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Interventions for hand eczema (Review)

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[Intervention Review]

Interventions for hand eczema

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ABSTRACT

Background

Hand eczema is an inflammation of the skin of the hands that tends to run a chronic, relapsing course. This common condition is often associated with itch, social stigma, and impairment in employment. Many different interventions of unknown effectiveness are used to treat hand eczema.

Objectives

To assess the effects of topical and systemic interventions for hand eczema in adults and children.

Search methods

We searched the following up to April 2018: Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, AMED, LILACS, GREAT, and four trials registries. We checked the reference lists of included studies for further references to relevant trials.

Selection criteria

We included randomised controlled trials (RCTs) that compared interventions for hand eczema, regardless of hand eczema type and other affected sites, versus no treatment, placebo, vehicle, or active treatments.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Primary outcomes were participant- and investigator-rated good/excellent control of symptoms, and adverse events.

Main results

We included 60 RCTs, conducted in secondary care (5469 participants with mild to severe chronic hand eczema). Most participants were over 18 years old. The duration of treatment was short, generally up to four months. Only 24 studies included a follow-up period. Clinical heterogeneity in treatments and outcome measures was evident. Few studies performed head-to-head comparisons of different interventions. Risk of bias varied considerably, with only five studies at low risk in all domains. Twenty-two studies were industry-funded.

Eighteen trials studied topical corticosteroids or calcineurin inhibitors; 10 studies, phototherapy; three studies, systemic immunosuppressives; and five studies, oral retinoids. Most studies compared an active intervention against no treatment, variants of the same medication, or placebo (or vehicle). Below, we present results from the main comparisons.

Corticosteroid creams/ointments: when assessed 15 days after the start of treatment, clobetasol propionate 0.05% foam probably improves participant-rated control of symptoms compared to vehicle (risk ratio (RR) 2.32, 95% confidence interval (CI) 1.38 to 3.91; number needed to treat for an additional beneficial outcome (NNTB) 3, 95% CI 2 to 8; 1 study, 125 participants); the effect of clobetasol compared to vehicle for investigator-rated improvement is less clear (RR 1.43, 95% CI 0.86 to 2.40). More participants had at least one adverse event with clobetasol (11/62 versus 5/63; RR 2.24, 95% CI 0.82 to 6.06), including application site burning/pruritus. This evidence was rated as moderate certainty.

When assessed 36 weeks after the start of treatment, mometasone furoate cream used thrice weekly may slightly improve investigator-rated symptom control compared to twice weekly (RR 1.23, 95% CI 0.94 to 1.61; 1 study, 72 participants) after remission is reached. Participant-rated symptoms were not measured. Some mild atrophy was reported in both groups (RR 1.76, 95% CI 0.45 to 6.83; 5/35 versus 3/37). This evidence was rated as low certainty.

Irradiation with ultraviolet (UV) light: local combination ultraviolet light therapy (PUVA) may lead to improvement in investigator-rated symptom control when compared to local narrow-band UVB after 12 weeks of treatment (RR 0.50, 95% CI 0.22 to 1.16; 1 study, 60 participants). However, the 95% CI indicates that PUVA might make little or no difference. Participant-rated symptoms were not measured. Adverse events (mainly erythema) were reported by 9/30 participants in the narrow-band UVB group versus none in the PUVA group. This evidence was rated as moderate certainty.

Topical calcineurin inhibitors: tacrolimus 0.1% over two weeks probably improves investigator-rated symptom control measured after three weeks compared to vehicle (14/14 tacrolimus versus 0/14 vehicle; 1 study). Participant-rated symptoms were not measured. Four of 14 people in the tacrolimus group versus zero in the vehicle group had well-tolerated application site burning/itching.

A within-participant study in 16 participants compared 0.1% tacrolimus to 0.1% mometasone furoate but did not measure investigator- or participant-rated symptoms. Both treatments were well tolerated when assessed at two weeks during four weeks of treatment.

Evidence from these studies was rated as moderate certainty.

Oral interventions: oral cyclosporin 3 mg/kg/d probably slightly improves investigator-rated (RR 1.88, 95% CI 0.88 to 3.99; 1 study, 34 participants) or participant-rated (RR 1.25, 95% CI 0.69 to 2.27) control of symptoms compared to topical betamethasone dipropionate 0.05% after six weeks of treatment. The risk of adverse events such as dizziness was similar between groups (up to 36 weeks; RR 1.22, 95% CI 0.80 to 1.86, n = 55; 15/27 betamethasone versus 19/28 cyclosporin). The evidence was rated as moderate certainty.

Alitretinoin 10 mg improves investigator-rated symptom control compared with placebo (RR 1.58, 95% CI 1.20 to 2.07; NNTB 11, 95% CI 6.3 to 26.5; 2 studies, n = 781) and alitretinoin 30 mg also improves this outcome compared with placebo (RR 2.75, 95% CI 2.20 to 3.43; NNTB 4, 95% CI 3 to 5; 2 studies, n = 1210). Similar results were found for participant-rated symptom control: alitretinoin 10 mg RR 1.73 (95% CI 1.25 to 2.40) and 30 mg RR 2.75 (95% CI 2.18 to 3.48). Evidence was rated as high certainty. The number of adverse events (including headache) probably did not differ between alitretinoin 10 mg and placebo (RR 1.01, 95% CI 0.66 to 1.55; 1 study, n = 158; moderate-certainty evidence), but the risk of headache increased with alitretinoin 30 mg (RR 3.43, 95% CI 2.45 to 4.81; 2 studies, n = 1210; high-certainty evidence). Outcomes were assessed between 48 and 72 weeks.

Authors' conclusions

Most findings were from single studies with low precision, so they should be interpreted with caution. Topical corticosteroids and UV phototherapy were two of the major standard treatments, but evidence is insufficient to support one specific treatment over another. The effect of topical calcineurin inhibitors is not certain. Alitretinoin is more effective than placebo in controlling symptoms, but advantages over other treatments need evaluating.

Well-designed and well-reported, long-term (more than three months), head-to-head studies comparing different treatments are needed. Consensus is required regarding the definition of hand eczema and its subtypes, and a standard severity scale should be established.

The main limitation was heterogeneity between studies. Small sample size impacted our ability to detect differences between treatments.

PLAIN LANGUAGE SUMMARY

Treatments for hand eczema

Review question

We reviewed evidence on the effects of topical and systemic (oral or injected medicines that work throughout the entire body) treatments for hand eczema when compared against placebo (an identical but inactive treatment), no treatment, vehicle (inactive ingredients that help deliver an active treatment), or another treatment. We included 60 randomised trials (5469 participants) published up to April 2018.

Background

Hand eczema is an inflammation of the skin of the hands that can be caused by contact allergens (i.e. substances that cause an allergic reaction) such as rubber chemicals, but other external factors (e.g. irritants such as water or detergents) and atopic predisposition are often important triggers. Hand eczema can cause a reduction in quality of life leading to many work-related problems. Various types of hand eczema exist, and different topical (creams, ointments, or lotions) and systemic treatments with unknown effectiveness can be used.

Study characteristics

Most participants were hospital outpatients over 18 years of age with mild to severe chronic hand eczema. Treatment was usually given for up to four months, and outcomes were mainly assessed after treatment. A large variety of treatments were studied and compared to no treatment, variants of the same medication, placebo, or vehicle. Twenty-two studies were funded by pharmaceutical companies.

Key results

Limited data are available to support the best way of managing hand eczema due to varying study quality and inability to pool data from studies with similar interventions. Corticosteroid creams/ointments and phototherapy (irradiation with UV light) are the major treatment options, although comparisons between these options are lacking. Below, we present results for the main comparisons of interest.

Corticosteroid creams/ointments: clobetasol propionate foam probably increases participant-rated good/excellent control of hand eczema when compared to vehicle (516 versus 222 per 1000), but the difference between groups was less clear for investigator-rated control, and more adverse events were reported with clobetasol propionate (178 versus 79 per 1000) (all based on moderate-certainty evidence).

Mometasone furoate cream used thrice weekly may slightly improve investigator-rated good/excellent control compared to twice weekly treatment, and participant-rated control was not measured. Mild skin thinning occurred in both groups, but cases were few (all based on low-certainty evidence).

Irradiation with UV light: various types of irradiation (i.e. exposure to radiation) were compared. Local PUVA may improve investigator-rated good/excellent control compared to narrow-band UVB (400 versus 200 per 1000); however, we are uncertain of this finding because results also show that local PUVA may make little or no difference. Participant-rated symptoms were not measured. Nine out of 30 participants in the narrow-band UVB group reported adverse events (mainly redness) compared to none in the PUVA group (all based on moderate-certainty evidence).

Topical calcineurin inhibitors: people receiving tacrolimus are probably more likely to achieve improved investigator-rated good/excellent symptom control compared to those given vehicle (14/14 participants with tacrolimus compared to none with vehicle), but participant-rated control of symptoms was not measured. Four of 14 people in the tacrolimus group versus zero in the vehicle group had well-tolerated application site burning/itching. One small study compared tacrolimus to mometasone furoate, which were both well tolerated, but did not measure investigator- or participant-rated control (all based on moderate-certainty evidence).

Oral interventions: oral immunosuppressant (a drug that hinders the immune response) cyclosporin probably slightly improves investigator- or participant-rated control of good/excellent symptoms compared to topical betamethasone cream (a corticosteroid). The risk of adverse events such as dizziness was similar between groups (all based on moderate-certainty evidence).

The oral vitamin A derivative (retinoid) alitretinoin (10 mg) achieved investigator-rated good/excellent symptom control in 307 compared to 194 participants per 1000 with placebo, and alitretinoin 30 mg achieved investigator-rated control in 432 compared to 157 participants per 1000 with placebo. Similar results were shown for participant-rated control (high-certainty evidence). When the dosage of alitretinoin was increased to 30 mg, risk of headache was higher compared to placebo (74 versus 251 per 1000; high-certainty evidence), but this probably does not differ between alitretinoin 10 mg and placebo (based on moderate-certainty evidence).

Quality of the evidence

The quality of evidence was mainly moderate, with most analyses based on single studies that had small sample sizes; therefore, some results should be interpreted with care.

Summary of findings for the main comparison. Corticosteroid creams/ointments: clobetasol propionate foam compared to vehicle foam for hand eczema

Corticosteroid creams/ointments: clobetasol propionate foam compared to vehicle foam for hand eczema

Patient or population: participants with moderate to severe hand eczema
Setting: secondary care with outpatients in Northern America
Intervention: clobetasol propionate 0.05% foam twice a day for 14 days
Comparison: vehicle/placebo foam twice a day for 14 days

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk[a]	Corresponding risk				
	Risk with vehicle foam	Risk with clobetasol propionate foam				
Primary: investigator-rated good/excellent control of symptoms Follow-up: day 15	**Study population**		**RR 1.43** (0.86 to 2.40)	125 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	-
	270 per 1000	**386 per 1000** (232 to 648)				
Primary: participants with self-rated good/excellent control of symptoms Follow-up: day 15	**Study population**		**RR 2.32** (1.38 to 3.91)	125 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	NNTB 3 (95% CI 2 to 8)
	222 per 1000	**516 per 1000** (307 to 869)				
Primary: adverse events - at least 1 adverse event Follow-up: day 15	**Study population**		**RR 2.24** (0.82 to 6.06)	125 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	-
	79 per 1000	**178 per 1000** (65 to 481)				
Primary: adverse events - any adverse event treatment-related (application site pruritus) Follow-up: day 15	**Study population**		**RR 1.02** (0.06 to 15.89)	125 (1 RCT)	⊕⊕⊕⊖ Moderate[d]	-
	16 per 1000	**16 per 1000** (1 to 252)				
Secondary: reduction in severity, participant-rated scoring Follow-up: day 15	**Study population**		**RR 1.57** (1.21 to 2.04)	125 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	NNTB 3 (95% CI 2 to 7)
	524 per 1000	**822 per 1000** (634 to 1000)				

Secondary: reduction in severity, investigator-rated scoring - improvement at least 2 grades Follow-up: day 15	**Study population**		**RR 1.47** (0.90 to 2.39)	125 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	-
	286 per 1000	**420 per 1000** (257 to 683)				

*__The risk in the intervention group__ (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; NNTB: number needed to treat for an additional beneficial outcome; RCT: randomised controlled trial; RR: risk ratio.

Kircik 2013

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The assumed risk is the mean control group risk.
[b]Downgraded by one level to moderate-certainty evidence for imprecision. Small sample size and small number of events.
[c]Downgraded by one level to moderate-certainty evidence for imprecision. Wide confidence interval with small sample size and small number of events.
[d]Downgraded by one level to moderate-certainty evidence for imprecision. Summary effect contains both appreciable benefit and harm; wide confidence interval with small sample size and small number of events.

Summary of findings 2. Corticosteroid creams/ointments: mometasone furoate cream 3 times/week versus 2 times/week for hand eczema

Corticosteroid creams/ointments: mometasone furoate cream thrice a week versus twice a week

Patient or population: people (all patch-tested) with hand eczema > 6 months that had cleared upon daily treatment for a maximum of 9 weeks with mometasone furoate cream
Settings: secondary care with outpatients from hospitals in Denmark
Intervention: mometasone furoate cream 3 times/week up to 36 weeks

Comparision: mometasone furoate cream 2 times/week up to 36 weeks

Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk[a]	**Corresponding risk**				

	Risk with mometasone furoatetwice a week	Risk with mometasone furoate thrice a week				
Primary: investigator-rated good/excellent control of symptoms Follow-up: 36 weeks	**Study population**		**RR 1.23** (0.94 to 1.61)	72 (1 RCT)	⊕⊕⊝⊝ Low[b]	-
	676 per 1000	**831 per 1000** (635 to 1000)				
Primary: participant-rated good/excellent control of symptoms Not measured	See comment	See comment	Not estimable	-	See comment	No data available
Primary: adverse events Follow-up: 36 weeks	**Study population**		**RR 1.76** (0.45 to 6.83)	72 (1 RCT)	⊕⊕⊝⊝ Low[c]	-
	81 per 1000	**143 per 1000** (36 to 554)				
Secondary: investigator-rated reduction in severity Not measured	See comment	See comment	Not estimable	-	See comment	No data available

*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; RCT: randomised controlled trial; RR: risk ratio.

Veien 1999

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

[a]The assumed risk is the mean control group risk.
[b]Downgraded by two levels to low-certainty evidence. Imprecision downgraded by one level: the event number was small as was the sample size. Downgraded one level for risk of bias, given the high risk of detection and performance bias.
[c]Downgraded by two levels to low-certainty evidence. Imprecision downgraded by one level: the summary effect contains both appreciable benefit and harm; sample size was small as was the event rate. Downgraded one level for risk of bias, given the high risk of detection and performance bias.

Summary of findings 3. Irradiation with UV light: local narrow-band UVB compared to local PUVA for hand eczema

Irradiation with UV light: local narrow-band UVB compared to local PUVA for hand eczema

Patient or population: people with hand eczema unresponsive to clobetasol propionate
Setting: secondary care with outpatients in the United Kingdom.
Intervention: local narrow-band UVB twice weekly for 12 weeks
Comparison: immersion PUVA twice weekly for 12 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk[a]	Corresponding risk				
	Risk with local PUVA	Risk with local narrow-band UVB				
Primary: investigator-rated good/excellent control of symptoms Follow-up: 12 weeks	**Study population**		**RR 0.50** (0.22 to 1.16)	60 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	-
	400 per 1000	**200 per 1000** (88 to 464)				
Primary: participant-rated good/excellent control of symptoms Not measured	See comment	See comment	Unable to estimate treatment effect	-	See comment	No data reported
Primary: adverse events - reported adverse events, mainly erythema Follow-up: 12 weeks	See comment	See comment	**RR 19.00** (1.16 to 312.42)	60 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	**PUVA:** No adverse events reported (0/30) **Narrow-band UVB:** 9 out of 30 participants reported an adverse event, mainly erythema Fisher's exact test P = 0.0019
Secondary: investigator-rated reduction in severity in mTLSS[d] Follow-up: 12 weeks	-	-	Unable to estimate treatment effect	43 (1 RCT)	⊕⊕⊕⊖ Moderate[e]	**Reduction in mTLSS PUVA:** Median mTLSS of 8.5 (range 0 to 16) and 8 (range 3 to 15) for the left and right hand,

to a median mTLSS 3 (range 0 to 13) and 3 (range 0 to 14) (n = 23)

Reduction mTLSS local narrow-band UVB group:

Median mTLSS of 7 (range 0 to 16) and 8.5 (range 1 to 15) to a median mTLSS5 (range 0 to 11) and 4.5 (range 0 to 11) (n = 20)

*__The risk in the intervention group__ (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; mTLSS: modified total lesion symptom score; PUVA: oral psoralen combined with UVA; RCT: randomised controlled trial; RR: risk ratio; UV: ultraviolet.

2015

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The assumed risk is the mean control group risk.
[b]Downgraded by one level to moderate-certainty evidence for imprecision. Small sample size, small number of events, and high dropout rate.
[c]Downgraded by one level to moderate-certainty evidence for imprecision. Wide confidence interval with small sample size, small number of events, and high dropout rate.
[d]The Modified Total Lesion Symptom Score (mTLSS) is the sum of seven items (erythema, oedema, vesiculation, scaling, lichenification/hyperkeratosis, fissures, and pruritus/pain) scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). A high mTLSS represents severe hand eczema.
[e]Downgraded by one level to moderate-certainty evidence for imprecision. Small sample size based on single study.

Summary of findings 4. Topical calcineurin inhibitors: tacrolimus 0.1% ointment compared to mometasone furoate ointment for vesicular hand eczema

Topical calcineurin inhibitors: tacrolimus 0.1% ointment compared to mometasone furoate ointment for vesicular hand eczema

Patient or population: people with moderate to severe chronic relapsing dyshidrotic eczema on hands
Setting: secondary care setting at a single dermatology department in Germany
Intervention: topical calcineurin inhibitors tacrolimus 0.1% ointment twice daily during 4 weeks
Comparison: topical corticosteroid mometasone furoate ointment twice daily during 4 weeks

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No. of participants	Certainty of the evidence	Comments

	Assumed risk	Corresponding risk				
	Risk with mometasone furoate ointment	Risk with topical calcineurin inhibitor tacrolimus 0.1% ointment		(studies)	(GRADE)	
Primary: investigator-rated good/excellent control of symptoms - Not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Primary: participant-rated good/excellent control of symptoms - Not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Primary: adverse events Follow-up: 2 weeks	See comment	See comment	Not estimable	16 pairs of hands (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Within-participant design None of the participants dropped out because of adverse events
Secondary: investigator-rated reduction in severity - DASI[b] Follow-up: 2 weeks	See comment	See comment	Not estimable	16 pairs of hands (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Within-participant design **Tacrolimus group:** Mean DASI from 18 (SD 12.68) to 6.6 (SD 6.18) **Mometasone furoate group:** Mean DASI from 18.5 (SD 14.09) to 6.9 (SD 7.7)

*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; DASI: Dyshydrotic Eczema Area and Severity Index; RCT: randomised controlled trial; RR: risk ratio; SD: standard deviation.

Schnopp 2002

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

Very low certainty: we are very uncertain about the estimate.

[a]Downgraded by one level to moderate-certainty evidence for imprecision: small sample size in a single study and small number of events.
[b]DASI: Dyshydrotic Eczema Area and Severity Index is an assessment of severity combining objective (vesicles, erythema, and desquamation) and subjective (itch) evaluations on a scale from 0 (no eczema) to 60 (severe hand eczema).

Summary of findings 5. Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus vehicle for hand eczema

Topical calcineurin inhibitor tacrolimus 0.1% ointment compared to vehicle for hand eczema

Patient or population: people with moderate to severe nickel sulphate-induced allergic contact dermatitis based on clinical history (hand eczema) and proven by patch testing, resistant to topical corticosteroids
Settings: secondary care setting in a single-centre study in Italy
Intervention: topical calcineurin inhibitor tacrolimus 0.1% ointment twice daily for 2 weeks

Comparison: vehicle twice daily for 2 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with vehicle	Risk with tacrolimus 0.1% ointment				
Primary: investigator-rated good/excellent control of symptoms Follow-up: 3 weeks	See comment	See comment	RR 29.00 (1.90 to 443.25)	28 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Unable to calculate assumed risk as no events in the control group - 14/14 participants in the tacrolimus group had good/excellent control of symptoms. Fisher's exact test P = 0.0001, NNTB 1, 95% CI 1 to 1
Primary: participant-rated good/excellent control of symptoms Not measured	See comment	See comment	Not estimable	-	See comment	No data reported
Primary: adverse events - burning/itching at application site	See comment	See comment	RR 9.00 (0.53 to 152.93)	28 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Unable to calculate assumed risk as no events in the control group - 4/14 participants in the tacrolimus group had burning/itching at the application site.

Follow-up: 3 weeks						Fisher's exact test P = 0.1129, RR 9.00, 95% CI 0.53 to 152.93 No data on "all adverse events"
Secondary: investigator-rated reduction in severity - Not measured	See comment	See comment	Not estimable	-	See comment	No data reported

*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; NNTB: number needed to treat for an additional beneficial outcome; RCT: randomised controlled trial; RR: risk ratio.

Pacor 2006

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

[a]Downgraded by one level to moderate-certainty evidence for imprecision: very small sample size, low event rate, and very large confidence intervals.

Summary of findings 6. Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate

Oral cyclosporin compared to topical betamethasone for patient with hand eczema

Patient or population: people with hand eczema, continuously for 6 months, significant disability, inadequate response to conventional treatment, confirmation by histopathology
Setting: secondary care setting at a single centre in Finland
Intervention: oral cyclosporin 3 mg/kg/d and placebo cream for 6 weeks
Comparison: topical betamethasone dipropionate 0.05% cream and placebo capsules for 6 weeks

Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk[a]	**Corresponding risk**				
	Risk with topical betamethasone	**Risk with oral cyclosporin**				
Primary: investigator- rated good/ excellent control of symptoms[b]	**Study population**		**RR 1.88** (0.88 to 3.99)	34 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	-

Follow-up: 6 weeks	**333 per 1000**	**627 per 1000** (293 to 1000)				
Primary: participant-rated good/ excellent control of symptoms[b] Follow-up: 6 weeks	**Study population**		**RR 1.25** (0.69 to 2.27)	34 (1 RCT)	⊕⊕⊕⊝ Moderate[c]	-
	500 per 1000	**625 per 1000** (345 to 1000)				
Primary: adverse events - at least 1 adverse event Follow-up: 36 weeks	**Study population**		**RR 1.22** (0.80 to 1.86)	55[d] (1 RCT)	⊕⊕⊕⊝ Moderate[c]	Because of partial cross-over design, a different number of participants is given for this outcome
	556 per 1000	**678 per 1000** (444 to 1000)				
Secondary: investigator-rated reduction in severity[b] Follow-up: 6 weeks	Mean investigator-rated reduction in severity in total disease activity score after 6 weeks of treatment was 5.7	**MD 0.30 higher** (2.50 lower to 3.10 higher)	-	34 (1 RCT)	⊕⊕⊕⊝ Moderate[c]	-

*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; MD: mean difference; RCT: randomised controlled trial; RR: risk ratio.

Granlund 1996

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

[a]The assumed risk is the mean control group risk.
[b]Observer-rated disease activity score: grading 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) on erythema, scaling, infiltration, excoriation, crusting, and vesicles for both hands. A high score represents severe hand eczema.
[c]Downgraded by one level to moderate-certainty evidence. Imprecision downgraded by one level: small sample size.
[d]The number of participants varies between different outcomes because this is a cross-over study, and adverse events were included from all different phases of the trial.

Summary of findings 7. Oral retinoids: alitretinoin 30 mg versus placebo for hand eczema

Oral retinoids: alitretinoin 30 mg versus placebo for hand eczema

Patient or population: people with moderate to severe chronic hand eczema
Settings: secondary care with outpatients in an international multi-centre setting
Intervention: oral retinoid alitretinoin 30 mg for 12 to 24 weeks

Comparison: oral placebo for 12 to 24 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk[a]	Corresponding risk				
	Risk with placebo	Risk with alitretinoin 30 mg				
Primary: investigator-rated good/excellent control of symptoms Follow-up: 48 weeks to 72 weeks	**Study population**		**RR 2.75** (2.20 to 3.43)	1210 (2 RCTs)	⊕⊕⊕⊕ High[b]	NNTB 4, 95% CI 3 to 5
	157 per 1000	**432 per 1000** (346 to 539)				
Primary: participant-rated good/excellent control of symptoms Folluw-up: 48 weeks to 72 weeks	**Study population**		**RR 2.75** (2.18 to 3.48)	1210 (2 RCTs)	⊕⊕⊕⊕ High[b]	NNTB 4, 95% CI 3 to 5
	143 per 1000	**394 per 1000** (312 to 498)				
Primary: adverse events - headache Folluw-up: 48 weeks to 72 weeks	**Study population**		**RR 3.43** (2.45 to 4.81)	1210 (2 RCTs)	⊕⊕⊕⊕ High[b]	All adverse events not stated in Ruzicka 2008 NNTH 6, 95% CI 4 to 11
	74 per 1000	**251 per 1000** (179 to 352)				
Secondary: investigator-rated reduction in severity in TLSS[c] and mTLSS[d]	See comment	See comment	Not estimable	-	See comment	Only incomplete data reported; therefore we were unable to extract these data

*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; NNTB: number needed to treat for an additional beneficial outcome; NNTH: number needed to treat for an additional harmful outcome; RCT: randomised controlled trial; RR: risk ratio.

Ruzicka 2008; Fowler 2014

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

[a]The assumed risk is the mean control group risk.
[b]Relatively high number of dropouts, although analysed via intention-to-treat analysis. Risk of bias was low, the two included studies were consistent, and the evidence is applicable to patients with (moderate to) severe hand eczema. Risk of publication bias was considered low, although the studies were sponsored by a pharmaceutical company.
[c]The total lesion symptom score (TLSS) is the sum of seven items (erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, and pruritus/pain) scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). A high TLSS represents severe hand eczema.
[d]The modified total lesion symptom score (mTLSS) is the sum of seven items (erythema, oedema, vesiculation, scaling, lichenification/hyperkeratosis, fissures, and pruritus/pain) scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). A high mTLSS represents severe hand eczema.

Summary of findings 8. Oral retinoids: alitretinoin 10 mg versus placebo for hand eczema

Oral retinoids: alitretinoin 10 mg versus placebo for hand eczema

Patient or population: people with moderate to severe chronic hand eczema
Settings: secondary care with outpatients in an international multi-centre setting
Intervention: oral retinoid alitretinoin 10 mg for 12 to 24 weeks

Comparison: oral placebo for 12 to 24 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk[a]	Corresponding risk				
	Risk with placebo	Risk with alitretinoin				
Primary: investigator-rated good/excellent control of symptoms Follow-up: up to 48 weeks	**Study population**		**RR 1.58** (1.20 to 2.07)	781 (2 RCTs)	⊕⊕⊕⊕ High[b]	NNTB 11, 95% CI 6.3 to 26.5
	194 per 1000	**307 per 1000** (233 to 402)				
Primary: participant-rated good/excellent control of symptoms Follow-up: up to 48 weeks	**Study population**		**RR 1.73** (1.25 to 2.40)	765 (2 RCTs)	⊕⊕⊕⊕ High[b]	NNTB 9, 95% CI 6 to 20
	144 per 1000	**249 per 1000** (180 to 345)				
Primary: all adverse events Follow-up: up to 48 weeks	**Study population**		**RR 1.01** (0.66 to 1.55)	158 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	NNTH 260, 95% CI -14.47 to 15.24
	346 per 1000	**350 per 1000** (228 to 537)				

Secondary: investigator-rated reduction in severity of TLSS[d] Follow-up: up to 48 weeks	See comment	See comment	-	158 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	Median % change in score from baseline (95% CI) **Placebo group:** -25% (95% CI -42 to -14) **Aitretinoin 10 mg:** –59 (95% CI –73 to –33)

*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; NNTB: number needed to treat for an additional beneficial outcome; NNTH: number needed to treat for an additional harmful outcome; RCT: randomised controlled trial; RR: risk ratio; TLSS: total lesion symptom score.

Ruzicka 2004; Ruzicka 2008

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

[a]The assumed risk is the mean control group risk.
[b] Both studies were at low risk of bias and results were precise.
[c]Downgraded by one level to moderate-certainty evidence: imprecision downgraded by one level: small sample size.
[d]The total lesion symptom score (TLSS) is the sum of seven items (erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, and pruritus/pain) scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). A high TLSS represents severe hand eczema.

BACKGROUND

Please note that unfamiliar terms may be listed in Appendix 1 ('Glossary of medical terms').

Future research would involve comparing different treatment groups. Focus on subgroups would provide reliable evidence for informed decisions about which treatment is effective in managing hand eczema.

The overall quality of evidence was very low. Many trials included in this review, particularly older ones, were of low quality with methodological weaknesses in design (small studies, short duration) or were biased (not blinded, sponsored by pharmaceuticals). Most included participants with chronic hand eczema in secondary care settings; some included only specific subtypes of hand eczema, thereby limiting direct application of study findings. Most analyses were based on single studies of small sample size and imprecise results.

Description of the condition

Definition and epidemiology

Hand eczema is an inflammation of the skin (dermatitis) that is confined to the hands. Hand eczema is a common condition with a point prevalence varying between 1% and 5% in the general population. When mild cases are included, one-year prevalence can reach 10% (Meding 2004; Thyssen 2010; Yngveson 2000). Thyssen et al conducted a review of seven epidemiological studies on hand eczema and concluded the median incidence rate of hand eczema was 5.5 cases/1000 person-years. For women, the incidence rate of hand eczema was 9.6 cases/1000 person-years, and for men, 4.0 cases/1000 person-years (Thyssen 2010). A possible explanation for this sex difference is greater exposure of women to wet work, such as cleaning, nursing, and hair dressing, for example (Mollerup 2014; Nilsson 1985). The incidence of notified (i.e. usually more severe) occupation-related cases is estimated to be above 0.7 per 1000 people per year, with much higher incidences (up to 1 in 100) in high-risk populations such as hairdressers (Diepgen 2003). Decreased prevalence has been observed in Swedish adults and was attributed to a decline in occupational exposure to irritants (Meding 2002).

Over the years, several authors have proposed a workable definition of hand eczema, whereby different subtypes have been recognised (Menné 2000). Hand eczema can be classified according to aetiological (causative) factors, clinical-morphological typology, or a combination of both (Coenraads 2012; Diepgen 2009a). However, due to multi-causality, it is difficult to assess the influence of each causative factor; therefore only one aetiological diagnosis might be insufficient. The Danish Contact Dermatitis Group developed a classification system based on morphology with clear definitions for each classification and one or more aetiological diagnoses (Menné 2011). This might facilitate the classification of hand eczema and was demonstrated to be a useful tool in general practice (Johansen 2011). However, there is an obvious need for international consensus regarding the classification of subgroups of hand eczema.

In the current literature, different names can be used for the same subgroups, or the same name can be used for different subgroups. An example of this is vesicular hand eczema (Veien 2009): this might be called pompholyx, dyshidrotic eczema, dyshidrosis, or vesicular eczema; no consensus has been reached regarding the definition. The original definition of 'pompholyx' states "an eruption of vesicles and bullae on the palms, which is accompanied by pain and severe itching". Fox 1873 hypothesised that pompholyx was caused by sweating of the palms and introduced the term 'dyshidrosis' (hydrosis from sweating); both terms were used for the same clinical vesicular type. Later, Kutzner 1986 demonstrated that sweat glands are not altered in vesicular hand eczema and discussed the histological features of eczema. However, despite this evidence, the term 'dyshidrosis' is still used in current literature.

Hand eczema may be accompanied by similar skin changes on the feet.

Causes

In many people, hand eczema has more than one cause and both predisposing and external factors play a part. Being atopic (a tendency to develop asthma, hay fever, or eczema) is a major predisposing factor responsible for hand eczema; one-third to one-half of people with hand eczema can be considered atopic (Coenraads 1998; Meding 1990; Svensson 1988). The role of genetic factors, especially the association between filaggrin (FLG) mutations and hand eczema, is still under investigation (Heede 2016; Kaae 2012; Molin 2015).

The most common external causes of hand eczema include contact with mild toxic agents or irritants (for instance, water and soaps). The resulting irritant contact dermatitis can be distinguished from allergic contact dermatitis, which is caused by skin contact with allergens. Allergic contact dermatitis is less common than irritant contact dermatitis, and it occurs only in persons who have developed a contact allergy to a specific substance such as rubber, nickel, or perfumes. Ingested allergens (e.g. nickel) may occasionally provoke hand eczema (Jensen 2006). Little evidence suggests that inhalation of house dust mites may increase the severity of vesicular hand eczema (Schuttelaar 2013). The relevance of psychosomatic factors remains speculative (Menné 2000). In many people with chronic hand eczema, a combination of the above-mentioned factors plays a role. In addition, for several types of hand eczema, the cause is still unknown.

Impact

Itch is common among those with hand eczema. The itch caused by hand eczema can be intense, leading to sleep loss in the sufferer and in other family members. A vicious cycle of symptoms causing skin damage can develop, the so-called itch/scratch/itch cycle. Cracks and blisters can be painful. Cracking, hyperkeratosis (callus-like thickening), and inflexibility of the hands are also problematic and may limit mobility of the hands.

A visible skin disease can be a great burden and can lead to a social stigma. The hands are important organs of communication and expression; therefore any visible skin disease on the hands may result in major psychosocial problems (e.g. anxiety, low self-esteem, social phobia).

Painful cracks and blisters, besides their negative effects on daily life outside work, can impede an individual's ability to carry out manual work, leading to significant disability and huge economic losses for both individuals and society. A systematic review estimated the mean annual total cost per hand eczema patient at

between €1712 and €9792 (Politiek 2016). Hand eczema accounts for an estimated 90% of occupational skin disease. Patients have substantial use of sick leave due to their hand eczema. Studies in patients with chronic severe hand eczema have reported job loss up to 20% (Cvetkovski 2005). Quality of life assessments have shown an impact on daily life and on employment (Agner 2008; Moberg 2009). A comparison between the generic quality of life instrument Short Form Health Survey (SF-36) and the skin-related Dermatology Life Quality Index (DLQI) revealed slightly higher impact of hand eczema on women compared to men for specific sub-items (Wallenhammar 2004). A comparison of physician-rated versus participant-rated assessments of severity showed a poor correlation, indicating that patients may evaluate several aspects of their hand eczema (including degree of erythema, vesicles, and fissures) differently from physicians (van Coevorden 2006).

Prognosis

Previous studies have suggested that hand eczema tends to run a chronic relapsing course, with the vast majority of people experiencing negative psychosocial consequences (Hald 2009; Meding 2005; Petersen 2014; Veien 2008).

Description of the intervention

Many diverse therapies are used to control the disease, such as:

- skin protection measures, including gloves;
- topical treatments (bland emollients, corticosteroid creams/ointments, calcineurin inhibitors, coal tar and derivatives, irradiation with ultraviolet (UV) light or X-rays); and
- systemic treatments (oral corticosteroids, oral retinoids, or other immunosuppressants such as cyclosporin).

The main groups of interventions covered by this review are topical corticosteroids, topical calcineurin inhibitors (immunomodulators), irradiation with UV light, and oral retinoids or systemic immunosuppressants.

Overall, after proper education and counselling, including the recommendation of emollients, application of topical corticosteroids remains the mainstream treatment for hand eczema (nationaleczema.org).

How the intervention might work

Theoretically, identifying and eliminating an allergic contact factor (e.g. nickel or rubber allergy) could result in cure of hand eczema, provided this is the sole cause. In clinical practice, however, such cases are rare, as hand eczema is often due to a combination of irritant and allergic contact exposure, as well as to endogenous factors.

This review deals with a great variety of interventions. Major types of interventions are topical corticosteroids, topical immunomodulators, irradiation with UV light, and oral retinoids.

Topical corticosteroids are the most frequently prescribed treatments for hand eczema (Soost 2012). They have overlapping mechanisms of action: like oral immunosuppressants (e.g. corticosteroids), they inhibit inflammation (anti-inflammatory) and production of inflammatory substances (immunosuppressive) (Ahluwalia 1998; Sakuma 2001; Schleimer 1993).

Topical immunomodulators, such as tacrolimus and pimecrolimus, are non-steroidal immunosuppressants that are more selective in their mode of action than corticosteroids. They inhibit the production of inflammatory substances in the body (such as synthesis and release of inflammatory cytokines from T-lymphocytes, and release of inflammatory mediators from mast cells). Calcineurin is present during activation of T-lymphocytes, and since tacrolimus and pimecrolimus block this step, they are called 'calcineurin inhibitors' (de Paulis 1992; Sakuma 2001).

Topical moisturisers or emollients can relieve dryness of the skin, can improve the skin barrier function, and can influence transepidermal water loss (depending on the composition of the emollient) (Lodén 2012b; Rawlings 2004). Moisturisers are available in various compositions such as oil-in-water, water-in-oil, lotions, gels, and emulsions, among others, and various adjuvants such as urea or salicylic acid can be added to reduce thickness and scaling of the skin.

Coal tar has been used to treat eczema since ancient times. It is claimed to increase epidermal differentiation and to up-regulate various key barrier proteins such as filaggrin, thus improving the skin barrier function (McLean 2013; van den Bogaard 2013). Moreover coal tar suppresses the Th2 cytokine response (McLean 2013; van den Bogaard 2013).

Irradiation with UV light can be performed with different types of UVA and UVB, depending on the wavelength. UVA treatment overall is combined with a topical or oral agent (psoralen) to make the skin more sensitive to UVA. Examples of different types of phototherapy include broad-spectrum UVB (280 to 315 nm), small-spectrum UVB (311 to 313 nm, also known as TL-01 or narrow-band UVB), UVA-1 (340 to 400 nm), and topical and oral psoralen combined with UVA (PUVA; 315 to 400 nm). UVA-1 phototherapy can be used at high (HD; 130 J/cm^2), medium (MD; 50 J/cm^2), and low doses (LD; 10 J/cm^2) (Hönigsmann 2003). The mechanism of photo(chemo)therapy is multi-factorial. In general, UV light locally decreases the activity of the immune system and inhibits the quantity of inflammatory cells. It suppresses the antigen-presenting function of the Langerhans cells and induction of apoptosis of T-cells (Majoie 2009). In addition, photo(chemo)therapy results in an increase in the amount of stratum corneum; in other words, the skin gets thicker (Jekler 1990). Finally, UVB reduces the number of microbes on the skin, including *Staphylococcus aureus* (Faergemann 1987).

Oral retinoids are vitamin A derivatives. Retinoids are thought to interfere at different steps in the inflammatory process. They have immunomodulatory properties and interfere with the epidermal differentiation process in various ways (Blair 2016; Kislat 2014; Schmitt-Hoffmann 2012). Both alitretinoin and acitretin are retinoids, although their mechanism of action is slightly different. Alitretinoin is thought to have anti-inflammatory and immunomodulatory effects on the skin. Alitretinoin binds with high affinity to both retinoic acid receptor (RAR) and retinoid X receptor (RXR) and presents anti-inflammatory and immunomodulatory activity, and acitretin binds only selectively to RAR, although both retinoids are thought to reduce inflammation (Blair 2016; Kislat 2014; Schmitt-Hoffmann 2012).

Hand eczema is a chronic condition that might be accompanied by flares and might improve as a result of the natural course; therefore, we believe a minimum treatment duration of three

months is required to document important data such as duration and frequency of disease relapse.

Why it is important to do this review

The high prevalence of hand eczema, along with its poor prognosis and associated disability with economic losses and impairment of quality of life, makes hand eczema an important disease to study from an individual and a societal perspective. This, coupled with the long list of diverse treatments of unknown effectiveness and several conflicting studies (Diepgen 2007; van Coevorden 2004b), suggests that a systematic review is needed. Even if methodological constraints do not permit sufficient clarification of existing conflicts to provide clear guidance in clinical practice, this review will be an important step in identifying research gaps and consequently providing directions for future research.

The plans for this review were published as a protocol "Interventions for hand eczema" (van Coevorden 2009). Differences between the review and the protocol are stated in the section Differences between protocol and review.

OBJECTIVES

To assess the effects of topical and systemic interventions for hand eczema in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of interventions for hand eczema regardless of hand eczema type and other affected localisations.

Types of participants

People (adults and children, occupational and non-occupational) with the diagnosis of hand eczema, regardless of the underlying assumed cause, were eligible. We also included participants with other parts of the body affected in addition to the hand. The terms 'eczema' and 'dermatitis' were acceptable whenever they referred to the hands. Other terms such as 'pompholyx', 'dyshidrosis', and 'pulpitis' were also deemed acceptable. We included participants with different types of hand eczema, for example, chronic hand eczema, hyperkeratotic palmar (also know as tylotic) hand eczema, and vesicular eczema (also known as dyshidrotic hand eczema or pompholyx).

We included in this review studies that included participants with other diagnoses besides hand eczema only when we were able to obtain separate data for hand eczema participants.

Types of interventions

We included only studies comparing the intervention versus no treatment, placebo, vehicle, or other active treatments. We considered all types of interventions, except interventions to prevent hand eczema (primary prevention). We excluded studies that focused on prevention of hand eczema and studies that investigated integrated care programmes or educational programmes (non-pharmacological interventions).

We considered studies comparing different interventions, for example, topical corticosteroids versus topical calcineurin inhibitors or oral cyclosporin versus topical corticosteroids, as most clinically relevant. For 'Summary of findings' tables, we included the following comparisons.

- Mometasone furoate cream on different treatment schedules.
- Local narrow-band UVB versus local PUVA.
- Tacrolimus 0.1% ointment versus vehicle.
- Tacrolimus 0.1% ointment versus mometasone furoate ointment.
- Oral cyclosporin versus topical betamethasone dipropionate.
- Oral alitretinoin at 10 mg and 30 mg a day versus placebo.

When a study reported on treatment during a remission- or clearance-induction phase for participants before they were randomised to a follow-up or maintenance phase, we considered only the latter (randomised) phase for this review.

Types of outcome measures

We extracted the following primary and secondary outcomes from the included studies.

Primary outcomes

- Percentage of participants with self-rated good/excellent control of symptoms.
- Percentage of participants with investigator-rated good/excellent control of symptoms.
- Adverse events: adverse effects (long- and short-term) of the intervention. Long-term adverse events are defined as adverse events occurring after completion of the treatment phase; short-term adverse events occur during the treatment phase.

Secondary outcomes

- Reduction in severity (participant-rated).
- Reduction in severity (investigator-rated).
- Time until relapse, defined as the number of days/weeks until the participant reported worsening of symptoms after initial response.
- Dose reduction: reduction in treatment dose per time unit or cumulative prescribed treatment dose. For example, a decrease in daily topical medication, or a decrease in weekly photo irradiation.

We did not exclude studies from the review that did not include these outcomes.

We believe that three months is the minimum study duration required to document important data such as duration and frequency of disease relapse.

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

The Cochrane Skin Information Specialist searched the following databases up to 19 April 2018, using strategies based on the draft

strategy for MEDLINE presented in our published protocol (van Coevorden 2009).

- Cochrane Skin Group Specialised Register (search strategy in Appendix 2).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 3), in the Cochrane Library (search strategy in Appendix 3).
- MEDLINE via Ovid (from 1946) (search strategy in Appendix 4).
- Embase via Ovid (from 1974) (search strategy in Appendix 5).
- Allied and Complementary Medicine (AMED) via Ovid (from 1985) (search strategy in Appendix 6).
- Latin American and Caribbean Health Science Information database (LILACS) (from 1982) (search strategy in Appendix 7).
- Global Resource of Eczema Trials. Centre of Evidence Based Dermatology (accessed at http://www.greatdatabase.org.uk on 19 April 2018), using the following terms in the title of the records: hand* or finger* or palm or palms.

Trials registries

We (WAC and PJC) searched the following trials registries up to 21 April 2018, using the following search terms: hand and (eczema or dermatitis).

- International Standard Randomized Controlled Trials Number (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/).

Searching other resources

Correspondence with authors

If we needed clarification regarding studies, we contacted study authors using the correspondence options stated in their papers (for studies published since 1999). If email addresses did not work, we tried to find recent publications by the same corresponding author with more recent contact data, or we searched Facebook, LinkedIn, and the Internet to connect with these authors. In addition, we tried to contact all authors of studies that included other dermatoses among hand eczema, to obtain separate data for hand eczema participants. We listed in the 'notes' section of the Characteristics of included studies tables whether we contacted study authors, and if they responded. We have not included in the review complete correspondence with all studies, but we have shown the relevant citations in the Characteristics of included studies tables. The full correspondence with study authors is available upon request.

References from published studies

We checked the bibliographies of included studies for further references to relevant trials.

Adverse events

We did not perform a separate search for adverse events. However, we did examine data on adverse events from the included studies.

Unpublished literature

We contacted authors and pharmaceutical companies in relation to ongoing trials that were recently completed according to the trial registries mentioned under Electronic searches. When results were published on the trial register websites, we included these in the results, and we tried to contact study authors for additional information if necessary.

Conference proceedings

We searched the conference proceedings of annual conferences of the European Academy of Dermatology and Venereology (EADV) from 2000 to 2011 for further relevant RCTs. Some were available from the JEADV; however, some others had to be obtained from the organisation itself, from which we requested the material on CD-ROM.

Handsearching

We handsearched using the terms 'eczema', 'dermatitis', 'hand(s)', 'palmoplantar', and 'inflammatory' in 16 English, two German, one Italian, one French, and one Dutch dermatology journal (all journals 1977 through 2003). We searched the journals listed in Appendix 8.

Data collection and analysis

Selection of studies

Three review authors (PJC, JLB, and WAC) independently checked titles and abstracts identified from the searches. Three review authors (PJC, TD, and ÅS) conducted an additional handsearch. If it was clear that the study did not refer to a randomised controlled trial on hand eczema, we excluded it. We retrieved all potential trials as full-text articles for further independent examination by two review authors (TD and ÅS). These two review authors decided which trials conformed to the inclusion criteria and resolved discrepancies by discussion in consensus meetings. We obtained missing data from the trial authors when possible. Whenever we found duplicate publications of the same trial, we used the paper with the most relevant data (usually we had a conference abstract and a full article) as the primary reference and listed the other publication in the additional references following the reference section.

Data extraction and management

Three review authors (PJC, TD, and ÅS) extracted data independently, using a standardised data extraction form. These review authors and future reviewers piloted the data extraction form during a meeting of the European Dermato-Epidemiology Network, in July 2000. This form was based on a preceding systematic review of psoriasis interventions and was later updated according to Cochrane recommendations. We resolved discrepancies and uncertainties in a series of consensus meetings, which were led by one review author (PJC).

Two other review authors (JLB and WAC) entered into Review Manager 5.3 and checked the outcome data extracted from the included studies (RevMan).

Assessment of risk of bias in included studies

Two review authors (ÅS and TD) independently assessed the risk of bias in included studies following the domain-based evaluation described in Chapter 8 of the *Cochrane Handbook for Systematic*

Reviews of Interventions and, using the Cochrane risk of bias tool, assessed all included studies from the following aspects for potential risk of bias (Higgins 2011b).

- Random sequence generation, which refers to selection bias due to inadequate generation of a randomised sequence.
- Allocation concealment, which also refers to selection bias but due to inadequate concealment of the allocation sequence before assignment.
- Blinding of participants and personnel, which refers to performance bias due to knowledge of intervention allocation by participants or personnel.
- Blinding of outcome assessment, which refers to detection bias due to knowledge of intervention allocation by the outcome assessor.
- Incomplete outcome data, which refers to the quantity, nature, or manner in which incomplete outcome data were handled.
- Selective reporting, which refers to reporting bias due to selective reporting.
- Other source of bias, which refers to any other types of bias not covered above, including inclusion of baseline comparisons, certainty of the diagnosis, and premature ending.

Whenever we encountered disagreement regarding assessment of risk of bias, we resolved this in a consensus meeting with a third review author (PJC or HW). Two review authors (JLB and WAC) assessed completed 'Risk of bias' forms and entered the data into RevMan.

Measures of treatment effect

We employed risk ratios (RR) with 95% confidence intervals (CIs) to measure the effect of a treatment for dichotomous outcomes. We expressed results as number needed to treat for an additional beneficial outcome (NNTB) when appropriate, along with different rates of baseline risk. We expressed results from analyses of continuous data as mean differences (MDs), along with CIs and respective P values. Whenever a small study (fewer than 30 participants) included zero events in one arm, we used Fisher's exact test to calculate the P value, and we provided numerical data for the numerator/denominator for each treatment (Grainge 2013). We calculated Fisher's exact test using GraphPad software (GraphPad).

We interpreted numerical data in charts and tables when possible. We tried to extract numerical data from graphical presentations by using a ruler, or we contacted study authors for recent trials if the data were unclear. For data that had been extracted from a graph, we added remarks.

For studies that exclusively presented median values for a particular outcome, we substituted the median for the mean, provided that data were not too skewed. When standard deviations were not available from a paper, we tried to calculate these from other available data. When confidence intervals were provided, we used the formula given in Chapter 7.7.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

For multi-arm studies, we analysed each arm in comparison with placebo when possible.

Unit of analysis issues

Cluster randomised trials

We checked cluster randomised trials (groups of individuals instead of individuals randomised to intervention or control) for unit of analysis errors based on advice provided in Section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

Cross-over studies

In cross-over studies (with each participant allocated to a sequence of interventions, instead of to only one intervention), unit of analysis issues can arise when participants have been randomised to multiple treatments over multiple periods, or when there has been an inadequate washout period. We dealt with cross-over studies by analysing only the first treatment period as a simple parallel-group study.

Within-participant studies (self-controlled, left-right designs)

Given that analysis of paired data was not possible with RevMan, we summarised the data from within-participant studies in the text. The unit of analysis in within-participant studies was one hand per participant, whereas in parallel-group studies, the unit of analysis was per participant. Relevant data were presented in the analysis as "other data", in table format.

Studies with multiple arms

For studies including multiple arms (more than two) in the analyses, we plotted the different comparisons in different forest plots when possible.

Dealing with missing data

For trials published from 1999 onwards and with uncertainty, we tried to contact trial authors if we felt that this may yield essential additional information. In these cases, we contacted the first author or, when stated, the corresponding author of the article. For the current review, we did not make any assumption or imputation to missing data. We extracted all outcome data as they were reported in the original studies. We stated when authors were contacted and whether additional information was provided under Characteristics of included studies.

Assessment of heterogeneity

We had planned to explore reasons for heterogeneity amongst studies and, if necessary, to carry out sensitivity analyses to examine the effects of excluding study subgroups (e.g. children versus adults, atopic versus allergic contact hand eczema) or studies with high risk of bias.

Clinical heterogeneity (or clinical diversity) is considered as variability among participants, interventions, and outcomes. In future updates of this review, we plan to assess clinical heterogeneity by examining characteristics of the studies and similarity between types of participants, interventions, and outcomes. If studies were sufficiently similar, we achieved statistical pooling by using a weighted treatment effect.

We used random-effects model meta-analysis because of anticipated differences across studies in, amongst other things, the participant base included. Statistical heterogeneity was investigated with the I^2 test. If the I^2 statistic had been greater

than 50%, reasons for heterogeneity in studies would have been explored.

Assessment of reporting biases

We planned on including statistical methods for detecting publication bias (e.g. Begg's funnel plots). However, funnel plots are recommended by the *Cochrane Handbook for Systematic Reviews of Interventions,* Section 10.4 (Higgins 2011c), when at least a substantial number of studies (10 or more) are included in the meta-analysis. This was not feasible due to the heterogeneity of included studies. For reporting bias, we studied the study authors and institutions involved (pharmaceutical companies or not), funding, sponsorship of commercially available supplements, and, finally, conflicts of interest.

Data synthesis

When data permitted, we had planned to conduct statistical pooling, using a random-effects model whenever studies appeared sufficiently similar.

Subgroup analysis and investigation of heterogeneity

We conducted no pre-planned subgroup analyses in the current review, but in future updates, we will carry out analyses, if data permit, to examine the effects of including specific study subgroups (e.g. children versus adults, recurrent vesicular versus hyperkeratotic hand eczema).

Sensitivity analysis

We conducted no pre-planned sensitivity analyses in this review, but for future updates, we will consider performing sensitivity analyses for pooled analysis involving only studies at low risk of bias.

