: 3.22 months (2.03) • Type of lesions: ○ Papule and plaque: azithromycin: 27 (77.1%); IMMA: 49 (84.5%) ○ Nodular: azithromycin: 6 (17.1%); IMMA: 7 (12.1%) ○ Ulcerative: azithromycin: 2 (5.8%); IMMA: 2 (2.8%)
Interventions	*Type of interventions*: • *Group 1*: "daily oral dose of 500 mg of azithromycin for 5 days/month in adults and 10 mg/kg in children; treatment cycles were repeated monthly when no favourable response was achieved, up to a maximum duration of 4 months"

	• *Group 2*: 60 mg/kg IMMA for 20 days *Duration of intervention*: up to 4 months (azithromicin) and 20 days (IMMA) *Co-interventions*: participants showing no favourable response after 4 months of azithromycin therapy would receive IMMA at the same dose as the other group, at the end of the study
Outcomes	*Clinical cure*: clinical response was determined on the basis of the lesions' size, border, induration, and infiltration of papulonodular lesions; ulcerative lesions were evaluated on the basis of the ulcer depth, diameter, crusting, and the extent of re-epithelialisation • Complete or significant improvement: decrease in the induration size > 75% or full re-epithelialisation of the le-scions and a negative direct skin smear (absence of parasites in the lesion) • No improvement: decrease in induration size < 30% • Partial improvement: any changes between above criteria *Recurrence* *Adverse effects* Time points reported: participants in the azithromycin group were evaluated monthly up to a maximum of 4 months, but participants in the IMMA group were evaluated both at the end of the treatment period (day 20) and 45 days later. Recurrence was reported after the 16-week follow-up period
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The 49 patients who met our inclusion criteria were randomly divided into two groups." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	48 of 50 participants randomised completed the study. 2/20 participants of the azithromycin group withdrew because of adverse effects. Applications of study drugs

Layegh 2007 (*Continued*)

		were conducted according to the protocol
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Layegh 2009

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Dermatology Clinic of Qaem Hospital in Mashad, Iran *Study period*: 10 months *Sample size calculation*: to detect a 22% difference in the cure rate between cryotherapy and ILMA groups and assuming a 57% cure rate in the cryotherapy group, with a 65% power and a 10% 2-sided type I error, 40 persons were needed in each group. The 79 participants who met our criteria were randomly divided into 2 groups: 40 participants received cryotherapy and 39 participants received ILMA
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: positive direct skin smears for CL, were ≤ 13 years of age, had visited the dermatology clinic from September 2006 through June 2007, and had lesions with a duration of < 12 weeks to exclude any natural self-healing during follow-up *Exclusion criteria*: > 13 years of age, had a lesion history > 3 months, allergic to antimonial drugs, simultaneously using any other therapeutic method *N randomised*: 79. Cryotherapy: 40, ILMA: 39 *Withdrawals*: 7: cryotherapy group: 4, ILMA: 3 *N assessed*: 72 (91.14%): cryotherapy group: 36 (90%), ILMA: 36 (92.31%) *Mean (SD) age*: 6.8 years (3.4) in cryotherapy group and 6.2 years (3.4) in ILMA group *Sex (male/female)*: cryotherapy: 18/22; ILMA: 20/19 *Baseline data*: • Mean number of lesions (SD): cryotherapy: 1.9 (1.02); ILMA: 1.4 (0.76) • Location of lesions by site: ○ Head and neck: cryotherapy: 24, ILMA: 31 ○ Upper limb (hand): cryotherapy: 10, ILMA: 13 ○ Lower limbs (foot): cryotherapy: 4, ILMA: 3 • Type of lesion: ○ Papule/plaque: cryotherapy: 35, ILMA: 37 ○ Nodule: cryotherapy: 2, ILMA: 3 ○ Ulcer: cryotherapy: 1, ILMA: 2 • Mean duration of lesions (SD): cryotherapy: 11.2 weeks (11.8); ILMA: 12.1 weeks (18.4)
Interventions	*Type of interventions*: • *Group 1*: cryotherapy group: liquid nitrogen (−195°C) was applied twice to the lesion. Each cycle was 10-15 s of freezing time with a thawing interval of 20 s. Care was taken to ensure that freezing reached up to a few millimetres within the healthy skin surrounding the lesion

	• *Group 2*: ILMA (Glucantime; Specia, Paris, France) in a volume of 0.5-2 cm^3 was injected into each lesion until the lesion was completely infiltrated (blanched) *Duration of intervention*: 6 weeks
Outcomes	*Clinical cure*: complete cure was defined as full re-epithelialisation; disappearance of oedema, induration, and other signs of inflammation; and a negative direct skin smear result. Score: 1. Complete improvement (full re-epithelialisation of the lesions and a negative direct skin smear result), 2. Significant improvement (decrease in induration size > 75%), 3. Partial improvement (decrease in induration size between 50% and 75%, 4. Slight improvement (decrease in induration size between 25% and 50% 5. No improvement (decrease in induration size < 25%) *Time to healing* *Adverse effects* Time points reported: at the end of treatment and 6 months (clinical cure); at 4, 5 and 6 weeks (time to healing); at the end of treatment, after 6 weeks (adverse effects)
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open trial; lesions of all participants were photographed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants in the cryotherapy group and 3 participants in the ILMA group were excluded because they received 2 medications simultaneously, did not complete the treatment course, did not visit the clinic for follow-up 6 months later, or changed their address and were lost to follow-up

Layegh 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	Protocol not available; not registered; however, pre-specified outcomes of the review were reported
Other bias	Low risk	Other items assessed correctly reported

Layegh 2011

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Dermatology Clinic of Ghaem Hospital, Mashhad, Iran *Study period*: March 2008 to September 2010 (30 months) *Sample size calculation*: to detect a 35% difference in the cure rate between the 2 groups of liposomal AmB and ILMA, assuming a 90% cure rate in liposomal AmB group with a 95% power and a 5% 2-sided type I error, 36 subjects were required in each group. Also regarding a loss to follow-up of 20%, this number was raised to 50 participants for each group
Participants	*Type of Leishmania*: *L tropica*, *L major* *Inclusion criteria*: cutaneous leishmaniasis approved by either a direct smear stained with Giemsa or a positive skin biopsy of lesions with less than 6-month duration, in cases with a previous history of anti-leishmaniasis therapy, a 3-month treatment-free interval from the last treatment course *Exclusion criteria*: pregnancy, breastfeeding, taking any other specific treatment while participating in the study, past medical history of any local or systemic disease during the last 2 months, a significant underlying disease such as cardiac, renal, or liver dysfunction *N randomised*: 110. Group 1: 50; group 2: 60 *Withdrawals*: 34 did not adhere. Group 1: 11; group 2: 23 *N assessed*: group 1: 39 (78%); group 2: 37 (61.7%) *Mean (SD) age*: group 1: 20.54 years (18.72); group 2: 25.30 years (15.70) *Sex (male/female)*: group 1: 23/27; group 2: 21/39 *Baseline data*: • Mean number of lesions (SD): group 1: 1.91 (1.02); group 2: 1.4 (0.76) • Location of the target lesion: ○ Group 1: head and neck, 26; hand, 18; leg and trunk, 6 ○ Group 2: head and neck, 22; hand 32; leg and trunk, 6 • Type of lesions: ○ Group 1: papule/plaque, 33; nodule, 8; ulcer, 9 ○ Group 2: papule/plaque, 53; nodule, 5; ulcer, 2
Interventions	*Type of interventions*: • *Group 1*: liposomal AmB was administered as 3-7 drops twice daily according to the lesion size • *Group 2*: ILMA (Glucantime; Specia, Paris, France) was injected into each lesion once a week, to the point when the lesion's surface became fully infiltrated and up to a maximum dose of 2 mL *Duration of intervention*: 8 weeks

Outcomes	*Clinical response*: determined on the basis of the lesion induration size of and the extent of re-epithelialisation in ulcerative ones. Scales: clinical response: • Slight improvement: decrease in induration size up to 25% • Mild improvement: decrease in induration size between 25 and 50% • Moderate improvement: decrease in induration size between 50 and 75% • Marked improvement: decrease in induration size more than 75% *Adverse effects* Time points reported: at the end of treatment, and 6 months after termination. Adverse effects were reported at the end of treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The 110 patients who met our inclusion criteria were randomly divided into two groups." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analyses performed Losses to follow-up per group: Intervention group: 11/50 (22%) Control group: 23/60 (38.3%)
Selective reporting (reporting bias)	Unclear risk	Number of lesions higher in the liposomal ampB group ($P < 0.05$) whereas number of papule and plaque lesions where higher in the ILMA group ($P = 0.011$) Outcomes described in the methods were reported in the results section. However, only one time point was reported Protocol not available; not registered in a clinical trial registry

Layegh 2011 (*Continued*)

Other bias	Low risk	Other items assessed correctly reported

Lynen 1992

Methods	*Study design*: randomised controlled trial *Setting/location*: school children, Sudan *Study period*: 80 days *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp not specified but *L major* was presumed to be the causative parasite. *Inclusion criteria*: all positive smears *Exclusion criteria*: children who had received diminazene aceturate or previous treatment in hospital *N randomised*: 70. 35 in each group *Withdrawals*: 8. Berelin: 3; Savlon: 5. 2 children in Berelin group were not enrolled because they received diminazene aceturate before. 2 in Savlon group were excluded because they were treated for CL in the hospital *N assessed*: 62. Berelin: 32; Savlon: 30 *Mean (SD) age*: Berelin: 9.3 years (4.6); Savlon: 10.4 years (2.8) *Sex (male/female)*: Berelin: 18/15; Savlon: 20/13 *Baseline imbalances*: comparability with regard to sex, age, number, size, duration and location of ulcer, and previous treatment taken • Size of lesion (% (n/N)): small lesions (< 2 cm): Berelin: 58% (19/33); Savlon: 61% (20/33); big lesions (≥ 2 cm): Berelin: 42% (14/33); Savlon: 39% (13/33) • Duration (% (n/N)): ≤ 2 months: Berelin: 52% (17/33); Savlon: 64% (21/33). >2 months: Berelin: 48% (16/33); Savlon: 36% (12/33)
Interventions	*Type of interventions*: • *Group 1*: Berelin (1.05 g diminazene aceturate in 2.36 g of granulate, dissolved in 12.5 cc of distilled water) daily except on Fridays for 50 days • *Group 2*: Savlon (cetrimide 15% + chlorhexidine 1.5% in a 2% solution) for 50 days *Duration of treatment*: 50 days *Duration of follow-up*: one month
Outcomes	*Primary outcome*: percentage of participants 'cured' at the end of treatment. Cure was defined when the skin lesion was completely closed and covered with scar tissue, without the possibility to evoke secretions on pressure and if this apparent cure was sustained for at least 2 weeks *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur 20 to 35 days after cure *Adverse effects* Time points reported: at the end of treatment and at the end of follow-up
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Lynen 1992 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A double-blind study design was attempted, but could not be sustained as Savlon is a well-known product and soapy on application
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of dropouts (8/70, < 2.5%)
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is probably that the published reports include all expected outcomes
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Maleki 2012

Methods	*Study design*: randomised controlled trial *Setting/location*: Imam Reza Hospital in Mashhad, Iran *Study period*: March to September 2004 (7 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: confirmation of cutaneous leishmaniasis based on direct smear, ≤ 3 lesions, duration of the disease < 12 weeks, aged 7-60 years, completion of informed consent form by participant or parents of minor participants, dry cutaneous leishmaniasis *Exclusion criteria*: pregnant or breastfeeding women; children < 7 years, lesions on ear, nose, joints, and near the eye; > 3 lesions; application of any kind of treatment for cutaneous leishmaniasis, duration of the disease longer than 12 weeks (to omit spontaneous healing cases during the follow-up period), recurrent infection, wet cutaneous leishmaniasis *N randomised*: 45 participants *Withdrawals*: 11

	N assessed: 34 participants (24, group 1; 10, group 2) *Age*: not described *Sex*: not described *Baseline data*: mean size of lesions (SD): group 1, 1.27 cm (0.81); group 2, 0.98 cm (0.61)
Interventions	*Type of interventions*: • *Group 1*: 2 bouts of intralesional 2% zinc sulphate was performed twice within 2 weeks interval • *Group 2*: 6 weekly bouts of ILMA *Duration of intervention*: group 1, 2 weeks; group 2, 6 weeks
Outcomes	*Clinical response* • Slight: partial reduction of erythema and oedema • Mild: reduction of lesion size up to 30% • Moderate: reduction of lesion size between 30% and 60% • Marked: reduction of lesion size more than 60% or negative smear • Total tolerance: complete healing of the lesion with negative smear Time points reported: 8 weeks
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This N randomised controlled trial was performed from March to September 2004 on patients with cutaneous leishmaniasis admitted to Imam Reza Hospital in Mashhad" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	45 participants were randomised into 2 groups. 11 were lost to follow-up (24%) No ITT analyses were performed

Maleki 2012 (*Continued*)

		High imbalance between groups
Selective reporting (reporting bias)	High risk	No baseline data. Side effects not clearly reported (no statistical analyses performed either)
Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability was not correctly reported

Mapar 2010

Methods	*Study design*: randomised controlled trial *Setting/location*: Ahvaz city, southern Iran *Study period*: 12 months (2002) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: clinically and parasitologically positive (Leishman bodies in Giemsa-stained direct smear of the lesion scrapings), duration of lesions < 3 months, aged 15-40 years, no evidence of secondary bacterial infections, no mucosal involvement, no history of previous treatment of cutaneous leishmaniasis, or of allergic reactions to MA or metronidazole *Exclusion criteria*: history of underlying disease (such as cardiac, renal, or pulmonary); pregnant or breastfeeding; cutaneous leishmaniasis localised on or near the joints *N randomised*: 36. Group 1: 18, group 2: 18 *Withdrawals*: 8. Group 1: 2, group 2: 6 *N assessed*: 28 (77.78%). Group 1: 16, group 2: 12 *Age*: mean 28.8 years (range 15-40) *Sex (male/female)*: 21/15 *Baseline data*: • Total lesions: group 1: 29, group 2: 27 • Group 1: lesions were of dry types (without any discharge), the longest diameters of the lesions were 0.5-2.5 cm • Group 2: clinically dry type skin lesions. The longest diameters of the lesions were 0.5-2.5 cm
Interventions	*Type of interventions*: • *Group 1*: weekly ILMA injections (150-600 mg = 0.5-2 mL of MA ampoule for each skin lesion). Intralesional injections were administered intradermally enough to blanch the lesions surface. • *Group 2*: weekly IL metronidazole (500 mg/100 mL vials were made by Fresenius, Bad Homburg), injected intradermally into each skin lesion enough to blanch the lesions surface (0.5-2 mL for each lesion) *Duration of intervention*: 8 weeks
Outcomes	• *Clinical cure of the lesions*: clinical criteria for cure were: complete re-epithelialisation, disappearance of oedema, induration, and other signs of

Mapar 2010 (*Continued*)

	inflammation, flattening of the lesions and change of colour from erythematous to blue or dark grey • *Adverse effects*: local or systemic adverse effect. Pain of intralesional injection. Local inflammatory reactions with oedema and induration. In both groups the participants complained of severe pain at the site of injections but group 2 had unbearable terrible pain Time points reported: clinical cure: after 8 injections. Adverse effects: after the treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The method of randomisation was selecting a card among 36 cards with odd or even numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	28/36 participants completed the study (77.8%)
Selective reporting (reporting bias)	High risk	No protocol available. Adverse effects not reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Mashood 2001

Methods	*Study design*: randomised controlled trial *Setting/location*: skin department of PNS Shifa, a naval hospital in Karachi. Endemic areas of Balochistan province, Pakistan *Study period*: not described *Sample size calculation*: not described

Mashood 2001 (*Continued*)

Participants	*Type of Leishmania*: *Leishmania* spp not mentioned *Inclusion criteria*: never received any treatment for their skin disease *Exclusion criteria*: very young and very old people, those who had received some treatment for the disease, people suffering from diffuse CL or leishmaniasis recidivans, people with some known cardiac, renal or hepatic disease *N randomised*: 40. 20 in each group *Withdrawals*: 0 Participants assessed: 40 (100%). 20 in each group *Age*: range 20-40 *Sex*: 100% male *Baseline data.* Nodular, ulcerative and crusted forms were the most common morphological patterns seen. Most lesions were on hands and feet • Group 1: MSL: 570.7 mm². MDLBT (range): 8.6 weeks (4-20) • Group 2: MSL: 960.3 mm². MDLBT: 12.6 weeks (8-24)
Interventions	*Type of interventions*: • *Group 1*: oral AL 20 mg/kg/d in 3-4 divided doses tablet • *Group 2*: IVSSG 20 mg/kg/d *Duration of intervention*: 15 days *Duration of follow-up*: 3 months
Outcomes	*Healing rates*: percentage of participants 'cured' at the end of treatment *Adverse effects* Time points reported: at the end of treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described

Mashood 2001 (*Continued*)

Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is probably that the published reports include all expected outcomes
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Mohebali 2007

Methods	*Study design*: randomised controlled trial *Setting/location*: Golestan province, in northeastern Iran *Study period*: 20 November 2005 to 20 July 2006 (8 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: observation of Leishman bodies (amastigotes) in dermal lesions, no previous use of anti-leishmanial drugs, no previously confirmed leishmaniasis (by scar or clinically compatible history), no pregnant or lactating women, no acute or chronic medical condition and no history of allergy, female participants of childbearing age were included after giving consent for effective contraception during therapy and until 3 months thereafter *Exclusion criteria*: not explicitly reported, but can be inferred from the above inclusion criteria *N randomised*: 63. Group 1: 32; group 2: 31 *Withdrawals*: 5. Group 1: 4 (lost after first week because lack of gastrointestinal tolerance) ; group 2: 1 (lost to follow-up after 3 months) *N assessed*: 63 (100%). Group 1: 28; group 2: 30 *Mean age*: group 1: 20.2 years; group 2: 16.8 years *Sex (male/female)*: 35/28. Group 1: 19/13; group 2: 16/15 *Baseline data*: • Location of the target lesion (%): < 20% of lesions were located on the face in each group: group 1: 12.5%; group 2: 16.1% • Mean number of lesions (range): group 1: 2.7 (1-15); group 2: 2.5 (1-10) • Mean size of lesions (range): group 1: 27.1 mm² (0.9-80.0); group 2: 19.3 mm² (3-67.3) • Mean duration of lesions: group 1: 45.5 days; group 2: 43.6 days
Interventions	*Type of interventions*: • *Group 1*: miltefosine orally 2.5 mg/kg daily for 28 days. Miltefosine capsules were administered as follows: 9-14 kg, 3 capsules of 10 mg; 15-29 kg, 1 capsule of 50 mg; 30-45 kg, 2 capsules of 50 mg; 46-84 kg, 3 capsules of 50 mg • *Group 2*: IMMA at 20 mg SbV ◦ /kg body weight daily for 14 days *Duration of intervention*: miltefosine: 28 days. IMMA: 14 days *Duration of follow-up*: 6 months

Outcomes	*Healing rates*: percentage of participants 'cured' 3 months after treatment *Secondary outcomes*: duration of remission and percentage of people with treated lesions that recur within 6 months *Adverse effects* Time points reported: 2 weeks, 3 months, 6 months
Notes	*Study funding sources*: this study was financially supported by Medical Sciences/University of Tehran, Iran (from grant for full professor) *Possible conflicts of interest*: not described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "For randomisation of patients into two groups, we used balanced block method"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This study was an open-label, N randomised comparison of miltefosine to meglumine antimonate in 63 patients"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers and reasons for missing data across intervention groups (4/32 = 12.5% miltefosine group; 1/31=3.22% IMMA group) Comment: the results for the dropouts were not excluded from the statistical analysis We think missing outcome data likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is probably that the published reports include all expected outcomes
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Momeni 1996

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: not described *Sample size calculation*: assuming a 30% spontaneous cure rate with placebo and the minimum usefulness of a 60% cure rate with itraconazole, and a 10% dropout rate, the sample size was calculated as 70 individuals in each group
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: age > 12 years, diagnosis of CL confirmed by laboratory test results, no previous treatment for leishmaniasis, no serious concomitant medical problems *Exclusion criteria*: age < 12 years, pregnant and nursing women, patients who had lesions on the face, lesions lasting > 4 months *N randomised*: 140. Itraconazole: 70; placebo: 70 Withdrawals: itraconazole: 5 *N assessed (lesions)*: 131. Itraconazole: 65 (219); placebo: 66 (262) *Age*: mean 26.3 years (range 12-46) *Sex (male/female)*: 90/41. Itraconazole: 44/21; placebo: 46/20 *Baseline data*: • Number of lesions: itraconazole: 219; placebo: 262 • Mean duration of lesions (SD): itraconazole: 38 days (1.45 months); placebo: 45 days (1.5 months)
Interventions	*Type of interventions*: • *Group 1*: itraconazole orally 7 mg/kg/d (max. 400 mg per day) • *Group 2*: placebo capsules *Duration of intervention*: 3 weeks *Duration of follow-up*: 51 days
Outcomes	*Healing rates*: percentage of participants 'cured' 51 days after treatment *Adverse effects* Time points reported: at the end of treatment (day 21); on day 51 (1 month after the end of treatment)
Notes	*Study funding sources*: this work was supported by the World Health Organization Special Program for Research and Training in Tropical Diseases and the research programme of Isfahan University of the Medical Sciences *Possible conflicts of interest*: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Carried out by the WHO Special Programme for Research and Training in Tropical Diseases group in Geneva, Switzerland" Comment: insufficient detail was reported about the method used to generate the allocation sequence

Momeni 1996 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules containing 100 mg of itraconazole or placebo were used in the study. The 2 treatment groups received either itraconazole as coded capsules for 21 days or placebo as coded capsules with the same dosages Review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified. The study published reports our primary outcomes: 'cured' and adverse effects
Other bias	Low risk	Other items assessed correctly reported

Momeni 2002

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Research Centre in Isfahan city. Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: age > 5 years, diagnosis of CL confirmed by laboratory test results, no previous treatment for leishmaniasis, no serious concomitant medical problems, signed written informed consent *Exclusion criteria*: pregnant and nursing women, age < 5 years, lesions lasting for > 4 months *N randomised*: 72. Group 1: 36; group 2: 36 *Withdrawals*: 6, lost to follow-up. Group 1: 5; group 2: 1 *N participants assessed (lesions)*: 66 (196). Group 1: 31 (91); group 2: 35 (105) *Mean age (male/female)*: 21.9 years/17.6 years (range 5-48 years). Group 1: 23.6 years/17.4 years; group 2: 20.2 years /18.1 years *Sex (male/female)*: 50 (75.7%)/16 (24.3%). Group 1: 26/5; group 2: 24/11

	Baseline data: • Number of lesions: group 1: 91; group 2: 105 • Mean duration of lesions (SD): group 1: 46.7 days (1.67 months); group 2: 45 days (1.58 months)
Interventions	*Type of interventions*: • *Group 1*: AL 20 mg/kg per day + low-dose IMMA 30 mg/kg/d for 20 days • *Group 2*: IMMA 60 mg/kg/d for 20 days *Duration of intervention*: 20 days *Duration of follow-up*: 51 days (1 month after the end of treatment)
Outcomes	*Healing rates*: percentage of participants 'cured' 51 days after treatment. On day 21 (end of therapy), the clinical response to treatment was coded subjectively as: apparent cure, partial response, and failure. After 1 month of follow-up (day 51), the participants were described as showing definitive cure if all the lesions had healed and direct smears of the lesions were negative *Adverse effects* *Tertiary outcomes*: microbiological or histopathological cure of skin lesions Time points reported: day 21, and 1 month after the end of treatment: day 51
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Seventy-two patients were assigned randomly to two groups." Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers across intervention groups: 5/36 (13.89%), AL + IMMA group; 1/36 (2.78%), IMMAgroup We think missing outcome data likely to be related to true outcome

Momeni 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Momeni 2003

Methods	*Study design*: randomised controlled trial *Setting/location*: endemic areas in the north of Isfahan city, Iran *Study period*: not described *Sample size calculation*: sample size calculation was based on 90% significance and 90% power to detect a difference between vehicle and ketoconazole. Assuming a 15% spontaneous cure with placebo, a minimum usefulness of a 60% cure with ketoconazole cream and about a 10% dropout, the sample size was calculated as 45 individuals in each group
Participants	*Type of Leishmania*: *Leishmania* spp: *L major* and *L tropica* *Inclusion criteria*: age > 5 years, laboratory-confirmed diagnosis of CL, no previous treatment for leishmaniasis, no serious concomitant medical problems *Exclusion criteria*: pregnant and nursing women, lesions on the face, lesions of > 4 months duration *N randomised*: 90 *Withdrawals*: 17 *N assessed*: 73 *Age*: mean 19.9 years (range 6-60) *Sex (male/female)*: 45/28 *Baseline data*: • Total number of lesions: 59 (group 1) and 43 (group 2) • Mean duration of lesions: 38 days (group 1) and 42 days (group 2)
Interventions	*Type of interventions*: • *Group 1*: ketoconazole cream • *Group 2*: vehicle *Duration of intervention*: twice daily for 21 days.
Outcomes	*Healing rates*: clinical response to treatment was coded subjectively as: apparent cure, partial response or failure. Definitive cure was defined if at day 51, the lesions were healed and direct smears of the lesions were negative *Adverse effects* Time points reported: the clinical response of the lesions was reported on days 21 (end of therapy) and 51
Notes	*Study funding sources*: supported by a research programme of Isfahan University of Medical Sciences *Possible conflicts of interest*: not described

Momeni 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was designed as a double-blind, N randomised, placebo-controlled trial" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and ketoconazole creams were identical cream containing either 25 ketoconazole 2% or placebo were used in the study. The two treatment groups received either the ketoconazole cream or placebo twice daily for 21 days as coded tubes with the same dosage"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	Low risk	Other items assessed correctly reported

Mostafavi 2013

Methods	*Study design*: randomised controlled trial *Setting/location*: skin and CL clinic in Gaz in Isfahan, Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: size of ulcer less than 5 cm in diameter, ≤ 5 lesions, duration of disease < 3 months *Exclusion criteria*: patients who had lesions on the face near the eyes or on the nose or ears, pregnancy, lactation, lupoid or sporotrichoid lesions, use of immunosuppressor drugs in the past 6 months and severe adverse effects, exacerbation of the disease

	N randomised: 40 participants (19 in prepared gel group and 21 vehicle gel mask) *Withdrawals*: 1 participant in prepared gel group *N assessed*: 39. 21 (100%) in vehicle gel group, and 18 in prepared gel group *Mean age*: 28.2 years *Sex (male/female)*: 25/15 *Baseline data*: not described
Interventions	*Type of interventions*: • *Group 1*: MA gel mask. Prepared by using polyvinyl alcohol (PVA), sodium carboxymethylcellulose, and hydroxypropyl methylcellulose as the base polymer and glycerin as the plasticizer, applied twice a day • *Group 2*: vehicle gel mask, applied twice a day *Duration of intervention*: 6 weeks *Co-interventions*: all of the participants received the standard treatment including ILMA weekly and cryotherapy every 2 weeks for a maximum of 6 weeks
Outcomes	*Treatment outcome*, defined as: • Complete healing: complete disappearance of the lesion • Moderate improvement: reduction in the size of the lesion more than 50% • Mild improvements: reduction in the size of the lesion less than 50% • No change: no considerable change in the size of the lesion • Worsening: increase in the size of lesion • Relapse: recurrence of lesion after complete healing Time points reported: 2 months after the end of treatment for relapse
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Open trials. Photography was done from all the lesions both at the first visit and all the follow-up visits

Mostafavi 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Protocol not available; not registered; in clinical trial registry; adverse effects not reported
Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability was not correctly reported

Mujtaba 1999

Methods	*Study design*: randomised controlled trial *Setting/location*: Pakistan *Study period*: around 4-5 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp not mentioned *Inclusion criteria*: clinical diagnosis of CL and positive Giemsa-stained smear of parasite *Exclusion criteria*: > 5 lesions and pregnant women *N participants randomised (lesions)*: 104 (215). Group 1: n = 49 (111); group 2: n = 55 (104) *Withdrawals*: 8 *N assessed*: 96. group 1: n = 49; group 2, n = 47 *Age*: • 0-10 years: group 1, 11; group 2, 12 • 11-20 years: group 1, 19; group 2, 17 • 21-30 years: group 1, 10; group 2, 11 • > 30 years: group 1, 9; group 2, 7 *Sex (male/female)*: 58/38 *Baseline imbalances*: comparability regarding age, sex, number, and site of lesions and duration of the disease • Duration of the disease (months) ◦ 0-2: group 1, 12; group 2, 11 ◦ 3-4: group 1, 13; group 2, 12 ◦ 5-6: group 1, 11; group 2, 13 ◦ >6: group 1, 13; group 2, 11 • No. of lesions in individual participants ◦ 1: group 1, 21; group 2, 19 ◦ 2: group 1, 12 ; group 2, 11 ◦ 3: group 1, 11; group 2, 10 ◦ > 3: group 1, 5; group 2, 7 • Total number of lesions at various anatomic sites in all participants ◦ Upper limbs: group 1, 48; group 2, 45 ◦ Face: group 1, 33; group 2, 31 ◦ Lower limbs: group 1, 29; group 2, 28 ◦ Trunk: group 1, 1; group 2, 0

Mujtaba 1999 (*Continued*)

Interventions	*Type of interventions*: • *Group 1*: ILMA injections weekly until complete cure or up to 8 weeks • *Group 2*: ILMA injections fortnightly until complete cure or up to 8 weeks *Duration of intervention*: until complete cure or up to 8 weeks
Outcomes	*Healing*: complete cure (100%); partial (> 50%; < 50%); failure (nil) *Speed of healing (time taken to be 'cured')* *Duration of remission and percentage of people with treated lesions that recur within 6 months and 1, 2*, and*3 years*:*time assessment not specified* *Prevention of scarring* *Adverse effects* Time points reported: at 2, 4, 6 and 8 weeks of treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two treatment groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients in group A were treated with weekly and those in group B with fortnightly intralesional injections" Comment: we think the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 8/104: 7.6% lost to follow-up Comment: the results for the defaulters were excluded from the statistical analysis. We think missing outcome data unlikely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes

Mujtaba 1999 (*Continued*)

Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Nassiri-Kashani 2005

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: October 2000 to February 2001 (5 months) *Sample size calculation*: to detect a clinically relevant difference of at least 25% between placebo (35% estimated response rate) and itraconazole (60% estimated response rate) in the primary outcome parameter with a power of 90% and a 2-sided type I error of 5%, a total of 164 subjects (82 in each group) were required. To compensate for dropouts, 20% more participants were enrolled in each group (in total 200 participants)
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: aged 12-60 years; presence of parasitologically confirmed lesion(s) of CL; healthiness on the basis of physical examination, medical history, and the results of blood biochemistry and haematology, carried out < 2 weeks before the start of the trial *Exclusion criteria*: women of child-bearing age without adequate effective contraception, pregnant or breastfeeding, duration of lesions > 45 days, presence of lesions on the face or near the mucous membranes, > 5 lesions, any lesion with a diameter > 3 cm, history of any systemic antileishmanial therapy, known hypersensitivity/allergy to itraconazole, receiving any drug with known interaction with itraconazole *N randomised*: 200 *Withdrawals*: 42 in total. 17 in the Itraconozale group and 25 in the placebo group *N assessed*: 158 *Age*: not described *Baseline imbalances*: comparable with regard to age, sex, and duration of the lesions • Group 1: mean number of lesions: 2.5, mean size of lesions: 7.76 mm • Group 2: mean number of lesions: 2.2, mean size of lesions: 8.58 mm • Duration of < 45 days
Interventions	*Type of interventions*: • *Group 1*: itraconazole 200 mg once daily • *Group 2*: placebo *Duration of intervention*: 8 weeks
Outcomes	*Healing rates*: for clinical assessment a 5-point scoring system was employed: cure (complete re-epithelialisation of all of the lesions), moderate improvement (more than 50% reduction in the size of the lesions), mild improvement (less than 50% reduction in the size of the lesions), no change, and worsening *Adverse effects*: at each visit, all of the participants were asked about any adverse effects Time points reported: after completion of treatment (8 weeks), and at the end of the 3 months follow-up (healing rates)
Notes	*Study funding sources*: supported by a grant from Janssen-Cilag Pharmaceuticals Inc *Possible conflicts of interest*: none declared

Nassiri-Kashani 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation sequence was generated from a random number table"
Allocation concealment (selection bias)	Low risk	Quote: "Concealed from the investigator until the data entry was completed and the data bank was locked"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients were randomly allocated to receive either itraconazole in the form of two 100-mg capsules or identical placebo capsules once daily for 8 weeks." Comment: we think the outcome is unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers and reasons for missing data across intervention groups (17% itraconozale group; 25% placebo group) Comment: the results for the defaulters were not excluded from the statistical analysis. We think missing outcome data likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	Low risk	Other items assessed correctly reported

Nilforoushzadeh 2004

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: not mentioned *Inclusion criteria*: CL confirmed with direct smear, aged 1-20 years, maximum number of lesions 3, maximum size of lesion 5 cm, duration of disease less than 8 weeks *Exclusion criteria*: history of allergy to MA, pregnancy or lactating

	N randomised: 210 *Withdrawals*: 53: 29/105 in group 1 and 24/105 in group 2 *N assessed*: 157. Group 1: 76, group 2: 81 *Age*: not described *Baseline data*: not described
Interventions	*Type of interventions*: • *Group 1*: combination triple therapy consisting of: 15% PR + 10% urea applied twice daily for 4 weeks, cryotherapy with liquid nitrogen repeated every 2 weeks till complete healing or for a maximum of 3 sessions, ILMA twice every week till complete healing or for a maximum of 6 weeks (in sessions that both cryotherapy and injections were used, cryo was done before injections) • *Group 2*: ILMA twice every week till complete healing or for a maximum of 6 weeks *Duration of intervention*: 6 weeks
Outcomes	*Healing rates*: percentage of participants 'cured' 2 weeks after treatment *Adverse effects* Time points reported: not described
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	High rates of dropouts: 53/210 (25.2%)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes

Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability were not correctly reported

Nilforoushzadeh 2006

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Disease and Leishmaniasis Research Center (SDLRC), Isfahan, Iran *Study period*: around 5 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: not mentioned *Inclusion criteria*: CL confirmed with direct smear *Exclusion criteria*: pregnant or nursing mothers, treated previously for CL, any known intercurrent illness or a history of allergy to MA, palpebral lesions, having > 5 lesions, lesion > 3 cm, duration of lesions was > 12 weeks *N randomised*: 80: 40 in each group *Withdrawals*: 7 *N assessed*: 73: 38 in group 1 and 35 in group 2 *Age*: range 5-75 years *Baseline data*: the most common clinical type of the lesions in both groups was papule (50% in TCA and 44% in the ILMA group) and nodule (25% in TCA and 24% in the ILMA group) Mean number of lesions: TCA: 1.2; ILMA: 1.4
Interventions	*Type of interventions*: • *Group 1*: TCA 50% (wt/vol) was applied on the lesions every 2 weeks up to 3 times • *Group 2*: ILMA weekly up to 6 weeks *Duration of intervention*: up to 6 weeks
Outcomes	*Healing*: complete cure was defined as complete healing and re-epithelialisation of the lesion(s); partial care as partial clinical improvement with reduction in erythema, induration and size of the lesions; treatment failure as the absence of any change or worsening of the lesion(s) *Duration of remission and percentage of people with treated lesions that recur after 3 months of follow-up* *Adverse effects* *Microbiological or histopathological cure of skin lesions* Time points reported: after the last treatment session, 1 and 3 months post-treatment. Complete cure was reported at 4 and 6 weeks of the treatment period. Recurrence was assessed at 3 months follow-up
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Nilforoushzadeh 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random digit table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Unblindness is a limitation of this study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "For 80 patients, which participated in the study, 73 cases completed the study" Comment: the results for the dropouts were excluded from the statistical analysis We think missing outcome data likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Nilforoushzadeh 2007

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Disease and Leishmaniasis Research Center (SDLRC), Isfahan, Iran *Study period*: 4 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: not mentioned *Inclusion criteria*: CL confirmed with direct smear, no history of systemic or topical therapy for CL, absence of the malnutrition or severe predisposing disease such as cardiac, renal or hepatic disease and other contraindication for MA *Exclusion criteria*: pregnant or lactating mothers, lesions > 3 months old and treated with the drugs that had interaction with MA *N randomised*: 100, 50 in each group *Withdrawals*: 23 (13 in the honey group and 10 in the ILMA group). However, in the abstract authors stated that 10 participants left the study *N assessed*: 90 (45 in each group)

	Age: range 7-70 years *Baseline data*: the most common clinical type of the lesions in both groups was plaque (60% in honey + ILMA and 55.6% in the ILMA-alone group). Mean number of lesions: honey + ILMA: 1.3; ILMA: 1.7
Interventions	*Type of interventions*: • *Group 1*: topical honey soaked gauze twice daily + ILMA • *Group 2*: ILMA *Duration of intervention*: once weekly until complete healing of the ulcer or for maximum of 6 weeks
Outcomes	*Healing*: complete healing was defined as disappearance of the induration and complete re-epithelialisation of the ulcer. Complete healing of the lesions was defined as complete clinical and parasitological healing (negative direct smear); partial healing of the lesions was defined as the decrease of the size and indurations of the lesions; non-responsive was defined as no clinical change or progression of the lesions *Speed of healing (time taken to be 'cured')*: expressed as mean healing time *Adverse effects* Time points reported: assessed weekly for 6 consecutive weeks and at the end of the 2nd, 3rd, and 4th month. Cure was assessed at the end of treatment and follow-up
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: no competing interests

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random allocation software (ver 1.0, May 2004; Saghaei)"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	We think the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Balance in numbers and reasons for missing data across intervention groups (13/45 (28.8%) in honey + ILMA group; 10/45 (22.2%) in ILMA-alone group) Comment: the results for the defaulters were excluded from the Kaplan-Meyer analysis

Nilforoushzadeh 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: relevant outcomes were reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Nilforoushzadeh 2008

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Skin Diseases and Leishmaniasis Research Center. Isfahan, Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* and *L major* *Inclusion criteria*: all the participants had positive smear for *Leishmania* body and had not received any topical or systemic therapy for leishmaniasis, aged 7-70 years, lesion not more than 3 months *Exclusion criteria*: pregnant or lactating; history of cardiac, renal, hepatic diseases; any contraindication for the treatment *N randomised*: 150. Group 1: 50; group 2: 50; group 3: 50 *Withdrawals*: 26. Group 1: 7; group 2: 14; group 3: 5 *N assessed*: 124 (82.66%). Group 1: 43 (86%); group 2: 36 (72%); group 3: 45 (90%) *Mean (SD) age*: group 1: 33.1 years (17.5); group 2: 27.8 years (9.8); group 3: 29.1 years (14.7) *Sex (male/female)*: 88 (70.97%)/36 (29.03%) • Group 1: 32 (74.4%)/11 (25.6%) • Group 2: 23 (63.9%)/13 (36.1%) • Group 3: 33 (73.3%)/12 (26.66%) *Baseline data*: • Type of lesion (no numbers): papule, nodule, plaque, ulcer, sporotrichid • Location of lesion (no numbers): face and neck, upper extremity, lower extremity, trunk
Interventions	*Type of interventions*: • *Group 1*: IMMA 60 mg/kg/d + placebo • *Group 2*: IMMA 30 mg/kg/d + 40 mg oral omeprazole for 3 weeks. Low dose of MA was prepared by adding normal saline to MA • *Group 3*: IMMA 30 mg/kg/d + oral placebo for 3 weeks The oral placebo was identical in appearance to omeprazole capsules and was administered in the similar way *Duration of intervention*: 3 weeks
Outcomes	*Clinical cure*: rate of complete response, 3 months (12 weeks) after starting treatment. *Scale*: complete healing of the lesions was regarded as complete clinical and parasitological healing (negative direct smear). Partial healing of the lesions was regarded as decrease of the size and indurations of the lesions, and no response was regarded as no clinical change or progression of the lesions

	Time to healing: proportion of complete improvement in the 3 groups during the course of treatment *Adverse effects*: at the end of treatment Time points reported: clinical cure: 12 weeks. Time to healing: 2, 4, 6, 8, 12 weeks. Adverse effects: at the end of treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: they declared no competing interests.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were selected and randomised by random allocation software into 3 groups
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The oral placebo was completely similar to omeprazole capsules and was administered in the similar way; low dose of IMMA was prepared by addition of normal saline to IMMA Both the investigating physicians and the participants were blinded to the type of treatment and drug codes were revealed only at the end of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Nilforoushzadeh 2012

Methods	*Study design*: randomised controlled trial *Setting/location*: Isfahan University of Medical Science, Isfahan, Iran *Study period*: March 2008 to March 2009 (12 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: unclear *Exclusion criteria*: pregnant, children < 5 years, palpebral lesions (less than 20 mm from palpebral margin), > 5 lesions, > 12 weeks duration of leishmaniasis, history of any specific anti-leishmaniasis therapy, significant underlying diseases *N randomised*: 80 lesions *Withdrawals*: 4 lesions *N assessed*: 76 lesions (38 lesions in each group) and 60 patients (30 patients in each group) *Mean (SD) age*: 5.11 years (13.3) (range 5-50) *Sex*: unclear *Baseline data*: • Lesions according to sex: ○ Female: group 1, 16 (42.1%); group 2, 23 (60.5%) ○ Male: group 1, 22 (57.9%) and group 2, 15 (39.5%) • Mean size of lesions at the beginning of study was not different between groups (P = 0.58) and was 2.66 cm (SD 0.37) in group and 13.18 cm (SD 0.89) in group 2 • Location of lesion: ○ 61/76 lesions in the upper extremities or head: 30/38 lesions (78.9%) in group 1 and 31/38 lesions (81.5%) in group 2 ○ 15/76 lesions in the lower extremities: 8 lesions (21.05%) in group 1 and 7 lesions (18.4%) in group 2
Interventions	*Type of interventions*: • *Group 1*: after cleansing the lesion with alcohol, TCA 50% (Merck, Berlin, Germany) was applied onto the lesion using a cotton swab, until frosting the lesion, once a week and for up to 2 weeks. Afterwards, a controlled localised heating of the lesions was performed using an RF heat generator (4 MHz, maximum output 90 W; Ellman International Inc, NY, USA). The area was heated to 42°C surface temperature for 30 s once a week and for 4 consecutive weeks • *Group 2*: ILMA (Sanofi-Aventis, France) administered twice a week and continued up to 8 weeks until absolute healing of lesions *Duration of intervention*: non-ablative radiofrequency + topical TCA 50%: 4 weeks; ILMA: 8 weeks
Outcomes	*Treatment responses*: • Complete cure: complete clinical healing was defined as complete re-epithelialisation of the lesions, flattening of the lesions and lack of indurations along with negative direct smear • Partial cure: partial clinical improvement along with decreased size of indurations, erythematic areas, and lesions at the end of the treatment • Non-cure or treatment failure: no clinical improvements along with unchanged or even increased size of lesions Time points reported: 6 months of treatment

Nilforoushzadeh 2012 (*Continued*)

Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "This computer-based randomised controlled trial was conducted from March 2008 to March 2009"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The examinations and measurements were performed by the investigators who were blinded to the type of treatment. "
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Originally 80 lesions were studied and randomly assigned to the 2 groups. However, due to missing data, only 76 were finally included in the analysis. No ITT analysis
Selective reporting (reporting bias)	High risk	Complete cure was described in Methods and Results, but partial cure and treatment failure was not reported in the Results section No adverse effects reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Nilforoushzadeh 2013

Methods	*Study design*: randomised controlled trial *Setting/location*: Cutaneous Leishmaniasis and Skin Diseases Research Center, Isfahan, Iran *Study period*: 2010 to 2011 (12 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: age older than 5 years, diameter less than 3 cm, the duration of disease less than 12 weeks, lesions with less than 2 cm distance from eyelid, < 5 lesions

	Exclusion criteria: pregnancy; lactation; colloid scar; lesions on cartilage, eyelids or joints; history of using other drugs against CL, treatment with immune system inhibitors *N randomised*: 90 (30 people in each group) *Withdrawals*: not described *N assessed*: 90 (30 people in each group) *Mean (SD) age*: 24.5years (14) *Sex (male/female)*:21/9, 23/7 and 21/9 *Baseline data*: Number of lesions:single lesion in 53 (58.9%), 2 lesions in 29 (32.2%) and 3 lesions in 8 patients (8.9%) *The type of lesion:* plaque in 32 patients (35.6%), nodule in 44 (48.4%), plaque and nodule in 8 (8.9%), and papule in 6 patients (6.7%) *Distribution of lesions:* hand 43, foot 15, face 8, trunk 5, hand and trunk 4, hand and neck 4, neck 4, hand and foot 4, hand and face 2, ear 1
Interventions	*Type of interventions*: • *Group 1*: ILMA twice a week for a maximum of 8 subsequent weeks. The tip of the insulin syringe was entered from a point out side of the lesion at the periphery of lesion and the injection was continued until the whole area was blanched. This was repeated in all areas of the lesion until whole lesion was blanched. • *Group 2*: ILMA + TCA 50% solution. Simultaneously with the MA injection twice a week, the TCA solution 50% was applied with cotton applicator once a week for 8 consecutive weeks until the lesion was frosted. The participants were visited at the beginning of the treatment and after 3 and 6 months. Final evaluation was done in the 6th month. • *Group 3*: ILMA + fractional laser. In this group IL injection was done twice a week with fractional laser every 2 weeks. The laser used was Dosis M&M, Q ray FRX system with energy of 25, 1 pass, dots cycle 6 and pixel pitch of 1 mm. In each session, before treatment with laser, first lesion was cleaned with a mild cleanser and 70% then alcohol. The laser treatment was done by an experienced dermatologist every 2 weeks for 2 sessions after IL injection. All patients in three groups were followed weekly for 3 months and then after 4 and 6 months to assess improvement of lesions and size of scar
Outcomes	*Clinical response*, according to standard quartile grading: • 0 < 25% (mild improvement) • 25% < score 1 < 50% (moderate improvement) • 50% < score 2 < 75% (good improvement) • < 75% (very good improvement) The quantitative 4-point scale used included: • 0 = unchanged size • 1 = the scar size became a bit small • 2 = the scar size became very small • 3 = the scar is almost removed Time points reported: 6 months
Notes	*Study funding sources*: Isfahan University of Medical Sciences *Possible conflicts of interest*: none declared
Risk of bias	

Nilforoushzadeh 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible for blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote "Evaluation of patients were done by two physicians who were not aware of the treatment group. These two physicians did the evaluations separately. The reduction in this size of ulcer and the scar was compared with the same lesion"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Nilforoushzadeh 2014a

Methods	*Study design*: prospective randomised controlled trial *Setting/location*: Central Research Center of Skin Diseases and Leishmaniasis and Novin Laser Center; Isfahan, Iran *Study period*: June 2010 to September 2011 (15 months) *Sample size calculation*: sample size was calculated as 60 cases in each group with further rate of 10% dropouts and exclusions
Participants	*Type of Leishmania*: not described *Inclusion criteria*: leishmaniasis scar diagnosed clinically on participants by a dermatologist *Exclusion criteria*: pregnancy, lactation, colloid scar, treatment with immune system inhibitors, use of isotretinoin or fillers for the past 6 months, use of dermabrasion or skin resurfacing for the past 12 months, skin types of IV to V1 *N randomised*: 120 (60 people in case group and 60 in control group) *Withdrawals*: not described *N assessed*: not described *Mean (SD) age*: 27.21 years (11.52) (range 6-45)

	Sex (male/female): 51%/49% *Baseline imbalances*: none *Severity of illness*: mean (SD) scar size: laser CO_2 group: 2.3 cm (0.3) and fractional CO_2 laser: 3.4 cm (0.4)
Interventions	*Type of interventions*: • *Group 1*: ablative CO_2 laser after applying the topical anaesthetic on scar site with pulsed CO_2, duration: 10 ns, frequency: use of 20 kHz, and power: 25 Kw for one session. The participants were visited at the beginning of the treatment and after 3 and 6 months. Final evaluation was done in the 6th month. • *Group 2*: fractional laser in each session by energy: 25, one pulse, pass: 1, dot cycle: 6, with the system of Qray FRX, Dosis M and M
Outcomes	*Clinical response*, according to standard quartile grading: • 0 < 25% (mild improvement) • 25% < score 1 < 50% (moderate improvement) • 50% < score 2 < 75% (good improvement) • < 75% (very good improvement) The quantitative 4-point scale used included: • 0 = unchanged size • 1 = the scar size became a bit small • 2 = the scar size became very small • 3 = the scar is almost removed Time points reported: 6 months
Notes	*Study funding sources*: Isfahan University of Medical Sciences *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "A photo was taken from patients before and after treatment with a digital camera ... Evaluation of participants were done by 2 physicians who were not aware of the treatment group. These 2 physicians did the evaluations separately. The reduc-