'Summary of findings' tables

We included in the 'Summary of findings' tables all primary outcomes and the secondary outcome 'investigator-rated reduction in severity' for the clinically most relevant studies (Ryan 2016). We assessed clinical relevance based on the clinical experiences of study authors. We tried to include studies from every group of interventions (topical corticosteroids, topical calcineurin inhibitors, UV therapy, and systemic treatments), and to keep the total number of included studies to a minimum. We therefore aimed to include studies that compared different groups of comparisons or studies that answered the questions that authors ask themselves on a regular basis in everyday practice. The 'Summary of findings' tables are based on the GRADE principles (GRADEPro, version 3.6.1). The GRADE approach is a sequential process that evaluates the quality of a body of evidence by considering the following domains.

- Study limitations, which refers to risk of bias in either study design or conduct that could lead to biased estimation of treatment effect.
- Inconsistency of results, which refers to unexplained heterogeneity of results.
- Indirectness of evidence, which refers to directness of comparisons of target populations, interventions, comparators, and outcomes of the included studies compared to those of the planned PICO of the systematic review.
- Imprecision, because results are generally imprecise when the study includes few participants, few events, or a wide confidence interval of the effect estimate.
- Publication bias.

Randomised controlled trials (RCTs) began as high-quality/certainty evidence, but If concerns were identified in the above domains, certainty was rated down by one or two levels depending on the severity of the concern. The GRADE approach completes assessments of the body of evidence by grading it in the high, moderate, low, or very low certainty category.

A duration of longer than three months was preferred for evaluating a clinically relevant effect. We considered interventions comparing different groups of interventions and studies providing different treatment regimens with regards to dosages or frequency as clinically most relevant. Therefore we included the following comparisons in the 'Summary of findings' tables.

- Clobetasol foam compared to vehicle (Summary of findings for the main comparison).
- Mometasone furoate cream in different treatment schedules (Summary of findings 2).
- Local narrow-band UVB compared to local PUVA (Summary of findings 3).
- Tacrolimus 0.1% ointment compared to mometasone furoate ointment (Summary of findings 4).
- Tacrolimus 0.1% ointment compared to vehicle (Summary of findings 5).
- Oral cyclosporin compared to topical betamethasone dipropionate (Summary of findings 6).
- Oral alitretinoin compared to placebo at 10 mg and 30 mg a day (Summary of findings 7; Summary of findings 8).

RESULTS

Description of studies

We included 60 RCTs on different interventions for hand eczema.

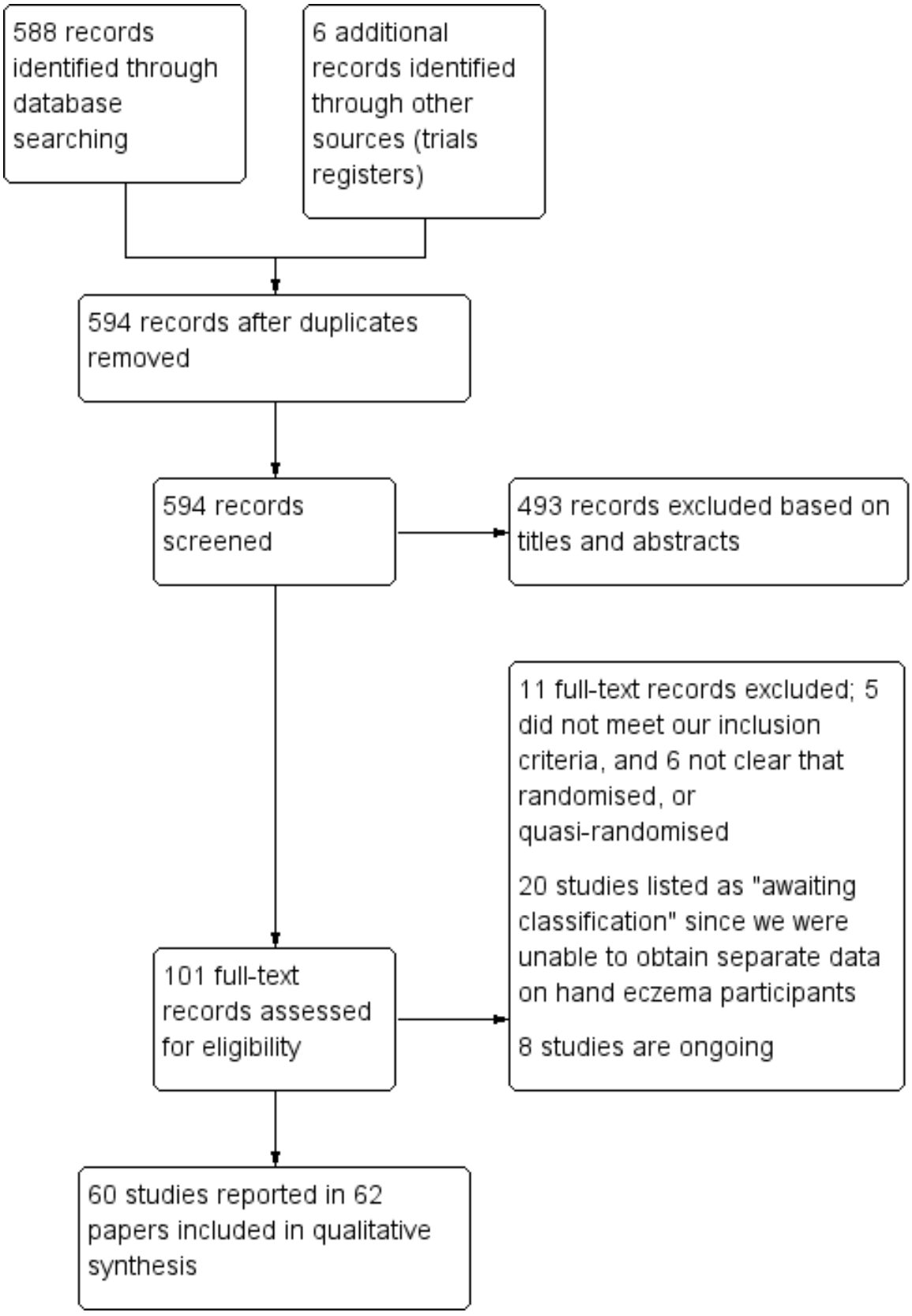
Results of the search

Our searches of the databases yielded 588 records (Electronic searches). Our searches of the trials registries identified six further studies. We therefore had a total of 594 records.

No duplicate records were identified, hence we screened 594 references. We excluded 493 records based on titles and abstracts. We obtained the full text of the remaining 101 records. We excluded 11 studies (Characteristics of excluded studies). We added 20 records to Characteristics of studies awaiting classification because we were unable to extract separate data on hand eczema patients. We identified eight ongoing studies (Characteristics of ongoing studies).

We included 60 studies reported in 62 references. For a further description of our screening process, see the study flow diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

Details of the 60 included studies with a total of 5469 participants are summarised in the Characteristics of included studies table. We included studies published from May 1967 to April 2018, as well as unpublished data from studies registered in trial registries up to April 2018.

Design

Of the 60 RCTs, 18 were within-participant studies (i.e. having a left-right design, comparing one hand with the other) (Adams 2007; Baskan 2005; Cartwright 1987; Chu 2009; Faghihi 2008; Fairris 1984; Fairris 1985; Fredriksson 1975; Grattan 1991; Kemper 1998; King 1984; Lindelöf 1987; Möller 1983; Odia 1996; Schnopp 2002; Sezer 2007; Sheehan-Dare 1989; Uggeldahl 1986). In total, 41 studies used a parallel-group design. Fowler 2005 used a parallel-group design but within each group chose a within-participant design as well. Two of these parallel-group studies used a cross-over design (Burrows 1986; Granlund 1996), but they were parallel before cross-over.

Participants

The original protocol stipulated diagnosis by a physician. Although only one of the identified studies stated this explicitly, all studies were based on participants being outpatients at hospitals. Therefore, we assumed that the diagnosis was established by a physician for all participants. Some studies included a specific subgroup of hand eczema, while others excluded these subgroups, for example, vesicular (or dyshidrotic) hand eczema was included by 11 studies (Adams 2007; Grattan 1991; Odia 1996; Pigatto 1990; Polderman 2003; Said 2010; Schnopp 2002; Sezer 2007; Sharma 2006; Sheehan-Dare 1989; Tzaneva 2009), and vesicular hand eczema was excluded by three studies (Bleeker 1989; Chu 2009; Hordinsky 2010). The same was true for atopic dermatitis and atopic dermatitis on the hands: six studies targeted atopic eczema specifically (Bauer 2012; Fowler 2005; Lauriola 2011; NCT01231854; Veien 1995; Yousefi 2012), while six other studies excluded participants with characteristics of atopic eczema (Bleeker 1989; Burrows 1986; Chu 2009; Hordinsky 2010; Katsarou 2012; Lodén 2012a).

All studies were performed in a secondary setting and included participants who had hand eczema for at least several weeks to months; therefore the review did not include acute hand eczema.

The studies included participants with different grades of severity, and not all studies included a severity grade as an inclusion criterion. Moderate to severe hand eczema was included in the following studies: Baskan 2005; Kircik 2013; Krejci-Manwaring 2008; Pacor 2006; Ruzicka 2004; Schnopp 2002; Tzaneva 2009; van Coevorden 2004a. Chu 2009 included only mild hand eczema. Mild to moderate hand eczema was included in Belsito 2004, Hordinsky 2010, Kucharekova 2003, Lauriola 2011, and Odia 1996. Cherill 2000, Fowler 2005, Hanifin 2004, and Uggeldahl 1986 included moderate hand eczema. Fowler 2014, NCT01231854, and Ruzicka 2008 included only severe hand eczema, and Bauer 2012 included moderate to very severe hand eczema. In two studies, the included severity was not completely clear (Veien 1995; Veien 1999).

Another inclusion criterion was poor response or resistance to conventional therapies such as topical corticosteroids (Adams 2007; Brass 2015; Cartwright 1987; Fairris 1984; Fairris 1985; Fowler 2014; Granlund 1996; King 1984; Lindelöf 1987; NCT01231854; Odia 1996; Pacor 2006; Ruzicka 2004; Ruzicka 2008; Sezer 2007; Sheehan-Dare 1989; Sjövall 1987; Tzaneva 2009). Only one study included a minimally affected area of hand eczema (Bayerl 1999). Disabling hand eczema was an inclusion criterion in two studies (Granlund 1996; Grattan 1991).

Overall, children were not included as a study population. One study included participants between 1.5 and 70 years of age (Uggeldahl 1986), another study included participants at least 10 years of age (Boroujeni 2017), four studies included participants 12 years of age and older (Faghihi 2008; Jowkar 2011; Jowkar 2014; Kircik 2013), and one study had a minimum inclusion age of 16 years (Grattan 1991). The remaining studies included only adults. A few studies excluded older participants. Two studies used an upper age limit of 60 years (Jowkar 2011; Yousefi 2012), three studies 65 years (Agarwal 2013; Bleeker 1989; Fowler 2005), three studies 70 years (Granlund 1996; Ruzicka 2004; Uggeldahl 1986), and three studies 75 years (Fowler 2014; NCT01231854; Ruzicka 2008).

One study included female participants exclusively (Kaaber 1983). The remaining studies included both female and male participants. Pregnant or lactating women, or both, were excluded from about half of the studies (32 studies).

Overall, participants were in general good health, and studies often excluded systemic diseases such as diabetes and renal or hepatic disease.

Sample size calculation

A total of 5469 participants were enrolled. Most studies were relatively small (12 to 158 participants), and sample size calculations often were not stated. A large proportion of the 5469 participants were included in five trials (Belsito 2004; Fowler 2014; Hordinsky 2010; Ruzicka 2004; Ruzicka 2008). Twelve studies included fewer than 25 participants (Burrows 1986; Fairris 1984; Grattan 1991; Kemper 1998; King 1984; Lindelöf 1987; Odia 1996; Pigatto 1990; Schnopp 2002; Sezer 2007; Sharma 2006; Sjövall 1987). In 27 studies, between 25 and 50 participants were included (Baskan 2005; Bauer 2012; Bayerl 1999; Cartwright 1987; Cherill 2000; Faghihi 2008; Fairris 1985; Fredriksson 1975; Granlund 1996; Gupta 1993; Hanifin 2004; Jowkar 2011; Kaaber 1983; Katsarou 2012; Krejci-Manwaring 2008; Kucharekova 2003; Lauriola 2011; Lodén 2012a; Odia 1996; Pacor 2006; Polderman 2003; Said 2010; Sheehan-Dare 1989; Thestrup-Pedersen 2001; Tzaneva 2009; Veien 1995; Whitaker 1996). Between 50 and 100 participants were included in eight studies (Bleeker 1989; Boroujeni 2017; Brass 2015; Fowler 2005; Jowkar 2014; Möller 1983; Uggeldahl 1986; Yousefi 2012). Between 100 and 500 participants were included in eight studies (Agarwal 2013; Belsito 2004; Bissonnette 2010; Hill 1998; Kircik 2013; Ruzicka 2004; van Coevorden 2004a; Veien 1999). Three studies included more than 500 participants (Fowler 2014; Hordinsky 2010; Ruzicka 2008).

NCT01231854 aimed to include 78 participants based on a sample size calculation; however the study was ended prematurely and included only 15 participants.

Setting

None of the studies were conducted in a primary care setting. As far as we know, all studies were conducted in a secondary care setting and included outpatients from hospitals. About half of the studies

were conducted as multi-centre studies, usually within the same country. Six studies were international multi-centre studies (Belsito 2004; Bissonnette 2010; Cherill 2000; Hordinsky 2010; Ruzicka 2004; Ruzicka 2008).

Although most studies did not declare the country in which the study was conducted, we assumed that they were conducted in the hospitals of the investigators. Based on this assumption, most studies were conducted in North America and Europe. A substantial number of studies were conducted in the United Kingdom (Brass 2015; Burrows 1986; Cartwright 1987; Fairris 1984; Fairris 1985; Grattan 1991; Hill 1998; King 1984; Sheehan-Dare 1989), Sweden (Bleeker 1989; Fredriksson 1975; Lindelöf 1987; Möller 1983; Sjövall 1987), Germany (Adams 2007; Bauer 2012; Bayerl 1999; Bissonnette 2010; NCT01231854; Odia 1996; Schnopp 2002), Denmark (Kaaber 1983; Thestrup-Pedersen 2001; Veien 1995; Veien 1999), and the Netherlands (Kemper 1998; Kucharekova 2003; Polderman 2003; van Coevorden 2004a).

A few studies were conducted in other parts of the world, including Iran (Boroujeni 2017; Faghihi 2008; Jowkar 2011; Jowkar 2014; Yousefi 2012), India (Agarwal 2013; Sharma 2006), Turkey (Baskan 2005; Sezer 2007), Singapore (Said 2010), South Africa (Whitaker 1996), and Taiwan (Chu 2009).

Treatment duration

Overall the studies were of relatively short duration. One study had a duration of only one week (Gupta 1993). The treatment episode was less than one month in 22 studies (Belsito 2004; Bleeker 1989; Boroujeni 2017; Chu 2009; Faghihi 2008; Fowler 2005; Fredriksson 1975; Hill 1998; Jowkar 2011; Jowkar 2014; Kemper 1998; King 1984; Kircik 2013; Lauriola 2011; Lodén 2012a; Odia 1996; Pacor 2006; Polderman 2003; Schnopp 2002; Sharma 2006; Uggeldahl 1986; Yousefi 2012), and it was less than two months (eight weeks) in 12 studies (Adams 2007; Baskan 2005; Bauer 2012; Bayerl 1999; Cherill 2000; Grattan 1991; Kucharekova 2003; Lindelöf 1987; Said 2010; Sheehan-Dare 1989; Sjövall 1987; Thestrup-Pedersen 2001); nine studies had a treatment duration between two and four months (Brass 2015; Cartwright 1987; Fairris 1984; Fairris 1985; Katsarou 2012; Krejci-Manwaring 2008; Pigatto 1990; Sezer 2007; van Coevorden 2004a).

Only 11 studies had a duration of active treatment longer than four months (Agarwal 2013; Bissonnette 2010; Fowler 2014; Hanifin 2004; NCT01231854; Ruzicka 2004; Ruzicka 2008; Tzaneva 2009; Veien 1995; Veien 1999; Whitaker 1996).

Studies with a cross-over design had an active treatment phase of six weeks for both drugs (Burrows 1986; Granlund 1996), and Hordinsky 2010 had an active treatment phase of six weeks, followed by an open-label phase.

The total duration of active treatment was unclear in two studies (Kaaber 1983; Möller 1983).

Follow-up

Most studies did not include a follow-up period. Only 24 studies included a follow-up period (Baskan 2005; Cartwright 1987; Fairris 1984; Fairris 1985; Fowler 2014; Granlund 1996; Grattan 1991; Jowkar 2011; Krejci-Manwaring 2008; Lindelöf 1987; NCT01231854; Pacor 2006; Polderman 2003; Ruzicka 2004; Ruzicka 2008; Said 2010; Schnopp 2002; Sezer 2007; Sharma 2006; Sheehan-Dare 1989; Sjövall 1987; Tzaneva 2009; van Coevorden 2004a; Whitaker 1996). This period varied from a week to several months and involved scheduled visits or just a single follow-up questionnaire. Veien 1999 clearly states that the treatment episode was 30 weeks, although data in the survival analyses suggest follow-up to 250 days.

Two studies were ended prematurely (Burrows 1986; NCT01231854).

Interventions and comparisons

In most studies, an active intervention was compared to no treatment, variants of the same medication, or placebo (or vehicle). Very few studies compared two different classes of interventions: one study compared coal tar paste with a corticosteroid (Kemper 1998), one study phototherapy (PUVA) with X-rays (Sheehan-Dare 1989), one study phototherapy (UVA-1) with a topical corticosteroid (Said 2010), two studies a calcineurin inhibitor with a corticosteroid (Katsarou 2012; Schnopp 2002), one study cyclosporin with a topical corticosteroid (Granlund 1996), and one study cromoglycate with a diet (Pigatto 1990). One study compared oral cyclosporin to oral alitretinoin (NCT01231854). We organised the remaining trials into the categories described below and provide details of the various dose regimens. Full details of interventions and comparisons for each included study are given in the Characteristics of included studies.

I. Skin protection measures, including gloves

These were not included in this review.

II. Topical treatments

A. Bland emollients

One study (Table 1) compared effects of two different emollients - an emollient with ceramides (Locobase Repair) in 17 participants versus a regular petrolatum-based emollient (Vaseline-lanette) in 15 participants - as adjuvants in the treatment of hand eczema over two months (Kucharekova 2003).

One within-participant study compared an emollient with E-DO lotion once daily to vehicle lotion. E-DO claims to be a potential agent for revitalising skin cells to regain their moisture retention capacity and might improve wound healing and inhibition of *Staphylococcus aureus* and *Propionibacterium acnes,* according to the study authors (Chu 2009).

B. Corticosteroid creams or ointments

Nine studies evaluated topical corticosteroids as the main intervention (Bleeker 1989; Faghihi 2008; Fowler 2005; Gupta 1993; Kircik 2013; Lodén 2012a; Möller 1983; Uggeldahl 1986; Veien 1999).

Bleeker 1989 compared two topical corticosteroids to determine whether the less potent fluprednidene (Cortoderm) cream was as effective as the more potent betamethasone-17-valerate (Betnovate) cream. Each product was applied once daily, in the evenings, for a study period of three weeks. In both study groups, a specific emollient was used if required.

In a within-participant study (Fowler 2005), the effectiveness of hydrocortisone butyrate (HB) 0.1% cream was compared with three other medium-potency corticosteroid creams (fluticasone propionate 0.05% cream (FP), prednicarbate emollient 0.1% cream (PC), and mometasone furoate 0.1% cream (MF)) for treatment of

chronic atopic and hand dermatitis. Participants were randomised to one of three treatment groups: HB versus FP, HB versus PC, or HB versus MF. Subsequently, participants applied twice-daily HB to one hand, and FP, PC, or MF to the other hand, for a duration of two weeks.

A double-blind within-participant study investigated whether the addition of zinc sulphate to clobetasol cream is effective in the treatment of chronic hand eczema (Faghihi 2008). Forty-seven participants were randomised and subsequently were treated twice daily with clobetasol + zinc sulphate cream on one hand and clobetasol 'only' cream on the other hand for two weeks.

In Gupta 1993, one group received betamethasone dipropionate polyacrylic film-forming lotion (Occlucort) twice a day for seven days. The other group received a traditional betamethasone dipropionate (Diprosone) lotion, slightly thickened to resemble the consistency of the other product.

In Kircik 2013, participants received clobetasol propionate 0.05% foam or vehicle foam twice daily for a period of 15 days.

In a double-blind randomised clinical trial (Lodén 2012a), twice-daily application of betamethasone-valerate 0.1% cream (BV group) was compared to once-daily application of betamethasone-valerate 0.1% cream in combination with once-daily application of a moisturiser cream containing 5% urea (BV + M group). The study duration was two weeks. Both groups were allowed to use urea 5% cream for additional hand treatment.

A multi-centre study was designed to investigate whether twice weekly application of a steroid was effective in keeping hand eczema, which had been brought into remission, under control (Möller 1983). To induce remission, 61 participants with symmetrical hand eczema of at least six months duration were treated with clobetasol propionate (Dermovate) cream twice weekly. Then, the 55 (out of 61) participants who were healed were included in a maintenance study and were followed for a mean period of 138 days (range 55 to 193 days); this occurred in the form of an RCT that compared one hand (receiving clobetasol (Dermovate) cream) with the other hand (receiving fluprednidene (Cortoderm) cream). When relapse occurred during the maintenance phase, the cream allocated to that hand could be applied more frequently; if this failed, the cream for the other (best) hand could be used temporarily. Participants were allowed to use an emollient (Essex cream) as needed.

Two strengths of the same topical corticosteroid were compared in a within-participant design (Uggeldahl 1986). Forty-six participants were treated twice daily with desonide (Tridesilon) cream 0.1% on one hand and desonide (Apolar) cream 0.05% on the other for two weeks. Participants had not been treated for eczema for at least one week before the study began.

The aim of one study was to compare mometasone (Elocon) ointment ("fatty cream") applied three times per week versus two times per week (Veien 1999). Initially, all participants were treated for three weeks with daily application of mometasone furoate to bring their dermatitis under control. This RCT investigated 106 participants whose dermatitis was brought under control. They were randomised to three parallel study groups for up to 36 weeks: treatment with mometasone furoate ointment once daily three times a week, treatment with mometasone furoate ointment once daily two times a week, and treatment with only emollients. In this study, in case of obvious bacterial infection, a course of oral antibiotics or potassium permanganate soaks, or both, was permitted. All participants were given an emollient to be used freely. Clinical evaluations were carried out after 3, 6, 12, 18, 24, and 30 weeks of maintenance treatment.

For an overview of the outcome 'Investigator-rated good/excellent control' in these studies, see the additional tables section (Table 2).

C. Coal tar and derivatives

Kemper 1998 investigated the efficacy of coal tar paste (pix lithanthracis) compared to zinc oxide paste and betamethasone-valerate. Nineteen participants with symmetrical hand eczema were included and were treated with coal tar paste on one hand and betamethasone-valerate ointment 0.1% or zinc oxide paste on the other hand. Participants were instructed to wear gloves on both hands for protection and bandage. Clinical evaluation of the hands was carried out once a week, and at that same visit, the corresponding treatment was applied, again to the hands. Treatment duration was four weeks.

For an overview of the outcome 'Investigator-rated good/excellent control' in this study, see the additional tables section (Table 3).

D. Irradiation with UV light

Variations in UV phototherapy (UVA, UVB, PUVA) were investigated in 10 studies (Adams 2007; Bayerl 1999; Brass 2015; Grattan 1991; Polderman 2003; Said 2010; Sezer 2007; Sjövall 1987; Tzaneva 2009; van Coevorden 2004a).

Said 2010 compared the efficacy of topical betamethasone-valerate 0,1% cream twice daily to UVA-1 phototherapy thrice weekly for six weeks. Twenty-four participants with chronic vesicular hand eczema were treated with phototherapy, and 23 participants were treated with topical corticosteroids.

Treatment with a portable UVB phototherapy unit, to be used at home, was compared with treatment by non-specific topical treatment in a study among 48 participants with occupational hand dermatitis (Bayerl 1999). It seems that the UVB-treated group also applied this non-specific topical treatment. The UVB-treated group irradiated their hands at home five days per week for eight weeks according to a predetermined dosage scheme.

Two studies compared oral PUVA with topical bath PUVA: van Coevorden 2004a and Tzaneva 2009.

Tzaneva 2009 compared oral PUVA versus bath PUVA. Immediately after immersion for 15 minutes, the hands and feet were exposed to UVA irradiation. The irradiation doses in both groups were increased depending on the degree of erythematous response. Treatment was given three to four times a week until complete clearance, or over a maximum period of 20 weeks. After clearing, participants were maintained on PUVA twice weekly for two weeks and then once weekly for another four weeks.

van Coevorden 2004a compared a randomised controlled parallel study of oral PUVA phototherapy whereby the hands were irradiated by participants themselves at home with bath PUVA; the hands were soaked in a psoralen (trioxsalen) solution followed by UVA in the clinic. The aim was to demonstrate equal clinical efficacy, assuming that costs for home treatment would be substantially

lower. Treatment was given for 10 weeks, and there was follow-up after the end of treatment for another eight weeks. Emollients were allowed in both groups.

Sezer 2007 compared UVA with UVB: 12 participants received local narrow-band UVB three times a week on one hand and local PUVA on the other hand for nine weeks. The initial dose was 150 mJ/cm^2 for each participant. A 20% increasing dose schedule was used until a final dose of 2000 mJ/cm^2 was reached versus local PUVA three times a week during nine weeks on 12/15 contralateral hands. The initial dose of psoralen plus UVA irradiation was 1.0 J/cm^2 with an increase of 0.5 J/cm^2 in every second session until a final dose of 7.5 J/cm^2 was achieved.

Brass 2015 compared the efficacy of narrow-band UVB with localised PUVA. Sixty participants received immersion PUVA or narrow-band UVB twice a week for 12 weeks.

Studies that employed UVA treatment were Adams 2007 and Grattan 1991.

A within-participant study compared the effectiveness of middle-dose UVA-1 irradiation to topical cream PUVA therapy (Adams 2007). UVA-1 is a newer form of UV therapy that contains only long-wavelength UVA-1 radiation (340 to 400 nm) and thus reduces the risk of burning. Participants with chronic relapsing dyshidrotic hand eczema received one treatment modality on one hand and one treatment modality on the other hand. Treatment was given three times a week during a period of five weeks (middle-dose UVA-1 irradiation three times a week during five weeks (cumulative dose of 600 J/cm^2) versus local 8-MOP-cream-PUVA irradiation three times a week during five weeks (cumulative dose of 17.4 J/cm^2)). 8-MOP-crème was applied 30 minutes before the start of irradiation. Grattan 1991 used topical PUVA three times weekly for eight weeks versus UVA (with placebo psoralen paint). The PUVA treatment was performed by applying a liquid ("paint") containing methoxypsoralen to one hand. On the contralateral hand, an inactive paint was applied, whereupon both hands were irradiated with UVA. Moisturisers were allowed on both hands, and both hands received a small fraction of UVB from UVA lamps.

Polderman 2003 used UVA-1 (long-wavelength UV radiation) irradiation 40 J/cm^2 on the hands five times weekly for three weeks versus placebo (simulated blue light). Emollients seem to have been allowed in both groups.

Sjövall 1987 used UVB irradiation only on the hands four times a week for eight weeks in six participants versus a placebo for UVB (filtered light) on the hands four times a week for eight weeks in six participants versus hand UVB followed by whole-body UVB + UVA four times a week during eight weeks in six participants. Their 'ordinary topical treatment' was permitted in all groups. Emollients were allowed in both groups.

For an overview of studies with UV therapy, see Table 4.

E. Irradiation with X-rays (ionising radiation)

X-rays/radiotherapy/Grenz rays were studied in five publications (Cartwright 1987; Fairris 1984; Fairris 1985; King 1984; Lindelöf 1987). One study compared conventional superficial radiotherapy to UV phototherapy (Sheehan-Dare 1989). All these studies used within-participant designs (i.e. comparing one hand with the contralateral hand).

Two of these studies used superficial X-rays 300 Rad as active treatment (Fairris 1984; King 1984).

King 1984 included 20 participants and treated one hand with three fractionated doses of 100 Rad (i.e. a total of 300 Rad) at 45 kV given at one-week intervals; Fairris 1984 treated participants with a combination of topical therapy and superficial X-ray therapy, and assessed them at 6, 9, and 18 weeks after the start of X-ray therapy. One hand was treated with 100 Rad at 50 kV on three occasions at intervals of 21 days (i.e. total 300 Rad), and the other hand with placebo. Participants continued treatment with tar paste or steroid ointments on both hands throughout the trial.

Lindelöf 1987 gave six fractionated doses of 3 Gy at one-week intervals for six weeks. Placebo therapy was achieved by allowing the apparatus to hum without emitting radiation.

In Cartwright 1987, one hand was irradiated three times with 3 Gy of Grenz rays (total 900 Rad), and the contralateral hand was treated in an exactly similar manner with sham radiation. Treatments were repeated at 21-day intervals for a total of three visits. Evaluations were performed by the doctor and the participant at 3, 6, 9, 12, 15, and 18 weeks after initial treatment.

One study compared superficial X-ray and Grenz ray irradiation (Fairris 1985). Both radiation therapies were given in three divided doses at 21-day intervals. One hand received 1 Gy of conventional superficial X-ray 50 kV, the other 3 Gy of Grenz ray 10 kV.

One study compared X-ray irradiation to UV phototherapy (Sheehan-Dare 1989). Superficial X-ray irradiation (0.9 Gy at 50 kV administered on three occasions at 21-day intervals) on one hand was compared with topical PUVA therapy (three times a week for six weeks) on the contralateral hand in 25 participants. Assessments were performed before and at 6, 9, and 18 weeks after the start of treatment.

For an overview of studies including irradiation with X-rays, see Table 5.

F. Topical calcineurin inhibitors

Tacrolimus was studied in four papers (Katsarou 2012; Krejci-Manwaring 2008; Pacor 2006; Schnopp 2002). Pimecrolimus was evaluated in three papers (Bauer 2012; Belsito 2004; Hordinsky 2010), as well as in two conference abstracts (Baskan 2005; Cherill 2000).

Topical tacrolimus 0.1% ointment (FK506) twice daily was compared with the topical corticosteroid mometasone furoate 0.1% ointment in a within-participant design (Schnopp 2002). Participants were encouraged to use emollients in addition. Treatment duration was four weeks, and treatment was followed by a washout period of two weeks. Tacrolimus ointment 0.1% twice daily during four weeks versus mometasone furoate 0.1% ointment twice daily was also used in Katsarou 2012 (with tapering mometasone furoate dose in the mometasone arm of the trial).

Katsarou 2012 compared topical tacrolimus 0.1% twice daily for 30 days and once daily for 31 to 90 days in 15 participants to mometasone furoate ointment twice daily for one week, once daily during week two and week three, once daily three times a week for weeks four and five, and once daily two times a week during the rest of the study (for 90 days) in 15 participants.

Two studies addressed tacrolimus ointment versus vehicle (Krejci-Manwaring 2008; Pacor 2006).

Twice-daily application of tacrolimus ointment was compared to its vehicle to study its effectiveness in keeping hand eczema in remission (Krejci-Manwaring 2008). Remission was induced after a three-week taper of prednisone. Simultaneous to the prednisone taper, participants started with tacrolimus or its vehicle for a total treatment duration of 12 weeks.

The aim of another trial was to evaluate the efficacy of 0.1% tacrolimus ointment for nickel sulphate-induced allergic contact dermatitis of the hands (Pacor 2006). Participants were randomised to twice-daily treatment with either 0.1% tacrolimus ointment or its vehicle during 14 days.

Five of our included studies addressed the use of pimecrolimus cream: Baskan 2005; Bauer 2012; Belsito 2004; Cherill 2000; Hordinsky 2010.

A large multi-centre study with 294 participants compared twice-daily application of pimecrolimus 1% cream to twice-daily application of vehicle in a three-week study (Belsito 2004). In both groups, the evening application was followed by six-hour occlusion. Time to relapse was compared between pimecrolimus 1% cream and vehicle in a randomised controlled parallel study (Bauer 2012). Before commencement, participants with atopic hand eczema used mometasone furoate for one to three weeks until symptoms had cleared. This was followed by an eight-week maintenance period with pimecrolimus versus vehicle cream. Another published abstract reporting a placebo-controlled randomised trial comparing pimecrolimus 1% cream with vehicle over eight weeks found pimecrolimus to be effective in suppressing all clinical signs of hand eczema apart from vesiculation (Baskan 2005). Only limited data could be extracted from one study comparing pimecrolimus 1% cream (with or without occlusion) to vehicle because this study was published as a conference abstract (Cherill 2000). In a large multi-centre study (Hordinsky 2010), 652 adults were randomised to pimecrolimus 1% or vehicle cream twice daily with overnight occlusion for six weeks.

For an overview of studies including topical calcineurin inhibitors, see Table 6.

G. Other topical interventions

Two antibacterial agents - clioquinol cream and fusidic acid cream - each combined with a corticosteroid (betamethasone-valerate) were compared in a multi-centre study on 120 hand eczema participants with confirmed or suspected secondary infection of their eczema (Hill 1998). The unblinded study had a duration of four weeks.

One study investigated urea cream (Fredriksson 1975), that is, Aquacare HP cream, a moisturising emulsion containing multi-sterols, phospholipids, and fatty diols (pH 6), twice a day (morning and evening) for four weeks, versus control of Calmurid cream containing betaine and lactic acid (pH 3), twice a day for four weeks.

Bexarotene, a novel type of retinoid, was evaluated in 55 participants by a three-arm unblinded (phase I to II open label) study lasting 22 weeks (Hanifin 2004). The intervention was bexarotene 1% gel applied in a stepwise accumulation every two weeks from once every other day to three times daily (bexarotene only group). Comparators were bexarotene application in combination with mometasone furoate (B + MF group) and in combination with hydrocortisone (B + HC group). All three groups used emollients.

One study compared topical furpalmate-containing cream (0.3%) with a topical corticosteroid (hydrocortisone acetate 0.5%) twice a day (Lauriola 2011).

Jowkar 2014 studied the efficacy of topical fumaric acid 5% cream twice daily compared to triamcinolone 0.1% cream twice daily in 92 participants.

Three studies investigated herbal topical treatments: one study compared a 2% oil extract of *Nigella sativa L.* to betamethasone ointment 0.1% and Eucerin (Yousefi 2012). *Nigella sativa L.* (family Ranunculaceae) is an annual flowering plant that grows in south and southwest Asia, of which the seeds can be used as spice. Another study compared a cream with 4% Fumaria parviflora Lam. twice daily to vehicle cream (Jowkar 2011). Fumaria parviflora Lam. extract (family Papaveraceae) is a Persian herbal medicine that is called 'Shahtareh' in Iran. The plants were dried, and from them an abstract was made for the cream. Finally, twice-daily application with an oil-in-water emulsion-based herbal cream containing fenugreek seeds 5%, marshmallow 5%, chamomile 5%, and walnut leaves 5% was compared with twice-daily application of the topical steroid fluocinolone acetonide cream 2%, in the study of Boroujeni 2017.

In a within-participant study, pulsed direct iontophoresis on one hand was compared with no iontophoresis on the contralateral hand (Odia 1996), in which one of the participants' hands received pulsed direct current iontophoresis, 20 times 15 minutes each during three weeks in 20 hands, or as a control, no iontophoresis on contralateral hands for three weeks. Both hands received steroid-free tar solution and zinc paste.

For an overview of other topical interventions, see Table 7.

III. Systemic treatments

A. Oral corticosteroids

We identified no RCTs addressing oral corticosteroids.

B. Immunosuppressants

We found two publications on cyclosporin (Granlund 1996), but these studies were based on the same trial, which had three phases. Oral cyclosporin 3 mg/kg/d and placebo cream for six weeks was compared with topical betamethasone dipropionate 0.05% cream and placebo capsules identical to cyclosporin. This was a cross-over trial, in which participants who failed to respond to their intervention in phase I were crossed over to the alternative intervention. The use of own emollients was allowed in both groups.

Agarwal 2013 investigated a low dose of azathioprine combined with topical clobetasol 0.05% cream compared to topical clobetasol 0.05% cream alone during 24 weeks.

NCT01231854 compared the effects of oral cyclosporin 2.7 to 4.0 mg/kg to those of alitretinoin 30 mg/d during 24 weeks. Please see Table 8.

C. Oral retinoids

We identified six studies evaluating oral retinoids (Bissonnette 2010; Fowler 2014; NCT01231854; Ruzicka 2004; Ruzicka 2008; Thestrup-Pedersen 2001). Ruzicka 2004 had previously been presented in part as a conference abstract (Larsen 2003, listed under Ruzicka 2004).

Three studies investigated the effect of 10 mg oral alitretinoin (Bissonnette 2010; Ruzicka 2004; Ruzicka 2008)

Two large multi-centre studies compared a total of four different oral doses of a novel retinoid (alitretinoin) with placebo capsules (Ruzicka 2004; Ruzicka 2008). In Ruzicka 2004, three groups, each receiving respectively, 10, 20, or 40 mg per day, were compared with a placebo group. The trial lasted 12 weeks. The other study (Ruzicka 2008; also known as Benefit of Alitretinoin in Chronic Hand Eczema or BACH study) compared two groups receiving, respectively, oral alitretinoin 10 or 30 mg once daily versus placebo up to 24 weeks. In both studies, participants were allowed to use a standard emollient.

The large multicenter study of Fowler 2014 compared alitretinoin 30 mg/d to placebo in 596 participants with severe chronic hand eczema. The treatment duration was 24 weeks, and afterwards participants were followed up for a substantial period of time.

NCT01231854 aimed to compare the effectiveness and safety of 30 mg alitretinoin to cyclosporin during 24 weeks in 78 participants.

In Bissonnette 2010, 117 participants suffering from chronic hand eczema were included who had been successfully treated with alitretinoin in an earlier study (Ruzicka 2008), and who had relapsed within the 24-week observation period after treatment. These 117 relapsed participants were randomised to receive their previous treatment or placebo in a 2:1 ratio. A total of 73 participants were included who had been treated with 30 mg alitretinoin in the previous BACH study (Ruzicka 2008). No other topical or systemic medication for hand eczema was allowed during the treatment period. Dose reductions of study medication were not allowed.

Thestrup-Pedersen 2001 compared acitretin given orally at 30 mg daily for eight weeks to placebo capsules given for eight weeks. Both groups were allowed to use topical emollients.

For an overview of studies on oral retinoids, see Table 9.

D. Other oral interventions

This group included six studies (Table 10) - one on triethylenetetramine (Burrows 1986), two on disulphiram (Kaaber 1983; Sharma 2006), one comparison of a low-nickel diet versus oral treatment with disodium cromoglycate (Pigatto 1990), one on oral ranitidine (Veien 1995), and one on evening primrose oil (Whitaker 1996).

Three studies aimed specifically to intervened on the imputed role of nickel allergy in hand eczema, and included exclusively nickel-sensitive participants (Burrows 1986; Kaaber 1983; Sharma 2006).

Burrows 1986 compared oral triethylenetetramine (Trientine) 300 mg daily for six weeks to placebo and was designed as a cross-over study, but this trial was terminated prematurely (23 participants had been included) because of literature reports on teratogenicity in rats.

Kaaber 1983 compared oral tetraethylthiuram disulphide 50 mg/d first week, increasing to 200 mg/d for at least six weeks, to placebo, and was performed in 30 nickel-sensitive (patch test-positive) women with pompholyx-type hand eczema. Half of the participants (n = 15) received tetraethylthiuram disulphide (Antabuse) with gradually increasing dosage (up to 20 mg/d) for "at least six weeks"; probably this maximum dose was given for six weeks. The other 15 women received placebo tablets. Both groups were allowed to use a topical corticosteroid (desoximethasone) and emollients.

Twenty-one nickel-sensitive participants (proven by means of patch testing) with vesicular hand eczema were included in a single-blinded trial and were randomised into two treatment groups (Sharma 2006); a low-nickel diet in combination with disulphiram was compared with a normal diet in combination with placebo.

Pigatto 1990 compared a low-nickel diet in eight participants to oral disodium cromoglycate (DSCG) 1500 to 2000 mg three times a day in nine participants to no treatment in seven participants for a period of three months; however this last group was not randomised and therefore was not included in the analyses.

Veien 1995 compared oral ranitidine 300 mg twice daily to placebo tablets in a trial of probably 16 weeks. Both groups were allowed to use betamethasone cream/ointment and emollients.

Evening primrose oil (GLA - gamma linolenic acid) 50 mg in 20 participants was compared to placebo capsules in 19 participants for 16 weeks (Whitaker 1996). Both groups were allowed to use unlimited qualities of emollients and a limited amount of group III corticosteroids. Participants were followed up for eight weeks after the end of treatment, resulting in a total study duration of 24 weeks.

For an overview, see Table 10.

Outcomes

The 60 included RCTs reported diverse outcomes. About half of these studies (n = 33) included our primary outcome good/excellent control either participant- or investigator-rated, although not all included reproducible data. Almost all studies reported our primary outcome 'adverse events' (n = 55). There was substantial heterogeneity between the studies in terms of outcome measures, duration, and timing of outcome assessments.

Most studies used a scale to score the (change in) severity of hand eczema or the rate of clearance. However, many different scoring systems were composed to score different items on different scales, and some did, while others did not, include the affected area. Most scoring systems were unnamed, non-validated, and self-created, and combined objective and subjective scores; in these cases, we provided a narrative account of study results and did not attempt quantitative analyses.

The Hand Eczema Severity Index (HECSI) is an assessment of the clinical severity of hand eczema that includes the extent and severity of hand eczema. The hands are divided into five areas (fingertips, fingers, palms, backs of hands and wrists). For each of these areas, the intensity of the six following clinical signs is scored on a grade from 0 (no skin changes) to 3 (severe changes): erythema, induration/papulation, vesicles, fissures, scaling, and oedema were graded on this scale. Moreover, the affected area for each is scored from 0 to 4 (0 = 0%; 1 = 1% to

25%; 2 = 26% to 50%; 3 = 51% to 75%; 4 = 76% to 100%) for the extent of clinical symptoms. Finally, the scores given for each extent location are multiplied by the total sum of the intensity of each clinical feature, resulting in a score of 0 (no hand eczema symptoms) to a maximum severity score of 360 points (very severe hand eczema). Scores above 28 represent severe hand eczema. This is a validated scoring system with excellent agreement for both interobserver and intraobserver reliability (Held 2005). Four studies used the HECSI (Agarwal 2013; Bauer 2012; NCT01231854; Yousefi 2012); three studies awaiting classification (EUCTR2005-005793-75-DE; IRCT201112018263N1; NCT01950494), as well as six ongoing studies, included this outcome parameter (IRCT2014012916412N1; ISRCTN80206075; NCT02664805; NCT03026907; NCT03026946; PACTR201704002194318).

The Dyshydrotic Eczema Area and Severity Index (DASI) is an assessment of severity combining objective (vesicles, erythema, and desquamation) and subjective (itch) evaluations. Each item has to be assessed on a scale ranging from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe), and the grading must be representative for all affected areas. The severity grading is multiplied by a number representative of the total affected area. DASI score = (Vesicles + Erythema + Desquamation + Itch) × Area score points. This results in a DASI ranging from 0 to 60. A DASI score between 0 and 15 represents mild dyshidrotic eczema, 16 to 30 is moderate, and between 31 and 60 represents severe dyshidrotic eczema. The DASI was first described by Odia (Odia 1996). It was used as primary outcome in five studies (Adams 2007; Odia 1996; Polderman 2003; Said 2010; Schnopp 2002); however, this regularly used instrument is not validated.

The Hand Eczema Area and Severity Score (HEAS) is used to assess clinical severity, corrected for the percentage of affected skin area (Simons 1997). The score ranges from 0 (no hand eczema) to 96 (very severe hand eczema) points. Two studies used the HEAS score, although this score is not validated for hand eczema (Chu 2009; Kucharekova 2003).

The Hand Eczema Extent Score (HEES) is a simple clinical score that is not validated (Meding 1989). The HEES scores only the extent of the presence of eczema signs on different locations of the hands, without including intensity of the lesions, with a range of 0 (no hand eczema) to 74 (very severe hand eczema) points. One study included the HEES (Lodén 2012a).

The Total Lesion Symptom Score (TLSS) is the sum of seven items (erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, and pruritus/pain) scored on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The TLSS was used in Ruzicka 2004, and afterwards a slightly modified version (modified Total Lesion Symptom Score - mTLSS) was used in Ruzicka 2008, Bissonnette 2010, Fowler 2014, and Brass 2015; the seven items were erythema, oedema, vesiculation, scaling, lichenification/hyperkeratosis, fissures, and pruritus/pain. A high mTLSS represents severe hand eczema. The mTLSS relates to the Physician Global Assessment, and a photographic guide has been developed to train observers.

Some studies used scoring systems derived and validated for atopic dermatitis. For example, the validated Eczema Area and Severity Index (EASI) was used (Jowkar 2011; Jowkar 2014), and this scoring system was adjusted to a Hand Eczema Area and Severity Index (HEASI) score (Hanifin 2004). NCT01231854 included the validated SCORing Atopic Dermatitis (SCORAD) next to the HECSI for participants with atopic hand eczema.

The Hand Eczema Area and Severity score is adapted from the well known EASI. The HEASI is calculated by (sum of severity scores for signs) × (involved hand area integer), whereby for the area, 1 = < 10% involvement, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%. Severity score is 0 = none, 1 = mild, 2 = moderate, 3 = moderately severe, and 4 = severe for the following signs: erythema, scaling, oedema, lichenification, vesiculation, and fissuring.

Investigator and Physician Global assessments (PGA and IGA) or variants of this scoring system (such as the Investigator's Static Global Assessment (ISGA)) were used in different studies, on a 4- or 5-point scale for both hands overall (Bauer 2012; Belsito 2004; Bissonnette 2010; Bleeker 1989; Brass 2015; Cartwright 1987; Chu 2009; Fairris 1984; Fairris 1985; Fowler 2014; Grattan 1991; Gupta 1993; Hill 1998; Hordinsky 2010; King 1984; Kircik 2013; Krejci-Manwaring 2008; Kucharekova 2003; Lauriola 2011; NCT01231854; Pacor 2006; Ruzicka 2004; Ruzicka 2008; Sheehan-Dare 1989; Sjövall 1987). In general, a low IGA or PGA score represents well-controlled hand eczema, whereas a high score represents severe hand eczema. PGA scores have been extensively studied and compared to, for example, HECSI and HEAS (Coenraads 2005; Van Der Valk 2013).

Itch was scored as subjective parameter in most studies (Agarwal 2013; Bayerl 1999; Bleeker 1989; Boroujeni 2017; Brass 2015; Cherill 2000; Chu 2009; Faghihi 2008; Fowler 2005; Fowler 2014; Granlund 1996; Gupta 1993; Hanifin 2004; Hill 1998; Hordinsky 2010; Jowkar 2014; Katsarou 2012; Kemper 1998; Kircik 2013; Krejci-Manwaring 2008; Kucharekova 2003; Lauriola 2011; Lindelöf 1987; Odia 1996; Pacor 2006; Pigatto 1990; Polderman 2003; Ruzicka 2004; Ruzicka 2008; Schnopp 2002; Sezer 2007; Sharma 2006; Thestrup-Pedersen 2001; Uggeldahl 1986; van Coevorden 2004a; Veien 1995).

Ten studies included quality of life as an outcome parameter; especially more recent studies and studies in trial registries included quality of life. The extensively studied and validated Dermatology Life Quality Index (DLQI from Finlay 1994) was used in seven studies (Bauer 2012; Brass 2015; Chu 2009; Kircik 2013; Lodén 2012a; Ruzicka 2004; Yousefi 2012). The DLQI contains 10 questions regarding the impact of skin conditions and their treatment on participants' lives, which are answered on a scale ranging from 0 (not at all) to 3 (very much). A total DLQI score between 0 and 1 represents no or minimal effect at all on a participant's life. A DLQI score of 10 or greater represents significant impact on life quality, whereas a score over 21 represents an extremely large effect on quality of life. A change in DLQI score of at least 4 points is considered clinically relevant in inflammatory skin conditions (Basra 2008; Basra 2015).

Another quality of life questionnaire that was used is the Eczema Disability Index (EDI) (Granlund 1996). The EDI includes 15 questions representing different dimensions of quality of life on a scale from 0 (not at all) to 6 (very much). The Skindex-29 was used by one study (Fowler 2014). Finally the Skindex-17 was used in another study (NCT01231854). The Skindex-17 is a dermatological health-related quality of life instrument that is derived from the Skindex-29 and includes only 17 items instead of 29, and a 3-point scale for answers instead of a 5-point scale. A high score on the

Skindex represents the huge impact of a skin condition on quality of life.

Economic losses such as sick days or out-of-pocket expenses were rarely registered as outcome parameters and were not included as outcome parameters before 2004. NCT01231854 and Brass 2015 contained an extensive cost-effectiveness analysis based on the EQ-5D. In addition, out-of-pocket expenses were registered in NCT01231854. van Coevorden 2004a registered travel expenses and time off work for participants. Two studies included the influence of hand eczema on work impairment with the Work Productivity and Activity Impairment Questionnaire (WPAI) (Kircik 2013; NCT01231854).

Cosmetic acceptability was considered as another outcome parameter in four studies (Fowler 2005; Fredriksson 1975; Kucharekova 2003; Lauriola 2011).

One of our secondary outcomes was 'dose reduction' - reduction in treatment dose per time unit or cumulative prescribed treatment dose. None of the included studies provided reproducible data regarding this outcome.

Funding

For many older studies, it is unclear who funded the study. More recent studies often declared funding for the study or clearly stated relationships with pharmaceutical companies. In total, 22 studies were funded by pharmaceutical industries or were (co-)authored by employees of pharmaceutical companies (Bauer 2012; Belsito 2004; Bissonnette 2010; Bleeker 1989; Cherill 2000; Chu 2009; Fowler 2005; Fowler 2014; Granlund 1996; Gupta 1993; Hill 1998; Hordinsky 2010; Kircik 2013; Krejci-Manwaring 2008; Lodén 2012a; Möller 1983; Ruzicka 2004; Ruzicka 2008; Uggeldahl 1986; Veien 1995; Veien 1999; Whitaker 1996). Thirteen studies were sponsored by governmental organisations, universities, or hospitals (Baskan 2005; Brass 2015; Faghihi 2008; Jowkar 2011; Jowkar 2014; Katsarou 2012; NCT01231854; Pacor 2006; Schnopp 2002; Sharma 2006; Tzaneva 2009; van Coevorden 2004a; Yousefi 2012).

Excluded studies

The excluded studies are summarised under Characteristics of excluded studies. The 11 excluded studies comprised studies that were excluded for different reasons such as:

- study on 'slightly irritated hands' in employees, which we did not accept as being hand eczema (Berndt 2001);
- quasi-randomised study, or unclear whether the study was randomised (Aertgeerts 1985; Güler Özden 2004; HogenEsch 1998; Petering 2004; Rosén 1987; Zimmerman 1967);
- study that did not examine hand eczema but rather colonisation with a bacterium - *Staphylococcus aureus* (Grivcheva-Panovska 2013);
- study without a comparator (Zeichner 2018);
- study on prevention of hand eczema after initial treatment of hand eczema (Gergovska 2017); and
- study from which we were unable to extract separate data on hand eczema because the study combined data on hand and foot eczema (Chen 2015).

Ongoing studies

The search yielded eight ongoing studies whose content we have summarised under Characteristics of ongoing studies:

Three studies are focused on topical treatments.

- NCT02664805: comparing the efficacy of twice daily applications of LEO 124249 ointment with LEO 124249 ointment vehicle for up to eight weeks for treatment of chronic hand eczema.
- IRCT2014012916412N1: comparing the efficacy of pumpkin ointment twice daily with betamethasone ointment twice daily, and almond ointment twice daily and Eucerin ointment twice daily.
- IRCT2017070922965N10: evaluating the effect of topical atorvastatin as adjuvant therapy for treatment of hand eczema.

One study is examining palmar botulinum toxin injections.

- PACTR201704002194318: evaluating the efficacy and tolerability of botulinum toxin type A for treatment of hand eczema.

Four are exploring systemic treatments.

- JPRN-UMIN000003326: determining the effect of olopatadine on itching in hand eczema.
- ISRCTN80206075: comparing alitretinoin 30 mg with PUVA twice weekly as first-line treatment for severe chronic hand eczema.
- NCT03026946: comparing the efficacy of alitretinoin 30 mg and cyclosporine for treatment for severe recurrent vesicular hand eczema.
- NCT03026907: comparing alitretinoin 30 mg with azathioprine in severe non-hyperkeratotic hand eczema.

Data from ongoing trials that have been completed at the time of the next update will be included in the review, if those results are available.

Studies awaiting classification

We added 20 records to Characteristics of studies awaiting classification. These include a lot of studies on different topical treatments such as hand creams and sanitisers for the treatment of hand eczema that were listed in different trial registries and, although they seem completed, results have never been posted and we were unable to obtain these results.

This section also contains studies that included different dermatoses among hand eczema, but for which we were unable to obtain separate data for hand eczema despite contacting the study investigator.

Risk of bias in included studies

Many studies were at high or unclear risk of bias in one or more components of trial design. We assessed only six studies as having low risk of bias in all components of trial design (Baskan 2005; Bauer 2012; Fowler 2005; Lindelöf 1987; Pacor 2006; Ruzicka 2004). Eight studies had only one unclear risk of bias with remaining domains rated as low risk (Bissonnette 2010; Fairris 1984; Fairris 1985; Fowler 2014; Kircik 2013; Ruzicka 2008; Sheehan-Dare 1989; Yousefi 2012). We rated 29 studies as having high risk of bias in at least one domain (Adams 2007; Agarwal 2013; Bayerl 1999; Brass 2015; Burrows 1986; Cartwright 1987; Fredriksson 1975; Hanifin

2004; Hill 1998; Jowkar 2014; Katsarou 2012; Kemper 1998; King 1984; Krejci-Manwaring 2008; Kucharekova 2003; Lauriola 2011; Möller 1983; NCT01231854; Odia 1996; Pigatto 1990; Said 2010; Schnopp 2002; Sharma 2006; Sjövall 1987; Thestrup-Pedersen 2001; Tzaneva 2009; van Coevorden 2004a; Veien 1995; Veien 1999).

Further information can be found in the risk of bias tables for each included study and in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

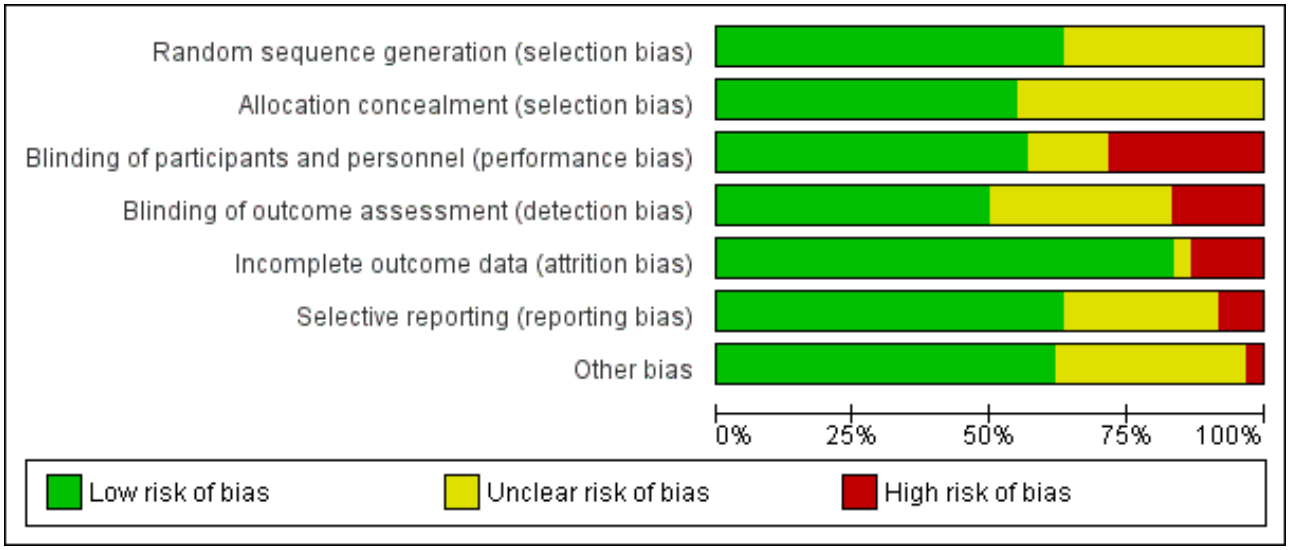


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

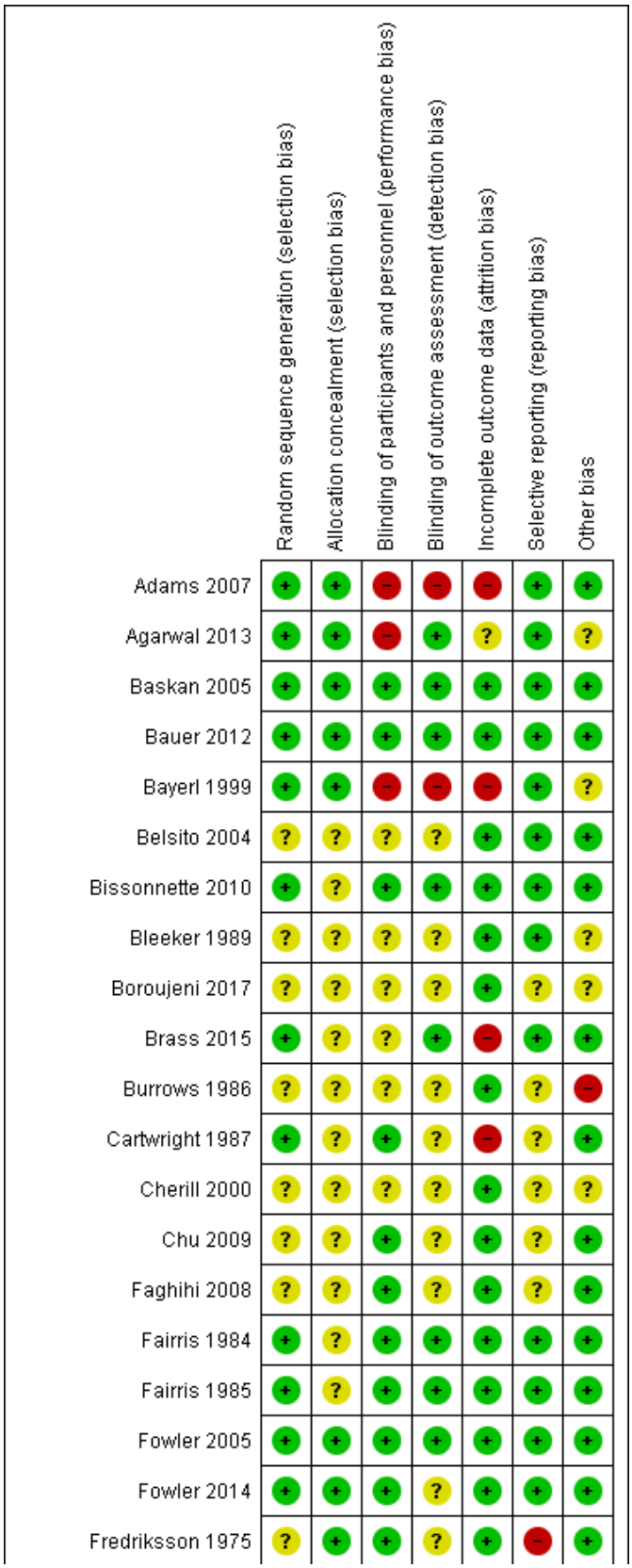


Figure 3. (Continued)

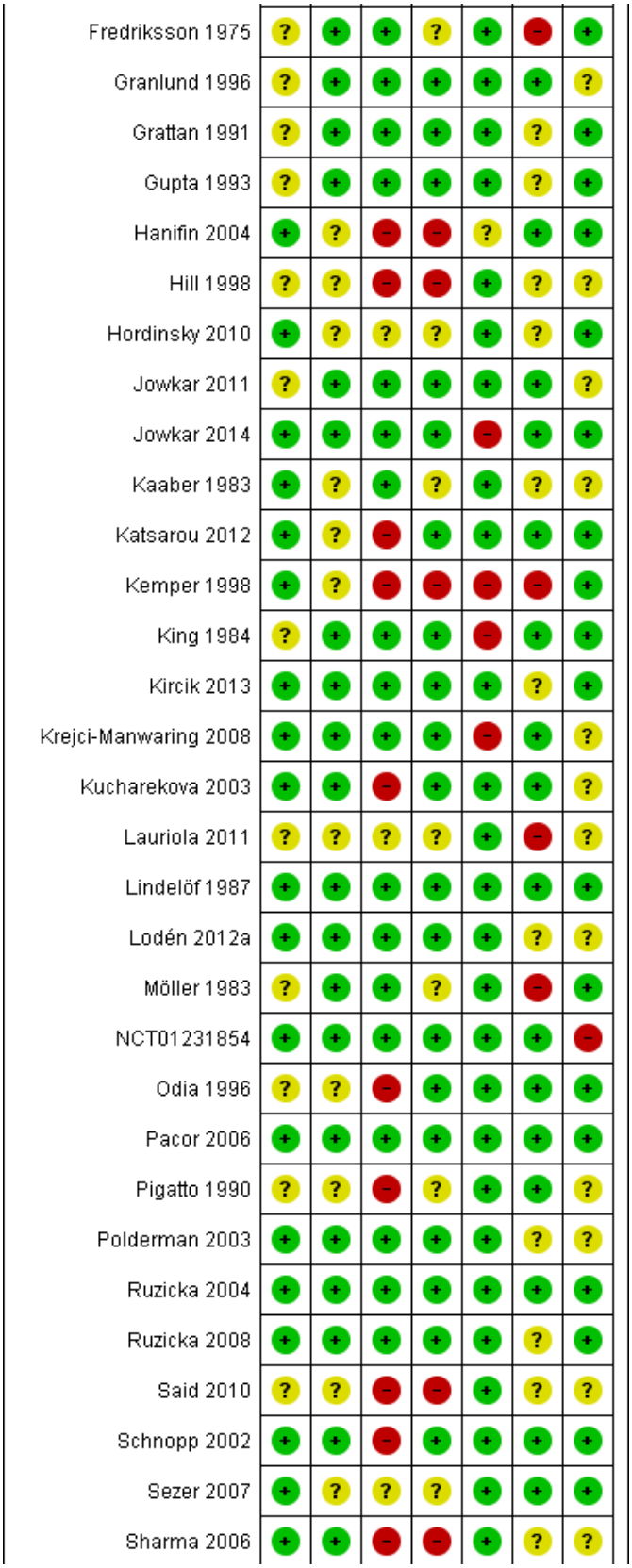
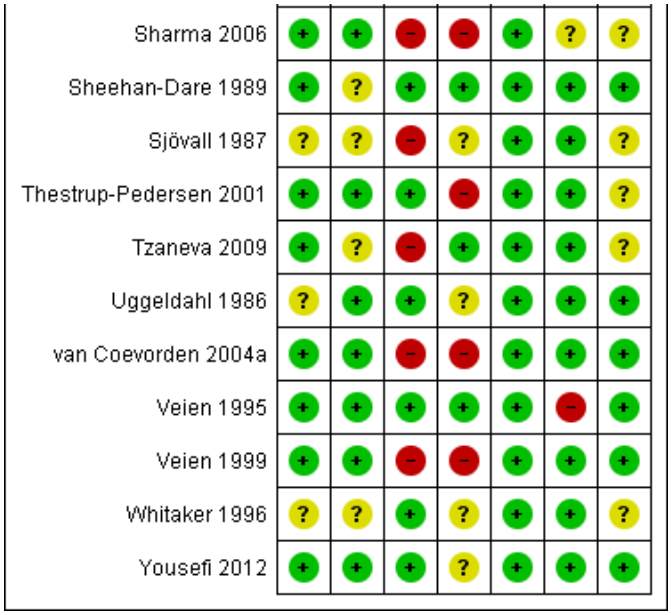


Figure 3. (Continued)



Allocation

Randomisation procedure

We judged the procedure as adequate (low risk of bias) when the allocation sequence was able to protect against biased allocation of comparison groups. If no details were given about the methods of sequence generation (i.e. if there was doubt about the adequacy of sequence generation), we judged studies as having unclear risk. We considered systematic methods that allow biased allocations, such as alternation or assignment based on day of admission, as inadequate (high risk of bias). References to a lottery system, throwing dice, or using a computer programme were considered as adequate (low risk of bias).

The randomisation procedure was unclear in 22 studies. For 25 studies, we judged the randomisation procedure as adequate based on the article (Adams 2007; Bauer 2012; Bayerl 1999; Cartwright 1987; Fairris 1984; Fairris 1985; Fowler 2014; Hanifin 2004; Hordinsky 2010; Kaaber 1983; Katsarou 2012; Kemper 1998; Kircik 2013; Krejci-Manwaring 2008; Lindelöf 1987; Lodén 2012a; NCT01231854; Polderman 2003; Ruzicka 2004; Ruzicka 2008; Sezer 2007; Sheehan-Dare 1989; Tzaneva 2009; van Coevorden 2004a; Yousefi 2012). For 13 studies, we were unable to base judgement on the article, but personal communication with study authors clarified that the randomisation procedure was adequate (Agarwal 2013; Baskan 2005; Bissonnette 2010; Brass 2015; Fowler 2005; Jowkar 2014; Kucharekova 2003; Pacor 2006; Schnopp 2002; Sharma 2006; Thestrup-Pedersen 2001; Veien 1995; Veien 1999). In total, we judged the randomisation procedure as adequate in 38 studies.

Concealment of allocation

We judged this as adequate (low risk of bias) when clinicians and participants were unaware of future allocations before participants gave consent to the study. Examples of these include randomisation by a third party or use of sequentially numbered, opaque, sealed envelopes. We judged this as unclear risk of bias if insufficient details are given about methods of allocation concealment. We judged the allocation inadequate (high risk of bias) when there was a possibility of knowledge of the next assignment, so when investigators could have successfully guessed the allocation before the participant gave consent.

Of the above-mentioned 38 studies with an appropriate randomisation procedure, concealment of allocation was adequate in 25 (Adams 2007; Agarwal 2013; Baskan 2005; Bauer 2012; Bayerl 1999; Fowler 2005; Fowler 2014; Jowkar 2014; Kircik 2013; Krejci-Manwaring 2008; Kucharekova 2003; Lindelöf 1987; Lodén 2012a; NCT01231854; Pacor 2006; Polderman 2003; Ruzicka 2004; Ruzicka 2008; Schnopp 2002; Sharma 2006; Thestrup-Pedersen 2001; van Coevorden 2004a; Veien 1995; Veien 1999; Yousefi 2012).

For eight studies, concealment of allocation was clear, but the randomisation procedure was unclear (Fredriksson 1975; Granlund 1996; Grattan 1991; Gupta 1993; Jowkar 2011; King 1984; Möller 1983; Uggeldahl 1986).

In total, in 33 studies the method used to conceal allocation was judged as adequate. In the remaining 27 studies, it is unclear if allocation was concealed.

Blinding

Performance bias

Performance bias refers to systematic differences between groups in the care provided, or in exposure to factors other than the interventions of interest (Higgins 2011a). After enrolment into the study, blinding of participants and site staff can reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes. Effective blinding can also ensure that the compared groups receive similar amounts of attention, ancillary treatment, and diagnostic investigation. With regards to performance bias, blinding of participants and of study personnel was judged separately. Use of identical looking study

and control drugs (vehicle or placebo) was considered an adequate method of blinding, if the study was double-blind.

If study authors made every attempt to blind the study to the best of their abilities, we judged the study as low risk. When, for example, the radiographer was the only person aware of treatment allocation but the study could not have been done in another way, we judged this as low risk of bias because we considered this the best possible way to minimise the risk of performance bias.

For 27 studies, both participants and staff were blinded in an adequate manner (Baskan 2005; Bauer 2012; Bissonnette 2010; Cartwright 1987; Chu 2009; Faghihi 2008; Fowler 2014; Fredriksson 1975; Granlund 1996; Grattan 1991; Gupta 1993; Jowkar 2011; Jowkar 2014; King 1984; Kircik 2013; Krejci-Manwaring 2008; Lindelöf 1987; Lodén 2012a; NCT01231854; Pacor 2006; Ruzicka 2004; Ruzicka 2008; Sheehan-Dare 1989; Thestrup-Pedersen 2001; Veien 1995; Whitaker 1996; Yousefi 2012). Seven studies were only participant-blinded (Fairris 1984; Fairris 1985; Fowler 2005; Kaaber 1983; Möller 1983; Polderman 2003; Uggeldahl 1986). Nine studies had unclear risk of blinding (Belsito 2004; Bleeker 1989; Boroujeni 2017; Brass 2015; Burrows 1986; Cherill 2000; Hordinsky 2010; Lauriola 2011; Sezer 2007).

For 17 studies, no blinding of participants was attempted, so the risk of performance bias was considered high (Adams 2007; Agarwal 2013; Bayerl 1999; Hanifin 2004; Hill 1998; Katsarou 2012; Kemper 1998; Kucharekova 2003; Odia 1996; Pigatto 1990; Said 2010; Schnopp 2002; Sharma 2006; Sjövall 1987; Tzaneva 2009; van Coevorden 2004a; Veien 1999). Some studies claimed a double-blind design but this was not feasible because participants had to follow lifestyle interventions such as a low-nickel diet (e.g. Pigatto 1990; Sharma 2006), or because treatment groups received completely different treatment such as whole-body irradiation versus local radiation (e.g. Sjövall 1987).

Detection bias

'Detection bias' refers to systematic differences between groups in how outcomes are determined. Blinding of outcome assessors reduces the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement (Higgins 2011a). We judged the procedure as having low risk of bias for detection when the outcome assessor was unaware of the allocation. When an article states only that the study was investigator-blinded or double-blinded, we considered this as too little information by which to judge the risk of bias and concluded that risk was unclear. We judged low risk of detection bias for studies that used independent observers, that received study drugs packed and dispensed by a third party, or that described another adequate method used to blind the observer.

The observer was blinded in an adequate manner in 30 studies (Agarwal 2013; Baskan 2005; Bauer 2012; Bissonnette 2010; Brass 2015; Fairris 1984; Fairris 1985; Fowler 2005; Granlund 1996; Grattan 1991; Gupta 1993; Jowkar 2011; Jowkar 2014; Katsarou 2012; King 1984; Kircik 2013; Krejci-Manwaring 2008; Kucharekova 2003; Lindelöf 1987; Lodén 2012a; NCT01231854; Odia 1996; Pacor 2006; Polderman 2003; Ruzicka 2004; Ruzicka 2008; Schnopp 2002; Sheehan-Dare 1989; Tzaneva 2009; Veien 1995).

Ten studies made no attempt to blind the observer (Adams 2007; Bayerl 1999; Hanifin 2004; Hill 1998; Kemper 1998; Said 2010; Sharma 2006; Thestrup-Pedersen 2001; van Coevorden 2004a; Veien 1999). For the remaining 20 studies, it is unclear whether the observer was truly blinded.

Incomplete outcome data

We tried to minimise the quantity of missing data by contacting all study authors from 1999 forward. We contacted them through personal communication by email, letters, or social media features such as LinkedIn. We asked questions with regard to uncertainty in the assessment of risks of bias or trial design. We also tried to search other sources such as trial registries, which may provide additional information with regards to study design, or we compared the study to similar studies done by the same authors.

We judged attrition bias as low risk in 50 studies (Baskan 2005; Bauer 2012; Belsito 2004; Bissonnette 2010; Bleeker 1989; Boroujeni 2017; Burrows 1986; Cherill 2000; Chu 2009; Faghihi 2008; Fairris 1984; Fairris 1985; Fowler 2005; Fowler 2014; Fredriksson 1975; Granlund 1996; Grattan 1991; Gupta 1993; Hill 1998; Hordinsky 2010; Jowkar 2011; Kaaber 1983; Katsarou 2012; Kircik 2013; Kucharekova 2003; Lauriola 2011; Lindelöf 1987; Lodén 2012a; Möller 1983; NCT01231854; Odia 1996; Pacor 2006; Pigatto 1990; Polderman 2003; Ruzicka 2004; Ruzicka 2008; Said 2010; Schnopp 2002; Sezer 2007; Sharma 2006; Sheehan-Dare 1989; Sjövall 1987; Thestrup-Pedersen 2001; Tzaneva 2009; Uggeldahl 1986; van Coevorden 2004a; Veien 1995; Veien 1999; Whitaker 1996; Yousefi 2012). We judged attrition bias as unclear in two studies (Agarwal 2013; Hanifin 2004), and as high in eight studies (Adams 2007; Bayerl 1999; Brass 2015; Cartwright 1987; Jowkar 2014, Kemper 1998; King 1984; Krejci-Manwaring 2008).

Loss to follow-up and intention-to-treat (ITT) analysis

We judged the risk of attrition bias (incomplete outcome bias) as adequate (low risk of bias) when more than 80% of participants were followed up and analysed in the groups to which they were originally randomised. In addition, we considered an intention-to-treat (ITT) analysis as having low risk of bias for the attrition bias. When more than 20% of participants dropped out and no ITT analysis was carried out, we considered the study element to have high risk of bias.

A total of 13 studies reported no dropouts (Cherill 2000; Faghihi 2008; Fredriksson 1975; Katsarou 2012; Lauriola 2011; Lodén 2012a; Odia 1996; Pacor 2006; Pigatto 1990; Schnopp 2002; Sharma 2006; Thestrup-Pedersen 2001; Veien 1999).

Despite loss of participants during follow-up, data were analysed according to the ITT analysis principle in 14 studies (Bauer 2012; Belsito 2004; Bissonnette 2010; Chu 2009; Fowler 2014; Granlund 1996; Hill 1998; Hordinsky 2010; Kircik 2013; Polderman 2003; Ruzicka 2004; Ruzicka 2008; van Coevorden 2004a; Veien 1995). NCT01231854 included an ITT analysis but included only 14 of the 78 planned participants due to early termination.

For 23 studies, at least 80% of participants were followed up and were included in the analyses (Agarwal 2013; Baskan 2005; Bleeker 1989; Boroujeni 2017; Burrows 1986; Fairris 1984; Fairris 1985; Fowler 2005; Grattan 1991; Gupta 1993; Jowkar 2011; Kaaber 1983; Kucharekova 2003; Lindelöf 1987; Möller 1983; Said 2010; Sezer 2007; Sheehan-Dare 1989; Sjövall 1987; Tzaneva 2009; Uggeldahl 1986; Whitaker 1996; Yousefi 2012).

The highest dropout rates were, respectively, 40%, 39%, 37%, and 37% (Cartwright 1987 ; Krejci-Manwaring 2008; Kemper 1998; Jowkar 2014). Eight studies analysed less than 80% (Adams 2007; Bayerl 1999; Brass 2015; Cartwright 1987; Jowkar 2014, Kemper 1998; King 1984; Krejci-Manwaring 2008).

For one study, it is unclear how many participants were analysed because the text states that less than 80% finished the protocol; however all participants seem to have been analysed without mention of ITT analyses (Hanifin 2004).

Selective reporting

We found a total 38 studies that we judged as having low risk of bias (Adams 2007; Agarwal 2013; Baskan 2005; Bauer 2012; Bayerl 1999; Belsito 2004; Bissonnette 2010; Bleeker 1989; Brass 2015; Fairris 1984; Fairris 1985; Fowler 2005; Fowler 2014; Granlund 1996; Hanifin 2004; Jowkar 2011; Jowkar 2014; Katsarou 2012; King 1984; Krejci-Manwaring 2008; Kucharekova 2003; Lindelöf 1987; NCT01231854; Odia 1996; Pacor 2006; Pigatto 1990; Ruzicka 2004; Schnopp 2002; Sezer 2007; Sheehan-Dare 1989; Sjövall 1987; Thestrup-Pedersen 2001; Tzaneva 2009; Uggeldahl 1986; van Coevorden 2004a; Veien 1999; Whitaker 1996; Yousefi 2012). We judged 17 studies as having unclear risk of reporting bias (Boroujeni 2017; Burrows 1986; Cartwright 1987; Cherill 2000; Chu 2009; Faghihi 2008; Grattan 1991; Gupta 1993; Hill 1998; Hordinsky 2010; Kaaber 1983; Kircik 2013; Lodén 2012a; Polderman 2003; Ruzicka 2008; Said 2010; Sharma 2006), and five as having high risk of reporting bias (Fredriksson 1975; Kemper 1998; Lauriola 2011; Möller 1983; Veien 1995). High risk of bias was assigned whenever we found severe discrepancies between the Materials and Methods section and the study protocol and Results section, when the stated primary outcome was neglected (Fredriksson 1975), and when significance levels were reached on subscores or on other scores, or were not stated at all (Kemper 1998; Lauriola 2011; Möller 1983). For example, Fredriksson 1975 used an unclear severity scale ranging from 0 to 5 and did not state the results of this outcome at all.

Many, especially older studies, did not register before commencement of the trial, so that the correspondence between actually reported outcomes and outcomes intended to be reported could not be assessed for most included studies. We found trial registration for 13 studies (Adams 2007; Bauer 2012; Bissonnette 2010; Brass 2015; Chu 2009; Fowler 2014; Hordinsky 2010; Jowkar 2011; Kircik 2013; Lodén 2012a; Ruzicka 2008; NCT01231854; Yousefi 2012), and we found discrepancies in Chu 2009, Hordinsky 2010, Kircik 2013, Lodén 2012a, and Ruzicka 2008 with regards to additional or missing outcome parameters. We found no major discrepancies between protocol and report in eight studies (Adams 2007; Bauer 2012; Bissonnette 2010; Brass 2015; Fowler 2014; Jowkar 2011; NCT01231854; Yousefi 2012), although one study was registered two years after the recruitment start date (Yousefi 2012).

For the other studies, we examined discrepancies between the Materials and Methods section and the Results section and noted no major discrepancies in most (Agarwal 2013; Baskan 2005; Bayerl 1999; Belsito 2004; Bleeker 1989; Fairris 1984; Fairris 1985; Fowler 2005; Granlund 1996; Hanifin 2004; Jowkar 2014; Katsarou 2012; King 1984; Krejci-Manwaring 2008; Kucharekova 2003; Lindelöf 1987; Odia 1996; Pacor 2006; Pigatto 1990; Schnopp 2002; Sezer 2007; Sheehan-Dare 1989; Sjövall 1987; Thestrup-Pedersen 2001; Tzaneva 2009; Uggeldahl 1986; van Coevorden 2004a; Veien 1999; Whitaker 1996), although in some studies we did find severe discrepancies, mainly involving missing information (Fredriksson 1975; Kemper 1998; Lauriola 2011; Möller 1983; Veien 1995).

Other potential sources of bias

Baseline comparison for severity of disease and diagnostic certainty

When assessing other potential sources of bias, we considered several aspects, namely, baseline balance for severity of disease and/or participants, diagnostic certainty, and whether the study was completed or ended prematurely.

Diagnostic certainty, meaning that the diagnosis was confirmed by a physician, was applicable to almost all studies. We judged this as low risk in all but one study (Said 2010).

For within-participant studies, we considered a baseline comparison dispensable. This was true for 18 within-participant studies (i.e. having a left-right design, comparing one hand with the other) (Adams 2007; Baskan 2005; Cartwright 1987; Chu 2009; Faghihi 2008; Fairris 1984; Fairris 1985; Fredriksson 1975; Grattan 1991; Kemper 1998; King 1984; Lindelöf 1987; Möller 1983; Odia 1996; Schnopp 2002; Sezer 2007; Sheehan-Dare 1989; Uggeldahl 1986). For three studies, we found significant differences at baseline and therefore declared them as having unclear risk of bias (Granlund 1996; Hill 1998; Krejci-Manwaring 2008). Sixteen studies did not state baseline comparisons (Agarwal 2013; Bayerl 1999; Boroujeni 2017; Burrows 1986; Cherill 2000; Kaaber 1983; Kucharekova 2003; Lauriola 2011; Lodén 2012a; Pigatto 1990; Polderman 2003; Said 2010; Sharma 2006; Sjövall 1987; Thestrup-Pedersen 2001; Tzaneva 2009), and these were unclear in three studies (Bleeker 1989; Jowkar 2011; Whitaker 1996). For the remaining studies, baseline comparisons were clearly stated (Adams 2007; Bauer 2012; Belsito 2004; Bissonnette 2010; Brass 2015; Fowler 2005; Fowler 2014; Gupta 1993; Hanifin 2004; Hordinsky 2010; Jowkar 2014; Katsarou 2012; Kircik 2013; NCT01231854; Pacor 2006; Ruzicka 2004; Ruzicka 2008; van Coevorden 2004a; Veien 1995; Veien 1999; Yousefi 2012).

Studies ending prematurely

Two studies were ended prematurely (Burrows 1986; NCT01231854). Burrows 1986 ended because teratogenicity in rats was reported during the study, and NCT01231854 ended because the investigator-initiated study was unable to include the planned number of participants. For this, we judged high risk of bias.

In total, we judged the risk of other potential sources of bias as high in two studies, unclear in 21 studies, and low in the remaining 37 studies.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroid creams/ointments: clobetasol propionate foam compared to vehicle foam for hand eczema; **Summary of findings 2** Corticosteroid creams/ointments: mometasone furoate cream 3 times/week versus 2 times/week for hand eczema; **Summary of findings 3** Irradiation with UV light: local narrow-band UVB compared to local PUVA for hand eczema; **Summary of findings 4** Topical calcineurin inhibitors: tacrolimus 0.1% ointment compared to mometasone furoate ointment for vesicular hand eczema; **Summary of findings 5** Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus vehicle for hand eczema; **Summary of**

findings 6 Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate; **Summary of findings 7** Oral retinoids: alitretinoin 30 mg versus placebo for hand eczema; **Summary of findings 8** Oral retinoids: alitretinoin 10 mg versus placebo for hand eczema

In the text below, where it has been possible to calculate an effect size, we have reported these with 95% confidence intervals. If no data were available for these analyses, we removed the result from this section and mentioned this in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10 for the primary outcome investigator-rated good/excellent control.

We considered statistical pooling, but the studies were too heterogeneous in terms of design, types of particular treatment compared, assessment of outcomes, duration of the trial, and presentation of data. The exceptions were two studies that compared 10 mg alitretinoin as active treatment versus placebo (Ruzicka 2004; Ruzicka 2008), along with studies regarding topical calcineurin inhibitors with regard to adverse events (Bauer 2012; Belsito 2004; Hordinsky 2010). Beside results of the pooled analysis, these studies also reported heterogeneity statistics. We considered, for example, pooling Brass 2015 and Sezer 2007, although treatment intensity (twice weekly versus thrice weekly) and study duration were too different. Moreover, only limited information was available on Brass 2015. Finally, Sezer 2007 was a within-participant study, and Brass 2015 was a parallel-group study.

In the additional tables section, we have tabulated the primary outcome investigator-rated good/excellent control for the different categories of interventions, that is, corticosteroids, irradiation with UV light, and irradiation with X-rays (respectively, Table 2 Table 4 and Table 5).

I. Skin protection measures, including gloves

We identified no randomised controlled trials.

II. Topical treatments

Comparison 1. Bland emollients: ceramide-containing emollients

A comparison was made between an emollient with ceramides (Locobase Repair) in 17 participants versus a regular petrolatum-based emollient (Vaseline-lanette) in 15 participants (Kucharekova 2003). Results were mainly depicted in graphic presentation (bar diagrams), and exact numbers cannot be extracted.

Primary outcome: adverse events

One participant in the ceramide group experienced an exacerbation of hand dermatitis, as did two participants in the comparison group (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.04 to 4.39; P = 0.49; Analysis 1.1). This showed no clear difference between groups.

Comparison 2. Bland emollients: emollient E-DO versus vehicle

Primary outcome: percentage of participants with self-rated good/excellent control at week 4

Chu 2009 conducted a within-participant study. After four weeks, the percentage of hands with a self-rated reduction of at least 50% on the participants' global assessment (PaGA) was 34.92% (22 hands) in the E-DO group, and 36.51% (23 hands) in the vehicle group (reported as 'other data'; see Analysis 2.1).

Primary outcome: percentage of participants with investigator-rated good/excellent control at week 4

We identified one within-participant study on E-DO (Chu 2009). After four weeks, 12 (19.0%) hands responded to E-DO only, 11 (17.5%) responded to vehicle only, and 25 (39.7%) responded to both. The overall response rate was 37 (58.73%) E-DO hands and 36 (57.14%) vehicle hands (reported as 'other data'; see Analysis 2.2). Also see Table 1.

Primary outcome: adverse events

At least one adverse event was reported by 19.4% of participants; 12 occurred on the E-DO hand (17.9%), and eight (11.9%) on the vehicle hand. Prurirtus was recorded for six E-DO hands and for two vehicle hands (reported as 'other data'; see Analysis 2.3). No serious adverse events were reported.

Comparison 3. Corticosteroid creams or ointments: fluprednidene acetate cream versus betamethasone-valerate

For an overview of studies on topical corticosteroids for the outcome investigator-rated good/excellent control, see the additional tables section (Table 2). That overview presents only the primary outcomes as defined according to our protocol (i.e. participant- or investigator-rated good or excellent control); consequently, this does not necessarily reflect the primary outcome that may be stated in the study report.

The point estimates (RRs) and confidence intervals (CIs), if available, are based on the per-protocol evaluation of participants, and are not based on an ITT analysis, unless stated otherwise. We considered statistical pooling, but the studies were too heterogeneous in terms of design, types of corticosteroid, assessment of outcomes, and presentation of data.

Primary outcome: percentage of participants with investigator-rated good/excellent control (healed) after three weeks of treatment

In a parallel study (Bleeker 1989), 14 out of 38 participants in the betamethasone group healed, as did 8 of 37 in the fluprednidene group. There was no clear difference between groups (RR 0.59, 95% CI 0.28 to 1.23; Analysis 3.1; Table 2).

Primary outcome: adverse events

Eight participants in the betamethasone group and seven in the fluprednidene group reported adverse events such as redness, smarting, swelling, irritation, or dryness (RR 0.90, 95% CI 0.36 to 2.23; Analysis 3.2), showing no clear differences between groups.

Secondary outcome: reduction in severity, investigator-rated scoring improvement > 50% after three weeks

After three weeks of treatment, 23 of 38 participants in the betamethasone group and 27 of 37 participants in the fluprednidene group showed improvement greater than 50% (Bleeker 1989). There were no clear differences between groups (RR 1.21, 95% CI 0.87 to 1.67; Analysis 3.3).

Comparison 4. Corticosteroid creams/ointments: betamethasone-dipropionate film-forming lotion versus betamethasone-dipropionate thick lotion

For this comparison, we found only one relevant trial (Gupta 1993).

Primary outcome: percentage of participants with investigator-rated good/excellent control of symptoms at day 7

Five of the 28 people in the betamethasone-dipropionate film-forming lotion group achieved good/excellent symptom control compared to zero of 26 in the control group. Fisher's exact test results in a P value of 0.051 (Analysis 4.1; Table 2).

Primary outcome: adverse events

No clear difference was found in relation to the occurrence of at least one adverse event (RR 1.33, 95% CI 0.33 to 5.44; Analysis 4.2).

In the betamethasone-dipropionate film-forming lotion group, two participants had stinging at the application site, one stinging in the eyes when opening the bottle close to the face, and one a "melting" feeling during the sauna visit compared to no application site reactions in the control group (Fisher's exact test P = 0.11). In the thickened lotion group, one participant experienced headache (probably not related to the study drug), and two had an exacerbation of hand eczema, compared to none in the control group (Fisher's exact test P = 1.00 and 0.49; also see Analysis 4.2). Zero events were reported in one of the arms for all of these three subgroups, and the confidence interval around the point of estimate was wide.

Secondary outcome: reduction in severity, investigator-rated scoring (not specified), and in overall severity at day 7

At day 7, 23 out of 28 participants in the film-forming group improved compared to 10 out of 26 participants in the thickened lotion group. There may be a difference between corticosteroid creams/ointments in favour of the betamethasone-dipropionate film-forming lotion at day 7 (RR 2.30, 95% CI 1.35 to 3.93; number needed to treat for an additional beneficial outcome (NNTB) 2, 95% CI 1 to 5; Analysis 4.3).

Secondary outcome: reduction in severity, investigator-rated global improvement, of eczema

The global comparison between treatments at day 7 showed improved eczema in 23 of 28 participants treated with polyacrylic film-forming lotion versus 18 of 26 participants treated with thickened lotion (RR 1.19, 95% CI 0.87 to 1.62; Analysis 4.4), indicating no clear difference in improvement between the two treatments.

Comparison 5. Corticosteroid creams/ointments: clobetasol propionate cream versus intermittent fluprednidene acetate cream

Primary outcome: percentage of participants with investigator-rated good/excellent control

No relapses were observed in 32 of 46 (70%) hands treated with clobetasol propionate cream and in 14 of 46 (30%) hands treated with fluprednidene acetate cream (Möller 1983). This is reported as 'other data'; see Analysis 5.1 and Table 2.

Primary outcome: adverse events

Adverse events occurred in four participants treated with clobetasol and in three participants treated with fluprednidene (reported as 'other data' in Analysis 5.2). One participant reported an adverse event from both glucocorticoids.

Comparison 6. Corticosteroid creams/ointments: clobetasol propionate foam 0.05% versus vehicle foam

This comparison included one study of 125 participants (Kircik 2013).

Primary outcome: percentage of participants with investigator-rated good/excellent control at day 15

In the clobetasol group, 38.7% (24/62 participants) had an Investigator Static Global Assessment (ISGA) score of 0 or 1 versus 27% (17/63 participants) in the vehicle group. There was no clear difference between groups (RR 1.43, 95% CI 0.86 to 2.40; Analysis 6.1; Summary of findings for the main comparison; Table 2).

Primary outcome: percentage of participants with self-rated good/excellent control at day 15

At the end of the study on day 15, 51.6% (32/62 participants) in the clobetasol group graded their hand eczema as clear or almost clear versus 22.2% (14/63 participants) in the vehicle group using the subject's global assessment (SGA). The relative risk of 2.32 favours clobetasol propionate foam over vehicle (RR 2.32, 95% CI 1.38 to 3.91; NNTB 3, 95% CI 2 to 8; Analysis 6.2; Summary of findings for the main comparison).

Primary outcome: adverse events

Adverse events were reported in 18% (11/62) of participants in the clobetasol propionate foam group and in 8% (5/63) of those in the vehicle foam group (RR 2.24, 95% CI 0.82 to 6.06; Analysis 6.3; Summary of findings for the main comparison). One participant reported application site burning/pruritus after clobetasol foam application. Three participants in the clobetasol group reported nasopharyngitis compared to one participant in the control group (RR 3.05, 95% CI 0.33 to 28.52; Analysis 6.3). No serious adverse events were reported in the clobetasol propionate foam group, and one participant in the vehicle group discontinued due to severe fissures (RR 0.34, 95% CI 0.01 to 8.16; Analysis 6.3). The wide confidence interval in this case could in part be the result of zero events in the clobetasol propionate foam group.

Secondary outcome: reduction in severity, participant-rated scoring, at day 15

At the end of treatment, 51 out of 62 participants (82.3%) had at least one grade improvement in SGA score, compared to 33 out of 63 participants (52.4%) in the vehicle group (RR 1.57, 95% CI 1.21 to 2.04; NNTB 3, 95% CI 2.2 to 7; Analysis 6.4; Summary of findings for the main comparison). This difference is statistically significant, but we have reduced confidence in it is clinical significance due to small sample size and limitation in study design.

Secondary outcome: reduction in severity, investigator-rated scoring, at day 15

In Kircik 2013, 26 out of 62 participants (41.9%) in the clobetasol group versus 18 out of 63 (28.6%) in the control group improved by two grades or more in ISGA score. There was no clear difference between groups (RR 1.47, 95% CI 0.90 to 2.39; Analysis 6.5).

In total, 45 participants (72.6%) in the clobetasol group versus 38 (60.3%) in the control group improved by at least one grade in ISGA score after 15 days of treatment. Again, there was no clear difference between groups (RR 1.20, 95% CI 0.94 to 1.55; Analysis 6.5).

Comparison 7. Corticosteroid creams/ointments: desonide cream 0.1% versus desonide cream 0.05%

Two strengths of the same topical corticosteroid were compared in a study using a within-participant (left/right) design (Uggeldahl 1986). Forty-six participants were treated twice daily with desonide (Tridesilone) cream 0.1% on one hand and desonide (Apolar) cream 0.05% on the other hand. These participants had not been treated for eczema for at least one week before the study. The duration of the study was only 14 days.

Primary outcome: adverse events

Two participants reported stinging upon application of desonide 0.05% cream (reported as 'other data'; Analysis 7.1).

Comparison 8. Corticosteroid creams/ointments: intermittent treatment with topical mometasone furoate at different frequencies (long term)

Veien 1999 included participants with chronic hand eczema that had cleared upon daily treatment for a maximum of 9 weeks with mometasone furoate cream.

Primary outcome: percentage of participants with investigator-rated good/excellent control

Mometasone furoate 3 times/week versus mometasone furoate 2 times/week

For this subgroup, we found only one relevant trial (n = 72) (Veien 1999). Among participants treated with mometasone three times a week, 29 out of 35 (83%) had no recurrences, compared to 25 out of 37 (68%) of those treated with mometasone two times a week. Mometasone furoate cream used thrice weekly may slightly improve investigator-rated good/excellent control of symptoms when compared to twice weekly application; however, the 95% confidence interval does include 1 (RR 1.23, 95% CI 0.94 to 1.61; Analysis 8.1; Summary of findings 2 Table 2).

Mometasone furoate 3 times/week versus emollients only

For this subgroup, we found only one relevant trial (n = 69) (Veien 1999). We noted a clear difference between corticosteroid creams/ointments: mometasone furoate cream 3 times weekly versus no steroids (RR 3.13, 95% CI 1.75 to 5.59; NNTB 2, 95% CI 1 to 3; Analysis 8.2; Table 2), but the difference may not be clinically significant due to imprecision of results caused by small sample size and limitations in study design/conduct.

Mometasone furoate 2 times/week versus emollients only

For this subgroup, we found only one relevant trial (n = 71) (Veien 1999). There was a statistically significant difference between corticosteroid creams/ointments: mometasone furoate cream 2 times weekly versus no steroids (RR 2.55, 95% CI 1.40 to 4.67; NNTB 2, 95% CI 2 to 5; Analysis 8.2), i.e. mometasone furoate twice a week was better than emollient only, but again, the difference may not be clinically significant due to imprecision of results caused by small sample size and limitations in study design/conduct.

Primary outcome: adverse events

Mometasone furoate 3 times/week versus mometasone furoate 2 times/week

In 10 participants, mild skin atrophy was noted at some point during the study. In five participants, atrophy disappeared during the study, and five participants had mild atrophy at the end of the study. The difference between groups was not clear (RR 1.76, 95% CI 0.45 to 6.83; Analysis 8.3; Summary of findings 2).

Comparison 9. Corticosteroid creams/ointments: 0.05% clobetasol and 2.5% zinc sulphate cream versus 0.05% clobetasol cream

Faghihi 2008 investigated whether zinc sulphate added to clobetasol cream is effective in the treatment of chronic hand eczema (n = 47 hands).

Primary outcome: percentage of participants with investigator-rated good/excellent control

After eight weeks, 25 out of 47 hands (53%) treated with clobetasol + zinc sulphate cream were clear from scaling compared to three hands (6%) treated with clobetasol cream alone (presented as 'other data' in Analysis 9.1; Table 2). Regarding erythema, 41 hands (87%) treated with clobetasol + zinc sulphate cream were clear after eight weeks compared to one hand (2%) treated with clobetasol cream alone (reported as 'other data' in Analysis 9.1). Last, 24 hands (51%) treated with clobetasol + zinc sulphate cream and seven hands (15%) treated with clobetasol cream alone were clear of lichenification (reported as 'other data' in Analysis 9.1). Absence of scaling, redness, and/or lichenification was seen as investigator-rated good/excellent control. An overall assessment of good/excellent control was not possible.

Primary outcome: adverse events

Treatments were well tolerated and no significant adverse events were reported or observed by participants in both groups. Trial authors concluded that treatments were generally well tolerated (no exact data given).

Comparison 10. Corticosteroid creams/ointments: betamethasone-valerate 0.1% cream twice daily versus betamethasone-valerate 0.1% cream and urea 5% cream

Lodén 2012a compared the application of betamethasone-valerate 0.1% cream twice daily versus the application of betamethasone-valerate 0.1% cream in the morning and a moisturiser containing urea 5% cream in the evening.

Primary outcome: percentage of participants with investigator-rated good/excellent control (cleared)

For this outcome, we found only one relevant trial (Lodén 2012a; n = 44). Clearance was defined as a score ≤ 3 on the HEES. There was no clear difference between betamethasone-valerate 0.1% cream (15 out of 22) and urea 5% cream (20 out of 22) (RR 0.75, 95% CI 0.55 to 1.03; Analysis 10.1; Table 2).

Secondary outcome: reduction in severity, participant-rated

For this outcome, we found only one relevant trial (Lodén 2012a; n = 44). The average reduction in VAS (mm) was 36.3 in the betamethasone-valerate 0.1% cream (BV) twice daily treatment group compared with 54.0 in the betamethasone-valerate and urea (BV + M) group. The mean difference with regards to the VAS score was -17.70, although the relatively wide confidence interval did borderline include zero; therefore the results should be interpreted with caution (mean difference (MD) -17.70, 95% CI -35.42 to 0.02; Analysis 10.2).

Secondary outcome: reduction in severity, investigator-rated

For this outcome, we found only one relevant trial (Lodén 2012a; n = 44). After two weeks, the average reduction in HEES was 12.5 (standard deviation (SD) 13.9) in the BV group compared to 10.5 (SD 9.0) in the BV + M group. There was no clear difference between groups (MD 2.00, 95% CI -4.92 to 8.92; Analysis 10.3).

Comparison 11. Topical others: coal tar paste versus betamethasone-valerate ointment 0.1% versus zinc oxide paste

In an unblinded randomised within-participant study (Kemper 1998), the efficacy of pix lithanthracis (coal tar paste) compared to zinc oxide paste and betamethasone-valerate was investigated (n = 19). Also see Table 3.

Primary outcome: adverse events

Six participants dropped out because they experienced problems with wearing gloves (the specific type of problem is not identified). One participant dropped out due to pompholyx as a result of allergy to 5% pix lithanthracis (reported as 'other data' in Analysis 11.1).

Comparison 12. Irradiation with UV light: UVB versus no UVB

For the phototherapy studies (UVA, UVB, PUVA), pooling was considered for two studies with data comparing UVB with no UVB or placebo (Bayerl 1999; Sjövall 1987); however, we found these studies too heterogeneous in terms of design, outcome assessment, and presentation of data to do so.

Treatment with a portable UVB phototherapy unit, to be used at home, was compared to no UVB treatment in a study among 48 participants with occupational hand dermatitis (Bayerl 1999).

Primary outcome: adverse events

In both groups, two participants showed an exacerbation. Other adverse events were stinging and burning sensations in some participants, which limited the increase in UVB therapy (RR 1.00, 95% CI 0.15 to 6.53; Analysis 12.1).

Comparison 13. Irradiation with UV light: whole body UVB versus placebo or local UVB hands

Primary outcome: percentage of participants with investigator-rated good/excellent control (cleared)

Local UVB hands alone versus placebo

For this subgroup, we found only one relevant trial. Three groups were compared in a trial of 18 participants with chronic hand eczema, and data for 10 participants were available (Sjövall 1987). Among participants receiving local UVB, two cleared, while in the group receiving filtered light (placebo UVB), one participant cleared (RR 2.00, 95% CI 0.26 to 15.62; Analysis 13.1; Table 4), but the confidence interval for the RR did not indicate clear differences between groups.

Whole-body UVB + local UVB hands versus placebo

For this subgroup, we found only one relevant trial (Sjövall 1987; n = 10). Five out of five participants in the whole-body UVB group showed good symptom control compared to one in the control group (RR 3.67, 95% CI, 0.90 to 14.97; Analysis 13.1; Table 4). However, the confidence interval around the effect estimate was wide and imprecise.

Whole-body UVB + local UVB hands versus local UVB hands alone

Five participants in the whole-body UVB irradiation group had good symptom control compared to two in the control group, but due to the small sample size, the intervention group did not demonstrate clear advantage over the group given local UVB of the hands alone (RR 2.20, 95% CI 0.83 to 5.84; Analysis 13.1; Table 4).

Primary outcome: adverse events

Adverse events were not seen in either group.

Secondary outcome: time until relapse (low score = better outcome)

A postal follow-up questionnaire three months after completion of treatment asked participants about the course of their hand dermatitis: the number of weeks in remission was presented in a descriptive way. In the local UVB group, two participants were still in remission after 15 weeks. The other three participants relapsed after 1 to 12 weeks (median 5 weeks). In the UVB local + whole-body group, all participants relapsed within 3 to 10 weeks (median 6 weeks). The participant in the placebo group who had reached remission relapsed after three weeks. This difference was not statistically significant for local UVB hands alone versus placebo (MD 4.10, 95% CI -3.25 to 11.45); for whole-body UVB + local UVB hands versus placebo (MD 0.50, 95% CI -4.98 to 5.98); nor for whole body UVB + local UVB hands versus local UVB hands alone (MD -3.60, 95% CI -9.68 to 2.48) (Analysis 13.2).

Comparisons 14 and 15. Irradiation with UV light: local narrow-band UVB versus local PUVA

For this outcome, we found two relevant trials (Sezer 2007, n = 24; and Brass 2015, n = 60). Brass 2015 was a parallel-group study that investigated local narrow-band UVB twice weekly compared to local PUVA twice weekly over a period of 12 weeks. Sezer 2007 studied local narrow-band UVB thrice weekly for nine weeks compared to local PUVA thrice weekly in a left-right study.

Primary outcome: percentage of participants with investigator-rated good/excellent control (clearance) in UVB versus PUVA

In Brass 2015, six out of 30 participants treated with narrow-band UVB improved compared to 12 out of 30 participants on local PUVA after 12 weeks (RR 0.50, 95% CI 0.22 to 1.16; Analysis 14.1; Summary of findings 3; Table 4).

In Sezer 2007, two out of 12 hands treated with UVB cleared (17%). On the PUVA-treated side, one hand cleared (8%), as presented in Analysis 15.1 and in Table 4.

Primary outcome: adverse events

Brass 2015 reported no serious treatment-related adverse events. An adverse event (mainly erythema) was reported in nine participants treated with local narrow-band UVB and in none of the participants treated with local PUVA (Fisher's exact test P = 0.0019; RR 19.00, 95% CI 01.16 to 312.42; Analysis 14.2; Summary of findings 3).

In Sezer 2007, one participant dropped out because of an exacerbation of eczema in both hands (unclear from which group). Palmar hyperpigmentation due to PUVA was observed in three participants (see Analysis 15.2).

Secondary outcome: reduction in severity, investigator-rated, by local narrow-band UVB versus local PUVA

The data for Brass 2015 were not reproducible; however in the PUVA group, the mTLSS was reduced from a median of 8.5 (range 0 to 16) and 8 (range 3 to 15) for the left and right hand, to a median of 3 (range 0 to 13) and 3 (range 0 to 14) (n = 23). In the local narrow-band UVB group, the median mTLSS was reduced from 7 (range 0 to 16) and 8.5 (range 1 to 15) to 5 (range 0 to 11) and 4.5 (range 0 to 11) after 12 weeks of treatment (n = 20) (Summary of findings 3).

We identified Sezer 2007 as the only relevant trial for this comparison (Sezer 2007, n = 24). For both treatments, researchers observed a marked clinical improvement in nine out of 12 hands (75%). The difference in total clinical scores between irradiation with UV light, local narrow-band UVB, and local PUVA was not clear (see Analysis 15.3).

Comparison 16. Irradiation with UV light: oral PUVA versus topical bath PUVA

Two studies investigated oral PUVA and bath PUVA (Tzaneva 2009; van Coevorden 2004a); however because the designs of these studies were substantially different, and because van Coevorden 2004a mainly focused on the at-home versus hospital-based version, we did not pool these studies. Also see Table 4.