Nilforoushzadeh 2014a (*Continued*)

		tion in this size of ulcer and the scar was compared with the same lesion"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Nilforoushzadeh 2014b

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Disease and Leishmaniasis Research Center, Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: participants with positive direct smear for CL; 6-60 years of age; without any previous history of systemic or topical therapy for CL; lesions < 3 cm, < 12 week duration, and not located within 2 cm distance of palpebral margin *Exclusion criteria*: pregnant and lactating women *N randomised*: 200 participants *Withdrawals*: not described *N assessed*: 187; group 1: 91; group 2: 96 *Mean (SD) age*: 10.7 years (22.04); group 1: 10 years (20.6); group 2: 11.3 years (23.3) *Sex (male/female)*: 101/86 *Baseline data*: mean (SD) lesion area was 329 mm^2 (118.7) in group 1 and 359 mm^2 (55.6) in group 2
Interventions	*Type of interventions*: • *Group 1*: ILMA + 50% TCA was performed twice a week • *Group 2*: ILMA alone was performed twice a week *Duration of intervention*: complete resolution of the lesions or end of 8 weeks
Outcomes	*Clinical cure*: complete re-epithelialisation of the lesion and lack of induration. Clinical response was measured at the end of treatment and was defined as complete cure (negative direct smear and clinical healing), partial cure (partial clinical improvement with decreasing erythema, induration, and lesion size), non-cure or treatment failure (no clinical change or worsening of the lesions) Time points reported: 8 weeks
Notes	*Study funding sources*: the study is self-funded *Possible conflicts of interest*: there is no conflict of interest
Risk of bias	

Nilforoushzadeh 2014b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software (version 1.0, May 2004, Saghaei) was used for randomisation
Allocation concealment (selection bias)	Low risk	Participants with confirmed cutaneous leishmaniasis referred to the Skin Diseases and Leishmaniasis Research Center were selected and randomised by random allocation software into 3 groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The measurements were done before treatment and at the end of eighth week by the investigators who were blinded to the type of treatment." Comment: Lesions were photographed before and after completion of the treatment course Not clear how blinding was preserved
Incomplete outcome data (attrition bias) All outcomes	Low risk	From a total of 200 randomised participants, 96 participants in ILMA group and 91 participants in the combination group completed the study Losses to follow-up were below 25% and homogeneous between the groups
Selective reporting (reporting bias)	High risk	Protocol not available, not registered. Adverse effects not reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Ranawaka 2010

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Anuradhapura Teaching Hospital, Anuradhapura, Sri Lanka *Study period*: 32 months. Participant selection: April 2006 to June 2007 (15 months) *Sample size calculation*: not described

Participants	*Type of Leishmania*: *L donovani* *Inclusion criteria*: participants with CL who attended to Anuradhapura Teaching Hospital, Anuradhapura, Sri Lanka from April 2006 to June 2007 *Exclusion criteria*: not described *N randomised*: a total of 154 participants with 229 lesions were included in the study. IL 7% HSCS: 67; ILSSG: 87 *Withdrawals*: (4.5%: 7/154). HSCS: 3, ILSSG: 4 *N assessed*: 147 (95.45%) CL participants with 222 lesions completed treatments. HSCS: 64 (95.52%); ILSSG: 83 (95.40%) *Age*: mean 32 years (range 16 months to 74 years) *Sex (male/female)*: 99/55, M:F ratio of 1.8:1 *Baseline data*: • N lesions: HSCS: 93, ILSSG: 136 • Location of the target lesion: head and neck 41, upper limb 123, lower limb 43, trunk 14, buttock 1. 93.2% of lesions being on exposed parts of the body • Clinical presentation (n(%)): papules ≤ 1 cm diameter: 52 (23.6%); nodules > 1 cm diameter: 28 (12.7%); plaques: 14 (6.34%); central ulcer with erythematous induration around the lesion: 121 (55%); chronic non-healing ulcers with undermined edges without surrounding induration; 5 (2.2%) • 19 lesions were wet lesions and all others (91.4%) were dry lesions
Interventions	*Type of interventions*: • *Group 1*: HSCS was prepared by dissolving 12.2 g of sodium chloride in 200 mL of 0.9% sodium chloride (normal saline) solutions. The solution was injected intralesionally and not subcutaneously • *Group 2*: ILSSG (Pentostam) *Duration of intervention*: HSCS: 1-29 weeks, depending on the size and the duration of the lesions (mean 8.78 weeks). SSG: 1-13 weeks, depending on the size and the duration of the lesions (mean 5.11 weeks) Participants were seen weekly for the first 3 injections; fortnightly for the fourth and fifth injections; then monthly until cure
Outcomes	*Clinical cure*: the percentage of lesions that were cured with SSG and HSCS *Number of injections required per each lesion in total for cure* (scales: 1-10 injections) *Adverse effects*: systemic side effects with SSG or HSCS. Local side effects: pain during injection. Scarring after healing, postinflammatory hyperpigmentation Time points reported: at the end of treatment. Participants were followed-up every 3 months after cure for 18 months to assess recurrences and evidence of visceralisation
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the al-

Ranawaka 2010 (*Continued*)

		location sequence
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double blind" Insufficient information to permit judgment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind", "At each visit the patients were examined by the primary investigator who was blind to the therapy" Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.5% (7/154) did not complete the study
Selective reporting (reporting bias)	Unclear risk	No protocol was available; not registered. Insufficient information to permit judgment SD not provided for duration of treatment and number of injections
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Ranawaka 2015

Methods	*Study design*: randomised double-blind clinical trial *Setting/location*: Skin Clinic of Anuradhapura Teaching Hospital, Sri Lanka *Study period*: January 2012 to February 2013 (14 months) *Sample size calculation*: approximately 473 participants per group were required to enable the detection of a treatment difference of 5% with a lowest cure rate of one group of 90%
Participants	*Type of Leishmania*: *L donovani* *Inclusion criteria*: the study recruited participants with suspected CL who consented to participation *Exclusion criteria*: pregnant or lactating women, subjects with a history of cardiac, renal, or hepatic disease *N participants randomised (lesions)*: 444 (643). 10% HSCS: 192 (297); 15% HSCS: 82 (101); ILSSG: 170 (245) *Withdrawals (lesions)*: 17 (20) lost to follow-up. 10% HSCS: 8 (7); 15% HSCS: 3 (3); ILSSG: 6 (10) *N assessed (lesions)*: 427 (623); 10% HSCS: 79 (98); 15% HSCS: 184 (290); ILSSG: 164 (235) *Age*: mean 32.7 years (range 14 months to 88 years). Most (60.8%) were aged 16-45 years

	Sex (male/female): 286/158 *Baseline data*: the average delay in presentation was 8 months (range: 4 weeks to 5 years) . 91% of lesions were located on exposed areas of the body. Most (69.8%) participants had a single lesion
Interventions	*Type of interventions*: • *Group 1*: 10% HSCS, prepared by dissolving 18.2 g of medical sodium chloride in 200 mL of 0.9% sodium chloride (normal saline) solutions • *Group 2*: 15% HSCS, prepared by dissolving 28.2 g of medical sodium chloride in 200 mL of 0.9% sodium chloride (normal saline) solutions • *Group 3*: ILSSG *Duration of intervention*: participants were seen weekly for the first 3 injections, fortnightly for the 4th and 5th injections, and then monthly until a cure was achieved
Outcomes	*Clinical and parasitological cure*: responses were graded as slight (10% improvement from the initial status of the lesion), mild (20%-30% improvement), moderate (50% improvement), marked (80%-90% improvement), or as total if the lesion had cleared and parasites were not detected in the affected area by smear or culture. Both marked improvements and total clearance were considered to represent a cure. Reported at the end of treatment *Duration of treatment*: in weeks, mean (range) *Time required to achieve the cure of the lesion*: mean and median times taken for cure for the different treatments groups. Every 5 weeks until achieve 30 weeks *Injections per lesion*, mean (range): number of injections for cure per lesion *Relapse*: *L recidivans* *Adverse effects*: *local side effects*: at the site of the lesion caused by the injections: pain during injections, postinflammatory hyperpigmentation, scarring, postinflammatory depigmentation, ulceration and necrosis, *L recidivans*. *Systemic side effects*: no systemic or significant local side effects with either SSG or 10% HSCS Time points reported: participants were followed up every 3 months after cure for more than 6 months to assess recurrences and evidence of visceralisation
Notes	*Study funding sources*: none reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The treatment options were documented separately and packed in opaque envelopes numbered consecutively according to the randomisation schedule at a ratio of 2: 2: 1
Allocation concealment (selection bias)	Low risk	The allocation sequence was concealed from the researcher who enrolled and assessed the participants by the use of sequentially numbered, opaque, sealed, and stapled envelopes that were impermeable even

Ranawaka 2015 (*Continued*)

		to intense light
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and the investigator (who assessed the participants for their clinical response) were blind to the type of therapy allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At each visit, the participant was examined by the primary investigator, who was blinded to the therapy
Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers of withdrawals were similar and small in the 3 groups: 4.1% (8/192) in group 1, 3.6% (3/82) in group 2, and 3.5% (6/170) in group 3
Selective reporting (reporting bias)	Low risk	The study published reports our primary outcome and adverse effects
Other bias	Low risk	Other items assessed correctly reported

Reithinger 2005

Methods	*Study design*: randomised controlled trial *Setting/location*: Khair Khana Clinic; Kabul, Afghanistan *Study period*: 100 days *Sample size calculation*: to detect a 20% difference in the cure rate between the SSG and thermotherapy groups, assuming an 80% cure rate in the SSG groups, with a 90% power and a 5% 2-sided type I error, 98 subjects were needed in each group. To compensate for anticipated loss to follow-up, 40% more participants were enrolled in each group
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: age > 5 years; the presence of a single, parasitologically confirmed CL lesion; no prior history of disease and/or antimonial treatment *Exclusion criteria*: the presence of a CL lesion located on or immediately adjacent to the nose, lips, or eyes; pregnancy; breastfeeding; major surgery in the previous 3 months; presence of any uncontrolled medical condition; anticipated unavailability for follow-up *N randomised*: 431. Group 1: 148, group 2: 144, group 3: 139 *Withdrawals*: 172 in total: 30 decided to withdraw after allocation and 142 did not complete the 4 visits or the follow-up *N assessed*: 259. Group 1: 93, group 2: 58, group 3: 108 *Age*: range 10-20 years *Sex (male/female)*: 200/201 *Baseline data*: the lesions were primarily located on the face (43.4% of participants), on the hands (38.2%), legs (15.9%) and arms (2.4%) • Group 1: MNL: 1. MSL: 12.75 mm. MDLBT: 6 months

	• Group 2: MNL: 1. MSL: 13.75 mm. MDLBT: 5.5 months • Group 3: MNL: 1. MSL: 10.25 mm. MDLBT: 6 months
Interventions	*Type of interventions*: • *Group 1*: ILSSG, 5 injections of 2-5 mL every 5-7 days depending on the lesion size for up to 29 days • *Group 2*: IMSSG (20 mg/kg) daily for 21 days • *Group 3*: thermotherapy using radiofrequency waves (1 treatment of > 1 consecutive application at 50ºC for 30 s depending on lesion size) *Duration of intervention*: not described
Outcomes	*Percentage of p*articipant*s 'cured' at 100 days after treatment initiation and by time to cure*: cure was defined as the complete re-epithelialisation of the CL lesion, with no evidence of papules, inflammation, or induration *Speed of healing (time taken to be 'cured')* *Adverse effects*: the occurrence of adverse effects was evaluated blindly by means of participant interviews and physical examinations during follow-up visits Time points reported: trial endpoint was 100 days after start of therapy
Notes	*Study funding sources*: the HNI Malaria and Leishmaniasis Control Program is funded by the European Union. This study was supported by the United Nation Children's Fund/ United Nation Development Program/WorldBank/World Health Organization Special Program for Research and Training in Tropical Diseases, the Afghan Research Evaluation Unit, and the Leveen Family Fund *Possible conflicts of interest*: since March 2004, R Reithinger has been a part-time employee of Thermosurgery Technologies. All other authors: no conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients then proceeded to pick 1 of 3 identical cardboard pieces out of a hat (the cardboard had been labelled with different treatment codes on one of its sides, the codes being non-visible to the patient) . After patients were randomly assigned to receive a treatment, the cardboard piece picked was returned to the hat."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding of participants and personnel seemed to be performed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The occurrence of adverse effects was evaluated blindly by means of patient interviews and physical examinations dur-

Reithinger 2005 (*Continued*)

		ing follow-up visits", "Microscopic examination was performed blindly." *Comment*: microscopic examination and adverse effects were performed blindly but no description about clinical examination was given
Incomplete outcome data (attrition bias) All outcomes	Low risk	172/431 (39.9%) withdrew from the study. However, ITT analyses were performed Quote: "An intention-to-treat analysis of the data (... including the patients lost to follow-up, who were considered to have had treatment failure) yielded similar results for the comparison of the odds of cure for the different treatments"
Selective reporting (reporting bias)	Low risk	Comment: relevant outcomes were reported
Other bias	Low risk	Other items assessed correctly reported

Sadeghian 2006a

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: 3 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: CL in whom the diagnosis was confirmed by laboratory demonstration of the parasite in the lesions by direct smear *Exclusion criteria*: allergic to antimonial drugs or pentoxifylline, lactating or pregnant, history of systemic illness *N randomised*: 64, 32 in each group *Withdrawals*: 1 participant withdrew from the MA + placebo group *N participants assessed (lesions)*: 63. Group 1: 32 (143), group 2: 31 (164) *Mean age*: group 1: 27 years, group 2: 31 years *Sex (male/female)*: 29/34 *Baseline data*: duration of the disease approximately 1.3 months. • Group 1: 59.5% had plaque, 24.5% nodule and 16% papule type of lesions, and they were primarily located in the face (35%), upper limbs (24.5%), lower limbs (21%) and trunk (19.5%). MNL: 4, MDLBT: 1.2 months • Group 2: 42.7% had plaque, 33.6% nodule and 23.7% papule type of lesions, and they were primarily located in the face (33.5%), upper limbs (24.3%), lower limbs (22%) and trunk (20.2%). MNL: 5, MDLBT: 1.3 months
Interventions	*Type of interventions*: • *Group 1*: IMMA (20 mg pentavalent antimony/kg/d) + pentoxifylline (400 mg 3

	times daily) • *Group 2*: IMMA (20 mg pentavalent antimony/kg/d) + placebo (3 tablets daily) *Duration of intervention*: 20 days *Duration of follow-up*: 3 months
Outcomes	*Healing rates*: • Complete improvement defined as flattened lesions, no induration and appearance of epidermal creases • Partial improvement defined as reduction in the size of the lesions but without the appearance of epidermal creases • Poor response defined as no reduction in the size of the lesions *Adverse effects* Time points reported: after end of treatment and 3 months' follow-up
Notes	*Study funding sources*: not described *Possible conflicts of interest*: not described

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Study was described as "double blind" but has no description about allocation method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was described as "double blind" but has no description about the blinding method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient withdrew in the placebo group. Reasons for withdrawal were reported. However, no ITT analyses were performed
Selective reporting (reporting bias)	Low risk	Comment: relevant outcomes were reported
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Sadeghian 2006b

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Diseases and Leishmaniasis Research Center in Isfahan, Iran *Study period*: not described *Sample size calculation*: not described
Participants	*Type of Leishmania*:*L major* endemic in the area. *Inclusion criteria*: participant with positive smear for Leishman bodies, of both sexes and > 5 years old who did not have indication for systemic therapy *Exclusion criteria*: facial lesions or lesions on joints, sporotrichoid type, lupoid leishmaniasis, erysipeloid type and other atypical forms of CL, pregnant women, history of cardiovascular and renal diseases *N randomised*: 72, 36 in each group *Withdrawals*: 0 *N assessed*: 72 *Mean age*: HSCS, 20.52 years; ILMA group, 18.67 years *Baseline data*: the most common site of lesions was on the extremities and the least common site was the trunk in both groups. The size range of lesions were from 0.5-4 cm^2 (IL HSCL group) and from 0.5-4 cm^2 (ILMA group)
Interventions	*Type of interventions*: • *Group 1*: IL HSCL (NaCl 5%; 0.5 to 1 mL) • *Group 2*: ILMA (0.5-1 mL) *Duration of intervention*: weekly 6-10 weeks *Duration of follow-up*: 6 months
Outcomes	*Healing*: complete improvement is defined as completely clinical re-epithelialisation with no signs of induration and inflammation with negative smear for Leishman bodies at the end of the treatment period. Partial improvement is defined as the re-epithelialising lesion has become smaller but not cured. If the lesion has become larger or has not been differed it will be called as no response to treatment Time points reported: at 6 and 10 weeks of treatment and 6 months follow-up
Notes	*Study funding sources*: not described *Possible conflicts of interest*: not described

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This N randomised controlled clinical trail study with simple sampling." "72 patients randomly divided in two equal groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence

Sadeghian 2006b (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	*Comment*: relevant outcomes were reported
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Sadeghian 2007

Methods	*Study design*: randomised controlled trial *Setting/location*: Skin Diseases and Leishmaniasis Research Center, Iran *Study period*: 7 months *Sample size calculation*: not reported
Participants	*Type of Leishmania*: not reported *Inclusion criteria*: smear from a suspected CL lesion was confirmed positive for *Leishmania* *Exclusion criteria*: pregnant women, children < 5 years of age, patients with facial lesions, those who had already received or were under other specific antileishmanial therapy, significant underlying diseases *N randomised*: 117 *Withdrawals*: 0 *N participants assessed (lesions)*: 117: 57 (83) lesions in group 1 and 60 (94) in group 2 *Mean age*: group 1, 25.12 years; group 2, 22.6 years *Sex (male/female)*: group 1, 37/20; group 2, 29/31 *Baseline data*: the shape of lesions was papule, nodule and plaque-like. Lesions were located in the trunk and upper and lower limbs • Group 1: mean number of lesions: 1.4. Mean duration of lesions: 4.42 weeks. Mean largest diameter: 15.6 mm • Group 2: mean number of lesions: 1.5. Mean duration of lesions: 3.85 weeks. Mean largest diameter: 14.7 mm
Interventions	*Type of interventions*: • *Group 1*: controlled localised heating using an RF heat generator (4 MHz, maximum output 90 W). The affected area was heated to 50ºC surface temperature for 30 s • *Group 2*: ILMA. The volume of the drug was 0.1-4 mL (each mL contains 85 mg

	MA), depending on lesion size *Duration of intervention*: once weekly for 4 consecutive weeks *Duration of follow-up*: 6 months
Outcomes	*Percentage of participants 'cured'*: • Complete (lesions flattened, no induration, and epidermal creases appeared) • Partial (size of the lesion decreased but without the appearance of epidermal creases) • Poor (size of induration was unchanged or had increased) *Duration of remission and percentage of people with treated lesions that recur within 6 months* *Prevention of scarring* *Adverse effects* Time points reported: at the end of treatment, and 6 months after
Notes	*Study funding sources*: technical and financial support from the joint WHO Eastern Mediterranean Region (EMRO), Division of Communicable Diseases (DCD) and the WHO Special Program for Research and Training in Tropical Diseases (TDR): the EMRO/TDR Small Grant Scheme for Operational Research in Tropical and other Communicable Disease *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to one of two treatment groups using a random number list generated by Epi Info (a software package designed to provide easy form and database construction, data entry, and analysis with epidemiologist statistics, map sand graphs)"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Group 1 was treated with controlled localised heating using an RF heat generator. Group 2 was treated with ILMA
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Follow-up evaluation was made by clinical assessment of treated lesions by a second dermatologist who was blinded to the method of treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Sadeghian 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Safi 2012

Methods	*Study design*: randomised controlled trial *Setting/location*: Leishmaniasis clinic of the National Malaria and Leishmaniasis Control Program in Darul-Aman District, Kabul City, Afghanistan *Study period*: not described *Sample size calculation*: to detect an 8% difference in the cure rate between the current standard therapy (ILMA) and thermotherapy by radio frequency groups, assuming 90% cure rate in the conventional therapy with an 80% power and a 5% type I error, 174 subjects were needed in each group. To compensate for anticipated loss to follow-up, sample size inflated by 10%. Hence, the final sample size, figuring research design, rounded to nearest 10 turned out to be 390 subjects, with 195 assigned to each treatment group
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: aged > 5 years; presence of a single, parasitologically confirmed CL lesion *Exclusion criteria*: history of previous infections from anthroponotic CL that was treated with antimonial medications, lesions located within 2 cm of the eyelids or on the lips or nose *N randomised*: 390 (195 assigned to each treatment group) *Withdrawals*: 8 participants (6 in group 1; 2 in group 2). *N assessed*: 382 (189 in group 1; 193 in group 2). *Median (interval) age*: group 1, 14 years (5-70); group 2, 13 years (5-75) *Sex (male/female)*: group 1, 85/104; group 2, 92/101 *Baseline data*: • Mean (SD) systolic blood pressure: group 1, 116.2 mmHg (13.5); group 2, 113 mmHg (13.6) • Mean (SD) diastolic blood pressure: group 1, 72.4 mmHg (7.9); group 2, 72.2 mmHg(10.7) • Mean (SD) body weight: group 1, 42.5 kg (23.3); group 2, 39.01 kg (18.3) • Location of lesion (n (%)) ○ Group 1: face/neck: 161 (50.8), upper extremity 26 (48.1), lower extremity 2 (25) ○ Group 2: face/neck: 156 (49.2), upper extremity 28 (51.9), lower extremity 6 (75), trunk 3 (100) • Type of lesion (n (%)) ○ Group 1: nodule 69 (41.1), papule 120 (57.7) ○ Group 2: ulcer 6 (100), nodule 99 (58.9), and papule 88 (42.3) • Size of the lesion: group 1: median 1 cm^2 and size interval 1-4; group 2, median 2

	cm² and size interval 1 -4.
Interventions	*Type of interventions*: • *Group 1*: single application of thermotherapy by radio frequency producing localised heat of 50°C (122°F) for 30 s • *Group 2*: 5 injections of ILMA (2-7 mL depending on the size of the lesion). The injections were given in 7-day intervals for 5 weeks. *Duration of intervention*: 5 weeks in ILMA group
Outcomes	*Cure* was defined as complete re-epithelialisation of the lesion with no inflammation and resolution of the papule and/or nodule. Failure was defined as no improvement, with the lesion unchanged or worse compared with its status at the start of treatment. Lesions that showed some improvement but did not meet the criteria for cure were considered treatment failures *Adverse effects* Time points reported: 6 months after treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were asked to pick one of two identical cardboard pieces out of a box (the cardboard had been labelled with different treatment codes on one of its sides) for their group assignment. After patients were assigned to a treatment group, the cardboard piece picked was returned to the box."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were losses to follow-up and no ITT analyses were performed. Also, the distribution of the lesions and the size was uneven between the 2 arms Quote: "More papules (57.7%) were treated by thermotherapy compared to (42.

Safi 2012 (*Continued*)

		3%) those which were treated by Glucantime. Nodules were mostly treated by Glucantime (58.9%), whereas all ulcers were treated by Glucantime. The lesion size interval was [1-4 cm²] with median of 1 cm² for thermotherapy by radio frequency and 2 cm² for Glucantime." This is important because the authors found out the following significant associations: Quote: "Type and size of lesion, were significantly associated with the outcome variable (cure/failure). Type of lesion was significantly associated with treatment outcome in this sample, taking papules as reference (Table V). Those who had nodules were 41% less likely and those with ulcers were 80% less likely to be cured compared with those with papules"
Selective reporting (reporting bias)	High risk	Adverse effects were described in Methods but not in Results. They mention them vaguely in the Discussion section
Other bias	Low risk	Other items assessed correctly reported

Salmanpour 2001

Methods	*Study design*: randomised controlled trial *Setting/location*: Iran *Study period*: 18 months *Sample size calculation*: not described
Participants	*Type of Leishmania*:*Leishmania* spp: *L tropica* and *L major* *Inclusion criteria*: patient with CL confirmed parasitologically by direct skin smears or skin biopsies *Exclusion criteria*: children < 3 years of age, pregnant and lactating women, cases with concomitant renal, liver or heart disease, and any event of any laboratory abnormality prior to initiation of treatment *N randomised*: 96 *Withdrawals*: 0 *N assessed*: 96 (100%): 64 in the ketoconazole group and 32 in the ILMA group *Age*: range 3-64 years *Sex (male/female)*: 44/52 *Baseline data*: In the ketoconazole group: • Mean duration of lesions (SD): 2.6 months (1.4) • Mean number of lesions: 2.5

Salmanpour 2001 (*Continued*)

	In the MA group: • Mean duration of lesions (SD): 3.1 months (1.4) • Mean number of lesions: 2.3
Interventions	*Type of interventions*: • *Group 1*: ketoconazole orally (adults: 600 mg/d for 30 days and children: 10 mg/kg/d for 30 days) • *Group 2*: ILMA 6 injections (some received up to 8) *Duration of intervention*: 30 days in the ketoconazole group. There is no mention about frequency of injections in MA group
Outcomes	*Healing rates*: • Cured if lesions had completely re-epithelialised with little or no scarring at 6 weeks post-treatment. • Failure if participants showed one of the following findings: < 25% reduction in the diameter of induration after 4 weeks of treatment; the persistence of lesions 6 weeks post-treatment • Relapse of disease after initial healing at 6 weeks post-treatment *Adverse effects* Time points reported: participants were followed every 2 weeks for the duration of the treatment and every 6 weeks after cessation of treatment up to 24 weeks
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to two treatment groups using a simple randomisation method" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Group 1, which included 64 participants, was designated as the group treated with oral ketoconazole. Group 2, which included 32 participants, was designated as the group that received ILMA. The outcome is likely to be influenced by lack of blinding

Salmanpour 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	Imbalance in numbers and reasons for missing data across intervention groups: 7/57, ketoconazole; 9/23, ILMA
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Salmanpour 2006

Methods	*Study design*: randomised controlled trial *Setting/location*: Dermatology Clinic of Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran *Study period*: unclear *Sample size calculation*: not reported
Participants	*Type of Leishmania*: not reported *Inclusion criteria*: participant with CL confirmed *Exclusion criteria*: not described *N randomised*: 60 *Withdrawals*: 0 *N assessed*: 60 participants distributed into the 3 groups of equal number (n = 20) *Age*: not reported *Sex*: not reported *Baseline data*: lesions were located on the head, neck and lower and upper extremities. Lesion duration was divided in 2 groups: a duration of < 3 months and > 3 months. Regarding lesion size, the authors divided the sizes in 3 groups: < 1 cm, 1-3 cm and > 3 cm
Interventions	*Type of interventions*: • *Group 1*: cryotherapy. The freezing time was 10-30 s with a thawing interval of 20 s • *Group 2*: cryotherapy + ILMA. The participants first received cryotherapy and after 5-10 min were given ILMA • *Group 3*: ILMA. The solution was injected into each lesion (0.2 to 1.5 cm^3 per session per week, depending on the size) *Duration of intervention*: weekly for a total of 6-8 times for each case
Outcomes	*Healing rates*: percentage of participants 'cured': timing not reported *Adverse effects* Time points reported: not reported

Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	High risk	The outcome is likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	No explanation was provided for missing outcome data.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports included all expected outcomes, including those that were pre-specified
Other bias	High risk	Sample size calculation, reporting of *Leishmania* spp involved and baseline comparability were not correctly reported

Shamsi Meymandi 2011

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: dermatology clinic and leishmaniasis research centre of Afzalipour hospital of Kerman, province of Iran *Study period*: 21 months *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: aged 7-60 years, confirmed CL *Exclusion criteria*:chronic systemic disease (such as renal failure, myocarditis, hepatitis and pancreatitis), immune suppression, breastfeeding, pregnancy, sporotrichoid and lupoid forms, maximum diameter of lesions > 3 cm, disease duration more than 1 year, more than 2 lesions present, history of sensitisation to MA,facial and joint lesions, receiving

	other specific anti *Leishmania* therapies *N randomised*: 191. Group 1: 96, group 2: 95 *Withdrawals*: group 1: 16 (14: no follow-up, 2 enrolled in other treatment), group 2: 15 (8 no follow-up, 4 enrolled in other treatment, 3 did not adhere to treatment schedule) *N assessed*: 160 (83.77%). Group 1: participants: 80 (83.33%), group 2: participants: 80 (84.21%) *Age*: range 7-60 years *Sex (male/female)*: Randomised patients: group 1: 50(52%)/46 (48%), group 2 39 (41%) /56 (59%). Assessed patients: group 1: 42 (50%)/38 (46%); group 2: 31 (39%)/49 (61%) *Baseline data (N lesions)*: group 1: 80, GB: 80 Location*of the target lesion*: • Group 1: head and neck 1 (1.3%), upper limb 68 (85%), lower limb 7 (8.8%), trunk 4 (5%) • Group 2: head and neck 5 (6.3%), upper limb 64 (80%), lower limb 10 (12.5%), trunk 1 (1.3%) *Type of lesions*: • Group 1: plaque or ulcerated plaque 33 (40.5%), nodule or ulcerated nodule 47 (59.5) • Group 2: plaque or ulcerated plaque 25 (31.3%), nodule or ulcerated nodule 55 (68.7%) *Case type*: New, group 1: 67 (83.3%); group 2: 69 (86.3%) Recurrence, group 1: 0 (0%); group 2: 1 (1.3%) Failure of previous treatment, group 1: 8 (10%); group 2: 0 (0%) Missed previous treatment, group 1: 5 (6.3%); group 2: 10 (12.5%)
Interventions	*Type of interventions*: • *Group 1*: CO 2 laser. Lesions were locally anaesthetised by injection of 2% lidocaine. The CO 2 laser (6-8 W continuous wave) was applied to the lesions and an area 2-3 mm² around it. The procedure was repeated until the ulcer bed turned brown (maximum 3-5 times) • *Group 2*: participants were treated with combined cryotherapy (biweekly) and ILMA (weekly). Cryotherapy with liquid nitrogen was performed using dipstick technique. Then ILMA (Amp 1.5 gr in 5 Ml solution) was injected in lesions *Duration of intervention*: 16 weeks
Outcomes	*Clinical cure of the lesions*: defined as complete re-epithelialisation of 100% (± scar), complete flattening of induration *Laboratory cure of the lesions*: negative smear of the lesions compared with baseline Cure rate based on weeks of follow-up *Adverse effects* of 2 types of treatments Time points reported: weeks 2, 6, 12 and 16
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was generated by the use of a randomisation Table. A simple block randomisation list with block size of 4 was prepared by a member of the study
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation allocation concealment was performed by sending the randomisation number in envelopes to a member who was responsible for giving the assigned treatment after each eligible patient was enrolled. The recruited patients were referred to this member to receive their assigned treatments." Comment: unclear because no mention of opaque and numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were 31 withdrawals (16/96 (16.7%) in the ILMA + cryotherapy and 15/95 (15.8%) in the CO_2 laser group) Comment: no ITT analyses were performed. However, withdrawals accounted for < 20% and were homogeneous among the treatment groups
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Not registered. Some pre-specified outcomes were reported. Data on individuals not presented. Conflicting data is presented between the abstract and the tables
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Shanehsaz 2015

Methods	*Study design*: randomised double-blind placebo-controlled clinical trial *Setting/location*: Aleppo University Hospital Clinic, Aleppo, Syria *Study period*: 12 months (from July 2009 to July 2010) *Sample size calculation*: not described
Participants	*Type of Leishmania*: not described *Inclusion criteria*: parasitological confirmation; aged 5-65 years; normal values of liver, kidney, and pancreas function tests and electrocardiogram before treatment *Exclusion criteria*: pregnant and lactating women; history of cardiac, renal, and hepatic diseases; treatment with other drugs during the month before commencement of the study *N randomised*: 90, 30 in each group *Withdrawals*: not described, but it seems that there were no dropouts *N assessed*: 90, 30 in each group *Sex (male/female)*: group 1, 21 (70%)/9 (30%); group 2, 17 (56.7%)/13 (43.4%); group 3, 20 (66.7%)/10 (33.3%) *Mean (SD) age*: group 1, 26.3 years (11.2); group 2, 24.2 years (12.5); group 3, 25.1 years (12.4) *Baseline data*: Mean number of lesions (SD): group 1, 3.0 (1.92); group 2, 3.0 (1.92); group 3, 3.0 (1.92)
Interventions	*Type of interventions*: • *Group 1*: IMMA 60 mg/kg/d (Glucantime; Aventis, Paris Cedex, France) + oral placebo. The drug was available in 5 mL vials. • *Group 2*: IMMA 30 mg/kg/d + oral cimetidine 1200 mg/d • *Group 3*: IMMA 30 mg/kg/d and oral placebo *Duration of intervention*: 3 weeks for 3 groups
Outcomes	*Clinical and parasitological cure*: the effectiveness of the treatment was classified in 3 levels: complete response of the lesions was regarded as complete clinical and parasitological healing (negative direct smear). Partial response of the lesions was regarded as decrease of the size and indurations of the lesions, and no response was regarded as no clinical change or progression of the lesions *Time to healing*: proportion of complete response in 3 groups during the course of treatment *Adverse effects*: complications Time points reported: clinical and parasitological cure: 12 weeks. Adverse effects: 6, 8, 12 weeks
Notes	*Study funding sources*: this project was funded by the University of Aleppo, Aleppo, Syria *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were recruited and randomised by random allocation software into 3 treat-

Shanehsaz 2015 (*Continued*)

		ment groups of 30 subjects each
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; the oral placebo was completely identical in appearance to the cimetidine tablet, they were the same colour, and drug codes were revealed only at the end of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study. The adverse effects are not properly described, although questionnaires regarding response to treatment and drug side effects were completed and in Table 2 there are data, numbers (%)
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Sharquie 1997

Methods	*Study design*: randomised controlled trial *Setting/location*: Baghdad, Iraq *Study period*: October 1994 to November 1995 (8 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp: *L major* and *L tropica* endemic in the area *Inclusion criteria*: confirmed cases of CL by smear or culture, or both; acute CL with a history of 12 weeks or less *Exclusion criteria*: cases of reinfection *N randomised*: 85 *Withdrawals*: 22 participants (participants who did not show up after the first or second injection were excluded). Losses were not reported by group *N assessed*: 63. Group 1, 19; group 2, 17; group 3, 18; group 4, 9 *Age*: range 3 months to 65 years

Sharquie 1997 (*Continued*)

	Sex (male/female): 28/37 *Baseline data*: • Group 1: MNL: 2.0. MDLBT: 6.89 weeks • Group 2: MNL: 2.35. MDLBT: 7.65 weeks • Group 3: MNL: 1.94. MDLBT: 7.00 weeks • Group 4: MNL: 4.22. MDLBT: 8.89 weeks
Interventions	*Type of interventions*: • *Group 1*: IL ZS with a solution of 2% • *Group 2*: IL 7% HSCS • *Group 3*: ILSSG 100 mg/mL • *Group 4*: a few lesions on unimportant and unexposed parts of the body were left as controls *Duration of intervention*: not described
Outcomes	*Healing*: responses were graded according to scale (Sharquie 1988): • Slight: decreased erythema and oedema of the lesion; mild: reduction in the size of the lesion of up to 30% • Moderate: reduction in the size of the lesion of 30%-60% • Marked: reduction in the size of the lesion by ≥ 60% and parasite not detected in the lesion by smear and/or culture • Total clearance of the lesion: with parasites not detected in the affected area by smear and/or culture *Speed of healing (time taken to be 'cured')*; expressed in days *Prevention of scarring* *Adverse effects* Time points reported: participants were followed up every 10-15 days for a period of 45 days. At the end of the 6 weeks follow-up period, the lesions were reassessed and parasitological proof of cure or otherwise was sought by smear and/or culture
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding

Sharquie 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 85 participants initially recruited, 63 participants were followed-up for the full observation period. Participants who did not show up after the first or second injection were excluded. We do not know numbers of missing data across intervention groups
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were pre-specified
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported.

Sharquie 2001

Methods	*Study design*: randomised controlled trial *Setting/location*: Iraq (outpatient department) *Study period*: October 1994 to May 1995 and November 1995 to May 1996 (15 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* and *L tropica* *Inclusion criteria*: CL confirmed by smear/culture; acute CL of ≤ 12 weeks duration (to exclude the possibility of self healing); those for whom systemic treatment was indicated including those for whom having multiple lesions (> 5) or large lesions (> 4 cm^2), that could not be injected, or who had lesions near to critical areas such as the eye; very young children for whom no local injection was attempted; participants who refused local treatment (2%) *Exclusion criteria*: received antileishmanial treatment, either local or systemic, cases of reinfection *N randomised*: 130. Group 1, 39; group 2, 37; group 3, 39; group 4, 15 *Withdrawals*: 27. Group 1, 8; group 2, 8; group 3, 7; group 4, 3 *N assessed*: 104. Group 1, 31; group 2, 29; group 3, 32; group 4, 12 *Mean (SEM) age*: group 1, 20.57 years (3.20); group 2, 22.55 years (2.72); group 3, 13. 83 years (2.45); group 4, 25.74 years (4.45) *Sex (male/female)*: 62/68. Group 1, 13/18; group 2, 19/10; group 3, 11/21; group 4, 6/6 *Baseline data*: • Lesions (Total): group 1, 161; group 2, 145; group 3, 149; group 4, 42 • Mean number of lesions (SEM): group 1, 5.19 (0.56); group 2, 5.00 (0.73); group 3, 4.65 (0.7); group 4, 3.50 (0.88)

	• Site of lesion (groups 1, 2, 3, and 4, respectively)
	  ○ Head and neck: 45; 19; 50; 3
	  ○ Lower limb: 21; 57; 52; 24
	  ○ Upper limb: 90; 69; 44; 14
	  ○ Trunk: 5;2;3;1
	• -Type of lesion:
	  ○ Wet: group 1, 41; group 2, 32; group 3,: 20; group 4, 7.
	  ○ Dry: group 1, 120; group 2, 113; group 3, 129; group 4, 36.
	• Mean duration of lesions (SEM): group 1, 8.1 weeks (0.56); group 2, 7.95 weeks (0.49); group 3, 8.50 weeks (0.54); group 4, 8.89 weeks (1.11)

Interventions	*Type of interventions*: • *Group 1*: ZS orally 2.5 mg/kg • *Group 2*: ZS orally 5 mg/kg • *Group 3*: ZS orally 10 mg/kg • *Group 4*: without treatment *Duration of intervention*: ZS groups one capsule every 8 hours *Duration of follow-up*: 6 weeks
Outcomes	*Healing*: responses were graded according to scale (Sharquie 1988): • Slight: decreased erythema and oedema of the lesion; mild: reduction in the size of the lesion of up to 30% • Moderate: reduction in the size of the lesion of 30%-60% • Marked: reduction in the size of the lesion by ≥ 60% and parasite not detected in the lesion by smear and/or culture • Total clearance of the lesion: with parasites not detected in the affected area by smear and/or culture *Speed of healing (time taken to be 'cured')*; expressed in days *Prevention of scarring* *Adverse effects* Time points reported: participants were followed up every 10-15 days for a period of 45 days. At the end of the 6 weeks follow-up period, the lesions were reassessed and parasitological proof of cure or otherwise was sought by smear and/or culture
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: none declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated

Sharquie 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts: 26/130 (25%)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Shazad 2005

Methods	*Study design*: randomised controlled trial *Setting/location*: Military Base Clinic, Iran *Study period*: January to October 2001 (10 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L major* *Inclusion criteria*: proven cases of CL, healthy apart from CL, lesions not in close proximity to a vital organ or joint, number of lesions 1 to 3, ulcer size < 5 cm in diameter, onset of the lesions < 3 months, no previous standard anti-*Leishmania* treatment, no history of allergy to the paromomycin family *Exclusion criteria*: not reported *N randomised*: 60, 30 in each group *Withdrawals*: 4. Group 1: 1; group 2: 3, *N assessed*: 36. Group 1: 29; group 2: 27 *Age*: Group 1: approx 20.6 years; group 2: approx 21.7 years *Sex*: all men *Baseline data*: • Group 1: 76.7% had ulcerative, 8.3% nodular, and 15% papular type of lesions, and they were primarily located in the head and neck (25%), upper extremities (41.7%), lower extremities (31.7%) and trunk (1.7%). MNL: 2. MSL 21.7 mm. MDLBT: 37.8 days • Group 2: 69.7% had ulcerative, 11.8% nodule, and 18.4% papule type of lesions, and they were primarily located in the head and neck (13.2%), upper extremities (47.4%), lower extremities (36.8%) and trunk (2.6%). MNL: 2.4. MSL: 25 mm. MDLBT: 39 days

Shazad 2005 (*Continued*)

Interventions	*Type of interventions*: • *Group 1*: 15% PR sulphate and 10% urea. Dose: 0.5 mg/mm²/d • *Group 2*: intradermal MA every other day *Duration of intervention*: 20 days
Outcomes	*Healing rates*: • Complete cure was defined as complete re-epithelialisation of all lesions at one week after cessation of treatment. Participants with multiple lesions were considered to be cured if all the lesions were healed. • Partial cure (parasitological cure) was defined when clinical cure had not occurred in any lesion in a participant but no *L amastigote* was found in a direct smear of the lesions(s), 3 slides were prepared, and stained from each active ulcer, and 1000 fields were checked (approximately 3 slides). • Failure of treatment was defined as no clinical cure and no parasitological cure at one week after cessation of treatment; relapse was defined as a reappearance of the lesion after complete cure. *Adverse effects* Time points reported: follow-up and clinical evaluation were performed at week 1 and 6 after completion of treatment. Participants were visited once at 6 months after treatment was completed
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was described as open and no blinding was done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was described as open and no blinding was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	*Comment*: relevant outcomes were reported
Selective reporting (reporting bias)	Low risk	*Comment*: relevant outcomes were reported

Shazad 2005 (*Continued*)

Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Stahl 2014

Methods	*Study design*: single-centre, 3-armed, open label, randomised, controlled, phase IIb trial *Setting/location*: Leishmania and Malaria Centre (LMC) of the Provincial Balkh Civil Hospital Mazar-e-Sharif (Afghanistan) *Study period*: November 2010 to March 2011 (15 months) *Sample size calculation*: the sample size calculation was based on the per protocol (PP) analysis, defined as all participants evaluable with respect to the primary endpoint
Participants	*Type of Leishmania*: in 44/69 participants analysed, 28 (64%) lesions were infected with *L tropica* and 16 (36%) with *L major* *Inclusion criteria*: CL lesions with *Leishmania*-positive Giemsa smears without prior CL treatment *Exclusion criteria*: age < 12 years; more than one skin lesion (to exclude intra-individual variations in this phase IIb analysis); lesion age > 3 months; lesions located on eye lids, lips or nose; drug addiction; coinfection with *Mycobacterium tuberculosis*, HIV, or diabetes *N randomised*: 87 participants: group 1, 24 (27.5%), group 2, 32 (36.8%), and group 3, 31 (35.6%) *Withdrawals*: lost after registration: group 2, 3; group 3, 3. Not followed up for the full treatment period: SSG, 1; group 2, 6; group 3, 3. Mixed treatment: group 3, 2 *N assessed*: 81 (93.10%). group 1: 24; group 2: 29; group 3: 28 *Mean age*: 29 years (95% CI 25-33) *Sex (male/female)*: 32 (46%)/37 (54%) *Baseline data*: comparable in all 3 regimens
Interventions	*Type of interventions*: • *Group 1*: intradermal injections of 0.6 mL SSG according to a protocol used by Zeglin 2009 • *Group 2*: aseptic MWT with 0.045% DAC N-055 following a single initial superficial wound debridement with HF-EC, which was performed under local anaesthesia after wound cleansing and disinfection with gauzes soaked in physiological saline solution containing 320 ppm chlorine dioxide (pH 5.5 acidified 0.09% DAC N-055) for 15 min • *Group 3*: MWT with 0.045% DAC N-055 alone *Duration of intervention*: for all groups: daily treatments (with the exception of Fridays) during the first week, followed by topical treatments at the centre twice a week until the end of week 4 and thereafter once a week until wound closure In group 1, the SSG treatment was discontinued after week 4. In groups 2 and 3, participants dressed their lesion themselves after week 4 with the topical $NaClO_2$ -basic-crème between their visits at the centre until lesion closure
Outcomes	*Primary outcome* was the ratio of closed versus open wounds at day 75 (D75) in the PP analysis for each regimen *Speed of healing*: not reported in Methods

	Adverse effects: not reported in Methods 6 visits were scheduled in the first week, 2 visits per week from weeks 2 to 4, and 1 visit per week thereafter until complete wound closure. Follow-up visits were required once a month until day 180 after treatment start
Notes	The funders had no role in study design, data collection, data analysis, and interpretation, decision to publish, or preparation of the manuscript. KWS and HCS are members of the Board and CB is a member of the non-profit NGO Waisenmedizin PACEM e.V. promoting access to essential medicine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Each patient was randomly assigned to one of the 3 regimens by the random allocation generator in the computer-based Leishmedoc system."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was described as open and no blinding was done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the present trial could not be conducted as either a double or a single blinded trial due to the physical nature of the applied interventions"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The intention-to-treat analysis (ITT) is solely added as additional information. Patients that could not be evaluated were patients that were lost immediately after registration before treatment started. 81 out of 87 patients (93.1%) were suitable for the ITT and 69 (79.3%) for the PP analysis"
Selective reporting (reporting bias)	Low risk	Clinicaltrials.gov ID: NCT00996463. Registered: 15 October 2009
Other bias	Low risk	Other items assessed correctly reported

Yazdanpanah 2011

Methods	*Study design*: randomised, prospective, double-blind trial *Setting/location*: Dermatology Department, Ghaem Hospital, Mashhad University of Medical Sciences, Iran *Study period*: October 2006 to May 2008 (19 months) *Sample size calculation*: not described
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: proven acute CL by a positive direct smear were selected for this study. Duration of lesions less than 6 months and no anti-leishmaniasis treatment received during 2 months ago *Exclusion criteria*: pregnant or nursing women, participants with hepatic, renal, and heart diseases *N randomised*: 115. Group 1: 30, group 2: 85 *Withdrawals*: excluded because of side effects: group 2, 6. Not followed up for the full treatment period: group 1, 4; group 2, 5 *N assessed*: 100 (86.96%). Group 1: 26 (86.67%); group 2: 74 (87.06%) *Mean (SD) age*: group 1, 32 years (23), group 2: 25 years (19) *Sex (male/female)*: group 1, 11/15, group 2: 39/35 *Baseline data*: • Total lesions: group 1, 43; group 2, 127 • Location of the target lesion: ○ Group 1: head and neck 19 (44.3%), upper limb 18 (44.9%), lower limb 5 (11.6%), trunk 1 (2.3%) ○ Group 2: head and neck 56 (44.1%), upper limb 56 (44.1%), lower limb 14 (11%), trunk 1 (0.8%) • Mean duration of lesions (SD): group 1, 4.5 months (1.5); group 2, 4 months (1.5)
Interventions	*Type of interventions*: • *Group 1*: received oral zinc sulphate (ZS) in a dose of 10 mg/kg/d during 45-day period before meal in 3 divided times • *Group 2*: IMMA (Glucantime; MA, Specia, Paris, France) 20 mg/kg/d for 20 days with a maximum of 3 vials *Duration of intervention*: group 1: 45 days, group 2: 20 days
Outcomes	*Decreased indurations of lesion* (lesions were measured by palpation and ruler): in aspect of response to treatment in comparison with first visit participants graded as 4 improvement rate groups: 1. Slight (up to 25% decreased indurations of lesion) 2. Mild (25%-50% decreased indurations of lesion) 3. Moderate (more than 50% and less than 75% decreased indurations of lesion) 4. Total clearance (75% or more improvement or complete re-epithelialisation without any indurations) *Decreased indurations of lesion after 45 days from completing treatment period*: the same scale *Adverse effects*: severe muscular pain and topical reaction of inoculation site (severe erythema and pruritus) Time points reported: at the end of clinical treatment. After 45 days from completing treatment period

Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using simple randomisation".
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not done. At each visit all lesions were reexamined by the same dermatologist. The size and induration of lesions were measured by palpation and ruler. No photographs were taken
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	100 out of 115 participants completed the study. 6 participants who received systemic MA were excluded because of side effects that included severe muscular pain and topical reaction of inoculation site (severe erythema and pruritus)
Selective reporting (reporting bias)	High risk	Protocol not available. Not registered. Alhtough most pre-specified outcomes were reported, adverse effects were not clearly reported (only for those excluded from the analysis)
Other bias	Unclear risk	There was not enough information in the publication to assess if there were other biases present