Primary outcome: adverse events

van Coevorden 2004a included only adverse events that constituted a reason to discontinue. From the oral/home PUVA group, three participants dropped out because of adverse events (nausea). From the hospital/bath PUVA group, one dropped out because of adverse events (burn). There were no clear differences between groups (nausea Fisher's exact test P = 0.1180; RR 7.18, 95% CI 0.38 to 136.71; burn Fisher's exact test P = 1.00; RR 0.34, 95% CI 0.01 to 8.26; Analysis 16.1).

In Tzaneva 2009, investigators gave oral PUVA (8-methoxypsoralen capsules) to 14 participants and topical bath PUVA therapy with 8-methoxypsoralen to 13 participants. Erythema occurred in 10 participants (71%) in the oral PUVA group, and in eight participants (62%) in the bath PUVA group (Fisher's exact test P = 0.49; RR 1.16, 95% CI 0.67 to 2.00; Analysis 16.1). In the oral PUVA group, 10 participants reported nausea (Fisher's exact test P = 0.0002; RR 19.60, 95% CI 1.26 to 304.14; number needed to treat for an additional harmful outcome (NNTH) 1, 95% CI 1 to 2), five reported dizziness (Fisher's exact test P = 0.04; RR 10.27, 95% CI 0.62 to 169.16), and three reported headache (Fisher's exact test P = 0.22; RR 6.53, 95% CI 0.37 to 115.49). Adverse events were observed most often at the beginning of therapy and improved during subsequent treatments. None of these adverse events led to dropouts.

With the exception of 'erythema', all other subgroups in this outcome had zero events in one of the arms, which could have been responsible in part for the wide confidence interval around the point of estimate, and for which FIsher's exact test was used.

Secondary outcome: reduction in severity, investigator-rated improvement, in mean eczema scores at week 10

For this outcome, we found only one relevant trial (van Coevorden 2004a, n = 158). At the end of the treatment phase (10 weeks) in the home PUVA group, 56/78 participants (72%) showed improvement (mean 3.3, SD 3.8) versus 49/80 participants (61%) in the hospital/bath PUVA group (mean 2.5, SD 3.4) (MD 0.80, 95% CI -0.33 to 1.93; Analysis 16.2).

Secondary outcome: reduction in severity, investigator-rated improvement, in mean scores at week 18 (low score = better outcome)

For this outcome, we found only one relevant trial (van Coevorden 2004a, n = 158). At eight weeks after the treatment phase, the reduction in mean score from baseline was 3.1 (SD 4.05) versus 2.7 (SD 3.4), respectively; there was no clear difference between irradiation with UV light: oral PUVA and topical bath PUVA (MD 0.40, 95% CI -0.77 to 1.57; Analysis 16.3).

Comparison 17. Irradiation with UV light: topical PUVA versus UVA

In a 16-week within-participant (left-right) study, topical PUVA was compared with UVA (Grattan 1991) in 15 participants (n = 30 hands).

Primary outcome: adverse events

Only one participant who completed the study experienced a burning sensation on the back of his PUVA-treated hand (see Analysis 17.1). Probably two participants had to be withdrawn due to exacerbation of eczema - one from each group (see Analysis 17.1).

Comparison 18. Irradiation with UV light: UVA-1 versus betamethasone-valerate 0.1% cream

Irradation with UVA-1 three times a week was compared to topical betamethasone-valerate 0.1% twice a day over a six-week period in 47 participants (Said 2010).

Primary outcome: adverse events

Tolerance of both treatments was good. The only adverse event noted was post-phototherapy pigmentation, which occurred in 18 of the 24 participants treated with UVA-1 compared to none of the participants in the control group (Fisher's exact test P = 0.0001; RR 35.52, 95% CI 2.26 to 557.08; NNTH 1, 95% CI 1 to 2; Analysis 18.1). Zero events in the control group is likely to explain the wide confidence interval.

Comparison 19. Irradiation with UV light: UVA-1 versus placebo

UVA-1 irradiation for three weeks in 15 participants with dyshidrotic hand eczema was compared with placebo (simulated blue light) in 13 participants (Polderman 2003).

Primary outcome: adverse events

Apart from some minor erythemal reactions, no adverse events occurred. Three of 13 participants in the placebo group dropped out after two weeks because of exacerbation, but no clear differences was identified between groups (Fisher's exact test P = 0.2258; RR 0.13, 95% CI 0.01 to 2.22; Analysis 19.1). Zero events in the intervention group is likely to explain the wide confidence interval.

Secondary outcome: reduction in severity of itch, participant-rated decrease in VAS, at week 3 (higher score = greater reduction)

For this outcome, we found only one relevant trial (Polderman 2003, n = 28). Although there was a notable difference between irradiation with UV light: UVA-1 (mean 2.31, SD 2.01) and placebo (mean -1.37, SD 4.05) with regards to VAS scores for itch (MD 3.68, 95% CI 1.25 to 6.11; Analysis 19.2), we have low confidence about the strength of the finding due to limited sample size (i.e. imprecision).

Secondary outcome: reduction in severity, investigator-rated improvement in DASI, at week 3 (higher score = greater reduction)

In the same group of participants (Polderman 2003), the severity score on the Dyshydrotic eczema Area and Severity Index (DASI) decreased in the UVA-1 group (mean 8.67, SD 6.72) compared to the placebo group (mean -0.38, SD 8.87) in week 3 (MD 9.05, 95% CI 3.15 to 14.95; Analysis 19.3).

Comparison 20. Irradiation with UV light: PUVA versus UVA-1

In a within-participant study, the effectiveness of middle-dose UVA-1 irradiation was compared with topical cream PUVA therapy in 15 participants with chronic relapsing dyshidrotic hand eczema (Adams 2007).

Primary outcome: adverse events

Burning occurred in three participants in the topical cream PUVA group and in one participant in the UVA-1 group, and increased pruritus occurred in five participants in the topical PUVA group versus three in the UVA-1 group (Analysis 20.1).

Comparison 21. Irradiation with X-rays (ionising radiation)

Among trials evaluating the effects of ionising radiation (X-rays), we considered pooling the results of four studies comparing X-rays with placebo irradiation (Cartwright 1987; Fairris 1984; King 1984; Lindelöf 1987), but dosages, presentation of results, and follow-up times were considered too heterogeneous in most cases. Moreover, all these studies used a within-participant design (i.e. comparing one hand versus the contralateral hand). Superficial X-ray irradiation on one hand was compared with topical PUVA on the contralateral hand in 25 participants (Sheehan-Dare 1989). Also see Table 5.

Comparison 21A. Irradiation with X-rays: X-rays versus placebo

Primary outcomes: percentage of participants with investigator-rated good/excellent control

After one month in seven out of 15 participants, hands treated with X-rays were categorised as showing good response (defined as 'clear' or 'nearly clear'), whereas all 15 placebo-treated hands were categorised as showing poor response (defined as 'partly clear', 'no change', or 'relapse') (King 1984; see Analysis 21.1 and Table 5). After three months, ten irradiated hands and six placebo-treated hands were categorised as showing good response (see Analysis 21.1), and after six months there was a good response in 11 irradiated and eight placebo-treated hands (see Analysis 21.1). There were no clear differences between groups.

Primary outcome: adverse events

No systemic or local adverse events were noted.

Comparison 21B. Irradiation with X-rays: Grenz ray

The effect of 3 Gy Grenz ray therapy six times in weekly intervals was investigated in within-participant studies (Lindelöf 1987; 24 participants, 48 hands in a within-participant design; Cartwright 1987; 30 participants, 60 hands in a within-participant design).

Primary outcome: adverse events

Six participants had hyperpigmentation in treated hands, and no participants in the placebo group experienced adverse events (see Analysis 21.2); however, there is no clear difference between groups.

Comparison 21C. Irradiation with X-rays: X-rays versus Grenz rays

A within-participant study on 25 participants compared superficial X-ray and Grenz ray irradiation (Fairris 1985).

Primary outcome: adverse events

Fairris 1985 reported no adverse events from either therapy.

Comparison 22. Topical calcineurin inhibitors: tacrolimus ointment versus mometasone furoate

An overview of all of the studies on topical calcineurin inhibitors can be found in Table 6.

The current comparison included two studies (Schnopp 2002, n = 16; Katsarou 2012, n = 30).

Primary outcome: adverse events

Both treatments were well tolerated. None of the participants in Schnopp 2002 dropped out because of adverse events.

Katsarou 2012 investigated adverse events but did not report any.

Secondary outcome: reduction in severity, investigator-rated

Although the reduction in mean DASI equalled improvement in scores for both treatments after two weeks, no clear difference was found between groups. The mean DASI score was reduced from 18 (SD 12.68) to 6.6 (SD 6.18) in the tacrolimus group, and from 18.5 (SD 14.09) to 6.9 (SD 7.7) in the mometasone furoate group, respectively (Schnopp 2002; see Analysis 22.1 and Summary of findings 4).

Comparison 23. Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus vehicle cream

Two studies addressed this comparison (Krejci-Manwaring 2008, n = 32; Pacor 2006, n = 28).

Primary outcome: percentage of participants with investigator-rated good/excellent control (remarkable improvement/complete remission)

Pacor 2006: In the tacrolimus group, complete remission at the end of treatment was observed in six participants (6/14), and remarkable improvement in eight participants (8/14). Treatment with vehicle cream did not lead to remarkable improvement (0/14) and led to only mild improvement in 4 of 14 participants (Fisher's exact test P = 0.0001; RR 29.00, 95% CI 1.90 to 443.25; NNTB 1, 95% CI 1 to 1; Analysis 23.1; Summary of findings 5 Table 6). Zero events in the control group is likely to explain the wide confidence interval.

Primary outcome: adverse events

In Krejci-Manwaring 2008, researchers observed one case of each of the following adverse events: acute contact dermatitis at the site of the necklace, flare of atopic dermatitis on the foot, acne-like rash on the face, leg cramps, and worsening of hand dermatitis. Stinging was not reported.

In Pacor 2006, four participants (4/14) in the tacrolimus group experienced transient burning and itching at the application site, which was well tolerated (Fisher's exact test P = 0.1129; RR 9.00, 95% CI 0.53 to 152.93; Analysis 23.2; Summary of findings 5).

RR given above is based on zero events in one arm, which is likely to explain the wide confidence interval.

Comparison 24. Topical calcineurin inhibitors: pimecrolimus 1% cream versus vehicle

Five of the included studies addressed this comparison: Belsito 2004 (n = 294), Hordinsky 2010 (n = 652), Bauer 2012 (n = 36), Cherill 2000 (n = 48), and Baskan 2005 (n = 25).

Primary outcome: percentage of participants with investigator-rated good/excellent control (clear or almost clear) with pimecrolimus cream versus vehicle at three weeks

For this subgroup, we found only one relevant trial (Belsito 2004, n = 294). In all, 42 of 151 versus 26 of 143 participants had good investigator-rated symptom control in intervention and control groups, respectively. The favourable outcome for pimecrolimus was borderline because the confidence interval includes 1 and therefore should be interpreted with care (RR 1.53, 95% CI 0.99 to 2.36; NNTB 10, 95% CI 5 to 1111; Analysis 24.1). When the subgroups were analysed based on aetiology, we did not find significant differences for irritant, allergic, or endogenous hand eczema (Analysis 24.1; Table 6).

Primary outcome: percentage of participants with investigator-rated good/excellent control (clear or almost clear) with pimecrolimus cream versus vehicle at six weeks

For this subgroup, we found only one relevant trial (Hordinsky 2010, n = 652). Treatment success (IGA score 0 = clear and 1 = almost clear) was achieved in 97 of 325 participants (29.8%) in the pimecrolimus cream 1% group and in 76 of 327 participants in the vehicle group. Favourable outcomes for pimecrolimus were borderline significant because the confidence interval included 1 and should be interpreted with care (RR 1.28, 95% CI 0.99 to 1.66; Analysis 24.1).

Primary outcome: adverse events

Bauer 2012, Belsito 2004, and Hordinsky 2010 reported adverse events (Analysis 24.2). Hordinsky 2010 found no clear differences between groups in terms of treatment-related erythema or irritation (RR 0.56, 95% CI 0.30 to 1.06; n = 652); itching (RR 0.89, 95% CI 0.52 to 1.53; n = 652); warmth, stinging, and burning (RR 0.82, 95% CI 0.52 to 1.29; n = 652); or herpes simplex infection (RR 0.60, 95% CI 0.15 to 2.51; n = 652). No adverse events were stated in Cherill 2000 and Baskan 2005.

Secondary outcome: reduction in severity, participant-rated

For pruritus relief between pimecrolimus 1% and vehicle, we found only one relevant trial (Hordinsky 2010, n = 652). There appears to be greater pruritus relief in the intervention group (pimecrolimus 1% cream) than in the vehicle group (RR 1.15, 95% CI 1.06 to 1.25; NNTB 9, 95% CI 6 to 22; Analysis 24.3); however, benefit relative to the control group appears to be marginal.

Secondary outcome: time until relapse

Time to relapse was compared between pimecrolimus 1% cream and vehicle in Bauer 2012 (n = 36). Time to relapse did not differ significantly between groups according to the trial authors (pimecrolimus: 39.35 days; vehicle: 33.19 days); this was represented in a survival graph. We were unable to reproduce these analyses.

Comparison 25. Topical antibacterial agents: betamethasone-valerate/clioquinol cream versus betamethasone-valerate/ fusidic acid

Primary outcomes: percentage of participants with investigator-rated good/excellent control (intention-to-treat) after four weeks

For this outcome, we found one relevant trial (Hill 1998, n = 120). In the ITT analysis, 34 of 62 participants (54.8%) in the betamethasone-valerate/clioquinol group and 31 of 58 (53,4%) in the betamethasone-valerate/fusidic acid group had a good response (RR 1.03, 95% CI 0.74 to 1.43; Analysis 25.1; Table 7).

Primary outcome: adverse events

In the clioquinol group, 11 of 62 participants experienced adverse events versus nine of 58 participants in the fusidic acid group (RR 1.14, 95% CI 0.51 to 2.56; Analysis 25.2). Several other adverse events were observed, including chest infection (1/62 versus 0/58), application-related irritation (5/62 versus 5/58), deterioration of eczema (4/62 versus 4/58), eye watering (1/62 versus 0/58), hands coloured yellow (1/62 versus 0/58), hands feeling thick (0/62 versus 1/58), and vesicle on the hands (0/62 versus 1/58), but none of these showed between-group differences (Analysis 25.2).

As shown above, quite a few subgroups under this outcome had zero events in one of the arms; this is likely to explain the wide 95% confidence interval.

Comparison 26. Topical retinoids: bexarotene 1% gel versus bexarotene with corticosteroids

Primary outcomes: percentage of participants with investigator-rated good/excellent control (> 90% clearance on physician response rates)

Treatment success (> 90% clearance) was achieved by 39% in the bexarotene only group, by 46% in the B + MF group, and by 21% in the B + HC group.

Bexarotene only versus bexarotene + mometasone

For this subgroup, we found only one relevant trial (Hanifin 2004, n = 41). There was no clear difference between topical retinoids: bexarotene 1% gel and bexarotene with mometasone (RR 0.85, 95% CI 0.40 to 1.8; Analysis 26.1; Table 7).

Bexarotene only versus bexarotene + hydrocortisone

For this subgroup, we found only one relevant trial (Hanifin 2004, n = 42). There was no clear difference between topical retinoids: bexarotene 1% gel and bexarotene with hydrocortisone (RR 1.83, 95% CI 0.61 to 5.53; Analysis 26.1; Table 7).

Bexarotene + mometasone versus bexarotene + hydrocortisone

For this subgroup, we found only one relevant trial (Hanifin 2004, n = 27). There was no clear difference between topical retinoids: bexarotene 1% gel and mometasone versus bexarotene with hydrocortisone (RR 2.15, 95% CI 0.67 to 6.89; Analysis 26.1; Table 7).

Primary outcome: adverse events

Forty-one participants (75%) had one or more adverse events during the study, of whom 27 (49%) had one or more events possibly related to the study drugs. The bexarotene group had irritation/rash in eight participants; stinging/burning in two; and dermatitis flare in five. The B + MF group had irritation/rash in four

participants and stinging/burning in four participants. The B + HC group had irritation/rash in four participants; stinging/burning in four participants, and dermatitis flare in zero participants (which is likely to explain the wide 95% confidence interval). None of the adverse events occurred significantly more often in a study or control group (Analysis 26.2; Analysis 26.3).

Secondary outcome: reduction in severity, investigator-rated: > 90% and > 50% reduction in hand eczema area and severity index (HEASI)

The percentage with > 90% reduction in Hand Eczema Area and Severity Index (HEASI) score in the bexarotene only group was 36%, in the B + MF group 38%, and in the B + HC group 14%. But there was no clear difference between groups according to the study authors. For > 50% reduction in HEASI, the percentages were, respectively, 79%, 85%, and 64%.

Bexarotene only versus bexarotene + mometasone

For this subgroup, we found only one relevant trial (Hanifin 2004, n = 41). There was no clear difference between topical retinoids: bexarotene 1% gel and bexarotene with mometasone (RR 0.93, 95% CI 0.69 to 1.26; Analysis 26.4).

Bexarotene only versus bexarotene + hydrocortisone

For this subgroup, we found only one relevant trial (Hanifin 2004, n = 42). There was no clear difference between topical retinoids: bexarotene 1% gel and bexarotene with hydrocortisone (RR 1.22, 95% CI 0.79 to 1.89; Analysis 26.4).

Bexarotene + mometasone versus bexarotene + hydrocortisone

For this subgroup, we found only one relevant trial (Hanifin 2004, n = 27). There was no clear difference between topical retinoids: bexarotene 1% gel and mometasone versus bexarotene with hydrocortisone (RR 1.32, 95% CI 0.84 to 2.07; Analysis 26.4).

Comparison 27. Other topical agents: calmurid versus Aquacare

A within-participant study compared topical Aquacare HP cream to a calmurid cream (Fredriksson 1975).

Primary outcome: adverse events

In the calmurid group, 13 participants experienced a burning sensation upon application compared to no adverse events in the Aqua HP group (see Analysis 27.1).

Comparison 28. Fumaric acid 5% cream versus triamcinolone 0.1% cream

This study compared topical fumaric acid twice daily to triamcinolone cream twice daily for four weeks in 58 participants (Jowkar 2014).

Primary outcome: adverse events

Erythema and pruritus were noted in two participants in each treatment group (RR 0.93, 95% CI 0.14 to 6.18; Analysis 28.1).

Comparison 29. Furpalmate 0.3% cream versus hydrocortisone acetate 0.5% cream

Primary outcome: percentage of participants with investigator-rated and/or self-rated good/excellent control (complete remission)

For this outcome, we found only one relevant trial (Lauriola 2011, n = 40). In the study report, treatments were shown to be equally effective in "curing" or "improving" hand dermatitis after 14 days. In the furpalmate group, 18 of 20 participants (90%) were cured or improved after 14 days, and this occurred in 20 of 20 participants in the hydrocortisone group (100%) (RR 0.90, 95% CI 0.76 to 1.07; Analysis 29.1; Table 7).

Comparison 30. Fumaria parviflora versus vehicle cream

Studies using a parallel-group design compared use of 2% Nigella sativa L. (family Ranunculaceae) ointment (a traditional medicine) twice daily with 0.1% betamethasone ointment twice daily and with Eucerin cream twice daily in 60 participants over four weeks (Yousefi 2012, n = 60).

A parallel-group study (Jowkar 2011, n = 44) compared the effect of an extract of 4% Fumaria parviflora Lam. cream twice a day versus vehicle cream (placebo) twice daily in 44 participants for four weeks.

Primary outcome: adverse events

Yousefi 2012 reported no adverse events for treatment with Nigella sativa L. and Eucerin cream.

In Jowkar 2011, one participant dropped out due to development of redness and papules in the Fumaria parviflora Lam. cream group (RR 3.00, 95% CI 0.13 to 69.87; Analysis 30.1). Zero events in the vehicle group is likely to explain the wide confidence interval and Fisher's exact test results with a P value of 1.00.

III. Systemic treatments

We identified no randomised controlled trials on oral corticosteroids.

Comparison 31. Oral immunosuppressants: oral azathioprine and topical clobetasol propionate versus topical clobetasol propionate only

Agarwal 2013 compared oral azathioprine with topical clobetasol propionate 0.05% cream to topical clobetasol propionate 0.05% cream alone in 108 participants; 91 participants completed the trial.

Primary outcome: percentage of participants with investigator-rated good/excellent control

After eight weeks, 36.95% in the clobetasol only group had a good response (defined as 75% improvement in signs and symptoms) versus 73.3% in the clobetasol with additional azathioprine 50 mg group (RR 1.98, 95% CI 1.31 to 3.01; NNTB 3, 95% CI 2 to 6; Analysis 31.1). After 24 weeks, 39.13% in the clobetasol only group improved, as did 91.1% in the clobetasol and azathioprine group (RR 2.33, 95% CI 1.61 to 3.38; NNTB 2, 95% CI 1 to 3; Analysis 31.1; Table 8).

Primary outcome: adverse events

No adverse events that would require reduction of dosage or discontinuation of treatment were reported.

Secondary outcomes: reduction in severity, investigator-rated (higher score = greater reduction)

This was measured by the hand eczema severity index (HECSI): after 24 weeks, 64.66% in the control group showed improvement, as did 91.29% in the intervention group (MD 10.79, 95% CI 4.77 to 16.81; Analysis 31.2).

Secondary outcome: reduction in severity of itch, participant-rated (higher score = greater reduction)

After 24 weeks, the itch score difference was 6.04 (SD 2.35) in the intervention group, and 4.56 (SD 2.26) in the control group (MD 1.48, 95% CI 0.53 to 2.43; Analysis 31.3). This is a participant-rated outcome, measured on a numerical scale from 0 to 10.

Comparison 32. Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate

Primary outcome: percentage of participants with investigator-rated good/excellent control

Overall assessment of good/very good efficacy was 60% in the cyclosporin group and 31% in the betamethasone group (Granlund 1996). There was no apparent difference between groups (RR 1.88, 95% CI 0.88 to 3.99; n = 34; Analysis 32.1; Summary of findings 6; Table 8).

Primary outcome: percentage of participants with self-rated good/excellent control

One study addressed this (Granlund 1996, n = 34; the original randomised number was n = 41, but seven people left the study early; hence data were available for only 34 people). Overall assessment of good/very good efficacy was 60% in the cyclosporin group and 48% in the betamethasone group; the difference between groups was unclear (RR 1.25, 95% CI 0.69 to 2.27; Analysis 32.2; Summary of findings 6).

Primary outcome: adverse events

"Some kind of adverse event" occurred in 19 of 28 participants on cyclosporin and in 15 of 27 participants in the betamethasone group (RR 1.22, 95% CI 0.80 to 1.86; Analysis 32.3; Summary of findings 6). In the cyclosporin group, one participant experienced dizziness, vomiting, and facial oedema versus zero events in the control group (Fisher's exact test P = 1.00; RR 2.90, 95% CI 0.12 to 68.15; Analysis 32.3). In the betamethasone group, one participant had insomnia versus zero events in the cyclosporin group (Fisher's exact test P = 0.49; RR 0.32, 95% CI 0.01 to 7.57; Analysis 32.3) (Granlund 1996). Two people in the cyclosporin group had an increase in serum creatinine of greater than 30% versus zero events in the betamethasone group (Fisher's exact test P = 0.49; RR 4.83, 95% CI 0.24 to 96.16; Analysis 32.3). Zero events in some of the above analyses is likely to explain the wide 95% confidence interval.

The number of participants in this section is different from that in the other sections because in the publication, adverse events in the run-in and cross-over phases are combined.

Secondary outcome: reduction in severity, investigator-rated total disease activity score (six weeks; higher score = greater reduction)

For this outcome, we found only one relevant trial (n = 34) (Granlund 1996).

The mean total decrease in total disease activity score was 6.0 (SD 4.3) in the cyclosporin group and 5.7 (SD 4.0) in the betamethasone group (MD 0.30, 95% CI -2.50 to 3.10; Analysis 32.4; Summary of findings 6).

Comparison 33. Oral immunosuppressants: oral cyclosporin versus alitretinoin

NCT01231854 compared cyclosporin to alitretinoin but was ended prematurely due to inability to include the total number of participants. According to the sample size calculation, 78 participants should have been included; however, only 15 participants were included and 14 were analysed.

Primary outcome: percentage of participants with investigator-rated good/excellent control (IGA) after 24 weeks

In the cyclosporin group, three out of seven participants (42.9%) reached complete or nearly complete clearance of hand eczema according to the Investigator Global Assessment (IGA), as did two out of seven participants (28.6%) in the alitretinoin group, after 24 weeks. There was no apparent difference between groups (Fisher's exact test P = 1.00; RR 1.50, 95% CI 0.35 to 6.40; Analysis 33.1; Table 8).

Primary outcomes: percentage of participants with participant-rated good/excellent control (PGA) after 24 weeks

In the cyclosporin group, four out of seven participants (57.1%) reached complete or nearly complete clearance of hand eczema according to the Patient Global Assessment (PGA), as did two out of seven participants (28.6%) in the alitretinoin group. There was no apparent difference between groups (Fisher's exact test P = 0.59; RR 2.00, 95% CI 0.53 to 7.60; Analysis 33.2).

Primary outcome: adverse events

Six adverse events were documented, of which two were possibly related to the use of cyclosporin (fatigue, bone ache, dry lips in one participant, and exacerbation of atopic eczema in another participant). No serious adverse events were recorded throughout the trial. At least one adverse event occurred in 3 of 7 cyclosporin participants and in 2 of 7 alitretinoin participants (Fisher's exact test P = 1.00; RR 1.50, 95% CI 0.35 to 6.40; Analysis 33.3).

Secondary outcome: time until relapse

None of the participants relapsed during the 24 weeks of follow-up (0 of 7 versus 0 of 7).

Comparison 34. Oral retinoids: acitretin versus placebo

Oral acitretin was compared with placebo capsules in a study that enrolled 29 participants with hyperkeratotic dermatitis of the palms (Thestrup-Pedersen 2001). Fourteen participants were allocated to 30 mg acitretin once daily for eight weeks, and 15 participants received identical looking placebo capsules. This study did not provide useable data for analysis, as only subscale mean score was available, without SD.

Primary outcome: adverse events

No adverse events were reported and all biochemical parameters were within normal limits in both groups.

Secondary outcome: reduction in severity, investigator rated, after four and eight weeks

Trial authors used a score system composed of subscales with hyperkeratosis, fissures, scaling, itch, and redness. After four weeks of treatment, a 51% reduction in all symptoms was seen in the acitretin group compared to a 9% reduction in the placebo group. No further improvement was seen after eight weeks of treatment (Thestrup-Pedersen 2001). No reproducible data were given.

Secondary outcome: reduction in severity, participant-rated number of participants with improvement in itch

After eight weeks of treatment, itch was reduced by 41% in the acitretin group compared to 19% in the placebo group (Thestrup-Pedersen 2001). No reproducible data were given.

Comparison 34A. Oral retinoids: alitretinoin versus placebo

Four studies investigated the effect of oral alitretinoin: Bissonnette 2010, Fowler 2014, Ruzicka 2004, and Ruzicka 2008.

Primary outcome: percentage of participants with investigator-rated good/excellent control (clear or almost clear) at week 12, at week 24, or at end of treatment

In Ruzicka 2004 and Ruzicka 2008, clearance or almost clearance of eczema occurred more often in all groups treated with alitretinoin compared to placebo after 12 weeks. Fowler 2014 studied this after 24 weeks.

Alitretinoin 40 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 159). There might be a difference between groups, as 43 out of 81 participants in the 40 mg group had clear or almost clear status for PaGA compared to 21 of 78 in the placebo group (RR 1.97, 95% CI 1.30 to 3.00; NNTB 4, 95% CI 2 to 9; Analysis 34.1; Table 9).

Alitretinoin 30 mg versus placebo

For this subgroup, we found two relevant trials (Ruzicka 2008, n = 614; Fowler 2014, n = 596). There was a clear difference between alitretinoin 30 mg and placebo, and the alitretinoin group was 2.75 times more likely to achieve symptom-clear status compared to the placebo group (RR 2.75, 95% CI 2.20 to 3.43; NNTB 4, 95% CI 3 to 5; Analysis 34.1; Summary of findings 7; Table 9).

Alitretinoin 20 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 158). There was no clear difference between groups, as 32 out of 80 participants in the 20 mg group had clear or almost clear status for PaGA, compared to 21 of 78 in the placebo group (RR 1.49, 95% CI 0.94 to 2.34; Analysis 34.1; Table 9).

Alitretinoin 10 mg versus placebo

For this subgroup, we found two relevant trials (n = 781). According to both studies (Ruzicka 2004; Ruzicka 2008), alitretinoin 10 mg was more effective for this outcome (respectively, 39% and 28%) compared to placebo (RR 1.58, 95% CI 1.20 to 2.07; NNTB 11, 95% CI 6.3 to 26.5; Analysis 34.1; Summary of findings 8; Table 9). There might be a difference between groups, but we are uncertain of the strength of the evidence due to imprecision of the estimates.

Primary outcome: percentage of participants with self-rated good/excellent control (clear or almost clear) with PaGA at week 12, at week 24, or at end of treatment

Ruzicka 2004 shows that for all doses of alitretinoin, statistically significantly more participants rated their eczema as clear or almost clear compared to those given placebo.

Alitretinoin 40 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 147). Of 74 participants in the 40 mg group, we judged that 32 had clear or almost clear status for PaGA compared to nine of 73 in the placebo group (RR 3.51, 95% CI 1.80 to 6.82; NNTB 3, 95% CI 2 to 6; Analysis 34.5). There might be a difference between groups, but we are uncertain of the strength of the evidence due to imprecision of the estimates.

Alitretinoin 30 mg versus placebo

For this subgroup, we found two relevant trials (Ruzicka 2008, n = 614; Fowler 2014, n = 596). There might be a difference in the study of Ruzicka 2008: 163 out of 409 participants in the 30 mg group were judged as having clear or almost clear status for PaGA after 200 days or at the end of treatment, compared to 31 of 205 in the placebo group (RR 2.64, 95% CI 1.87 to 3.72; Analysis 34.5), but we are uncertain of the strength of the evidence due to imprecision of the estimates.

Pooling the data for alitretinoin 30 mg (heterogeneity statistics: Chi^2 test = 0.11, P = 0.74; I^2 = 0) gives an effect estimate that clearly favours the intervention group and demonstrates that the alitretinoin group was 2.75 times more likely to achieve improvement relative to the placebo group (RR 2.75, 95% CI 2.18 to 3.48; NNTB 4, 95% CI 3 to 5; Analysis 34.5; Summary of findings 7).

Alitretinoin 20 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 147). Of 74 participants in the 20 mg group, 25 were judged to have clear or almost clear status for PaGA compared to 9 of 73 in the placebo group (RR 2.74, 95% CI 1.37 to 5.46; NNTB 5, 95% CI 3 to 13; Analysis 34.5). There might be a difference between groups, but we are uncertain of the strength of the evidence due to imprecision of the estimates.

Alitretinoin 10 mg versus placebo

For this subgroup, we found two relevant trials (n = 765). Both studies found that 10 mg alitretinoin was more effective (respectively, 29% and 24% clear or almost clear) than placebo (Ruzicka 2004; Ruzicka 2008). Pooling these data for 10 mg alitretinoin (heterogeneity statistics: Chi^2 test = 0.89, P = 0.35; I^2 = 0) shows there might be a difference between groups, but we are uncertain of the strength of the evidence due to imprecision of the estimate (RR 1.73, 95% CI 1.25 to 2.40; NNTB 9, 95% CI 6 to 20; Analysis 34.5; Summary of findings 8).

Primary outcome: adverse events

Studies listed in detail the adverse events observed; headache was one of the most frequent events (22 in 40 mg group, eight in 20 mg group, four in 10 mg group, and seven in the placebo group in Ruzicka 2004; and 87 of 296 and 81 of 409 participants using alitretinoin 30 mg in Fowler 2014 and Ruzicka 2008, respectively). There was no clear difference between groups for 10 mg (Analysis 34.6), 20 mg (Analysis 34.7), or 40 mg (Analysis 34.9) versus placebo. However, the 30 mg versus placebo subgroup comparison produced a few notable between-group differences (Analysis 34.8), specifically for the following adverse events: headache (RR 3.43, 95% CI 2.45 to 4.81; NNTH 6, 95% CI 4 to 11), flushing (RR 7.28, 95% CI 2.05 to 25.86; NNTH 25, 95% CI 17 to 50), erythema (RR 5.79, 95% CI 2.09 to 16.06; NNTH 25, 95% CI 14 to 100), nausea (RR 3.82, 95% CI 1.67 to 8.76; NNTH 27, 95% CI 18 to 56), elevated blood triglycerides (RR 7.05, 95% CI 1.89 to 26.28; NNTH 33, 95% CI 20 to 50), vomiting (RR 8.00, 95% CI 1.01 to 63.57; NNTH 50, 95% CI 23 to 250), and tinnitus (RR 4.33, 95% CI 1.25 to 15.05; NNTH 33, 95% CI 17 to 100). With the exception of headache, we have limited confidence in the

clinical significance of the differences mentioned above because in most of these analyses, the number of events was too small; hence, this reduced the precision of the effect estimates. Limitations in the quality of the trial further compromised our confidence in this finding.

Some of the outcomes above had zero events in one arm, which is likely to explain the wide 95% confidence interval. These outcomes are dry lips, fatigue, rigours, tonsillitis, and elevated blood triglycerides.

Secondary outcome: reduction in severity, investigator-rated, in total lesion symptom score

Ruzicka 2004 observed a higher median % reduction in total lesion symptom score for all doses of alitretinoin compared to placebo: 25% in the placebo group (stated 95% CI -42 to -14) versus 52% in the 20 mg group (stated 95% CI -73 to -42) and 71% in the 40 mg group (stated 95% CI -80 to -44; Analysis 34.10). The difference between alitretinoin and placebo was apparent for both doses according to study authors (Analysis 34.10). There was also reporting of a decrease in extent of disease in all groups, but no details were given. We have plotted these data (Analysis 34.11) based on the medians. Because the original data were not available to us, we were unable to assess whether the data were skewed; therefore, it is uncertain whether the medians are close to the means.

Alitretinoin 40 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 159). Only median data were available; hence, we reported these as 'other data' in a table (Analysis 34.11). The median of the alitretinoin group is evidently higher than that of the placebo group; however, we are unsure of the clinical importance of the observed difference.

Alitretinoin 20 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 158). Only median data were available; hence, we reported these as 'other data' in a table (Analysis 34.11). Similar to the previous analysis, the median of the alitretinoin group is evidently higher than that of the placebo group; however, we are unsure of the clinical importance of the observed difference.

Alitretinoin 10 mg versus placebo

For this subgroup, we found only one relevant trial (Ruzicka 2004, n = 158). Only median data were available; hence, we reported these as 'other data' in a table (Analysis 34.11). The median of the alitretinoin group is evidently higher than that of the placebo group, as in the previous analysis, and we are unsure of the clinical importance of the observed difference.

Secondary outcome: reduction in severity, investigator-rated, in modified total lesion symptom score

Fowler 2014: the modified total lesion symptom score showed a change of -53.99% in the alitretinoin 30 mg group after 24 weeks and a change of -29.86% in the placebo group. For the mean difference in reduction, these numbers were inverted, so the mean difference in reduction of severity was 24.13 (MD 24.13, 95% CI 17.87 to 30.39; Analysis 34.12).

Ruzicka 2008: the median reduction in the modified total lesion symptom score was 75% in the 30 mg group and 56% in the 10 mg group, compared to 39% in the placebo group (Analysis 34.10).

Secondary outcome: time to relapse

Fowler 2014 included a follow-up phase up to 48 weeks after end of treatment. The median time to relapse after end of treatment was 83.0 weeks, with a 95% CI of 48.3 to 83.0, according to trial authors.

For Ruzicka 2008, the median time to relapse was 5.5 months for alitretinoin 30 mg, 6.2 months for alitretinoin 10 mg, and 5.4 months for placebo.

Comparison 35. Oral retinoids: re-treatment with alitretinoin versus placebo

In Bissonnette 2010, 117 participants with chronic hand eczema were successfully treated with alitretinoin in an earlier study (Ruzicka 2008); 24 withdrew.

Primary outcome: percentage of participants with investigator-rated good/excellent control (clear or almost clear)

Alitretinoin 30 mg versus placebo

For this subgroup, we found only one relevant trial (Bissonnette 2010, n = 73). A total of 39 out of 49 participants (80%) who were re-treated with 30 mg alitretinoin were rated as 'clear' or 'almost clear' according to the PGA, compared to 2 of 24 participants (8%) who were re-treated with placebo. There appears to be a large effect favouring the intervention group (RR 9.55, 95% CI 2.51 to 36.27; NNTB 1, 95% CI 1 to 2; Analysis 35.1; Table 9); however, we have limited confidence in this finding due to the small sample size and risk of bias in the study itself.

Alitretinoin 10 mg versus placebo

For this subgroup, we found only one relevant trial (Bissonnette 2010, n = 31). Ten out of 21 participants were cleared or almost cleared again under re-treatment with 10 mg alitretinoin in comparison to 1 out of 10 participants who were re-treated with placebo (10%) (RR 4.76, 95% CI 0.70 to 32.25; Analysis 35.1; Table 9). In the group that was re-treated with placebo, 9 out of 13 participants (69%) responded again.

Primary outcome: adverse events

Headache was the most frequently reported adverse event in the 30 mg group; 7 of 50 participants reported headache in the intervention group compared with zero events in the placebo group (Fisher's exact test P = 0.0129; RR 13.82, 95% CI 0.81 to 235.45; Analysis 35.3). None of the participants in the alitretinoin 10 mg group or in the placebo group reported headache. Adverse events occurred similarly in both groups (Analysis 35.2; Analysis 35.3). Three serious adverse events were reported: one case of acute cardiac failure with fatal outcome in the 10 mg group, which was not related to the study drug; one case of aortic aneurysm and one case of coronary artery disease (both in the 30 mg group) were assessed as having a remote relationship to the study drug.

Comparison 36. Other oral interventions: oral triethylenetetramine versus placebo

Burrows 1986 (n = 23) studied oral triethylenetetramine versus placebo and included exclusively nickel-sensitive participants.

Primary outcome: percentage of participants with investigator- and participant-rated good/excellent control

We found one study for this outcome (Burrows 1986), including 23 participants in a cross-over design, of which 20 were analysed. Because the data before cross-over are not available, rather than analysing the post-cross-over data, we have presented them in a table for the readers' review (Analysis 36.1; Table 10). This outcome was based on a global assessment (improved/no change/deterioration) by participant and doctor, probably by consensus, and included both phases of the cross-over study.

Primary outcome: adverse events

None of the participants in Burrows 1986 reported adverse events; however, this trial was ended prematurely due to increased teratogenicity among rats who received trientine.

Comparison 37. Other oral interventions: tetraethylthiuram disulfide (TETDS) versus placebo

Kaaber 1983 studied oral tetraethylthiuram disulfide (TETDS) versus placebo in 24 nickel-sensitive participants.

Primary outcome: percentage of participants with investigator-rated good/excellent control during treatment period

For this outcome, we found only one relevant trial (Kaaber 1983, n = 24). Among participants receiving the active compound, 5 out of 11 'healed' versus 2 out of 13 in the placebo group. Analysis 37.1 shows no clear difference between the two groups in that the 95% CI includes 1 and is wide (Fisher's exact test P = 0.1819; RR 2.95, 95% CI 0.71 to 12.34). Also see Table 10.

Primary outcome: adverse events

In the group receiving tetraethylthiuram disulphide, hepatic toxicity was experienced in two participants (Fisher's exact test P = 0.48; RR 5.00, 95% CI 0.26 to 96.13; Analysis 37.2) and headache in one (Fisher's exact test P = 1.00; RR 3.00, 95% CI 0.13 to 68.26; Analysis 37.2). Two participants had mild acne, but it is not clear to which group they were assigned. In the intervention group, there was one case of discontinuation due to depression and one case of discontinuation due to dyspepsia, whereas neither event occurred in the control group (Fisher's exact test P = 1.00; Analysis 37.2). There were zero events in placebo group for all of the above subgroups; this is likely to explain the wide 95% confidence intervals.

Comparison 38. Other oral interventions: low-nickel diet (LND) and disulphiram versus normal diet and placebo

Sharma 2006 (n = 21) compared a low-nickel diet combined with disulphiram versus a normal diet and placebo and included exclusively nickel-sensitive participants.

Primary outcomes: percentage of participants with self-rated good/excellent control (clearance of eczema) after four weeks

For this outcome, we found only one relevant trial (Sharma 2006, n = 21). Ten of the 11 participants in the LND group reached good/excellent control compared to 1 of 10 in the control group (Fisher's exact test P = 0.0003; RR 9.09, 95% CI 1.40 to 58.91; NNTB 1, 95% CI 1 to 2; Analysis 38.1).

Primary outcome: adverse events

Three out of 11 participants treated with disulphiram experienced a metallic taste (Fisher's exact test P = 0.2143; RR 6.42, 95% CI 0.37 to 110.71; Analysis 38.2), and two had mild drowsiness (Fisher's exact test P = 0.4762; RR 4.58, 95% CI 0.25 to 85.33; Analysis 38.2). Three participants treated with disulphiram showed mild elevation of liver enzymes (Fisher's exact test P = 0.2143; RR 6.42, 95% CI 0.37 to 110.71; Analysis 38.2).

Comparison 39. Other oral interventions: oral evening primrose oil versus placebo

Secondary outcome: reduction in severity, investigator-rated score at week 24

For this outcome we only found one relevant trial (Whitaker 1996, n = 34) on oral gamma-linoleic acid (GLA, evening primrose oil, Epogam). Mean and SD of the evening primrose oil group is 18 ± 12.37, and for the placebo group is 30.4 ± 23.36. There was no clear difference between the oral interventions (MD -12.40, 95% CI -25.46 to 0.66, Analysis 39.1).

Comparison 40. Other oral interventions: ranitidine versus placebo

Primary outcome: percentages of participants with self- and/or investigator-rated good/excellent control (clearance / marked alleviation)

For this outcome, we found only one relevant trial (Veien 1995, n = 47). Although it is not clear whether this was participant- or investigator-rated, 17 out of 23 with ranitidine cleared or were markedly improved versus 8 out of 24 receiving placebo (RR 2.22, 95% CI 1.20 to 4.10; NNTB 2, 95% CI 2 to 7; Analysis 40.1; Table 10).

Primary outcome: adverse events

No adverse events were reported in the ranitidine or placebo group.

Comparison 41. Other oral interventions: disodium cromoglycate diet (DSCG) versus low-nickel diet

For this comparison, we found one study (Pigatto 1990), which included 16 participants in three different treatment groups (disodium cromoglycate diet (DSCG) versus low-nickel diet versus a non-randomised control for eight participants who did not give consent for the study and were only followed up). Because participants were not randomised, this subgroup is deleted from the review.

Primary outcomes: number of participants with self-rated good/excellent control of itch after three months

For this outcome, we found only one relevant trial (n = 16) (Pigatto 1990). The numbers of events in the disodium cromoglycate and low-nickel groups were 5 of 8 and 1 of 8, respectively (Fisher's exact test P = 0.1189; RR 5.00, 95% CI 0.74 to 33.78; Analysis 41.1).

DISCUSSION

Summary of main results

Hand eczema is a common condition. In light of the high prevalence of hand eczema, it is striking that the results of all 60 identified randomised controlled trials (RCTs) are based on approximately 5469 participants, whereby about half of them (n = 2893) were enrolled in five RCTs: three on the oral retinoid alitretinoin

(Fowler 2014; Ruzicka 2004; Ruzicka 2008), and two on the topical calcineurin inhibitor pimecrolimus (Belsito 2004; Hordinsky 2010).

Although many systematic reviews focus on a single treatment modality or its closely related variants, we have tried to include all interventions in this review in an attempt to determine which therapy would reflect current standard treatment and the extent to which there is evidence for its effectiveness. The wide range of available treatments underlines the fact that there does not seem to be a single candidate for standard therapy. Topical corticosteroids and ultraviolet (UV) phototherapy are the major treatment options for chronic hand eczema, although in this review, we found little strong or consistent evidence that one intervention for hand eczema should be recommended over the other.

About half of the studies (n = 33) included our primary outcome of good/excellent control of symptoms rated by participants or by investigators. The definition of good/excellent control varied across studies because a wide variety of outcome measures were used. Most studies included the primary outcome adverse events (n = 55). None of the adverse events were life-threatening, and most were mild (local irritation with stinging, erythema, and burning).

Of the nine trials on topical corticosteroids, each dealt with a different type of steroid. The duration of six studies was rather short, namely, one week (Gupta 1993), two weeks (Faghihi 2008; Fowler 2005; Kircik 2013; Lodén 2012a; Uggeldahl 1986), and three weeks (Bleeker 1989). Treatment in Veien 1999 lasted up to 36 weeks, and treatment duration in Möller 1983 is unknown. Three trials compared two different corticosteroids. The comparators used in the remaining trials were the same corticosteroids as those used for the intervention, the same treatment but in a different vehicle, or a different dosage, or they were applied at a different frequency or were combined with zinc sulphate or urea, or consisted of vehicle alone.

Based on one study (125 participants), which compared clobetasol propionate foam with vehicle, clobetasol probably improves participant-rated good/excellent symptom control more than vehicle; however, the difference between groups on observer-rated scales is less clear (moderate-certainty evidence) (Kircik 2013). Another study (72 participants) compared mometasone furoate cream used thrice weekly compared to twice weekly, and mometasone furoate cream used thrice weekly may slightly improve investigator-rated good/excellent control of symptoms (low-certainty evidence); participant-rated symptoms were not measured (Veien 1999). See Summary of findings for the main comparison and Summary of findings 2.

The 10 trials on UV phototherapy were too heterogeneous for pooling. Three studies provided UVB as the main intervention, three gave UVA-1, and six used oral psoralen combined with UVA (PUVA) as the main intervention or comparator. Other comparators included no treatment, placebo, UVB, the same treatment as the intervention but at different sites, UVA, and topical betamethasone-valerate cream. One study had a treatment duration of less than one month (Polderman 2003), five had a treatment duration of less than two months (Adams 2007; Bayerl 1999; Grattan 1991; Said 2010; Sjövall 1987), three had a treatment duration of two to four months (Brass 2015; Sezer 2007; van Coevorden 2004a), and one had a treatment duration greater than four months (Tzaneva 2009).

In one of the studies comparing local narrow-band UVB to local PUVA, results showed that PUVA may lead to an improvement in investigator-rated good/excellent symptom control (60 participants), but the 95% confidence interval indicates that local PUVA might make little or no difference (moderate-certainty evidence). Participant-rated symptoms were not measured (Brass 2015). See Summary of findings 3.

The topical calcineurin inhibitors were studied in nine RCTs, and almost all studies compared tacrolimus or pimecrolimus to vehicle. Based on one small study comparing tacrolimus over two weeks to vehicle, investigator-rated good/excellent symptom control is probably more likely to be achieved in those treated with tacrolimus (14/14 participants in the tacrolimus group versus zero people in the vehicle group), but participant-rated good/excellent control of symptoms was not measured (28 participants) (moderate-certainty evidence) (Pacor 2006). Tacrolimus was compared to mometasone in a within-participant trial but did not measure investigator- or participant-rated good/excellent symptoms (Schnopp 2002). See Summary of findings 4 and Summary of findings 5.

Three studies assessed immunosuppressants, which were compared against a steroid or a retinoid. In one cross-over RCT comparing oral cyclosporin to topical betamethasone dipropionate, cyclosporin probably slightly improves participant- or investigator-rated good/excellent control of symptoms (34 participants) (moderate-certainty evidence) (Granlund 1996). See Summary of findings 6.

A relatively new treatment option is oral alitretinoin, which has been compared with placebo in three large trials, with a total enrolment of 1947 participants (Fowler 2014; Ruzicka 2004; Ruzicka 2008). These trials investigated, in addition to other dosages, a daily dosage of 10 mg. Ruzicka 2004 and Ruzicka 2008 were considered sufficiently equivalent to pool the data for 10 mg daily, which showed that alitretinoin was more effective than placebo in both investigator- and participant-rated good/excellent control of symptoms (high-certainty evidence). Even larger risk ratios were observed when a higher dosage of alitretinoin (30 mg) was compared to placebo for both outcomes (Fowler 2014; Ruzicka 2008) (high-certainty evidence). See Summary of findings 7 and Summary of findings 8.

Oral alitretinoin has not yet been compared to other treatment modalities such as corticosteroids or UV phototherapy. Unfortunately, the study that was expected to further clarify the position of systemic treatments with retinoids or systemic immunosuppressants (alitretinoin versus cyclosporin) in the treatment of hand eczema was ended prematurely (NCT01231854). Although this study shows low risk of bias in all other domains, it included only 15 of the required 78 participants.

Adverse events were reported by 55 of the 60 studies; they were generally mild and similar between groups. Mild atrophy was reported with mometasone furoate thrice weekly or twice weekly (low-certainty evidence), but more adverse events (e.g. application site burning/pruritus after intervention application, nasopharyngitis, one incident of severe fissures) were noted when clobetasol propionate foam was compared to vehicle placebo (moderate-certainty evidence). In the study comparing local narrow-band UVB to local PUVA, only the narrow-band UVB group reported adverse events (mainly erythema) (moderate-

certainty evidence). When tacrolimus was compared to vehicle, well-tolerated burning/itching was reported only in the tacrolimus group (moderate-certainty evidence). With systemic treatment, the risk of adverse events with oral cyclosporin compared to topical betamethasone was similar, and dizziness was reported (moderate-certainty evidence). The occurrence of headaches and flushing was similar when alitretinoin 10 mg was compared to placebo (moderate-certainty evidence), but risk of headache was greater with alitretinoin 30 mg than with placebo (high-certainty evidence).

Overall completeness and applicability of evidence

We included 60 RCTs with a total of 5469 participants. Overall, studies included adults of both genders in general good health, which in our opinion is applicable to an important part of the hand eczema population, since hand eczema can be related to occupation.

The applicability of evidence is limited by several methodological weaknesses of the included studies; one of the most prominent of these is the varied definition of hand eczema. Furthermore, the definition of hand eczema was different in almost all trials. Studies defined 'chronic hand eczema' as duration longer than six months or longer than three months, or did not include a minimal duration of disease at all. We intended to conduct subgroup analyses, but a minority of the trials defined subgroups (e.g. Ruzicka 2004 and Ruzicka 2008 did include subgroups). In general, it is not clear which participants had hyperkeratotic hand eczema or vesicular hand eczema, and clinical experience suggests that the clinical subtype might influence treatment success. Without logical and comprehensive definitions of hand eczema with clear diagnostic criteria for hand eczema and its subgroups, RCTs are seriously flawed, which is one of the main pitfalls of this review.

Furthermore, in this review, we found a wide range of severity scoring systems for hand eczema, which prevented meaningful data pooling.

Finally, some studies, especially older studies, did collect useable data with regard to the effectiveness of treatment but did not report these data (Fredriksson 1975). Since these were all single-study results, which could not have been pooled anyway, we do not believe that this influenced the overall completeness of the evidence.

Of all treatment categories, the largest number of studies focus on topical steroids (nine RCTs) and UV therapy (10 RCTs). Nevertheless, most trials do not include one of these treatments as a comparator. In fact, most trials provide placebo, vehicle, or a variant of the intervention as a comparator, making it difficult to draw conclusions on the comparative advantages of different treatments. We did identify some ongoing studies, for example, ISRCTN80206075, NCT03026907, and NCT03026946; results of these trials might eventually help to fill some of the gaps. With regard to phototherapy, it is difficult to compare different studies because different treatment regimens were used. Although in daily practice the treatment regimens are highly dependent on patient skin type and on the occurrence of adverse events, it might be challenging to align treatment protocols. Topical steroids were assessed in nine studies, although different treatment regimens were not investigated intensively, nor was the strength of different corticosteroids. Topical calcineurin inhibitors were investigated in nine studies. Topical calcineurin inhibitors were compared with placebo and with active treatment (topical corticosteroids), although this last comparator might have been used more often. Alitretinoin was examined in well-designed studies with a substantial number of participants. Other oral treatments such as cyclosporin, methotrexate, or acitretin were barely/not investigated, which is a severe shortcoming in the overall completeness of evidence.