Zerehsaz 1999

Methods	*Study design*: randomised controlled trial *Setting/location*: Fars province, Iran *Study period*: not described *Sample size calculation*: not described

Zerehsaz 1999 (*Continued*)

Participants	*Type of Leishmania*: *Leishmania* spp: *L major* and *L tropica* in the area *Inclusion criteria*: diagnosed as having CL based on positive smears from lesions, and in some cases, cultures and histopathologic studies were also performed *Exclusion criteria*: pregnant, nursing, or serious concomitant diseases. *N randomised*: 171 *Withdrawals*: 0 *N assessed*: 171 participants: 86 participants in the herbal extract Z-HE group and 85 participants in the IMMA (15 to 20 mg/kg/d) *Age*: range 10 months to 69 years *Sex (male/female)*: 84/87 *Baseline data*: the duration of the disease was < 4 months. Most participants had papular and papulonodular lesion(s), although other clinical forms including ulcerative, eczematoid, hyperkeratotic, and erysipeloid types were also present. Most participants had multiple lesions, and the most common sites were the face and the extremities
Interventions	*Type of interventions*: • *Group 1*: herbal extract Z-HE as a black paste applied to the lesions and covered by a dressing for 5 consecutive days + placebo (saline) injected (0.5 mL) for 20 consecutive days • *Group 2*: IMMA (15-20 mg/kg/d) for 20 consecutive days + vehicle (petrolatum and charcoal powder) applied on the lesions as a black paste covered by a dressing for 5 consecutive days *Duration of intervention*: 20 consecutive days
Outcomes	*Healing rates*: complete cure was defined as clinical improvement with complete healing and re-epithelialisation of the lesion(s), partial cure as partial clinical improvement with reduction in infiltration erythema, and size of the lesion(s), and failure as the absence of any changes in the lesion(s) or progression and worsening of the lesion(s) *Adverse effects* Time points reported: 6 weeks post-treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgment
Blinding of participants and personnel (performance bias)	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blind-

Zerehsaz 1999 (*Continued*)

All outcomes		ing could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

Özgöztasi 1997

Methods	*Study design*: randomised controlled trial *Setting/location*: Turkey *Study period*: around 8 weeks *Sample size calculation*: not described
Participants	*Type of Leishmania*: *Leishmania* spp: *L tropica* in the area *Inclusion criteria*: confirmed diagnosis of CL *Exclusion criteria*: pregnant, nursing, or serious concomitant diseases *N randomised*: 72 *Withdrawals*: 0 *N assessed*: 72 (100%): 40 participants in group 1 and 32 participants in group 2 *Age*: most were children aged 10 years or younger *Sex*: both sexes *Baseline data*: the most common site of the lesion was the face and most of the participants had one papulonodular lesion, with duration of the lesions varying from 1 to 12 months • Group 1: MNL: 1. MDLBT: 4.3 months • Group 2: MNL: 1. MDLBT: 4.3 months
Interventions	*Type of interventions*: • *Group 1*: 15% PR sulphate + 12% MBCL twice daily for 15 days • *Group 2*: ketoconazole orally 400 mg per day for 30 days (reduced to 200 mg if participants < 12 years old) *Duration of intervention*: 4 weeks
Outcomes	*Healing rates*: percentage of participants 'cured' one month after treatment *Adverse effects* Time points reported: at the end of treatment and 4 weeks post-treatment
Notes	*Study funding sources*: not reported *Possible conflicts of interest*: none declared

Özgöztasi 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were divided randomly into two treatment groups" Comment: insufficient detail was reported about the method used to generate the allocation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "An open-labeled, N randomised controlled trial to evaluate the efficacy of paromomycin ointment as compared with ketoconazole" Comment: we think the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No subjects withdrew because of this adverse effect" Comment: no dropouts, so ITT analyses were performed.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes
Other bias	High risk	Sample size calculation and reporting of *Leishmania* spp involved was not correctly reported

ACL: anthroponotic cutaneous leishmaniasis; **AL**: allopurinol; **CCR**: complete clinical response; **CL**: cutaneous leishmaniasis; **HF-EC**: high frequency electrocauterisation; **HSCS**: hypertonic sodium chloride solution; **IL**: intralesional; **ILMA**: intralesional meglumine antimoniate; **ILSSG**: intralesional sodium stibogluconate; **IM**: intramuscular; **IMMA**: intramuscular meglumine antimoniate; **IQR**: interquartile range; **IV**: intravenous; **MA**: meglumine antimoniate; **MBCL**: methyl benzethonium chloride; **MDLBT**: median duration of lesions before therapy; **MNL**: median number of lesions; **MSL**: median size of lesions; **MWT**: moist wound treatment; **PDT**: topical photodynamic therapy; **PR**: paromomycin; **RF**: radiofrequency; **RFHT**: radiofrequency heat therapy; **SD**: standard deviation, **SEM**: standard error of the mean; **SSG**: sodium stibogluconate; **TCA**: trichloroacetic acid; **TM**: ThermoMed; **ZS**: zinc sulphate;

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alavi-Naini 2012	Review
Banihashemi 2015	Inclusion criteria of the patients: patients with lupoid leishmaniasis, chronic recurrent leishmaniasis, that typically follows an acute form of cutaneus leishmaniasis
Bumb 2010	Not an RCT. "Selected patients were categorised into two groups (groups A and B) of 110 persons each. Alternate patients were included in group A and B, respectively"
Dogra 1986	They stated that participants were randomly selected for the study, but not randomly assigned to the treatment groups
Dogra 1994	They stated that participants were randomly selected for the study, but not randomly assigned to the treatment groups
Dorlo 2012	Review
El On 1992	Cross-over study
Frankenburg 1993	It measured immunity parameters but did not show any clinical results
Kim 2009	This was a meta-analysis.
Moosavi 2005	The method of generation of randomisation was inappropriate. The author was contacted and stated that after enrolling the participants, they did consecutively allocate ILMA for odd number participants and used topical paromomycin for even number participants
Nilforoushzadeh 2010	They stated that participants were randomly selected for the study, but not randomly assigned to the treatment groups
Nilforoushzadeh 2011	Included immunocompromised and chronically ill patients
Siavash 2013	Only studied electrocardiogram and biochemical adverse effects of meglumine antimoniate
Singh 1995	They stated that participants in both groups were randomly selected. However, they did not have an initial population eligible for the study that was randomly divided in the 2 treatment groups. But rather one group of people that were randomly selected for one group and another group of participants that were also randomly selected to form part of the other group. Besides, the duration of treatments was not the same and the follow-up was also different for both treatment groups
Trau 1987	No clear data is available for multiple lesions. Only lesions from participants with multiple lesions were randomised. The lesions from participants with single lesions a cross-over study was performed

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Farajzadeh 2016a

Methods	Double-blind randomised controlled trial This study was carried out in some clinics of Kerman University of Medical Sciences (Iran), from October 2008 to December 2010 *Sample size calculation*: a sample size of 40 participants per treatment group was planned, a probability of a type I error at alpha = 0.05 and beta = 0.1 to determine a 20% difference between intralesional injection of ZS 2 % solution with ILMA (Glucantime)
Participants	*Type of Leishmania*: *L tropica* *Inclusion criteria*: the presence of parasitological confirmed lesion(s) of CL and aged 5-60 years *Exclusion criteria*: disease duration more than 6 months, those with a history of hypersensitivity to MA (Glucantime) or ZS, pregnant or nursing women, those with more than 5 lesions, those with lesions with size of 5 cm or more, and a history of any anti-leishmanial therapy during last 4 weeks *N randomised*: 80, 40 in each group *Withdrawals*: 34, 18 in the ZS-treated group and 16 patients in the MA (Glucantime)-treated group (lost to follow-up in all of the participants except in one in the ZS-treated group, who had severe necrosis) *N assessed*: 46; 22 patients in the ZS-treated group and 24 patients in the MA (Glucantime)-treated group There was no significant difference between compared groups' baseline characteristics
Interventions	*Group 1*: intralesional injection of ZS 2% vials once a week for 10 weeks or sooner in case of complete resolution of the lesions *Group 2*: ILMA once a week for 10 weeks or sooner in case of complete resolution of the lesions *Co-intervention*: in both groups cryotherapy was performed once every other week for 10 weeks
Outcomes	*Clinical response*: no response to treatment was defined if the area of a lesion decreased less than 75%, partial treatment if decreased 75% to 99%, and complete treatment if decreased 100% compared to its baseline area *Time to healing* (partial/complete treatment) *Adverse effects*: there were no major side effects in either group. Pain was observed in all participants of both groups. In ZS group 4 participants developed necrosis of the site of the injection while this was not observed in MA (Glucantime) group at all Time points reported: on average, each participant was followed for 4.1 weeks (SD 2.6)
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: there is no conflict of interest

Farajzadeh 2016b

Methods	Triple-blind randomised controlled trial Performed in Shahid Dadbin Clinic of Leishmaniasis Research Center (Iran), at Kerman University of Medical Sciences, between 2008 and 2010 *Sample size calculation*: a sample size of 44 participants per treatment group was planned with a probability of a type I error at alpha = 0.05 and beta = 0.1 to determine a 20% difference between topical terbinafine and vehicle in outcome
Participants	*Type of Leishmania*: *L major* and *L tropica* in the area *Inclusion criteria*: < 2 years of age; parasitological diagnosis of cutaneous leishmaniasis from all lesions with direct smear; ulcerative lesions with duration of less than one month that were not on exposed areas or joints; the size

Farajzadeh 2016b (*Continued*)

	of lesions has to be < 3 cm; ≤ 3 lesions; no anti-leishmanial therapy during last 2 weeks, and with no history of hypersensitivity to MA *Exclusion criteria*: pregnant or nursing women, patients with hepatic, renal, or heart diseases *N randomised*: 88, 44 in each group *Withdrawals*: 36 in topical terbinafine + MA; 29 in vehicle + MA *N assessed (3 months)*: 9 in topical terbinafine + MA; 15 in vehicle + MA There are significant differences between participants' sex in intervention and control groups
Interventions	*Group 1*: IMMA 20 mg/kg/d + topical terbinafine for 20 days 3 months follow-up after completing of the treatment phase *Group 2*: IMMA 20 mg/kg/d + vehicle (Mahan Vaseline) for 20 days *Visited at days*: 0, 14, 30 and 44
Outcomes	*Clinical cure*, defined as: • Complete improvement: full re-epithelialisation for ulcerative lesions and decrease in induration size(75%, with or without a negative direct smear result) • Partially improved: decrease in the indurations size between 25% and 75% • No change: decrease in the indurations size of 25% *Time to healing* (partial/complete treatment)
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: there is no conflict of interest.

Hanif 2016

Methods	Randomised controlled study Department of Dermatology, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, Pakistan, from November 2013 to June 2014 *Sample size*: was calculated by using a formula for 2 proportions; expected proportion for duration of treatment in one group was taken as 55, and in second group 51 days; power of study was taken as 80, and standard error of 5%
Participants	*Type of Leishmania*: not reported *Inclusion criteria*: patients of all age groups except neonates, with single or multiple parasitologically confirmed lesions of cutaneous leishmaniasis with no past history of disease and not previously treated with SSG or MA *Exclusion criteria*: retinal abnormality or visual field defects, pregnancy, hepatic dysfunction, known hypersensitivity to chloroquine and those having visceral leishmaniasis *N randomised*: 86; 48 intralesional chloroquine, 38 oral chloroquine *Withdrawals*: 0 *N assessed*: 86; 48 intralesional chloroquine, 38 oral chloroquine
Interventions	Intralesional and oral chloroquine administration *Co-interventions*: lesions with secondary bacterial infection before, during, or after treatment were treated with topical antibiotics. If such infections required systemic treatment, an antibiotic that has no activity against *Leishmania* (e.g. erythromycin) was given.
Outcomes	*Cure* was defined as the complete re-epithelialisation of the ulcerated lesions, with no evidence of papules, inflammation, or induration Quantitative variables like, *duration, cost* and *total dose of treatment* were calculated

Hanif 2016 (*Continued*)

	Adverse effects Time points reported: < 4 weeks, 5-8 weeks, ≥ 9 weeks
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: none declared

Jaffary 2016

Methods	Interventional randomised controlled study was conducted in the Skin Disease and Leishmaniasis Research Center of Isfahan University of Medical Sciences, Isfahan, Iran, between April 2010 and May 2011 *Sample size calculation*: not described
Participants	*Leishmania type*: not described *Inclusion criteria*: patients older than 5 years with biopsy-confirmed cutaneous leishmaniasis were eligible if they had the following criteria: lesion diameter < 3 cm, disease duration < 12 weeks, lesion-to-eyelid distance > 2 cm, and no history of systemic or topical therapy for cutaneous leishmaniasis *Exclusion criteria*: pregnancy, lactation, immunosuppressive therapy, and serious side effects of medication *N randomised*: 90. 30 in each group (ILMA (Glucantime) alone, ILMA + TCA 50%, or fractional CO_2 laser) *Withdrawals*: 14 *N assessed*: 76 participants (84.5%) completed treatment and were followed up for 60 days
Interventions	ILMA alone, ILMA + TCA 50% or fractional CO_2 laser for up to 8 weeks Participants in all 3 groups were followed up weekly for the next 6 months
Outcomes	The *clinical response* was rated as complete improvement (complete re-epithelialisation of the lesion with negative direct skin smear result), partial improvement (50%-75% improvement of the lesion size), and no change in the lesion appearance *Time to healing* *Adverse effects* The improvement of scar was also evaluated according to the *participant's satisfaction, the morphology of the lesion, the level of induration, and the level of atrophy* and scored as follows: score of 1 (less than 5% improvement), score of 2 (25% to 50% improvement), score of 3 (51% to 75% improvement), and score of 4 (76% to 100% improvement)
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: there is no conflict of interest.

Na-Bangchang 2016

Methods	Exploratory phase II, randomised, vehicle-controlled, single-centre (Ankober Health Center, North Shewa zone of Amhara region, Ethiopia) study *Sample size calculation*: not described
Participants	*Leishamania type*: not described *Inclusion criteria*: patients with localised cutaneous leishmaniasis (LCL) aged 18-65 years with a new, uncomplicated, localised, single lesion on the face or arms and positive parasite smear by microscopy *Exclusion criteria*: cutaneous leishmaniasis with secondary infection, concomitant diseases (mucocutaneous or visceral leishmaniasis), history of anti-leishmanial treatment within the past 6 months, abnormality of biochemical and/or

Na-Bangchang 2016 (*Continued*)

	haematological laboratory tests, known hypersensitivity to any of the Shiunko components, or pregnancy (positive urine HCG test), breastfeeding, or possibility of becoming pregnant during the study *N randomised*: 40 were randomised to receive vehicle and Shiunko ointment (20 participants for each group) *Withdrawals*: 2 participants did not receive complete treatment, and 9 were not completely followed up. In the vehicle group, 2 and 5 cases did not have complete treatment and follow-up, respectively *N assessed*: 38 participants had complete treatment and 31, complete follow-up. In the vehicle group, 18 and 15 cases had complete treatment and follow-up, respectively
Interventions	*Group 1*: the composition of Shiunko was as follows: 2.04 g shikon, 1.02 g tohki, 16.92 g sesame oil, and 6.76 g honeycomb wax *Group 2*: the vehicle contained 20 g wax *Co-interventions*: cryotherapy was to be offered to all participants who were withdrawn or discontinued from the study for safety reasons Vehicle and Shiunko ointment applied on the lesion twice a day for 4 weeks Follow-up: 16 weeks
Outcomes	*Cure*: *complete cure* was defined as complete wound closure and re-epithelialisation without inflammation or infiltration and absence of parasite (amastigotes) within 12 weeks after the end of treatment. *Partial response* was defined as improvement of *Leishmania* signs (skin oedema, erythema, and/or hardening) and/or reduction in size but not total disappearance of the lesion and absence of parasite (amastigotes) within 12 weeks after the end of treatment. *Treatment failure* was defined as failure of the lesion size to decrease and/or lack of lesion sign improvement or re-epithelialisation and/or presence of leishmanial amastigotes in the lesion 12 weeks after end of treatment (week 16) *Adverse effects* *Clinical and parasitological assessments* were performed before treatment, weekly for 4 weeks, and then 4, 8, and 12 weeks after the end of treatment
Notes	*Study funding sources*: the study was supported by the Institute of Tropical Medicine, Nagasaki University (Japan), ArmauerHansen Research Institute (Ethiopia), and Okusa Co., Ltd. (Japan) *Possible conflicts of interest*: there is no conflict of interest.

Rajabi 2016

Methods	Clinical randomised trial conducted from March 2008 through 2009 in the dermatology department of Quaem University Hospital, Mashhad, Iran *Sample size calculation*: not described
Participants	*Leishamania type*: not described *Inclusion criteria*: positive smear for leishmaniasis with disease duration of less than 12 weeks, no treatment for the current condition before and volunteer to participate in the study *Exclusion criteria*: pregnancy, breastfeeding, history of simultaneous treatment with other methods before or during the trial, history of local cutaneous or systemic diseases in the past 2 months, history of intolerance or allergy to macrolides, severe underlying diseases such as cardiovascular, renal, or hepatic diseases *N randomised*: 96; 26 (43 lesions) azithromycin, 40 (54 lesions) MA (Glucantime) *Withdrawals*: 2 azithromycin group *N assessed*: 94; 24 (40 lesions) azithromycin, 40 (54 lesions) MA
Interventions	*Group 1*: topical liposomal form of azithromycin was administered for the first group twice daily. *Group 2*: the other group was treated by weekly ILMA with a volume of 0.5-2 cm^3 into each lesion till complete

Rajabi 2016 (*Continued*)

	blanching of the lesion occurred Clinical evaluations were performed every week during the treatment course (8 weeks) by a single dermatologist in both groups The participants were followed up for recurrence or complications 6 and 12 months after the end of the treatment course
Outcomes	*Complete cure* was defined as full re-epithelialisation, disappearance of oedema, induration, and other signs of inflammation, and a negative direct skin smear result *Improvement rate (%)*: complete improvement (full re-epithelialisation of the lesions for ulcerative ones or disappearance of induration and erythema; significant improvement (decrease in induration size > 60%); moderate improvement (decrease in induration size between 30% and 60%; slight improvement (decrease in induration size of < 30%) *Adverse effects*
Notes	*Study funding sources*: none declared *Possible conflicts of interest*: none declared

Refai 2016

Methods	Interventional randomised study *Setting*: Sri Lanka *Sample size calculation*: not described
Participants	*Leishmania type*:*L donovani* *Inclusion criteria*: Laboratory-confirmed CL patients with single lesions *Exclusion criteria*: - *N randomised*: test group (n = 98); control group (n = 115) *Withdrawals*: - *N assessed*: -
Interventions	*Group 1*: single session of radiofrequency induced heat therapy (RFHT) at 50ºC for 30 s *Group 2*: received weekly ILSSG until cure or 10 doses Participants were followed up fortnightly for 12 weeks to assess clinical response and adverse effects
Outcomes	*Cure rate* *Adverse effects* Time points reported: 8, 10, and 12 weeks
Notes	Poster

Sattar 2012

Methods	Randomised controlled trial
Participants	40 participants (no more data described in abstract)
Interventions	Topical ointment prepared from the stem extract of Morinda citrifolia (no more data described in abstract)
Outcomes	Improvement (no more data described in abstract)

Sattar 2012 (*Continued*)

Notes	Article request to authors

CL: cutaneous leishmaniasis; **HCG**: human chorionic gonadotropin; **ILMA**: intralesional meglumine antimoniate; **IM**: intramuscular; **MA**: meglumine antimoniate; **SSG**: sodium stibogluconate; **ZS**: zinc sulphate.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12614001288617

Trial name or title	A clinical trial to assess the safety and effect of heat therapy in comparison to standard intra-lesional sodium stibogluconate for cutaneous leishmaniasis
Methods	Randomised controlled trial
Participants	*Inclusion criteria*: suggestive skin lesions (papules, nodules, plaques, ulcers and nodule-ulcers) who were clinically diagnosed by a consultant dermatologist and parasitologically confirmed as CL *Exclusion criteria*: non-localised leishmaniasis (VL, MCL, leishmaniasis recidivans, diffuse cutaneous leishmaniasis and post-kala-azar dermal leishmaniasis); use of prior concomitant treatment for leishmaniasis including any traditional medicines; lesions close to nasal, oral, urogenital, anal areas (mucosae) and the eyes; multiple lesions; any chronic or concomitant illnesses and people on pace makers and any metallic devices; pregnancy and breastfeeding mothers; children < 12 years of age; immunocompromised states including HIV/AIDS and use of immunosuppressants like steroids; alcohol abuse; not capable of understanding and complying with the study protocol; known hypersensitivity or allergy to treatment *Age*: 12-90 years
Interventions	The device used was the ThermoMed 1.8, ThermoSurgery Technologies portable battery operated device. The generator has received clearance by the US Food and Drug Administration for the treatment of CL. It delivers precisely controlled localised radiofrequency waves to selectively destroy diseased tissue. Heat therapy was administered as a single session. The lesion and surrounding normal skin was cleaned with normal saline. Then the area was anaesthetised with 2% lignocaine using a 1 cc syringe. The device was used in according to manufacturers instructions (ThermoMed 1.8; Thermosurgery). It generates a 6.78 mHz frequency applied with a hand set that is attached to 2 applicator electrodes which were placed on the diseased skin. A temperature of 50^{o}C was applied for 30 s to cover an area about 49-73 mm^{2}, according to the size of electrodes (3 sizes are provided). Then the applicator is moved to another area of the lesion until the entire area is treated. Once treatment begins the temperature is measured by a thermistor embedded in the applicator which ensures that the applied temperature remains constant. After treatment the lesions were covered with gauze to prevent secondary infections and participants were given an antibiotic cream (soframycin 1% per 30 g depending on the size of lesion to cover the lesion) to be applied twice a day for 3 days
Outcomes	*Recurrence* *Treatment efficacy* was measured by the percentage of participants clinically cured by 8 weeks, 10 weeks, 12 weeks and 16 weeks after initiation of treatment in both groups • Cure was defined as complete re-epithelialisation of the CL lesion with no evidence of papules, active inflammation or induration. • Partially cured if healing was 50%-100% • Non-responders or treatment failures were those who had lesions that were less than 50% healed at the

ACTRN12614001288617 (*Continued*)

	end of 3 months or if new lesions occur while on treatment Any adverse effects like secondary bacterial infections, allergy to treatment or hypersensitivity and worsening of the lesion clinically was recorded during or after treatment with either therapy
Starting date	December 2014
Contact information	Dr Fathima Wardha Refa PGIM address: No. 160, Professor Nandadasa Kodagoda Mawatha (Norris Canal Road), 00700, Colombo 7. 2.Department of Parasitology, Faculty of Medicine Colombo University of Colombo address: No 25, Kynsey Road, Colombo 8 0080, Sri Lanka. 7 MACLEOD ROAD COLOMBO 4, Sri Lanka +94 727800003 or +94 11 2580093 or+94 11 2699284 wardharefai@yahoo.com
Notes	-

IRCT138904091159N7

Trial name or title	Comparison between the efficacy of intralesional placebo and nitric oxide releasing patch versus placebo patch and Glucantime in the treatment of cutaneous leishmaniasis
Methods	Randomised, placebo-controlled trial
Participants	*Inclusion criteria*: diagnosis of acute zoonotic cutaneous leishmaniasis, proven parasitology by direct smear; aged 18-50 years; lesion diameter ≤ 3 cm; 1 lesion, not located on the face near the eyes, joints, cartilage, on the nose and ears; < 3 months passed from diseases times *Exclusion criteria*: pregnancy and lactation; risk of presence or incidence of sporotrichoid or satellite lesions; history of hepatitis, heart, or kidney disorder; taking immunosuppressive medications (over the last 6 months) ; local or systemic treatment against leishmaniasis in the last 3 months; history of heart attack or high blood pressure; liver disease; anaemia; history of surgery for head and brain haemorrhage; taking blood pressure medications, antidepressants, or drugs used for angina
Interventions	*Group 1*: nitroglycerin patch (the pharmacy of Nour and Ali Asghar hospital in Isfahan) once a day covering 5.08 to 7.62 cm of lesion + intralesional injection of placebo (injection of distilled water) once a week (15-30 mg) until whitening of base of the ulcer for 8 weeks or until complete cure *Group 2*: ILMA (Meglusan) from Avenue de Scheut company in Belium, once a week (15-30 mg) until whitening of base of the ulcer + placebo patch (the pharmacy of Nour and Ali Asghar hospital in Isfahan) once a day covering 5.08 to 7.62 cm of lesion for 8 weeks or until complete cure
Outcomes	*Improvement rate*. Timepoint: 1, 2, 3, 4, 7, 8 weeks during treatment and 12, 16, 20 weeks after end of treatment. Method of measurement: observation and examination *Induration*. Timepoint: 1, 2, 3, 4, 7, 8, 12, 16, 20 weeks after end of treatment. Method of measurement: physical examination *Lesion area*. Timepoint: 8, 12, 20 weeks after end of treatment
Starting date	August 2013
Contact information	Fariba Jaffary Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Sedigheh Tahereh

IRCT138904091159N7 (*Continued*)

	(AS) Research Centers Complex, Khorram Ave., Isfahan, Iran Isfahan Iran, Islamic Republic Of Iran 00983113373736 jaffary@pharm.mui.ac.ir
Notes	-

IRCT2013092414746N1

Trial name or title	The effect of MJ1 (topical dairy extract) versus routine care for treatment of cutaneous leishmaniasis (rural) in Isfahan Iran:a randomised controlled clinical trial (RCTs)
Methods	Randomised controlled trial
Participants	*Inclusion criteria*: cutaneous leishmaniasis of parasitology confirmed that they have not been previously treated; any other medical problem (such as heart disease, renal, hepatic, or haematological); available for follow-up; informed consent to participate in the study *Exclusion criteria*: secondary infections, history of allergic reactions
Interventions	*Group 1*: in this group patients apply MJ1 skin cream 3 times a day, they are trained to use it for a month with a diameter of 3 mm on the rub of the lesion without dressing *Group 2*: skin cream MJ1 - 3 times a day - for a month
Outcomes	*Lesion size*, lesion diameters measured Timepoint: 1, 2, 3, 4 and 8 weeks after starting treatment, participants are evaluated Method of measurement: at each visit, the 2 dimensions are measured and the area calculated
Starting date	December 2013
Contact information	Dr Mohsen Janghorbani Hezar jarib Street, School of Public Health, Isfahan University of Medical Sciences Isfahan Iran, Islamic Republic Of 00983117922774 janghorbani@hlth.mui.ac.ir
Notes	-

NCT00840359

Trial name or title	Phase 2 study of the efficacy of daylight activated photodynamic therapy in the treatment of cutaneous leishmaniasis
Methods	Randomised, parallel assignment, open label
Participants	*Age:* ≥ 18 years
Interventions	*Group 1*: photodynamic therapy Application of Metvix 16% cream followed by exposure to daylight for 2.5 h *Group 2*: cryotherapy for 2 times 20 s

NCT00840359 (*Continued*)

Outcomes	Eradiation of amastigotes
Starting date	September 2009
Contact information	Prof Claes D. Enk, Hadassah Medical Organization
Notes	-

NCT01050777

Trial name or title	Pilot study of efficacy of topical nano-liposomal meglumine antimoniate (Glucantime) or paromomycin in combination with systemic Glucantime for the treatment of anthroponotic cutaneous leishmaniasis (ACL) caused by *Leishmania tropica*
Methods	Randomised, parallel assignment, double-blind
Participants	*Inclusion criteria*: aged 12-60 years; parasitologically proven CL due to*L tropica*; history of failure to at least one full course of systemic meglumine antimoniate (Glucantime); general good health based on history and physical examination; ≤ 4 lesions; lesion size < 3 cm; signed informed consent voluntarily and knowingly; guardian's signature for volunteer less than 18 years old *Exclusion criteria*: pregnant or lactating women and those who are planning to be pregnant in next 60 days; use of other types of treatment for CL; involvement in any other drug or vaccine trial during the study period; known heart, kidney, liver diseases based on history and physical exam; abnormal ECG *Age*: 12-60 years
Interventions	*Group 1*: liposomal paromomycin (liposomes containing 10% paromomycin) + liposomal MA *Group 2*: liposomal MA (Glucantime) *Group 3*: placebo + liposomal MA
Outcomes	*Complete cure* equal to complete re-epithelialisation of all lesions
Starting date	March 2011
Contact information	Ali Khamesipour, Tehran University of Medical Sciences
Notes	-

SLCTR/2014/028

Trial name or title	Randomised, double-blind, controlled study on efficacy and safety of intralesional metronidazole vs intralesional sodium stibogluconate in *L donovani* cutaneous leishmaniasis
Methods	Randomised controlled trial
Participants	*Inclusion criteria*: > 12 years of age, positive slit skin smear and/or skin biopsy for *Leishmania* parasites *Exclusion criteria*: pregnancy, breastfeeding, known renal impairment, known liver impairment, congestive cardiac failure

SLCTR/2014/028 (*Continued*)

Interventions	*Group 1*: intralesional metronidazole 0.2-4 mL per lesion depending on the size of the lesion, weekly until cure or maximum of 10 injections *Group 2*: intralesional stibogluconate 0.2-4 mL per lesion depending on the size of the lesion, weekly until cure or maximum of 10 injections
Outcomes	*Rate of clinical cure* *Adverse effects* - anticipated local side effects are pain, ulceration, scarring, postinflammatory hyperpigmentation or depigmentation. Systemic side effects are not anticipated as the drug is given intralesionally
Starting date	November 2014
Contact information	Ranthilaka R Ranawaka 0112855200 ranthilaka37@yahoo.com
Notes	-

CL: cutaneous leishmaniasis; **ECG**: electrocardiogram; **ILMA**: intralesional meglumine antimoniate.

DATA AND ANALYSES

Comparison 1. ILMA weekly versus ILMA fortnightly for up to 8 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. ILMA (every other day) versus IMMA (6 d/week) for up to 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 3. IMMA (30 mg/kg/d for 3 weeks) + cimetidine versus IMMA (30 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. IMMA (30 mg/kg/d for 3 weeks) + cimetidine versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 5. IMMA (60 mg/kg/d for 3 weeks) + placebo versus IMMA (30 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 6. IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	2	148	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.71, 0.96]
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Serious adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Skin reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Cardiac toxicity 'QT prolongation'	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 7. IMMA (30 mg/kg/d for 3 weeks) + 40 mg omeprazole versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 8. IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 9. IMMA (30 mg/kg/d for 3 weeks) + 40 mg omeprazole versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 10. ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects (itching and burning)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects (oedema)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 11. ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects (itching and burning)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects (oedema)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 12. ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects (itching and burning)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects (oedema)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 13. ILMA (weekly injections for 6 weeks) + gel mask twice a day versus ILMA (weekly injections for 6 weeks) + vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 14. ILSSG (20 mg/kg/d) + IMSSG (remaining total dose days 1, 3, 5) versus ILSSG (1000 mg/mL days 1, 3, 5)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 15. ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 d for 29 days) versus IMSSG (20 mg/kg/d for 3 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects (mild heart symptoms)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 16. Ketoconazole 600 mg/d for 6 weeks versus ketoconazole 800 mg/d for 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects (nausea and vomiting)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 17. Ketoconazole 600 mg/d for 30 d versus ILMA (6 to 8 biweekly injections)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effect (liver enzymes increase)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 18. ILSSG (100 mg/mL days 1, 3, 5) + oral ketoconazole (600 mg/d for 4 weeks) versus ILSSG (100 mg/mL days 1, 3, 5)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 19. ILSSG (100 mg/mL days 1, 3, 5) + ketoconazole (600 mg/d for 4 weeks) versus ILSSG (20 mg/kg/d) + IMSSG (remaining total dose days 1, 3, 5)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 20. Itraconazole (200 mg for 6 weeks) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected

Comparison 21. Itraconazole (200 mg for 3 weeks) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected

Comparison 22. Itraconazole (200 mg for 6 to 8 weeks) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	3	244	Risk Ratio (M-H, Random, 99% CI)	3.70 [0.35, 38.99]
2 Adverse effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Mild abdominal pain and nausea	3	204	Risk Ratio (M-H, Random, 95% CI)	2.36 [0.74, 7.47]
2.2 Mild abnormal liver function	3	84	Risk Ratio (M-H, Random, 95% CI)	3.08 [0.53, 17.98]
2.3 Headache and dizziness	1	20	Risk Ratio (M-H, Random, 95% CI)	2.63 [0.16, 43.63]
3 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected

Comparison 23. Itraconazole (200 mg for 6 to 8 weeks) versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
2 Adverse effects (headache and dizziness)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 24. Fluconazole (200 mg for 6 weeks) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 25. Fluconazole (400 mg/d for 6 weeks) versus fluconazole (200 mg/d for 6 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Rise creatinine and liver enzymes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Cheilitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 26. Oral dapsone (200 mg/d for 6 weeks) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete Cure	2	160	Risk Ratio (M-H, Random, 95% CI)	24.08 [1.44, 403.43]
2 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Nausea	2	160	Risk Ratio (M-H, Random, 95% CI)	21.86 [3.04, 157.29]

Comparison 27. Allopurinol (15 mg/kg/d for 3 weeks) + IMMA (20 mg/kg/d for 2 weeks) versus allopurinol (15 mg/kg/d for 3 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1	100	Risk Ratio (M-H, Random, 95% CI)	3.83 [1.71, 8.60]

Comparison 28. Allopurinol (15mg/kg/d for 3 weeks)+ IMMA (20 mg/kg/d for 2 weeks) versus IMMA (20 mg/kg/d for 2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1	100	Risk Ratio (M-H, Random, 95% CI)	1.92 [1.08, 3.41]

Comparison 29. Allopurinol (15 mg/kg/d for 3 weeks) versus IMMA (20 mg/kg/d for 2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions Cured	1	100	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.35, 1.62]

Comparison 30. Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Mild abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Skin eruption	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Muscle pain and weakness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Microbiological cure of skin lesions	1	72	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.88, 1.41]

Comparison 31. Allopurinol (20 mg/kg/d for 3 weeks)+ IMMA (10 mg/kg/d for 20 d) versus IMMA (20 mg/kg/d for 28 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Secondary infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Myalgia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 ECG changes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Chest pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Pain injection site	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Abscess	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 32. Allopurinol (20 mg/kg/d for 3 weeks) versus IVSSG (20 mg/kg/d for 15 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Abdominal symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Liver abnormalities	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Myalgia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Rash	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 33. Oral rifampicin (10 mg/kg/d for 4 to 6 weeks) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Evaluated 3 months after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Evaluated after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 34. Oral rifampicin (10 mg/kg/d) + omeprazole (20 mg/d) for 6 weeks versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 35. Azythromicin (500 mg/d for 5 d/month up to 4 months) versus IMMA (60 mg/kg/d for 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Nausea and vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 36. Azythromicin (10 mg/kg/d) + allopurinol (10 mg/kg/d) for 1 month versus IMMA (20 mg/kg/d for 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Gastrointestinal complaints and headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Gastrointestinal complications	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Myalgia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 37. Oral pentoxifylline (400 mg 3 times daily) + IMMA (20 mg/kg/d) for 20 d versus placebo + IMMA (20 mg/kg/d) for 20 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Allergic macule-papular	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 38. Oral miltefosine (2.5 mg/kg/d for 4 weeks) versus IMMA (60 mg/kg/d for 2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 39. Oral miltefosine (2.5 mg/kg/d for 4 weeks) versus IMMA (60 mg/kg/d for 2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 40. Oral zinc sulphate 2.5 mg/kg/d for 45 days versus oral zinc sulphate 5 mg/kg/d for 45 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Nausea and vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 41. Oral zinc sulphate 2.5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Nausea and vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 42. Oral zinc sulphate 5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Nausea and vomiting	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 43. Oral zinc sulphate (10 mg/kg/d for 45 d) versus IMMA (20 mg/kg/d for 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 44. Artesunate 400 mg + sulphamethoxypyrazine/pyrimethamine 1000 mg/50 mg 4 times daily for 4 d versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 45. Topical 2% miconazole (twice a day) versus topical 1% clotrimazole (twice a day) for 30 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 46. Topical ketoconazole (twice a day) versus vehicle (twice a day) for 30 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 47. Topical amphotericin B (3 to 7 drops twice daily for 8 weeks) versus ILMA (max 2 mL) once a week for 8 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure (ITT)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Hypersensitivity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Mild pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Erithema and oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 48. Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Scarring	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 49. Paromomycin (twice daily for 30 d) versus vehicle (twice daily for 30 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1	80	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.25, 2.06]

Comparison 50. Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	2	383	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.17]
2 Adverse effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Skin/local reaction	3	463	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.45, 1.93]
3 Microbiological cure of skin lesions	2	383	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.88, 1.20]

Comparison 51. Paromomycin 15% (daily for 20 d) versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 52. Paromomycin 15% + gentamicin 0.5% (daily for 20 d) versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 53. Paromomycin 15% + gentamicin 0.5% (daily for 20 d) versus paromomycin 15% alone (daily for 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 54. Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Scarring	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 55. Paromomycin 15% + 10% urea (twice daily for 20 d) versus ILMA (weekly for up to 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Cutaneous reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 56. Paromomycin + MBCL (twice daily for 15 d) versus ketoconazole (weekly for up to 30 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 57. Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Scarring	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
3 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 58. Paromomycin (4 weeks) versus paromomycin (2 weeks) + vehicle (2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 59. IL zinc 2% (twice a week for 2 weeks) versus ILSSG (100 mg/mL) for 2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 60. IL zinc 2% (twice a week for 2 weeks) versus IL 7% HSCS for 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 61. ILSSG (100 mg/mL) for 2 weeks versus IL 7% HSCS for 2 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 62. IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participants complete cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Itching	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Inflammation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Pruritus and erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Severe pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 63. IL zinc 2% (twice a week for 2 weeks) versus ILMA (60 mg/kg/d for 2 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Inflammation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 64. Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participants with treated lesions that recur	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Itch and burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 65. IL 7% HSCS (0.2 mL to 7 mL per lesion) versus ILSSG (max 2 mL) max 5 injections

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 66. IL 5% HSCS (0.5 mL to 1 mL per lesion) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 6 to 10 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Sporotrichotic dissemination	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 67. IL 7% HSCS (0.1 mL to 0.5 mL per lesion) versus IL 2% ciprofloxacin solution (0.1 mL to 0.5 mL per lesion)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 68. IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Ulceration and necrosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 69. ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Ulceration and necrosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 70. ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
3 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Ulceration and necrosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 71. IL IFN-γ (weekly for 5 weeks) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 5 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 72. WR279,396 (twice a day for 20 d) versus vehicle (twice a day for 20 d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Mild pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Hearing acuity problems	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 73. IL metronidazole (2.5 mg to 10 mg each lesion) versus ILMA (150 mg to 600 mg each lesion) for up to 8 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Local inflammatory reactions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 74. Topical miltefosine 6% (once daily) versus ILMA (twice a week) for up to 28 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 75. Dapsone gel 5% (twice a day) + ILMA (weekly) versus cryotherapy (every 2 weeks) + IMMA (weekly) for up to 16 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 76. DAC-055 + MWT (for 15 min) versus DAC-055 alone for up to 75 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Reulceration	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Keloïd scars	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 77. DAC-055 + heat (for 15 min) versus ILSSG (0.6 mL) for up to 75 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Reulceration	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Keloïd scars	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 78. DAC-055 alone (for 15 min) versus ILSSG (0.6 mL) for up to 75 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Reulceration	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Keloïd scars	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 79. Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Dizziness and nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Hypersensitive reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 80. CO laser (30 W continuous) versus IMMA (50 mg/kg/d) for up to 15 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1	433	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.55]
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Hyperpigmentation and redness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Hypertrophic scarring	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Systemic symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 81. CO laser (30 W continuous) versus cryotherapy (fortnightly) + ILMA (weekly) for up to 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Hyperpigmentation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Atrophic scar	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Hypopigmentation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 82. Ablative CO laser (25 kW for 1 session) versus 3 weeks fractional CO laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Partcipants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 83. TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Mild erythema and itch	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Microbiological cure of skin lesions	1	80	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.26]

Comparison 84. Topical TCA 50% + local heat versus ILMA twice a week for up to 8 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Lesions cured	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected
2.1 Males	1		Risk Ratio (M-H, Random, 99% CI)	0.0 [0.0, 0.0]
2.2 Females	1		Risk Ratio (M-H, Random, 99% CI)	0.0 [0.0, 0.0]

Comparison 85. TCA + ILMA (weekly for up to 8 weeks) versus ILMA alone (twice a week for up to 8 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 86. Fractional laser + ILMA (fortnightly 2 sessions) versus ILMA alone (twice a week for up to 8 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 87. TCA + ILMA (weekly for up to 8 weeks) versus fractional laser + ILMA (fortnightly 2 sessions)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 88. TCA fortnightly up to 8 weeks + ILMA (twice a week) versus ILMA alone (weekly for up to 8 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 89. Cryotherapy + ILMA (weekly) versus cryotherapy (weekly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Erythema and oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 90. Cryotherapy + ILMA (weekly) versus ILMA (weekly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Erythema and oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 91. Cryotherapy + ILMA (weekly) versus ILMA alone (weekly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Erythema and oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 92. Cryotherapy (weekly) versus ILMA (weekly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 93. Cryotherapy + ILMA (weekly) versus cryotherapy alone (weekly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Hypopigmentation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 94. Cryotherapy + ILMA (weekly) versus ILMA (fortnightly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Hypopigmentation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 95. Cryotherapy alone (weekly) versus ILMA (fortnightly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1	390	Risk Ratio (M-H, Random, 95% CI)	14.64 [0.86, 247.99]
2.1 Hypopigmentation	1	390	Risk Ratio (M-H, Random, 95% CI)	14.64 [0.86, 247.99]

Comparison 96. Cryotherapy (fortnightly) + 15% paromomycin + 10% urea cream (twice a day) + ILMA (twice a day for 4 weeks) versus ILMA (twice a week) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 97. Cryotherapy (weekly) + 3% salicylic + 3% sodium nitrite cream (twice a day) for up to 12 weeks versus cryotherapy (weekly) + 3% salicylic cream (twice a day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Mild skin symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 98. Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participants complete cure	2	499	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.97, 1.55]
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 99. Radiofrequency waves (50 uCTM applied for 30 s) versus ILSSG (10 days of 20 mg/kg/d)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects (serious)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 100. Radiofrequency waves (1 treatment of > 1 consecutive application at 50°C for 30 s) versus IMSSG (20 mg/kg/d for 3 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse event (secondary infection)	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected

Comparison 101. Radiofrequency waves (1 treatment of > 1 consecutive application at 50°C for 30 s) versus ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 days)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse event (secondary infection)	1		Risk Ratio (M-H, Random, 99% CI)	Totals not selected

Comparison 102. Radiofrequency waves versus ILSSG

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 103. Electrocauterisation + DAC n-055 (daily) versus electrocauterisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Superinfection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Keloid formation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 104. PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesions cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Scarring	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 105. Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Development of cell-mediated immunity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 106. Diminazene aceturate solution (weekly) versus cetrimide + chlorhexidine solution for 50 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 107. Topical garlic (twice a day) versus vehicle for 3 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 108. Topical herbal extract + placebo (5 d) versus IMMA (15-20/mg/kg/d) + vehicle for 20 d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 109. Topical honey (twice a day) + ILMA (weekly) versus ILMA (weekly) for 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 110. *Cassia fistula* (topical gel) + ILMA (0.5 mL to 2 mL), twice a week versus ILMA (0.5 mL to 2 mL), twice a week + vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Itching	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 111. *Cassia fistula* boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 112. *Cassia fistula* hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Speed of healing (weeks)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Adverse reaction	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 113. *Cassia fistula* boiled (topical) versus*C fistula* hydroalcoholic (topical) for 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Speed of healing (days)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 114. Topical gel *Achilles millefollium* (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks

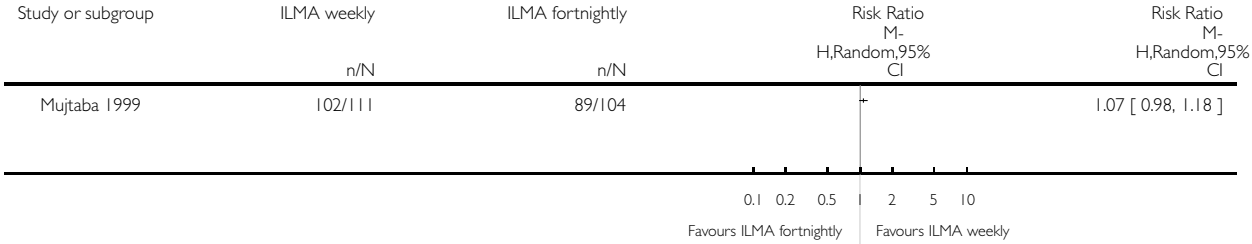
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants complete cure	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Itching	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Microbiological cure of skin lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 ILMA weekly versus ILMA fortnightly for up to 8 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 1 ILMA weekly versus ILMA fortnightly for up to 8 weeks

Outcome: 1 Lesions cured

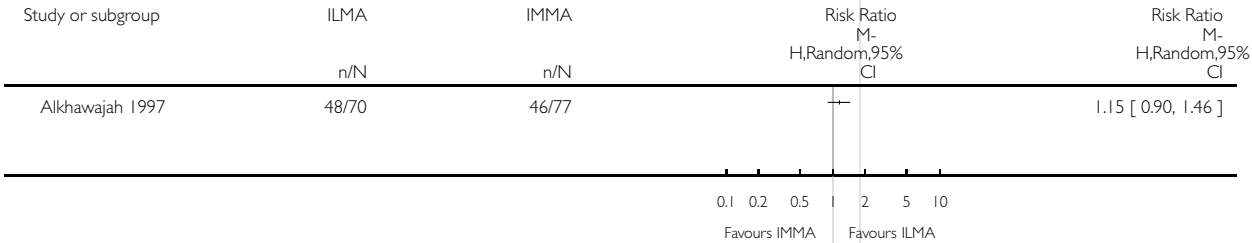


Analysis 2.1. Comparison 2 ILMA (every other day) versus IMMA (6 d/week) for up to 4 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 2 ILMA (every other day) versus IMMA (6 d/week) for up to 4 weeks

Outcome: 1 Lesions cured

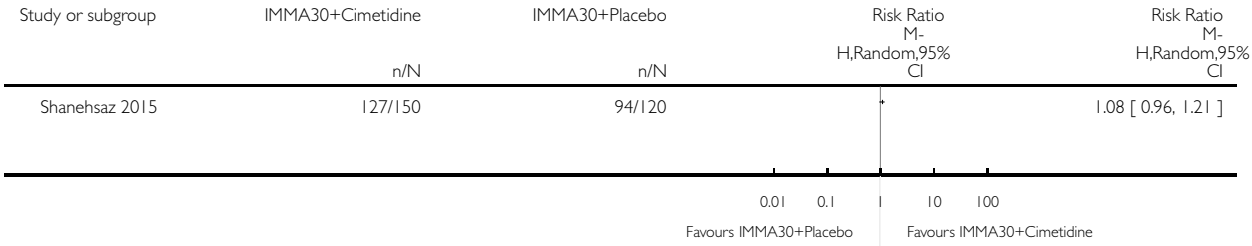


Analysis 3.1. Comparison 3 IMMA (30 mg/kg/d for 3 weeks) + cimetidine versus IMMA (30 mg/kg/d for 3 weeks) + placebo, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 3 IMMA (30 mg/kg/d for 3 weeks) + cimetidine versus IMMA (30 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Lesions cured

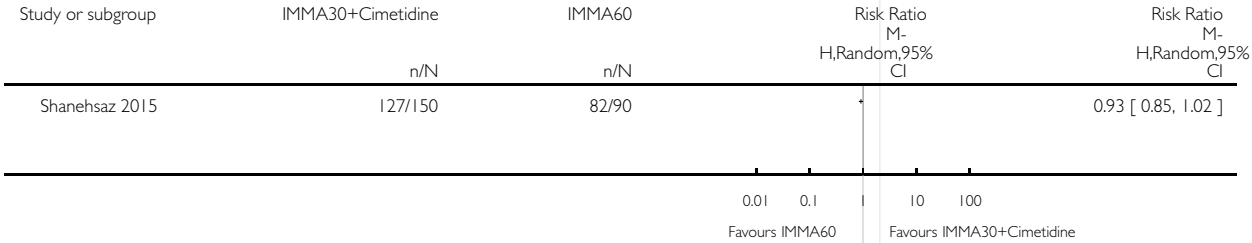


Analysis 4.1. Comparison 4 IMMA (30 mg/kg/d for 3 weeks) + cimetidine versus IMMA (60 mg/kg/d for 3 weeks) + placebo, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 4 IMMA (30 mg/kg/d for 3 weeks) + cimetidine versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Lesions cured

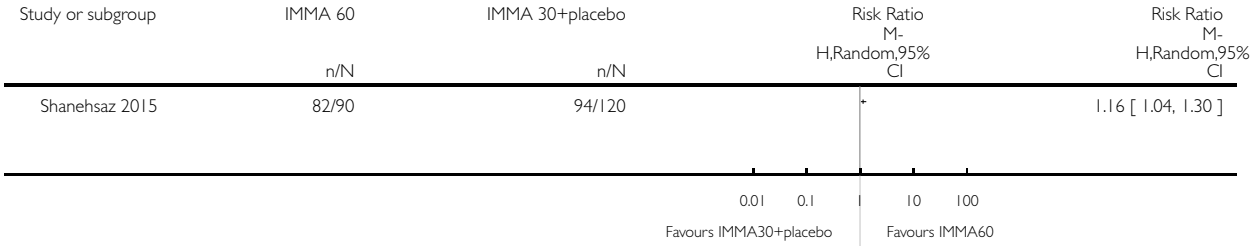


Analysis 5.1. Comparison 5 IMMA (60 mg/kg/d for 3 weeks) + placebo versus IMMA (30 mg/kg/d for 3 weeks) + placebo, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 5 IMMA (60 mg/kg/d for 3 weeks) + placebo versus IMMA (30 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Lesions cured

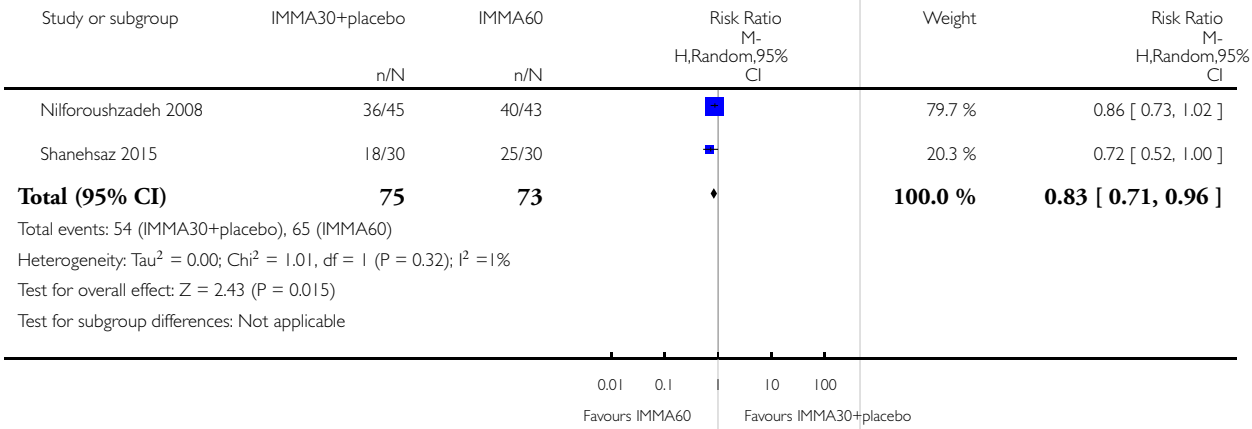


Analysis 6.1. Comparison 6 IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 6 IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Participants complete cure

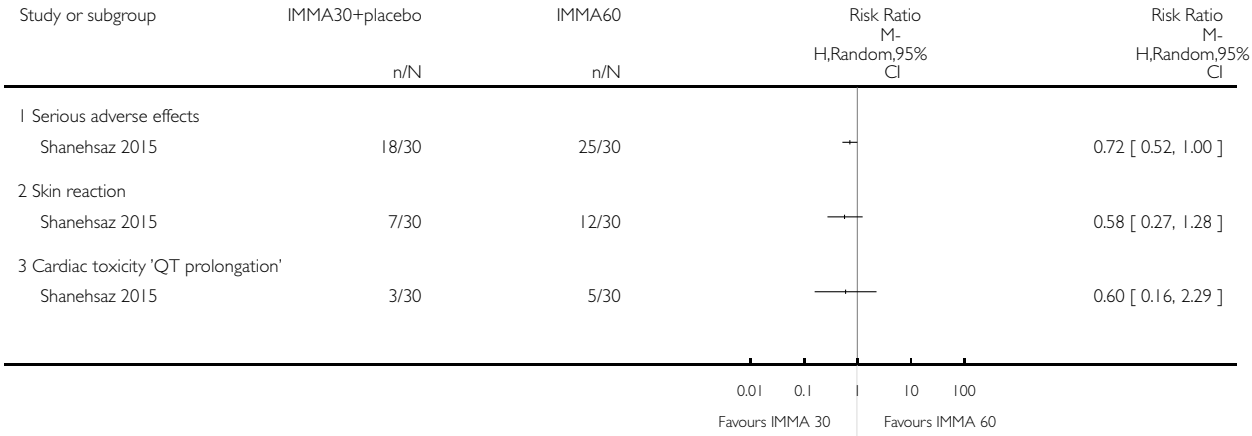


Analysis 6.2. Comparison 6 IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 6 IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome: 2 Adverse effects

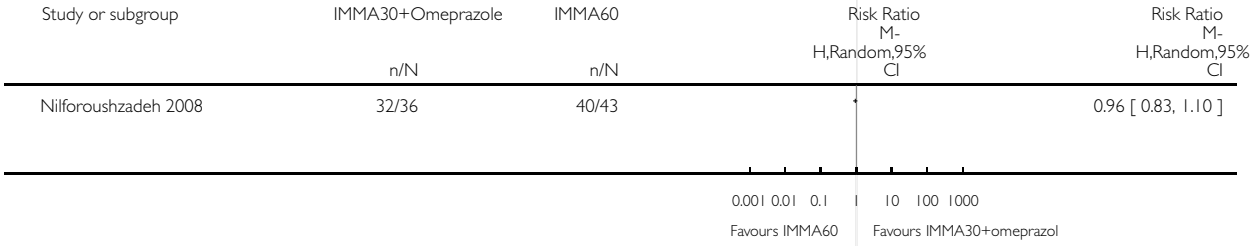


Analysis 7.1. Comparison 7 IMMA (30 mg/kg/d for 3 weeks) + 40 mg omeprazole versus IMMA (60 mg/kg/d for 3 weeks) + placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 7 IMMA (30 mg/kg/d for 3 weeks) + 40 mg omeprazole versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Participants complete cure



Analysis 8.1. Comparison 8 IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 8 IMMA (30 mg/kg/d for 3 weeks) + placebo versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Participants complete cure

Study or subgroup	IMMA30+placebo n/N	IMMA60 n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2008	36/45	40/43		0.86 [0.73, 1.02]

Analysis 9.1. Comparison 9 IMMA (30 mg/kg/d for 3 weeks) + 40 mg omeprazole versus IMMA (60 mg/kg/d for 3 weeks) + placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 9 IMMA (30 mg/kg/d for 3 weeks) + 40 mg omeprazole versus IMMA (60 mg/kg/d for 3 weeks) + placebo

Outcome: 1 Participants complete cure

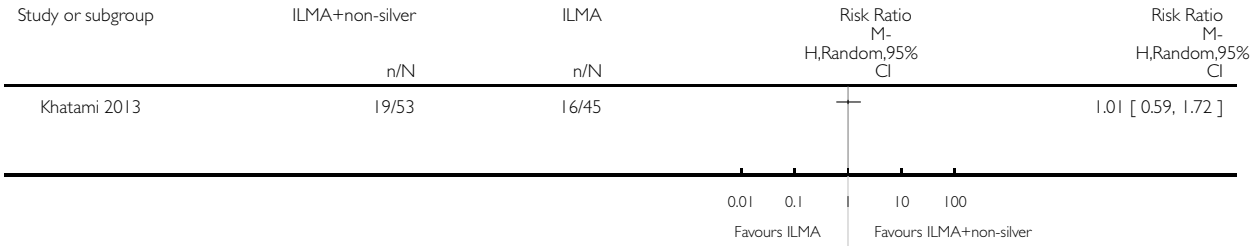
Study or subgroup	IMMA30+Omeprazole n/N	IMMA30+Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2008	32/36	36/45		1.11 [0.92, 1.34]

Analysis 10.1. Comparison 10 ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 10 ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome: 1 Lesions cured

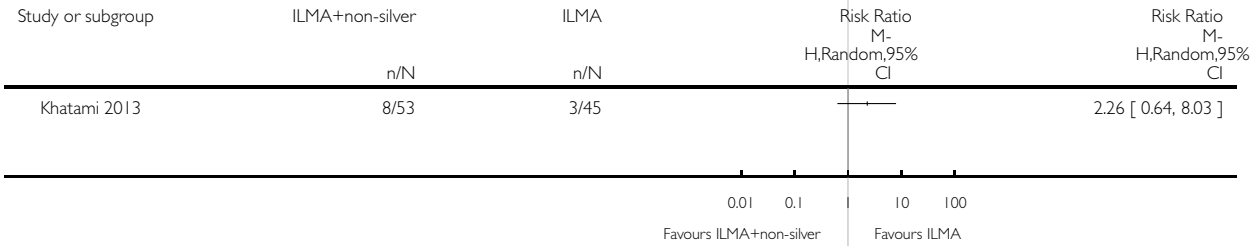


Analysis 10.2. Comparison 10 ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks), Outcome 2 Adverse effects (itching and burning).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 10 ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome: 2 Adverse effects (itching and burning)

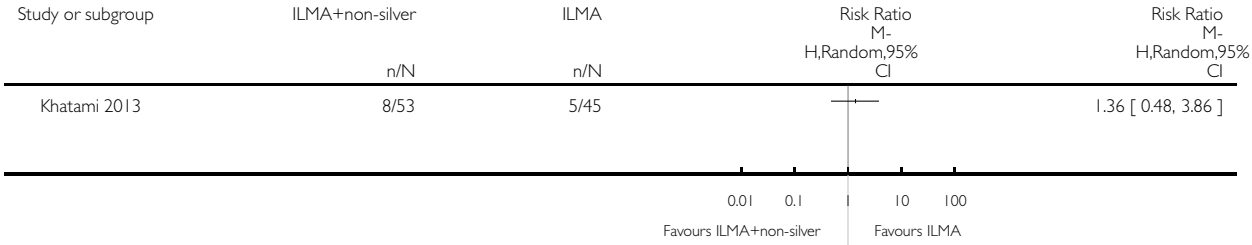


Analysis 10.3. Comparison 10 ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks), Outcome 3 Adverse effects (oedema).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 10 ILMA + non-silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome: 3 Adverse effects (oedema)

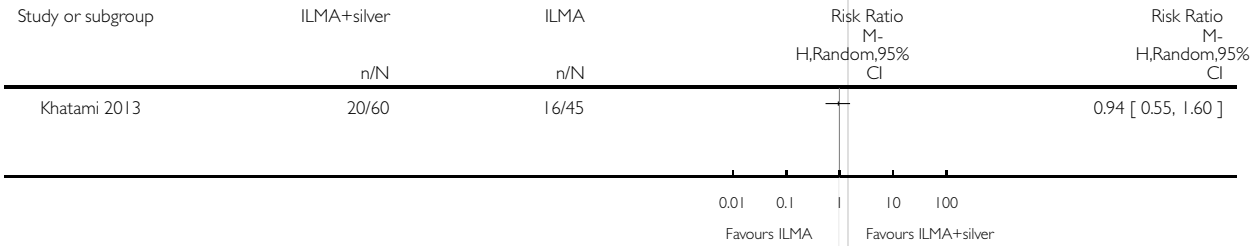


Analysis 11.1. Comparison 11 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 11 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome: 1 Lesions cured

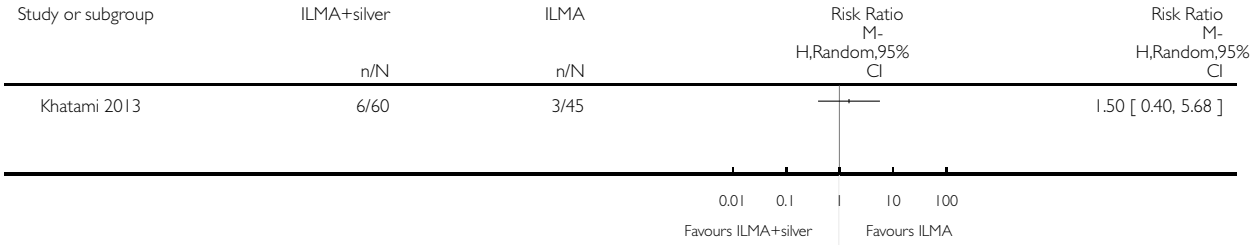


Analysis 11.2. Comparison 11 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks), Outcome 2 Adverse effects (itching and burning).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 11 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome: 2 Adverse effects (itching and burning)

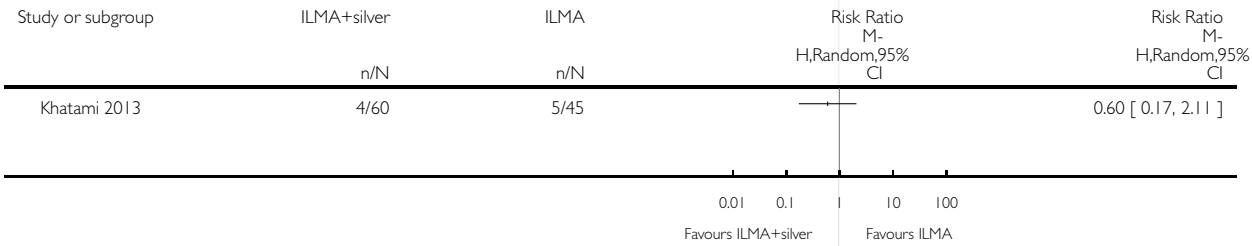


Analysis 11.3. Comparison 11 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks), Outcome 3 Adverse effects (oedema).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 11 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks)

Outcome: 3 Adverse effects (oedema)

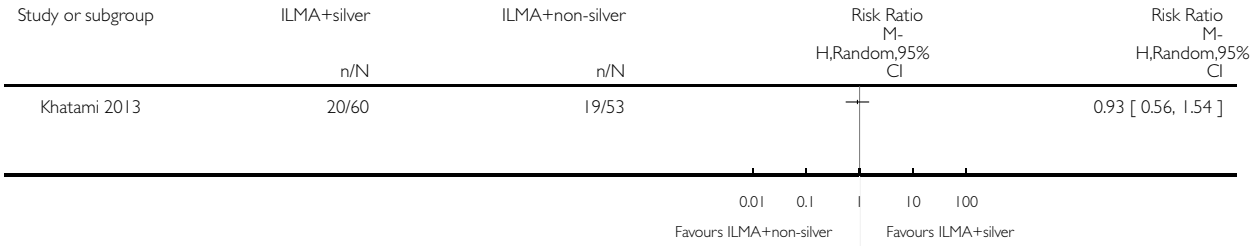


Analysis 12.1. Comparison 12 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 12 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing

Outcome: 1 Lesions cured

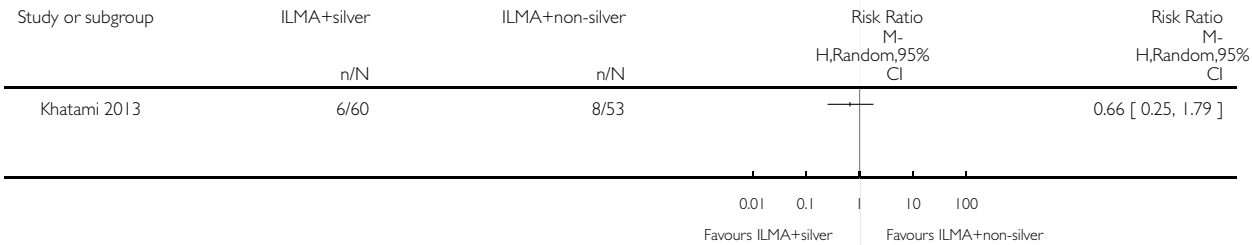


Analysis 12.2. Comparison 12 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing, Outcome 2 Adverse effects (itching and burning).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 12 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing

Outcome: 2 Adverse effects (itching and burning)

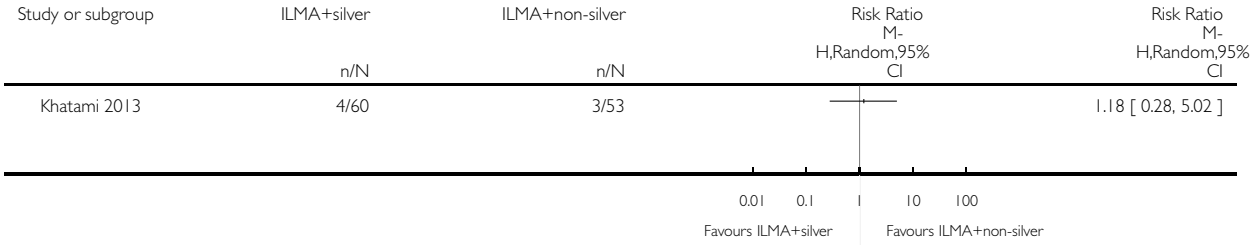


Analysis 12.3. Comparison 12 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing, Outcome 3 Adverse effects (oedema).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 12 ILMA (weekly injections for 6 weeks) + silver polyester dressing versus ILMA (weekly injections for 6 weeks) + non-silver polyester dressing

Outcome: 3 Adverse effects (oedema)

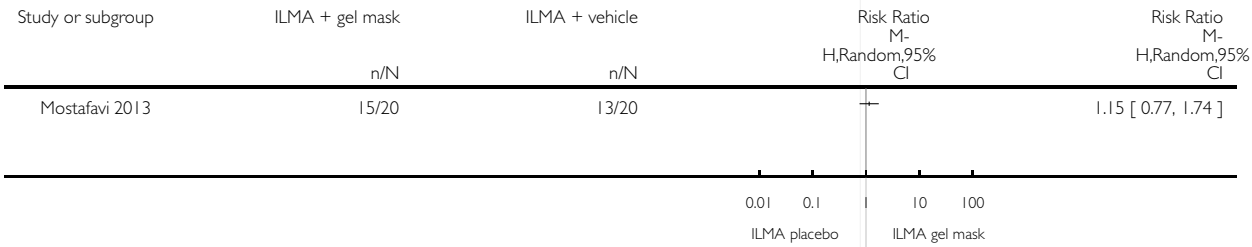


Analysis 13.1. Comparison 13 ILMA (weekly injections for 6 weeks) + gel mask twice a day versus ILMA (weekly injections for 6 weeks) + vehicle, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 13 ILMA (weekly injections for 6 weeks) + gel mask twice a day versus ILMA (weekly injections for 6 weeks) + vehicle

Outcome: 1 Participants complete cure

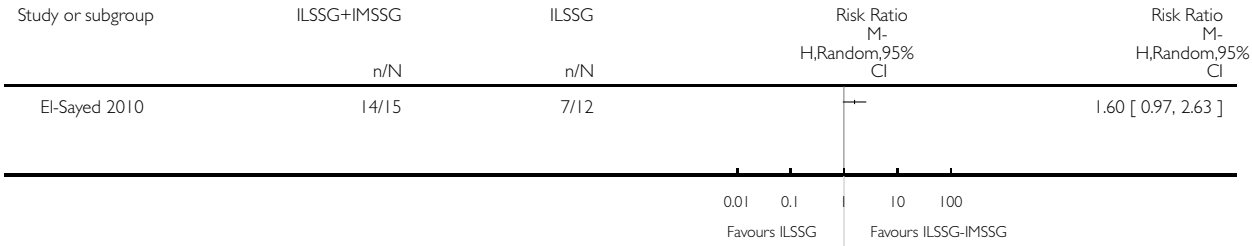


Analysis 14.1. Comparison 14 ILSSG (20 mg/kg/d) + IMSSG (remaining total dose days 1, 3, 5) versus ILSSG (1000 mg/mL days 1, 3, 5), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 14 ILSSG (20 mg/kg/d) + IMSSG (remaining total dose days 1, 3, 5) versus ILSSG (1000 mg/mL days 1, 3, 5)

Outcome: 1 Lesions cured

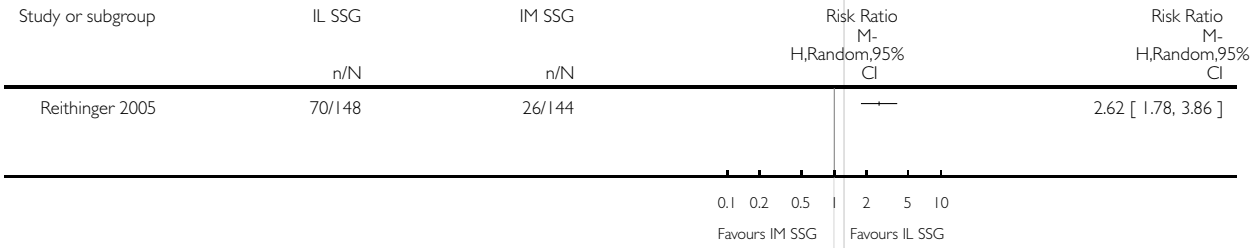


Analysis 15.1. Comparison 15 ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 d for 29 days) versus IMSSG (20 mg/kg/d for 3 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 15 ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 d for 29 days) versus IMSSG (20 mg/kg/d for 3 weeks)

Outcome: 1 Participants complete cure

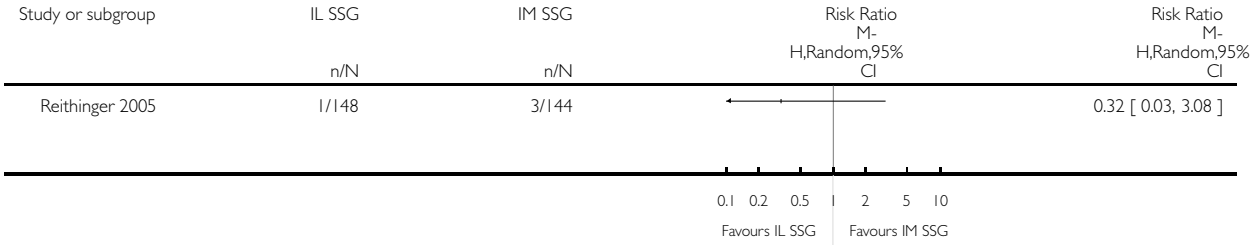


Analysis 15.2. Comparison 15 ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 d for 29 days) versus IMSSG (20 mg/kg/d for 3 weeks), Outcome 2 Adverse effects (mild heart symptoms).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 15 ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 d for 29 days) versus IMSSG (20 mg/kg/d for 3 weeks)

Outcome: 2 Adverse effects (mild heart symptoms)

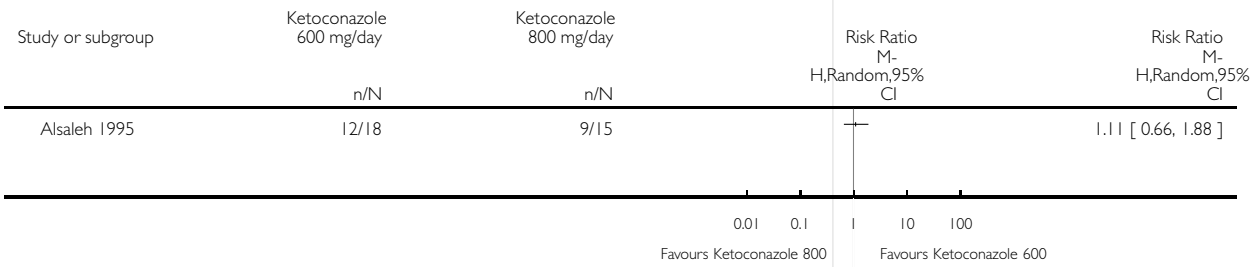


Analysis 16.1. Comparison 16 Ketoconazole 600 mg/d for 6 weeks versus ketoconazole 800 mg/d for 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 16 Ketoconazole 600 mg/d for 6 weeks versus ketoconazole 800 mg/d for 6 weeks

Outcome: 1 Participants complete cure

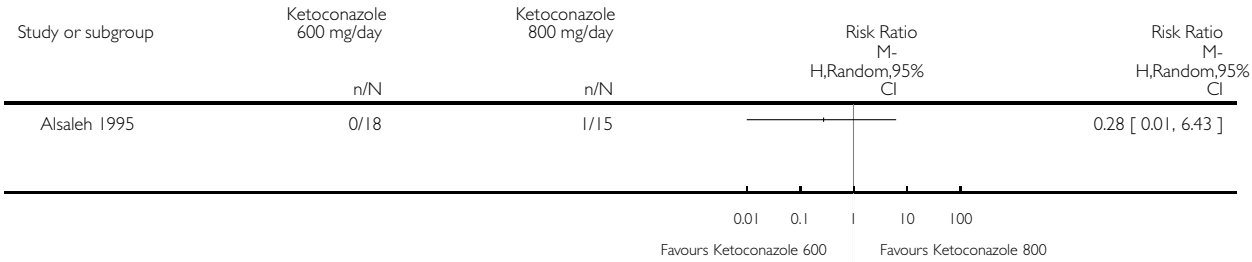


Analysis 16.2. Comparison 16 Ketoconazole 600 mg/d for 6 weeks versus ketoconazole 800 mg/d for 6 weeks, Outcome 2 Adverse effects (nausea and vomiting).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 16 Ketoconazole 600 mg/d for 6 weeks versus ketoconazole 800 mg/d for 6 weeks

Outcome: 2 Adverse effects (nausea and vomiting)

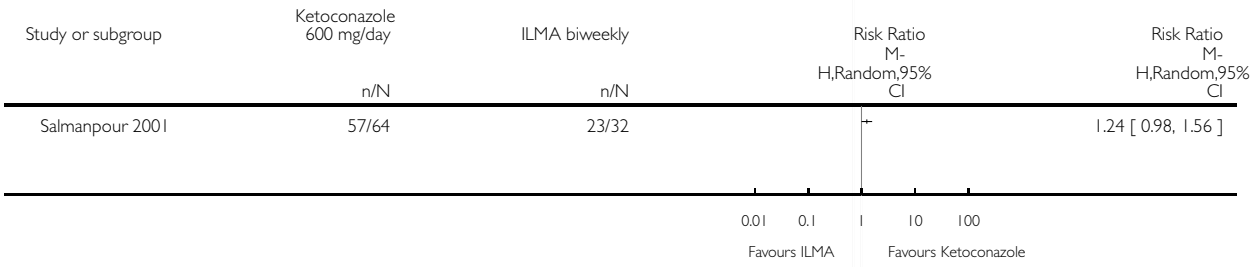


Analysis 17.1. Comparison 17 Ketoconazole 600 mg/d for 30 d versus ILMA (6 to 8 biweekly injections), Outcome 1 Participants cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 17 Ketoconazole 600 mg/d for 30 d versus ILMA (6 to 8 biweekly injections)

Outcome: 1 Participants cured

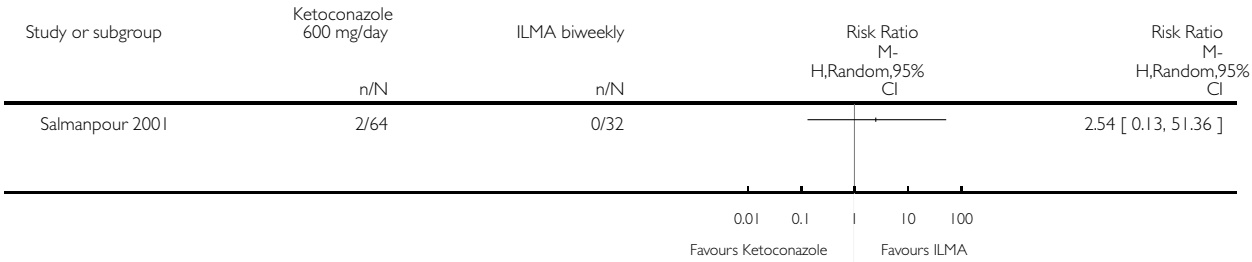


Analysis 17.2. Comparison 17 Ketoconazole 600 mg/d for 30 d versus ILMA (6 to 8 biweekly injections), Outcome 2 Adverse effect (liver enzymes increase).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 17 Ketoconazole 600 mg/d for 30 d versus ILMA (6 to 8 biweekly injections)

Outcome: 2 Adverse effect (liver enzymes increase)

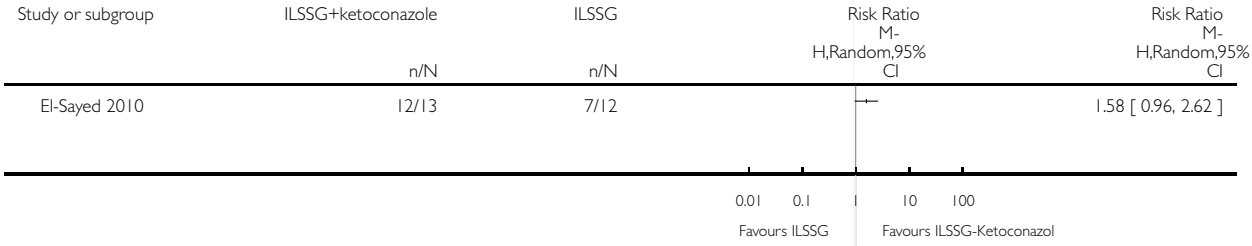


Analysis 18.1. Comparison 18 ILSSG (100 mg/mL days 1, 3, 5) + oral ketoconazole (600 mg/d for 4 weeks) versus ILSSG (100 mg/mL days 1, 3, 5), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 18 ILSSG (100 mg/mL days 1, 3, 5) + oral ketoconazole (600 mg/d for 4 weeks) versus ILSSG (100 mg/mL days 1, 3, 5)

Outcome: 1 Lesions cured

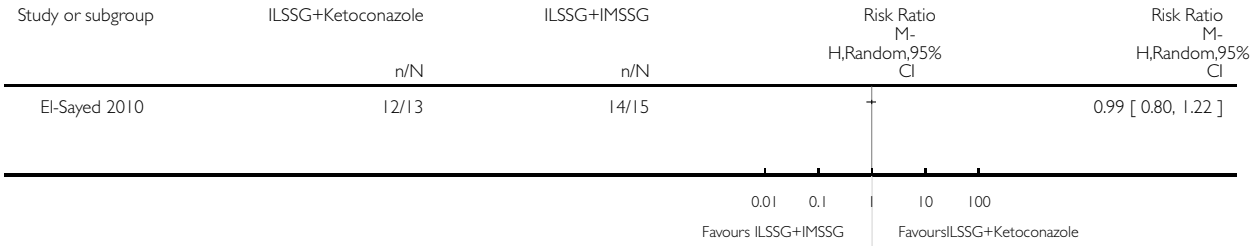


Analysis 19.1. Comparison 19 ILSSG (100 mg/mL days 1, 3, 5) + ketoconazole (600 mg/d for 4 weeks) versus ILSSG (20 mg/kg/d) + IMSSG (remaining total dose days 1, 3, 5), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 19 ILSSG (100 mg/mL days 1, 3, 5) + ketoconazole (600 mg/d for 4 weeks) versus ILSSG (20 mg/kg/d) + IMSSG (remaining total dose days 1, 3, 5)

Outcome: 1 Lesions cured

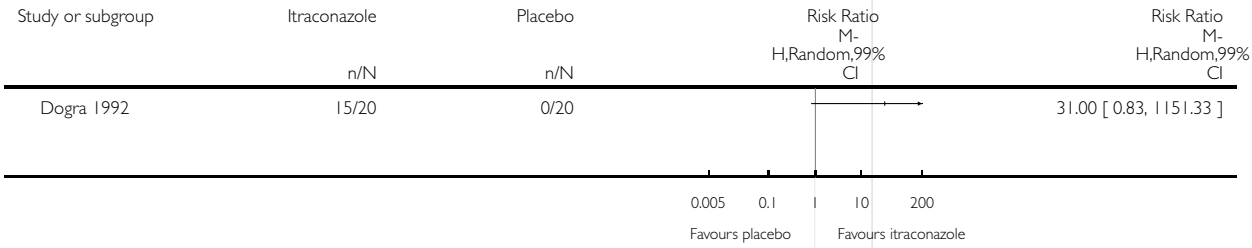


Analysis 20.1. Comparison 20 Itraconazole (200 mg for 6 weeks) versus placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 20 Itraconazole (200 mg for 6 weeks) versus placebo

Outcome: 1 Participants complete cure



Analysis 21.1. Comparison 21 Itraconazole (200 mg for 3 weeks) versus placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 21 Itraconazole (200 mg for 3 weeks) versus placebo

Outcome: 1 Participants complete cure

Study or subgroup	Itraconazole n/N	Placebo n/N	Risk Ratio M-H,Random,99% CI	Risk Ratio M-H,Random,99% CI
Momeni 1996	36/70	27/70		1.33 [0.82, 2.18]

Analysis 22.1. Comparison 22 Itraconazole (200 mg for 6 to 8 weeks) versus placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 22 Itraconazole (200 mg for 6 to 8 weeks) versus placebo

Outcome: 1 Participants complete cure

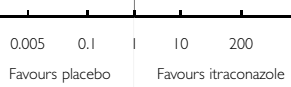
Study or subgroup	Itraconazole n/N	Placebo n/N	Risk Ratio M-H,Random,99% CI	Weight	Risk Ratio M-H,Random,99% CI
Nassiri-Kashani 2005	67/100	53/100		46.7 %	1.26 [0.93, 1.71]
Dogra 1996	7/10	1/10		30.7 %	7.00 [0.57, 85.38]
Al-Fouzan 1991	11/15	0/9		22.6 %	14.38 [0.40, 512.25]
Total (99% CI)	**125**	**119**		**100.0 %**	**3.70 [0.35, 38.99]**

Total events: 85 (Itraconazole), 54 (Placebo)

Heterogeneity: $Tau^2 = 1.78$; $Chi^2 = 7.52$, df = 2 (P = 0.02); $I^2 = 73\%$

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable

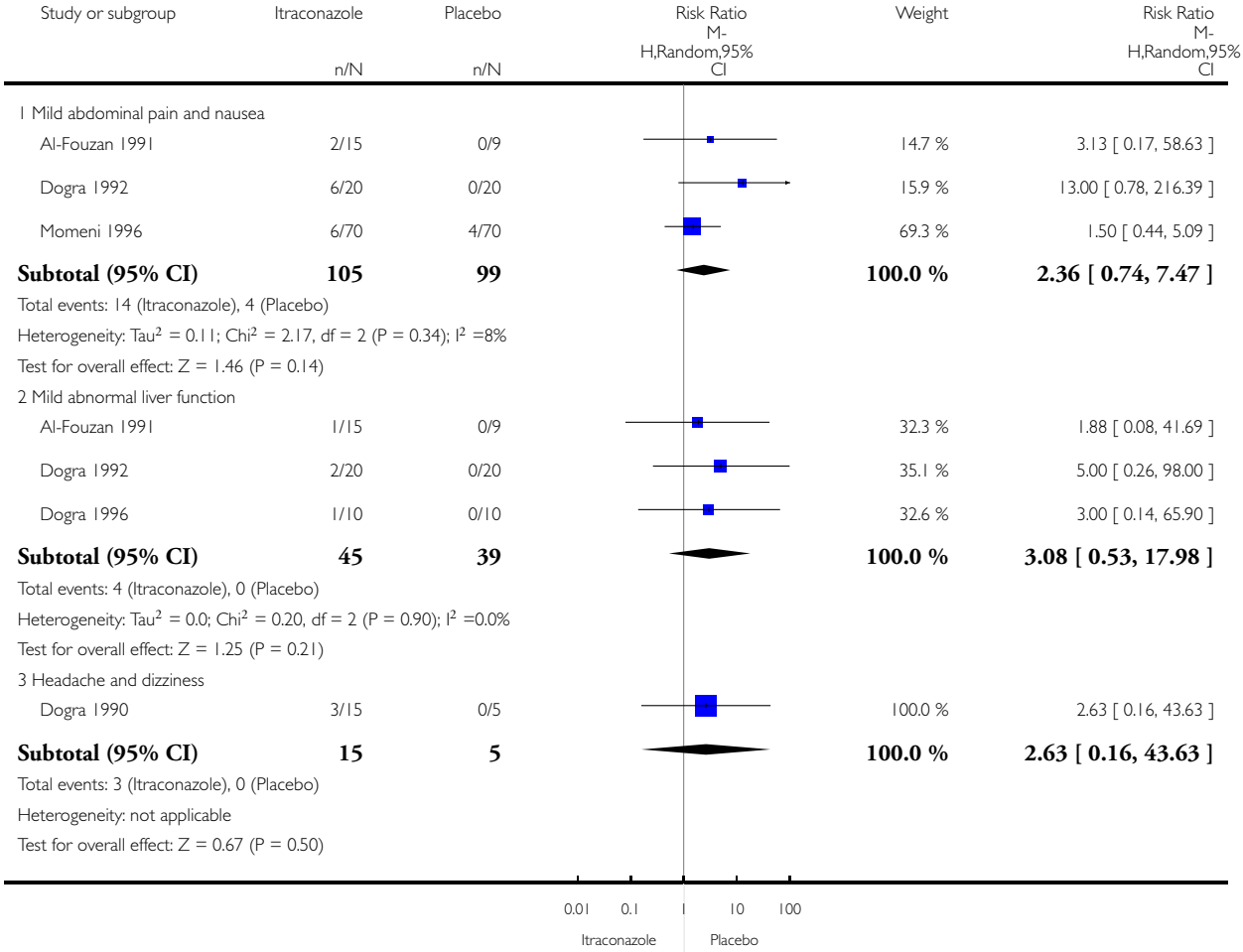


Analysis 22.2. Comparison 22 Itraconazole (200 mg for 6 to 8 weeks) versus placebo, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 22 Itraconazole (200 mg for 6 to 8 weeks) versus placebo

Outcome: 2 Adverse effects



Analysis 22.3. Comparison 22 Itraconazole (200 mg for 6 to 8 weeks) versus placebo, Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 22 Itraconazole (200 mg for 6 to 8 weeks) versus placebo

Outcome: 3 Microbiological cure of skin lesions

Study or subgroup	Itraconazole n/N	Placebo n/N	Risk Ratio M-H,Random,99% CI	Risk Ratio M-H,Random,99% CI
Dogra 1996	8/10	0/10		17.00 [0.47, 612.21]

Analysis 23.1. Comparison 23 Itraconazole (200 mg for 6 to 8 weeks) versus no treatment, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 23 Itraconazole (200 mg for 6 to 8 weeks) versus no treatment

Outcome: 1 Participants complete cure

Study or subgroup	Itraconazole n/N	No treatment n/N	Risk Ratio M-H,Random,99% CI	Risk Ratio M-H,Random,99% CI
Dogra 1990	10/15	0/5		7.88 [0.23, 265.70]

Analysis 23.2. Comparison 23 Itraconazole (200 mg for 6 to 8 weeks) versus no treatment, Outcome 2 Adverse effects (headache and dizziness).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 23 Itraconazole (200 mg for 6 to 8 weeks) versus no treatment

Outcome: 2 Adverse effects (headache and dizziness)

Study or subgroup	Itraconazole n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dogra 1990	3/15	0/5		2.63 [0.16, 43.63]

Analysis 23.3. Comparison 23 Itraconazole (200 mg for 6 to 8 weeks) versus no treatment, Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 23 Itraconazole (200 mg for 6 to 8 weeks) versus no treatment

Outcome: 3 Microbiological cure of skin lesions

Study or subgroup	Itraconazole n/N	No treatment n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dogra 1990	10/15	0/5		7.88 [0.54, 114.56]

Analysis 24.1. Comparison 24 Fluconazole (200 mg for 6 weeks) versus placebo, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 24 Fluconazole (200 mg for 6 weeks) versus placebo

Outcome: 1 Lesions cured

Study or subgroup	Fluconazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Dandashli 2005	75/264	10/102		2.90 [1.56, 5.38]

Analysis 24.2. Comparison 24 Fluconazole (200 mg for 6 weeks) versus placebo, Outcome 2 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 24 Fluconazole (200 mg for 6 weeks) versus placebo

Outcome: 2 Participants complete cure

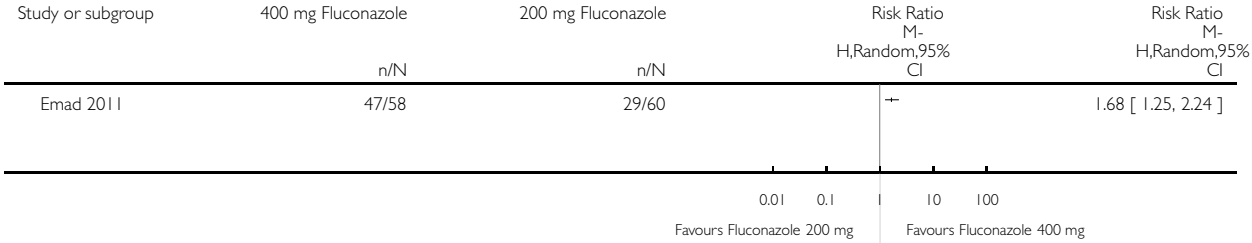
Study or subgroup	Fluconazole n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Alrajhi 2002	63/106	22/103		2.78 [1.86, 4.16]

Analysis 25.1. Comparison 25 Fluconazole (400 mg/d for 6 weeks) versus fluconazole (200 mg/d for 6 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 25 Fluconazole (400 mg/d for 6 weeks) versus fluconazole (200 mg/d for 6 weeks)

Outcome: 1 Participants complete cure

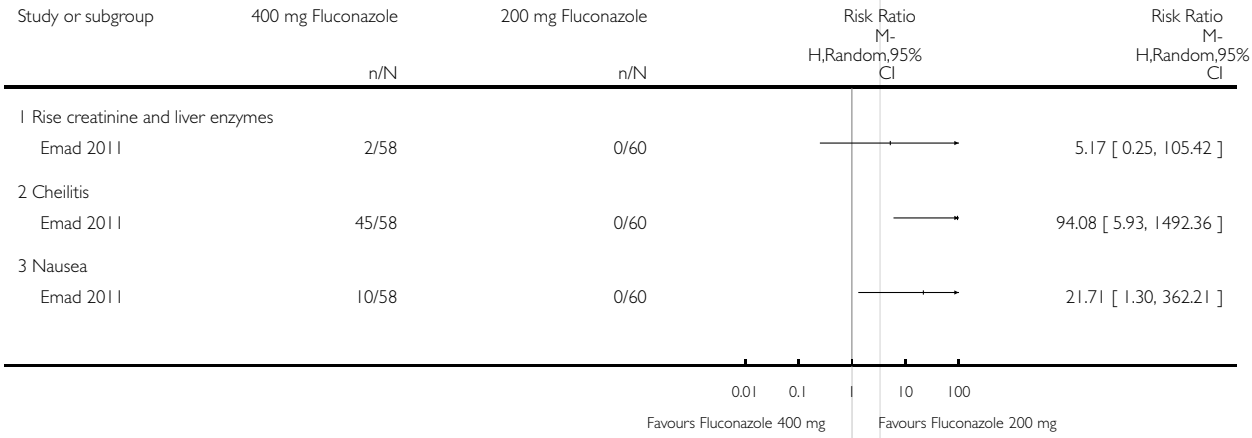


Analysis 25.2. Comparison 25 Fluconazole (400 mg/d for 6 weeks) versus fluconazole (200 mg/d for 6 weeks), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 25 Fluconazole (400 mg/d for 6 weeks) versus fluconazole (200 mg/d for 6 weeks)

Outcome: 2 Adverse effects



Analysis 26.1. Comparison 26 Oral dapsone (200 mg/d for 6 weeks) versus placebo, Outcome 1 Participants complete Cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 26 Oral dapsone (200 mg/d for 6 weeks) versus placebo

Outcome: 1 Participants complete Cure

Study or subgroup	Dapsone 200 mg/day n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dogra 1991	49/60	0/60		41.0 %	99.00 [6.25, 1569.00]
Dogra 1992	18/20	2/20		59.0 %	9.00 [2.40, 33.79]
Total (95% CI)	**80**	**80**		**100.0 %**	**24.08 [1.44, 403.43]**

Total events: 67 (Dapsone 200 mg/day), 2 (Placebo)

Heterogeneity: $Tau^2 = 3.05$; $Chi^2 = 3.50$, df = 1 (P = 0.06); $I^2 = 71\%$

Test for overall effect: Z = 2.21 (P = 0.027)

Test for subgroup differences: Not applicable

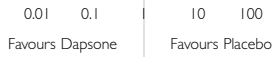
Analysis 26.2. Comparison 26 Oral dapsone (200 mg/d for 6 weeks) versus placebo, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 26 Oral dapsone (200 mg/d for 6 weeks) versus placebo

Outcome: 2 Adverse effects

Study or subgroup	Dapsone 200 mg/day n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Nausea					
Dogra 1991	9/60	0/60		48.9 %	19.00 [1.13, 319.27]
Dogra 1992	12/20	0/20		51.1 %	25.00 [1.58, 395.48]
Subtotal (95% CI)	**80**	**80**		**100.0 %**	**21.86 [3.04, 157.29]**
Total events: 21 (Dapsone 200 mg/day), 0 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.06 (P = 0.0022)					
Test for subgroup differences: Not applicable					



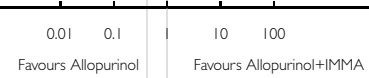
Analysis 27.1. Comparison 27 Allopurinol (15 mg/kg/d for 3 weeks) + IMMA (20 mg/kg/d for 2 weeks) versus allopurinol (15 mg/kg/d for 3 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 27 Allopurinol (15 mg/kg/d for 3 weeks) + IMMA (20 mg/kg/d for 2 weeks) versus allopurinol (15 mg/kg/d for 3 weeks)

Outcome: 1 Lesions cured

Study or subgroup	Allopurinol+ IMMA n/N	Allopurinol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Esfandiarpour 2002	23/50	6/50		100.0 %	3.83 [1.71, 8.60]
Total (95% CI)	**50**	**50**		**100.0 %**	**3.83 [1.71, 8.60]**
Total events: 23 (Allopurinol+ IMMA), 6 (Allopurinol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Test for subgroup differences: Not applicable					



Analysis 28.1. Comparison 28 Allopurinol (15mg/kg/d for 3 weeks)+ IMMA (20 mg/kg/d for 2 weeks) versus IMMA (20 mg/kg/d for 2 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 28 Allopurinol (15mg/kg/d for 3 weeks)+ IMMA (20 mg/kg/d for 2 weeks) versus IMMA (20 mg/kg/d for 2 weeks)

Outcome: 1 Lesions cured

Study or subgroup	Allopurinol +MMA n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Esfandiarpour 2002	23/50	12/50		100.0 %	1.92 [1.08, 3.41]
Total (95% CI)	**50**	**50**		**100.0 %**	**1.92 [1.08, 3.41]**

Total events: 23 (Allopurinol +MMA), 12 (IMMA)

Heterogeneity: not applicable

Test for overall effect: Z = 2.21 (P = 0.027)

Test for subgroup differences: Not applicable

Analysis 29.1. Comparison 29 Allopurinol (15 mg/kg/d for 3 weeks) versus IMMA (20 mg/kg/d for 2 weeks), Outcome 1 Lesions Cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 29 Allopurinol (15 mg/kg/d for 3 weeks) versus IMMA (20 mg/kg/d for 2 weeks)

Outcome: 1 Lesions Cured

Study or subgroup	Allopurinol n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Esfandiarpour 2002	9/50	12/50		100.0 %	0.75 [0.35, 1.62]
Total (95% CI)	**50**	**50**		**100.0 %**	**0.75 [0.35, 1.62]**

Total events: 9 (Allopurinol), 12 (IMMA)

Heterogeneity: not applicable

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable

Analysis 30.1. Comparison 30 Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 30 Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d)

Outcome: 1 Lesions cured

Study or subgroup	Allopurinol +IMMA n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Momeni 2002	25/36	26/36		0.96 [0.71, 1.29]

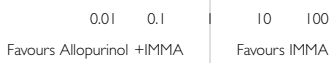
Analysis 30.2. Comparison 30 Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 30 Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d)

Outcome: 2 Adverse effects

Study or subgroup	Allopurinol +IMMA n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Mild abdominal pain				
Momeni 2002	6/36	0/36		13.00 [0.76, 222.53]
2 Skin eruption				
Momeni 2002	0/36	1/36		0.33 [0.01, 7.92]
3 Muscle pain and weakness				
Momeni 2002	0/36	4/36		0.11 [0.01, 1.99]