With regard to outcomes, our primary outcomes percentage of participants with investigator-rated and/or self-rated good/excellent control of symptoms and/or adverse events were reported in most of the included studies. However, the secondary outcome dose reduction was not stated in any of the included studies. Moreover, various studies did not report on time until relapse.

The enrolled participants had typical long-standing eczema. Studies included overall chronic hand eczema with long-lasting disease and included patients in secondary care settings; therefore acute eczema is not included in these studies. Consequently, the results are less applicable for the primary care setting. This review included participants of all ages; however, most of the included studies did not include children. Only four studies included participants under the age of 16 years and did not provide separate results for this subgroup; therefore, the results of this review may not be applicable to children. With regard to external validity, these studies were conducted all over the world, supporting the generalisability of the results.

The objective of this Cochrane Review was to assess the effects of topical and systemic interventions for hand eczema in adults and children. Because of the above-mentioned implications, it is difficult to answer our review question with a single answer. As stated before, we cannot comment on children based on the included studies, which mainly include adults. However, this review does provide a clear overview of different studies on potential topical and systemic interventions for adult patients with chronic hand eczema. A pitfall is the lack of head-to-head studies, which makes it impossible to know whether one treatment is favoured over another.

Quality of the evidence

We found some serious limitations in the quality of reporting and aimed to discuss these according to the GRADE considerations*(study limitations, consistency of effect, imprecision, indirectness, and publication bias).*

Limitations in study design and implementation

We included only RCTs in this review. Overall, the older studies had more shortcomings with regard to risk of bias, and we judged them as having 'high' or 'unclear' risk of bias with regard to allocation concealment, blinding, and/or loss to follow-up. Frequent shortcomings included missing information on randomisation and blinding, no justification of the number of participants, and no analysis of dropouts. Studies that were conducted more recently had an overall low or unclear risk of bias for most of the risks (allocation concealment, blinding, intention-to-treat analysis, and selective reporting of outcomes), although they sometimes were sponsored by pharmaceutical industries. Over a third of the studies used a within-participant design (left-right studies). Although these studies show strengths in terms of power to obtain statistically significant results with

small numbers of participants, this is done at the expense of problems in interpreting studies finding no difference in effect. This might be a consequence of cross-contamination of topical interventions, possible systemic effects of topical preparations, or both. In general, we consider the body of evidence in this review as having 'unclear risk of bias'.

As a consequence, we downgraded evidence only for one of our main comparisons (mometasone furoate cream three times per week versus two times per week; Summary of findings 2), as we considered the included study to be at high risk of detection and performance bias (Veien 1999).

Indirectness of evidence

Overall the included studies were of relatively small sample size and short duration. Although hand eczema usually has a chronically relapsing course, less than half of the studies had a duration longer than three months, which in our opinion is the minimum duration required to document important data such as duration and frequency of disease relapse. Therefore, this is considered as a form of indirectness. This review analysed the efficacy of many different interventions, of which various included a placebo. Moreover, because the number of studies comparing different groups of interventions (e.g. corticosteroids, oral retinoids, phototherapy) is limited and the number of participants for each intervention is limited (with the exception of alitretinoin), the evidence is mostly indirect. Overall, participants in a secondary care setting with chronic eczema were included. As mentioned above, the definition of 'chronic hand eczema' was not always clear; this could be defined as having a minimal duration of six weeks to six months. Some studies included participants with specific subtypes of hand eczema such as recurrent vesicular hand eczema, whereas others excluded this subgroup. We were unable to pool the data for different subgroups of hand eczema, for example, to focus on hyperkeratotic palmar hand eczema, since the data for specific subgroups often were not stated. A wide range of outcome parameters was presented, most of which were not validated. Some studies used a validated outcome measure such as the Hand Eczema Severity Index (HECSI), whereas most created their own non-validated, un-named scoring system. Another limitation arose from the comparators used: most interventions were compared to an inactive placebo, which is less effective than standard treatment in most settings. We decided not to downgrade the evidence in our main comparisons for indirectness, as we judged this to be a less serious concern than imprecision (see below).

Consistency of results

It is difficult to judge the consistency of the results because we were unable to pool the study results for most of the outcomes assessed because only a single study was available, or because of clinical heterogeneity in interventions (and co-interventions), treatment duration, comparison groups, and outcomes measured or reported. As a direct consequence of the overwhelming diversity in study characteristics (i.e. clinical heterogeneity), most of the comparisons are based on single studies, hence making it difficult for the review authors to draw any firm conclusions with confidence. We can interpret this review only as a scoping review. Hence, we could not downgrade any evidence for inconsistency.

Imprecision of results

Most of the analyses are based on a single study of small sample size, and often with low event rates (in some cases, zero events), and the 95% confidence interval of effect estimates was often very wide, resulting in a low-precision assessment. Hence, we downgraded most of the outcomes included in the summary of findings tables for imprecision because we believe the small sample size means there was not enough power to detect any differences between groups. The effectiveness outcomes in two of our main comparisons comparing alitretinoin 10 mg or 30 mg versus placebo were not downgraded for imprecision because the analyses included two studies equalling a larger sample size, and the results had fairly narrow 95% confidence intervals, which did not include one showing high-certainty evidence supporting the effectiveness of alitretinoin (see Summary of findings 7 and Summary of findings 8).

Probability of publication bias

We did not produce funnel plots due to insufficient numbers of included trials for all given outcomes. Publication bias may especially be present in the wide range of studies on different moisturisers to treat hand eczema: we did find various registered trials in trial registries that were not (yet) published. Contact with study authors in some cases revealed that the results were minimal and would not be published, or study authors did not respond to our writings at all. In other cases, study authors were not at liberty to disclose results but referred us to pharmaceutical sponsors, who often remained unresponsive.

Potential biases in the review process

We acknowledge that there was potential for bias at all stages of the review process, but we made various attempts to restrict the level of bias.

We comprehensively searched for randomised controlled trials from a wide range of databases to avoid the risk of publication bias, and we used clinically relevant outcome measures. We tried to compare respective trial registrations with published trials to ascertain whether there was lack of correspondence between what was intended to be an outcome and actually reported outcomes. We attempted to be as inclusive as possible in our search strategy and included studies reported in languages other than English. The different language backgrounds of review authors enabled us to include Dutch - Kemper 1998 - and German articles - Adams 2007; Bayerl 1999. We translated a Turkish article to minimise language bias (Baskan 2005). Nevertheless, the studies included in this review were predominantly conducted in European or North American countries and were published in European or American journals.

The authors of this review independently assessed the eligibility of studies for inclusion in this review; two other review authors extracted data and assessed risk of bias to minimise the potential for additional bias beyond that detailed in the 'Risk of bias in included studies' tables. Discrepancies between review authors were resolved by discussion to reach consensus. However, we acknowledge that our assessments may occasionally have been subjective, for example, in the case of the not-blinded radiographers (Cartwright 1987; Fairris 1984; Fairris 1985; King 1984). Therefore, readers may not agree with all of our decisions.

Review authors who were involved as trialists for certain studies were not involved in selection, assessment, and data extraction for those studies. Pieter-Jan Coenraads was involved in the studies of Ruzicka 2004, Ruzicka 2008, and van Coevorden 2004a. Thomas L Diepgen was involved in the studies of Bauer 2012 and Ruzicka 2008 (Declarations of interest).

The authors of this review are aware that some differences between protocol and review (see Differences between protocol and review) may have been a source of bias. The protocol was published in 2009, and Cochrane guidance has since developed. Such differences include changing adverse events to a primary outcome, adding a time point of a minimum of three months for measuring outcomes such as relapse, changing the way measures of treatment effect are expressed, and making changes to the literature search. We tried to not make these decisions based on the data we had extracted, but rather on the new Cochrane guidance.

We judged a lot of studies to have unclear risk of bias, especially with regard to selection bias, since a substantial number of studies did not describe the way allocation concealment and sequence generation were performed. To obtain more clarity on this matter, we contacted all authors from studies published after 1999 by email or through other forms of social media such as LinkedIn. Study authors with a personal or professional relation to one of the authors of this review may have been reached more easily and might have been more prone to respond to our requests. Therefore, these studies may have been judged more often as having low risk of bias. For studies pre-1999 and for reports for which study authors were unresponsive, we had less information and had to deal with more ambiguity, which we were unable to resolve; this may have contributed to some bias in assessments of these studies, and these studies were more often judged as having unclear risk of bias.

The time frame for the studies included in this review inevitably shows that there is a time trend in treatments that are evaluated: earlier studies tend to focus on corticosteroids, UV phototherapy, or X-rays, and more recent trials evaluate the effects of novel medicaments such as oral retinoids and topical calcineurin inhibitors.

The fact that 20 studies have not yet been incorporated into this review may be a source of potential bias.

Agreements and disagreements with other studies or reviews

This Cochrane Review studies a wide range of treatments that have been evaluated by RCTs since 1967. Within the same time frame, many uncontrolled and non-randomised controlled studies have been published. van Coevorden 2004b conducted a review to describe study design and the quality of studies on hand eczema, covering the time period from 1977 up to 2003. These review authors included 90 studies, of which 44 were case series, 15 non-randomised controlled trials, and 31 RCTs. In total, 11 different categories of treatment were found, and most trials studied ultraviolet irradiation (n = 32) or corticosteroids (n = 13). This review concluded that the overall quality of reporting on hand eczema was poor, and most hand eczema trials were not considered adequate to guide clinical practice. Since the current Cochrane Review was conducted in part by the same review authors and incorporated the same RCTs, it is not surprising that the results and conclusions of both reviews overlap. However, since we tried to obtain more information by contacting authors in this Cochrane Review, and since we sought additional published and unpublished data, we had fewer uncertainties with regard to the quality of evidence. We also included RCTs that were conducted after 2003, and in general these studies are of better quality than the older studies. We maintain that the overall quality of reporting in hand eczema is low, and that there is a need for well-designed head-to-head studies of adequate duration, reported according to the CONSORT guidelines.

Over the years, various groups have composed guidelines for the management of (chronic) hand eczema (Veien 2003; Diepgen 2007; Diepgen 2009b; English 2009; Lynde 2010; Menné 2011). These guidelines have in common that they all acknowledge the lack of RCTs. All guidelines recommend topical corticosteroids as one of the first steps in pharmacological treatment for all types of hand eczema. Thereafter, the guidelines recommend different steps, in which the subtype of hand eczema can be a leading factor, usually starting with topical treatments (e.g. more potent or prolonged use of corticosteroids or calcineurin inhibitors).

For severe hand eczema that is unresponsive to topical treatment, basically all guidelines recommend a treatment regimen with tar, phototherapy, and systemic (oral) treatment (acitretin, alitretinoin, cyclosporin, corticosteroids, or others). Since alitretinoin was recently licensed for the treatment of hand eczema in Europe and Canada (not yet in the United States), the more recent guidelines include this treatment option for severe chronic hand eczema (Diepgen 2009b; English 2009; Lynde 2010; Menné 2011).

English 2009 published a consensus statement on the management of chronic hand eczema in the view of general practitioners and dermatologists. The authors did not conduct a systematic review but based their statement on a mix of clinical experience and a variety of RCTs and non-RCTs on hand eczema and atopic dermatitis. In general, they advise a skin protection programme and topical treatment with corticosteroids or calcineurin inhibitors in a primary care setting whenever possible. For referrals to secondary care (dermatologist), PUVA, cyclosporin, azathioprine, and alitretinoin are preferred treatment options for hyperkeratotic and vesicular hand eczema, with emphasis on the importance of patient preference and local availability. Furthermore, PUVA (also in our review a well-studied intervention) is recommended for hyperkeratotic hand eczema. Methotrexate and mycophenolate are recommended after failure of other systemic interventions; however, this recommendation is not supported because of lack of RCTs examining these interventions.

The German Dermatologic Society stresses the importance of education and prevention (Diepgen 2009b). Topical corticosteroids, topical calcineurin inhibitors, and iontophoresis are the first treatment steps. For moderate to severe hand eczema, highly potent corticosteroids, UV therapy, and alitretinoin are recommended, while other systemic treatment options such as cyclosporin are the final resort. This recommendation is based largely on the fact that alitretinoin is registered for the treatment of hand eczema, while cyclosporin is an off-label therapy.

The Canadian guideline states that treatment of hand eczema can be difficult and unsatisfactory (Lynde 2010). Researchers distinguish three important clinical types: irritant contact dermatitis, allergic contact dermatitis, and atopic hand eczema. This guideline provides a clear flow diagram for acute hand

eczema and chronic hand eczema, which is divided into mild, moderate, and severe. Topical corticosteroids are the mainstream of treatment, and phototherapy is recommended for moderate chronic hand eczema unresponsive to topical corticosteroids. For severe cases that are unresponsive to potent topical corticosteroids, phototherapy and alitretinoin are recommended. When this is insufficient as well, cyclosporin can be considered. Because the comparative study NCT01231854 was ended prematurely, we do not know whether alitretinoin should be preferred over cyclosporin.

Danish guidelines state that treatment for hand eczema should be tailored to the individual and that skin care education is very important (Menné 2011). They classify hand eczema into six different clinical types: chronic fissured hand eczema, recurrent vesicular hand eczema, hyperkeratotic palmar hand eczema, pulpitis, interdigital eczema, and nummular hand eczema. Furthermore, they distinguish between mild/moderate hand eczema and severe hand eczema. Mild/moderate hand eczema should be treated with topical corticosteroids, potentially in rotation with calcineurin inhibitors. For severe hand eczema, a step-up with topical corticosteroids and "possibly potassium permanganate baths" for vesicular hand eczema and "silver nitrate solutions" for hyperkeratotic eczema is recommended. However, our review did not find evidence for these treatment options. If topical treatment is insufficient, a further step-up regimen is recommended with tar, phototherapy, and systemic treatment (acitretin, alitretinoin, cyclosporin, corticosteroids, or others), although the guideline does not given an order of priority and does not make further recommendations regarding the different subtypes of hand eczema.

The American Academy of Dermatology has published guidelines on the use of topical glucocorticoids - the mainstay of treatment for hand eczema (Drake 1996). The British Photodermatology Group developed a guideline on phototherapy and included a comment on the use of phototherapy in hand eczema (Halpern 2000). Although the evidence for topical PUVA over oral PUVA is scarce, this group suggests a commonsense approach, which is not contradictory to the findings of this review.

The studies included in this review regarding alitretinoin did find an increase in the number of participants reporting headache while taking alitretinoin compared to placebo with a high level of evidence (Bissonnette 2010; Ruzicka 2004; Ruzicka 2008), which is in line with multiple daily life studies that have reported headache as a well known side effect of alitretinoin (Diepgen 2012; Augustin 2016).

Overall, we can conclude that most guidelines do not give a single recommendation based on the current literature, which is consistent with the main finding of this review.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review cannot be used to inform clinical practice with regard to the best way of managing hand eczema, especially in the long term. Until such data are forthcoming, physicians will be tempted to use an array of treatments.

For the comparison of clobetasol propionate versus vehicle foam, the percentage of participants with self-rated good/excellent control of symptoms probably improves with clobetasol propionate, but the effect is less clear for investigator-rated symptoms (moderate-quality evidence). Mometasone furoate cream thrice weekly may slightly improve investigator-rated symptoms compared to twice weekly application (low-quality evidence); participant-rated control was not measured.

Tacrolimus ointment probably improves investigator-rated good/excellent control of symptoms compared to vehicle foam (moderate-quality evidence); participant-rated control was not measured.

A relatively new systemic treatment (an oral retinoid called alitretinoin) for patients with severe chronic hand eczema showed clearance or almost clearance of about half the participants in three large RCTs (Fowler 2014; Ruzicka 2004, Ruzicka 2008). We found high-quality evidence that relative to placebo, people who are given alitretinoin were more likely to achieve good symptom control (investigator or participant rated). The benefit became more apparent with increased dosage (10 mg versus 30 mg).

Local PUVA may lead to improvement compared to local narrow-band UVB; however, the 95% confidence interval indicates that local PUVA might make little or no difference (moderate-quality evidence). Participant-rated control was not measured.

Oral cyclosporin probably slightly improves investigator-/participant-rated control of symptoms compared with topical betamethasone dipropionate (moderate-quality evidence).

For the comparison tacrolimus 0.1% ointment versus mometasone furoate ointment, investigator-rated symptoms and participant-rated control was not measured.

Adverse events: adverse (long- and short-term) effects of the interventions

- Clobetasol propionate led to more adverse events (including application site burning/pruritus after intervention application, nasopharyngitis, and one incident of severe fissures) compared to vehicle foam (moderate-quality evidence)
- With regard to mometasone furoate cream used thrice weekly compared to twice weekly, mild atrophy was reported in both groups (low-quality evidence)
- When compared to local PUVA, adverse events (mainly erythema) were reported in the local narrow-band UVB group only (moderate-quality evidence)
- With regard to tacrolimus ointment compared to mometasone furoate ointment, both treatments were well tolerated; none of the participants dropped out due to adverse events (moderate-quality evidence)
- When compared to vehicle foam, adverse events (well-tolerated burning/itching at the application site) were reported in the group taking tacrolimus ointment only (moderate-quality evidence)
- The risk of adverse events such as dizziness was fairly similar between those taking oral cyclosporin and those taking topical betamethasone dipropionate (moderate-quality evidence)

The 20 studies listed under Studies awaiting classification may alter the conclusions of the review once assessed.

Implications for research

The most important implication of this review is the need to conduct high-quality RCTs of people with hand eczema to compare commonly used interventions by using simple outcome measures that can be understood by participants and clinicians.

- E (Evidence): current evidence for managing hand eczema is mainly of low to moderate certainty and especially head-to-head trials are missing. Recently**,** head-to-head trials for different (systemic) treatments have been registered in trial registries (ISRCTN80206075; NCT03026907; NCT03026946), which might alter the outcomes of this review in the near future.
- P (Population): people with chronic (longer than six months) moderate to severe hand eczema should be included in future trials. Subgroup analyses on participants with different variants of hand eczema are recommended, although lack of consensus regarding the classification of hand eczema is a major limitation. We need international consensus regarding the definition of (chronic) hand eczema and subgroups of hand eczema, based on morphology or aetiology. Subgroups of especial interest include participants with hyperkeratotic hand eczema and participants with recurrent vesicular hand eczema. Studies on acute hand eczema were not included in this review but may be of interest, especially in primary care settings. Not many children were included in these studies, and this is a potential subgroup of interest for future studies.
- I (Intervention): all sources of treatment can be included, although we would recommend including the main interventions (topical corticosteroids, UV therapy, topical calcineurin inhibitors, acitretin, alitretinoin, and cyclosporin).
- C (Comparison): head-to-head trials, in which different groups of commonly used interventions are compared, are highly desirable, for example, cyclosporin versus alitretinoin or UVA therapy versus topical corticosteroids. If an RCT includes placebo (or vehicle or inactive treatment) as the only comparator instead of an established treatment modality, this should be clearly and convincingly justified.
- O (Outcome): at the moment, international consensus on a standard severity scale for hand eczema is lacking. Many of the scales used were not validated, and validation of commonly used scoring systems is needed. Alternatively, a simple global rating measure with, for example, photographic anchors is highly recommended (Charman 2005; Weistenhöfer 2010). We would like to recommend the same procedure as is currently ongoing in atopic dermatitis: Harmonising Outcome Measures for Eczema (HOME) (Schmitt 2010). The HOME group is a worldwide initiative with the aim of developing a consensus-based set of core outcome domains for trials and clinical record keeping in atopic dermatitis. This is important, to allow comparison of data across trials - one of the difficulties that we encountered in this review on interventions for hand eczema. Duration of remission, the way the disease is brought under control, adverse events, focus on patient-reported outcomes, and simple outcome measures applicable to all participants are preferable. Hand eczema is known to influence quality of life; therefore quality of life should be an important outcome. In addition, trials should focus on economic consequences, since hand eczema is a common occupational disease. A major limitation of almost all reviewed trials is that no measure of effect size including precision is given. This is necessary to enable judgement of whether advantages of treatments are not only statistically significant but also meaningful.
- T (Time stamp): our latest search was conducted in April 2018. Older studies focused mainly on topical corticosteroids, UV therapy, and irradiation, and more recent (namely, industry-funded) studies focus on topical calcineurin inhibitors (pimecrolimus and tacrolimus) and alitretinoin. The included studies were predominantly of short duration. Future studies should have adequate treatment duration, preferably longer than three months, which in our opinion is the minimum duration required to document important data such as duration and frequency of disease relapse. Furthermore, studies on chronic hand eczema should include a follow-up period of at least equal duration. Acute hand eczema, especially the allergic type, tends to respond quickly to treatment and needs only a short follow-up, in which case a few weeks of treatment and follow-up should be sufficient.

It is obvious in many of the reviewed trials that the approach to statistical analyses was limited. Several parametric and non-parametric statistical procedures that are able to model both within (person and/or time) and between subject (treatment) factors simultaneously have been offered by most statistical packages for many years. A major limitation of many of the treatment comparisons is that they did not control for baseline variation. In addition, omnibus factorial designs (allowing contrasts to be specified a priori) reduce the type 1 error rate because they test several hypotheses at the same time. Post-hoc comparisons would be necessary only should the data reveal surprising results. These analyses, of course, would have to be viewed in an explorative fashion. Future studies need to overcome said limitations.

Many deficiencies in trial reporting thus far can be avoided if all specialist dermatology journals adopt the CONSORT guidelines (Moher 2001), especially since many of the 'unclear' risks, turned out to be based on missing information in the report instead of flaws in the study design. All future studies should adhere to these guidelines. Future studies should ensure they are adequately powered to detect any differences between treatment groups and to reduce imprecision.

Practical recommendations for upcoming studies include the above-mentioned recommendations on chronic hand eczema. Studies that are highly recommended include the comparison of phototherapy (e.g. bath-PUVA) versus alitretinoin 30 mg in a large cohort of participants with chronic hand eczema with a duration of at least three months and follow-up of at least equal length. This study is already registered (ISRCTN80206075), and results of this trial might influence the outcomes of this review in future updates.

Another recommendation would be to compare alitretinoin 30 mg to cyclosporin in participants with vesicular hand eczema and with hyperkeratotic hand eczema, since participants with vesicular hand eczema seemed to respond less to alitretinoin in the included trials on alitretinoin. This study design is already registered for vesicular hand eczema as well, and we are awaiting the results (NCT03026946). Other potential research options include comparison of a potent topical corticosteroid, since this is the mainstream of treatment, to alitretinoin 30 mg or to phototherapy. The comparative advantage over other treatments needs further evaluation, since the only study that did compare alitretinoin to

another immunosuppressant (cyclosporin) was ended prematurely (NCT01231854).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adams 2007

Methods	Within-participant, randomised controlled study (left-right design). This study was carried out in the secondary care setting; it was a single-centre study conducted in Germany
Participants	15 participants at least 18 years old suffering from chronic relapsing dyshidrotic hand eczema with a minimal duration of 1 month that was resistant to conventional therapies Dropouts: 4 **Inclusion criteria of the trial** • At least 18 years old • Chronic relapsing dyshidrotic hand eczema with a duration of at least 1 month • Resistant to conventional therapies **Exclusion criteria of the trial** • Other dermatological diseases • Pregnancy • Light therapy during the last 4 weeks • Topical corticosteroids during the last week • > 200 PUVA treatments in the past • Medication or alcohol abuse • Immune suppressive therapy **Study population** • Gender: 8 female, 3 male • Age: median 45.1 years, range 28 to 66 years
Interventions	**Intervention** • Middle-dose UVA-1 irradiation 3 times a week (cumulative dose of 600 J/cm^2) in 11/15 hands during 5 weeks • Local 8-MOP-cream-PUVA irradiation 3 times a week during 5 weeks (cumulative dose of 17.4 J/cm^2) in 11/15 contralateral hands. 8-MOP-crème was applied 30 minutes before the start of irradiation **Duration** 5 weeks
Outcomes	**Primary outcomes of the trial** • Observer-rated assessment of improvement (DASI score) **Other outcomes** • Adverse events
Notes	Therapeutic efficacy was shown with relatively low cumulative doses of UVA and UVA-1

Adams 2007 *(Continued)*

	The secondary outcome - reduction in severity, investigator-rated - was included but did not provide reproducible data Study authors were contacted by mail on 6 March 2014 and responded 10 March 2014 Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The article states that randomisation was done by an independent third person. No information regarding random sequence generation appeared in the article; however personal communication clarified that this was done appropriately: "cards with the characterisation "A" and "B" were enclosed in envelopes by a third person, mixed like a card play by a third person, then numbered consecutively by a third person and opened by the study doctor consecutively after informed consent to the study"
Allocation concealment (selection bias)	Low risk	Quote: "randombriefe wurden nach Wűrfeln von einer von der Studie unabhängigen Person erstellt" (free translation: the randomisation letter was created by an independent person after throwing dices) Comment: adequate allocation concealment as randomisation was accomplished by a third party
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "eine Verblindung der Studie erfolgte nicht" (free translation: the study was not blinded) Comment: no attempts were made to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "eine Verblindung der Studie erfolgte nicht" (free translation: the study was not blinded) Comment: observers were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (11 of 15 = less than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found; however all outcomes listed in Materials and Methods are given in the Results section
Other bias	Low risk	Baseline comparisons revealed no significant differences between groups, as within-participant study was not applicable Diagnostic certainty: yes The study was completed

Agarwal 2013

Methods	Parallel-group, randomised controlled trial

Agarwal 2013 *(Continued)*

	This study was probably carried out in a secondary care setting as a single-centre study at a Department of Dermatology in India
Participants	108 participants with clinically diagnosed hand eczema included; 91 completed the study Dropouts: 17 **Inclusion criteria of the trial** • Clinical diagnosis of hand eczema with duration longer than 6 months **Exclusion criteria of the trial** • Pregnancy • Lactating mothers • Younger than 18 years or older than 65 years • Any associated systemic disease (diabetes, hypertension, thyroid disorders, any renal or liver disease, malignancy, etc.) • Hypersensitivity to azathioprine **Study population** • Gender: 29 female, 62 male • Age: group A mean 36.86 years, SD 11.55 years; group B mean 35.82 years, SD 10.67 years
Interventions	**Intervention** • Topical clobetasol propionate 0.05% cream twice daily with oral azathioprine 50 mg daily in 46 participants for 24 weeks **Control intervention** • Topical clobetasol propionate 0.05% cream twice daily alone in 45 participants for 24 weeks Participants were instructed to use the topical clobetasol intermittently and to stop application whenever the signs and symptoms disappeared and restart when the complaints returned **Duration** 24 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Reduction in severity, investigator-rated scoring measured by the Hand Eczema Scoring Index (HECSI) at 2, 4, 8, 12, and 24 weeks • Reduction in severity of itch, participant-rated, measured on a numerical scale from 0 to 10 • Number of exacerbations • Adverse events
Notes	The total quantity of corticosteroids used was not registered Study authors were contacted on 27 February 2014 by email and responded 1 March 2014 Declarations of interest: not stated Funding: not stated

Agarwal 2013 *(Continued)*

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised into 2 groups using block randomization" Comment: unclear from the article how these blocks were generated; however contact with study authors clarified that a valid computer-generated table was used
Allocation concealment (selection bias)	Low risk	No information is provided in the article on how allocation was concealed from participants and investigators, but personal communication revealed that randomisation was done by a third person
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "patients paid for the medicine themselves" Comment: participants were not blinded because they had to buy their own study drugs, and no placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an observer blinded randomized comparative trial" Comment: study authors stated that the study was observer blinded but gave no details as to how this was achieved. Contact with study authors clarified that observers were independent and were not involved in treatment nor in dispensation of study drugs
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	91 of the 108 (84.3%) included participants were analysed. No intention-to-treat analysis. Dropouts were not evenly distributed between the 2 groups
Selective reporting (reporting bias)	Low risk	No trial registration found. However, all mentioned outcomes are described in the Results section
Other bias	Unclear risk	No baseline comparisons were conducted or reported Diagnostic certainty: yes The study was completed

Baskan 2005

Methods	Within-participant, placebo-controlled, randomised controlled trial The study was conducted in the secondary setting at a single centre in Turkey
Participants	25 participants with moderate to severe bilateral hand dermatitis with a minimal duration of 6 months Dropouts: 1 **Inclusion criteria of the trial** • Bilateral hand dermatitis • Moderate to severe hand eczema with a minimal duration of 6 months • 18 years of age or older **Exclusion criteria of the trial**

Baskan 2005 *(Continued)*

- Pregnancy
- Lactation
- Use of systemic immunosuppressants
- Other diagnosis such as urticaria, psoriasis, bacterial or fungal infection
- Illness in the previous 4 weeks

Study population

- Gender: 15 female, 9 male
- Age: mean 35.8 years, range 18 to 63 years

Interventions	**Intervention** • Pimecrolimus 1% cream twice daily in 24/25 hands presumably for 8 weeks **Control intervention** • Placebo cream twice daily presumably for 8 weeks in 24/25 hands • Participants were followed up for the same period **Duration** 16 weeks (8 weeks active treatment, 8 weeks follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Clinical response to therapy; erythema, desquamation, lichenification, oedema, vesiculation, and fissuring were scored between 0 and 4 and were controlled at 2nd, 4th, 6th, and 8th weeks of therapy • Clinical response to therapy for pruritus • At the end of therapy, participants were followed up for the same period to observe recurrences • Adverse events
Notes	Conference abstract from which only limited information can be extracted Study authors were contacted for additional information, which led to review of an additional full-text article in Turkish. The secondary outcome - reduction in severity, investigator-rated - was included but did not provide reproducible data Declarations of interest: not stated Funding: not stated in the paper, but personal communication clarified that study authors did not receive any funding Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors stated randomised but gave no clear description of how this was attained. Personal communication with study authors clarified that they used a card drawing system Quote: "a simple randomisation method by card drawing was performed"

Baskan 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	No information on how allocation was concealed from participants and investigators is provided in the abstract Personal communication clarified that one investigator drew the cards after participants gave their consent. The topical drugs were packed in yellow and red boxes, and staff gave participants the corresponding boxes for treatment, without knowledge about the content of those boxes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not clear from the abstract; however personal communication clarified that dispensation of study drug was done by a third person in boxes labelled for each hand. The vehicle and pimecrolimus were packed in similar boxes and were indistinguishable for participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not clear from the abstract; however personal communication clarified that observation was done by another physician who was not involved in randomisation or drug dispensation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Unclear whether an intention-to-treat analysis was conducted; however 24 of the 25 included participants completed the study, which is more than 80%
Selective reporting (reporting bias)	Low risk	No trial registration found. All relevant clinical signs were scored in the symptom score, and all described outcomes were depicted in the Results section
Other bias	Low risk	No baseline comparisons were conducted or reported, as within-participant study was not applicable Diagnostic certainty: yes The study was completed

Bauer 2012

Methods	Parallel-group, randomised controlled trial. Multi-centre study at the outpatient clinics of the University Hospitals Heidelberg and Dresden, Germany
Participants	40 adult outpatients Dropouts: 4. **Inclusion criteria of the trial** • Patients with moderate to very severe chronic relapsing atopic hand dermatitis (IGA ≥ 3) • 18 years of age or older • Responded to treatment with mometasone furoate 0.1% once daily over 1 to 3 weeks (IGA ≤ 2) once IGA ≤ 2; participants received pimecrolimus cream or vehicle for up to 56 days **Exclusion criteria of the trial** • Atopic dermatitis covering over 20% of the body surface area • Use of phototherapy • Systemic prednisone or systemic immunosuppressive agents 4 weeks before screening visit • Use of topical tar, pimecrolimus, and tacrolimus 7 days before screening visit • Hypersensitivity to ingredients of the study medication and/or vehicle • Women without adequate contraception or pregnancy or lactation • Patients with malignant diseases within the last 5 years

Bauer 2012 *(Continued)*

- Concomitant skin disease
- Infections of the hands

Study population

- Gender: 22 female, 14 male
- Age: mean 33.06 years, SD 10.78 years, range 18 to 54 years

Interventions	Participants were randomly allocated in a ratio of 1:1 to receive the following **Intervention** • Pimecrolimus 1% cream twice a day for 8 weeks after clinical response (IGA 2) to 1 to 3 weeks of treatment with mometasone furoate 0.1% in 20/20 participants **Control intervention** • Vehicle twice a day for 8 weeks after clinical response (IGA 2) to 1 to 3 weeks of treatment with mometasone furoate 0.1% in 16/20 participants To control for compliance, study medication was weighed at every visit **Duration** 8 weeks after 1 to 3 weeks of start-up treatment
Outcomes	**Primary outcomes of the trial** • Proportion of participants maintaining a stable remission (IGA 2) with twice-daily application of pimecrolimus or vehicle. The study endpoint was defined as the time interval from commencement of treatment to relapse (IGA 3) during the 8-week active treatment period **Secondary outcomes of the trial** • Mean change IGA, patient self-assessment, HECSI, and DLQI **Other outcomes** • Mean change in IGA from baseline during study period • Mean change in patient self-assessment (PSA) from baseline during study period • Mean change in HECSI from baseline during study period • Mean change in DLQI from baseline during study period • Adverse events
Notes	Secondary outcomes - reduction in severity, participant- and observer-rated - were included but did not provide reproducible data Study authors were contacted on 27 February 2014 and provided additional information on 27 February 2014 Funding: the study was funded by a grant from Novartis Pharma GmbH, Nurnberg, Germany, the manufacturer of the study drug Study authors gave lectures for Novartis, although they claim this is not directly related to the study. One study author was an employee of Novartis Pharma, the manufacturer of the pimecrolimus cream Sample size rationale: adequate

Risk of bias

Bias	Authors' judgement	Support for judgement

Bauer 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "randomization was performed by allocation of the consecutive patients to the lowest available number from the randomisation list. The allocation sequence was generated by use of a permutated block randomisation list in blocks of 4 with equal allocation to pimecrolimus and vehicle" Comment: this is considered as adequate random sequence generation
Allocation concealment (selection bias)	Low risk	This was unclear from the article. Personal communication with study authors clarified that the investigators had no access to the randomisation code and used sealed envelopes for the allocation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "verum and vehicle creams were prepared from the commercial product and blinded labelled for this study by Novartis Pharma GmbH. Patients and investigators were blinded to assignment of patients during the entire study period until the closing of the data bank" Comment: participants and personnel of the study at the study site (except personnel for Novartis, which was located somewhere else) were unaware of the allocation during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "verum and vehicle creams were prepared from the commercial product and blinded labelled for this study by Novartis Pharma GmbH. Patients and investigators were blinded to assignment of the patients during the entire study period until the closing of the data bank" Comment: investigators were blinded during the entire study, and only the investigators from Novartis were aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "ITT analysis was performed" Comment: intention-to-treat analysis for primary outcome as well as per protocol (35/36 ≥ 80%)
Selective reporting (reporting bias)	Low risk	The trial was registered under Eudra CT Nr 2005-0003644-59 before the start of the study. We found no discrepancy between outcomes stated in the protocol and reported in the publication
Other bias	Low risk	Baseline comparison: no statistically significant differences were found between the pimecrolimus (n = 20) and vehicle (n = 16) groups with regards to age, sex, body weight, height, and ethnicity, and in IGA at baseline Diagnostic certainty: yes The study was completed

Bayerl 1999

Methods	Parallel-group, randomised controlled trial The study was conducted in the secondary setting at 2 different dermatology departments in Germany
Participants	48 participants with chronic hand eczema (21 irritant, 18 allergic, 9 atopic) > 3 months' duration, more than 30% of the hands involved. All had occupation-related hand eczema: 41% were in a wet occupation Dropouts: 12 **Inclusion criteria of the trial** • Occupational chronic hand eczema of > 3 months' duration

Bayerl 1999 *(Continued)*

- > 30% involvement of hands

Exclusion criteria of the trial

- Non-compliance
- Liver disease
- Porphyria
- Polymorphic light dermatitis
- Use of light-sensitive medication
- Malignancies
- Use of chemotherapies or immunosuppressives
- History of skin malignancies
- Specific topical or systemic therapy (including corticosteroids and coal tar)

Study population

- Gender: not stated
- Age: not stated

Interventions

Intervention

• UV-B phototherapy 5 days/week for 8 weeks in 19/24 participants

Control intervention

• No UVB for 8 weeks in 17/24 participants

Both groups were allowed to use non-specific creams/emollients

Duration

8 weeks

Outcomes

Primary outcomes of the trial

Not defined

Other outcomes

- Observer-rated extent of hand eczema, and scoring 1 to 4 (1 = absent, 2 = mild, 3 = moderate, 4 = severe) on erythema, oedema, maceration, excoriation, lichenification, fissuration, infection, scaling, itch
- Participant-rated VAS (0 to 10) on itching and restrictions in daily life
- TEWL and Nitrazinyellow-test
- Adverse events

Notes

Study authors rightly state that this is a pilot study. Only graphic presentation of a few components of some outcome parameters. Not clear, but assumed, that 24 participants were randomised to each group. The secondary outcome - reduction in severity, investigator-rated - was included but did not provide reproducible data

Study authors were contacted on 7 March 2014 and responded 10 March 2014

Declarations of interest: not stated

Funding: not stated

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Bayerl 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	The article states only that the study is randomised, without details about the method of randomisation. Personal communication clarified that the same method was used as in Adams 2007: "cards with the characterisation "A" and "B" were enclosed in envelopes by a third person, mixed like a card play by a third person, then numbered consecutively by a third person and opened by the study doctor consecutively after informed consent to the study" This is an adequate method
Allocation concealment (selection bias)	Low risk	No details about whether the allocation was concealed from participants and investigators in the article, but personal communication clarified that this was done appropriately by a third person, and that the study doctor and participants opened the consecutively numbered envelopes after informed consent was retrieved
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded during the study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Observers were not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (36 of 48 = less than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found; however outcomes described in Materials and Methods are depicted in the Results section and are adequate
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons regarding group differences (randomisation check) Diagnostic certainty: yes The study was completed

Belsito 2004

Methods	Parallel-group, randomised controlled trial The study was carried out in a secondary care setting This was a multi-centre study that was conducted in Brazil, Canada, and the USA
Participants	294 participants with mild to moderate chronic hand eczema (117 irritant, 94 endogenous, 32 irritant + endogenous, 32 irritant + allergic, 9 allergic, 4 allergic + endogenous, 4 irritant + allergic + endogenous, 2 unknown aetiology) Dropouts: 22 **Inclusion criteria of the trial** • At least 18 years old • Mild to moderate chronic hand eczema for a minimum duration of 6 weeks **Exclusion criteria of the trial** • Pregnancy

Belsito 2004 *(Continued)*

- Treatments that possibly interfere with study evaluations
- Hand-foot-and-mouth disease
- Contact urticaria
- Severe vesicobullous dermatitis of hands
- Latex allergy
- Mosaic warts
- History of malignancies or current pre-malignant disease of hands
- Concurrent flaring atopic dermatitis
- Psoriasis or skin disease of hands requiring therapy
- Use of systemic therapy in previous month and use of systemic antibiotics for hand infection or topical therapy within the previous 7 days

Study population

- Gender: 176 female, 118 male
- Age: mean age 44.6 years, range 18 to 86 years

Interventions	**Intervention** • Pimecrolimus 1% cream twice daily with 6 hours of love occlusion in the evenings for 3 weeks in 140/151 participants **Control intervention** • Vehicle cream twice daily with 6 hours of glove occlusion in the evenings for 3 weeks in 132/143 participants Barrier creams or emollients were allowed in both groups if applied more than 1 hour before study cream **Duration** 3 weeks
Outcomes	**Primary outcomes of the trial** • Investigator Global Assessment (IGA) on a 5-point scale: ranging from 0 = clear to 4 = severe • Efficacy measured was proportion of treatment successes at end of study (day 22) in each group; treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) **Other outcomes** • Adverse events
Notes	Overall efficacy (proportion of treatment successes) for both groups at end of study presented as graph (bar chart); exact figures not given. In separate table, exact figures for treatment successes, with strata of selected groups overlapping ("to identify groups highly responsive") Study authors contacted by email and LinkedIn 27 February 2014, but we were unable to obtain additional information Declarations of interest: some study authors were employees of pharmaceutical companies Funding: the study was supported by a grant from Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, which is the manufacturer of pimecrolimus cream. Four study authors had an ongoing financial relationship with Novartis, and four were employees of Novartis Sample size rationale: not stated
Risk of bias	

Belsito 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a multicenter, randomized, vehicle-controlled 3 week study..." Comment: the article states only that subjects were randomised, without further information. Insufficient information provided to judge the risk of bias
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "study design - the study was a double-blind, multicenter, vehicle-controlled trial of ...." Comment: unclear; participants and personnel probably blinded as this is stated in the paper, but no further details are given. It is unclear whether vehicle and placebo were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "study design - the study was a double-blind, multicenter, vehicle-controlled trial of ...." Comment: no details regarding blinding of observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the intention-to-treat (ITT) and safety populations consisted of all randomized patients who received the study medication, and the per-protocol population included all patients from the ITT population who did not violate the protocol in ways that would affect efficacy evaluations" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No trial registration found; however all outcomes listed in the Methods section are described in the Results section
Other bias	Low risk	Baseline comparisons: no significant differences in demographic or disease characteristics between groups Diagnostic certainty: yes The study was completed

Bissonnette 2010

Methods	Parallel-group, placebo-controlled, randomised study with participants who initially responded in a previous BACH study (Ruzicka 2008), but who relapsed in the observational period This study was carried out in a secondary care setting This was a multi-centre study conducted in Canada, France, and Germany
Participants	117 participants with chronic hand eczema who relapsed after they were successfully treated with alitretinoin 30 mg, 10 mg, or placebo Dropouts: 24 **Inclusion criteria of the trial** • Participants who relapsed after successful treatment with alitretinoin or placebo in a previous trial (Ruzicka 2008) **Exclusion criteria of the trial** • Well defined

Bissonnette 2010 *(Continued)*

	Study population • Gender: placebo group 23 female, 24 male; alitretinoin 10 mg 5 female, 15 male; alitretinoin 30 mg 24 female, 25 male • Age: mean placebo group 50.4 years; alitretinoin 10 mg 49.0 years; alitretinoin 30 mg 52.0 years
Interventions	**Intervention** • Alitretinoin 10 mg once daily for 12 to 24 weeks in 21 participants • Alitretinoin 30 mg once daily for 12 to 24 weeks in 49 participants **Control intervention** • Placebo for 12 to 24 weeks in 47 participants Participants were re-treated with the same dose that they had received in the previous study, or they were treated with placebo Participants who were initially treated with placebo in the first trial were treated with placebo again No other topical or systemic therapy for hand eczema was allowed **Duration** 12 to 24 weeks
Outcomes	**Primary outcome of the trial** • Physician's Global Assessment (PGA): whereby physician global assessment is categorised as clear, almost clear, mild, moderate, severe. Responders were defined as clear or almost clear at week 12 or last evaluation **Other outcomes** • Patient's Global Assessment (PaGA) • Modified Total Lesion Symptom Score (mTLSS) • Extent of disease • Time to response • Adverse events
Notes	Study included participants who relapsed after successful treatment in a previous study (Ruzicka 2008). No other active treatment as comparator. Analysis of efficacy based on intention-to-treat principle. Study included a safety assessment by careful medical and laboratory monitoring. The primary outcome percentages of participants with self-rated good/excellent and secondary outcome reduction in severity, investigator-rated scoring were included in the study, but we were unable to reproduce the data Study authors were contacted and referred us for further information to GSK, which provided additional information Declarations of interest: various study authors were investigators or consultants for Basilea Pharmaceutica International Ltd. Funding: the study was supported and funded by Basilea Pharmaceutica International Ltd, Basel, Switzerland, the manufacturer of alitretinoin. Study authors were investigators in Basilea clinical trials, or were consultants or employees of Basilea Pharmaceutica International Ltd. Sample size rationale: not stated Quote: "the sample size was not prespecified, and all relapsing patients from the BACH trial were eligible for trial screening"

Bissonnette 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to the same dose they received in the BACH study or to placebo" Comment: no further details given. In personal communication, the study authors clarified: "the study was a follow on from the BACH study BAP00089, which was a randomised double blind placebo controlled study of subjects in a 2:2:1 randomisation of treatment to alitretinoin 30 mg, alitretinoin 10 mg, or placebo, respectively. Patients who responded in study BAP00089 and relapsed during the posttreatment observation period were assigned to the same dose they had received or to placebo in a 2:1 ratio. Responding patients who had received placebo in study BAP00089 were assigned to continue receiving placebo. Each was assigned a coded allocation of study drug containing either placebo or a dosage of active drug. The randomisation was computer generated"
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators. In personal communication, the study authors stated: "it is unclear how this knowledge was imparted, but it is clear from the protocols that those subjects who had received placebo in the original trial BAP00089, and who had been successfully treated but had subsequently relapsed, would upon entering this study be given placebo again, as it was considered unethical to expose them unnecessarily to drug"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the investigator, sponsor and all participants remained blinded throughout the course of the BACH and re-treatment studies" Comment: Study authors stated that they conducted a double-blind study but made no statements about how this was done Quote: "the placebo and active drug were indistinguishable and packaged in the same way" Comment: use of identical packages is a sufficient form of blinding; however it is unclear whether site staff were also blinded because the study was a follow-up study in which most participants received the same treatment as in the previous study Personal communication clarified: "a list of treatment assignments was sealed and kept in a central repository by the Biometrics Department and by the Drug Safety Department. No open key to the code was available at the Study Center, or to monitors or members of the project team"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded throughout the study; however no details regarding blinding were given. The observers might have been the same as in the study of Ruzicka 2008. Personal communication clarified: "the investigator had access to coded, sealed envelopes for each participant to be used in an emergency that would have required knowledge of the study medication to manage the emergency. If the investigator wished to know the identity of the treatment given to study subjects for any other purpose, this request was first to be discussed with Basilea Pharmaceutica"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "efficacy evaluations are based on the intention-to-treat population, which included all randomized patients" Comment: intention-to-treat analysis

Bissonnette 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	The trial was registered at clinicialtrials.gov (NCT00124436 and BAP00091 and EUCTR2004-000432-85-HU). No major changes in primary or secondary outcomes. The only difference is that the trial registration states enrolment of 300 participants, and the actual trial included only 117 participants; this was done so all participants from the BACH study who relapsed could be included
Other bias	Low risk	Baseline comparison of disease severity in table, but no significance of differences in tests provided. Personal communication clarified that there were no statistically significant differences Diagnostic certainty: yes The study was completed

Bleeker 1989

Methods	Parallel-group, randomised controlled trial This study was conducted as a multi-centre study at dermatology departments and private clinics in Sweden
Participants	76 participants (22 male, 54 female; ages 18 to 65) with different subtypes of hand eczema. Vesicular and infected dermatitis excluded Dropouts: 1 **Inclusion criteria of the trial** • Allergic or trauma-induced contact dermatitis or atopic dermatitis for at least 3 months • Age limits: 18 to 65 years **Exclusion criteria of the trial** • Infected or vesicular dermatitis • Use of steroid therapy in the last 2 weeks **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Fluprednidene cream once daily in the evening for 3 weeks in 37/38 participants • Betamethasone cream once daily in the evening for 3 weeks in 38/38 participants Emollient (Unguentum Merck) was allowed in both groups if required **Duration** 3 weeks
Outcomes	**Primary outcomes of the trial** Not stated **Other outcomes** • Observer- and participant-rated general assessment of therapeutic result (0 = healed, 1 = improved, 2 = unchanged, 3 = worse)

Bleeker 1989 *(Continued)*

- Reduction in scoring based on symptoms (erythema, scaling, papules, vesicles, lichenification, fissures, excoriation, pruritus) on a scale from 0 to 3 (0 = healed, 1 = improved, 2 = unchanged, 3 = worse)
- Adverse events

Notes	Unclear whether severity score as stated in Methods was used in analysis. Aim was to study equivalency of treatment effect The secondary outcome - reduction in severity, participant-rated - was included but did not provide reproducible data Declarations of interest: not stated Funding: E. Merck A.B. Sweden, which was the manufacturer of unguentum Merck, supported the study Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "each patient was allocated a patient number and assigned at random to one of the two treatment groups" Comment: the article states only that each participant was allocated a participant number and was assigned at random, without further details
Allocation concealment (selection bias)	Unclear risk	Quote: "each patient was allocated a patient number and assigned at random to one of the two treatment groups" Comment: no details about how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a double blind study design was used" Comment: participants and personnel probably blinded, as this is stated in the paper, but no details are given as to how this was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a double blind study design was used" Comment: the article states a double-blind design; however no details are given regarding blinding of observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (75 of 76 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found; however all important clinical outcomes described in Materials and Methods are depicted in the Results. The only drawback is that with regards to the participant-rated general assessment, the Results section states only that this was "significantly improved ($P < 0.001$) after 1 week in both treatment groups"; however no details are given
Other bias	Unclear risk	Baseline comparison: a baseline comparison of disease severity is depicted in a table, but no significance of differences in tests is provided Diagnostic certainty: yes The study was completed

Boroujeni 2017

Methods	Parallel-group, randomised controlled study The study was conducted at a single centre in Iran
Participants	64 participants with hand eczema Dropouts: 4 **Inclusion criteria of the trial** • Patients over 10 years of age **Exclusion criteria of the trial** • Pregnancy • History of oral and topical medication use before and during treatment • Having systemic disease or other skin condition such as fungus infection **Study population** • Gender: herbal group 19 female, 13 male; fluocinolone acetonide group 21 female, 9 male • Age: the most frequent age was 30 to 40 years old; no further details were given
Interventions	**Intervention** • Twice-daily application with an oil-in-water emulsion-based herbal cream. Concentrations of plant material were as follows: fenugreek seeds 5%, marshmallow 5%, chamomile 5%, and walnut leaves 5% • Twice-daily application of fluocinolone acetonide cream 2% **Duration** Two weeks
Outcomes	**Primary outcomes of the trial** Reduction in severity of symptoms such as burning, itching, erythema level, papules and vesicles bumps, and fissures of the skin (method and scale not stated) **Other outcomes** • Questionnaires at baseline and follow-up at week 2
Notes	Study authors were contacted for additional information in April 2018 but remained unresponsive Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "64 patients with hand eczema were randomly divided into two groups of 32 patients each" Comment: no further details on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "this study is a double blind clinical trial" Comment: no details regarding blinding

Boroujeni 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "this study is a double blind clinical trial" Comment: no details regarding observer blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (60 of 64 = more than 80%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found We did not find major differences between what was stated in the Methods and Result sections; however it is unclear how the outcomes were scored
Other bias	Unclear risk	Baseline comparison: not stated Diagnostic certainty: yes The study was completed

Brass 2015

Methods	Parallel-group, randomised controlled pilot study The study was conducted at a single centre in the United Kingdom
Participants	60 participants with hand eczema unresponsive to clobetasol propionate Dropouts: 17 **Inclusion criterion** • Patient has provided written informed consent for participation in the study before undergoing any study-specific procedures • Palmar eczema not responsive to topical treatments • Over 18 years of age • No topical treatments (except emollients for 48 hours) • No systemic treatments for eczema for 3 months • Absence of clinical evidence of bacterial, fungal, or viral infection • Not pregnant **Exclusion criteria of the trial** • Inability to give informed consent • Significant eczema on the dorsal surface of the hands • Previous phototherapy within the last 3 months • Previous sun bed use within the last 3 months • Current involvement in other investigational studies or trials, or involvement within 3 months before study entry **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention**

Brass 2015 *(Continued)*

	• Immersion PUVA twice weekly for 12 weeks with 4-weekly assessments in 30 participants • NB-UVB twice weekly for 12 weeks with 4-weekly assessments in 30 particiBpants **Duration** 12 weeks
Outcomes	**Primary outcomes of the trial** Number of participants achieving a 'clear' or 'almost clear' treatment response at 12 weeks **Other outcomes** • Percentage improvement based on the mTLSS (modified total lesion symptom score) at weeks 0, 4, 8, and 12 • Change in quality of life based on the Dermatology Life Quality index (DLQI) at weeks 0, 4, 8, and 12 • Change in health economic evaluation with the EuroQol health outcome score (EQ-5D) at weeks 0, 4, 8, and 12 • Adverse events
Notes	Data are based on a conference abstract with limited data. Study authors were contacted and provided some additional information Additional information was extracted from the trial register (ISRCTN18213910) Declarations of interest: not stated Funding: the study was sponsored by Newcastle upon Tyne Hospitals NHS Foundation Trust (UK) Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Personal communication with study authors clarified that a computerised randomisation programme was used
Allocation concealment (selection bias)	Unclear risk	Personal communication with study authors stated that before recruitment no one knew what the treatment allocation would be, as the trial was randomised
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "we performed a randomized, observer-blinded pilot study of PUVA vs. NB-UVB for the treatment of hand eczema" Comment: no data available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "we performed a randomized, observer-blinded pilot study of PUVA vs. NB-UVB for the treatment of hand eczema" Comment: the abstract states that observers were blinded Personal communication clarified that only the research co-ordinator was aware of the treatment allocation. All observers carrying out assessments were blind
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (43 of 60 = less than 80%)

Brass 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	The trial was registered at http://www.isrctn.com/ISRCTN18213910 before the start. No significant differences between the trial register and the abstract were found
Other bias	Low risk	Baseline comparison: a baseline comparison of disease severity was provided Diagnostic certainty: yes The study was completed

Burrows 1986

Methods	Parallel-group, randomised controlled study; cross-over design This multi-centre study was conducted in Ireland and in the UK in a secondary setting at 3 different centres
Participants	23 participants with chronic eczema on palms or dorsa, with positive patch test to nickel Dropouts: 3 **Inclusion criteria of the trial** • Chronic hand eczema and a positive patch test to 5% nickel sulphate **Exclusion criteria of the trial** • Pregnancy • Atopic eczema • History of peptic ulcer, hepatic or renal disease • Aberrations in serum iron, CPK, bilirubin, alkaline phosphatase, LDH, AST, ALT, creatinine, urea, urine analysis, and antinuclear factor **Study population** • Gender: 21 female, 2 male • Age: mean age 29.3 years, SD 13.3 years, range 19 to 66 years
Interventions	**Intervention** • Triethylenetetramine (Trientene) 300 mg daily for 6 weeks in an unknown number of participants **Control intervention** • Placebo for 6 weeks Cross-over after 4-week washout. The total expected duration of the study was thus 16 weeks; however the trial was terminated prematurely **Duration** 6 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated: improvement/no change/deterioration • Participant-rated: improvement/no change/deterioration

Burrows 1986 *(Continued)*

- Urinary nickel and copper excretion
- Adverse events

Notes	The trial was terminated due to a literature report on potential adverse events (teratogenicity). Study results were based on participants entered before termination. Results table is difficult to interpret in view of the cross-over; probably based on 20 participants Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were allocated randomly" Comment: no further details on randomisation procedure
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a multicentre, double-blind, crossover trial was initiated to test the ability of...." Comment: participants and staff were probably blinded, as this is stated in the paper, and a placebo was used, but no details are given as to how this was achieved. It is not clear whether placebo was identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a multicentre, double-blind, crossover trial was initiated to test the ability of...." Comment: no details regarding observer blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (20 of 23 = more than 80%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found. The outcome parameters used are very concise. The Materials and Methods section describes that observer- and participant-rated scores would be used with regard to improvement/no change/deterioration; however, only one table shows improvement versus no improvement and worse, and it is unclear whether this was participant- or observer-rated
Other bias	High risk	No baseline comparisons Diagnostic certainty: yes The study was ended prematurely

Cartwright 1987

Methods	Within-participant, randomised controlled trial This was a single-centre study, conducted in the UK

Cartwright 1987 *(Continued)*

Participants	30 participants with bilateral symmetrical constitutional hand eczema, resistant to previous treatment Dropouts: 12 **Inclusion criteria of the trial** • Resistant bilateral hand eczema **Exclusion criteria of the trial** • Not defined **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Superficial X-ray 300 Rad 10 kV 3 times with a 21-day interval in 18/30 hands **Control intervention** • Placebo-radiation in 18/30 contralateral hands 3 times with a 21-day interval Participants were followed up for 18 weeks after initial treatment Participants continued application of tar paste or steroid ointments throughout the trial **Duration** 21 weeks (3 weeks active treatment, 18 weeks follow-up)
Outcomes	**Primary outcomes of the trial** Not defined. **Other outcomes** • Participant-rated severity score on scale 0 to 10 with increasing severity • Observer-rated score 0 to 4 (0 = no eczema; 1 = eczema, mild scaling; 2 = erythema, scaling, fissures; 3 = erythema, severe scaling, bleeding fissures; 4 = active pompholyx) • Adverse events
Notes	Secondary outcomes - reduction in severity, investigator- and participant-rated scoring - were included but provided no reproducible data. Only graphic representation of outcome scores. Graphs in Figures 1 and 2 seem to have been exchanged. High dropout: 12 out of 30. Reasons given for the 12 dropouts: unwilling to attend, mostly because eczema improved Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to a predetermined random code known by the radiographer..."