Analysis 30.3. Comparison 30 Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d), Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 30 Allopurinol (20 mg/kg/d for 3 weeks) + IMMA (30 mg/kg/d for 20 days) versus IMMA (60 mg/kg/d for 20 d)

Outcome: 3 Microbiological cure of skin lesions

Study or subgroup	Allopurinol + IMMA n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Momeni 2002	30/36	27/36		100.0 %	1.11 [0.88, 1.41]
Total (95% CI)	**36**	**36**		**100.0 %**	**1.11 [0.88, 1.41]**

Total events: 30 (Allopurinol + IMMA), 27 (IMMA)

Heterogeneity: not applicable

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable

Analysis 31.1. Comparison 31 Allopurinol (20 mg/kg/d for 3 weeks)+ IMMA (10 mg/kg/d for 20 d) versus IMMA (20 mg/kg/d for 28 d), Outcome 1 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 31 Allopurinol (20 mg/kg/d for 3 weeks)+ IMMA (10 mg/kg/d for 20 d) versus IMMA (20 mg/kg/d for 28 d)

Outcome: 1 Adverse effects

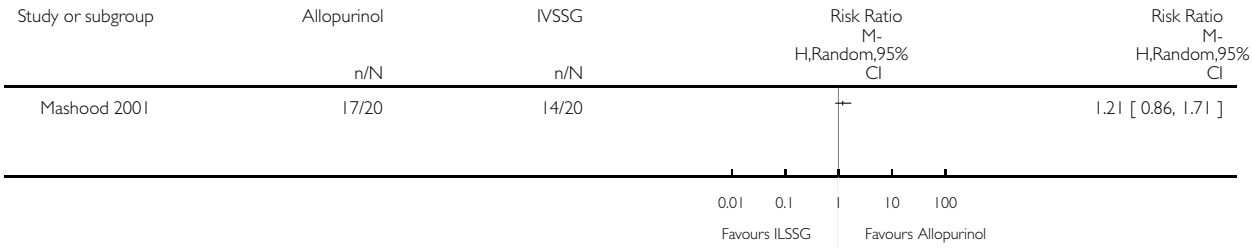
Study or subgroup	Allopurinol + IMMA n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Secondary infection				
Ejaz 2014	21/175	19/152		0.96 [0.54, 1.72]
2 Myalgia				
Ejaz 2014	10/175	12/152		0.72 [0.32, 1.63]
3 ECG changes				
Ejaz 2014	1/175	3/152		0.29 [0.03, 2.75]
4 Chest pain				
Ejaz 2014	0/175	1/152		0.29 [0.01, 7.06]
5 Pain injection site				
Ejaz 2014	0/175	2/152		0.17 [0.01, 3.59]
6 Abscess				
Ejaz 2014	0/175	5/152		0.08 [0.00, 1.42]

Analysis 32.1. Comparison 32 Allopurinol (20 mg/kg/d for 3 weeks) versus IVSSG (20 mg/kg/d for 15 d), Outcome 1 Participants complete cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 32 Allopurinol (20 mg/kg/d for 3 weeks) versus IVSSG (20 mg/kg/d for 15 d)

Outcome: 1 Participants complete cured

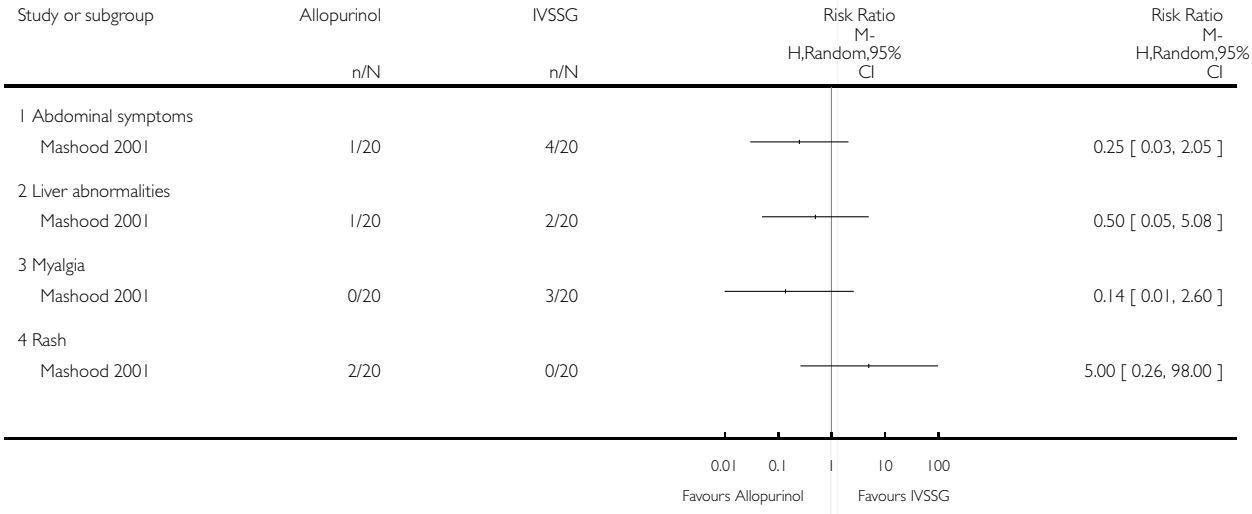


Analysis 32.2. Comparison 32 Allopurinol (20 mg/kg/d for 3 weeks) versus IVSSG (20 mg/kg/d for 15 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 32 Allopurinol (20 mg/kg/d for 3 weeks) versus IVSSG (20 mg/kg/d for 15 d)

Outcome: 2 Adverse effects



Analysis 33.1. Comparison 33 Oral rifampicin (10 mg/kg/d for 4 to 6 weeks) versus placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 33 Oral rifampicin (10 mg/kg/d for 4 to 6 weeks) versus placebo

Outcome: 1 Participants complete cure

Study or subgroup	Oral rifampicin n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Evaluated 3 months after treatment				
Jaffar 2006	21/46	3/16		2.43 [0.84, 7.08]
2 Evaluated after treatment				
Kochar 2000	17/25	1/25		17.00 [2.45, 118.19]

Analysis 33.2. Comparison 33 Oral rifampicin (10 mg/kg/d for 4 to 6 weeks) versus placebo, Outcome 2 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 33 Oral rifampicin (10 mg/kg/d for 4 to 6 weeks) versus placebo

Outcome: 2 Microbiological cure of skin lesions

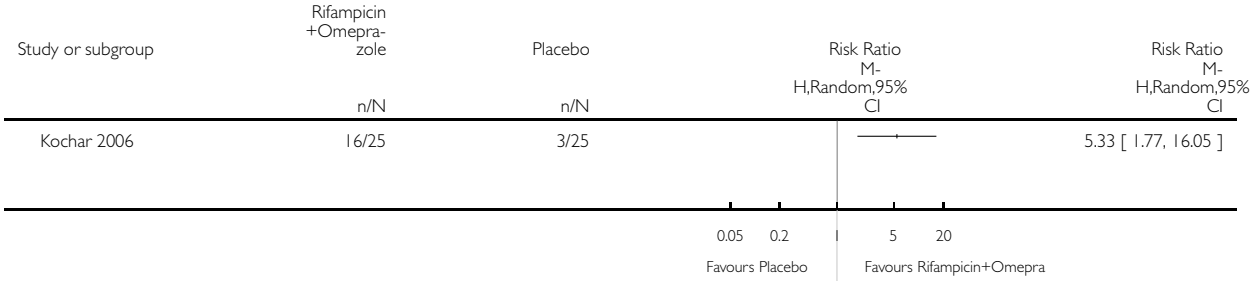
Study or subgroup	Oral rifampicin n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kochar 2000	2/25	8/25		0.25 [0.06, 1.06]

Analysis 34.1. Comparison 34 Oral rifampicin (10 mg/kg/d) + omeprazole (20 mg/d) for 6 weeks versus placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 34 Oral rifampicin (10 mg/kg/d) + omeprazole (20 mg/d) for 6 weeks versus placebo

Outcome: 1 Participants complete cure

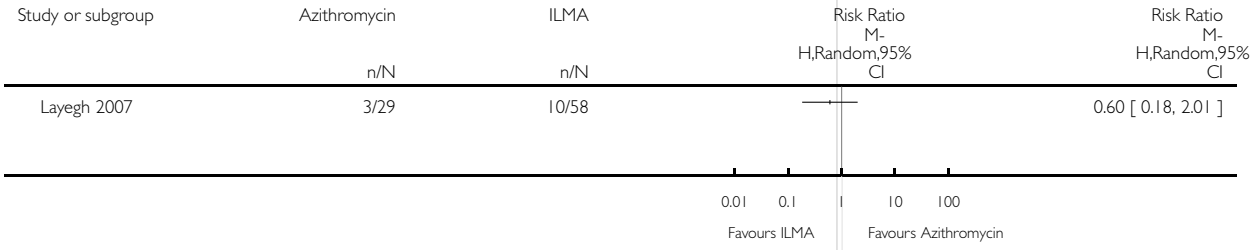


Analysis 35.1. Comparison 35 Azythromicin (500 mg/d for 5 d/month up to 4 months) versus IMMA (60 mg/kg/d for 20 d), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 35 Azythromicin (500 mg/d for 5 d/month up to 4 months) versus IMMA (60 mg/kg/d for 20 d)

Outcome: 1 Lesions cured

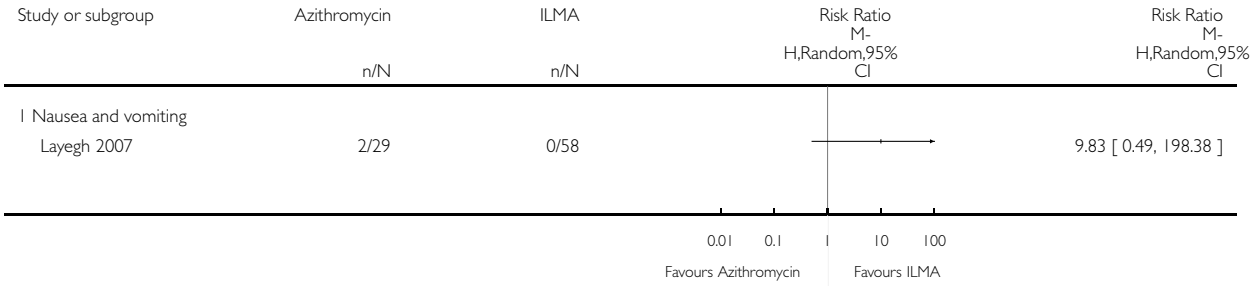


Analysis 35.2. Comparison 35 Azythromicin (500 mg/d for 5 d/month up to 4 months) versus IMMA (60 mg/kg/d for 20 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 35 Azythromicin (500 mg/d for 5 d/month up to 4 months) versus IMMA (60 mg/kg/d for 20 d)

Outcome: 2 Adverse effects

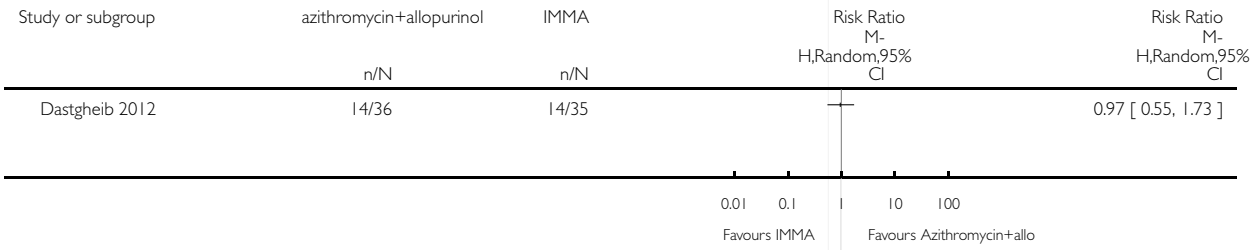


Analysis 36.1. Comparison 36 Azythromicin (10 mg/kg/d) + allopurinol (10 mg/kg/d) for 1 month versus IMMA (20 mg/kg/d for 20 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 36 Azythromicin (10 mg/kg/d) + allopurinol (10 mg/kg/d) for 1 month versus IMMA (20 mg/kg/d for 20 d)

Outcome: 1 Participants complete cure



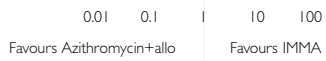
Analysis 36.2. Comparison 36 Azythromicin (10 mg/kg/d) + allopurinol (10 mg/kg/d) for 1 month versus IMMA (20 mg/kg/d for 20 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 36 Azythromicin (10 mg/kg/d) + allopurinol (10 mg/kg/d) for 1 month versus IMMA (20 mg/kg/d for 20 d)

Outcome: 2 Adverse effects

Study or subgroup	azithromycin+allopurinol n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Gastrointestinal complaints and headache				
Dastgheib 2012	1/36	0/35		2.92 [0.12, 69.32]
2 Gastrointestinal complications				
Dastgheib 2012	3/36	0/35		6.81 [0.36, 127.23]
3 Myalgia				
Dastgheib 2012	0/36	2/35		0.19 [0.01, 3.91]



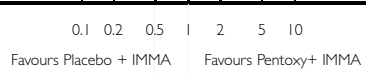
Analysis 37.1. Comparison 37 Oral pentoxifylline (400 mg 3 times daily) + IMMA (20 mg/kg/d) for 20 d versus placebo + IMMA (20 mg/kg/d) for 20 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 37 Oral pentoxifylline (400 mg 3 times daily) + IMMA (20 mg/kg/d) for 20 d versus placebo + IMMA (20 mg/kg/d) for 20 d

Outcome: 1 Participants complete cure

Study or subgroup	Oral pentoxyfill-ine+IMMA n/N	Placebo+IMMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Sadeghian 2006a	26/32	16/32		1.63 [1.11, 2.39]

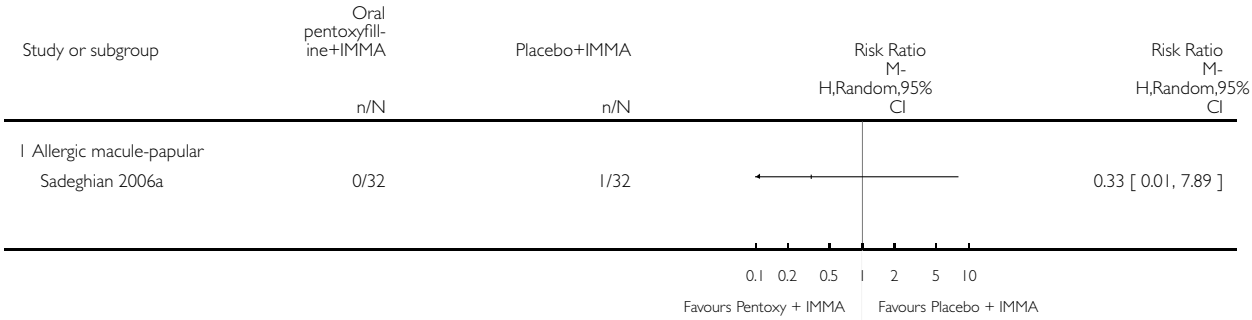


Analysis 37.2. Comparison 37 Oral pentoxifylline (400 mg 3 times daily) + IMMA (20 mg/kg/d) for 20 d versus placebo + IMMA (20 mg/kg/d) for 20 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 37 Oral pentoxifylline (400 mg 3 times daily) + IMMA (20 mg/kg/d) for 20 d versus placebo + IMMA (20 mg/kg/d) for 20 d

Outcome: 2 Adverse effects

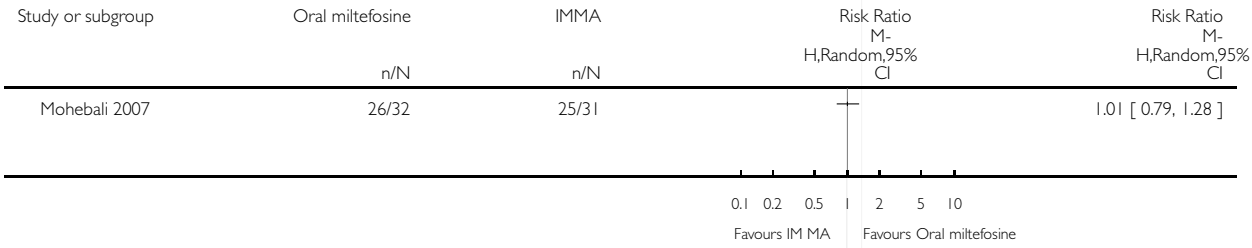


Analysis 38.1. Comparison 38 Oral miltefosine (2.5 mg/kg/d for 4 weeks) versus IMMA (60 mg/kg/d for 2 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 38 Oral miltefosine (2.5 mg/kg/d for 4 weeks) versus IMMA (60 mg/kg/d for 2 weeks)

Outcome: 1 Participants complete cure

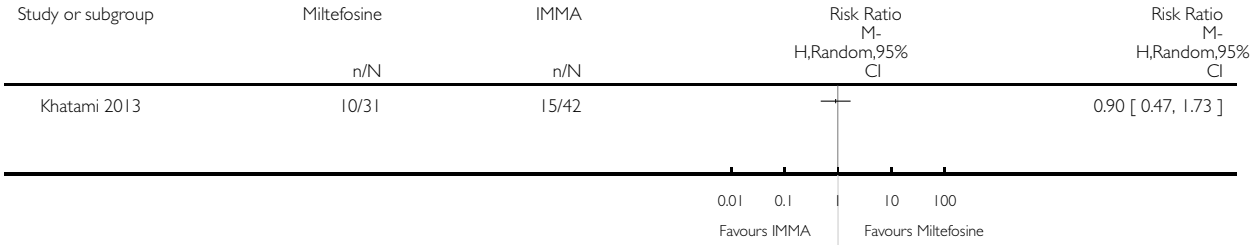


Analysis 39.1. Comparison 39 Oral miltefosine (2.5 mg/kg/d for 4 weeks) versus IMMA (60 mg/kg/d for 2 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 39 Oral miltefosine (2.5 mg/kg/d for 4 weeks) versus IMMA (60 mg/kg/d for 2 weeks)

Outcome: 1 Participants complete cure

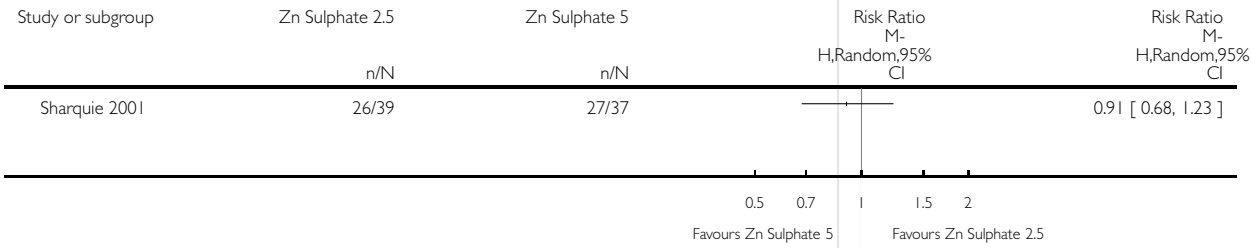


Analysis 40.1. Comparison 40 Oral zinc sulphate 2.5 mg/kg/d for 45 days versus oral zinc sulphate 5 mg/kg/d for 45 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 40 Oral zinc sulphate 2.5 mg/kg/d for 45 days versus oral zinc sulphate 5 mg/kg/d for 45 d

Outcome: 1 Participants complete cure

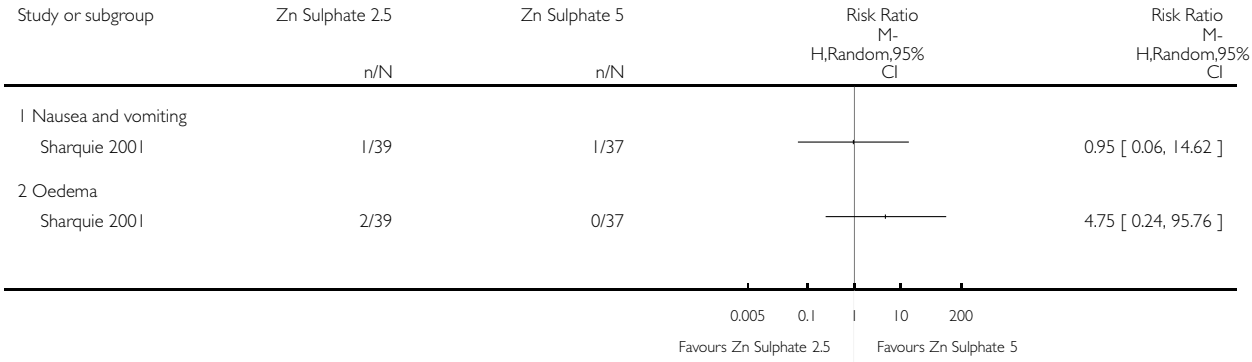


Analysis 40.2. Comparison 40 Oral zinc sulphate 2.5 mg/kg/d for 45 days versus oral zinc sulphate 5 mg/kg/d for 45 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 40 Oral zinc sulphate 2.5 mg/kg/d for 45 days versus oral zinc sulphate 5 mg/kg/d for 45 d

Outcome: 2 Adverse effects

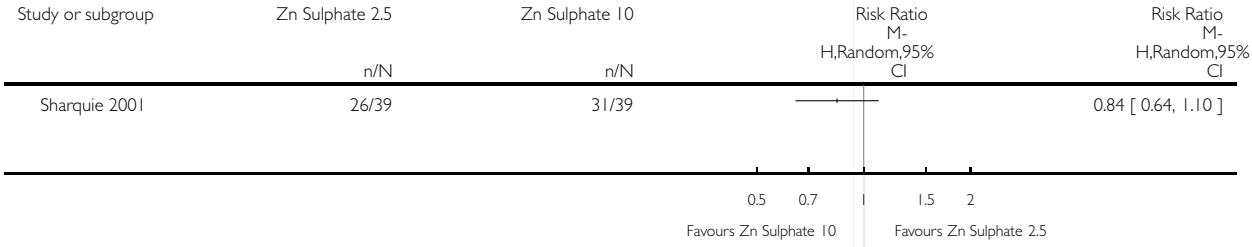


Analysis 41.1. Comparison 41 Oral zinc sulphate 2.5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 41 Oral zinc sulphate 2.5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d

Outcome: 1 Participants complete cure

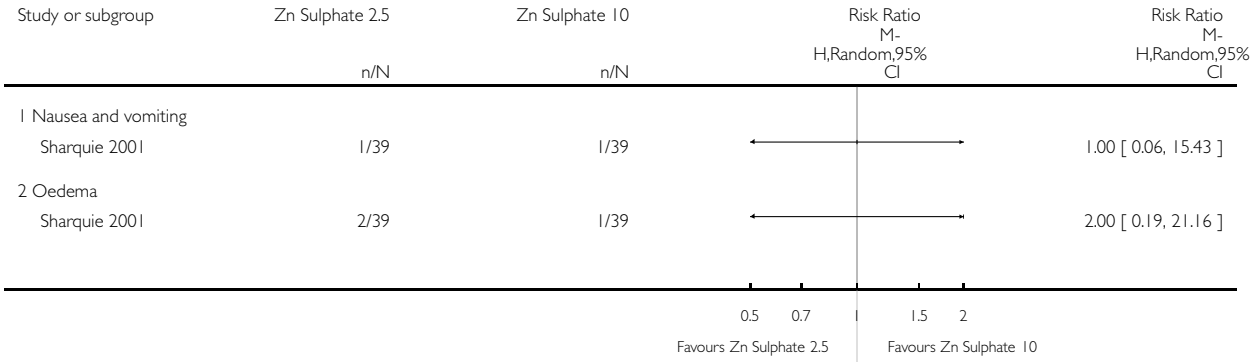


Analysis 41.2. Comparison 41 Oral zinc sulphate 2.5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 41 Oral zinc sulphate 2.5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d

Outcome: 2 Adverse effects

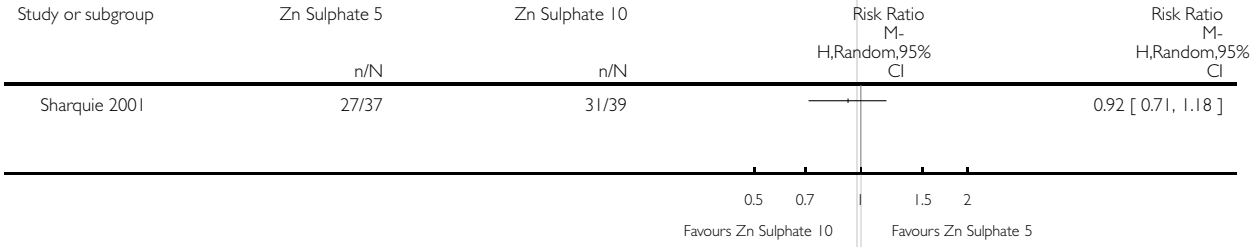


Analysis 42.1. Comparison 42 Oral zinc sulphate 5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 42 Oral zinc sulphate 5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d

Outcome: 1 Participants complete cure

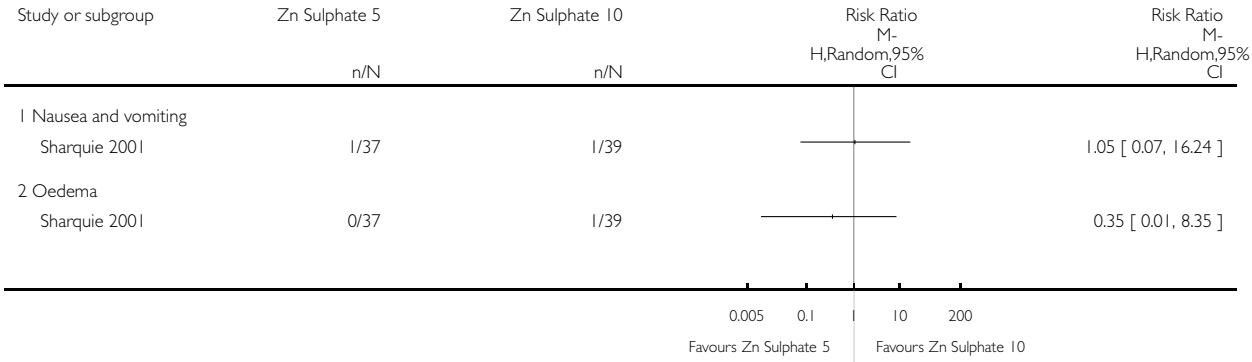


Analysis 42.2. Comparison 42 Oral zinc sulphate 5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 42 Oral zinc sulphate 5 mg/kg/d for 45 d versus oral zinc sulphate 10 mg/kg/d for 45 d

Outcome: 2 Adverse effects

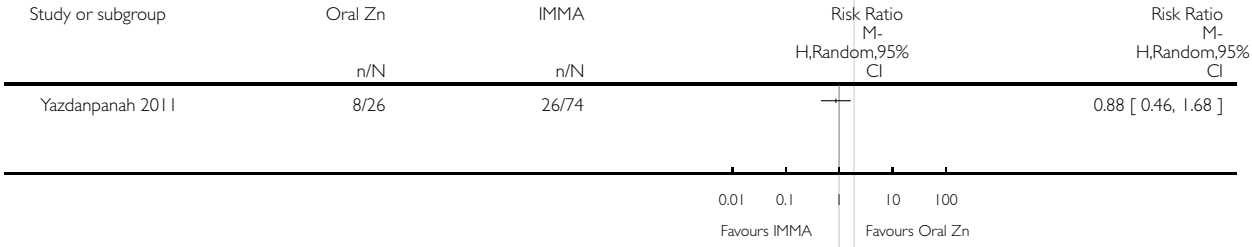


Analysis 43.1. Comparison 43 Oral zinc sulphate (10 mg/kg/d for 45 d) versus IMMA (20 mg/kg/d for 20 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 43 Oral zinc sulphate (10 mg/kg/d for 45 d) versus IMMA (20 mg/kg/d for 20 d)

Outcome: 1 Participants complete cure

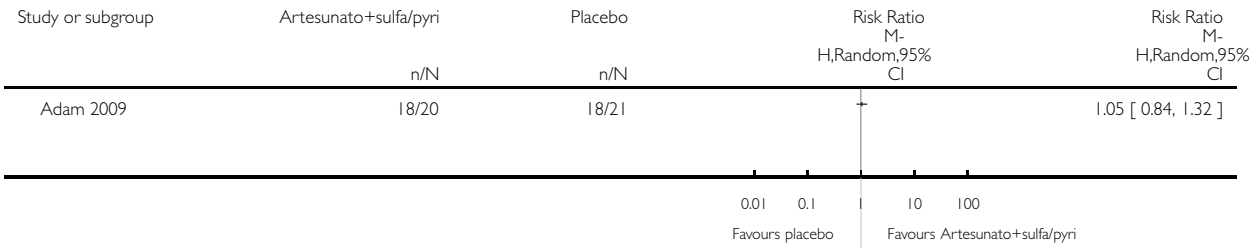


Analysis 44.1. Comparison 44 Artesunate 400 mg + sulphamethoxypyrazine/pyrimethamine 1000 mg/50 mg 4 times daily for 4 d versus placebo, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 44 Artesunate 400 mg + sulphamethoxypyrazine/pyrimethamine 1000 mg/50 mg 4 times daily for 4 d versus placebo

Outcome: 1 Participants complete cure

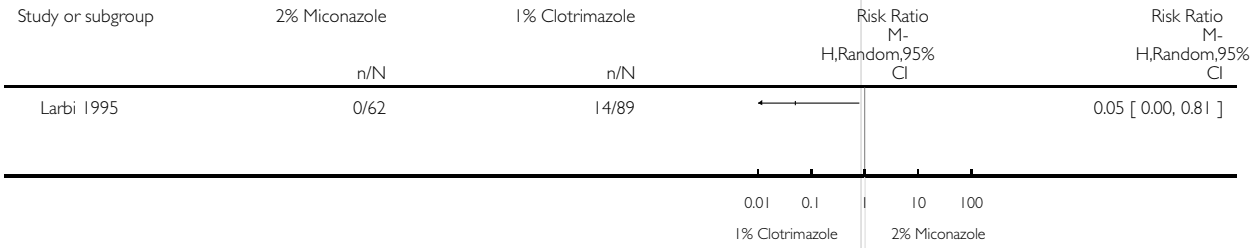


Analysis 45.1. Comparison 45 Topical 2% miconazole (twice a day) versus topical 1% clotrimazole (twice a day) for 30 d, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 45 Topical 2% miconazole (twice a day) versus topical 1% clotrimazole (twice a day) for 30 d

Outcome: 1 Lesions cured

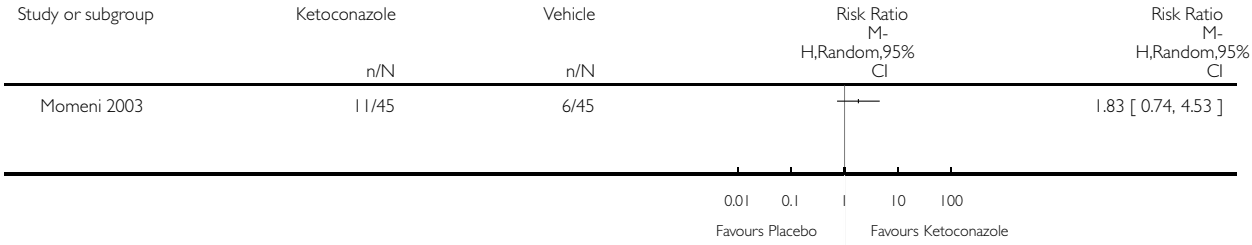


Analysis 46.1. Comparison 46 Topical ketoconazole (twice a day) versus vehicle (twice a day) for 30 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 46 Topical ketoconazole (twice a day) versus vehicle (twice a day) for 30 d

Outcome: 1 Participants complete cure

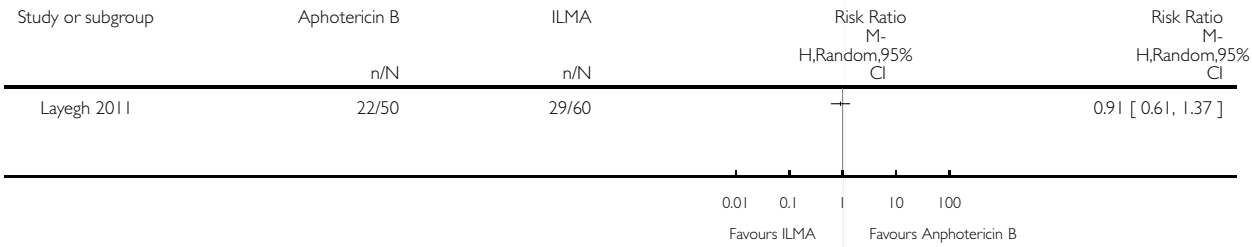


Analysis 47.1. Comparison 47 Topical amphotericin B (3 to 7 drops twice daily for 8 weeks) versus ILMA (max 2 mL) once a week for 8 weeks, Outcome 1 Participants complete cure (ITT).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 47 Topical amphotericin B (3 to 7 drops twice daily for 8 weeks) versus ILMA (max 2 mL) once a week for 8 weeks

Outcome: 1 Participants complete cure (ITT)

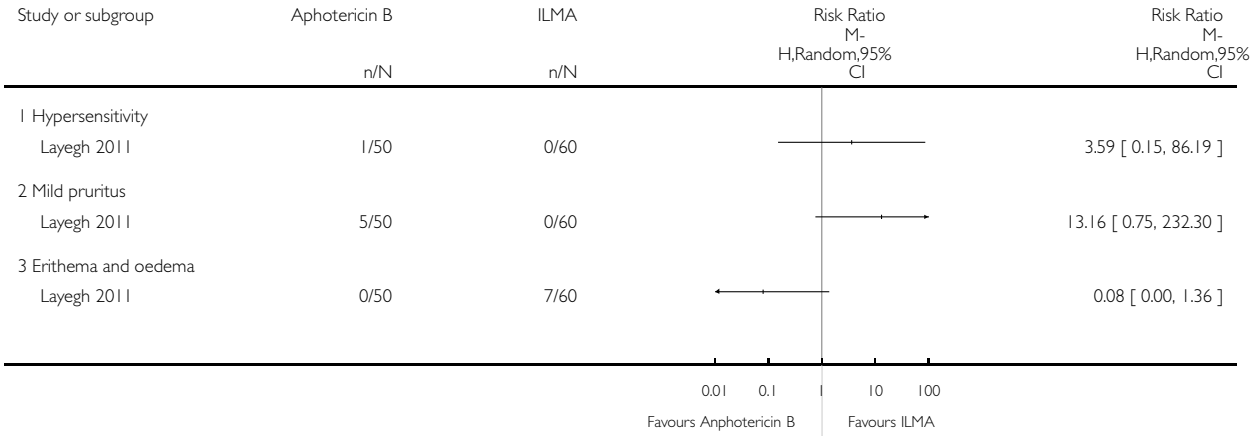


Analysis 47.2. Comparison 47 Topical amphotericin B (3 to 7 drops twice daily for 8 weeks) versus ILMA (max 2 mL) once a week for 8 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 47 Topical amphotericin B (3 to 7 drops twice daily for 8 weeks) versus ILMA (max 2 mL) once a week for 8 weeks

Outcome: 2 Adverse effects

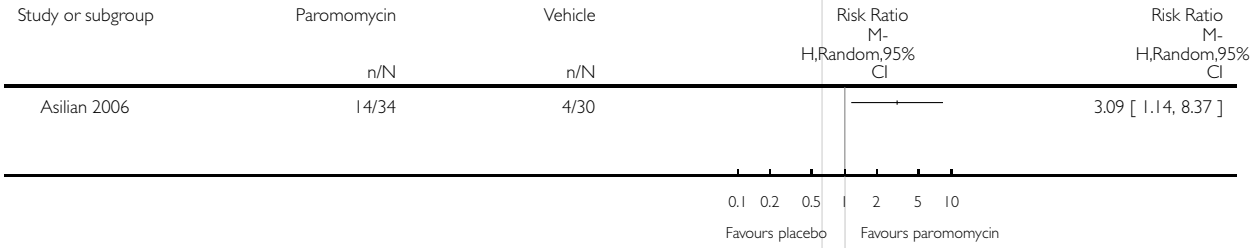


Analysis 48.1. Comparison 48 Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 48 Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d)

Outcome: 1 Lesions cured

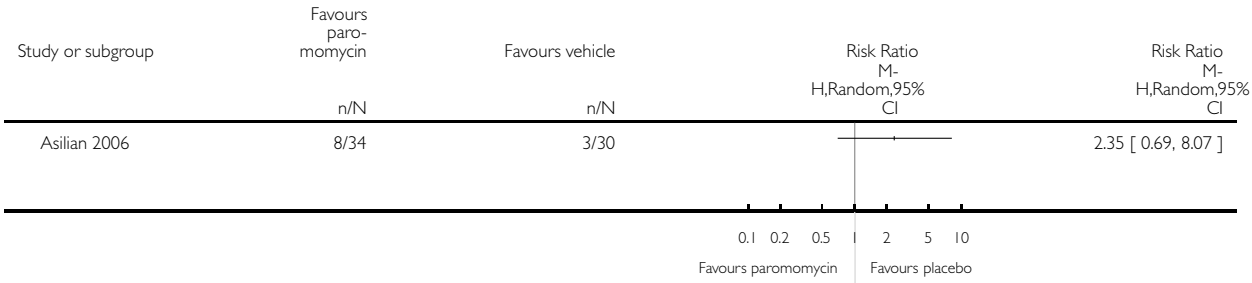


Analysis 48.2. Comparison 48 Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d), Outcome 2 Scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 48 Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d)

Outcome: 2 Scarring

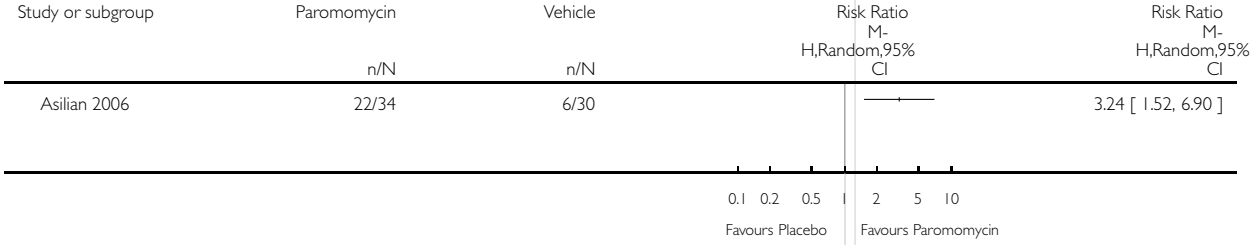


Analysis 48.3. Comparison 48 Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d), Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 48 Paromomycin 15% + 12% MBCL (twice daily for 28 d) versus vehicle (twice daily for 28 d)

Outcome: 3 Microbiological cure of skin lesions



Analysis 49.1. Comparison 49 Paromomycin (twice daily for 30 d) versus vehicle (twice daily for 30 d), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 49 Paromomycin (twice daily for 30 d) versus vehicle (twice daily for 30 d)

Outcome: 1 Lesions cured

Study or subgroup	Paromomycin n/N	Vehicle n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Iraji 2005	5/40	7/40		100.0 %	0.71 [0.25, 2.06]
Total (95% CI)	**40**	**40**		**100.0 %**	**0.71 [0.25, 2.06]**

Total events: 5 (Paromomycin), 7 (Vehicle)

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 50.1. Comparison 50 Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 50 Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d)

Outcome: 1 Participants complete cure

Study or subgroup	Paromomycin n/N	Vehicle n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Asilian 1995	80/126	79/125		68.1 %	1.00 [0.83, 1.21]
Ben Salah 1995	40/66	40/66		31.9 %	1.00 [0.76, 1.32]
Total (95% CI)	**192**	**191**		**100.0 %**	**1.00 [0.86, 1.17]**

Total events: 120 (Paromomycin), 119 (Vehicle)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 0.04 (P = 0.97)

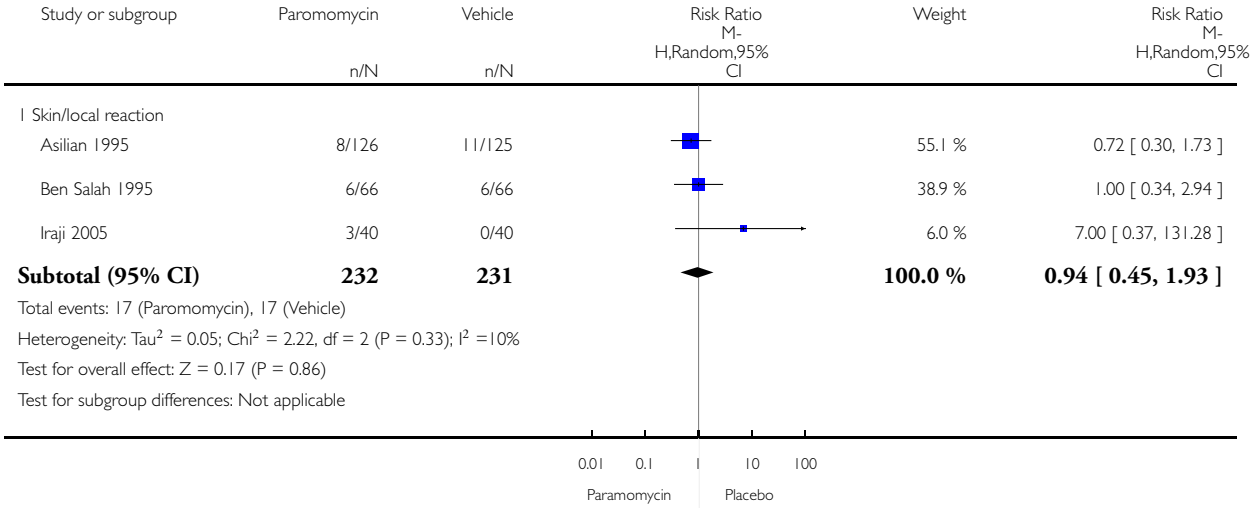
Test for subgroup differences: Not applicable

Analysis 50.2. Comparison 50 Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 50 Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d)

Outcome: 2 Adverse effects

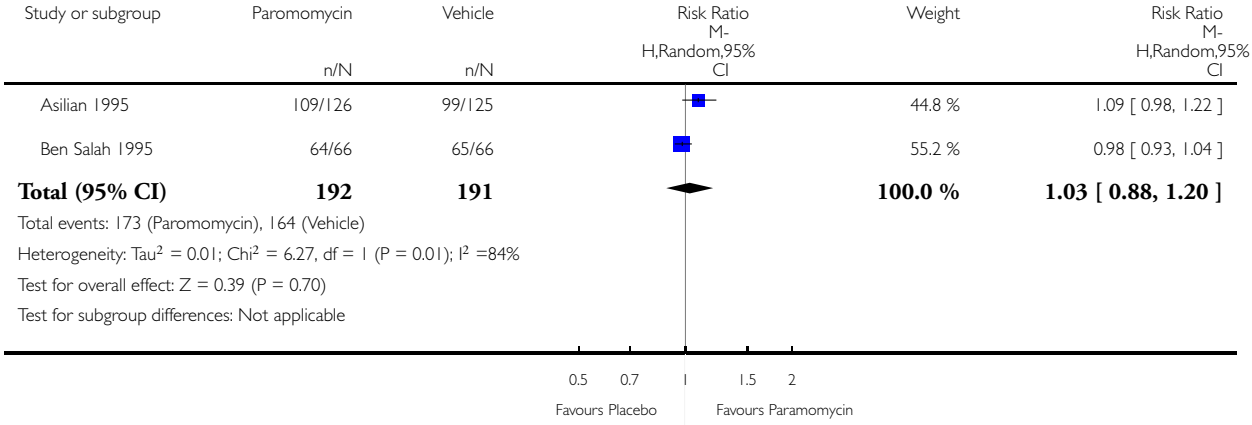


Analysis 50.3. Comparison 50 Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d), Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 50 Paromomycin 15% + 10% urea (twice daily for 14 d) versus vehicle (twice daily for 14 d)

Outcome: 3 Microbiological cure of skin lesions

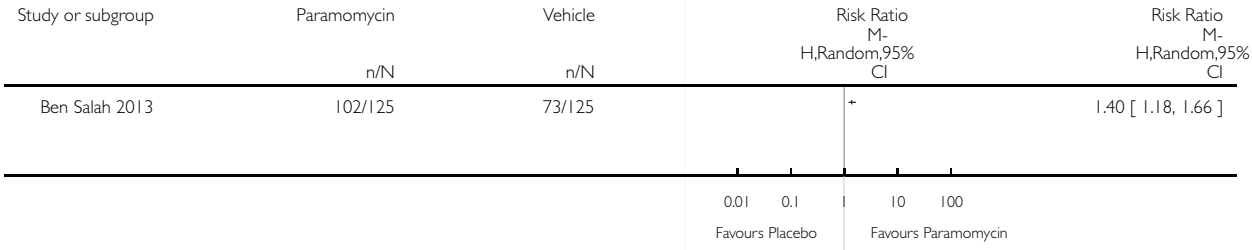


Analysis 51.1. Comparison 51 Paromomycin 15% (daily for 20 d) versus vehicle, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 51 Paromomycin 15% (daily for 20 d) versus vehicle

Outcome: 1 Participants complete cure



Analysis 52.1. Comparison 52 Paromomycin 15% + gentamicin 0.5% (daily for 20 d) versus vehicle, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 52 Paromomycin 15% + gentamicin 0.5% (daily for 20 d) versus vehicle

Outcome: 1 Participants complete cure

Study or subgroup	Paramomycin+Gentamicin n/N	Vehicle n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ben Salah 2013	101/125	73/125		1.38 [1.17, 1.64]

Analysis 53.1. Comparison 53 Paromomycin 15% + gentamicin 0.5% (daily for 20 d) versus paromomycin 15% alone (daily for 20 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 53 Paromomycin 15% + gentamicin 0.5% (daily for 20 d) versus paromomycin 15% alone (daily for 20 d)

Outcome: 1 Participants complete cure

Study or subgroup	Paramomycin+Gentamicin n/N	Paramomycin n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ben Salah 2013	101/125	102/125		0.99 [0.88, 1.12]

Analysis 54.1. Comparison 54 Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 54 Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months)

Outcome: 1 Participants complete cure

Study or subgroup	Paromomycin+urea n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Faghihi 2003	8/48	20/48		0.40 [0.20, 0.82]

Analysis 54.2. Comparison 54 Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months), Outcome 2 Recurrence.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 54 Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months)

Outcome: 2 Recurrence

Study or subgroup	Paromomycin+urea n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Faghihi 2003	3/48	3/48		1.00 [0.21, 4.71]

Analysis 54.3. Comparison 54 Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months), Outcome 3 Scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 54 Paromomycin 15% + 10% urea (twice daily for 45 d) versus ILMA (weekly for up to 3 months)

Outcome: 3 Scarring

Study or subgroup	Paromomycin+urea n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Faghihi 2003	2/48	4/48		0.50 [0.10, 2.60]

Analysis 55.1. Comparison 55 Paromomycin 15% + 10% urea (twice daily for 20 d) versus ILMA (weekly for up to 20 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 55 Paromomycin 15% + 10% urea (twice daily for 20 d) versus ILMA (weekly for up to 20 d)

Outcome: 1 Participants complete cure

Study or subgroup	Paromomycin+urea n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Shazad 2005	20/30	18/30		1.11 [0.75, 1.64]

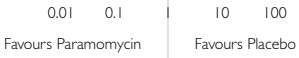
Analysis 55.2. Comparison 55 Paromomycin 15% + 10% urea (twice daily for 20 d) versus ILMA (weekly for up to 20 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 55 Paromomycin 15% + 10% urea (twice daily for 20 d) versus ILMA (weekly for up to 20 d)

Outcome: 2 Adverse effects

Study or subgroup	Paromomycin n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Cutaneous reaction				
Shazad 2005	1/30	3/30		0.33 [0.04, 3.03]



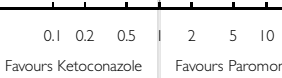
Analysis 56.1. Comparison 56 Paromomycin + MBCL (twice daily for 15 d) versus ketoconazole (weekly for up to 30 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 56 Paromomycin + MBCL (twice daily for 15 d) versus ketoconazole (weekly for up to 30 d)

Outcome: 1 Participants complete cure

Study or subgroup	Paromomycin+MBCL n/N	Ketoconazole 600 mg/kg n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Özgöztasi 1997	15/40	0/32		24.95 [1.55, 401.63]

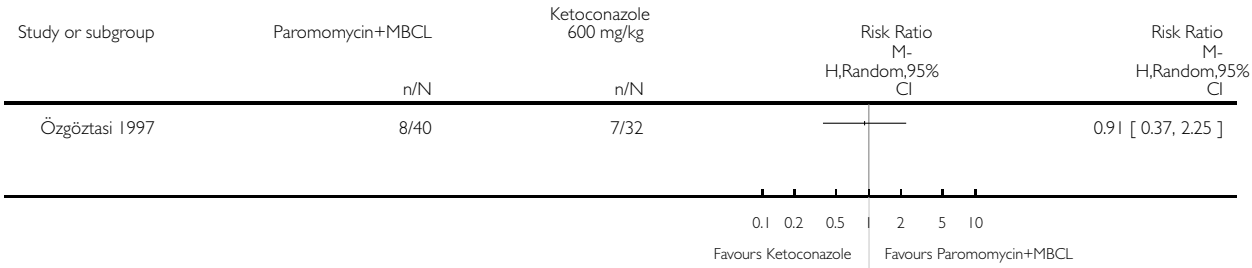


Analysis 56.2. Comparison 56 Paromomycin + MBCL (twice daily for 15 d) versus ketoconazole (weekly for up to 30 d), Outcome 2 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 56 Paromomycin + MBCL (twice daily for 15 d) versus ketoconazole (weekly for up to 30 d)

Outcome: 2 Microbiological cure of skin lesions

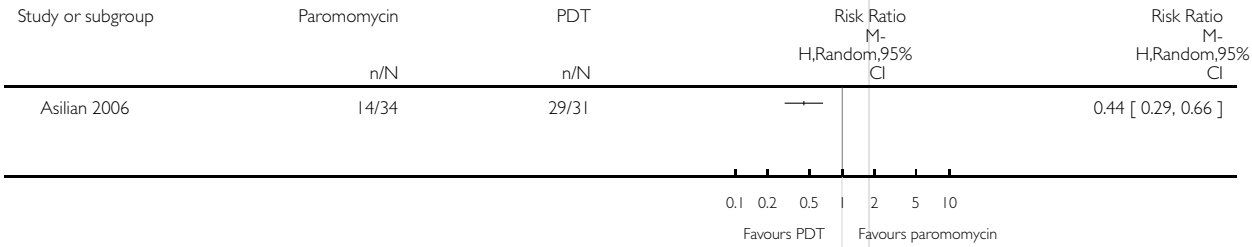


Analysis 57.1. Comparison 57 Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 57 Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks)

Outcome: 1 Lesions cured



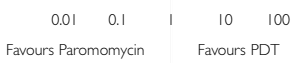
Analysis 57.2. Comparison 57 Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks), Outcome 2 Scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 57 Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks)

Outcome: 2 Scarring

Study or subgroup	Paromomycin n/N	PDT n/N	Risk Ratio M-H,Random,99% CI	Risk Ratio M-H,Random,99% CI
Asilian 2006	8/34	0/31		15.54 [0.39, 625.57]



Analysis 57.3. Comparison 57 Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks), Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 57 Paromomycin (15% + 12% MBCL twice daily for 28 days) versus PDT (weekly for 4 weeks)

Outcome: 3 Microbiological cure of skin lesions

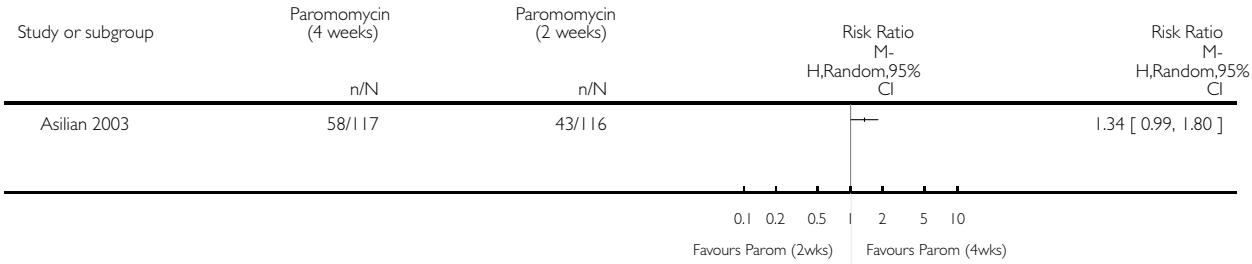
Study or subgroup	Paromomycin n/N	PDT n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Asilian 2006	22/34	31/31		0.65 [0.51, 0.84]

Analysis 58.1. Comparison 58 Paromomycin (4 weeks) versus paromomycin (2 weeks) + vehicle (2 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 58 Paromomycin (4 weeks) versus paromomycin (2 weeks) + vehicle (2 weeks)

Outcome: 1 Participants complete cure

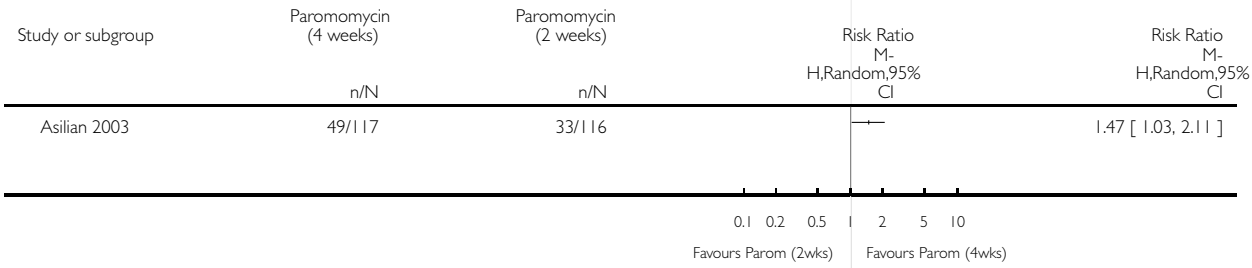


Analysis 58.2. Comparison 58 Paromomycin (4 weeks) versus paromomycin (2 weeks) + vehicle (2 weeks), Outcome 2 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 58 Paromomycin (4 weeks) versus paromomycin (2 weeks) + vehicle (2 weeks)

Outcome: 2 Microbiological cure of skin lesions



Analysis 59.1. Comparison 59 IL zinc 2% (twice a week for 2 weeks) versus ILSSG (100 mg/mL) for 2 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 59 IL zinc 2% (twice a week for 2 weeks) versus ILSSG (100 mg/mL) for 2 weeks)

Outcome: 1 Lesions cured

Study or subgroup	Zinc Sulfate n/N	ILSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Sharquie 1997	36/38	31/35		1.07 [0.93, 1.23]

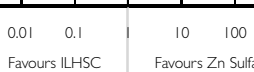
Analysis 60.1. Comparison 60 IL zinc 2% (twice a week for 2 weeks) versus IL 7% HSCS for 2 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 60 IL zinc 2% (twice a week for 2 weeks) versus IL 7% HSCS for 2 weeks

Outcome: 1 Lesions cured

Study or subgroup	Zinc Sulfate n/N	ILHSC n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Sharquie 1997	36/38	34/40		1.11 [0.96, 1.30]

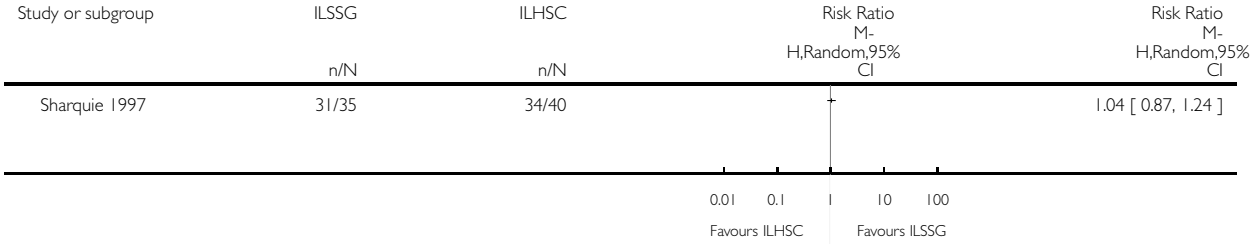


Analysis 61.1. Comparison 61 ILSSG (100 mg/mL) for 2 weeks versus IL 7% HSCS for 2 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 61 ILSSG (100 mg/mL) for 2 weeks versus IL 7% HSCS for 2 weeks

Outcome: 1 Lesions cured

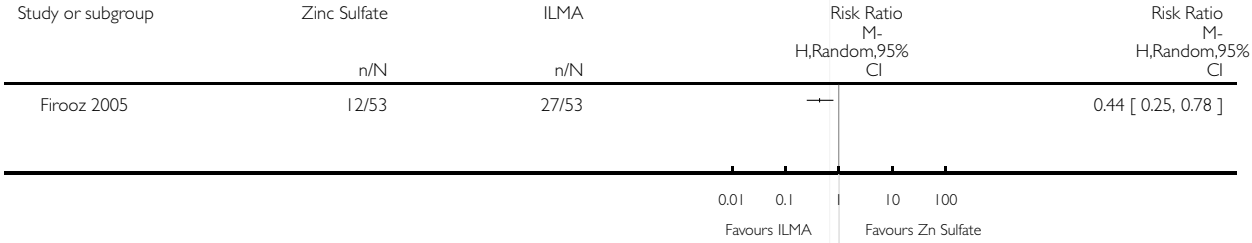


Analysis 62.1. Comparison 62 IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 62 IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks)

Outcome: 1 Lesions cured



Analysis 62.2. Comparison 62 IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks), Outcome 2 Participants complete cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 62 IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks)

Outcome: 2 Participants complete cured

Study or subgroup	Zinc Sulfate n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Iraji 2004	26/49	21/55		1.39 [0.91, 2.13]

Analysis 62.3. Comparison 62 IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks), Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 62 IL zinc 2% (weekly for up to 6 weeks) versus ILMA (max 2 mL weekly for up to 6 weeks)

Outcome: 3 Adverse effects

Study or subgroup	Zinc Sulfate n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Pain				
Firooz 2005	13/36	5/36		2.60 [1.03, 6.54]
2 Burning				
Firooz 2005	3/36	0/36		7.00 [0.37, 130.82]
3 Itching				
Firooz 2005	3/36	0/36		7.00 [0.37, 130.82]
4 Inflammation				
Firooz 2005	7/36	8/36		0.88 [0.35, 2.16]
5 Pruritus and erythema				
Iraji 2004	3/49	0/55		7.84 [0.42, 148.08]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Zinc Sulfate	ILMA	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
6 Severe pain				
Iraji 2004	2/49	0/55		5.60 [0.28, 113.87]

Analysis 63.1. Comparison 63 IL zinc 2% (twice a week for 2 weeks) versus ILMA (60 mg/kg/d for 2 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 63 IL zinc 2% (twice a week for 2 weeks) versus ILMA (60 mg/kg/d for 2 weeks)

Outcome: 1 Lesions cured

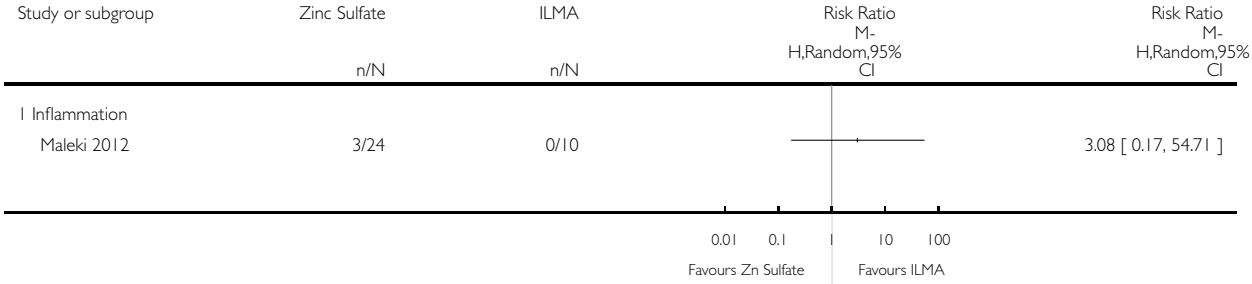
Study or subgroup	Zinc Sulfate	ILMA	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Maleki 2012	8/24	8/10		0.42 [0.22, 0.79]

Analysis 63.2. Comparison 63 IL zinc 2% (twice a week for 2 weeks) versus ILMA (60 mg/kg/d for 2 weeks), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 63 IL zinc 2% (twice a week for 2 weeks) versus ILMA (60 mg/kg/d for 2 weeks)

Outcome: 2 Adverse effects

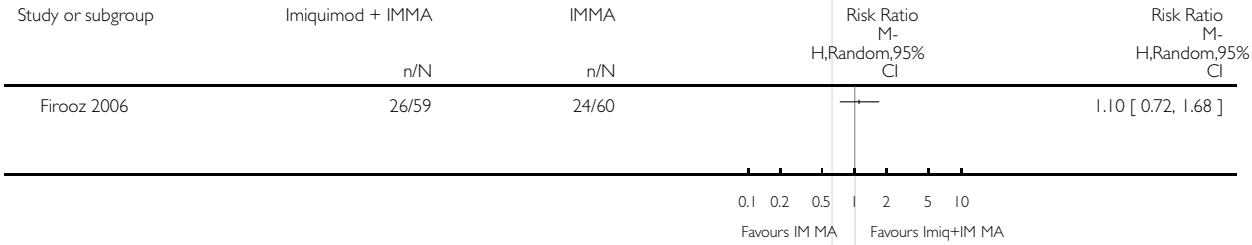


Analysis 64.1. Comparison 64 Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 64 Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA

Outcome: 1 Participants complete cure

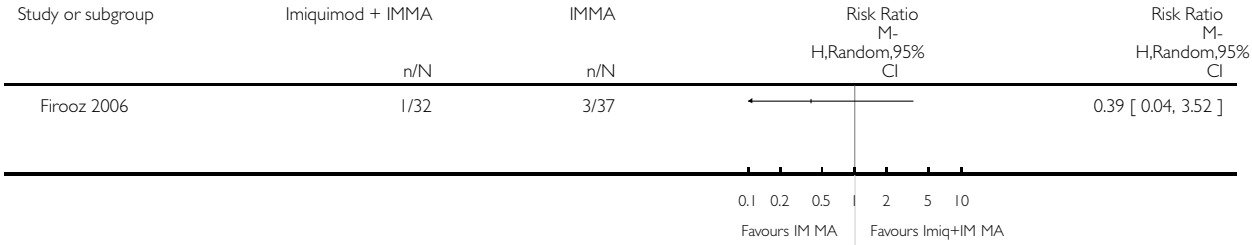


Analysis 64.2. Comparison 64 Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA, Outcome 2 Participants with treated lesions that recur.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 64 Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA

Outcome: 2 Participants with treated lesions that recur

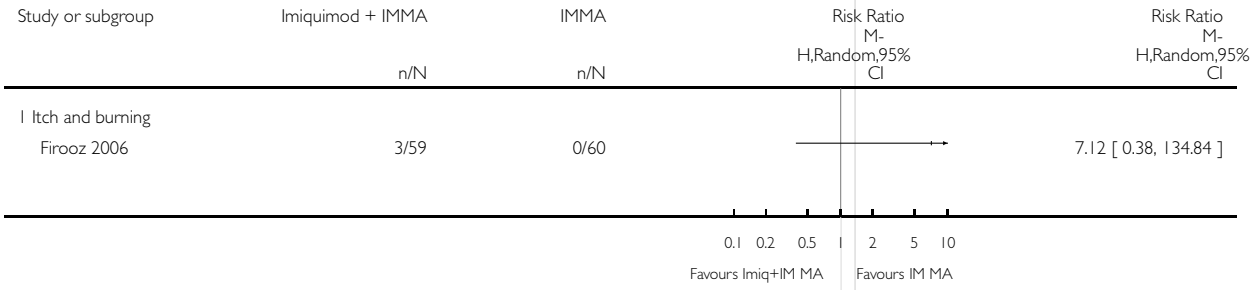


Analysis 64.3. Comparison 64 Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA, Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 64 Imiquimod (5% 3 times/week for 28 d) + IMMA (20 mg/kg/d for 14 d) versus vehicle + IMMA

Outcome: 3 Adverse effects



Analysis 65.1. Comparison 65 IL 7% HSCS (0.2 mL to 7 mL per lesion) versus ILSSG (max 2 mL) max 5 injections, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 65 IL 7% HSCS (0.2 mL to 7 mL per lesion) versus ILSSG (max 2 mL) max 5 injections

Outcome: 1 Lesions cured

Study or subgroup	Hypertonic Saline n/N	ILSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ranawaka 2010	56/64	83/83		0.87 [0.79, 0.96]

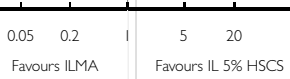
Analysis 66.1. Comparison 66 IL 5% HSCS (0.5 mL to 1 mL per lesion) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 6 to 10 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 66 IL 5% HSCS (0.5 mL to 1 mL per lesion) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 6 to 10 weeks

Outcome: 1 Lesions cured

Study or subgroup	IL 5% HSCS n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Sadeghian 2006b	9/36	12/36		0.75 [0.36, 1.56]

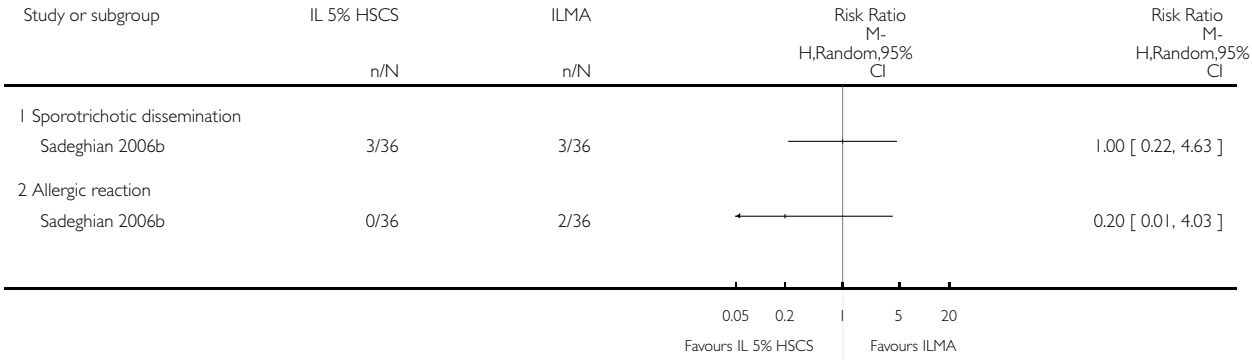


Analysis 66.2. Comparison 66 IL 5% HSCS (0.5 mL to 1 mL per lesion) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 6 to 10 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 66 IL 5% HSCS (0.5 mL to 1 mL per lesion) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 6 to 10 weeks

Outcome: 2 Adverse effects

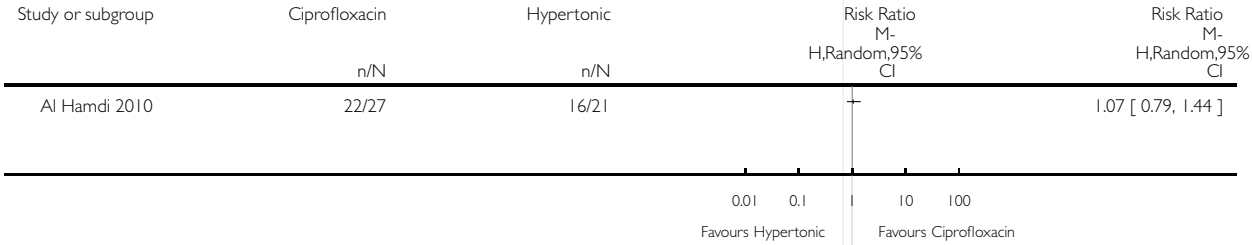


Analysis 67.1. Comparison 67 IL 7% HSCS (0.1 mL to 0.5 mL per lesion) versus IL 2% ciprofloxacin solution (0.1 mL to 0.5 mL per lesion), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 67 IL 7% HSCS (0.1 mL to 0.5 mL per lesion) versus IL 2% ciprofloxacin solution (0.1 mL to 0.5 mL per lesion)

Outcome: 1 Lesions cured

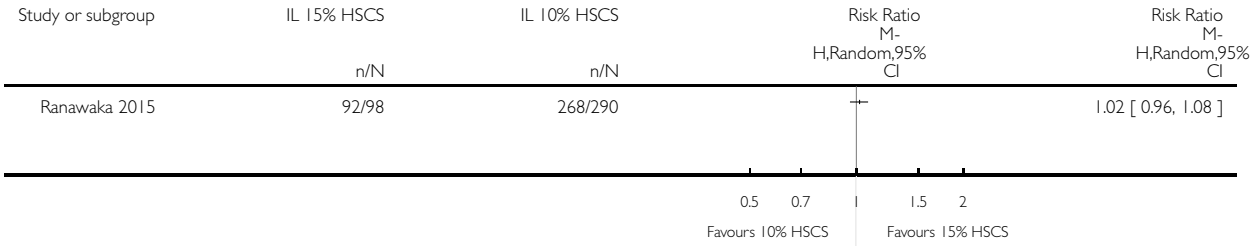


Analysis 68.1. Comparison 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 1 Lesions cured

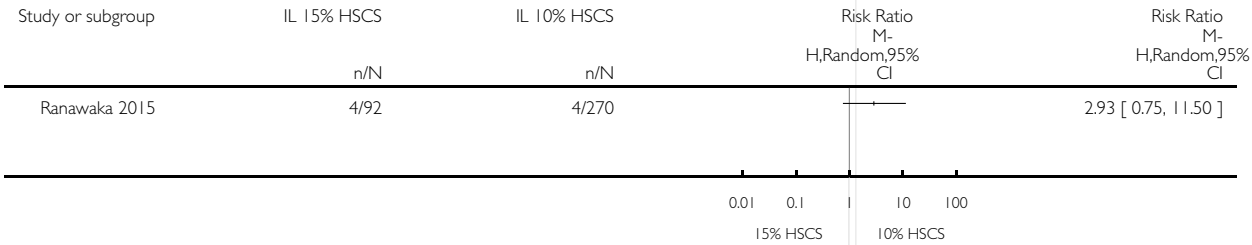


Analysis 68.2. Comparison 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 2 Recurrence.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 2 Recurrence



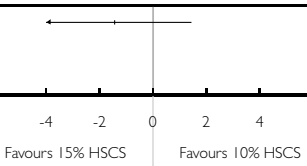
Analysis 68.3. Comparison 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 3 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 3 Speed of healing (weeks)

Study or subgroup	IL 15% HSCS N	Mean(SD)	IL 10% HSCS N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Ranawaka 2015	290	11.2 (8.65)	98	12.65 (13.71)		-1.45 [-4.34, 1.44]



Analysis 68.4. Comparison 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 4 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 68 IL 15% HSCS (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 4 Adverse effects

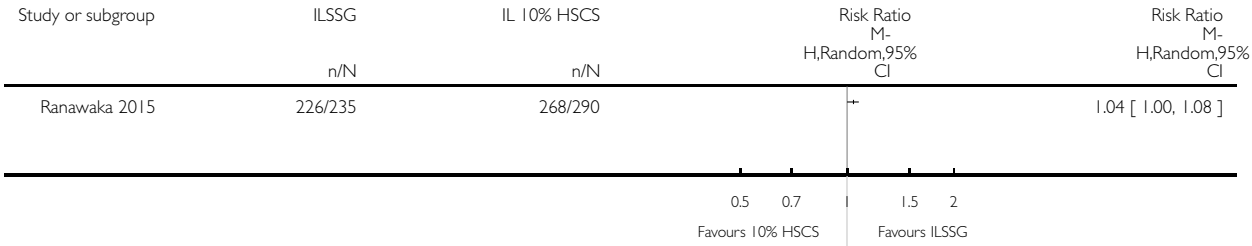
Study or subgroup	IL 15% HSCS n/N	IL 10% HSCS n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Ulceration and necrosis				
Ranawaka 2015	30/98	9/290		9.86 [4.86, 20.04]

Analysis 69.1. Comparison 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 1 Lesions cured

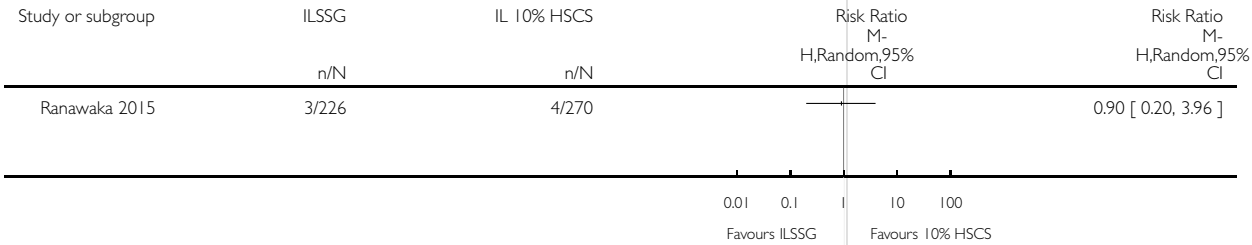


Analysis 69.2. Comparison 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 2 Recurrence.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 2 Recurrence



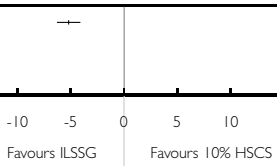
Analysis 69.3. Comparison 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 3 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 3 Speed of healing (weeks)

Study or subgroup	ILSSG N	Mean(SD)	IL 10% HSCS N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Ranawaka 2015	235	6 (3.89)	290	11.2 (8.65)		-5.20 [-6.31, -4.09]



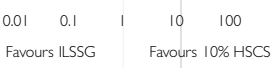
Analysis 69.4. Comparison 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion), Outcome 4 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 69 ILSSG (0.2 mL to 4 mL per lesion) max 5 injections versus IL 10% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 4 Adverse effects

Study or subgroup	ILSSG n/N	IL 10% HSCS n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Ulceration and necrosis				
Ranawaka 2015	0/235	9/290		0.06 [0.00, 1.11]

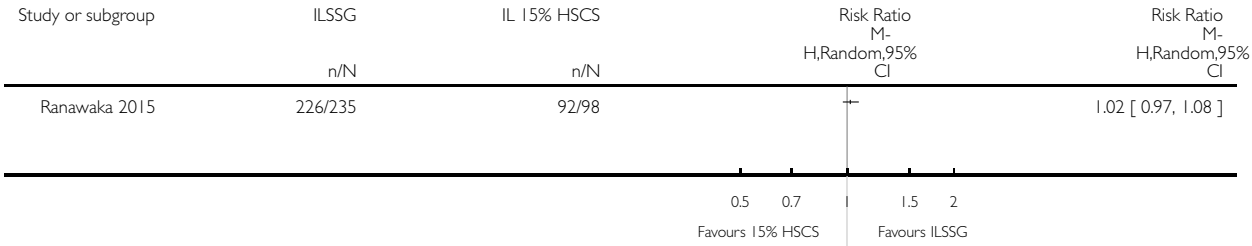


Analysis 70.1. Comparison 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 1 Lesions cured

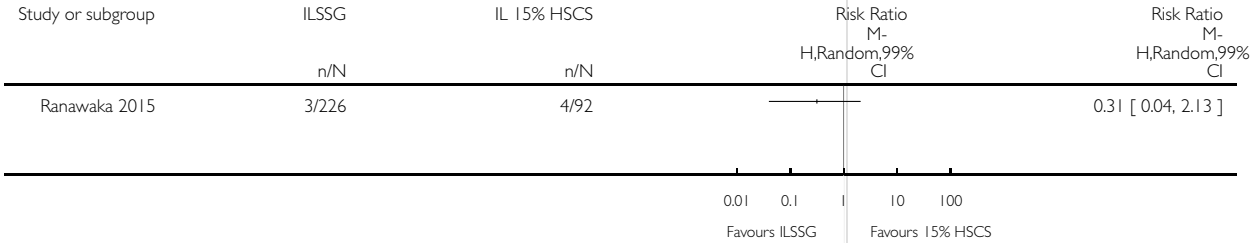


Analysis 70.2. Comparison 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion), Outcome 2 Recurrence.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 2 Recurrence



Analysis 70.3. Comparison 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion), Outcome 3 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 3 Speed of healing (weeks)

Study or subgroup	ILSSG N	Mean(SD)	IL 15% HSCS N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Ranawaka 2015	235	6 (3.89)	98	12.65 (13.71)		-6.65 [-9.41, -3.89]

Analysis 70.4. Comparison 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion), Outcome 4 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 70 ILSSG (0.2 mL to 4 mL per lesion) maximum 5 injections versus IL 15% HSCS (0.2 mL to 4 mL per lesion)

Outcome: 4 Adverse effects

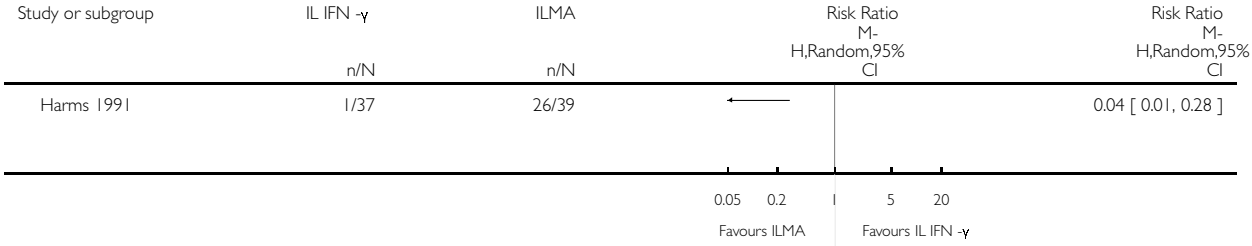
Study or subgroup	IL 15% HSCS n/N	ILSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Ulceration and necrosis				
Ranawaka 2015	30/98	0/235		145.41 [8.98, 2354.65]

Analysis 71.1. Comparison 71 IL IFN-γ (weekly for 5 weeks) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 5 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 71 IL IFN-γ (weekly for 5 weeks) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 5 weeks

Outcome: 1 Lesions cured

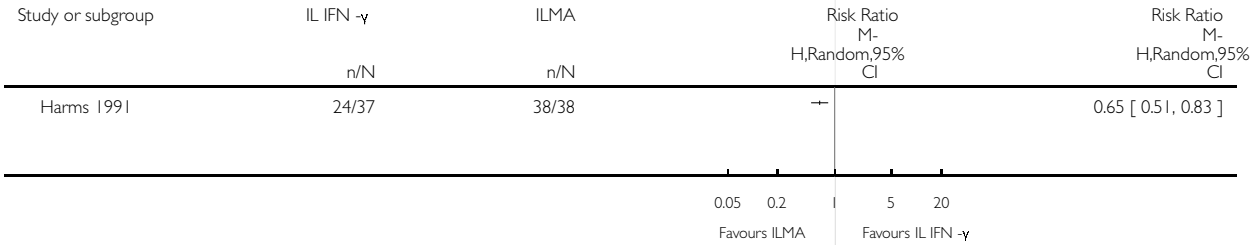


Analysis 71.2. Comparison 71 IL IFN-γ (weekly for 5 weeks) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 5 weeks, Outcome 2 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 71 IL IFN-γ (weekly for 5 weeks) versus ILMA (0.5 mL to 1 mL per lesion) weekly for 5 weeks

Outcome: 2 Microbiological cure of skin lesions



Analysis 72.1. Comparison 72 WR279,396 (twice a day for 20 d) versus vehicle (twice a day for 20 d), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 72 WR279,396 (twice a day for 20 d) versus vehicle (twice a day for 20 d)

Outcome: 1 Participants complete cure

Study or subgroup	WR279,396 n/N	Vehicle n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Ben Salah 2009	43/50	27/42		1.34 [1.04, 1.72]

Analysis 72.2. Comparison 72 WR279,396 (twice a day for 20 d) versus vehicle (twice a day for 20 d), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 72 WR279,396 (twice a day for 20 d) versus vehicle (twice a day for 20 d)

Outcome: 2 Adverse effects

Study or subgroup	WR279,396 n/N	Vehicle n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Erythema				
Ben Salah 2009	15/50	10/42		1.26 [0.63, 2.50]
2 Mild pain				
Ben Salah 2009	7/50	6/42		0.98 [0.36, 2.69]
3 Hearing acuity problems				
Ben Salah 2009	14/50	9/42		1.31 [0.63, 2.71]

Analysis 73.1. Comparison 73 IL metronidazole (2.5 mg to 10 mg each lesion) versus ILMA (150 mg to 600 mg each lesion) for up to 8 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 73 IL metronidazole (2.5 mg to 10 mg each lesion) versus ILMA (150 mg to 600 mg each lesion) for up to 8 weeks

Outcome: 1 Participants complete cure

Study or subgroup	IL metronidazole n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Mapar 2010	3/18	13/18		0.23 [0.08, 0.67]

Analysis 73.2. Comparison 73 IL metronidazole (2.5 mg to 10 mg each lesion) versus ILMA (150 mg to 600 mg each lesion) for up to 8 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 73 IL metronidazole (2.5 mg to 10 mg each lesion) versus ILMA (150 mg to 600 mg each lesion) for up to 8 weeks

Outcome: 2 Adverse effects

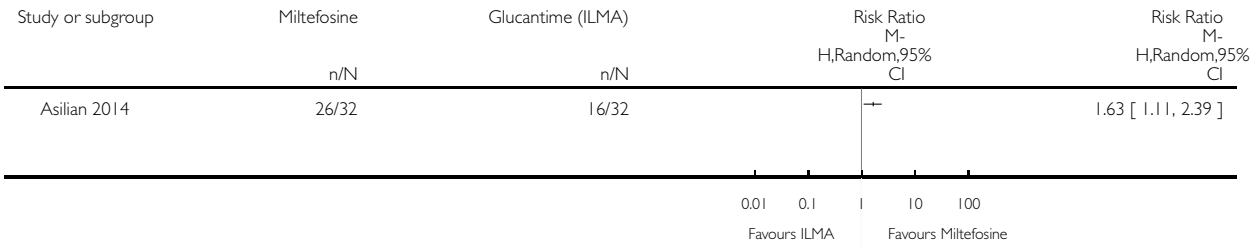
Study or subgroup	IL metronidazole n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Local inflammatory reactions				
Mapar 2010	0/18	2/18		0.20 [0.01, 3.89]

Analysis 74.1. Comparison 74 Topical miltefosine 6% (once daily) versus ILMA (twice a week) for up to 28 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 74 Topical miltefosine 6% (once daily) versus ILMA (twice a week) for up to 28 d

Outcome: 1 Participants complete cure

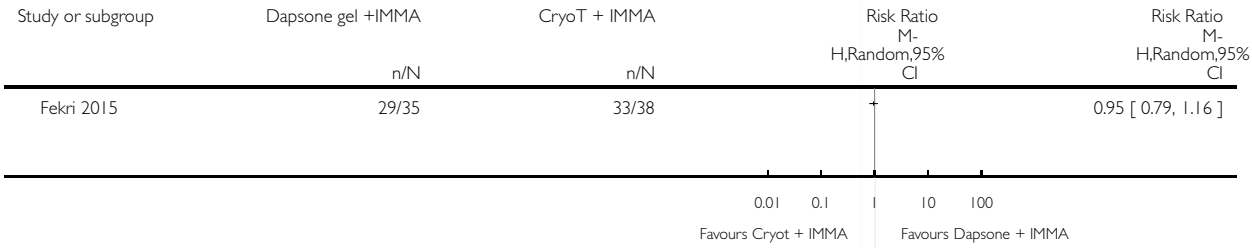


Analysis 75.1. Comparison 75 Dapsone gel 5% (twice a day) + ILMA (weekly) versus cryotherapy (every 2 weeks) + IMMA (weekly) for up to 16 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 75 Dapsone gel 5% (twice a day) + ILMA (weekly) versus cryotherapy (every 2 weeks) + IMMA (weekly) for up to 16 weeks

Outcome: 1 Lesions cured

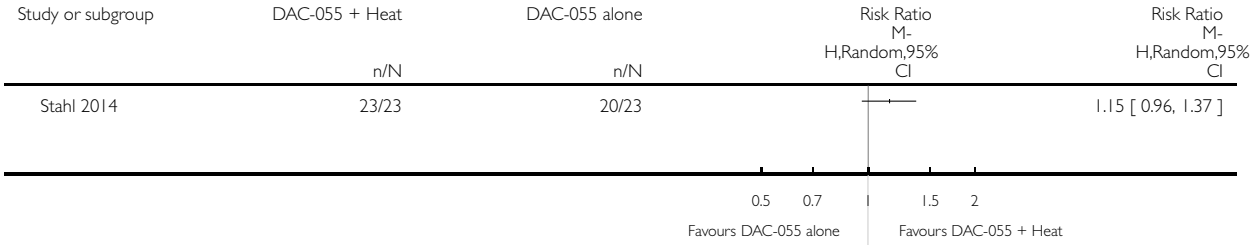


Analysis 76.1. Comparison 76 DAC-055 + MWT (for 15 min) versus DAC-055 alone for up to 75 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 76 DAC-055 + MWT (for 15 min) versus DAC-055 alone for up to 75 d

Outcome: 1 Participants complete cure

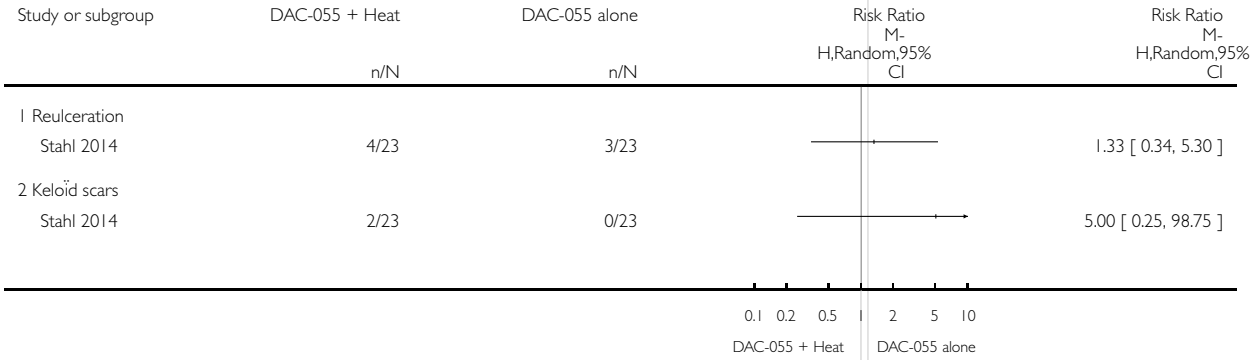


Analysis 76.2. Comparison 76 DAC-055 + MWT (for 15 min) versus DAC-055 alone for up to 75 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 76 DAC-055 + MWT (for 15 min) versus DAC-055 alone for up to 75 d

Outcome: 2 Adverse effects



Analysis 77.1. Comparison 77 DAC-055 + heat (for 15 min) versus ILSSG (0.6 mL) for up to 75 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 77 DAC-055 + heat (for 15 min) versus ILSSG (0.6 mL) for up to 75 d

Outcome: 1 Participants complete cure

Study or subgroup	DAC-055 + Heat n/N	ILSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Stahl 2014	23/23	15/23		1.52 [1.12, 2.05]

Analysis 77.2. Comparison 77 DAC-055 + heat (for 15 min) versus ILSSG (0.6 mL) for up to 75 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 77 DAC-055 + heat (for 15 min) versus ILSSG (0.6 mL) for up to 75 d

Outcome: 2 Adverse effects

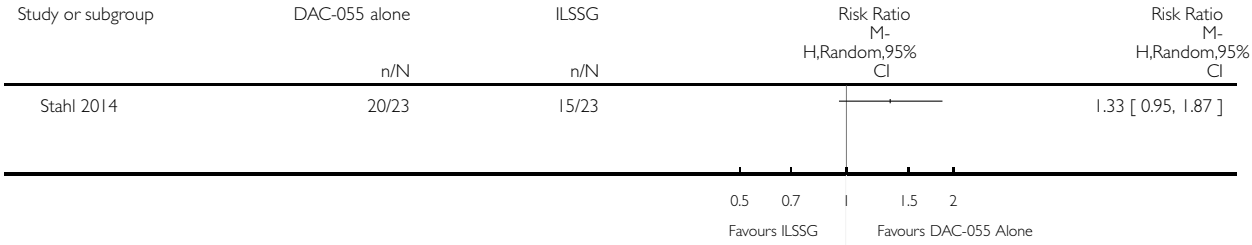
Study or subgroup	DAC-055 + Heat n/N	ILSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Reulceration				
Stahl 2014	4/23	7/23		0.57 [0.19, 1.69]
2 Keloïd scars				
Stahl 2014	2/23	0/23		5.00 [0.25, 98.75]

Analysis 78.1. Comparison 78 DAC-055 alone (for 15 min) versus ILSSG (0.6 mL) for up to 75 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 78 DAC-055 alone (for 15 min) versus ILSSG (0.6 mL) for up to 75 d

Outcome: 1 Participants complete cure

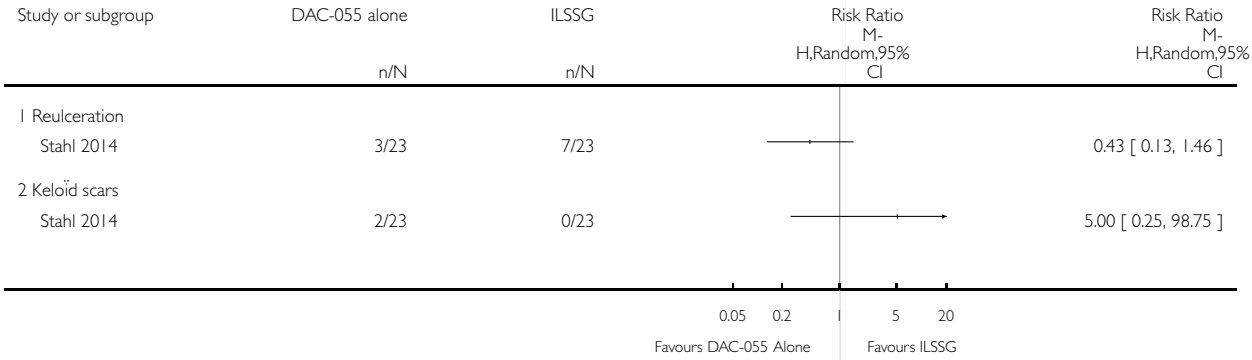


Analysis 78.2. Comparison 78 DAC-055 alone (for 15 min) versus ILSSG (0.6 mL) for up to 75 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 78 DAC-055 alone (for 15 min) versus ILSSG (0.6 mL) for up to 75 d

Outcome: 2 Adverse effects



Analysis 79.1. Comparison 79 Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 79 Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks

Outcome: 1 Lesions cured

Study or subgroup	Thio Ben+ Cryo n/N	Cryo+ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Daie Parizi 2015	20/22	23/25		0.99 [0.83, 1.18]

Analysis 79.2. Comparison 79 Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks, Outcome 2 Recurrence.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 79 Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks

Outcome: 2 Recurrence

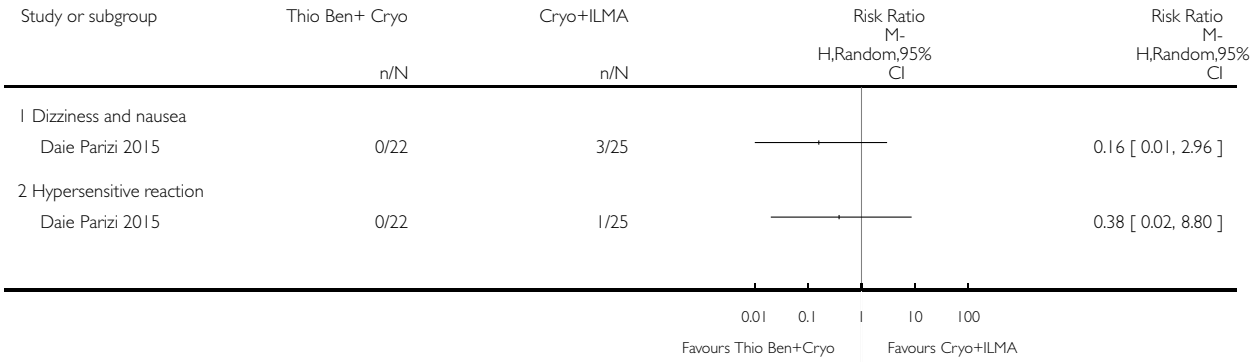
Study or subgroup	Thio Ben+ Cryo n/N	Cryo+ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Daie Parizi 2015	4/22	3/25		1.52 [0.38, 6.04]

Analysis 79.3. Comparison 79 Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks, Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 79 Thio-Ben (1 mL to 2 mL daily) + cryotherapy (fortnightly) versus ILMA (0.5 mL to 2 mL per lesions) weekly + cryotherapy (fortnightly) for up to 12 weeks

Outcome: 3 Adverse effects

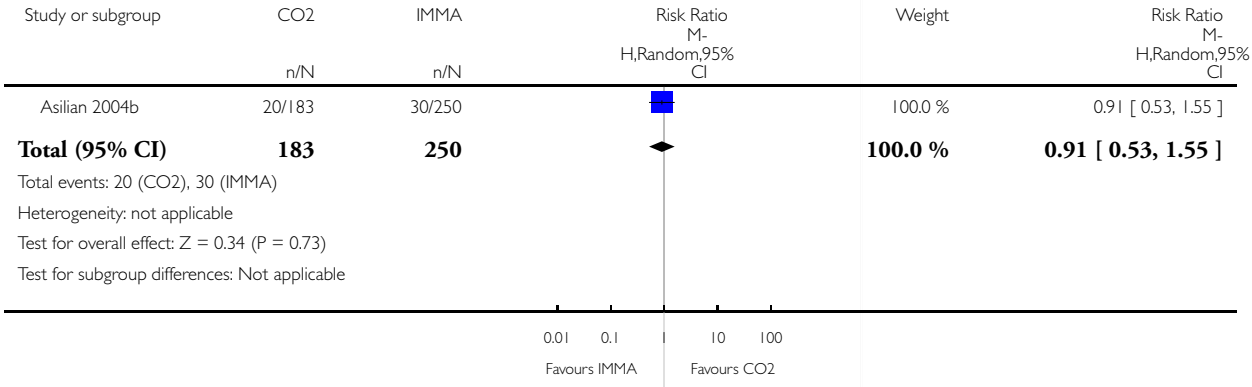


Analysis 80.1. Comparison 80 CO_2 laser (30 W continuous) versus IMMA (50 mg/kg/d) for up to 15 d, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 80 CO_2 laser (30 W continuous) versus IMMA (50 mg/kg/d) for up to 15 d

Outcome: 1 Lesions cured



Analysis 80.2. Comparison 80 CO_2 laser (30 W continuous) versus IMMA (50 mg/kg/d) for up to 15 d, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 80 CO_2 laser (30 W continuous) versus IMMA (50 mg/kg/d) for up to 15 d

Outcome: 2 Adverse effects

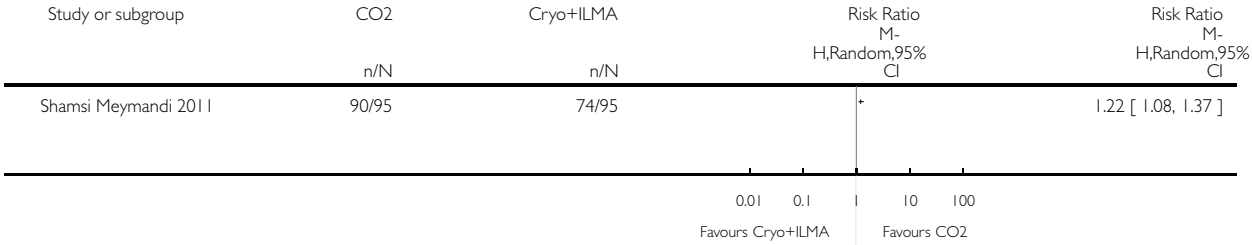
Study or subgroup	CO2 n/N	IMMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Hyperpigmentation and redness				
Asilian 2004b	4/183	0/250		12.28 [0.67, 226.62]
2 Hypertrophic scarring				
Asilian 2004b	5/183	0/250		15.01 [0.83, 269.67]
3 Systemic symptoms				
Asilian 2004b	0/183	22/250		0.03 [0.00, 0.50]

Analysis 81.1. Comparison 81 CO_2 laser (30 W continuous) versus cryotherapy (fortnightly) + ILMA (weekly) for up to 12 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 81 CO_2 laser (30 W continuous) versus cryotherapy (fortnightly) + ILMA (weekly) for up to 12 weeks