Cartwright 1987 *(Continued)*

		Reference to a predetermined random code known only by the radiographer
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators, although the article states that only the radiographer knew the randomisation code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "according to a predetermined random code known by the radiographer and unknown to patient and observer, one hand was irradiated with 300 rad (3 Gy) of Grenz rays (...) and the other hand treated in an exactly similar manner, except that sham therapy was given" Comment: participants were truly blinded and received placebo-radiation. The radiographer was the only one aware of the randomisation code in that he had to programme the radiation; however in our opinion, this study could not have been done in another fashion; therefore we judged this trial to have low risk, although not all staff were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "according to a predetermined random code known by the radiographer and unknown to patient and observer..." Comment: the observer was unaware of the allocation; however no further details are provided
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (18 of 30 = less than 80%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found. Outcomes mentioned in the Methods section are depicted in graphs and tables in the Results section; however participant- and observer-rated graphs probably are switched because results in the participant section range from 0 to 3, and results for the observer range from 0 to 7
Other bias	Low risk	Baseline comparisons: within-participant study was not applicable Diagnostic certainty: yes The study was completed

Cherill 2000

Methods	Parallel-group (4 groups), randomised controlled trial; proof of concept Single-centre study, probably conducted in the USA, although not clear from abstract
Participants	48 adult participants with chronic irritant hand dermatitis of moderate severity No dropouts **Inclusion criteria of the trial** • Chronic irritant hand dermatitis of moderate severity **Exclusion criteria of the trial** • Not defined **Study population** • Gender: not stated • Age: not stated

Cherill 2000 *(Continued)*

Interventions	**Intervention** • Pimecrolimus 1% cream twice daily for 6 weeks in 12 participants • Pimecrolimus 1% cream under occlusion twice daily for 6 weeks in 12 participants **Control intervention** • Vehicle twice daily for 6 weeks in 12 participants • Vehicle under occlusion for 6 weeks in 12 participants **Duration** 6 weeks
Outcomes	**Primary outcome of the trial** • Observer-rated (?) total key sign/symptom score (0 to 3 for erythema, excoriation, oedema/ papulation, pruritus) at days 8, 15, 22, 29, 36, and 43 **Other outcomes** • (Serious) adverse events • Key scores for erythema, excoriation, oedema/papulation, pruritus rated on a scale from 0 to 3 at days 8, 15, 22, 29, 36, and 43
Notes	Study was published as a conference abstract; therefore information on quality issues is limited. Study authors were contacted by email and LinkedIn but were unresponsive. Similar abstract published in JEADV 2000;14(S1):128 The secondary outcome - reduction in severity, investigator-rated - was included but did not provide reproducible data Declarations of interest: some study authors were employee of Novartis Pharma AG Funding: study authors were employees of Novartis Pharmaceuticals Corp., East Hanover, New Jersey, USA, and Novartis Pharma AG, Basel, Switzerland, the manufacturer of the study drug Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "within each treatment group, patients were randomly assigned (1:1) to occlusion or no occlusion" Comment: not stated whether participants were randomly assigned to pimecrolimus or vehicle - only that participants in both groups were randomly assigned to occlusion or no occlusion. No further details are given
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a 6-week, randomized, double-blind, vehicle controlled, single center study" Comment: title suggests double-blinded; however, no details about how this was accomplished. Participants used pimecrolimus or vehicle: it is unclear whether these were similar in appearance

Cherill 2000 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a 6-week, randomized, double-blind, vehicle controlled, single center study" Comment: no details regarding blinding of observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included participants were analysed
Selective reporting (reporting bias)	Unclear risk	No trial registration found, and only limited information could be extracted from the abstract. In the abstract, only the overall scores were given - not the key scores for each item
Other bias	Unclear risk	No baseline comparisons conducted or reported Diagnostic certainty: yes The study was completed

Chu 2009

Methods	Within-participant, randomised controlled trial This study was conducted at a single centre in Taiwan
Participants	67 participants with chronic hand eczema **Inclusion criteria of the trial** • Males or females 20 years of age or older • Participants must have chronic hand dermatitis based on clinical diagnosis and at least mild dermatitis of both hands at baseline, as defined by an Investigator Global Assessment score of 2 (mild) to 5 (very severe) • Participants must have been informed of study procedures and therapies and must have given their written informed consent **Exclusion criteria of the trial** • Women who are pregnant or who are breast-feeding • Participants who have received systemic corticosteroids (i.e. oral, intravenous, intra-articular, rectal, intramuscular) within 1 month before first application of study medication • Participants who have received phototherapy (e.g. UVB, PUVA) or systemic therapy (e.g. immunosuppressants, cytostatics) known or suspected to have an effect on hand dermatitis within 1 month before first application of study medication • Patients who were treated with topical therapy (e.g. tar, topical corticosteroids) known or suspected to have an effect on hand dermatitis within 7 days before first application of study medication • Patients who have a diagnosis on the hands of active atopic dermatitis, dyshidrotic eczema, psoriasis, urticaria, active fungal or bacterial infection, or identified allergic contact dermatitis (e.g. poison ivy dermatitis) • Patients with hypersensitivity to vitamin B, vitamin C, vitamin E, beta-carotene **Study population** • Gender: 52 female, 15 male • Age: mean age 42.95 years, range 20.5 to 72.6 years
Interventions	**Intervention**

Chu 2009 *(Continued)*

	• E-DO (HK-03) topical lotion, once daily (evening), for 4 weeks, applied to 1 hand in 67 participants **Control intervention** • Placebo applied once daily on the contralateral hand for 4 weeks, on 67 contralateral hands **Duration** 4 weeks
Outcomes	**Primary outcome of the trial** • Observer-rated therapeutic response rate (clear or almost clear) based on Investigator Global Assessment (IGA) at week 4 (or at time of early discontinuation) **Secondary outcomes of the trial** • Participant-rated reduction in severity: the proportion of participants with at least 50% improvement (clinically significant response) base on the patient's global assessment (PaGA) at week 4 (or at time of early discontinuation) • Observer-rated reduction in severity: the percent change in HEAS (Hand Eczema Area and Severity Score) from baseline to post treatment during 4 weeks • Change in pruritus score and pain score from baseline to post treatment during 4 weeks • Change in the degree of moisture on the skin's surface, and water evaporation on skin surfaces by transepidermal water loss (TEWL) after 4 weeks • Change in quality of life scores (DLQI) from baseline to end of study during 4 weeks • Safety and tolerability of E-DO including adverse events/serious adverse events reported during 4 weeks
Notes	This study is (not yet) published but was registered on clinicaltrials.gov, and Dr. Chu released the results in personal communication after obtaining consent from HenKan Pharmaceutical The secondary outcomes - reduction in severity, investigator-rated and participant-rated - were included but did not provide reproducible data Declarations of interest: not stated, although the study was sponsored by HenKan Pharmaceutical Co. Funding: the study was sponsored by HenKan Pharmaceutical Co., Ltd., and results of this negative study (E-DO was not statistically significant better than vehicle) were not published, although HenKan Pharmaceuticals did give Dr. Chai-Yu consent to release the results Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The report and the trial register claim a randomised design; however it is unclear how randomisation was done Personal communication did not reveal further information
Allocation concealment (selection bias)	Unclear risk	Not described in the protocol; personal communication did not reveal further details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind, vehicle controlled..." Comment: double-blind study in which a placebo vehicle was used
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "randomized, double-blind, vehicle controlled..."

Chu 2009 *(Continued)*

All outcomes		Comment: double-blind study; unclear how this was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "sixty-three subjects received at least one dose of each investigational product (..) and [having] at least one post-baseline assessment on both hands were included in the ITT population" Comment: intention-to-treat analysis was carried out on all participants who received the study drug. Only 63 of the 67 randomised participants received the study drug (94%)
Selective reporting (reporting bias)	Unclear risk	The trial was registered at clinicaltrials.gov (NCT00556855). We found no major discrepancies between the trial registration and the final study report; however for most of the secondary outcomes (quality of life, TEWL, HEAS, pain score), the report states only that no statistically significant differences were found and does not provide actual numbers
Other bias	Low risk	Baseline comparisons: a baseline comparison with regards to disease severity is provided; however because this trial used a within-participant design, this is not further applicable Diagnostic certainty: yes The study was completed

Faghihi 2008

Methods	Within-participant, randomised controlled trial This study was conducted in a secondary setting at 2 different centres in Iran
Participants	47 participants with nearly symmetrical chronic hand eczema with a duration > 4 weeks No dropouts **Inclusion criteria of the trial** • Symmetrical chronic hand eczema with duration > 4 weeks • Older than 12 years of age **Exclusion criteria of the trial** • Pregnancy • No topical treatment during the last 2 weeks nor systemic medication treatment in the last month • Systemic illness **Study population** • Gender: 35 female, 12 male • Age: range 17 to 74 years
Interventions	**Intervention** • 0.05% clobetasol + 2.5% zinc sulphate cream on 1 hand in 47 participants for 2 weeks • 0.05% clobetasol cream alone on the other hand in 47 participants for 2 weeks **Duration** 2 weeks

Faghihi 2008 *(Continued)*

Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Assessment and scoring of different characteristics of hand eczema, namely, scaling, erythema, lichenification, and itch, on a 3-point scale • Severity of itching evaluated by means of the visual analogue scale (VAS) • Adverse events
Notes	Overall severity of hand eczema was not an outcome. Use of the Mann-Whitney U-test for statistical analysis appears incorrect, as the data were related (within-subject design) The secondary outcomes - reduction in severity, participant-rated, and time until relapse - were included but did not provide reproducible data Study authors were contacted by mail on 28 February 2014 but remained unresponsive Declarations of interest: not stated Funding: the study was funded and supported by Isfahan University of Medical Sciences Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... right or left hand of them were randomised to be treated..." Comment: no further details given
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the patients and investigators were blinded to type of treatment" Comment: the drugs were made in "similar shape" by a third party; this is considered an adequate way to blind participants Quote: "drugs were made by the Isfahan Pharmacy School in the similar shape, and the patients and investigators were blinded to the type of treatment" Comment: the code of drugs was revealed only at the end of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "drugs were made by the Isfahan Pharmacy School in the similar shape, and the patients and investigators were blinded to the type of treatment. The code of drugs was revealed only at the end of the study" Comment: no details regarding blinding of outcome assessors, although study authors mention a double-blind design; this is insufficient information to judge the risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "overall, 47 patients (94 samples) were evaluated and all of them completed the study" Comment: all participants completed the study and were included in the analyses
Selective reporting (reporting bias)	Unclear risk	No trial registration found. All outcomes described in Subjects and Methods are described in the Results section, although for itch, only the statistical sig-

Faghihi 2008 *(Continued)*

		nificance level is stated, but the other outcomes are stated in tables with exact numbers
Other bias	Low risk	Baseline comparisons revealed no significant differences between groups in terms of erythema, scaling, lichenification, and pruritus; further within-participant design Diagnostic certainty: yes The study was completed

Fairris 1984

Methods	Within-participant, randomised controlled trial The study was conducted at a single centre in the UK and was carried out in a secondary care setting
Participants	24 participants with chronic constitutional therapy-resistant hand eczema Dropouts: 1 **Inclusion criteria of the trial** • Chronic symmetrical constitutional hand eczema resistant to topical therapy **Exclusion criteria of the trial** • Not defined **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Ionising radiation 100 rad 50 kV 3 times with 21-day interval in 23/24 hands **Control intervention** • Placebo radiation 3 times with a 21-day interval in 23/24 contralateral hands Participants were followed up until 18 weeks after initial treatment **Duration** 21 weeks (3 weeks active treatment, 18 weeks follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant-rated comparisons between both hands based on best improvement at weeks 6, 9, and 18: greater improvement in irradiated hand, placebo hand, or no difference • Participant-rated severity score of hand eczema on a scale of 0 to 10 at weeks 6, 9, and 18 • Observer-rated severity score (0 = normal skin, 1 = mild scaling and erythema, 2 = moderate scaling and erythema and shallow fissures, 3 = severe scaling erythema and deep bleeding fissures, 4 = active pompholyx) • Adverse events

Fairris 1984 *(Continued)*

Notes	The secondary outcomes - reduction in severity, participant-rated and investigator-rated - were included but did not provide reproducible data. Only graphic presentation of scores with statistical significance Declarations of interest: not stated Funding: not stated. Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the radiographer (D.P.M.) treating the patient gave the active radiation or placebo treatment according to a predetermined code" Comment: reference to a predetermined code
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators; only that the code was broken after the end of the trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study: participants were unaware of which hand received treatment and which one placebo due to the placebo-irradiation. The radiographer did know the code of randomisation and gave placebo-X-ray therapy to participants that was indistinguishable from actual X-ray therapy. Although the radiographer (staff) was aware of the treatment, this study could not have been done in another fashion; therefore we judged low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the observer (G.M.F.) did not know which hand was receiving X-ray therapy until the code was broken at the end of the trial" Comment: the observer was unaware of the treatment group, and we judged this as low risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (23 of 24 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. However all outcomes described in the Methods section are clearly described in the Results section
Other bias	Low risk	Baseline comparisons: within-participant study was not applicable Diagnostic certainty: yes The study was completed

Fairris 1985

Methods	Within-participant, randomised controlled trial The study was conducted at a single centre in the UK and was carried out in secondary care setting
Participants	25 participants with chronic constitutional therapy-resistant hand eczema Dropouts: 5 **Inclusion criteria of the trial**

Fairris 1985 *(Continued)*

	• Chronic symmetrical constitutional hand eczema resistant to topical therapy **Exclusion criteria of the trial** • Not defined **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Superficial X-ray 300 Rad 10 kV 3 times with 21-day interval in 20/25 hands • 100 Rad 50 kV 3 times with 21-day interval in 20/25 contralateral hands Participants were followed for 18 weeks after initial treatment **Duration** 21 weeks (3 weeks active treatment, 18 weeks follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant-rated comparisons between both hands based on best improvement at weeks 3, 6, 12, and 18 • Participant -rated score of increasing severity 0 to 10 on VAS. All 3 ratings at weeks 3, 6, 12, and 18 • Observer-rated score (0 = normal skin, 1 = mild scaling and erythema, 2 = moderate scaling and erythema and shallow fissures, 3 = severe scaling, erythema, and deep bleeding fissures, 4 = active pompholyx) • Adverse events
Notes	The secondary outcomes - reduction in severity, participant-rated and investigator-rated - were included but did not provide reproducible data. Only graphic presentation of scores with statistical significance Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "one hand received 100 rad (1 Gy) of conventional superficial X-ray (...), the other 300 rad (3 Gy) of Grenz ray (...) according to a predetermined random code operated by the radiographer..." Comment: reference to a predetermined random code operated by the radiographer
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and investigators

Fairris 1985 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...operated by the radiographer and unknown to the observer" Comment: no information about participant blinding; however the difference between grenz ray and X-ray therapy is indistinguishable for a participant. Although the radiographer (staff) was aware of the treatment, this study could not have been done in another fashion; therefore we judged low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "...operated by the radiographer and unknown to the observer" Comment: the study claims to be double-blinded and thus observer-blinded, which was probably adequate as in Fairris 1984, because the study designs are similar
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (20 of 25 = 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found; however, all outcomes described in the Methods section are clearly described in the Results section
Other bias	Low risk	Baseline comparisons: within-participant study was not applicable Diagnostic certainty: yes The study was completed

Fowler 2005

Methods	Within-participant, randomised controlled trial of 3 parallel groups This was a multi-centre study conducted in the USA and carried out in a secondary care setting
Participants	86 participants with chronic hand eczema Dropouts: 4 **Inclusion criteria of the trial** • Between 18 and 65 years old • Symmetrical hand or atopic dermatitis of moderate severity for at least 2 weeks **Exclusion criteria of the trial** • Use of systemic treatments in the last month or topical corticosteroids in the last week before study entry **Study population** • Gender: 52 female, 34 male • Age: mean 46 years
Interventions	**Intervention** • Hydrocortisone butyrate 0.1% cream on the one hand vs fluticasone propionate 0.05% cream twice daily on the other hand for 2 weeks in 26 participants • Hydrocortisone butyrate 0.1% cream on the one hand vs prednicarbate emollient 0.1% cream twice daily on the other hand for 2 weeks in 28 participants • Hydrocortisone butyrate 0.1% cream on the one hand vs mometasone furoate 0.1% cream twice daily on the other hand for 2 weeks in 31 participants **Duration**

Fowler 2005 *(Continued)*

	2 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Investigator-rated severity of hand eczema on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) for 4 clinical signs (erythema, cracking/ fissuring, scaling, papules/vesicles) • Investigator-rated severity total sum score • Participant-rated severity of hand eczema on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) for 6 clinical signs (erythema, cracking/ fissuring, scaling, papules/vesicles, pruritus, burning/pain) • Participant-rated severity total sum score • Investigator-rated mean reduction in percentage of hand involvement • Participants-rated preference and cosmetic acceptability • Adverse events
Notes	Three participants with atopic dermatitis participated in the study. Percentage of hand involvement was the only outcome whereby exclusively participants with hand eczema were analysed. Each intervention group had a within-participant design. in addition, the difference in efficacy between the 3 groups was evaluated The study did include a participant- and investigator-rated severity score, but we were unable to use the data. The study also included adverse events, but we were unable to use this information because only numbers for both treatment groups combined were stated Study authors were contacted on 4 March 2014 and replied 6 March 2014 Declarations of interest: 2 study authors acted as consultants Funding: the study was funded by Ferndale Laboratories, Inc., manufacturer of the study drugs. Two study authors were investigator and consultant for Ferndale Laboratories, Inc. Sample size rationale: not stated; personal communication clarified this was not conducted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised in balanced cohorts to 3 parallel treatment groups" Comment: no further details given in the article; personal communication with the study author clarified that a computer programme was used to create the randomisation code
Allocation concealment (selection bias)	Low risk	No details in the article about how allocation was concealed from participants and investigators. Personal communication revealed that allocation was conducted by the sponsor, who was at a remote site. Participants were enrolled without knowledge of the expected treatment group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the medication[s] were dispensed to the subjects in blind-labelled tubes that were clearly marked with the subject's identification number and the word left or right" Comment: study authors state double-blind design. The sponsor and the study co-ordinator had access to the randomisation code list; treating physicians and participants were unaware of this

Fowler 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study, which includes observer blinding. Observers had no access to the randomisation code and were truly blinded (personal communication)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (82 of 86 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found; however all outcomes described in the Methods section are described in the Results
Other bias	Low risk	Baseline comparisons: no significant differences among the 3 groups in terms of age, gender, race, and eczema severity Diagnostic certainty: yes The study was completed

Fowler 2014

Methods	Randomised, parallel-group, placebo-controlled trial This study was carried out in a secondary care setting This was a multi-centre study conducted at 70 centres in the United States The study consisted of 4 phases: screening, run-in, treatment, and follow-up
Participants	596 participants with severe chronic hand eczema refractory to potent topical corticosteroids Dropouts during treatment phase: 307 participants 162 participants entered the follow-up period after achieving a PGA rating of clear or almost clear Dropouts during follow-up: 35 A total of 467 entered the safety follow-up phase Dropouts during safety follow-up: 116 **Inclusion criteria of the trial** • All types of chronic hand eczema lasting for at least 6 months since initial diagnosis • Rated as severe by the physician after at least 2 weeks of treatment with potent topical corticosteroids • Unresponsive to highly potent topical corticosteroids, such as clobetasol • History of unsatisfactory treatment outcomes • 18 to 75 years of age **Exclusion criteria of the trial** • Patients with known allergens and irritants who have not made a reasonable effort to avoid these substances • Patients with psoriasis lesions • Active fungal, bacterial, or viral infections of the hands • Female patients who are pregnant or breastfeeding • Female patients of child-bearing potential who cannot use or will not commit to using 2 effective methods of contraception • Atopic dermatitis lesions requiring medication • Acute episodes of pompholyx/dyshidrosis or contact dermatitis

Fowler 2014 *(Continued)*

- Metabolic bone disease, disease affecting the bone, or patients receiving bone active drugs
- Active psychiatric disorder and/or > 1 in question 9 or overall score > 15 on the Patient Health Questionnaire
- History of hearing loss or otological or balance disorders deemed medically relevant

Study population

- Gender: alitretinoin 30 mg female 133, male 165; placebo female 149, male 149
- Age: alitretinoin 30 mg mean 47.1 years, SD 12.6 years, median 48.0 years; placebo mean 47.5 years, SD 13.0 years, median 50.0 years

Interventions	**Intervention** • Oral alitretinoin 30 mg once daily for 24 weeks in 298 participants **Control intervention** • Placebo capsules once daily for 24 weeks in 298 participants **Duration** 72 weeks (24 weeks of active treatment and follow-up up to 48 weeks after the end of treatment)
Outcomes	**Primary outcomes of the trial** • The proportion of responding participants with a PGA of "clear" or "almost clear" after 24 weeks or at the latest assessment for patients withdrawing maturely **Secondary outcomes of the trial** • Change from baseline in mTLSS (modified Total Lesion Symptom Score) • PaGA (Patient Global Assessment) • Time to response • Duration of response • Time to relapse **Other outcomes** • Extent of disease at baseline and at end of treatment • Quality of life assessment (Skindex-29) • Adverse events • Other safety monitors (PHQ-9 and Brief Symptom Inventory (BSI-53), depression screening questionnaires, bone markers, skeletal X-rays, dual-energy X-ray absorptiometry, ophthalmological and audiological evaluations)
Notes	The treatment phase was included in this review Study authors were contacted for additional information Declarations of interest: the first study author was a sponsored investigator and served as consultant to GSK The other study authors were employed by Stiefel, a GSK Company Funding: the study was supported and funded by Stiefel, a GlaxoSmithKline Company (GSK), manufacturer of the study drug. No information was provided about external monitoring or quality control Sample size rationale: adequate

Risk of bias

Fowler 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "participants were randomized 1:1 to receive once-daily alitretinoin 30 mg or placebo through a central randomization system that used an interactive voice response system" Comment: randomisation method adequate
Allocation concealment (selection bias)	Low risk	Quote: "investigators, study personnel, patients and statisticians were unaware of assigned study treatment" Comment: the central randomisation point was used at a distance location
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote from the clinical trial register: "patients receive matching placebo for up to 24 weeks" Comment: placebo was used to achieve blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not clear who assessed the outcome - probably the 70 providers of the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the intent-to-treat (ITT) population (randomised patients who were dispensed medication) was used for efficacy analyses" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	The study was registered at clinicaltrials.gov NCT00817063. Except for some small differences in the exclusion criteria, no substantial differences between protocol and study report were found
Other bias	Low risk	Baseline comparison: no significant differences were reported Diagnostic certainty: yes The study was completed

Fredriksson 1975

Methods	Within-participant, randomised controlled trial The study was probably conducted at a single centre in Sweden
Participants	30 participants with bilateral eczematous dermatitis of the hands were selected from a clinical pool No dropouts **Inclusion criteria of the trial** • Patients with bilateral eczematous dermatitis of the hands were selected from a clinical pool for treatment **Exclusion criteria of the trial** • Not stated **Study population** • Gender: not stated

Fredriksson 1975 *(Continued)*

- Age: not stated

Interventions	**Intervention** • Aquacare HP cream, a moisturising emulsion containing multi-sterols, phospholipids, and fatty diols (pH 6) twice a day (morning and evening) for 4 weeks in 30 hands **Control intervention** • Calmurid cream containing betaine and lactic acid (pH 3) twice a day for 4 weeks in 30 contralateral hands **Duration** 4 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant preference rating based on efficacy • Investigator preference rating on basis of efficacy • Participant preference rating on basis of cosmetic acceptability • Adverse events • An unclear scale for effectiveness ranging from 0 to 5: 0 = no objective symptoms; 5 = severest possible condition. Unclear whether this was observer or participant rated
Notes	The last outcome is unclear, and results are not depicted in the article. Study authors state only that Aquacare was statistically significantly more effective over Calmurid; no exact results or data are given Declarations of interest: not stated. Funding: not stated. Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "tubes containing 90 gpm of Aqaucare HP cream and Calmurid cream were packed into identical cartons after being randomly marked left and right" Comment: no clarification on how random marking of left and right was done; therefore risk was judged as unclear
Allocation concealment (selection bias)	Low risk	Quote: "tubes containing 90 gpm of Aqaucare HP cream and Calmurid cream were packed into identical cartons after being randomly marked left and right. These were dispensed in a double-blind fashion" Comment: the drugs were dispensed in identical looking cartons that at random were marked with left or right, without any organisation; therefore physicians and participants were unaware of treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...double-blind fashion..." Comment: study authors stated double-blinded design. Randomly marked tubes were dispensed in a "double-blind fashion", which is considered an adequate way to blind participants

Fredriksson 1975 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double-blind fashion..." Comment: double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included participants were analysed
Selective reporting (reporting bias)	High risk	No trial registration found. The article describes an unclear severity scale ranging from 0 to 5; however the results for this outcome are not registered in the article
Other bias	Low risk	No baseline comparisons; however within-participant study was not applicable Diagnostic certainty: yes The study was completed

Granlund 1996

Methods	Randomised, parallel-group design, with a partial cross-over design in the second phase Randomisation procedure unclear The study was carried out in a secondary care setting This was a single-centre study conducted in Finland
Participants	41 participants with hand eczema, continuously for 6 months, significant disability, inadequate response to conventional treatment, confirmation by histopathology Dropouts: 6 in the first phase, 1 in the second phase **Inclusion criteria of the trial** • 18 to 70 years old • Continuous hand eczema for at least 6 months • Causing significant disability • Inadequate response to conventional treatment **Exclusion criteria of the trial** • Other skin disorders • Treatment with systemic corticosteroids within 4 weeks or topical steroids or UV radiation within 2 weeks before the study • Standard exclusion criteria for participants undergoing cyclosporin treatment **Study population** • Gender: cyclosporin group 13 female, 7 male; betamethasone group 10 female, 11 male • Age: cyclosporin group mean 36 years, SD 9 years, 95% CI 32 to 40; betamethasone group mean 40 years, SD 11 years, 95% CI 35 to 45
Interventions	**Intervention** • Oral cyclosporin 3 mg/kg/d and placebo cream for 6 weeks in 17/20 participants • Topical betamethasone dipropionate 0.05% cream and placebo capsules identical to cyclosporin in 19/21 participants

Granlund 1996 *(Continued)*

At week 6, cross-over of those who had treatment failure in the first 6 week phase: 8 participants switched to betamethasone, and 6 to cyclosporin

In the third phase, a 24-week follow-up period without intervention

Use of own emollients was allowed in both groups

Duration

Maximum 36 weeks with 6 to 12 weeks of active treatment

Outcomes

Grandlund 1996:

Primary outcomes of the trial

Not defined

Other outcomes

- Participant-rated overall assessment of efficacy (1 = very good, 2 = good, 3 = moderate, 4 = slight, 5 = none)
- Observer-rated overall assessment of efficacy (1 = very good, 2 = good, 3 = moderate, 4 = slight, 5 = none)
- Observer-rated disease activity score: grading 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) on erythema, scaling, infiltration, excoriation, crusting, vesicles
- Observer-rated extent of disease
- Use of emollients
- Participant-rated itch and sleep disturbances for the final 2 weeks on a VAS
- Treatment success, defined as decrease in disease activity score (see first outcome above) to < 5.0% of baseline score
- Adverse events

Grandlund 1997:

Primary outcome of the trial

- Quality of life assessed by the Eczema Disability Index (EDI) at week 6 and week 12

Other outcomes

- Observer-rated disease activity score: grading 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) on erythema, scaling, infiltration, excoriation, crusting, vesicles for both hands
- Observer-rated extent of disease
- Use of emollients
- Participant-rated itch and sleep disturbances for the final 2 weeks on a VAS

Notes

Grandlund 1996: study had 3 phases, which were partially overlapping. The second phase dealt with participants who had treatment failure in phase 1. In this second phase, participants were switched over to the alternative intervention. The third phase includes only participants who had treatment success in phase 1. Outcome assessment based on intention-to-treat analysis. This review deals with only phase 1 and phase 3

Granlund 1997: paper is based on the same trial (same participants) as Granlund 1996, but deals only with phases 1 and 2. The study had 3 phases, which were partially overlapping. The second phase dealt with participants who had treatment failure in phase 1. In this second phase, participants were switched over to the alternative intervention. The third phase includes only participants who had treatment success in phase 1. In this review, only results of the first phase will be discussed. Outcome assessment was based on intention-to-treat analysis

The secondary outcomes - reduction in severity, participant-rated scoring, time until relapse, and dose reduction - were included in the study but did not provide reproducible data

Granlund 1996 *(Continued)*

	Declarations of interest: not stated Funding: the study was supported by Sandoz Pharmaceuticals, Switzerland (manufacturer of the study drug) and Finland, and by a grant from Finska Läkaresällskapet, Finland Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were given numbers 1-41 in consecutive order, which had been reassigned to treatment with..." Comment: however, neither article clarifies how this reassignment was done
Allocation concealment (selection bias)	Low risk	Quote: "the codes were not opened until all participants had finished all parts of the study" Comment: the study used identical placebos for topical and oral treatment, and participants were given consecutive numbers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "soft gelatine capsules containing 25, 50 or 100 mg and identical placebo capsules were supplied by ..." "Identical 100 tubes were used for the creams" Comment: study authors stated double-blinded design. Sufficient information provided about how participant blinding was achieved and identical tubes and placebos were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the codes were not opened until all patients had finished all parts of the study" Comment: double-blind design; because identical placebos were used and the randomisation code was not broken before the end of the study, it is unlikely that assessors were aware of the treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "results were analyzed on an intention to treat basis" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No trial registration found; however all relevant outcomes are addressed in the Materials and Methods sections of the 2 articles and are depicted in graphs in the Results section
Other bias	Unclear risk	Baseline comparisons revealed a significant difference between groups in terms of pre-study antibiotics treatment Diagnostic certainty: yes The study was completed

Grattan 1991

Methods	Within-participant, randomised controlled trial The study was probably conducted in a secondary care setting at a single centre in the UK
Participants	15 participants with vesicular hand eczema for at least 6 months Dropouts: 3

Grattan 1991 *(Continued)*

Inclusion criteria of the trial

- 16 years of age or older
- Recurrent disabling symmetrical vesicular hand eczema for at least 6 months with periods of remission (complete clearance) not exceeding 1 month in the previous 6

Exclusion criteria of the trial

- Pustular psoriasis
- Chronic hyperkeratotic dermatitis
- Chronic fungal infection
- Relevant allergy
- Predominantly irritant dermatitis
- Pregnancy
- Phototoxicity
- Use of immunosuppressive drugs

Study population

- Gender: 3 female, 9 male
- Age: mean 49.7 years, SEM 4.1 years, range 24 to 69 years

Interventions	**Intervention** • Topical PUVA 3 times a week for 8 weeks on 12/15 hands **Control intervention** • UVA (with placebo psoralen paint) on 12/15 contralateral hands Moisturisers were allowed on both hands, and both hands received a small fraction of UVB from UVA lamps During an unclear follow-up period, participants received a questionnaire **Duration** 8 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated global rating on a 5-point scale (0 = clear, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe) at a weekly interval • Participant-rated VAS to indicate improvement at weeks 0, 4, 8, 12, and 16 • Observer-rated severity score: T-120 scores: multiplying surface area involved with severity scores (0 to 4) for vesiculation, erythema and scaling in weeks 0, 4, 8, 12, and 16 • Questionnaire after completion of the study • Adverse events
Notes	Small number of participants. The secondary outcomes - reduction in severity, investigator-rated and participant-rated, and time until relapse - were included but did not provide reproducible data. Exact figures for main outcomes are not given; instead there are graphic presentations. Questionnaire assessment was performed after completion of the study, but duration of follow-up in this questionnaire assessment remains unclear Declarations of interest: not stated Funding: not stated

Grattan 1991 *(Continued)*

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "psoralen and placebo were randomised and coded by one independent investigator (GJS) and supplied in bottles labelled left and right" Comment: no further details
Allocation concealment (selection bias)	Low risk	Quote: "psoralen and placebo were randomised and coded by one independent investigator (GJS) and supplied in bottles labelled left and right" Comment: randomisation and coding were accomplished by an independent investigator, and bottles were supplied labelled 'left' and 'right'; therefore the physician was unaware of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "psoralen and placebo were randomised and coded by one independent investigator (GJS) and supplied in bottles labelled left and right" Quote: "the placebo was...." Comment: double-blind study with a similar looking placebo; it was not possible for the participant to distinguish these
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the code was not broken until completion of the study" Comment: double-blind design in which an independent investigator supplied the treatments. It was not possible for observers to know the treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (12 of 15 = 80%)
Selective reporting (reporting bias)	Unclear risk	No trial register found. No major differences between outcomes described in the Methods section and outcomes described in the Results section; however although the article text claims that separate scores for the T-120 are described, we were unable to find a score for separate items
Other bias	Low risk	Baseline comparisons: as within-participant study not applicable Diagnostic certainty: yes The study was completed

Gupta 1993

Methods	Parallel-group, randomised controlled trial The study was conducted at a single dermatology centre in Canada
Participants	58 participants with steroid-responsive dermatitis limited to the hands Evaluable: 54 Dropouts: 6, of whom 4 permitted a protocol violation and 2 ended prematurely because of an exacerbation of hand eczema **Inclusion criteria of the trial**

Gupta 1993 *(Continued)*

- Corticosteroid-responsive dermatitis limited to the hands

Exclusion criteria of the trial

- Medically significant cutaneous conditions other than hand eczema
- Clinically infected hand dermatitis
- Known sensitivity to study medication
- Use of topical corticosteroids in the last 14 days, other topical treatments in last week, systemic corticosteroids during last 12 weeks. Systemic antimicrobials, all other investigational drugs and radiation therapy last 30 days, systemic or topical antihistamines in last 14 days, and topical anaesthetics or topical and systemic analgesics in last 48 hours

Study population

- Gender: not stated
- Age: 18 to 70 years

Interventions	**Intervention** • Betamethasone dipropionate film-forming lotion in 28/29 participants daily for 7 days • Betamethasone dipropionate thickened lotion in 26/29 participants for 7 days **Duration** 1 week
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Investigator-rated overall severity of hand eczema:(0 = absent, 1 = mild, 2 = moderate, 3 = severe) at days 2, 4, and 7 • Investigator-rated scores (0 = absent, 1 = mild, 2 = moderate, 3 = severe) of pruritus, scaling, erythema, induration at days 2, 4, and 7 • Physician global assessment of eczema relief (+3 = cleared to -2 = much worse) at days 2, 4, and 7 • Adverse events
Notes	Very short study of only 7 days. Unclear about withdrawals in lotion group. Exact number allocated to each treatment not specified. Among the different outcomes, unclear how change in overall severity was calculated Declarations of interest: not stated. Funding: the study was supported in part by a grant from GenDerm Corporation, Montreal, Canada, manufacturer of the study drugs Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "participants were randomly assigned to 2 groups..." Comment: no further details
Allocation concealment (selection bias)	Low risk	Quote: "bottles were dispensed in their marketed containers with identical overlabels and the contents were not known to the patients or the investiga-

Gupta 1993 *(Continued)*

		tor who assessed the results. Only the study coordinator was aware of the contents of the bottles" Comment: sequentially numbered drug containers of identical appearance are considered as adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "bottles were dispensed in their marketed containers with identically appearing overlabels and the contents were not known to the patients or the investigator who assessed the results. Only the study coordinator was aware of the contents of the bottles" Comment: double-blind study; identical looking containers were used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "bottles were dispensed in their marketed containers with identically appearing overlabels and the contents were not known to the patients or the investigator who assessed the results. Only the study coordinator was aware of the contents of the bottles" Comment: observers were unaware of the study drug, which was identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (54 or 52 of 58 = more than 80%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found. No major differences between the Methods and Results sections found; however for erythema and pruritus, study authors state only that no significant differences were found
Other bias	Low risk	Baseline comparisons: at baseline, significant differences in scaling between groups, but controlled for by statistical procedure. No significant differences at baseline with regard to age, gender, race, erythema, induration, pruritus, or area of eczematous involvement Diagnostic certainty: yes The study was completed

Hanifin 2004

Methods	A phase I-II, open-label, randomised controlled, parallel-group (3 groups) study The study was conducted at various dermatology departments in the USA
Participants	55 participants with chronic severe hand dermatitis (32 atopic, 18 irritant, 5 dyshidrotic or other): duration at least 6 months and severity score 3 or 4 Dropouts: 13 **Inclusion criteria of the trial** • Hand eczema for at least 6 months with a score of 3 or 4 on 3 out of 6 severity scales **Exclusion criteria of the trial** • Psoriasis on the hands • Urticaria • Active fungal or bacterial infection on the hands • Identified allergic contact dermatitis • Use of oral retinoids was contraindicated with a washout period of 12 weeks

Hanifin 2004 *(Continued)*

- Use of other oral therapies (washout 4 weeks), topical retinoids, or immunomodulating therapies in the last 4 weeks
- Use of topical steroids in the last 2 weeks
- Pregnancy
- Lactating women

Study population

- Gender: 37 female, 18 male
- Age: median 42 years, range 20 to 74 years

Interventions	**Intervention** • Bexarotene 1% gel escalated stepwise from 1× every other day to 3× daily in 28 participants for 22 weeks • Bexarotene gel stepwise plus mometasone furoate 0.1% ointment 2× daily in 13 participants for 22 weeks • Bexarotene gel stepwise plus hydrocortisone 1% ointment 2× daily in 14 participants for 22 weeks In all 3 groups, daily use of emollients was allowed **Duration** 22 weeks
Outcomes	**Primary outcome of the trial** • Observer-rated treatment success defined by 90% or better clearance using a physician assessment score (not exactly defined) **Secondary outcomes of the trial** • Observer-rated percentage improvement in HEASI (adaptation of EASI for the hands) score. The HEASI equals (sum of severity scores for signs) × (involved hand area integer), whereby for the area 1 = < 10% involvement, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%. Severity score of signs is 0 = none, 1 = mild, 2 = moderate, 3 = moderately severe, and 4 = severe for, respectively, erythema, scaling, oedema, lichenification, vesiculation, and fissuring at weeks 2, 4, 6, 8, 10, 14, 18, and 22 **Other outcomes** • Observer-rated clinically significant response, defined by 50% improvement using a physician assessment score (not exactly defined) • Participant-rated pruritus on a scale from 0 = none to 4 = severe • Adverse events
Notes	Phase I to II open-label study. Intention-to-treat principle not stated, but the proportion of participants with treatment success is based on the number of all participants enrolled in each treatment group. Of the 12 dropouts/withdrawals, it is unknown to which treatment group they belong The secondary outcome - reduction in severity, participant-rated scoring - was included but no reproducible data were provided Study authors were contacted by email and LinkedIn; however they were unable to answer all of our questions Declarations of interest: one of the study authors was an employee of Ligand Pharmaceuticals, San Diego, USA Funding: not stated

Hanifin 2004 *(Continued)*

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized at 2:1:1 into three treatment arms..." Comment: no further details given in the article; personal communication clarified that a computer-generated scheme was used
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "a phase I-II open label randomized clinical study...." Comment: no blinding of participants or observers as open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "a phase I-II open label randomized clinical study...." Comment: observers were not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No intention-to-treat analysis according to the text; however in the tables, 55 participants seems to be included, where the text clearly states that 13 participants withdrew before completing the 22 weeks of the study 42 of 55 = less than 80%
Selective reporting (reporting bias)	Low risk	No trial registration found; however, relevant outcomes were described, such as HEASI score, and we found no major discrepancies between participants in the Methods section and the Results section
Other bias	Low risk	Baseline comparisons: no significant difference among groups in demographic or disease characteristics Diagnostic certainty: yes The study was completed

Hill 1998

Methods	Randomised, parallel-group design. The study was conducted in a secondary care setting at different dermatology departments in the UK
Participants	120 participants with diagnosis of eczema on one or both hands, and with suspected or confirmed infection Dropouts: 10 **Inclusion criteria of the trial** • Clinical diagnosis of hand eczema with secondary bacterial infection • Presence of erythema induration or itching (2 out of 3) • 18 years of age or older **Exclusion criteria of the trial**

Hill 1998 *(Continued)*

- Psoriasis of the hands
- Primary cutaneous infections on the hands
- Non-eczematous lesions with secondary infection on the hands
- Topical or systemic antibiotics in previous week
- Use of other drugs in the past 4 weeks that could affect eczema
- Known hypersensitivity to study medication
- Women with inadequate contraception, pregnancy, and breastfeeding
- Patients unable to comply with the study protocol

Study population

- Gender: 40 female, 18 male
- Age: mean 35.6 years, range 18 to 79 years

Interventions	**Intervention** • Betamethasone-valerate 0.1% + clioquinol 3% cream twice daily for 4 weeks in 57/61 participants • Betamethasone-v 0.1% + fusidic acid 2% cream twice daily in 53/55 participants for 4 weeks **Duration** 4 weeks
Outcomes	**Primary outcome of the trial** • Observer-rated proportion of participants with satisfactory (i.e. good or excellent) response at the last on-treatment visit based on global rating: excellent, good, fair, or poor **Other outcomes** • Participant-rated response to treatment: excellent, good, fair, or poor at weeks 1, 2, and 4 • Observer-rated changes in scores for erythema, pruritus, induration, dryness/scaling, cracking/fissuring, clinical signs of infection (for each: 0 = absent, 1 = mild, 2 = moderate, 3 = severe) at weeks 1, 2, and 4 • Participant-rated severity of itching: 0 = absent, 1 = mild, 2 = moderate, 3 = severe at weeks 1, 2, and 4 • Participants' assessment of treatment acceptability with regards to stickiness, staining of skin and/or clothing, ease of application, and overall acceptability • Bacterial culture at entry and at end of treatment: successful if pretreatment pathogen, if present, was eradicated • Adverse events
Notes	Primary outcome assessed at last on-treatment visit: probably for most participants at week 4, but unclear how much earlier for dropouts (graph suggests after week 4). Not clear if data for secondary outcome number 2 (participant-rated response) are presented The primary outcome percentage of participants with self-rated good/excellent control and the secondary outcomes - reduction in severity, investigator- and participant-rated scoring - were included but provided no reproducible data Declarations of interest: one study author was an employee of Leo Pharmaceuticals, Princes Risborourg, UK Funding: the study was designed and sponsored by Leo Pharmaceuticals, Princes Risborough, UK, manufacturer of the study drug Sample size rationale: not stated

Risk of bias

Hill 1998 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "treatment was allocated at random" Comment: the article states only that treatment was allocated at random, without further details
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "this was a multicentre, prospective, randomized, open-parallel-group comparison" Comment: not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "this was a multicentre, prospective, randomized, open-parallel-group comparison" Comment: not blinded, which might have affected observer-rated outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "... and were included in an intention-to-treat analysis in respect of the primary efficacy criterion only" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	No trial registration found. We did not find major differences between what was stated in the Methods section and in the Results section; however the subscores for clinical signs and symptoms were not given, and it was stated only whether they were statistically significantly different
Other bias	Unclear risk	Baseline comparisons: more 'severe' classification of signs in the betamethasone/fusidic acid group; unclear whether this constitutes a significant difference and was controlled for Diagnostic certainty: yes The study was completed

Hordinsky 2010

Methods	Randomised controlled, parallel-group design This was a multi-centre study conducted at 57 centres in 7 countries (Austria, Canada, Denmark, Hungary, Italy, Norway, USA)
Participants	652 (246 male, 406 female) with diagnosis of mild to moderate hand dermatitis as defined by IGA 555 participants completed the double-blind phase, 544 (269 in the pimecrolimus group and 275 in vehicle group) entered the open extension phase, and 512 (248 and 264, respectively) completed the study **Inclusion criteria of the trial** • History of hand eczema (according to IGA: mild to moderate) of at least 90 days' duration • Minimum age of 18 years **Exclusion criteria of the trial** • Medication or concomitant conditions that could interfere with conduct of the study or results

Hordinsky 2010 *(Continued)*

- Immunocompromised participants
- History of malignant disease
- Endogenous dermatoses: dyshidrotic dermatitis, psoriasis of the hands, flares of atopic dermatitis

Study population

- Gender: pimecrolimus group 185 female, 130 male; vehicle group 211 female, 116 male
- Age: pimecrolimus group mean 43.9 years, SD 14.4 years, range 18 to 84 years; vehicle group mean 44.1 years, SD 15.1 years, range 18 to 85 years

Interventions	**Intervention** • Pimecrolimus 1% ointment twice daily with daily occlusion by use of vinyl gloves of at least 6 hours after second (evening) application for up to 43 weeks in 325 participants **Control intervention** • Vehicle ointment twice daily with daily occlusion by use of vinyl gloves of at least 6 hours after second (evening) application for up to 43 weeks in 327 participants **Duration** Up to 43 weeks
Outcomes	**Primary outcome of the trial** • Investigators Global Assessment (IGA) of the target hand at day 43 or at time of early discontinuation (according to trial registration, not clear from article) (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) **Other outcomes** • Observer rated: clear or almost clear of hand dermatitis at end of trial as defined by IGA (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) at weekly intervals • Participant-rated: pruritus severity 0 to 3 (0 = absent, 3 = severe) at weekly intervals • Participant-rated: burning sensation/severity of burning 0 to 3 (0 = absent, 3 = severe) • Safety and tolerability (adverse events)
Notes	Participants could enter open-label phase before 42nd day if hand dermatitis had remained cleared on 2 consecutive weekly assessments. However, efficacy comparisons were made at day 42 in intention-to-treat analysis. Not clear how many participants were blind to treatment during assessments at days 29, 36, and 43, as open-label phase could already have started We were unable to obtain additional information from study authors Declarations of interest: one study author was an employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA Funding: the study was supported by Novartis Pharma AG, manufacturer of the study drug Sample size rationale: provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were randomized in a 1:1 ratio to receive..." Quote: "randomization was performed using a validated automated system and was stratified by baseline IGA score at each centre" Comment: randomisation method was considered adequate

Hordinsky 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...double-blind and vehicle-controlled..." Comment: study authors state double-blinded design, although unclear whether pimecrolimus and vehicle were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double-blind and vehicle-controlled..." Comment: double-blind study; however, insufficient details are given about investigator blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all the efficacy assessments were done in the intent-to-treat population using a last observation carried forward approach" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Trial registration was found on clinicaltrials.gov (NCT00226707) Work productivity and activity impairment questionnaires are included in the trial registration but are not mentioned in the article The trial register stated that the primary outcome was IGA on day 43, although this is not clearly stated in the article
Other bias	Low risk	Baseline comparisons conducted: "there were no clinically relevant differences in baseline demographic characteristics or disease history between the pimecrolimus cream 1% and vehicle groups" Diagnostic certainty: yes The study was completed

Jowkar 2011

Methods	Randomised controlled, parallel-group design This study was conducted at a single dermatology centre in Iran
Participants	44 "healthy patients with hand eczema that did not use topical medication in 2 weeks ago or systemic medication in 1 month ago were enrolled" (participants aged 12 to 60 years with hand eczema) No dropouts **Inclusion criteria of the trial** • Healthy participants with hand eczema **Exclusion criteria of the trial** • Use of topical medication in the 2 weeks before the study • Systemic treatments 1 month before the study • Pregnancy • Lactation • Hypersensitivity to study drugs **Study population**

Jowkar 2011 *(Continued)*

- Gender: 30 female, 14 male
- Age: mean 33.3 years, range 13 to 58 years

Interventions	**Intervention** • 4% topical cream of Fumaria parviflora L. alcoholic extract for 4 weeks twice daily, 10 grams on hand surface skin in probably 22 participants, although this is not clearly described in the article **Control intervention** • Placebo twice daily in probably 22 participants for 4 weeks Participants were followed up until 2 weeks after the end of treatment **Duration** 6 weeks (4 weeks active treatment, 2 weeks follow-up)
Outcomes	**Primary outcome of the trial** • Investigator-rated reduction in severity of hand eczema at week 0 and week 6 (2 weeks after termination of therapy) by means of the Eczema Area and Severity Index (EASI), which is validated for atopic dermatitis and scores erythema, papules, excoriation, and lichenification on a scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe and multiplies this by an area score **Other outcomes of the trial** • Adverse events
Notes	The number of participants in each group is not described, and the ratio intervention vs placebo is unclear Because the data are presented in a graphical manner, they are difficult to reproduce. The secondary outcome - reduction in severity investigator-rated - was included but did not provide reproducible data Study authors were contacted on 28 February 2014 and replied the same day Declarations of interest: none declared Funding: the study was supported by Shiraz University of Medical Science Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was conducted based on block randomization design" Comment: randomisation block design suggests the use of a randomisation code list; however study authors denied the existence of a randomisation list in personal communication
Allocation concealment (selection bias)	Low risk	No details about allocation concealment in the article; however personal communication clarified that treatment allocation was done by a third person
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind (patient-physician) placebo-controlled study" Comment: no additional information is provided in the article. Personal communication clarified that placebo and actual treatment were the same in appearance, and the secretary (third party, not involved in actual treatment) dispensed the study drugs

Jowkar 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "both dermatologist and patients were blind to study groups. Data were recorded by an assessor" Comment: physicians were blinded and unaware of treatment allocation, which was done by a third person
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "a total of 44 patients completed the study" Comment: one patient was excluded from the study due to side effects; however more than 80% completed the study
Selective reporting (reporting bias)	Low risk	No discrepancy between the registered trial (IRCT 1388103030741N1) and the original article with regard to outcomes
Other bias	Unclear risk	Baseline characteristics depicted in graphs; not stated whether there was a significant difference between groups Diagnostic certainty: yes The study was completed

Jowkar 2014

Methods	Randomised controlled, parallel-group study This study was conducted at teaching dermatology clinics of the Shiraz University of Medical Sciences
Participants	92 consecutive patients with a clinical diagnosis of hand eczema Dropouts: 58 participants were analysed, of whom 4 were excluded due to adverse events; unclear what happened to the remaining 34 participants **Inclusion criteria of the trial** • Clinical diagnosis of hand eczema **Exclusion criteria of the trial** • Pregnancy • Lactation • Use of any topical or systemic immunosuppressants during the last month • Patients under 12 years of age • Psoriasis proven by a biopsy in clinically probable cases • Patients who used topical therapy during the last 2 weeks • Patients who used systemic therapy during the last month • Development of adverse events during the study **Study population** • Gender: fumaric acid group 21 female, 9 male; triamcinolone group 19 female, 11 male • Age: fumaric acid group mean 28.7 years; triamcinolone group mean 31 years
Interventions	**Interventions** • Topical fumaric acid 5% cream twice a day for 1 month in 30 participants • Triamcinolone 0.1% cream twice a day for 1 month in 28 participants **Duration** 4 weeks

Jowkar 2014 *(Continued)*

Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes of the trial** • Signs of the disease including erythema, excoriation, population, and lichenification at week 0 and week 4 • Disease score based on the EASI (Eczema Area and Severity Index) at week 0 and week 4 • Degree of pruritus ranging from 0 to 3 (0 = no pruritus, 3 = severe) at week 0 and week 4
Notes	92 consecutive patients were recruited; a substantial portion of these patients were lost to follow-up Study authors were contacted for additional information by email and provided additional information regarding design and risk of bias Declarations of interest: none declared Funding: the study was sponsored by Shiraz University of Medical Sciences. Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a list of randomized coded groups was given to the study investigator, and as patients consecutively were enrolled in the study, they were assigned to the next available randomized group on the list" Comment: consecutive patients were enrolled, and the investigator was given a list of randomised coded groups Study authors clarified they used a random number table generated by a statistical computer programme
Allocation concealment (selection bias)	Low risk	No details about how allocation was concealed from participants and clinicians besides the above stated. Study authors clarified that assignment of study medication was done by a third party - the hospital pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind study" Comment: no additional information is provided in the article, but study authors stated that study drugs were prescribed in similar looking bottles of 40 grams
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind study" Comment: no additional information is provided in the article, but study authors explained that observers were unaware of the allocation and were not involved in application or distrubution of study drugs
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (58 of 92 = less than 80%). A substantial number of the 92 participants were lost to follow-up, and 4 left the study due to adverse events (explanation of the study author)
Selective reporting (reporting bias)	Low risk	No trial registration found; however all outcomes listed in the Materials and Methods section are also listed in the Results section
Other bias	Low risk	Baseline comparisons were conducted, and no differences were found regarding age, gender, and duration of disease Diagnostic certainty: yes

Jowkar 2014 *(Continued)*

	The study was completed

Kaaber 1983

Methods	Randomised controlled, parallel-group design This study was probably conducted in a secondary care setting at 2 Danish departments of dermatology
Participants	30 female participants with pompholyx more than 6 months, and positive patch test to nickel Dropouts: 6 **Inclusion criteria of the trial** • Pompholyx of the hands of more than 6 months' duration • At least 1 flare every 2 weeks • A positive patch test to nickel **Exclusion criteria of the trial** • Not defined **Study population** • Gender: 30 female, no male • Age: median 25 years, range 19 to 67 years
Interventions	**Intervention** • Oral tetraethylthiuram disulphide (TETDS) 50 mg/d first week, increasing to 200 mg/d for at least 6 weeks in 11/15 participants for at least 6 weeks **Control intervention** • Placebo tablets in 13/15 The total duration of the study was probably 8 weeks (?); however run-in time and total duration of treatment are not completely clear Both groups were allowed to use desoximetasone ointment and emollients **Duration** Probably 8 weeksIS
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant-rated (?) number of flares at each 2- to 3-week visit • Observer-rated score of severity: area involved 0 to 4, erythema 0 to 3, number of vesicles 0 to 3, scaling 0 to 3 • Number of participants healed (not specified in Methods) • Amount of corticosteroid ointment used since last visit • Adverse events
Notes	Study duration unclear. Timing of outcome assessments not clear. Comparison based on slopes of linear regression of scores.