Outcome: 1 Lesions cured

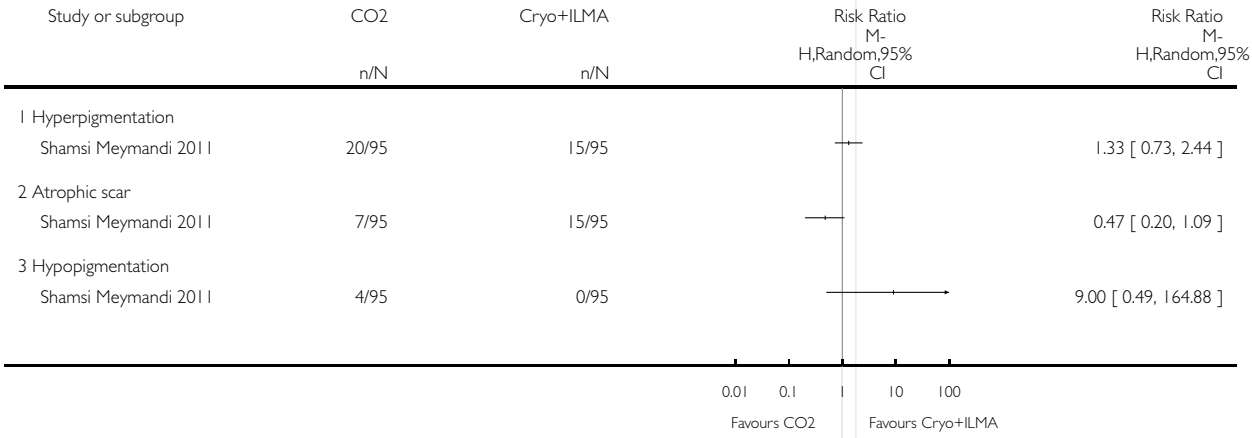


Analysis 81.2. Comparison 81 CO_2 laser (30 W continuous) versus cryotherapy (fortnightly) + ILMA (weekly) for up to 12 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 81 CO_2 laser (30 W continuous) versus cryotherapy (fortnightly) + ILMA (weekly) for up to 12 weeks

Outcome: 2 Adverse effects



Analysis 82.1. Comparison 82 Ablative CO_2 laser (25 kW for 1 session) versus 3 weeks fractional CO_2 laser, Outcome 1 Partcipants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 82 Ablative CO_2 laser (25 kW for 1 session) versus 3 weeks fractional CO_2 laser

Outcome: 1 Partcipants complete cure

Study or subgroup	Ablative CO2 n/N	Fractional CO2 n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2014a	28/60	46/60		0.61 [0.45, 0.83]

Analysis 82.2. Comparison 82 Ablative CO_2 laser (25 kW for 1 session) versus 3 weeks fractional CO_2 laser, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 82 Ablative CO_2 laser (25 kW for 1 session) versus 3 weeks fractional CO_2 laser

Outcome: 2 Adverse effects

Study or subgroup	Ablative CO2 n/N	Fractional CO2 n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Erythema				
Nilforoushzadeh 2014a	2/60	4/60		0.50 [0.10, 2.63]

Analysis 83.1. Comparison 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks)

Outcome: 1 Participants complete cure

Study or subgroup	TCA	ILMA	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Nilforoushzadeh 2006	26/40	23/40		1.13 [0.80, 1.60]

Analysis 83.2. Comparison 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks), Outcome 2 Recurrence.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks)

Outcome: 2 Recurrence

Study or subgroup	TCA	ILMA	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
Nilforoushzadeh 2006	5/40	4/40		1.25 [0.36, 4.32]

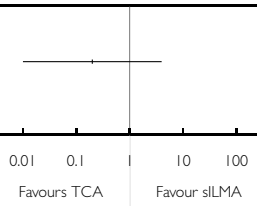
Analysis 83.3. Comparison 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks), Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks)

Outcome: 3 Adverse effects

Study or subgroup	TCA n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Mild erythema and itch				
Nilforoushzadeh 2006	0/40	2/40		0.20 [0.01, 4.04]



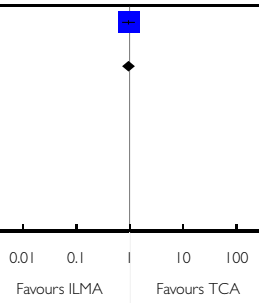
Analysis 83.4. Comparison 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks), Outcome 4 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 83 TCA (50% wt/vol) fortnightly up to 3 times versus ILMA alone (weekly for up to 6 weeks)

Outcome: 4 Microbiological cure of skin lesions

Study or subgroup	TCA n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2006	29/40	30/40		100.0 %	0.97 [0.74, 1.26]
Total (95% CI)	**40**	**40**		**100.0 %**	**0.97 [0.74, 1.26]**
Total events: 29 (TCA), 30 (ILMA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
Test for subgroup differences: Not applicable					



Analysis 84.1. Comparison 84 Topical TCA 50% + local heat versus ILMA twice a week for up to 8 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 84 Topical TCA 50% + local heat versus ILMA twice a week for up to 8 weeks

Outcome: 1 Participants complete cure

Study or subgroup	TCA+Heat n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2012	16/30	24/30		0.67 [0.46, 0.97]

Analysis 84.2. Comparison 84 Topical TCA 50% + local heat versus ILMA twice a week for up to 8 weeks, Outcome 2 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 84 Topical TCA 50% + local heat versus ILMA twice a week for up to 8 weeks

Outcome: 2 Lesions cured

Study or subgroup	TCA+Heat n/N	ILMA n/N	Risk Ratio M-H,Random,99% CI	Risk Ratio M-H,Random,99% CI
1 Males				
Nilforoushzadeh 2012	8/22	8/15		0.68 [0.26, 1.77]
2 Females				
Nilforoushzadeh 2012	8/16	16/23		0.72 [0.34, 1.50]

Analysis 85.1. Comparison 85 TCA + ILMA (weekly for up to 8 weeks) versus ILMA alone (twice a week for up to 8 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 85 TCA + ILMA (weekly for up to 8 weeks) versus ILMA alone (twice a week for up to 8 weeks)

Outcome: 1 Participants complete cure

Study or subgroup	TCA+ILMA n/N	ILMA alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2013	27/30	10/26		2.34 [1.42, 3.86]

Analysis 85.2. Comparison 85 TCA + ILMA (weekly for up to 8 weeks) versus ILMA alone (twice a week for up to 8 weeks), Outcome 2 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 85 TCA + ILMA (weekly for up to 8 weeks) versus ILMA alone (twice a week for up to 8 weeks)

Outcome: 2 Speed of healing (weeks)

Study or subgroup	TCA+ILMA N	Mean(SD)	ILMA alone N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Nilforoushzadeh 2013	30	5.2 (1)	26	6.8 (1.7)		-1.60 [-2.35, -0.85]

Analysis 86.1. Comparison 86 Fractional laser + ILMA (fortnightly 2 sessions) versus ILMA alone (twice a week for up to 8 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 86 Fractional laser + ILMA (fortnightly 2 sessions) versus ILMA alone (twice a week for up to 8 weeks)

Outcome: 1 Participants complete cure

Study or subgroup	Fracional+ILMA n/N	ILMA alone n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2013	20/23	10/26		2.26 [1.36, 3.77]

Analysis 87.1. Comparison 87 TCA + ILMA (weekly for up to 8 weeks) versus fractional laser + ILMA (fortnightly 2 sessions), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 87 TCA + ILMA (weekly for up to 8 weeks) versus fractional laser + ILMA (fortnightly 2 sessions)

Outcome: 1 Participants complete cure

Study or subgroup	TCA+ILMA n/N	Laser+ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2013	27/30	20/23		1.04 [0.85, 1.26]

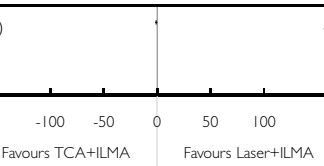
Analysis 87.2. Comparison 87 TCA + ILMA (weekly for up to 8 weeks) versus fractional laser + ILMA (fortnightly 2 sessions), Outcome 2 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 87 TCA + ILMA (weekly for up to 8 weeks) versus fractional laser + ILMA (fortnightly 2 sessions)

Outcome: 2 Speed of healing (weeks)

Study or subgroup	TCA+ILMA N	Mean(SD)	Laser+ILMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Nilforoushzadeh 2013	30	5.2 (1)	23	6.3 (3)		-1.10 [-2.38, 0.18]



Analysis 88.1. Comparison 88 TCA fortnightly up to 8 weeks + ILMA (twice a week) versus ILMA alone (weekly for up to 8 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 88 TCA fortnightly up to 8 weeks + ILMA (twice a week) versus ILMA alone (weekly for up to 8 weeks)

Outcome: 1 Participants complete cure

Study or subgroup	TCA n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2014b	78/91	76/95		1.07 [0.94, 1.22]

Analysis 89.1. Comparison 89 Cryotherapy + ILMA (weekly) versus cryotherapy (weekly) for up to 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 89 Cryotherapy + ILMA (weekly) versus cryotherapy (weekly) for up to 6 weeks

Outcome: 1 Participants complete cure

Study or subgroup	Cryotherapy + ILMA n/N	Cryotherapy n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Salmanpour 2006	18/20	14/20		1.29 [0.93, 1.77]

Analysis 89.2. Comparison 89 Cryotherapy + ILMA (weekly) versus cryotherapy (weekly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 89 Cryotherapy + ILMA (weekly) versus cryotherapy (weekly) for up to 6 weeks

Outcome: 2 Adverse effects

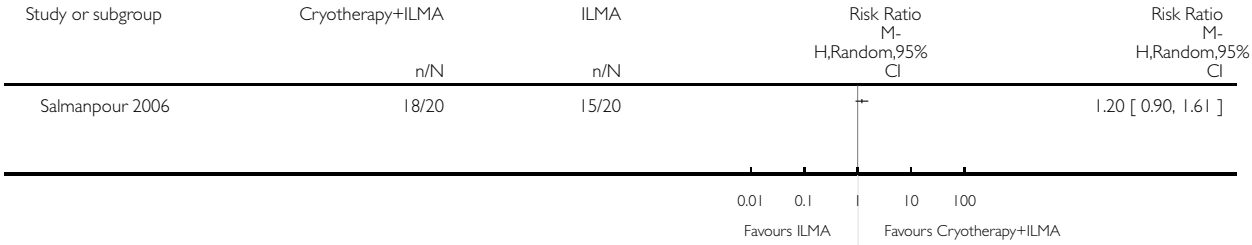
Study or subgroup	Cryotherapy + ILMA n/N	Cryotherapy n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Erythema and oedema				
Salmanpour 2006	7/20	6/20		1.17 [0.48, 2.86]

Analysis 90.1. Comparison 90 Cryotherapy + ILMA (weekly) versus ILMA (weekly) for up to 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 90 Cryotherapy + ILMA (weekly) versus ILMA (weekly) for up to 6 weeks

Outcome: 1 Participants complete cure

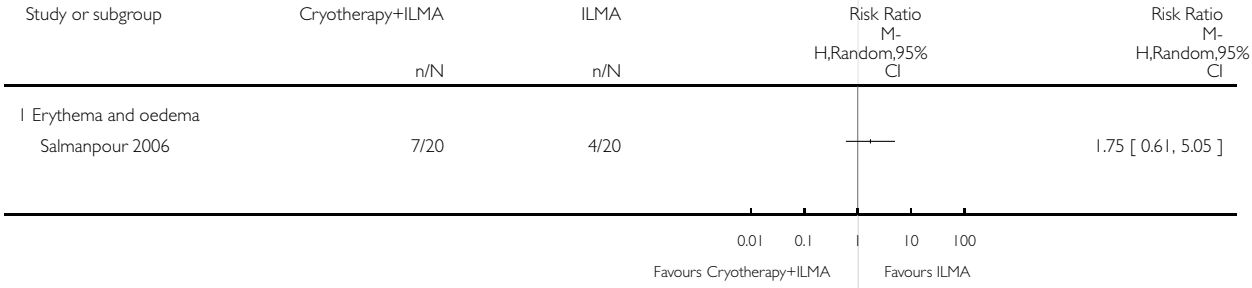


Analysis 90.2. Comparison 90 Cryotherapy + ILMA (weekly) versus ILMA (weekly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 90 Cryotherapy + ILMA (weekly) versus ILMA (weekly) for up to 6 weeks

Outcome: 2 Adverse effects



Analysis 91.1. Comparison 91 Cryotherapy + ILMA (weekly) versus ILMA alone (weekly) for up to 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 91 Cryotherapy + ILMA (weekly) versus ILMA alone (weekly) for up to 6 weeks

Outcome: 1 Participants complete cure

Study or subgroup	Cryotherapy n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Salmanpour 2006	14/20	15/20		0.93 [0.64, 1.37]

Analysis 91.2. Comparison 91 Cryotherapy + ILMA (weekly) versus ILMA alone (weekly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 91 Cryotherapy + ILMA (weekly) versus ILMA alone (weekly) for up to 6 weeks

Outcome: 2 Adverse effects

Study or subgroup	Cryotherapy n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Erythema and oedema				
Salmanpour 2006	6/20	4/20		1.50 [0.50, 4.52]

Analysis 92.1. Comparison 92 Cryotherapy (weekly) versus ILMA (weekly) for up to 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 92 Cryotherapy (weekly) versus ILMA (weekly) for up to 6 weeks

Outcome: 1 Participants complete cure

Study or subgroup	Cryotherapy n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Layegh 2009	21/36	10/36		2.10 [1.16, 3.81]

Analysis 93.1. Comparison 93 Cryotherapy + ILMA (weekly) versus cryotherapy alone (weekly) for up to 6 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 93 Cryotherapy + ILMA (weekly) versus cryotherapy alone (weekly) for up to 6 weeks

Outcome: 1 Lesions cured

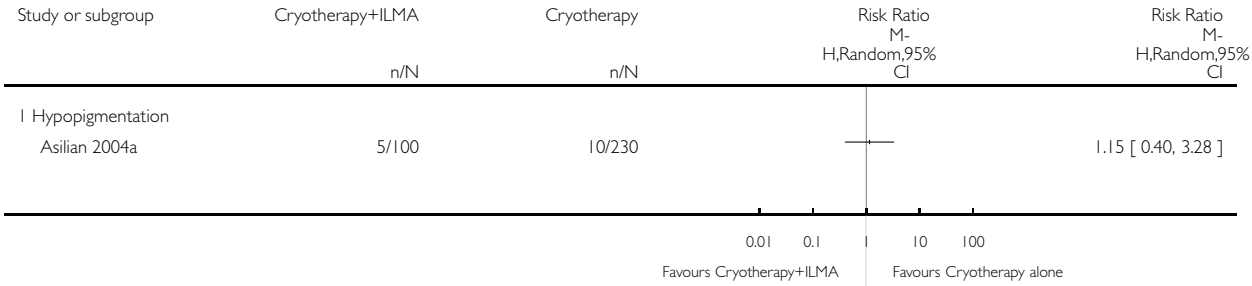
Study or subgroup	Cryotherapy+ILMA n/N	Cryotherapy n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Asilian 2004a	120/149	120/230		1.54 [1.33, 1.79]

Analysis 93.2. Comparison 93 Cryotherapy + ILMA (weekly) versus cryotherapy alone (weekly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 93 Cryotherapy + ILMA (weekly) versus cryotherapy alone (weekly) for up to 6 weeks

Outcome: 2 Adverse effects

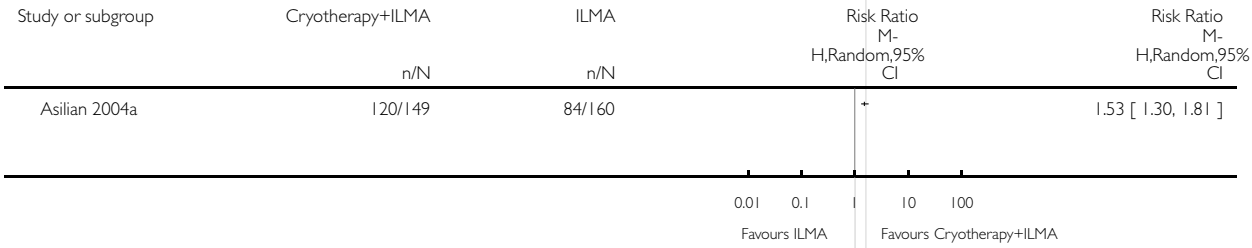


Analysis 94.1. Comparison 94 Cryotherapy + ILMA (weekly) versus ILMA (fortnightly) for up to 6 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 94 Cryotherapy + ILMA (weekly) versus ILMA (fortnightly) for up to 6 weeks

Outcome: 1 Lesions cured

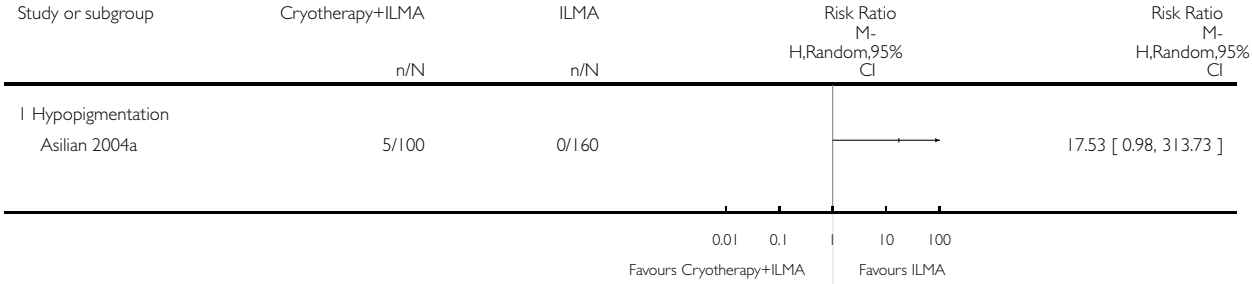


Analysis 94.2. Comparison 94 Cryotherapy + ILMA (weekly) versus ILMA (fortnightly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 94 Cryotherapy + ILMA (weekly) versus ILMA (fortnightly) for up to 6 weeks

Outcome: 2 Adverse effects

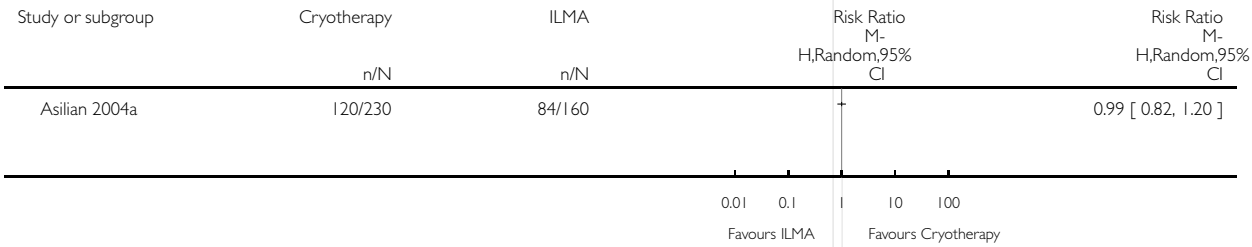


Analysis 95.1. Comparison 95 Cryotherapy alone (weekly) versus ILMA (fortnightly) for up to 6 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 95 Cryotherapy alone (weekly) versus ILMA (fortnightly) for up to 6 weeks

Outcome: 1 Lesions cured

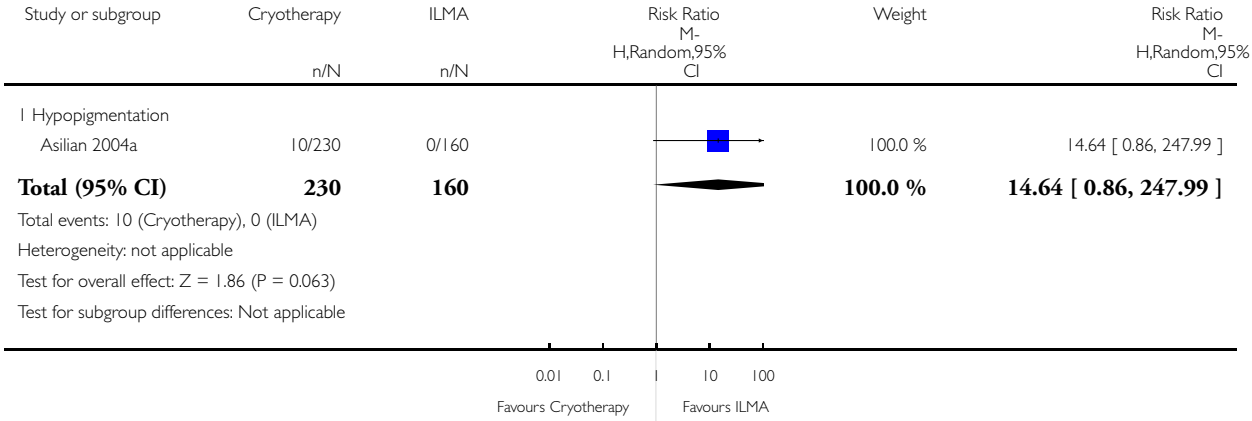


Analysis 95.2. Comparison 95 Cryotherapy alone (weekly) versus ILMA (fortnightly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 95 Cryotherapy alone (weekly) versus ILMA (fortnightly) for up to 6 weeks

Outcome: 2 Adverse effects

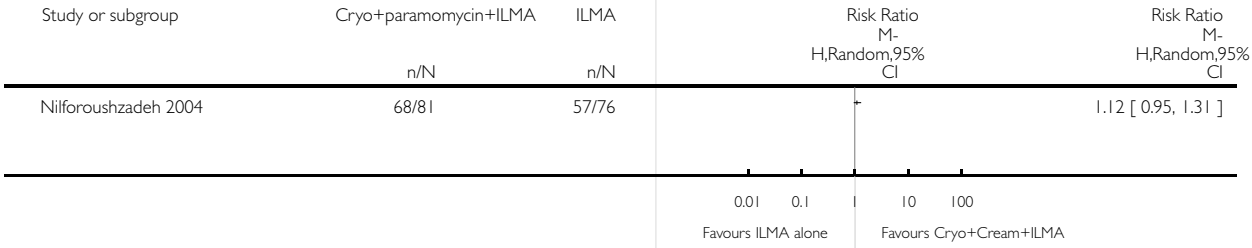


Analysis 96.1. Comparison 96 Cryotherapy (fortnightly) + 15% paromomycin + 10% urea cream (twice a day) + ILMA (twice a day for 4 weeks) versus ILMA (twice a week) for up to 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 96 Cryotherapy (fortnightly) + 15% paromomycin + 10% urea cream (twice a day) + ILMA (twice a day for 4 weeks) versus ILMA (twice a week) for up to 6 weeks

Outcome: 1 Participants complete cure

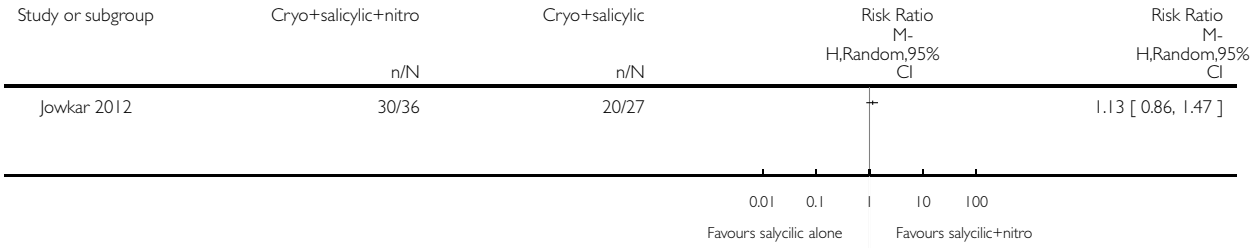


Analysis 97.1. Comparison 97 Cryotherapy (weekly) + 3% salicylic + 3% sodium nitrite cream (twice a day) for up to 12 weeks versus cryotherapy (weekly) + 3% salicylic cream (twice a day), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 97 Cryotherapy (weekly) + 3% salicylic + 3% sodium nitrite cream (twice a day) for up to 12 weeks versus cryotherapy (weekly) + 3% salicylic cream (twice a day)

Outcome: 1 Lesions cured

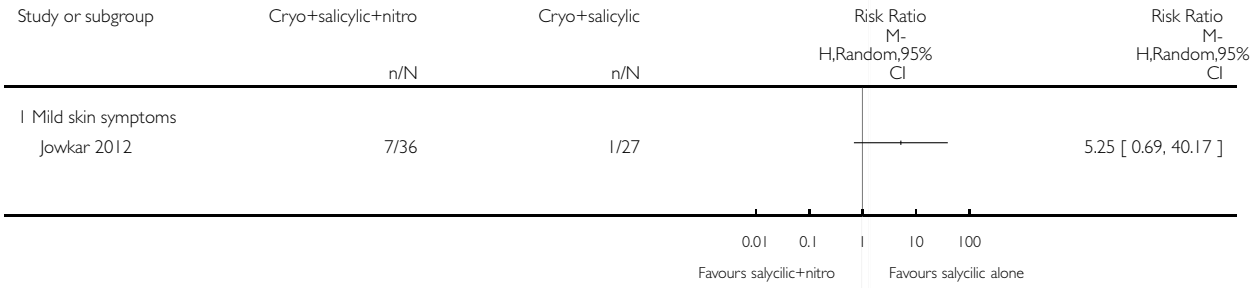


Analysis 97.2. Comparison 97 Cryotherapy (weekly) + 3% salicylic + 3% sodium nitrite cream (twice a day) for up to 12 weeks versus cryotherapy (weekly) + 3% salicylic cream (twice a day), Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 97 Cryotherapy (weekly) + 3% salicylic + 3% sodium nitrite cream (twice a day) for up to 12 weeks versus cryotherapy (weekly) + 3% salicylic cream (twice a day)

Outcome: 2 Adverse effects

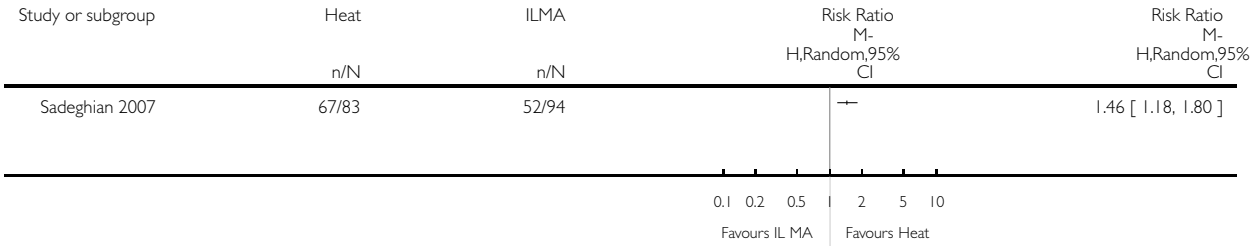


Analysis 98.1. Comparison 98 Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks, Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 98 Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks

Outcome: 1 Lesions cured

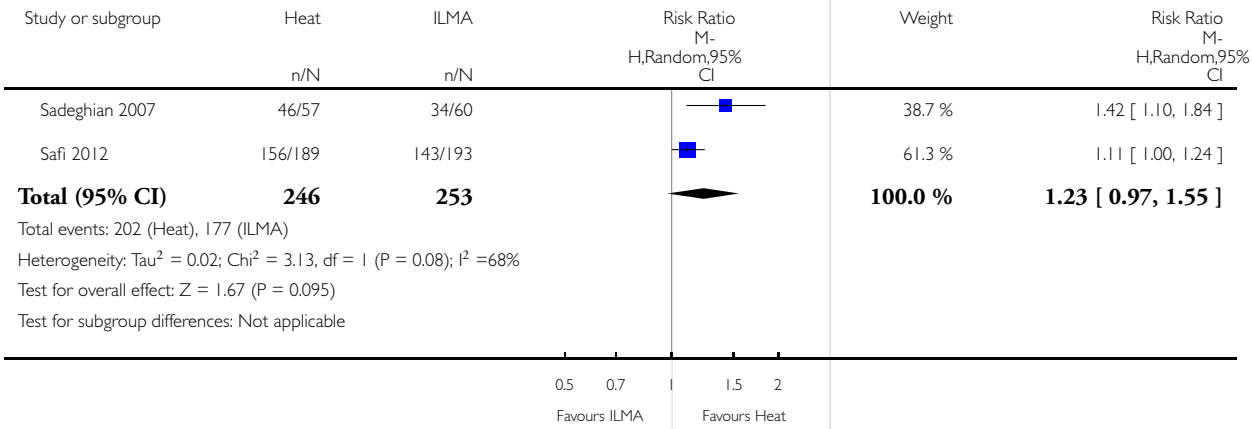


Analysis 98.2. Comparison 98 Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks, Outcome 2 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 98 Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks

Outcome: 2 Participants complete cure



Analysis 98.3. Comparison 98 Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks, Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 98 Radiofrequency waves versus ILMA (1 mL to 7 mL per lesion) weekly for 4 weeks

Outcome: 3 Adverse effects

Study or subgroup	Heat n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Allergic reaction				
Sadeghian 2007	0/57	11/60		0.05 [0.00, 0.76]

Analysis 99.1. Comparison 99 Radiofrequency waves (50 uCTM applied for 30 s) versus ILSSG (10 days of 20 mg/kg/d), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 99 Radiofrequency waves (50 uCTM applied for 30 s) versus ILSSG (10 days of 20 mg/kg/d)

Outcome: 1 Lesions cured

Study or subgroup	Thermotherapy n/N	SSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Aronson 2010	63/86	50/84		1.23 [0.99, 1.53]

Analysis 99.2. Comparison 99 Radiofrequency waves (50 uCTM applied for 30 s) versus ILSSG (10 days of 20 mg/kg/d), Outcome 2 Adverse effects (serious).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 99 Radiofrequency waves (50 uCTM applied for 30 s) versus ILSSG (10 days of 20 mg/kg/d)

Outcome: 2 Adverse effects (serious)

Study or subgroup	Thermotherapy n/N	ILSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Aronson 2010	4/86	3/84		1.30 [0.30, 5.64]

Analysis 100.1. Comparison 100 Radiofrequency waves (1 treatment of > 1 consecutive application at 50°C for 30 s) versus IMSSG (20 mg/kg/d for 3 weeks), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 100 Radiofrequency waves (1 treatment of > 1 consecutive application at 50 C for 30 s) versus IMSSG (20 mg/kg/d for 3 weeks)

Outcome: 1 Participants complete cure

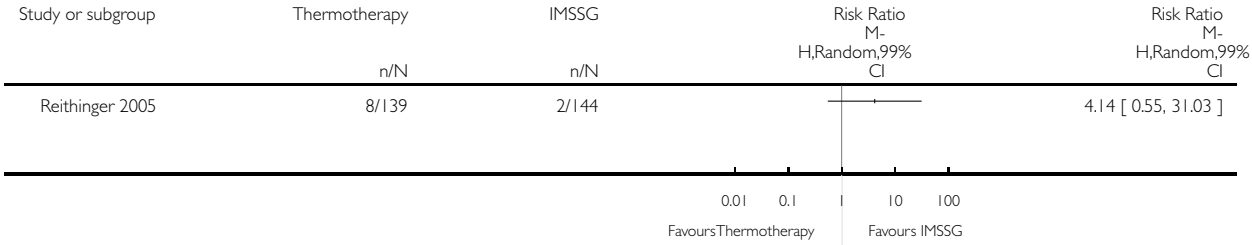
Study or subgroup	Thermotherapy n/N	IMSSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Reithinger 2005	75/139	26/144		2.99 [2.04, 4.37]

Analysis 100.2. Comparison 100 Radiofrequency waves (1 treatment of > 1 consecutive application at 50ºC for 30 s) versus IMSSG (20 mg/kg/d for 3 weeks), Outcome 2 Adverse event (secondary infection).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 100 Radiofrequency waves (1 treatment of > 1 consecutive application at 50 C for 30 s) versus IMSSG (20 mg/kg/d for 3 weeks)

Outcome: 2 Adverse event (secondary infection)

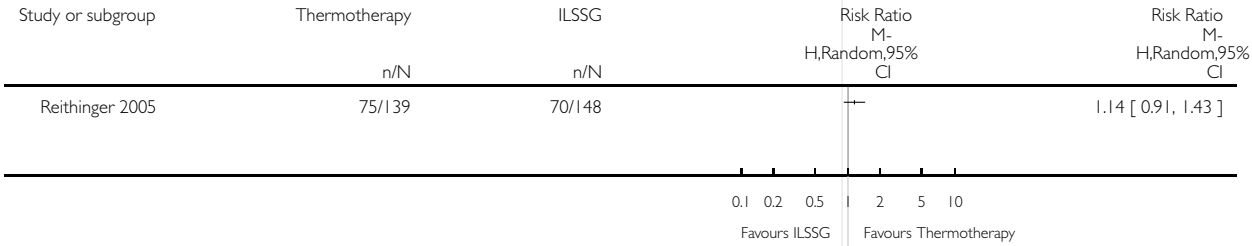


Analysis 101.1. Comparison 101 Radiofrequency waves (1 treatment of > 1 consecutive application at 50ºC for 30 s) versus ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 days), Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 101 Radiofrequency waves (1 treatment of > 1 consecutive application at 50 C for 30 s) versus ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 days)

Outcome: 1 Participants complete cure



Analysis 101.2. Comparison 101 Radiofrequency waves (1 treatment of > 1 consecutive application at 50ºC for 30 s) versus ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 days), Outcome 2 Adverse event (secondary infection).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 101 Radiofrequency waves (1 treatment of > 1 consecutive application at 50 C for 30 s) versus ILSSG (5 injections of 2 mL to 5 mL every 5 to 7 days)

Outcome: 2 Adverse event (secondary infection)

Study or subgroup	Thermotherapy n/N	iLSSG n/N	Risk Ratio M-H,Random,99% CI	Risk Ratio M-H,Random,99% CI
Reithinger 2005	8/139	5/148		1.70 [0.41, 7.17]

Analysis 102.1. Comparison 102 Radiofrequency waves versus ILSSG, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 102 Radiofrequency waves versus ILSSG

Outcome: 1 Participants complete cure

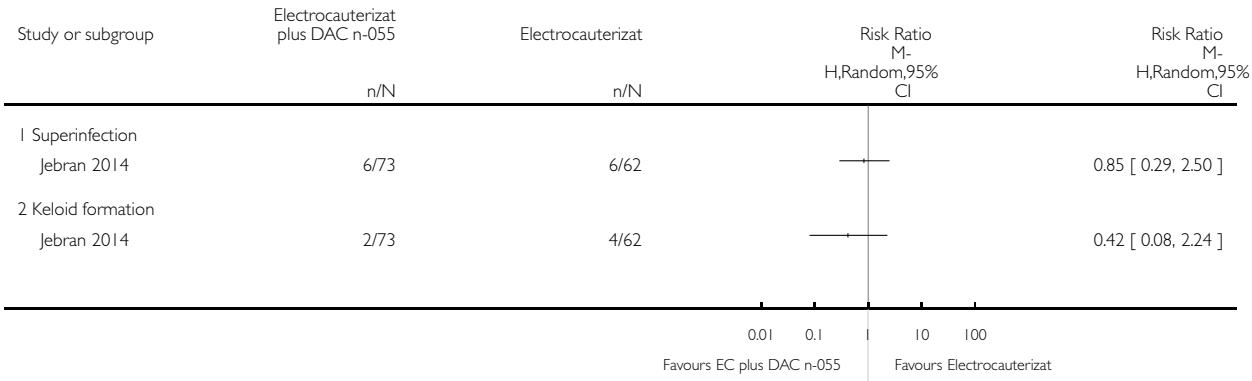
Study or subgroup	RFHT n/N	IL SSG n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Bumb 2013	49/50	47/50		1.04 [0.96, 1.13]

Analysis 103.1. Comparison 103 Electrocauterisation + DAC n-055 (daily) versus electrocauterisation, Outcome 1 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 103 Electrocauterisation + DAC n-055 (daily) versus electrocauterisation

Outcome: 1 Adverse effects

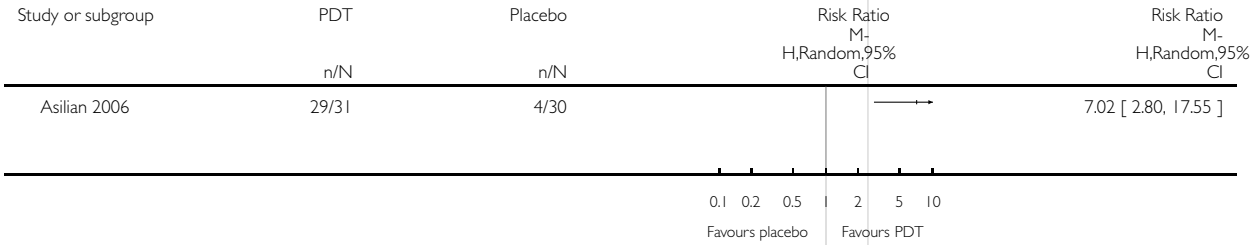


Analysis 104.1. Comparison 104 PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks), Outcome 1 Lesions cured.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 104 PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks)

Outcome: 1 Lesions cured

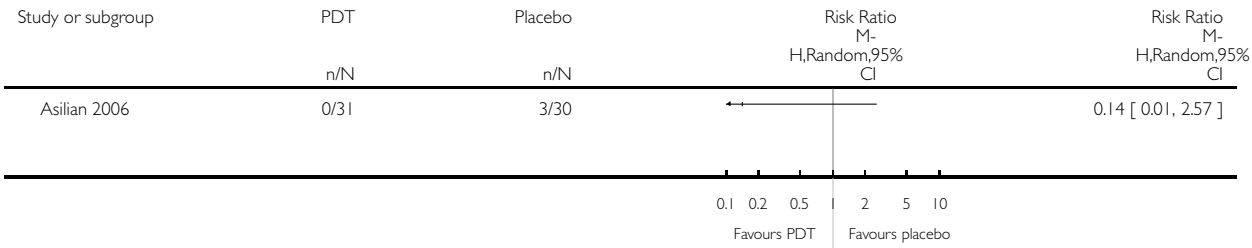


Analysis 104.2. Comparison 104 PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks), Outcome 2 Scarring.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 104 PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks)

Outcome: 2 Scarring

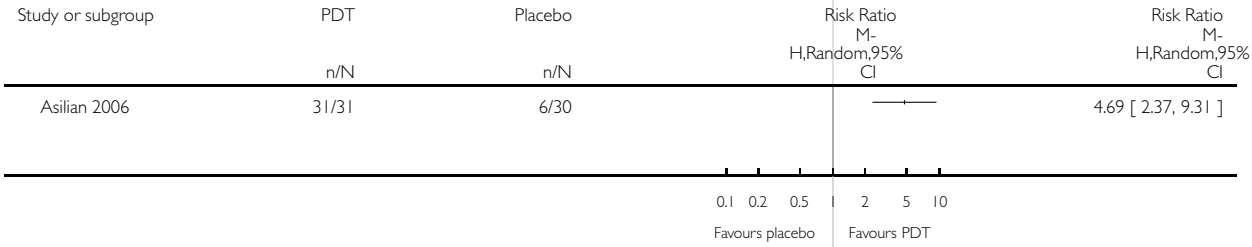


Analysis 104.3. Comparison 104 PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks), Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 104 PDT (weekly for 4 weeks) versus placebo (twice a day for 4 weeks)

Outcome: 3 Microbiological cure of skin lesions



Analysis 105.1. Comparison 105 Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 105 Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks

Outcome: 1 Participants complete cure

Study or subgroup	Mesotherapy n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kashani 2010	25/30	26/30		0.96 [0.78, 1.19]

Analysis 105.2. Comparison 105 Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 105 Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks

Outcome: 2 Adverse effects

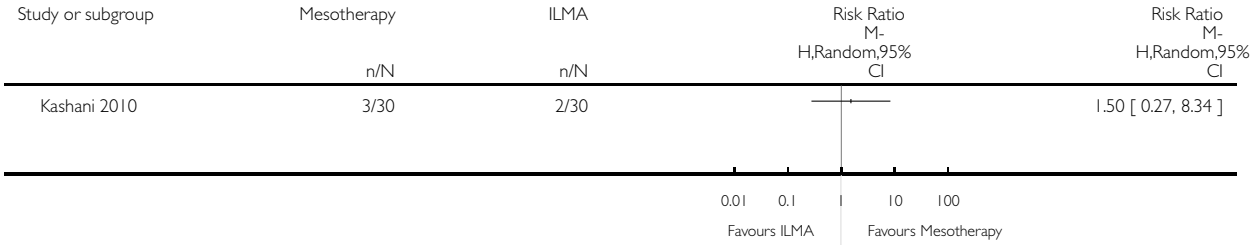
Study or subgroup	Mesotherapy n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Allergic reaction				
Kashani 2010	2/30	1/30		2.00 [0.19, 20.90]

Analysis 105.3. Comparison 105 Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks, Outcome 3 Development of cell-mediated immunity.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 105 Mesotherapy gun (0.5 mL of MA weekly) versus ILMA (0.1 mL weekly) for up to 6 weeks

Outcome: 3 Development of cell-mediated immunity

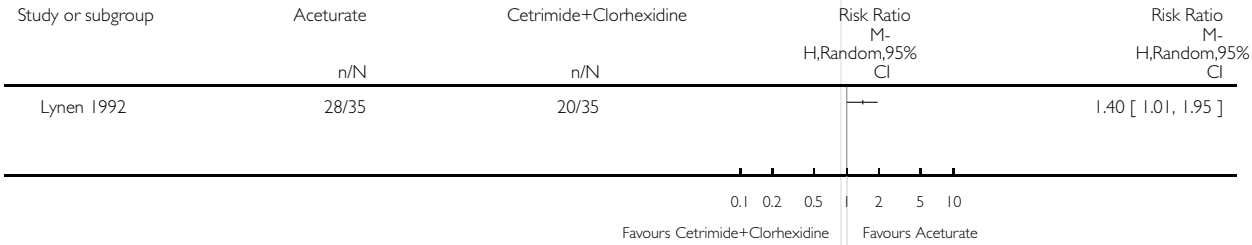


Analysis 106.1. Comparison 106 Diminazene aceturate solution (weekly) versus cetrimide + chlorhexidine solution for 50 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 106 Diminazene aceturate solution (weekly) versus cetrimide + chlorhexidine solution for 50 d

Outcome: 1 Participants complete cure

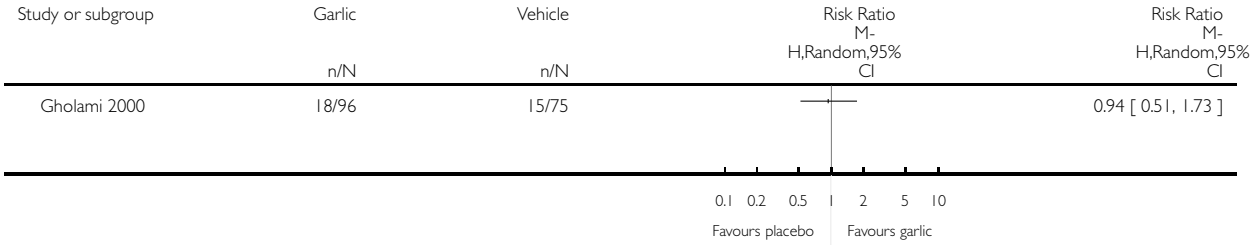


Analysis 107.1. Comparison 107 Topical garlic (twice a day) versus vehicle for 3 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 107 Topical garlic (twice a day) versus vehicle for 3 weeks

Outcome: 1 Participants complete cure

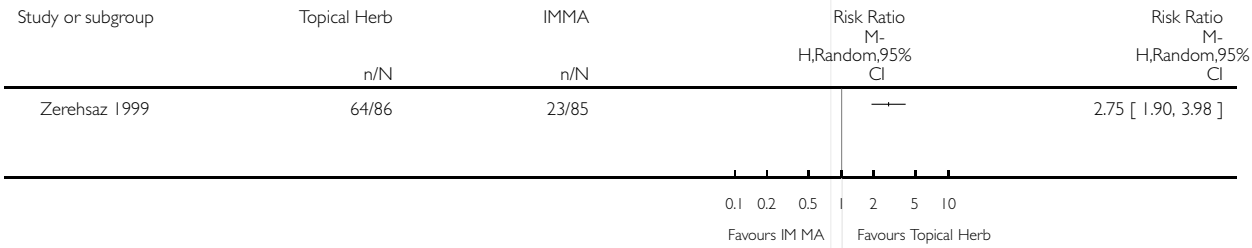


Analysis 108.1. Comparison 108 Topical herbal extract + placebo (5 d) versus IMMA (15-20/mg/kg/d) + vehicle for 20 d, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 108 Topical herbal extract + placebo (5 d) versus IMMA (15-20/mg/kg/d) + vehicle for 20 d

Outcome: 1 Participants complete cure



Analysis 109.1. Comparison 109 Topical honey (twice a day) + ILMA (weekly) versus ILMA (weekly) for 4 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 109 Topical honey (twice a day) + ILMA (weekly) versus ILMA (weekly) for 4 weeks

Outcome: 1 Participants complete cure

Study or subgroup	Honey + ILMA n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Nilforoushzadeh 2007	23/50	32/50		0.72 [0.50, 1.04]

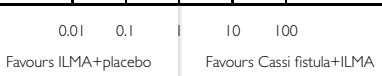
Analysis 110.1. Comparison 110 Cassia fistula (topical gel) + ILMA (0.5 mL to 2 mL), twice a week versus ILMA (0.5 mL to 2 mL), twice a week + vehicle, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 110 *Cassia fistula* (topical gel) + ILMA (0.5 mL to 2 mL), twice a week versus ILMA (0.5 mL to 2 mL), twice a week + vehicle

Outcome: 1 Participants complete cure

Study or subgroup	*Cassi fistula* + ILMA n/N	Vehicle + ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Jaffary 2010	47/70	29/70		1.62 [1.17, 2.24]



Analysis 110.2. Comparison 110 Cassia fistula (topical gel) + ILMA (0.5 mL to 2 mL), twice a week versus ILMA (0.5 mL to 2 mL), twice a week + vehicle, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 110 *Cassia fistula* (topical gel) + ILMA (0.5 mL to 2 mL), twice a week versus ILMA (0.5 mL to 2 mL), twice a week + vehicle

Outcome: 2 Adverse effects

Study or subgroup	*Cassi fistula* + ILMA n/N	Vehicle + ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Itching				
Jaffary 2010	9/70	9/70		1.00 [0.42, 2.37]

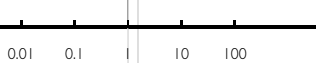
Analysis 111.1. Comparison 111 Cassia fistula boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 111 *Cassia fistula* boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome: 1 Participants complete cure

Study or subgroup	C. fistula Boiled n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Jaffary 2014b	22/55	36/55		0.61 [0.42, 0.89]



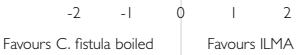
Analysis 111.2. Comparison 111 Cassia fistula boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks, Outcome 2 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 111 *Cassia fistula* boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome: 2 Speed of healing (weeks)

Study or subgroup	C. fistula Boiled		ILMA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Jaffary 2014b	55	4.6 (3.7)	55	6.4 (5.2)		-1.80 [-3.49, -0.11]



Analysis 111.3. Comparison 111 Cassia fistula boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks, Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 111 *Cassia fistula* boiled (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome: 3 Adverse effects

Study or subgroup	C. fistula Boiled	ILMA	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
1 Allergic reaction				
Jaffary 2014b	3/55	2/55		1.50 [0.26, 8.63]

Analysis 112.1. Comparison 112 Cassia fistula hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 112 *Cassia fistula* hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome: 1 Participants complete cure

Study or subgroup	C. fistula Hydroalcoholic n/N	ILMA n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Jaffary 2014b	20/55	36/55		0.56 [0.37, 0.83]

Analysis 112.2. Comparison 112 Cassia fistula hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks, Outcome 2 Speed of healing (weeks).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 112 *Cassia fistula* hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome: 2 Speed of healing (weeks)

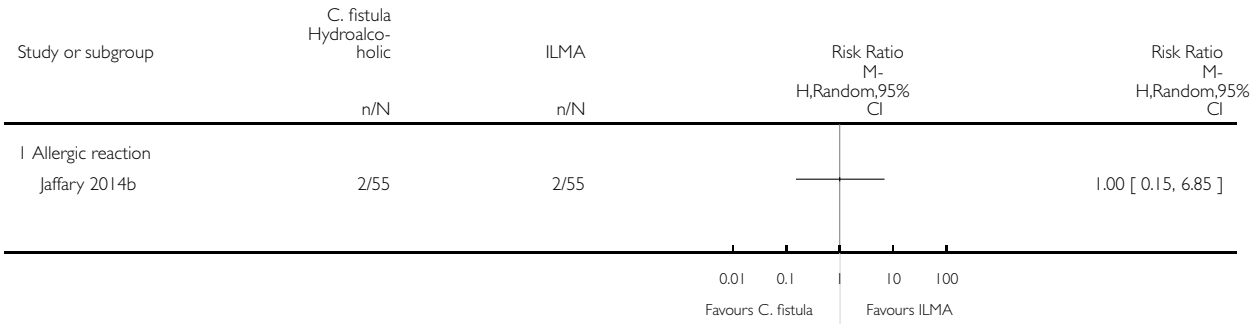
Study or subgroup	C. fistula Hydroalcoholic N	Mean(SD)	ILMA N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Jaffary 2014b	55	4.9 (3.8)	55	6.4 (5.2)		-1.50 [-3.20, 0.20]

Analysis 112.3. Comparison 112 Cassia fistula hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks, Outcome 3 Adverse reaction.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 112 *Cassia fistula* hydroalcoholic (topical) versus ILMA (0.5 mL to 2 mL), twice a week for 4 weeks

Outcome: 3 Adverse reaction

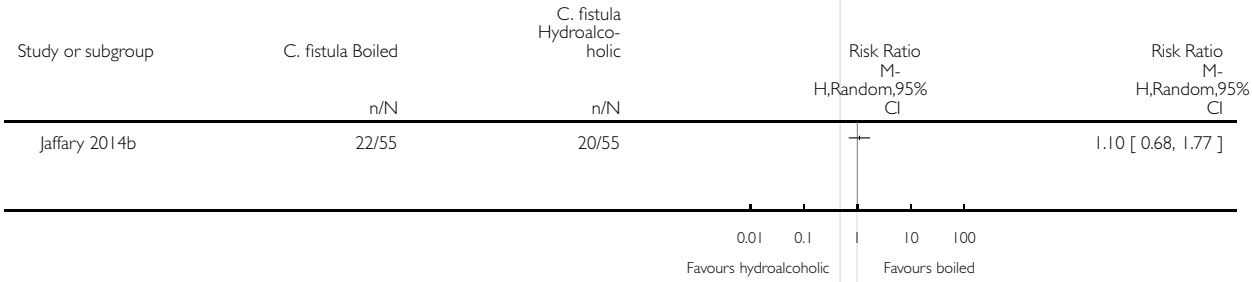


Analysis 113.1. Comparison 113 Cassia fistula boiled (topical) versusC fistula hydroalcoholic (topical) for 4 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 113 *Cassia fistula* boiled (topical) versus *C fistula* hydroalcoholic (topical) for 4 weeks

Outcome: 1 Participants complete cure



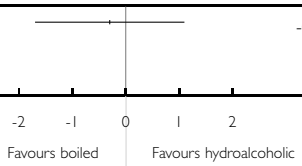
Analysis 113.2. Comparison 113 Cassia fistula boiled (topical) versusC fistula hydroalcoholic (topical) for 4 weeks, Outcome 2 Speed of healing (days).

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 113 *Cassia fistula* boiled (topical) versus *C fistula* hydroalcoholic (topical) for 4 weeks

Outcome: 2 Speed of healing (days)

Study or subgroup	C. fistula Boiled		C. fistula Hydroalcoholic		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Jaffary 2014b	55	4.6 (3.7)	55	4.9 (3.8)		-0.30 [-1.70, 1.10]



Analysis 113.3. Comparison 113 Cassia fistula boiled (topical) versusC fistula hydroalcoholic (topical) for 4 weeks, Outcome 3 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 113 *Cassia fistula* boiled (topical) versus *C fistula* hydroalcoholic (topical) for 4 weeks

Outcome: 3 Adverse effects

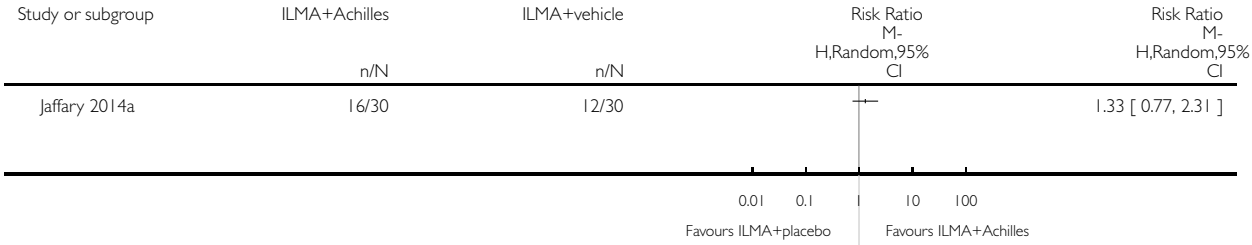
Study or subgroup	C. fistula Boiled	C. fistula Hydroalcoholic	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
	n/N	n/N		
1 Allergic reaction				
Jaffary 2014b	3/55	2/55		1.50 [0.26, 8.63]

Analysis 114.1. Comparison 114 Topical gel Achilles millefollium (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks, Outcome 1 Participants complete cure.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 114 Topical gel *Achilles millefollium* (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks

Outcome: 1 Participants complete cure

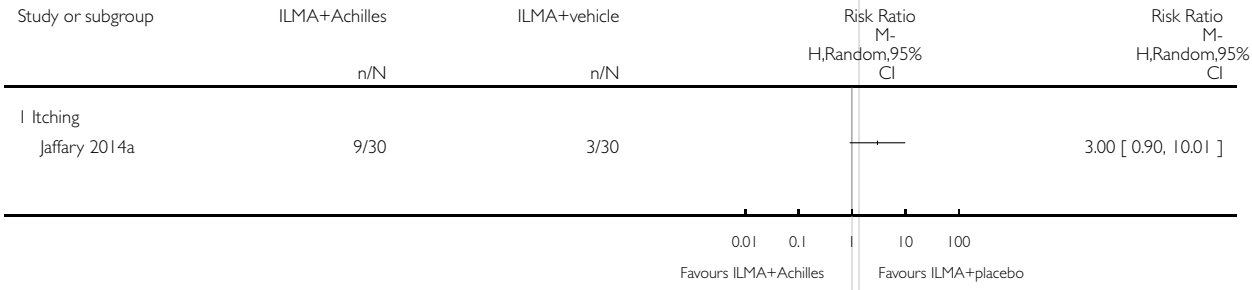


Analysis 114.2. Comparison 114 Topical gel Achilles millefollium (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks, Outcome 2 Adverse effects.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 114 Topical gel *Achilles millefollium* (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks

Outcome: 2 Adverse effects

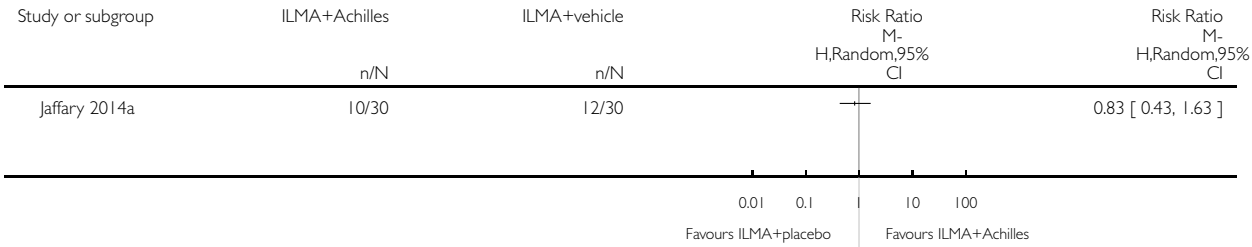


Analysis 114.3. Comparison 114 Topical gel Achilles millefollium (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks, Outcome 3 Microbiological cure of skin lesions.

Review: Interventions for Old World cutaneous leishmaniasis

Comparison: 114 Topical gel *Achilles millefollium* (twice daily) + ILMA (weekly 20 mg/kg/d) versus ILMA (weekly 20 mg/kg/d) + vehicle (twice daily) for 4 weeks

Outcome: 3 Microbiological cure of skin lesions



ADDITIONAL TABLES

Table 1. Glossary

Term	Definition
Antimonials	Pharmaceutical agents containing antimony. Antimony-containing compounds (meglumine antimoniate and sodium stibogluconate) are the principal medications used to treat leishmaniases, an infection caused by a protozoan parasite
Arthralgia	Pain in the joints. The causes of arthralgia are varied and range, from a joints perspective, from degenerative and destructive processes such as osteoarthritis and sports injuries to inflammation of tissues surrounding the joints, such as bursitis
Cardiac arrhythmia	An arrhythmia is an abnormal heart rhythm. Many types of arrhythmia have no symptoms. When symptoms are present these may include palpitations or feeling a pause between heartbeats. More seriously there may be lightheadedness, passing out, shortness of breath, or chest pain
Cutaneous necrosis	The death of living tissues in response to disease or injury
Cytolysis	The degeneration or dissolution of cell caused by the disruption of cell membrane
Exudate	A fluid with a high content of protein and cellular debris that has escaped from blood vessels and has been deposited in tissues or on tissue surfaces, usually as a result of inflammation
Human monocytes	Monocytes are the biggest type of white blood cell in the immune system. Originally formed in the bone marrow, they are released into our blood and migrate into the connective tissue

Table 1. Glossary (*Continued*)

	where they differentiate into macrophages. When certain germs enter the body, they quickly rush to the site of attack
Hypotension	A systolic blood pressure reading (the top number) of 90 millimetres of mercury (mmHg) or less a diastolic blood pressure reading (the bottom number) of 60 mmHg or less is generally considered low blood pressure. The causes of low blood pressure can range from dehydration to serious medical or surgical disorders
Immune response modifier	Any of a broad family of biomolecules that up- or down-regulate, or restore immune responsiveness, which are generated after T cells recognise an antigen present on the surface of a self-antigen-presenting cell, which, once activated, produce multiple cytokines
Immunolabeling	A biochemical process that enables the detection and localisation of an antigen to a particular site within a cell, tissue, or organ. Antigens are organic molecules, usually proteins, capable of binding to an antibody. These antigens can be visualised using a combination of antigen-specific antibodies as well as a means of detection, called a tag, that is covalently linked to the antibody. If the immunolabeling process is meant to reveal information about a cell or its substructures, the process is called immunocytochemistry. Immunolabeling of larger structures is called immunohistochemistry
In vitro	Biological processes or reactions made to occur outside the living organism in an artificial environment, such as a culture medium
Intralesional meglumine antimoniate	Meglumine antimoniate (or Glucantime) is a medicine used for treating leishmaniasis. It belongs to a group of compounds known as the pentavalent antimonials
Lymphadenopathies	Lymph nodes that have an abnormal in size, number or consistency; often used as a synonym for swollen or enlarged lymph nodes. Common causes of lymphadenopathy are infection, autoimmune disease, or malignancy
Lymphatic channels	The vessels that transport lymph throughout the body. Lymph is a clear fluid that contains cells important for forming antibodies that fight infection
Lymphokine	Any of various soluble protein mediators released by sensitised lymphocytes on contact with antigen, and believed to play a role in macrophage activation, lymphocyte transformation, and cell-mediated immunity. They regulate immune responses through differentiation, amplification, and inhibition of cell functions. Lymphokines may also have a cytotoxic effector function. Used as biologic response modifiers in the treatment of cancer
Macrophages	White blood cells (activated monocytes) that protect the body against infection and foreign substances by breaking them down into antigenic peptides recognised by circulating T cells
Miltefosine	An oral alkyl phosphocholine analogue used to treat cutaneous and visceral leishmaniasis. Interacts with lipids and sterols in the Leishmania membrane resulting in inhibition of mitochondria and apoptotic cell death
Mucous membranes	The mucous membranes (or mucosae or mucosas; singular mucosa) are linings of mostly endodermal origin, covered in epithelium, which are involved in absorption and secretion. They line cavities that are exposed to the external environment and internal organs

Table 1. Glossary (*Continued*)

Myalgia	Myalgia, or muscle pain, is a symptom of many diseases and disorders. The most common causes are the overuse or over-stretching of a muscle or group of muscles. Myalgia without a traumatic history is often due to viral infections. Long-term myalgias may be indicative of a metabolic myopathy, some nutritional deficiencies or chronic fatigue syndrome
Nodular lymphangitis	Nodular lymphangitis is a distinct clinical entity, separate from lymphangitis. This disorder is characterised by inflammatory nodules along the lymphatics draining a primary skin infection
Papule	A solid, rounded growth that is elevated from the skin, usually inflammatory but nonsuppurative. A papule is usually less than 1 cm across
Parenteral	Administration of a medicinal or therapeutic substance, other than through the gastrointestinal or respiratory tracts, e.g. by intravenous, intramuscular or subcuticular injection
Pentamidine	Pentamidine (e.g. isethionate) is an antiprotozoal and antifungal agent of the class of aromatic diamidines, administered intravenously or intramuscularly in treatment of early African trypanosomiasis and leishmaniasis, and intravenously, intramuscularly, or by oral inhalation in treatment and prophylaxis of *Pneumocystis carinii* pneumonia.
Pentavalent antimony	Pentavalent antimonials are a group of compounds used for the treatment of leishmaniasis. The first pentavalent antimonial used was urea stibamine: first introduced in the 1930s, it fell out of favour in the 1950s due to higher toxicity compared to sodium stibogluconate. The compounds currently available for clinical use are: sodium stibogluconate (Pentostam; manufactured by GlaxoSmithKline; available in the USA and UK), which is administered by slow intravenous injection, intralesional or intramuscular injection, and meglumine antimoniate (Glucantime; manufactured by Aventis; available in Brazil, France and Italy), which is administered by intramuscular, intralesional, or intravenous injection
Promastigotes	Term now generally used instead of 'leptomonad' or 'leptomonad stage' to avoid confusion with the flagellate genus Leptomonas. It denotes the flagellate stage of a trypanosomatid protozoan in which the flagellum arises from a kinetoplast in front of the nucleus and emerges from the anterior end of the organism; usually an extracellular phase, as in the insect intermediate host (or in culture) of *Leishmania* parasites.
Protozoan	Any of a group of single-celled, usually microscopic, eukaryotic organisms, such as amoebas, ciliates, flagellates, and sporozoans
ThermoMed device	The ThermoMed is a battery-operated device that delivers precisely controlled localised current field radiofrequency heat to selectively destroy certain diseased tissue and is recommended by the World Health Organization as an alternative therapy for cutaneus leishmaniasis
Thermotherapy	The treatment of disease by the application of heat. Thermotherapy may be administered as dry heat with heat lamps, diathermy machines, electric pads, or hot water bottles or as moist heat with warm compresses or immersion in warm water. Warm soaks or compresses may be used to treat local infections, relax muscles and relieve pain in patients with motor problems, and promote circulation in peripheral vascular disorders such as thrombophlebitis

Table 2. Interventions for Old World cutaneous leishmaniasis

Drug	Doses
Systemic antimonials	
Sodium stibogluconate (Pentostam, Stibanate) Meglumine antimonate (Glucantime) Combined with pentoxifylline	20 mgSb $^{v+}$/kg/d intramuscularly or intravenously for 20-30 days 400 mg orally 3 times a day for 10-20 days
Intralesional antimonials	
Sodium stibogluconate (Pentostam, Stibanate) Meglumine antimonate (Glucantime)	1-5 mL per session every 3-7 days. Up to 10 sessions depending on the clinical response, but most patients require $\leq$ 5 sessions
Non-antimonial systemic treatments	
Fluconazole	200 mg orally daily for 6 weeks
Miltefosine	50 mg orally three times daily for 28 days
Liposomal amphotericin B	3 mg/kg/d IV on days 1-5 and 10 (18 mg/kg total dose)
Non-antimonial topical or intralesional therapies	
15% paromomycin/12% methylbenzethonium chloride	Ointment twice daily for 10-20 days
15% paromomycin/0.5% gentamicin sulphate	Twice a day for 20 days
Physical therapies	
Cryotherapy with liquid nitrogen	Frozen for 10-30 s and thaw applied locally 2-3 times in each session, repeated every 1-4 weeks to complete healing (usually 2-4 sessions)
Local heat therapy	50°-55°C for 30 s by: Infrared light Direct current electrical stimulation Ultrasound Laser Radiofrequency waves ThermoMed device

Table 3. Adverse effects of oral antibiotics

Study	Method of assessment	Timing	Interventions	Adverse effects
Kochar 2000	Quote: "Biochemical tests were done to detect any toxic effects of the drug."	Biochemical tests were done at the end of 1 week, 2 weeks and 4 weeks post-treatment	I1: oral rifampicin 1200 mg/d I2: placebo	**Intervention** 23 participants evaluated for AEs. Quote: "The drug was well-tolerated and no side-effects were seen in any participant." **Placebo** 23 participants evaluated for AEs. Not reported
Jaffar 2006	Quote: "clinical examination, liver function tests, renal function tests"	Quote: "Before, during, and after completion of treatment"	I1: oral rifampicin 10 mg/kg/d I2: placebo	**Intervention** 46 participants evaluated for AEs. Elevation liver enzymes: 1 (2%) **Placebo** 16 participants evaluated for AEs. Not reported
Kochar 2006	Haemoglobin, leukocyte count, and liver test	Biochemical tests were done at the end of 2 week, 4 weeks and 6 weeks post-treatment	I1: oral rifampicin + omeprazole I2: placebo	**Intervention 1** 23 participants evaluated for AEs. **Intervention 2** 21 participants evaluated for AEs. Quote: "All participants tolerated the drug and placebo very well and no side effect was reported."
Layegh 2007	Not described	Azythromycin group: monthly up to 4 months	I1: azithromycin 500 mg/d I2: IMMA 60 mg/kg/d	**Intervention 1** 22 participants evaluated for AEs (35 lesions). Nausea and vomiting: 2 (9%) **Intervention 2** 27 participants evaluated for AEs (58 lesions). Myalgia: 3 (11%); Erythema: 1 (3.7%).
Adam 2009	Quote: "Complete haemogram, including haemoglobin and liver and renal function tests Participants were questioned about expected adverse effects for 3 days	Haemogram: 1 and 2 months Clinical AEs: days 5-7; 19-21; 33-35; 47-19.	I1: artesunate I2: placebo	**Intervention 1** 20 participants evaluated for AEs. **Placebo** 21 participants evaluated for AEs. Skin rash with itching: 1

Table 3. Adverse effects of oral antibiotics (*Continued*)

	(Days 5-7) following administration of the doses."			(4.7%) Quote: "There was no significant difference in biological tests (liver and renal function tests) in all the participants before and after treatment."
Ben Salah 2009	Interview, physical examination, laboratory test, evaluation for pain, standardised questionnaire for the occurrence of systemic side effects (e.g. vertigo, tinnitus). Diminished hearing was verified with audiometer Laboratory test.	Quote: "Investigators observed each participant each day that the topical creams were administered and at follow-up study visits (days 50-100-180). Clinical and laboratory evidence of side effects was determined on D10 and D20."	I1: WR 279,396 I2: placebo	**Intervention** 50 participants evaluated for AEs. Erythema at the site of application: 15 (30%); mild pain within 30 minutes of application: 7 (14 %); mild increases and decreases in hearing acuity from baseline: 14 (28%); change hearing acuity: 14 (28%) ; vertigo: 0 (0%); Increase serum creatinine: 0 (0%); Death: 0 (0%) **Placebo** 42 participants evaluated for AEs. Erythema at the site of application: 10 (24%); mild pain within 30 minutes of application: 6 (14 %); mild increases and decreases in hearing acuity from baseline: 9 (21%); change hearing acuity: 9 (21%); vertigo: 0 (0%); increase serum creatinine: 0 (0%); death: 0 (0%)
Dastgheib 2012	Quote: "Participants were interviewed and underwent laboratory tests three times"	Quote: "In Allopurinol group, the participants which were visited and received medication underwent laboratory tests three times (before, one month a2fter, and end of the treatment)	I1: azithromycin + allopurinol I2: IMMA	**Intervention 1** 36 participants evaluated for AEs. Gastrointestinal complaints and headache severe: 1 (2.7%); slight gastrointestinal complications (nausea, heartburn, and epigastric pain): 3 (8.3%) **Intervention 2** 35 participants evaluated

Table 3. Adverse effects of oral antibiotics (*Continued*)

				for AEs. Myalgia: 2 (5.7%)

AE: adverse effect; **IMMA**: intramuscular meglumine antimoniate.

Table 4. Adverse effects of topical paromomycin

Study	Method of assessment	Timing	Interventions	Adverse effects
Asilian 1995	Clinical evaluation and laboratory tests	Days 15, 45 and 105	I1: paromomycin I2: placebo	126 participants evaluated for AEs. *During treatment*: oedema, local pain, vesiculation: 1 (0.7%) *After treatment*: redness, pain, vesiculation, and inflammation: 8 (6.3%) Quote: "There were no significant differences in four laboratory test results of safety (SGOT, BUN, Hb, and WBC) between the groups either before or after treatment."
Ben Salah 1995	Clinical evaluation, physical examination, advice to participants, laboratory test: liver function, haemoglobin and white blood cell count	Days 15, 45 and 105	I1: paromomycin I2: placebo	57 participants evaluated for AEs. Quote: "A local reaction (inflammation, vesication, pain and/or red ness) was recorded for 12 participants, with no significant difference between the 2 groups." Laboratory test changes: 0 (0%)
Özgöztasi 1997	Not described	At the end of treatment (day 30) and 1 month post-treatment	I1: paromomycin + MBCL I2: oral ketoconazole	40 participants (62 lesions) evaluated for AEs Quote: "Treatment-related adverse effects were only observed in the paromomycin group. The most common side-effect was the development of irritant contact dermatitis. No subjects withdrew because of this adverse effect."

Table 4. Adverse effects of topical paromomycin (*Continued*)

Asilian 2003	Clinical evaluation	Days 15, 29, 45 and 105	I1: paromomycin I2: placebo	108 participants evaluated for AEs. Quote: "Treatment was well tolerated, and no adverse reactions to the ointment were observed or reported in either group."
Faghihi 2003	Not described	Quote "Clinical evaluation and follow-up were performed fortnightly until 1 month post treatment and then monthly until 3 months post treatment, and finally every 3 months until 1 year post treatment"	I1: paromomycin + urea I2: ILMA weekly	Not described
Shazad 2005	Not described	Week 1 and week 6 post-treatment and at 6 months after treatment was completed	I1: paromomycin + urea I2: ILMA weekly	30 participants evaluated for AEs. Cutaneous reactions (erythematosus, urticaria or lymphadenitis with pain): 1 (3%) Quote: "No systemic toxic reaction attributable to the drug was observed."
Iraji 2005	Clinical evaluation	Days 7, 14, 21 and 30	I1: paromomycin I2: placebo	30 participants evaluated for AEs. Mild contact dermatitis: 3 (10%)
Asilian 2006	Not described	Weekly during treatment and monthly for up 2 months	I1: photodynamic therapy I2: paromomycin I3: placebo	19 participants (34 lesions) evaluated for AEs. Quote: "Adverse side-effects seen in some participants in all groups were pruritus, burning, redness, discharge, oedema, and pain, but all were generally mild and tolerable."
Ben Salah 2009	Quote: "Renal toxic effects and ototoxic effects from aminoglycoside exposure were ascertained by means of serum creatinine measurements at the end	Quote: "Safety end points were assessed daily during therapy (20 days)."	I1:Paromomycin - Gentamicin I2: paromomycin Alone I3: vehicle Control	**Intervention 1**: 125 participants evaluated for AEs. Erythema: 6 (5%); local infection: 0 (0%); inflammation: 0 (0%); vesicles

Table 4. Adverse effects of topical paromomycin (*Continued*)

	of therapy (at 20 days) and participants' daily reports of tinnitus and vertigo."			mild-moderate: 31 (25%) ; mild oedema: 2 (2%); pain: 2 (2%); mild bronchitis: 5 (4%) ; paronychia: 2 (2%); superinfection: 3 (2%); upper respiratory tract infection: 0 (0%); oropharyngeal pain: 4 (3%); skin irritation: 3 (2%); tinnitus: 0 (0%); vertigo: 0 (0%); creatinine serum changes: 0 (0%) **Intervention 2**: 125 participants evaluated for AEs. Erythema: 7 (6%); local infection: 0 (0%); inflammation: 0 (0%); vesicles mild-moderate: 32 (26%); mild-moderate oedema: 3 (3%); pain: 2 (2%); bronchitis mild-moderate: 3 (3%); paronychia: 0 (0%) ; superinfection: 0 (0%); upper respiratory tract infection: 2 (2%); oropharyngeal pain: 3 (2%); skin irritation: 9 (7%); tinnitus: 0 (0%); vertigo: 0 (0%); creatinine serum changes: 0 (0%)

AE: adverse effect; **BUN**: blood urea nitrogen; **Hb**: haemoglobin; **ILMA**: intralesional meglumine antimoniate; **SGOT**: serum glutamic-oxaloacetic transaminase; **WBC**: white blood cells.

Table 5. Adverse effects of intralesional zinc sulphate

Study	Method of assessment	Timing	Interventions	Adverse effects
Sharquie 1997	Not described	Quote: "Participants were seen at 10-15 day intervals after injection, and at 6 weeks post treatment"	I1: IL 2% zinc sulphate I2: IL 7% sodium chloride I3: ILSSG 2-5 mL per lesion	19 participants evaluated for AEs. Quote: "Apart from pain at the time of injection, no appreciable side-effect was noted."

Table 5. Adverse effects of intralesional zinc sulphate (*Continued*)

Iraji 2004	Not described	Not described	I1: IL zinc sulphate I2: ILMA weekly	31 participants evaluated for AEs. Severe pain caused vasovagal shock: 2 (6.4%)
Firooz 2005	Not described	Not described	I1: IL zinc sulphate I2: ILMA weekly	36 participants evaluated for AEs. Pain: 13 (36.1%); burning at site injection: 3 (8.4%) ; itching: 3 (8.4%); inflammation: 7 (19.4%)
Maleki 2012	Not described	14, 28, 42, and 56 days after starting the treatment	I1: IL 2% zinc sulphate I2: ILMA weekly	24 participants evaluated for AEs. Quote: "The side effects seen in both groups were pain after injection and hyperpigmentation." Burning after injection and necrosis of the lesions: 24 (100%); inflammation and swelling: 3 (12.5%)

AE: adverse effect; **IL**: intralesional; **ILMA**: intralesional meglumine antimoniate; **ILSSG**: intralesional sodium stibogluconate.

Table 6. Adverse effects of intralesional hypertonic sodium chloride solution

Study	Method of assessment	Timing	Interventions	Adverse effects
Sharquie 1997	Not described	Quote: "Participants were seen at 10-15 day intervals after injection, and at 6 week post treatment"	I1: IL 2% zinc sulphate I2: IL 7% HSCS I3: ILSSG 2-5 mL per lesion	17 participants evaluated for AEs. Quote: "No side-effect other than pain at the time of injection was noted."
Sadeghian 2006b	Not described	Not described	I1: IL 5% HSCS I2: ILMA 0.5-1 mL/week	36 participants evaluated for AEs. Allergic reaction (erythema, oedema, and pruritus): 0 (0%); sporotrichoid dissemination: 3 (8.3%)
Ranawaka 2010	Not described	Quote: "Participants were seen weekly for the first three injections; fortnightly for the fourth and fifth injections; then	I1: ILSSG I2: IL 7% HSCS	67 participants evaluated for AEs. Leishmaniasis recidivans: 0 (0%) Quote: "There were no sys-

Table 6. Adverse effects of intralesional hypertonic sodium chloride solution (*Continued*)

		monthly until cure. Participants were followed-up every 3 months after cure for 18 months to assess recurrences and evidence of visceralization."		temic side effects with SSG or HS. Pain during injection was the only local side effect noted with both therapies. After healing, scarring was minimal, but postinflammatory hyperpigmentation was observed in all participants for both treatments, which faded out over 6-8 months."

AE: adverse effect; **IL**: intralesional; **ILSSG**: intralesional sodium stibogluconate; **HSCS**: hypertonic sodium chloride solution.

Table 7. Adverse effects of laser

Study	Method of assessment	Timing	Interventions	Adverse effects
Asilian 2004b	Not described	1, 3, 4, 8, 12 and 24 weeks after treatment	I1: CO_2 I2: IMMA 50 mg/kg/d	123 participants evaluated for AEs. Quote: "Complications were seen in (4) 4.5% of participants and included hyperpigmentation, persistent redness." Hypertonic scars: 5 (4%)
Shamsi Meymandi 2011	Quote: "Follow-up was performed and any side-effects were recorded."	Quote: "Follow-up evaluation was performed by clinical assessment of treated lesions at weeks 2, 6, 12 and 16."	I1: CO_2 I2: cryotherapy + MA	80 participants (95 lesions) evaluated for AEs. Hyperpigmentation + trivial scar: 20 (25%); atrophic scar: 7 (8.75%) ; hypertrophic scar: 1 (1.25%); sporotrichoid: 1 (1.25%); raised papular lesions: 1 (1.25%) ; persistent erythema: 3 (3.75%); hypopigmentation + trivial scar: 4 (5%)
Nilforoushzadeh 2014a	Not described	Quote: "Participants were followed in the first, third, and sixth months after treatment with the final evaluation in the sixth month."	I1: ablative CO_2 laser I2: fractional CO_2 laser	**Intervention 1**: 30 participants evaluated for AEs. Erythema: 2 (6.7%) **Intervention 2**: 30 participants evaluated

Table 7. Adverse effects of laser (*Continued*)

				for AEs. Erythema: 4 (13.3%)

AE: adverse effect; **IMMA**: intramuscular meglumine antimoniate; **MA**: meglumine antimoniate.

Table 8. Adverse effects of cryotherapy

Study	Method of assessment	Timing	Interventions	Adverse effects
Asilian 2004a	Not described	Fortnightly until 6 months post-treatment and 2 weeks and 4 weeks post-treatment	I1: cryotherapy + ILMA I2: cryotherapy alone I3: ILMA alone	**Intervention 1**: 100 participants evaluated for AEs. Postinflammatory hypopigmentation: 5 (5%) **Intervention 2**: 200 participants evaluated for AEs. Postinflammatory hypopigmentation: 10 (5%)
Salmanpour 2006	Not described	Not described	I1: ILMA alone I2: cryotherapy alone I3: cryotherapy + ILMA	I**ntervention 2**: 20 participants evaluated for AEs. Erythema and oedema of the lesions and perilesional area: (28%) **Intervention 3**: 20 participants evaluated for AEs. Erythema and oedema of the lesions and perilesional area: (33%) Quote: "There were no serious side-effects in any of the treatment groups"
Layegh 2009	Not described	Quote: "Weekly for up to six weeks of treatment and six months after."	I1: cryotherapy I2: ILMA	36 participants evaluated for AEs. Hypopigmentation: 2 (5.5%); hyperpigmentation: 7 (19.4%). Quote: "the most common adverse reactions were erythema and oedema of the treated site, which appeared during the initial hours of

Table 8. Adverse effects of cryotherapy (*Continued*)

				treatment, and blistering of the treatment site, which became evident 1-2 days after treatment and responded well to local treatment."
Shamsi Meymandi 2011	Quote: "Follow-up was performed and any side-effects were recorded."	Quote: "Follow-up evaluation was performed by clinical assessment of treated lesions at weeks 2, 6, 12 and 16."	I1: CO_2 I2: cryotherapy + MA	80 participants (95 lesions) evaluated for AEs. Hyperpigmentation + trivial scar: 15 (18.7%); atrophic scar: 6 (7.5%) ; hypertrophic scar: 0 (0%); sporotrichoid: 0 (0%); raised papular lesions: 0 (0%); persistent erythema: 0 (0%); hypopigmentation + trivial scar: 15 (18.8%)
Jowkar 2012	Quote: "During these visits the healing process of the ulcer, change of diameter and induration of lesions and complications were assessed."	Quote: "The participants were evaluated every 2 weeks up to 12 weeks."	I1: cryotherapy + 3% salicylic + 3% sodium nitrite I2: cryotherapy + 3% salicylic + placebo	**Intervention 1**: 36 participants evaluated for AEs. Erythema, a burning sensation and skin irritation: 7 (19.4%) **Intervention 2**: 27 participants evaluated for AEs. Erythema, a burning sensation and skin irritation: 1 (3.7%)

AE: adverse effect; **ILMA**: intralesional meglumine antimoniate; **MA**: meglumine antimoniate.

Table 9. Adverse effects of thermotherapy

Study	Method of assessment	Timing	Interventions	Adverse effects
Reithinger 2005	Quote: "The occurrence of adverse effects was evaluated blindly by means of participant interviews and physical examinations."	Quote: "The occurrence of adverse effects was evaluated … during follow-up visits."	I1: ILSSG 2-5 mL per lesion I2: IMSSG 20 mg/kg I3: thermotherapy	138-108 participants evaluated for AEs. Secondary infections: 8 (5.7%). Quote: "The original CL ulcer often increased in size immediately after and up to 2 weeks after treatment."

Table 9. Adverse effects of thermotherapy (*Continued*)

Sadeghian 2007	Quote: "Appearance of lesions at subsequent follow-up visits and occurrence of unwanted side-effects were also recorded on the form. "	Weekly 4 weeks and monthly up to 6 months	I1: thermotherapy I2: ILMA weekly	57 participants (83 lesions) evaluated for AEs. Satellite lesions: 1 (1.7%)
Aronson 2010	Quote: "Interview, physical examination, laboratory testing (complete blood count, creatine phosphokinase, amylase, lipase, complete metabolic profile), and electrocardiograms."	Quote: "Daily for the first 10 days and follow-up at 2, 6, and 12-24 months post treatment"	I1: thermotherapy I2: ILSSG	27 participants evaluated for AEs. Serious AE: 4 (15%); ECG changes: 10 (37%) ; abdominal discomfort: 1 (4%); wound infection: 5 (19%); musculoskeletal: 5 (19%); headache: 3 (11%) ; fatigue: 5 (19%); rash: 1 (4%); blister reaction: 25 (93%); erythema: 7 (26%) ; oozing: 21 (78%)
Safi 2012	Quote: "The occurrences of adverse effects were evaluated by means of participant interviews and physical examinations during follow-up visits."	Quote: "During treatment, all participants were then followed for four visits at weekly intervals … After initial treatment, all participants were scheduled for four subsequent follow-up visits: 10 days after baseline and 1-month, 2 months and 6 months after treatment."	I1: thermotherapy I2: ILMA weekly	189 participants evaluated for AEs Not reported
Bumb 2013	Not described	Not described	I1: radiofrequency heat treatment I2: ILSSG	Quote: "RFHT was cosmetically acceptable because it was associated with less scarring and hyperpigmentation compared with intralesional SSG injections."
Jebran 2014	Quote: "In case of clinical signs for a superinfection, a smear was taken, Gram stained and microscopically evaluated for the presence of bacteria and/or fungi."	Quote: "Adverse events such as bacterial or fungal superinfections of the wounds, the formation or scars and the rate of re-ulcerations were monitored during the treatment and follow-up period."	I1: electrocauterisation + DAC N-055. I2: electrocauterisation + placebo.	**Intervention 1**: 38 participants evaluated for AEs. Bacterial and fungal superinfections: 3 (8.0%); Keloïd formation: 2 (5%) **Intervention 2**: 32 participants evaluated for AEs.

Table 9. Adverse effects of thermotherapy (*Continued*)

				Bacterial and fungal superinfections: 3 (9.0%); Keloïd formation: 2 (6%)

AE: adverse effect; CL: cutaneous leishmaniasis; **ILMA**: intralesional meglumine antimoniate; **ILSSG**: intralesional sodium stibogluconate; **IMSSG**: intramuscular sodium stibogluconate.

APPENDICES

Appendix 1. Cochrane Skin Specialised Register/CRS

(solitary or limited or "old world" or localised or diffuse or cutaneous) AND (leishmania*))

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Leishmaniasis, Cutaneous] this term only
#2 (solitary or limited or localised or old world or diffuse or cutaneous):ti,ab,kw
#3 leishmania*:ti,ab,kw
#4 #2 and #3
#5 #1 or #4

Appendix 3. MEDLINE (Ovid) search strategy

1. leishmania$.mp.
2. (solitary or limited or old world or localised or diffuse or cutaneous).mp.
3. 1 and 2
4. Leishmaniasis, Cutaneous/
5. 3 or 4
6. randomised controlled trial.pt.
7. controlled clinical trial.pt.
8. randomized.ab.
9. placebo.ab.
10. clinical trials as topic.sh.
11. randomly.ab.
12. trial.ti.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp animals/ not humans.sh.
15. 13 not 14
16. 5 and 15

[Lines 6-15: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. skin leishmaniasis/
2. leishmania$.mp.
3. (solitary or limited or old world or localised or diffuse or cutaneous).mp.
4. 2 and 3
5. 1 or 4
6. crossover procedure.sh.
7. double-blind procedure.sh.
8. single-blind procedure.sh.
9. (crossover$ or cross over$).tw.
10. placebo$.tw.
11. (doubl$ adj blind$).tw.
12. allocat$.tw.
13. trial.ti.
14. randomised controlled trial.sh.
15. random$.tw.
16. or/6-15
17. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
18. human/ or normal human/
19. 17 and 18
20. 17 not 19
21. 16 not 20
22. 5 and 21

Appendix 5. LILACS search strategy

(cutaneous and leishmaniasis) or (cutanea and leishmaniosis) or (old and world and leishman$) or ((solitar$ or locali$ or limited) and leishman$)
In LILACS we searched using the above terms and the Controlled clinical trials topic-specific query filter.

Appendix 6. Adverse effects search strategy in MEDLINE (Ovid)

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. adverse event$.mp.
3. adverse effect$.mp.
4. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5. exp hypersensitivity, immediate/ or exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
6. side effect$.mp.
7. exp Poisoning/
8. exp Substance-Related Disorders/
9. exp Drug Toxicity/
10. exp Abnormalities, Drug-Induced/
11. exp Teratogens/
12. exp Mutagens/
13. exp Carcinogens/
14. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
15. photoallergic reaction$.mp.
16. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
17. sensiti?ation.mp.

18. fetal abnormalit$.mp.
19. exp Drug Monitoring/
20. harm$ effect$.mp.
21. (toxic effect$ or drug effect$).mp.
22. undesirable effect$.mp.
23. (safe or safety).mp.
24. toxicity.mp.
25. noxious.mp.
26. serious reaction$.mp.
27. complication$.mp.
28. tolerability.mp.
29. (adverse adj3 (effect$ or reaction$ or event$ or outcome$)).mp.
30. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
31. *Itraconazole/
32. *Ketoconazole/
33. *Paromomycin/
34. *Allopurinol/
35. *Amphotericin B/
36. aminosidine sulphate.mp.
37. pentamidine isethionate.mp. or *Pentamidine/
38. *Aminoglycosides/
39. miltefosine.mp.
40. thermotherapy.mp.
41. *Granulocyte-Macrophage Colony-Stimulating Factor/
42. *Mefloquine/
43. *Immunotherapy/
44. *BCG Vaccine/ or bacillus calmette guerin.mp.
45. *Meglumine/
46. sodium stibogluconate.mp.
47. or/1-30
48. or/31-46
49. 47 and 48
50. (solitary or limited or old world or localised or diffuse or cutaneous).mp.
51. leishmania$.mp.
52. 50 and 51
53. exp Leishmaniasis, Cutaneous/
54. 52 or 53
55. 49 and 54

WHAT'S NEW

Last assessed as up-to-date: 17 November 2016.

Date	Event	Description
15 November 2017	New citation required and conclusions have changed	The incorporation of GRADE into this updated review means that compared with the previous version of the review, we are now less certain of the evidence on which we base our conclusions

(*Continued*)

15 November 2017	New search has been performed	The corresponding author is now Julio Heras-Mosteiro. Of the authors from the first review, only Mariona Pinart and Ludovic Reitez have participated in this update. There are seven new authors: Begoña Monge-Maillo, Patricia Lopez-Pereira, Emely Garcia-Carrasco, Pedro Campuzano Cuadrado, Rogelio López-Vélez, Irene Mendez Roman, and Ana Royuela. We have not searched CINAHL for this update

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2008

Date	Event	Description
17 May 2012	Amended	The lead author's contact details have been edited.
18 April 2008	Amended	Converted to new review format.
21 December 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JHM was the contact person with the editorial base; he coordinated contributions from the co-authors and wrote the final draft of the review.

PLP, EGC, BMM, and JHM screened papers against eligibility criteria.

PLP obtained data on ongoing and unpublished studies.

MP, JHM, and PLP appraised the quality of papers.

MP, PLP, EGC, PC, and JHM extracted data for the review and sought additional information about papers.

JHM, PLP, EGC, BMM, MP, RLV, and PC entered data into RevMan.

AR, JHM, BMM, and RLV analysed and interpreted data.

AR and JHM worked on the Methods sections.

BMM and RLV drafted the clinical sections of the Background and responded to the clinical comments of the referees.

AR and JHM responded to the methodology and statistics comments of the referees.

IMR was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes were relevant to consumers.

JHM Is the guarantor of the update.

Disclaimer

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Skin Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DECLARATIONS OF INTEREST

Julio Heras-Mosteiro: none known.

Begoña Monge-Maillo: none known.

Mariona Pinart: none known.

Patricia Lopez Pereira: none known.

Emely Garcia-Carrasco: none known.

Pedro Campuzano Cuadrado: none known.

Ana Royuela: none known.

Irene Mendez Roman: none known.

Rogelio López-Vélez: none known.

Iraj Sharifi, one of the clinical referees, was a co-author on the included studies Khatami 2012 and Daie Parizi 2015.

SOURCES OF SUPPORT

Internal sources

- Cochrane Madrid. Hospital Universitario Ramón y Cajal. Carretera de Colmenar Km 3.1 Madrid 28034, Spain.
Methodology support

External sources

- Office of Control of Neglected Tropical Diseases (WHO/CDS/NTD/IDM), Communicable Disease Cluster, World Health Organization, Switzerland.
- The National Institute for Health Research (NIHR), UK.
The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the protocol and the current update

For differences between other published versions, please see the 'Differences between protocol and review' section within the original publications.

The protocol of this review was first entitled 'Interventions for solitary or limited cutaneous leishmaniasis'. However, the clinical subject was split into two reviews. The title of this review was amended to 'Interventions for Old World cutaneous leishmaniasis' (Gonzalez 2008). A Cochrane Review entitled 'Interventions for American cutaneous and mucocutaneous leishmaniasis' was also published (González 2009). This decision stemmed from the fact that the *Leishmania* species in the geographical areas involving the Old World differ from the ones affecting the New World. Due to the title change and also in response to referee comments, we modified the Background considerably. Also, our Objectives are now focused on the localised form of cutaneous leishmaniasis (CL) in the Old World rather than the solitary or limited form of CL.

Compared with the published protocol, there were some alterations in the tasks completed by review authors: JHM, PC, PLP, BMM, or EGM checked the titles and abstracts identified from the searches rather than UG and LR; BMM and EGM obtained the full text study for independent assessment when it was unclear if a study was relevant rather than NH and WF. Any disagreements were discussed with AR rather than UG, and MP, LR, JHM, or PLP carried out data extraction rather than MC, NH, or UG. This is because they are no longer authors of the updated version of the systematic review.

Types of participants: we modified this to 'immunocompetent people who have localised OWCL' in accordance with the aforementioned changes.

Types of interventions: we added a list of interventions in response to past referees' comments and to ease readability. We also changed the scope of the interventions from 'all doses and regimens of therapeutic interventions (including topical, systemic, and non-pharmacological treatments) for solitary or localised cutaneous leishmaniasis' to interventions for Old World cutaneous leishmaniasis, in accordance with the aforementioned changes. We also replaced placebo as a comparison with vehicle because a topical comparison in an RCT should correctly be termed a vehicle rather than a placebo, as the vehicle in a dermatologic drug product enhances delivery and efficacy of the active compound.

Types of outcome measures: also following advice from past referees, we clarified the primary outcomes, and we added a phrase to define emergence of resistance to the tertiary outcomes. We also added a second primary outcome following advice from past referees: 'Percentage of participants with a complete cure after the end of treatment'. We omitted the term "around 3 months" in our primary outcome because it was not precise. We decided not to limit both primary outcomes by length of follow-up since the studies reporting these outcomes prior to 3 months of follow-up may report interesting clinical information.

Electronic searches: for the update of this review, we did not search the CINAHL database. This database focuses on nursing and allied health literature, content not particularly relevant to our review topic. We did not search the Cochrane Database of Abstracts of Reviews of Effectiveness (DARE) or MedCarib. DARE contains information on systematic reviews, and the MedCarib database is focused on the Caribbean region. We did not update our search of the American College of Physicians (ACP) journal club. We considered these databases unlikely to yield further references to relevant trials, based on our search results from the previous edition of this review. For the update of this review, we searched the following databases, which we considered relevant for the identification of ongoing trials.

- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources > Unpublished literature: although planned in the protocol, we did not contact Centro Dermatológico Federico Lleras Acosta, Colombia, because the Leishmania species in Colombia differ from the ones affecting the Old World. Instead we wrote to National Programme Managers, General Coordinators, Directors, Clinicians, and WHO-EMRO Regional Officers of endemic countries in order to find relevant studies. Although planned in the protocol, we did not update our search of the conference proceedings. Conference proceedings were considered unlikely to yield further references to relevant trials, based on our search results from the previous edition of this review.

Searching other resources >Adverse effects: although planned in the protocol, we did not contact adverse reaction-reporting bodies. The review team considered it preferable and more efficient to search MEDLINE for adverse or side effects using the search strategy in Appendix 6.

Data collection and analysis: we updated some of the methods from what we had planned in the protocol, which was published many years ago.

Measures of treatment effect: we planned in the protocol to express results as number needed to treat where appropriate, for a range of plausible control event rates. We did not do this because the great variety found among different participant populations made it impossible to obtain a range of plausible control event rates. As the *Cochrane Handbook for Systematic Reviews of Interventions* says, "Risk

ratios and relative risk reductions remain crucial because relative effect tends to be substantially more stable across risk groups than does absolute benefit" (Higgins 2011). We decided to describe hazard ratios (HR) for time-to-event outcomes data when the studies did. We have followed the recommendation, "Conducting a meta-analysis using summary information from published papers or trial reports is often problematic as the most appropriate summary statistics are typically not presented", and we have not calculated them because we did not have enough information from studies (Higgins 2011).

Assessment of heterogeneity: In the protocol, we had not planned how to assess clinical heterogeneity, but we recorded this in the update. Also, we had planned to explore reasons for heterogeneity using sensitivity and/or subgroup analyses, but we did not do this because there were too few studies to perform a sensitivity and/or subgroup analyses.

Data synthesis: Although not planned in the protocol, we decided to only undertake data synthesis if we were able to identify two or more studies investigating similar treatments and reporting data that could be pooled. We did this because the previous systematic review chose this approach, and we consider that defining a minimum number of studies is necessary to be informative in the data synthesis phase. Where it was not possible to perform a meta-analysis, we summarised the data for each trial.

We decided not to meta-analyse studies when I^2 was above 75% and effect estimates crossed the no-effect line. However, we did meta-analyse studies with a high I^2 if none of the confidence intervals crossed the line of no effect, and we discuss the reasons for such significant heterogeneity.

Although not planned in the protocol, where an ITT was not stated, we used the numbers originally randomised to the groups in order to calculate effect estimates. We did this to avoid overestimating the effect of the intervention (to reduce attrition bias). Concerning the losses to follow-up, it was not always possible to determine within which arm the losses occurred, and therefore perform ITT analyses.

In the protocol, we had planned that for each trial, we would report other commonly reported outcomes in a table with the cure rates at follow-up, based on the reported clinical, microbiological, histopathological, or polymerase chain reaction (PCR) results. We did not do this because there were few studies assessing all outcomes. In our manuscript we stated that: "Two RCTs reported results where *Leishmania* was detected by parasitological diagnostic methods (e.g. PCR or culture, positive smears) (Jaffary 2014A; Jebran 2014). No studies reported emergence of resistance.."

Unit of analysis issues: in the protocol we planned to list quasi-randomised and non-randomised controlled studies but not discuss them further; however, in the review, we decided to focus only on RCTs, as in our inclusion criteria.

Dealing with missing data: in the protocol, we did not specify how to deal with missing data; therefore, in this review, we specified that we would treat missing data as treatment failures.

Reporting bias: in the protocol we did not specify if we would investigate reporting bias. In the review we planned to investigate it but was unable to due to low number of studies included in the meta-analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Infective Agents [therapeutic use]; Antiprotozoal Agents [therapeutic use]; Complementary Therapies; Cryotherapy; Hot Temperature [therapeutic use]; Laser Therapy; Leishmania major; Leishmania tropica; Leishmaniasis, Cutaneous [*therapy]; Photochemotherapy; Randomized Controlled Trials as Topic

MeSH check words

Animals; Humans