Kaaber 1983 *(Continued)*

	The secondary outcomes - reduction in severity, investigator-rated, and dose reduction - were included but did not provide reproducible data Declarations of interest: not stated Funding: Hoechst Danmark and Dumex Ltd. Danmark supplied the study drugs Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "referring to a system of random numbers, the patients received..." Comment: reference to a system of random numbers
Allocation concealment (selection bias)	Unclear risk	Unclear if this concerned an open list and unclear how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the tablets were identical in appearance" Comment: study authors stated double-blinded design; this is considered an adequate way to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind design. No information is given about how observer blinding was achieved
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (24 of 30 = 80%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found. For observer-rated severity score, the Results section states only that this was not statistically significant, only with regards to scaling and the frequency of flares. The Results section is very concise
Other bias	Unclear risk	Baseline comparisons: not stated Diagnostic certainty: yes The study was completed

Katsarou 2012

Methods	Randomised controlled, parallel-group study This study was conducted in a specialised unit for contact dermatitis at a single centre in Greece
Participants	30 participants with chronic hand eczema and a relevant allergic contact dermatitis No dropouts **Inclusion criteria of the trial** • Adult participants with chronic hand eczema (present at least 6 months before referral to clinic) • Positive relevant patch test reaction • Absence of atopy

Katsarou 2012 *(Continued)*

	• No use of systemic corticosteroids and/or immunosuppressants 2 weeks before inclusion **Exclusion criteria of the trial** • Not stated **Study population** • Gender: tacrolimus group 8 female, 7 male; mometasone group 9 female, 6 male • Age: tacrolimus group mean for females 39 years, mean for males 34 years; mometasone group mean for females 40 years, mean for males 32 years
Interventions	**Intervention** • Tacrolimus 0.1% twice daily for 30 days and once daily for 31 to 90 days in 15 participants • Mometasone furoate ointment twice daily for 1 week, once daily during week 2 and week 3, once daily 3 times a week for weeks 4 and 5, and once daily 2 times a week during the rest of the study until 90 days in 15 participants **Duration** 90 days
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Investigator-rated severity of erythema judged on a 5-point VAS scale at days 0, 30, 60, and 90 • Investigator-rated severity of infiltration judged on a 5-point VAS scale • Investigator-rated severity of vesiculation judged on a 5-point VAS scale • Investigator-rated severity of desquamation judged on a 5-point VAS scale • Investigator-rated severity by presence of cracks judged on a 5-point VAS scale • Investigator-rated severity of itching judged on a 5-point VAS scale • Adverse events
Notes	The secondary outcome - reduction in severity, participant-rated - was included but not provide reproducible data. The conducted analyses are inappropriate and insufficient, and in consequence, the conclusions are invalid Study authors were contacted on 28 February 2014 but were not responsive Declarations of interest: none declared Funding: no financial support received Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to the study design, patients were randomized according to random numbers in a computerized way" Comment: the study used randomisation according to random numbers generated in a computerised way

Katsarou 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "an investigator's assistant enrolled and assigned the treatment of the participants while the clinical evaluation was performed by a group of three investigators..." Comment: an investigator's assistant enrolled and assigned treatment; unclear whether this person was aware of treatment allocations
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an investigator's assistant enrolled and assigned the treatment of the participants while the clinical evaluation was performed by a group of three investigators, in order to make the assessments more objective as the investigators were unaware of the patient's group" Comment: assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included participants completed the study
Selective reporting (reporting bias)	Low risk	No trial registration found; however all outcomes listed in the Materials and Methods section are also listed in the Results section
Other bias	Low risk	Baseline comparison: there were no statistical differences in baseline variables according to study authors Diagnostic certainty: yes The study was completed

Kemper 1998

Methods	Within-participant, randomised controlled study This study was conducted in a secondary care setting at 2 Dutch departments of dermatology
Participants	19 participants with hand eczema (all types) Dropouts: 7 **Inclusion criteria of the trial** • Bilateral hand eczema of all types **Exclusion criteria of the trial** • Not stated **Study population** • Gender: 8 female, 4 male • Age: not stated
Interventions	**Intervention** • Coal tar 5% paste (pix lithanthracis) once weekly on the one hand in 12 participants for 4 weeks • Betamethasone valerate 0.1% ointment once weekly in 6 contralateral hands for 4 weeks

Kemper 1998 *(Continued)*

	• Zinc oxide paste once weekly during 4 weeks in the remaining 6 contralateral hands All participants had to wear gloves for an entire week after application of the ointment Use of oral antihistamines was allowed in all groups **Duration** 4 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes of the trial** • Investigator-rated improvement in total score based on erythema, vesicles, papules, scaling/hyperkeratosis, and lichenification multiplied by the affected area at week 0 and week 4 • Participant's assessment of subjective complaints (itch, pain, and insomnia) • Adverse events
Notes	The only trial included studying the effect of coal tar paste. Small number of participants with relatively high dropout rate. The secondary outcomes - reduction in severity, investigator-rated and participant-rated - were included but did not provide reproducible data. The results are listed as overall mean scores. No exact data are given Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "door middel van loting werd bepaald welke hand..." (free translation: "by means of a draw was decided which hand...") Comment: the paper refers to a lottery system
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, which is also difficult given the colour and smell of coal tar treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded, which might have affected the investigator-rated outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (12 of 19 = less than 80%)
Selective reporting (reporting bias)	High risk	No trial registration found. In the Methods section, study authors list a scoring system based on erythema, vesicles, papules, scaling/hyperkeratosis, and lichenification multiplied by the affected area, and refer to 2 different references with scoring systems; however in the Results section, a total sum score

Kemper 1998 *(Continued)*

		is given, along with scores for inflammation, hyperproliferation, and lichenification; these are not explained in the article, nor in the references
Other bias	Low risk	Baseline comparisons: as within-participant study not applicable Diagnostic certainty: yes The study was completed

King 1984

Methods	Within-participant, randomised controlled study This study was conducted at a single centre in a secondary care setting in the UK
Participants	20 participants with chronic palmar eczema Evaluable: 15 (8 hyperkeratotic, 7 pompholyx). Dropouts: 5 **Inclusion criteria of the trial** • Chronic symmetrical palmar eczema unresponsive to topical steroids or tar • Stable for at least 3 months before the beginning of the study **Exclusion criteria of the trial** • Pregnancy • Under 25 years of age • Treatment with oral steroids or cytotoxic agents • History of skin neoplasia or previous radiotherapy **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Superficial ionising radiation fractionated 100 rad at 45 kV once weekly for 3 weeks; total dose 300 rad in 15/20 hands **Control intervention** • Placebo radiation once weekly for 3 weeks in 15/20 contralateral hands In both groups, the topical medication was continued unchanged **Duration** 3 weeks' active treatment with follow-up until 6 months
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated assessment of extent of lesions: good response (clear and nearly clear) vs poor response (partly clear, no change, relapse). Response was assessed at 1, 3, and 6 months

King 1984 *(Continued)*

	• Photographs
Notes	Outcome 2 (photographs) was not used in the presentation of results Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the radiographer randomly selected one palm..." Comment: no further details are given
Allocation concealment (selection bias)	Low risk	Quote: "neither patient nor doctor was aware which hand had received treatment, but a record was kept by a radiographer in a sealed envelope" Comment: the study used sealed envelopes. This is a clear description of an adequate allocation concealment procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "neither patient nor doctor was aware which hand had received treatment, but a record was kept by a radiographer in a sealed envelope" Comment: double-blinded. One hand received actual radiotherapy; the other received "simulated radiotherapy" in the same regimen. This was considered as an adequate way to blind participants. The radiographer (staff) was aware of the treatment arm, but we consider this the best possible way to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "neither patient nor doctor was aware which hand had received treatment, but a record was kept by a radiographer in a sealed envelope" Comment: double-blind design. At the end of the study, the records of the radiographer were studied. Observers had no direct access to the randomisation code due to the sealed envelope and were not involved in administration of treatment. This is considered an adequate method to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (15 of 20 = less than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. We did not find discrepancies between Methods and Results sections
Other bias	Low risk	Baseline comparisons: as within-participant study not applicable Diagnostic certainty: yes The study was completed

Kircik 2013

Methods	Parallel-group, randomised controlled study

Kircik 2013 *(Continued)*

	This study was probably conducted in North America
Participants	125 participants with moderate to severe hand eczema **Inclusion criteria of the trial** • Capable of understanding and willing to provide signed informed consent • Male or female at least 12 years of age at time of consent and at time of first dose • Able to complete the study and to comply with study instructions • Moderate to severe hand dermatitis • Chronic hand dermatitis for at least 6 months **Exclusion criteria of the trial** • Females who are pregnant, trying to become pregnant, or breastfeeding • Current diagnosis of allergic contact dermatitis • Participated in a previous study of the same study product • Any major illness within 30 days before the screening/baseline visit • Considered immunocompromised • Clinically relevant history of or current evidence of abuse of alcohol or other drugs • Considered unable or unlikely to attend the necessary visits **Study population** • Gender: 70 female, 55 male • Age: mean 49.4 years, SD 15.5 years, median 51 years, range 15 to 84 years
Interventions	**Intervention** • Clobetasol propionate 0.05% foam twice a day for 14 days in 62 participants **Control intervention** • Vehicle/Placebo foam twice a day for 14 days in 63 participants **Duration** 2 weeks
Outcomes	**Primary outcome of the trial** • Number of participants with improvement of at least 2 grades in the Investigator's Static Global Assessment (ISGA) score from baseline to day 15. The ISGA is an investigator-rated 5-point scale for severity (0 = clear, 4 = severe) **Other outcomes of the trial** • Number of participants with improvement of at least 1 grade in ISGA score from baseline to day 15 • Number of participants with improvement of at least 2 grades in ISGA score from baseline to day 3 and to day 8 • Number of participants with improvement of at least 1 grade in ISGA score from baseline to day 3 and to day 8 • Number of participants with ISGA score of 0 or 1 at days 3, 8, and 15 • Number of participants with improvement of at least 1 grade in Subject Global Assessment (SGA) score from baseline to days 3, 8, and 15 • Number of participants with SGA score of 0 or 1 at days 3, 8, and 15 • Percentage change from baseline in pruritus, stinging, burning, and pain scores at days 3, 8, and 15 • Adverse events • Concomitant medication

Kircik 2013 *(Continued)*

- Participant-rated quality of life: for participants between 12 and 16 years of age, the Children's Dermatology Life Quality Index (CDLQI) was used; for participants 16 years of age and older, the Dermatology Quality of Life index (DLQI) was used at baseline, day 8, and day 15
- Participant-rated work productivity and activity impairment questionnaire

Notes	Sponsor: Stiefel, a GSK company We contacted study authors for additional information; however they remained unresponsive Declarations of interest: the primary study author has worked as consultant, researcher, or speaker for GSK Stiefel; 2 other study authors are employees of Stiefel, a GSK company Funding: the study was supported by Stiefel, a GSK company Sample size rationale: adequate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "subjects were randomized 1:1 at baseline using a computerized-generated schedule..." Comment: subjects were randomised 1:1 at baseline according to a computer-generated schedule, which is considered as low risk
Allocation concealment (selection bias)	Low risk	Quote: "study product assignments were unavailable to study personnel..." Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "both products were identical in packaging, labelling and ingredients except for the presence or absence of clobetasol propionate" Comment: the study claims to be double-blind. Identical looking placebos were used, which we consider an adequate method of blinding of participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "study product assignments were unavailable to study personnel until after all data had been collected and validated following applicable standard operating procedures" Comment: observers were unaware of treatment allocation and had no direct access to the randomisation code
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the intent-to-treat (ITT) population included all randomized subjects who were dispensed the study product. The per-protocol (PP) analysis set was used for the primary and key secondary analyses (which were also performed for the ITT analysis set)" Comment: an intention-to-treat analysis was carried out next to a per-protocol analysis
Selective reporting (reporting bias)	Unclear risk	The study design and results were registered on clinicaltrials.gov (NCT01323673). In the article, substantially more outcomes are listed that were not registered in the trial register, for example, quality of life and work impairment
Other bias	Low risk	Baseline comparisons: an extensive baseline comparison was given Diagnostic certainty: yes The study was completed

Krejci-Manwaring 2008

Methods	Parallel-group, randomised controlled study This study was conducted in a secondary care setting at a single centre in the USA
Participants	32 participants with moderate to severe hand dermatitis who did not use topical tacrolimus during the previous 28 days and did not use topical corticosteroids, non-steroidal immunosuppressants, or light treatment during the last 7 days Dropouts: 13 (including 1 participant who dropped out before the intervention was started) **Inclusion criteria of the trial** • Adults 18 years of age or older • Hand eczema with a combined severity score of 5 to 16 **Exclusion criteria of the trial** • Pregnancy • Use of topical tacrolimus 28 days before the study • Use of topical corticosteroids, immunosuppressants, or light treatments to the hand 1 week before the study • Use of systemic corticosteroids **Study population** • Gender: 24 female, 8 male • Age: mean 46 years, range 20 to 70 years
Interventions	**Intervention** • Topical tacrolimus twice daily for 12 weeks in addition to a daily dose of prednisone during 3 weeks; 30 mg in week 1, 20 mg in week 2, 10 mg in week 3 in 14/21 participants **Control intervention** • Vehicle ointment applied twice daily for 12 weeks; in addition, a daily dose of prednisone during 3 weeks: 30 mg in week 1, 20 mg in week 2, 10 mg in week 3 in 6/11 participants Participants were followed up at 5-week intervals until week 14 after initial treatment **Duration** 14 weeks (3 weeks active treatment, 11 weeks follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated reduction in severity based on symptom grading scale for erythema, scaling, induration, and fissuring (5-point scale; 0 = none to 4 = marked/intense) at weeks 1, 4, 8, 12 (end of treatment), and 14 (end of study) • Investigator's global assessment at weeks 1, 4, 8, 12, and 14 • Participant-rated visual analogue scale (VAS) of pruritus • Participant-rated improvement • Adverse events
Notes	Pilot study on maintenance therapy. Exact numbers of results for main outcomes not given - only whether there was a statistically significant difference between the 2 interventions

Krejci-Manwaring 2008 *(Continued)*

The study did include the secondary outcomes reduction in severity, investigator and participant-rated and time until relapse, but we were unable to reproduce these data

Declarations of interest: study authors received research, speaking, and/or consulting support from various pharmaceutical companies

Funding: the study was supported by a grant from Astellas Pharma Inc.

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the randomization code list, correlating the kit number with the content of each kit, was kept on file at Fuijsawa Healthcare Medical Information Department until the time of analysis" Comment: reference to a randomisation code list
Allocation concealment (selection bias)	Low risk	Quote: "the vehicle and tacrolimus ointments were packaged in identical containers labelled with the subject number, so neither the subject, coordinator, nor the investigator knew which treatment the patient received" Comment: randomisation was remote from the participant-recruitment centre. Vehicle and tacrolimus were packaged in pre-labelled identical containers corresponding to a participant number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the vehicle and tacrolimus ointments were packaged in identical containers labelled with the subject number, so neither the subject, coordinator, nor the investigator knew which treatment the patient received" Comment: double-blinded; this is considered an adequate blinding method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the vehicle and tacrolimus ointments were packaged in identical containers labelled with the subject number, so neither the subject, coordinator, nor the investigator knew which treatment the patient received" Comment: by the use of pre-labelled and identical containers, observers were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but per protocol (20 of 33 = less than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. All relevant outcomes described in the Materials section are described in the Results section
Other bias	Unclear risk	Baseline comparisons: at baseline, significant difference between groups for demographic characteristics was given. All participants had a combined symptom severity score of 5 to 16 Diagnostic certainty: yes The study was completed

Kucharekova 2003

Methods	Parallel-group, randomised controlled trial

Kucharekova 2003 *(Continued)*

	This study was carried out in a secondary care setting; it was a single-centre study. This study was conducted in the Netherlands
Participants	32 participants with bilateral chronic hand dermatitis for more than 6 months, with mild to moderate severity and good response to topical steroids Dropouts: 6 **Inclusion criteria of the trial** • Mild to moderate bilateral hand dermatitis since > 6 months • Good response to class I or II topical corticosteroids **Exclusion criteria of the trial** • Clinically relevant allergic or irritant contact dermatitis with inability to avoid exposure • Severe and very severe hand eczema • Severe vesiculation or bullae • History of contact urticaria and pustular disease • Recent therapy with class III or IV topical corticosteroids • Recent systemic therapy or phototherapy **Study population** • Gender: 22 female, 10 male • Age: mean 39.15 years, range 19 to 65 years
Interventions	**Intervention** • Emollient with ceramides twice daily for 2 months in 14/17 participants • Traditional pet-based emollient in 12/15 participants Both groups were allowed to use triamcinolone ointment in case of active dermatitis **Duration** 2 months
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant-rated efficacy of response (1 = worse, 2 = no change, 3 = minimal improvement, 4 = moderate improvement, 5 = marked improvement, 6 = clearing or almost clearing) • Participant-rated cosmetic acceptability (very poor, poor, acceptable, good, excellent) • Participant-rated use of corticosteroids and emollients • Participant-rated severity of itch • Observer-rated global assessment of severity with the Investigator Global Assessment (IGA) (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe) at baseline, after 1 and 2 months • Observer-rated Hand Eczema Area and Severity (HEAS) score, which divides the hands into 7 areas; involvement was assessed for each area on a scale of 0 to 4. In each area, intensity of erythema, vesicles, papules, scaling, fissures, excoriations, and hyperkeratosis was scored on a of 0 to 3 scale (0 = none, 1 = slight, 2 = moderate, 3 = severe). The affected area was multiplied by a correction factor and by the sum of intensities of symptoms. Finally, all areas were added up, resulting in a total symptom score • Adverse events
Notes	Unclear about 2 dropouts. Study authors state that this is a pilot study. Analysis may have been intention-to-treat, but procedure unclear. Results presented graphically, without exact numbers. Accuracy

Kucharekova 2003 *(Continued)*

of the statistics is unclear because all between-group comparisons were conducted at each time individually rather than comparing difference scores between groups.

The primary outcomes percentage of participants with self-rated and observer-rated improvement and the secondary outcomes reduction in severity, investigator-rated and participant-rated, were included in the study, although no useable data were provided. Data were given in a graphic presentation; no exact figures were given

Study authors were contacted for additional information on 4 March 2014 and responded 10 March 2014

Declarations of interest: not stated

Funding: not stated

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised into 2 groups" Comment: no further details given in the article. Personal communication with the study author revealed that sealed, numbered envelopes were used
Allocation concealment (selection bias)	Low risk	No details in the article about how allocation was concealed from participants and clinicians; personal communication clarified that the study author used sealed envelopes that were distributed after informed consent was obtained. Participants did not know the randomisation before signing informed consent but became aware of the allocation afterwards
Blinding of participants and personnel (performance bias) All outcomes	High risk	Observer-blinded, but not participant-blinded. Participants were aware of their treatment, and the study nurse who distributed study drugs was aware of the treatment arms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the same study investigator blindly assessed the dermatitis at various time-points" Comment: observer-blinded. Personal communication clarified that the study nurse was responsible for distribution of study drugs; outcomes were observed by a third person
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (26 of 32 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found; no major differences between Methods and Results sections
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons regarding group differences (randomisation check) Diagnostic certainty: yes The study was completed

Lauriola 2011

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary care setting at a single centre in Italy
Participants	40 participants with mild to moderate atopic dermatitis of hands No dropouts **Inclusion criteria of the trial** • Participants aged 18 years or older • Mild to moderate atopic dermatitis of hands, grading 3.0 to 5.0 **Exclusion criteria of the trial** • Topical treatment in the last 10 days • Systemic treatment in the last 2 weeks **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Furpalmate-containing creams (0.3%) twice a day for 14 days in 20 participants • Corticosteroid (hydrocortisone acetate 0.5%) twice a day for 14 days in 20 participants **Duration** 2 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated: physician's global evaluation of clinical response and of individual signs (erythema, xerosis) • Participant-rated assessment of itch (VAS) • Global response (unclear whether observer or participant rated) • Tolerability (adverse events) • Cosmetic compliance (unclear whether observer or participant rated)
Notes	Conference abstract, from which only limited information can be extracted The secondary outcomes - reduction in severity, participant- and investigator-rated - were included but did not provide reproducible data Study authors were contacted on 28 February 2014 but were not responsive Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Lauriola 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "a single-center, randomized, prospective, investigator blinded, controlled trial..." Quote: "...patients were randomly allocated..." Comment: study authors stated randomised but gave no clear description of how this was attained
Allocation concealment (selection bias)	Unclear risk	No details of how allocation was concealed from participants and investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "a single-center, randomized, perspective, investigator blinded, controlled trial..." Comment: study authors stated investigator-blinded; participants were not blinded (open-label?), although this is not clear
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a single-center, randomized, prospective, investigator blinded, controlled trial..." Comment: the article states only that the study was done in an investigator-blinded way. We considered this as insufficient information to judge this risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all patients completed the study period" Comment: all participants completed the study
Selective reporting (reporting bias)	High risk	No trial registration found. The abstract is very concise, and not all outcomes listed in the Methods section are described in the Results section, for example, cosmetic aspects or adverse events
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons regarding group differences (randomisation check) Diagnostic certainty: yes The study was completed

Lindelöf 1987

Methods	Within-participant, randomised controlled study This study was carried out in a secondary care setting at a single centre. The study was conducted in Sweden
Participants	24 participants with chronic hand eczema (13 allergic, 5 atopic, 3 irritant, 2 tylotic, 1 pompholyx) Dropouts: 1 **Inclusion criteria of the trial** • Chronic symmetrical hand eczema unresponsive to topical steroids • Stable for at least 3 months **Exclusion criteria of the trial** • Not defined **Study population**

Lindelöf 1987 *(Continued)*

- Gender: not stated
- Age: not stated

Interventions	**Intervention** • Ionising radiation (Grenz rays, 300 rad) 1× weekly for 6 weeks in 23/24 hands **Control intervention** • Placebo radiation once a week for 6 weeks in 23/24 contralateral hands Participants were followed up to 10 weeks after initial treatment **Duration** 10 weeks (6 weeks active treatment, 4 weeks follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated severity score (0 = no symptoms, 4 = very severe symptoms for erythema, scaling, itching, vesicles, fissures, and distribution (size of area involved)) at week 5 and week 10 • Comparison of number of participants who are better on the treated hand versus number of participants who are better on the placebo hand • Adverse events
Notes	The secondary outcome - reduction in severity, investigator-rated - was included but provided no reproducible data. Total scores are only graphically presented, without statistical analysis Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the treatments were administered by a nurse according to a predetermined randomized code unknown to both patients and doctors" Comment: reference to a predetermined randomisation code
Allocation concealment (selection bias)	Low risk	Quote: "the treatments were administered by a nurse according to a predetermined randomized code unknown to both patients and doctors" Comment: by including a third person, neither the physician/observer, nor the participants can be aware of the treatment allocation. Therefore we considered this as low risk of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the treatments were administered by a nurse according to a predetermined randomised code unknown to both patients and doctors" Comment: double-blinded. Placebo therapy was achieved by "allowing the apparatus to hum without emitting radiation", which could be considered as adequate; however the treatments were administered by a nurse who was aware of the predetermined randomised code. Although one might argue that part of

Lindelöf 1987 *(Continued)*

		the staff was aware of the treatment allocation, we decided this is the best way to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the treatments were administered by a nurse according to a predetermined randomized code unknown to both patients and doctors" Comment: the observer was blinded, and treatment was administered by someone else
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (23 of 24 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major differences between the Methods and Results sections
Other bias	Low risk	Baseline comparisons: as within-participant study not applicable Diagnostic certainty: yes The study was completed

Lodén 2012a

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary setting at 4 outpatient clinics in Norway This study consists of 2 parts (Lodén 2010); only the second part is included in this review
Participants	44 participants with a clinically proven history of hand eczema and a recent relapse participated in part 1 of this trial No dropouts **Inclusion criteria of the trial** • Clinically proven history of hand eczema with a recent relapse • Daily use of moisturising treatment • Either gender • Age 18 or older • Written informed consent **Exclusion criteria of the trial** • Possible allergy to ingredients in the study medications • At study start, active psoriatic lesions or active atopic eczema lesions on the hands • Active bacterial, fungal, or viral infection of the hands • Participants who are pregnant or breastfeeding, or who plan to become pregnant during the course of the study • Use of any concomitant medication that may interfere with study-related activities or assessment of efficacy • Any participant-related factor suggesting potentially poor compliance with study procedures (e.g. psychiatric disorders, history of alcohol or substance abuse) • Any serious medical condition that, in the opinion of the investigator, may interfere with evaluation of results • Inclusion in a study of an investigational drug within 60 days before the start of treatment

Lodén 2012a *(Continued)*

	Study population • Gender: 27 female, 17 male • Age: mean 46 years, range 22 to 76 years
Interventions	**Intervention** • Betamethasone 0.1% cream twice daily in 22 participants during 2 weeks • Betamethasone 0.1% cream once daily + urea 5% cream once daily in 22 participants during 2 weeks **Duration** 2 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant-rated severity on a 100-mm visual analogue scale (VAS), where 0 was no eczema and 100 extreme severe eczema. This was done daily • Investigator-rated severity of Hand Eczema Extent score (HEES); clearance was defined as a score ≤ 3 • Participant-rated quality of life using the validated Dermatology Life Quality Index (DLQI) at baseline and after 2 weeks
Notes	Short duration of 2 weeks Declarations of interest: study authors were paid consultants or employees of ACO Hud Nordic AB Funding: the study was funded by ACO Hud Nordic AB (manufacturer of the study drug) and by Knowledge Foundation, Stockholm, Sweden Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the coded tubes were sequentially numbered according to a randomization list which was prepared and retained by the contract research organization" Comment: reference to a prepared randomisation list
Allocation concealment (selection bias)	Low risk	Quote: "the coded tubes were sequentially numbered according to a randomization list which was prepared and retained by the contract research organization" Comment: the randomisation list was prepared and retained by the contract research organisation. The tubes were coded and sequentially numbered, and the clinicians who dispensed the tubes to participants were blinded. This is considered as low risk of selection bias because randomisation was done at a remote site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the patients, the clinicians, those assessing the outcomes and those making the data analyses were blinded" Quote: "the treatment was double-blinded and combined with a moisturizer cream (M) (5% urea, Canoderm, ACO Hud AB, Sweden). All patients received two coded tubes; one for evening applications, labelled 'evening' and contain-

Lodén 2012a *(Continued)*

		ing BV and one for morning applications, labelled 'morning' and containing either BV or M. The creams had a similar texture, were white and did not contain perfume" Comment: double-blind design. The different creams were identical in appearance and were labelled by a contract research organisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the patients, the clinicians, those assessing the outcomes and those making the data analyses were blinded" Comment: the observations and the data analysis were conducted by blinded assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all included participants received treatment and were analysed" Comment: no dropouts
Selective reporting (reporting bias)	Unclear risk	The trial was registered on clinicaltrials.gov (NCT00576550) as part 2. The primary outcomes registered in the trial register are for part 1 of the study (Lodén 2010), not for part 2. Therefore it is difficult to judge the risk of reporting bias In the article, there are no major discrepancies between the Methods and Results sections
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons regarding group differences (randomisation check) Diagnostic certainty: yes The study was completed

Möller 1983

Methods	Within-participant, randomised controlled trial This study was carried out in a secondary care setting; it was a multi-centre study involving 14 dermatological centres in Sweden
Participants	55 participants with chronic symmetrical hand eczema > 6 months, who had been treated with clobetasol twice daily in a preceding 3-week healing phase; 46 participants completed the trial Dropouts: unclear on status of 9 withdrawals **Inclusion criteria of the trial** • Symmetrical hand eczema of at least 6 months' duration **Exclusion criteria of the trial** • Not defined **Study population** • Gender: not stated • Age: not stated
Interventions	**Intervention** • Clobetasol propionate cream twice weekly for unclear duration (55 to 193 days) in 46/55 hands

Möller 1983 *(Continued)*

	• Fluprednidene acetate cream twice weekly in 46/55 contralateral hands Emollients were allowed on both hands When relapse occurred during the maintenance phase, the cream allocated to that hand could be applied more frequently; if this failed, the cream of the other (best) hand could be used temporarily **Duration** Unclear
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Number of hands that relapsed, and time of relapse • Efficacy judgement (not specified) by a dermatologist, at unknown point in time • Adverse events
Notes	Study on maintenance therapy. Handling of dropouts unclear: 9 participants were withdrawn because of unsatisfactory results (this could be an outcome). Study duration unclear. Difficult to interpret results for participants with relapses. Unclear which of the 2 treatments was the intervention or the comparator The secondary outcomes - reduction in severity investigator-rated and time until relapse - were included in the study but did not provide reproducible data Declarations of interest: 2 authors were employees of Glaxo Läkemedel AB, Mölndal, Sweden Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the side distribution was randomly allocated..." Comment: no further details given
Allocation concealment (selection bias)	Low risk	Quote: "the side distribution was randomly allocated and the creams were provided in coded samples of identical appearance except for the pairing in 'left' and 'right'" Comment: allocation was likely concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...identical appearance...." Comment: double-blind study in which an identical looking placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double-blind study..." Comment: although the study claims to be double-blind, no information was given about how observers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (46 of 55 = more than 80%)

Möller 1983 *(Continued)*

Selective reporting (reporting bias)	High risk	No trial registration found. It is not clear from the Methods section which are outcomes from the study, and the Results section contains various parameters that are not described in the Methods section
Other bias	Low risk	Baseline comparisons: within-participant study not applicable Diagnostic certainty: yes The study was completed

NCT01231854

Methods	Parallel-group, randomised controlled trial This study was conducted at a single centre in Germany
Participants	The study planned on 78 participants with severe atopic hand dermatitis but ended prematurely Included: 15 Dropouts: 6 **Inclusion criteria of the trial** • Male and female • Age > 18 years and ≤ 75 years • Body weight 50 to 100 kg • Chronic hand dermatitis (duration > 6 months) • Atopic constitution according to Erlanger Atopiescore 1 and/or positive personal history for atopic eczema, allergic rhinitis, allergic asthma, and/or elevated serum IgE • Severe hand dermatitis not responding to treatment with potent topical steroids for at least 4 weeks within the past 6 months due to IGA • Written informed consent **Exclusion criteria of the trial** • Participation in another clinical trial within past 4 weeks • Pregnancy/breastfeeding • Women of reproductive age except those who fulfil at least 1 of the following criteria throughout the total study and until at least 5 weeks after active study treatment in case of early study termination: post-menopausal women (12 months physiological amenorrhoea or 6 months amenorrhoea with serum FSH level > 40 mIU/mL), postoperative (6 weeks after bilateral ovariectomy with or without hysterectomy), regular and proper use of at least 2 methods of contraception, including at least 1 method of contraception with a failure rate < 1% per year (e.g. implants, depot preparations, oral contraceptives, IUD), or vasectomy of the partner. Women of reproductive age who do not meet all of the following criteria throughout the whole study or - in case of early study termination - up to 5 weeks after active therapy: ◦ The participant understands the teratogenic risk associated with taking the study medication ◦ The participant understands the need for strict monthly monitoring, the need for reliable, continuous contraception, and the need for regular pregnancy tests throughout the study and - in case of early study termination - up to 5 weeks of active therapy ◦ The participant is able to adequately and reliably apply methods of contraception ◦ The participant is informed about the possible consequences of pregnancy and knows that she must immediately contact her physician in case of suspected pregnancy ◦ The participant gives informed consent about knowing the potential risks and necessary measures to avoid pregnancy

NCT01231854 *(Continued)*

- Blood and/or plasma donation during the whole study period. In case of early study termination, blood and plasma donation is not allowed until 1 month after the end of active study treatment
- UV therapy within the past 3 months
- Concurrent photo- and/or photochemotherapy
- Known hypersensitivity/intolerance against cyclosporin, alitretinoin, or any other ingredients of Immunosporin or Toctino
- Known allergy against peanuts or soya
- Known hereditary fructose intolerance
- Acute and/or uncontrolled chronic infectious disease
- Known congenital or acquired immune deficiency
- Malignant tumour (past or present)
- Uncontrolled arterial hypertension (RR systolic ≥ 160 mmHg and/or RR diastolic ≥ 90 mmHg despite anti-hypertensive treatment)
- Renal insufficiency (serum creatinine above normal range)
- Liver insufficiency (CHILD ≥ Stadium B)
- Not sufficiently controlled hyperlipidaemia (LDL/HDL ratio > 4 despite medical treatment)
- Clinically significant thyroid hypofunction
- Known hypervitaminosis A
- Concurrent supplementation of vitamin A or treatment with other retinoids
- Concurrent tetracycline therapy
- Concurrent therapy with St. John's wort ("Johanniskraut")
- Known genetic diseases causing increased UV light sensitivity such as xeroderma pigmentosum, Cockayne syndrome, Bloom syndrome
- Known drug and/or alcohol abuse
- Known significant psychiatric morbidity

Study population

- Gender: cyclosporin group 1 female, 6 male; alitretinoin group 4 female, 3 male
- Age: cyclosporin group mean 42.1 years, SD 13.9 years; alitretinoin group mean 33.1 years, SD 12.7 years

Interventions

Intervention

• Oral cyclosporin depending on body weight: 50 to 74.9 kg: daily dosage 200 mg; 75 to 100 kg: daily dosage 300 mg (7 participants)

• Oral alitretinoin 30 mg once daily in 8 participants

Duration

24 weeks

Outcomes

Primary outcome of the trial

- Proportion of participants with complete or almost complete clearance according to the Investigator Global Assessment (IGA) within 24 weeks of active therapy in both groups

Secondary outcomes of the trial

- Time to complete or almost complete clearance according to IGA in both groups
- Proportion of participants with complete or almost complete clearance according to the Patient's Global Assessment (PGA) within 12 weeks and 24 weeks of active therapy
- Mean relative change in objective disease severity by means of the Hand Eczema Severity Index (HECSI) between baseline and weeks 4, 8, 12, 16, 20, and 24 in both groups
- Mean relative change in quality of life (Skindex 17) between baseline and week 24 in both groups
- Cost-effectiveness of studied treatment options (cost/QALY gained; assessed by the EQ-5D)

NCT01231854 *(Continued)*

- Mean relative change in work productivity (assessed by the work limitations questionnaire (WLQ)) in both groups
- Mean utilisation of topical steroids within the follow-up period in both groups
- Participant satisfaction with treatment in both groups (assessed using a 100-mm VAS)
- Proportion of participants with relapse (≥ 75% of baseline HECSI) within 24-week follow-up after previous complete/almost complete clearance
- For participants with atopic dermatitis on the body: measured percentage of participants with at least 50% improvement in disease severity with active therapy using SCORAD
- Tolerability and safety in both study groups

Notes	The study was ended prematurely. According to the sample size calculation, 78 participants should have been included; however only 15 participants were included, and 14 were analysed. Results are not yet published. The study author released the preliminary study results in personal communication and is aware of the fact that the data are used in this review. The secondary outcome - reduction in severity, investigator-rated - was included, but we were unable to reproduce the data Declarations of interest: not stated Funding: TU Dresden, Germany Sample size rationale: adequate, although the needed number of participants was not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "during the baseline visit patients underwent central randomization with the use of a randomization table with constant length of blocks and stratification according to the patients' body weights (50-74.9 kg vs. 75-100 kg) with equal allocation to ciclosporin and alitretinoin. The allocation sequence was generated by the KKS Dresden utilizing the trial software MACRO 3.0, and stored by the clinical trials pharmacist at the Technical University Dresden" Comment: random sequence generation method was considered adequate
Allocation concealment (selection bias)	Low risk	Quote: "treatment packs were prepared and labelled at the pharmacy. The research assistants used consecutively numbered packs to allocate new participants to treatment groups" Comment: study authors declared that they were blinded during allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants and assessors were blinded to group assignment during collection of the data" Comment: drug dispensation was done by a third party (the pharmacist). Unclear whether drugs were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "participants and assessors were blinded to group assignment during collection of the data. Database lock was on January 28, 2013. Unblinding occurred on March 07, 2013 before data analyses" Comment: the article claims that the observer had no access to the randomisation list, and a third party was used for drug dispensation. Unblinding occurred before data analyses
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all analyses were performed on the Intention-to-Treat (ITT) population. This population includes all patients that completed the baseline visit and used the trial medication at least once during the study"

NCT01231854 *(Continued)*

		The study aimed to include 78 participants but was terminated early due to inability to include this number of participants. Finally, 15 participants were randomised and 1 withdrew before the study drug was used. The intention-to-treat analysis included all participants who received the study drug (14 of 15 participants) Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	The trial was registered under NCT01231854 before it was begun. We found no major discrepancies between the trial register and the final study report
Other bias	High risk	Baseline comparison: groups were comparable at baseline with regards to disease severity Diagnostic certainty: yes The study was ended prematurely

Odia 1996

Methods	Within-participant, randomised controlled trial This study was most likely conducted at a single centre in Germany, although this is not clear from the article
Participants	20 participants with bilateral dyshidrotic hand eczema (13 male, 7 female). Atopic 7 and 9 with nickel allergy (4/9 also atopic) No dropouts **Inclusion criteria of the trial** • Mild to moderate dyshidrotic hand eczema in a stable phase • Poor response to steroid-free topical therapy **Exclusion criteria of the trial** • Not defined **Study population** • Gender: 7 female, 13 male • Age: range 18 to 30 years
Interventions	**Intervention** • One hand pulsed direct current iontophoresis, 20 times of 15 minutes each during 3 weeks in 20 hands **Control intervention** • No iontophoresis on 20 contralateral hands for 3 weeks Both hands received steroid-free tar solution and zinc paste **Duration** 3 weeks
Outcomes	**Primary outcomes of the trial**

Odia 1996 *(Continued)*

- Observer rated: decrease in authors' special investigator-rated score: sum of score points on vesicles, erythema, desquamation, itching, multiplied by size of affected area, which will become known as the Dyshidrotic eczema Area and Severity Index score (DASI)
- Participant-rated severity of pruritus

Notes	Unclear at which point in time outcome was assessed. Same scoring system (DASI) was used in Adams 2007, Polderman 2003, and Schnopp 2002 The report did not provide any useful data for analyses, although the secondary outcomes - reduction in severity, participant-rated and investigator-rated - were included Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...were subjected to tap water iontophoresis in a randomised one-side comparison..." Comment: no further details given
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants received unilateral iontophoresis, so one side was left untreated. Participants were allowed to use additional tar solutions and zinc paste. This might have influenced the amount of additional topical therapy used and thus the performance of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "scoring was performed by a second investigator, who did not know which side had been treated with iontophoresis" Comment: observer-blinded: scorings were performed by a third person who was not involved in the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included participants were analysed. (20 of 20 = 100%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major discrepancies between Methods and Results sections
Other bias	Low risk	Baseline comparisons: within-participant study not applicable Diagnostic certainty: yes The study was completed

Pacor 2006

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary care setting. It was a single-centre study conducted in Italy

Pacor 2006 *(Continued)*

Participants	28 participants with moderate to severe nickel sulphate-induced allergic contact dermatitis based on clinical history (hand eczema) and proven by patch testing, resistant to topical corticosteroids No dropouts **Inclusion criteria of the trial** • Moderate to severe nickel sulphate-induced allergic contact dermatitis based on clinical history (hand eczema) and prior patch testing • Resistant to topical corticosteroids **Exclusion criteria of the trial** • Treatment with systemic corticosteroids, cytotoxic agents, or phototherapy within 6 weeks before participation • Previous treatment with tacrolimus • Pregnancy and lactation **Study population** • Gender: 24 female, 4 male • Age: range 17 to 58 years
Interventions	**Intervention** • 0.1% tacrolimus ointment twice daily for 2 weeks in 14 participants **Control intervention** • Vehicle twice daily for 2 weeks in 14 participants 2 weeks of treatment was followed by 1 week of follow-up **Duration** 3 weeks (2 weeks active treatment, 1 week follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant's assessment of the following symptoms: erythema, oozing, scaling, itching, on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe on a daily diary card • Investigator's Global Assessment reduction in severity: 0 = no improvement, 1 = mild improvement, 2 = marked improvement, 3 = complete remission • Adverse events • Frequency of rescue medication usage
Notes	Unclear from the abstract whether all participants had hand eczema, but contact with study authors confirmed that all participants had active hand eczema at the beginning of the trial. Treatment started after a run-in period of 7 days The primary outcome percentage of participants with participant-rated good/excellent control and the secondary outcome - reduction in severity, investigator-rated - were included in the study, but no re-producible data were provided Study authors were contacted on 28 February 2014 and replied 2 March 2014 Declarations of interest: none declared Funding: the study was supported by grants from the Ministero Italiano Universita e Ricerca (MIUR)

Pacor 2006 *(Continued)*

	Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a randomized, double-blind, placebo-controlled, parallel-group study design..." Comment: study authors state this is a randomised study but gave no details in the article Personal communication clarified that StatsDirect Statistical software was used, which is considered to provide adequate random sequence generation
Allocation concealment (selection bias)	Low risk	No details in the article about how allocation was concealed from participants and clinicians. Personal communication revealed that the personnel recruiting participants were unaware of treatment allocation because this was done by a third party (the hospital pharmacist)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the test compounds were contained in opaque syringes and the treatment was not distinguishable from placebo and was blinded for both investigator and patients" Comment: the authors state that the study uses a double-blind design. The placebo ointment of tacrolimus was made of the same components as the study drug, only without the active component. All personnel involved in direct contact with participants were unaware of treatment allocation. Only the pharmacist was aware of the allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the test compounds were contained in opaque syringes and the treatment was not distinguishable from placebo and was blinded for both investigator and patients" Comment: the article claims to be double-blind. Personal communication with the study author clarified that the outcomes were observed by a blind observer and were analysed in blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study (28 of 28 = 100%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major discrepancies between Methods and Results sections
Other bias	Low risk	Baseline comparisons: no significant difference between groups in terms of age, gender, and severity of hand eczema Diagnostic certainty: yes The study was completed

Pigatto 1990

Methods	Parallel-group, randomised controlled trial (3 groups) This study was carried out in a secondary care setting at 1 centre in Italy

Pigatto 1990 *(Continued)*

Participants	16+8 participants with dyshidrotic eczema (pompholyx) and positive patch test to nickel, confirmed by reaction on oral challenge with nickel No dropouts **Inclusion criteria of the trial** • Hand eczema with palmar vesicles • Type IV allergy to nickel at 5% pet **Exclusion criteria of the trial** • Not defined **Study population** • Gender: unclear; in the entire study 21 female, 3 male, although 8 participants in the control group should be excluded from the review • Age: unclear; female from 23 to 45.3 years of age, male from 28 to 50 years of age
Interventions	**Intervention** • Low-nickel diet for 3 months in 8 participants • Oral disodium cromoglycate (DSCG) 1500 to 2000 mg 3× daily for 3 months in 8 participants **Control intervention** • No treatment for 3 months in 8 participants - not included in the review **Duration** 3 months
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated reduction in severity of itching: improvement/slight improvement/no improvement in degree of itching every 2 weeks • Observer-rated number of vesicles in an area (exact location not stated) of 2 × 2 cm every 2 weeks • Nickel urinary levels at beginning and at week 4 • Differences in intestinal permeability in a subgroup of 10 participants at day 0 and at day 15 • Adverse events
Notes	Unclear which of the 2 is intervention and which is comparator. The third group consisted of participants who did not give consent for the interventions and was observed without undergoing any treatment. This group was not randomised and therefore was not included in the analysis Unclear how the outcome 'Degree of itching' was assessed. In addition, an intestinal permeability study was performed in 5 DSCG and 5 diet participants The secondary outcome - reduction in severity, investigator-rated - was included but no reproducible data were provided The article states different numbers of participants included in intervention and control groups (8;8;8 vs 8;9;7) Declarations of interest: not stated Funding: not stated

Pigatto 1990 *(Continued)*

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were then randomly divided into 3 groups" Comment: groups 1 and 2 were probably randomised; however, the third group consisted of patients who did not give informed consent for the study and therefore were not randomised. Group 3 is not included in the analysis
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the patients avoided eating the foods indicated on a list, reduced the quantity of vegetables and of dairy products, and avoided using stainless steel utensils and ornaments" Comment: because the intervention group in group A had to follow a low-nickel diet with strict dietary restrictions for 3 months, blinding was not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the patients were evaluated blind by an observer...." Comment: observer blinded but no further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the participants dropped out, and all included participants were analysed (16 of 16 = 100%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major differences between Methods and Results sections
Other bias	Unclear risk	Baseline comparisons: no baseline analyses regarding group differences (randomisation check) Diagnostic certainty: yes The study was completed

Polderman 2003

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary care setting at a single dermatology clinic in the Netherlands
Participants	28 participants with dyshidrotic hand eczema, with duration of 4 months to 34 years Dropouts: 3 **Inclusion criteria of the trial** • Dyshidrotic hand eczema **Exclusion criteria of the trial** • Younger than 18 years old • Use of systemic immunosuppressive or immunomodulating medication in the last 2 months • Pregnancy

Polderman 2003 *(Continued)*

- History of UV sensitivity or skin malignancy

Study population

- Gender: not stated
- Age: not stated

Interventions	**Intervention** • UVA-1 irradiation 40 J/cm² on the hands in 15/15 participants 5 times weekly for 3 weeks **Control intervention** • Placebo (simulated blue light) in 10/13 participants Emollients probably were allowed in both groups Participants were followed until 6 weeks after the end of treatment **Duration** 9 weeks (3 weeks active treatment, 6 weeks follow-up)
Outcomes	**Primary outcomes of the trial** • Observer-rated severity by the dyshidrotic eczema area and severity index (DASI; based on sum score for severity 1 = mild, 2 = moderate, 3 = severe for, respectively, vesicles, erythema, desquamation, itch, multiplied by score for affected area); time point unclear **Other outcomes** • VAS for itch (probably participant-rated) at the end of each week and 3 and 6 weeks after treatment • Observer-rated reduction in severity for separate items of DASI at the end of each week and 3 and 6 weeks after treatment • Adverse events
Notes	Primary outcome probably at week 3 (i.e. at end of treatment). Analysis based on intention-to-treat principle. There was a follow-up 6 weeks after treatment, but only summary data were given for the treatment group Study authors were contacted on 28 February 2014 but remained not responsive Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "they were randomly assigned to either UVA-1 (n=15) or placebo treatment (n=13) by an independent investigator using a lottery system" Comment: reference to a lottery system, which is an adequate way to prevent selection bias
Allocation concealment (selection bias)	Low risk	Quote: "they were randomly assigned to either UVA-1 (n=15) or placebo treatment (n=13) by an independent investigator using a lottery system"

Polderman 2003 *(Continued)*

		Comment: participants were assigned to different study arms by an independent investigator using a lottery system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo treatment comprised of TL tubes, emitting visible light, covered with a blue plastic plate to mimic the blue UVA-1 light" Comment: participants: placebo design to mimic the intervention; participants wore protective eyewear and protection on their forearms during both interventions. For participants, the placebo is probably indistinguishable from the actual treatment; however personnel who delivered the treatment were not blinded. Given that the staff had to administer the treatment, and we could not think of a better way to blind participants and staff, this was considered as low risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "a blinded investigator was responsible for the evaluation of the parameters" Comment: observer-blinded; this was another person, then the one who assigned participants to treatment arms
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "analysis was performed according to the intention-to-treat principle" Comment: intention-to-treat analyses
Selective reporting (reporting bias)	Unclear risk	No trial registration found. No major differences between Methods and Results sections for results during the treatment phase, except that results 6 weeks after treatment are very scarce. Study authors remarked that for ethical reasons, a lot of participants were prescribed topical corticosteroids; therefore these results are less reliable and probably are poorly reported
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons regarding group differences (randomisation check) Diagnostic certainty: yes The study was completed

Ruzicka 2004

Methods	Randomised controlled, parallel-group design study of 1 placebo group and 3 treatment groups given different doses of the same (oral) medicament This study was carried out in a secondary care setting This was a multi-centre study involving 43 clinics in Belgium, Denmark, Finland, France, Germany, Holland, Hungary, Poland, Switzerland, and the United Kingdom
Participants	319 participants (235 male, 84 female) with moderate or severe chronic hand dermatitis of at least 3 months' duration and refractory to standard therapy. All types of hand dermatitis Dropouts: 75 **Inclusion criteria of the trial** • Moderate or severe hand eczema for at least 3 months • Refractory to standard therapy • 18 to 70 years of age **Exclusion criteria of the trial**

Ruzicka 2004 *(Continued)*

	• Well defined **Study population** • Gender: placebo group 22 female, 56 male; alitretinoin 10 mg group 24 female, 56 male; alitretinoin 20 mg group 21 female, 59 male; alitretinoin 40 mg group 17 female, 64 male • Age: placebo group mean 48.7 years; alitretinoin 10 mg group mean 48.7 years; alitretinoin 20 mg group mean 46.7 years; alitretinoin 40 mg group mean 48.7 years
Interventions	**Intervention** • Oral alitretinoin 10 mg daily for 12 weeks in 62/80 participants • Oral alitretinoin 20 mg/d in 67/80 participants for 12 weeks • Oral alitretinoin 40 mg/d in 63/81 participants for 12 weeks **Control intervention** • Placebo capsules in 62/78 participants for 12 weeks Standard emollients were allowed in all treatment groups Responders were followed up for 3 months **Duration** 6 months (12 weeks active treatment, 3 months follow-up)
Outcomes	**Primary outcomes of the trial** • Responders according to physician global assessment of overall severity, whereby physician global assessment is categorised as clear, almost clear, mild, moderate, or severe. Responders are defined as clear or almost clear at week 12 or at last evaluation **Secondary outcomes of the trial** • Observer-rated total lesion symptom score: sum of scores (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, and pruritus/pain • Participant-rated global assessment: clearing or almost clearing (> 90% clearing of signs and symptoms compared with baseline), marked improvement (> 75%), moderate improvement (> 50%), mild improvement (> 25%), no change, worsening • Observer-rated extent of disease: total percentage involvement of palm and dorsum of both hands • Dermatological life quality index (DLQI) • Adverse events
Notes	No other active treatment as comparator. More males enrolled because of exclusion of women of childbearing potential. Study included a safety assessment by careful medical and laboratory monitoring. Analysis of efficacy based on intention-to-treat principle Of the 127 responders, 117 were followed up for another 12 weeks after end of treatment; only summary data about this extra follow-up are presented Declarations of interest: some study authors were employees, received grants, or had received consultancy fees from Basilea Pharmaceutica Funding: the study was supported and funded by Basilea Pharmaceutica Ltd., Basel, Switzerland, manufacturer of the study drug Sample size rationale: provided
Risk of bias	

Ruzicka 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were randomized to treatment by center, in blocks of 4 without stratification, by use of computer-generated randomization codes...." Comment: computer-generated randomisation codes
Allocation concealment (selection bias)	Low risk	Quote: "eligible patients were randomized to treatment by center, in blocks of 4 without stratification, by use of computer-generated randomization codes provided by the study sponsor (Basilea Pharmaceutica Ltd, Basel, Switzerland) and incorporated into double-blind coded drug packaging" Comment: the site staff had no direct access to randomisation codes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo and active drug (as soft gelatine capsules) and packaging were indistinguishable" Comment: participant blinding. The double-blind coded packages were provided by the sponsor, which blinded site personnel and participants sufficiently
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "design: multicenter, randomized, double-blind, placebo-control, prospective trial" Comment: observers were blinded during the study because the identical looking package of study drugs was provided by a third party. One might argue that the observer could have guessed the treatment group due to headache and dry mucosa; however this was also seen in the control group and therefore was not conclusive. The trial was designed in such a way to minimise risk of bias; we agree that this could not have been done in a better way
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all statistical tests were 2 sided and based on a level of .05 and were carried out using SAS (version 8.1; SAS Institute Inc, Cary, NC) with the intention-to-treat population" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No trial register found. No major discrepancies between Methods and Results sections
Other bias	Low risk	Baseline comparisons: no significant differences between groups in demographic or disease characteristics Diagnostic certainty: yes The study was completed

Ruzicka 2008

Methods	Parallel-group, randomised controlled trial including 1 placebo group and 2 treatment groups given different doses of the same (oral) retinoid This study was carried out in a secondary care setting This was a multi-centre study at 111 clinics in Europe and Canada
Participants	1032 participants (582 male, 450 female) with severe chronic hand dermatitis of at least 6 months' duration and refractory to standard therapy. All types of hand dermatitis Dropouts: 273

Ruzicka 2008 *(Continued)*

Inclusion criteria of the trial

- Severe chronic hand eczema refractory to standard therapy
- 18 to 75 years of age

Exclusion criteria of the trial

- Well defined

Study population

- Gender: placebo group 84 female, 121 male; alitretinoin 10 mg group 180 female, 238 male; alitretinoin 30 mg group 186 female, 223 male
- Age: placebo group mean 48 years, SD 12 years; alitretinoin 10 mg group mean 47 years, SD 13 years; alitretinoin 30 mg group mean 48 years, SD 13 years

Interventions

Intervention

• Oral alitretinoin 10 mg once daily for 12 or 24 weeks (depending on moment of response according to the PGA) in 319/418 participants

• Oral alitretinoin 30 mg/d in 303/409 participants for 12 or 24 weeks

Control intervention

• Placebo capsules in 137/205 participants for 12 or 24 weeks

Standard emollient in all treatment groups

All participants were followed up for 4 weeks, and responders were observed for relapses for 24 weeks after end of treatment

Duration

Up to 48 weeks (12 to 24 weeks of active treatment, up to 24 weeks of follow-up)

Outcomes

Primary outcome of the trial

- Responders according to physician global assessment of overall severity, whereby physician global assessment is categorised as clear, almost clear, mild, moderate, or severe. Responders are defined as clear or almost clear at week 12 or at last evaluation

Other outcomes

- Time to response
- Partial response (PGA assessment of clear, almost clear, or mild)
- Observer-rated modified total lesion symptom score: sum of scores (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for erythema, oedema, vesicles, desquamation, hyperkeratosis, fissures, pruritus/pain
- Participant-rated global assessment: clearing or almost clearing (> 90% clearing of signs and symptoms compared with baseline), marked improvement (> 75%), moderate improvement (> 50%), mild improvement (> 25%), no change, worsening
- Time to relapse
- Observer-rated extent of disease: total percentage involvement of palm and dorsum of both hands
- Adverse events

Notes

No other active treatment as comparator. Analysis of efficacy based on intention-to-treat principle. Study included a safety assessment by careful medical and laboratory monitoring. More males were enrolled because of exclusion of women of child-bearing potential

Declarations of interest: some study authors were employees, received grants, or had received consultancy fees from Basilea Pharmaceutica

Funding: see above item

Ruzicka 2008 *(Continued)*

	Sample size rationale: provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "eligible patients were randomized to treatment by centre, in blocks of 5 without stratification, by the use of computer-generated randomization codes provided by the study sponsor (Basilea Pharmaceutica)..." Comment: computer-generated randomisation codes
Allocation concealment (selection bias)	Low risk	Quote: "eligible patients were randomized to treatment by centre, in blocks of 5 without stratification, by the use of computer-generated randomization codes provided by the study sponsor (Basilea Pharmaceutica) and incorporated into double-blind coded drug packaging. Placebo, active drug and packaging were indistinguishable. Investigators allocated consecutively numbered packages of medication to patients in their order of enrolment" Comment: codes provided by study sponsor. Sequentially numbered packages of different treatment modalities of identical appearance were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... incorporated into double-blind coded drug packaging. Placebo, active drug and packaging were indistinguishable" Comment: double-blinded; the identical looking packages were provided by the sponsor and by site staff, and participants were unaware of the treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observers were blinded during the study because the identical looking package of study drugs was provided by a third party. One might argue that the observer could have guessed the treatment group due to headache and dry mucosa; however these were also seen in the control group and therefore were not conclusive. The trial was designed in such a way as to minimise risk of bias; we agree that this could not have been done in a better way
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all efficacy evaluations were based on the intent-to-treat population. All randomized patients were included in this population, and were analysed according to their randomization with last observation carried forward (LOCF) in cases of missing data" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Trial registration on clinicaltrials.gov (NCT00124475). No differences in primary outcomes; however small discrepancies in other outcomes between trial registration and article
Other bias	Low risk	Baseline comparisons: no significant differences between groups in demographic or disease characteristics Diagnostic certainty: yes The study was completed

Said 2010

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary care setting in a single dermatology department in Singapore
Participants	47 participants with chronic vesicular hand eczema

Said 2010 *(Continued)*

	Dropouts: 7 **Inclusion criteria of the trial** • Chronic vesicular hand eczema **Exclusion criteria of the trial** • Not defined **Study population** • Gender: not stated • Age: not stated
Interventions	**Interventions** • UVA-1 phototherapy 3 times a week for 6 weeks in 24 participants • Betamethasone-valerate 0.1% cream twice a day for 6 weeks in 23 participants **Duration** 6 weeks active treatment, 6 weeks follow-up. Total duration: 12 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Degree of improvement based on the Dyshidrotic Area and Severity Index (DASI) at week 3, week 6, and week 12 • Adverse events
Notes	Conference abstract, from which only limited information can be extracted We were unable to contact the study authors Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "twenty-four patients were randomly assigned to..." Comment: insufficient data
Allocation concealment (selection bias)	Unclear risk	Insufficient data
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open-label study" Comment: no blinding
Blinding of outcome assessment (detection bias)	High risk	Quote: "open-label study"

Said 2010 *(Continued)*

All outcomes		Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	More than 80% of participants were analysed (40/47)
Selective reporting (reporting bias)	Unclear risk	No trial register was found
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons regarding group differences (randomisation check) Diagnostic certainty: no The study was completed

Schnopp 2002

Methods	Within-participant, randomised controlled study This study was carried out in a secondary care setting at a single dermatology department in Germany
Participants	16 participants with moderate to severe chronic relapsing dyshidrotic eczema on hands No dropouts **Inclusion criteria of the trial** • Moderate to severe chronic relapsing dyshidrotic hand eczema **Exclusion criteria of the trial** • Use of topical glucocorticoids or any systemic treatment with possible influence on the course of hand eczema **Study population** • Gender: 15 female, 1 male • Age: mean 43 years, range 23 to 54 years
Interventions	**Intervention** • Tacrolimus 0.1% ointment twice daily on 12/12 hands for 4 weeks • Mometasone furoate 0.1% ointment twice daily on 12/12 contralateral hands for 4 weeks Follow-up period was up to 8 weeks after the end of treatment **Duration** 12 weeks (4 weeks of active treatment, up to 8 weeks of follow-up)
Outcomes	**Primary outcome of the trial** • Observer-rated dyshidrotic eczema area and severity index (DASI) at baseline, week 2, and week 4 (based on sum-score for severity 1 = mild, 2 = moderate, 3 = severe for, respectively, vesicles, erythema, desquamation, and itch multiplied by score for affected area) **Other outcomes**

Schnopp 2002 *(Continued)*

- Adverse events

Notes	Originally, 20 participants with hand and/or foot involvement, 4 of whom were excluded due to poor disease control during the trial-preceding washout phase. Study in 16 participants, of whom 12 had their hands involved. The limited data on the 4-week post-treatment follow-up period are difficult to interpret. Outcome scores at week 4 presented graphically, without exact numbers Scoring of outcome (DASI) same as the study by Odia The secondary outcomes - reduction in severity, participant-rated, and time until relapse - were included but did not provide reproducible data Study authors were contacted 3 March 2014 and replied 4 March 2014 Declarations of interest: none declared Funding: no funding Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned....." Comment: no further details were given in the article; however personal communication with study authors clarified that they threw dice to create a randomisation list
Allocation concealment (selection bias)	Low risk	No details in the article about how allocation was concealed from participants and clinicians. Contact with study authors clarified that the randomisation list was composed by a third person. This person was involved in the distribution of study drugs, but not in the recruiting. The third person held office in a different building of the hospital that was not accessible for physicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "this study was a randomized, observer-blinded, intraindividual comparison study..." Comment: participants were not blinded during the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all assessments were performed by an independent observer on separate sheets on different premises. Patients were instructed not to talk about treatment modalities" Comment: study authors clearly described how they tried to prevent detection bias. Observers were blinded adequately
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the participants dropped out during the study; all participants were included in the analyses (16 of 16 = 100%)
Selective reporting (reporting bias)	Low risk	No trial registration found; however the DASI is a valid score for hand eczema and was described in the Methods and Results sections without major discrepancies
Other bias	Low risk	Baseline comparisons: within-participant study not applicable Diagnostic certainty: yes The study was completed

Sezer 2007

Methods	Within-participant, randomised controlled study This study was conducted in a secondary care setting at a single centre in Turkey
Participants	15 participants with chronic hand eczema of the dry or dyshidrotic type were randomised Dropouts: 3 **Inclusion criteria of the trial** • Diagnosis of biopsy-proven chronic hand eczema of dry and dyshidrotic types • Duration > 4 months • Resistant to conventional therapies **Exclusion criteria of the trial** • Hyperkeratotic hand eczema • Treatment with topical corticosteroids in the prefacing 2 weeks • Treatment with systemic corticosteroids or other immunosuppressive agents within the last 4 weeks • Unilateral disease • Pregnancy • Inability to meet for follow-up consultations **Study population** • Gender: 6 female, 9 male • Age: range 18 to 73 years
Interventions	**Intervention** • Local narrow-band UVB 3 times a week for 9 weeks in 12/15 hands. The initial dose was 150 mJ/cm^2 for each participant. A 20% increasing dose schedule was used until a final dose of 2000 mJ/cm^2 was reached • Local PUVA 3 times a week during 9 weeks in 12/15 contralateral hands. The initial dose of psoralen plus UVA irradiation was 1.0 J/cm^2 with an increase of 0.5 J/cm^2 at every second session until a final dose of 7.5 J/cm^2 was achieved Participants who completed the treatment sessions were followed up for 10 weeks after the last therapy **Duration** 19 weeks (9 weeks of active treatment, 10 weeks of follow-up)
Outcomes	**Primary outcomes of the trial** • Investigator-rated reduction in severity of a total sum score defined by degree of erythema, desquamation, induration, fissuring, and itching, as scored on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) in weeks 0, 3, 6, and 9 • Investigator-rated number of participants with clearance defined as a total sum score of 0; participants with marked improvement had a reduction of more than 70% at week 9 • Number of relapses during follow-up phase • Adverse events
Notes	Unblinded study with a small number of participants Study author was contacted on 4 March 2014 by email, but we were unable to obtain additional information

Sezer 2007 *(Continued)*

	Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the NB-UVB and PUVA treatments were randomly assigned to the left or right hand. The hand treated was selected using a computer-based program..." Comment: treatment was randomly assigned to the left or right hand using a computer-based programme
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on whether participant- and/or observer-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "clinical assessments were performed by the same investigator (E.S.) every 3 weeks during the 9-week treatment period" Comment: unclear. All observations were made by the same investigator, although it is unknown whether this observer was aware of the treatment modalities
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (12 of 15 = 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major differences between Methods and Results sections
Other bias	Low risk	Baseline comparisons: at baseline, no significant differences between groups in total clinical scores; however within-participant study not applicable Diagnostic certainty: yes The study was completed

Sharma 2006

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary care setting at a single centre in India
Participants	21 participants with proven nickel allergy by patch testing No dropouts **Inclusion criteria of the trial** • Chronic recurring vesicular hand eczema

Sharma 2006 *(Continued)*

- Solely allergic to nickel as proven by patch testing

Exclusion criteria of the trial

- Usage of prosthesis
- Pregnancy
- Lactation
- History of alcoholism
- Abnormal biochemistry (glucose and liver function tests) or blood counts

Study population

- Gender: 15 female, 6 male
- Age: mean 34.1 years, range 18 to 50 years

Interventions	**Intervention** • Low-nickel diet and disulphiram 125 mg daily in the first 2 weeks and 250 mg daily in weeks 3 and 4 in 11 participants **Control intervention** • Normal diet and placebo tablet (lactose) for 4 weeks in 10 participants Participants were followed up for 2 to 12 weeks after end of treatment **Duration** Up to 16 weeks (4 weeks of active treatment, 2 to 12 weeks of follow-up)
Outcomes	**Primary outcome of the trial** • Investigator-rated (?) severity of hand eczema (total severity scores for the parameters itching, vesicles, crusting, scaling, and fissuring) at baseline, week 2, and week 4 **Other outcomes** • Adverse events
Notes	Two weeks after the start of a low-nickel diet in the experimental group, disulphiram was started for a duration of 4 weeks. Participants in the control group were treated only with a placebo tablet during those 4 weeks. In addition, the low-nickel diet was continued during follow-up (i.e. 12 weeks after disulphiram was stopped) The secondary outcome - reduction in severity, investigator-rated - was included, but the article did not provide reproducible data Study authors were contacted for additional information with regards to the risk of bias table Declarations of interest: none declared Funding: no funding Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "all the 21 patients were randomly divided in 2 groups"

Sharma 2006 *(Continued)*

		Comment: no further details in the article. Personal communication with study authors clarified that they had used a lottery system
Allocation concealment (selection bias)	Low risk	No details about how allocation was concealed from participants and clinicians. Personal communication clarified that this was done by a third person
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "it was a comparative study and participants were not aware if they belonged to study group or control group (single blind trial)" Comment: participant blinding attempted with the use of placebo tablets (lactose tablets), although participants in the control group were allowed to continue with their normal diet, while the intervention group remained on the low-nickel diet. Site personnel probably were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "it was a comparative study and participants were not aware if they belonged to study group or control group (single blind trial)" Comment: observers were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the participants dropped out, and all participants were included in the analyses (21 of 21 = 100%)
Selective reporting (reporting bias)	Unclear risk	No trial registration found. In the Methods section, no clear description is given of the outcome parameters; in the Results section, outcomes are listed that are not described in the Materials section
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons Diagnostic certainty: yes The study was completed

Sheehan-Dare 1989

Methods	Within-participant, randomised controlled trial. Hands were unit of randomisation and analysis This study was conducted at a single department of dermatology in the UK
Participants	25 participants with chronic constitutional hand eczema; participants with irritant or allergic contact dermatitis were excluded Dropouts: 4 **Inclusion criteria of the trial** • Bilateral and symmetrical chronic, constitutional vesicular palmar eczema for at least 6 months with continued or episodic vesiculation • Resistant to topical emollients, steroid and tar preparations **Exclusion criteria of the trial** • Irritant and allergic dermatitis **Study population** • Gender: 14 female, 7 male • Age: mean 52.3 years, range 19 to 79 years
Interventions	**Intervention**

Sheehan-Dare 1989 *(Continued)*

	• Topical PUVA thrice weekly for 6 weeks in 21/24 hands • Radiotherapy 90 Rad 50 KV 3 times with 21-day interval in 21/24 contralateral hands for 6 weeks Participants were followed up until 18 weeks after initial treatment **Duration** 18 weeks (6 weeks of active treatment, 12 weeks of follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Participant-rated severity on linear analogue scale of 10 cm • Observer-rated severity score 0 to 4 (0 = normal skin; 1 = eczema, mild scaling, and erythema; 2 = moderate scaling, erythema, and shallow fissures; 3 = severe scaling, erythema, and deep bleeding fissures; 4 = active pompholyx) at baseline and at weeks 6, 9, and 18 • Adverse events
Notes	The primary outcome adverse events and the secondary outcomes reduction in severity, participant-rated and investigator-rated, were included but did not provide reproducible data. Means of outcome scores were not given as exact figures but in a graphical presentation Declarations of interest: not stated Funding: not stated Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated topical PUVA to one hand and superficial radiotherapy to the other using a pre-determined code" Comment: participants were randomly allocated using a predetermined code
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the procedure was carried out in such a way that patients were unable to tell which hand had received active treatment" Quote: "the topical PUVA treated hand received sham radiotherapy during which the X-ray machine appeared to function normally but the power supply to the tube was interrupted such that no X-rays were received by the patient" Quote: "the superficial radiotherapy treated hand was treated with a sham PUVA procedure. This consisted of an application of the organic solvent base without psoralen 5 min prior to exposure to the light source" Comment: participant blinding. We consider this an adequate way to blind participants, although personnel probably were not blinded to perform the procedures
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "patients were assessed by 2 observers (R.S-D and M.G) who were unaware of the treatment status of each hand until the codes were broken at the end of the study"

Sheehan-Dare 1989 *(Continued)*

		Comment: observer blinding; independent observers are considered an adequate method for detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (21 of 25 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No discrepancies between the Materials and Results sections
Other bias	Low risk	Baseline comparisons: within-participant design not applicable Diagnostic certainty: yes The study was completed

Sjövall 1987

Methods	Parallel-group, randomised controlled trial (3 groups) This study was carried out in a secondary care setting and was probably a single-centre study in Sweden
Participants	18 participants (3 male, 15 female) with chronic hand eczema of different types resistant to conventional therapy (11 patch test-proven relevant allergy, 4 atopic, 3 endogenous) Dropouts: 3 **Inclusion criteria of the trial** • Chronic hand eczema • Resistant to conventional topical treatment with potent corticosteroids and moisturisers **Exclusion criteria of the trial** • Not defined **Study population** • Gender: 15 female, 3 male • Age: mean 45 years, range 26 to 67 years
Interventions	**Intervention** • UVB irradiation only on hands 4 times a week for 8 weeks in 6 participants • Filtered light (placebo UVB, no UVB) on the hands 4 times a week for 8 weeks in 6 participants • Hand UVB followed by whole-body UVB + UVA 4 times a week during 8 weeks in 6 participants Their 'ordinary topical treatment' was permitted in all groups Three months after end of treatment, participants were mailed a questionnaire regarding the course of their hand eczema and their opinions on treatment **Duration** 8 weeks with an email follow-up after 3 months
Outcomes	**Primary outcomes of the trial** Not defined

Sjövall 1987 *(Continued)*

Other outcomes

- Observer-rated severity scoring system (0 = unchanged/worse, 1 = improved, 2 = cleared) after 4 weeks (16 exposures), if a participant cleared before the end of the study, or at 8 weeks (end of treatment after 32 exposures)
- Participant-rated follow-up questionnaire 3 months after end of treatment, regarding the course of hand dermatitis and the burden of treatment (time consuming)
- Adverse events

Notes	Small number of participants. Main table unclear: results at 8 weeks or at 20 weeks? Follow-up at 3 months presented in a descriptive way, without exact details Declarations of interest: not stated Funding: the study was supported by grants from Alfred Österlund and Finsen Foundations Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomly divided..." Comment: no further details
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the whole device was covered by green clothes, thus making it possible to perform a double blind trial between the patients in group 1 and 2" Comment: the investigators covered the machine with green clothes; by this method, 2 groups (A and B) were blinded; however the third group of participants was not blinded because they received whole-body irradiation. Staff probably was not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The investigators state a partly double-blind design; however it is unclear how observers were blinded, and if they were independent observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (15 of 18 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major differences between Materials and Methods sections
Other bias	Unclear risk	Baseline comparisons: no baseline comparisons Diagnostic certainty: yes The study was completed

Thestrup-Pedersen 2001

Methods	Parallel-group, randomised controlled trial

Thestrup-Pedersen 2001 *(Continued)*

	This study was conducted in a secondary care setting at 4 dermatology departments or clinics in Denmark
Participants	29 participants (21 male, 8 female) with hyperkeratotic eczema on palms, patch-test negative or irrelevant No dropouts **Inclusion criteria of the trial** • Hand eczema based on clinical diagnosis **Exclusion criteria of the trial** • Allergic contact dermatitis **Study population** • Gender: 8 female, 21 male • Age: median 54 years, range 30 to 76 years
Interventions	**Intervention** • Acitretin orally 30 mg daily for 8 weeks in 14/14 participants **Control intervention** • Placebo capsules for 8 weeks in 15/15 participants Both groups were allowed to use topical emollients **Duration** 8 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Mean observer-rated severity scores (0 = absent, 1 = slight, 2 = moderate, 3 = severe) combined of these signs: hyperkeratosis, fissures, scaling, itch, redness, and vesicles at week 4 and at week 8 • Change in biochemical parameters (Hb, hepatic function, cholesterol, triglyceride) • Adverse events
Notes	We contacted the study author for additional information by letter; however he was unable to respond to all of our questions No overall scores were presented as outcomes. Details of biochemical parameters were not given A proper between-group comparison was not conducted; only within-group comparisons with Wilcoxon-rank sum test were conducted The study did include the secondary outcomes - reduction in severity, participant- and investigator-rated - although we were unable to include these data because of missing data Declarations of interest: none declared Funding: Roche A/S, Copenhagen, supplied the study drug free of charge, but the investigators did not receive financial support nor consultant fees from Roche Sample size rationale: not stated

Thestrup-Pedersen 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "they were asked to take three 10-mg capsules of acitretin once daily for 8 weeks or identically looking placebo capsules" Comment: from the article, it is unclear whether the study was randomised at all. Personal communication with study authors clarified that randomisation was done by a third party according to a pre-defined randomisation list
Allocation concealment (selection bias)	Low risk	No details about how allocation was concealed from participants and clinicians. Personal communication clarified that the sponsor shipped 4 identical boxes to all participating centres, which could at random be dispensed to participants. The investigators were unaware of the content of the boxes; therefore we judged this as low risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "they were asked to take three 10-mg capsules of acitretin once daily for 8 weeks or identically looking placebo capsules" Comment: the study contained an identical looking placebo in an attempt to blind participants, and randomisation and dispensation of drugs were done at a remote site by a third party. Therefore we judged this as adequate blinding of participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "as several patients in the active treatment group experienced dryness of the lips, we have called our study single-blind" Comment: study authors declared this a single-blind study because the observers could have guessed the acitretin group due to adverse events of acitretin
Incomplete outcome data (attrition bias) All outcomes	Low risk	None of the participants dropped out, and all participants were included in the analyses
Selective reporting (reporting bias)	Low risk	No trial registration found. However we found no major discrepancies between Methods and Results sections
Other bias	Unclear risk	Baseline comparisons: not stated whether there was a significant difference in disease severity between groups Diagnostic certainty: yes The study was completed

Tzaneva 2009

Methods	Parallel-group, randomised controlled trial This study was carried out in a secondary care setting at a dermatology department in Austria
Participants	29 participants with moderate to severe dyshidrotic or hyperkeratotic palmar and/or plantar eczema, with symmetrical distribution Dropouts: 2 **Inclusion criteria of the trial** • Moderate to severe dyshidrotic or hyperkeratotic palmar and/or plantar eczema for at least 1 year • Symmetrical distribution

Tzaneva 2009 *(Continued)*

- Unsatisfactory response to conventional topical treatment

Exclusion criteria of the trial

- Pregnant or lactating women
- Age < 18 years
- History of abnormal UVA sensitivity
- Intake of photo-sensitising drugs
- Local therapy within 2 weeks or systemic therapy within 4 weeks before study entry

Study population

- Gender: oral PUVA group 10 female, 4 male; bath PUVA group 8 female, 5 male
- Age: oral PUVA group mean 49.7 years, SD 16.4 years; bath PUVA group mean 44.2 years, SD 13.5 years

Interventions

Intervention

• Oral PUVA: 8-MOP at a dose of 0.6 mg/kg 1 hour before irradiation with UVA in 14 participants. Irradiation dose: 1.5 J/cm^2 for the palms and soles and 1.0 J/cm^2 for the backs of the hands and feet in participants with skin type III/IV. Respective doses for skin type I/II were 1.2 and 0.8 J/cm^2

• Bath PUVA: 2 mL of a 0.5% 8-MOP concentration of 5 mg/L in 13/15 participants. Immediately after immersion for 15 minutes, the hands and feet were exposed to UVA irradiation. Skin type III/IV: initial dose of 0.7 J/cm^2 for the backs of the hands and feet. Skin type I/II: 0.8 and 0.55 J/cm^2, respectively

Irradiation doses in both groups were increased depending on the degree of an erythematous response. Treatment was given 3 to 4 times a week until complete clearance or over a maximum period of 20 weeks. After clearing, participants were maintained on PUVA twice weekly for 2 weeks, then once weekly for another 4 weeks

At the end of treatment, participants were followed up until relapse, or for a maximum of 40 months

Duration

Up to 40 months (up to 20 weeks of active treatment, up to 40 months of follow-up)

Outcomes

Primary outcome of the trial

- Investigator-rated reduction in severity of eczema score at end of treatment: score based on extent of involvement (0 = 0%, 1 = 1% to 25%, 3 = 51% to 75%, 4 = 76% to 100%), intensity (0 = absent, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe) of erythema, and infiltration of vesicles and scaling

Other outcomes

- Investigator-rated reduction in severity of eczema: score based on extent of involvement (0 = 0%, 1 = 1% to 25%, 3 = 51% to 75%, 4 = 76% to 100%), intensity (0 = absent, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe) of erythema, and infiltration of vesicles and scaling at baseline and at weeks 4, 8, 12, 16, and 20 during treatment, and at 1, 3, 6, 12, 18, 30, and 40 months after end of treatment
- Time until relapse defined as an eczema score > 50% of baseline score during a follow-up period of maximal 40 months
- Cumulative UVA exposure dose and number of exposures required for achieving a good or excellent response (> 75% reduction of eczema score)
- Tolerability of the 2 regimens (adverse events)

Notes

From the article, it is unclear whether all participants had hand eczema. After writing to study authors, it became clear that all participants had hand eczema, and some also had plantar eczema

Study authors were contacted with an additional request for allocation on 4 March 2014, but we were unable to obtain further data

The secondary outcome - reduction in severity, investigator-rated - was used, and study authors did not find a statistically significant difference in dyshidrotic hand eczema (stated P = 0.67; multi-factorial

Tzaneva 2009 *(Continued)*

ANOVA) and a significant difference in the hyperkeratotic group (stated P = 0.03; multi-variate ANOVA), although we were unable to reproduce these data because the standard deviation was not available

The secondary outcome - time until relapse - was included, but we were unable to reproduce these data

Declarations of interest: none declared

Funding: no clear indication of funding that might lead to conflict of interest

Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly allocated to receive either oral or bath PUVA therapy by means of a computer-generated sequentially numbered randomization list" Comment: randomisation method was adequate
Allocation concealment (selection bias)	Unclear risk	Insufficient details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "...observer-blinded study..." Comment: participants and personnel were not blinded, and no placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "eczema severity was determined by a blinded investigator (A. T.) at baseline and every 4 weeks..." Comment: a single, blinded observer assessed all outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (27 of 29 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major discrepancies between Methods and Results sections. The Methods section gives a clear description of the definitions of relapse and clearance
Other bias	Unclear risk	Baseline comparisons: not stated Diagnostic certainty: yes The study was completed

Uggeldahl 1986

Methods	Within-participant, randomised controlled trial This study was conducted in a secondary care setting, probably at 2 centres in Finland
Participants	50 (46) participants (1.5 to 70 years) with bilateral moderate hand/wrist/lower arm eczema, with left-right comparable severity, were included; 4 were excluded because of asymmetrical hand eczema Dropouts: 2

Uggeldahl 1986 *(Continued)*

	Inclusion criteria of the trial • Bilateral and symmetrical moderate eczema of the hand, wrist, and lower arm **Exclusion criteria of the trial** • Not stated **Study population** • Gender: not stated • Age: mean 27 years, range 1.5 to 70 years
Interventions	**Intervention** • Desonide cream 0.1% twice daily for 2 weeks in 44/46 hands • Desonide cream 0.05% twice daily in 44/46 contralateral hands for 2 weeks **Duration** 2 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated score 0 to 4 (0 = absent and 4 = maximum severity) for inflammation, infiltration, desquamation, lichenification, itching, tenderness, and chapping, after 4 to 7 days and after 11 to 14 days • Participant-rated therapeutic effect: both hands equal or one hand better than the other at days 11 to 14 • Adverse events
Notes	In fact, 50 participants were randomised, but 4 participants were excluded at the start. Not clear whether inclusion criteria of the trial (hand/wrist/lower arm) stipulated that the hands had to be involved in all participants. The youngest participant was 1.5 years old Aim was to study equivalency, but this was not reflected in the analysis The secondary outcomes - reduction in severity, investigator-rated and participant-rated - were included but did not provide reproducible data Declarations of interest: 2 study authors were employees of the research department at Apothekernes Laboratorium A.S., Oslo, Norway, the manufacturer of the study drugs Funding: see above item Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the study consisted of a double-blind, randomized, left-right comparative study..." Comment: stated only that this was a randomised study. No further details provided

Uggeldahl 1986 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "each patient was given 2 tubes identical in appearance...." Quote: "according to the double-blind nature of the study, the creams were randomly allocated to the left and right side..." Comment: no details about how allocation was concealed from participants and clinicians. The identical tubes were randomly allocated to left and right sides
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "each patient was given 2 tubes identical in appearance...." Comment: the only difference between the 2 tubes was the concentration, wherefore this is considered as low risk
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...double-blind nature..." Comment: unclear whether observers were aware of the treatment modalities, although study authors claim double-blind design
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (44 or 46 of 50 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. No major discrepancies between Methods and Results sections
Other bias	Low risk	Baseline comparisons: within-participant study not applicable Diagnostic certainty: yes The study was completed

van Coevorden 2004a

Methods	Parallel group, open-label randomised controlled trial This study was conducted at 2 university hospital outpatient clinics in the Netherlands
Participants	158 participants (88 male, 70 female) with chronic hand eczema of at least 1 year's duration, with at least 2 relapses of at least 3 weeks' duration, moderate to severe, grade 6 on a hand eczema score at start of treatment Dropouts: 33 during treatment, 8 during follow-up **Inclusion criteria of the trial** • Bilateral or unilateral hand eczema since at least 1 year • At least 2 relapses or more than 3 consecutive weeks with visible signs in the last 3 months • Moderate to severe hand eczema with a score of at least 6 **Exclusion criteria of the trial** • Active eczematous lesions elsewhere on the body • Use of photosensitive drugs or anticoagulants • Treatment with cytostatics or ionising radiation or PUVA of the hands in the last 6 months • Other forms of photosensitivity • Alcohol abuse • Liver or renal dysfunction • Congestive heart failure

van Coevorden 2004a *(Continued)*

- Hypertension
- Epilepsy
- (Pre)malignant skin tumours
- Pregnancy (wish)

Study population

- Gender: 70 female, 88 male
- Age: mean 42 years, range 18 to 70 years; SD 14 years; SE 1.1 years

Interventions	**Intervention** • Oral PUVA (methoxypsoralen) phototherapy at home on both hands thrice weekly for 10 weeks in 63/78 participants • Topical bath PUVA (trioxsalen) twice weekly in hospital for 10 weeks in 62/80 participants Emollients were allowed in both groups Participants were followed up for an additional 8 weeks after the end of treatment **Duration** 18 weeks (10 weeks of active treatment, 8 weeks of follow-up)
Outcomes	**Primary outcome of the trial** • Observer-rated severity score based on sum of scores 0 to 3 (0 = none, 1 = slight, 2 = moderate, 3 = severe) for erythema, desquamation, vesiculation, infiltration, fissures, itch, and pain at week 10 (end of treatment) **Other outcomes** • Observer-rated severity score (as described above) at weeks 3 and 6 of treatment and at weeks 4 and 8 after end of treatment • Participant-registered travel costs and time off work • Number of participants improved at week 10 • Adverse events
Notes	Blinding of participants impossible. Observers of outcomes not blinded. Analysis based on intention-to-treat principle. Scoring of eczema was similar to the scoring used by Rosén 1987a Secondary outcome number 3 (number of participants improved at week 10) not specified in the Methods. Study authors mention adherence to CONSORT statement. Missing standard deviations were calculated according to formula provided in Chapter 7.7.3.2 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) Declarations of interest: none declared Funding: the study was supported in part by the Netherlands Healthcare Insurance Board, Amstelveen, the Netherlands Sample size rationale: provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization lists with blocks of 4 were created by a secretary" Comment: randomisation method was considered adequate

van Coevorden 2004a *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "consecutive patients were given consecutive numbers on the list and randomized accordingly by the trial's dermatologists. The randomization sequence was kept concealed by the secretary until the end of the trial" Comment: allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "blinding of the patient and the outcome assessor was not practically feasible: patients are aware of their treatment modality and assessors can easily identify a hand treated with bath PUVA because of its rim of pigmentation" Comment: no blinding was attempted. Study authors state that blinding was not practically feasible. In addition, outcomes of this study were time off work and travel time. When participants would have received placebo in hospital or at home radiation, this outcome would not be applicable
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "hand eczema severity was assessed by one of the unblinded trial's dermatologists (trained in assessment of hand eczema)" Quote: "blinding of the patient and the outcome assessor was not practically feasible: patients are aware of their treatment modality and assessors can easily identify a hand treated with bath PUVA because of its rim of pigmentation" Comment: no blinding; study authors state in a comment that blinding of observers was practically not feasible because observers would be able to guess the difference based on the rim of pigmentation in the bath PUVA-treated group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the statistical analysis was based on the intention-to-treat principle, using the "last value carried forward" method" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No trial registration found. The article provides a clear participant flow chart based on CONSORT guidelines. With regards to one of the important outcomes - travel costs and time of work - study authors stated only that "patients treating themselves at home had substantially lower travel costs and substantially less time of work"; however additional information is provided in a separate report
Other bias	Low risk	Baseline comparisons did not reveal significant differences in hand eczema between groups Diagnostic certainty: yes The study was completed

Veien 1995

Methods	Parallel-group, randomised controlled trial This study was conducted at 4 dermatological departments and clinics in Denmark
Participants	47 participants (11 male and 36 female) with hand eczema of at least 6 months' duration. All had or previously had atopic dermatitis. All without positive reaction to standard patch test series Dropouts: 9 **Inclusion criteria of the trial** • Eczema of the hands and/or fingers for at least 6 months

Veien 1995 *(Continued)*

- A minimum score of 5 according to the adopted scoring system
- At least 18 years of age
- Current or past atopic dermatitis according to criteria of Hanifin and Rajka

Exclusion criteria of the trial

- Type IV allergy

Study population

- Gender: 36 female, 11 male
- Age: not stated

Interventions	**Intervention** • Oral ranitidine 300 mg twice daily (21/23 participants) for 16 weeks **Control intervention** • Placebo tablets (17/24 participants) for 16 weeks Both groups received betamethasone cream/ointment and emollient **Duration** 16 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated severity scoring based on scoring (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for erythema, vesicles, scaling, pruritus, and fissures, and 1 to 3 score for area involved • Participant-rated treatment result: 0 = unchanged/aggravated, 1 = slight improvement, 2 = marked improvement, 3 = clear at baseline and at weeks 4, 8, 12, and 16 • Observer-rated treatment result: 0 = unchanged/aggravated, 1 = slight improvement, 2 = marked improvement, 3 = clear at baseline and at weeks 4, 8, 12, and 16 • Participant- and physician-rated (combined?) overall result: successful (marked alleviation or clear) or failed (unchanged/aggravated) • Scores of separate items for outcome 1 • Adverse events
Notes	Published as brief communication. Analysis according to intention-to-treat principle, but no details given The secondary outcome - reduction in severity, investigator-rated - was included, although because standard deviations were missing, we were unable to reproduce the data Study authors were contacted by email but were unable to answer all of our questions because the study was conducted such a long time ago Declarations of interest: not stated Funding: the study drugs were provided by Glaxo Denmark A/S, and Glaxo provided an employee to assist with the study. The emollients were provided by Rhône-Poulene, and statistical analyses were performed by Biomedica, Copenhagen, Denmark Sample size rationale: not stated

Risk of bias

Veien 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patients were randomly selected" Comment: no further details given in the article; personal communication with study authors clarified that a computer-generated code was used
Allocation concealment (selection bias)	Low risk	No details in the article about how allocation was concealed from participants and clinicians. Personal communication with study authors clarified the following: "The allocation was concealed from patients and investigators by numbers on identical boxes of tablets containing either ranitidine or placebo". Because randomisation was done by a third party, boxes were identical, and investigators received the randomisation code only in a sealed envelope, this was considered an adequate method to prevent selection bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the patients were randomly selected to receive oral ranitidine, 300 mg twice daily, or placebo tablets of identical appearance" Comment: double-blind design. Because randomisation was done by a third party and staff received identical looking boxes for ranitidine and placebo, it was not possible for participants and staff to know the treatment arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the code was broken when all the patients had completed the study and all results were recorded" Comment: randomisation was carried out by a third party; therefore observers could not have known the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "statistical evaluations were based on the intention-to-treat principle" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	High risk	No trial registration found. The Results section is very concise. In the Results section, it is unclear whether the outcome was based on participants' or investigators' scores or on a combination of these, and only total scores or significance levels are given
Other bias	Low risk	Baseline comparisons: the 2 groups were comparable with regard to age, duration of dermatitis, eczema at other sites, and presence of other atopic symptoms Diagnostic certainty: yes The study was completed

Veien 1999

Methods	Parallel-group (3 groups), randomised controlled trial This study was conducted in a secondary care setting at 3 centres in Denmark (study was carried out at a university department as well as at 2 private dermatology clinics)
Participants	106 participants were randomised (all patch tested) with hand eczema > 6 months that had cleared upon daily treatment for a maximum of 9 weeks with mometasone furoate cream 120 participants were recruited, and 14 dropped out during the initial phase No dropouts after randomisation (see notes)

Veien 1999 *(Continued)*

Inclusion criteria of the trial

- Eczematous hand dermatitis for longer than 6 months with a minimum score of 6 according to the adopted scoring system

Exclusion criteria of the trial

- Infection to the hands
- Hyperkeratotic hand eczema
- Other hand dermatoses
- Contact allergy to the topical remedies used in the study
- Fungal infection of hands/feet
- Pregnant and lactating women
- Use of systemic immunosuppressants

Study population

- Gender: 100 female, 20 male in the recruited group
- Age: median 31 years, range 17 to 70 years, in the recruited group

Interventions	**Intervention** • Mometasone furoate cream thrice weekly (Sunday/Tuesday/Thursday) for up to 36 weeks or 30 (?) in 35/35 participants • Mometasone cream twice weekly (Saturday/Sunday) for up to 36 weeks in 37/37 participants **Control intervention** • No corticosteroids in 34/34 participants Emollients (Essex cream and ointment) used in all groups In case of recurrence, all groups were permitted to use mometasone daily for a maximum of 3 weeks at separate period Additional treatment was permitted in all groups in case of a bacterial infection **Duration** Up to 36 weeks
Outcomes	**Primary outcome of the trial** • Number of recurrences of hand eczema and times at which recurrence occurred (recurrence defined as eczema score equal to or higher than initial score) **Other outcomes** • Length of time it took to control the dermatitis during the initial treatment period • Numbers and times of recurrence in subgroups. Data analysis by survival analysis • Adverse events
Notes	All randomised participants were supposed to be free of eczema due to preceding treatment (induction of remission) with mometasone, yet recurrence was defined as a score equal to or higher than before this remission induction phase. In each group, a few participants received additional treatment. Dropout was defined as participant who had more than 2 recurrences The secondary outcome - time until relapse - was included in the study, but data were not reproducible Study authors were contacted on 7 March 2014 but responded on 13 March 2014 that they were unable to provide additional information

Veien 1999 *(Continued)*

	Declarations of interest: not stated Funding: Schering-Plough A/S Farum, Denmark, supplied the study drugs and covered the expenses of processing the data Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients.... were randomised into 1 of 3 groups" Comment: no further details in the article. Personal contact with the study author clarified that the randomisation table was computer generated with blocks of 5, and this was carried out by Schering-Plough A/S, Farum, Denmark
Allocation concealment (selection bias)	Low risk	No details in the article about how allocation was concealed from participants and clinicians; however personal contact with study authors clarified that randomisation was created by a third party. The investigators received sealed and numbered envelopes for allocation to a treatment arm
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "ideally, the maintenance phase should have been double-blind. This would, however, have required a very complicated distribution of the medicaments, with many different tubes for various days of the week. We felt the risks of mistakes by the patients and of poor compliance to be too great" Comment: no blinding; blinding was difficult because participants had to follow different treatment schedules
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the investigation was carried out as an open, prospective, randomized trial" Comment: no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "the intention-to-treat principle was used to calculate the effect of the treatments" Comment: intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	No trial registration found. Severity of pruritus, erythema and vesicles, scaling, and fissures is described in the Materials and Methods section, but separate results for these are not given in the Results section; however, because these are not listed as outcome, we judged this as low risk. All (clearly described) outcomes listed in the Materials and Methods section are included in the Results section
Other bias	Low risk	Baseline comparisons: "there were no statistically significant differences in the demographic features represented in the 3 centres or in the 3 randomisation groups" Diagnostic certainty: yes The study was completed

Whitaker 1996

Methods	Parallel-group, randomised controlled trial

Whitaker 1996 *(Continued)*

	This study was carried out in a secondary setting for outpatients at a single centre in South Africa
Participants	39 participants with chronic stable hand eczema of > 12 months' duration Dropouts: 5 **Inclusion criteria of the trial** • Stable hand eczema for at least 12 months **Exclusion criteria of the trial** • Inflammatory skin disorders other than eczema • Allergic contact dermatitis that resolves after avoidance of the relevant contact allergens • Severe intercurrent illness • Currently treated with oral steroids, PUVA, immune suppressants, phenothiazines, or antidepressants **Study population** • Gender: not stated • Age: range 19 to 75 years
Interventions	**Intervention** • GLA (gamma linolenic acid) 50 mg (in 500 mg evening primrose oil capsules) daily for 16 weeks in 19/20 participants **Control intervention** • Gelatine capsules with 500 mg sunflower oil daily for 16 weeks in 15/19 participants Both groups were allowed to use unlimited quantities of standard emollient and a limited quantity of group III corticosteroids Participants were followed up for 8 weeks after the end of treatment **Duration** 24 weeks (16 weeks of active treatment, 8 weeks of follow-up)
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Observer-rated clinical evaluations (using a 100-mm visual analogue scale to evaluate dryness, redness, itch, cracking, vesiculation, oedema, and overall impression) at 4-week intervals, up to 24 weeks, from which score decreases (improvements) from baseline to week 16 and week 24 are analysed • Change in epidermal GLA content • Decrease in steroid usage
Notes	Part of the study was a laboratory investigation in 10 matched healthy controls. At the beginning of the study, all participants had blood taken for laboratory parameters, as well as biopsies for histology and electron microscopy. No participant-rated outcomes Study authors were contacted for additional information but remained unresponsive Declarations of interest: not stated Funding: the study was planned and funded by Scotia Pharmaceuticals Sample size rationale: not stated

Whitaker 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a blind random method was used..." Comment: no further details
Allocation concealment (selection bias)	Unclear risk	No details about how allocation was concealed from participants and clinicians, although study authors stated that they used a "blind random method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo was given to 19 patients as identical-appearing gelatine capsules..." Comment: study authors stated double-blinded design and included a placebo of identical appearance, which is an adequate way to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a parallel, double-blind, placebo-controlled trial..." Comment: study authors stated a double-blind design but provided no information regarding observer blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (34 of 39 = more than 80%)
Selective reporting (reporting bias)	Low risk	No trial registration found. All results described in the Materials and Methods section are depicted in the Results section
Other bias	Unclear risk	Baseline comparisons: redness was significantly more severe in the placebo group than in the intervention group Diagnostic certainty: yes The study was completed

Yousefi 2012

Methods	Parallel-group, randomised controlled trial This study was conducted in a secondary care setting at a single centre in Iran
Participants	60 participants with chronic hand eczema Dropouts: 8 **Inclusion criteria of the trial** • Participants with chronic hand eczema that is confirmed by 2 dermatologists • 18 to 60 years of age • Hand eczema could be due to occupational dermatitis, atopic dermatitis, or irritant dermatitis of the hands (bilateral or unilateral) **Exclusion criteria of the trial** • History of allergic reactions to the study medication • Use of systemic corticosteroids or immunosuppressive drugs during the last 4 weeks • Synchronous local infection at the site of eczema • Women during pregnancy or lactation • Obsessive-compulsive disorder concerning over-washing

Yousefi 2012 *(Continued)*

- Any other medical or mental conditions that interfered with participation in this study

Study population

- Gender: Eucerin group 14 female, 4 male; Nigella group 15 female, 4 male; betamethasone group 10 female, 5 male
- Age: Eucerin group mean 31.89 years, 11.61 SD years; Nigella group mean 35.79 years, 15.03 SD years; betamethasone group mean 32.60 years, 13.74 SD years

Interventions	**Intervention** • Nigella sativa oil extract 2% with Eucerin base applied twice a day for a period of 4 weeks in 19 participants • 0.1% betamethasone ointment applied twice a day for a period of 4 weeks in 15 participants **Control intervention** • Only Eucerin ointment applied twice a day for a period of 4 weeks in 18 participants **Duration** 4 weeks
Outcomes	**Primary outcomes of the trial** • Resolution of severity and intensity of lesions after 2 weeks measured by Hand Eczema Severity Index (HECSI) • Quality of life after 2 weeks measured by Dermatology Life Quality Index (DLQI) **Other outcomes** • Irritant or allergic contact dermatitis after 4 weeks measured by physician assessment • Adverse events
Notes	The secondary outcomes - reduction in severity, participant-rated and investigator-rated - were included but did not provide reproducible data Declarations of interest: none declared Funding: the study was planned and funded by Shahid Beheshti University of Medical Science, Tehran, Iran Sample size rationale: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "assigning patients to the treatment groups was performed based on randomly permuted blocks of size 6. The project biostatistician prepared the randomization list" Comment: this was considered an adequate method to generate a randomisation sequence
Allocation concealment (selection bias)	Low risk	Quote: "they were pre-packed in tubes and consecutively numbered for each participant according to the randomization list. This was done by the project pharmacologist. Each participant was assigned an order number and the dermatology resident used the corresponding numbered packs to allocate participants to treatment groups. Both patients and dermatologists were blind to the assigned drugs due to randomization procedure"

Yousefi 2012 *(Continued)*

		Comment: this is considered an adequate and well-described procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes (Iranian Clinical Trial Register IRCT201111266959N3): "blinding: single blind" "For blinding the participants but not investigators, all 3 creams(Nigella, Betamethasone, Eucerin as placebo) will be prepared in the identical tubes which only labelled A, B, and C with no other information" Comment: the trial registrations stated a single-blind study, although the original article claims that the study is double-blind Quotes (from article): "in this randomised, controlled, double-blind clinical trial..." "The therapeutic medications were manufactured identical in appearance, odour and other characteristics by adding ineffective ingredients. We added the essence of 0.1% mint oil to create the same smell in all ointments" "Each participant was assigned an order number and the dermatology resident used the corresponding numbered packs to allocate participants to treatment groups. Both patients and dermatologists were blind to the assigned drugs due to randomization procedure" Comment: we assume that participants were unaware of their treatment modality by this method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote (from Iranian Clinical Trial Register IRCT201111266959N3): "for blinding the participants but not investigators, all 3 creams (Nigella, Betamethasone, Eucerin as placebo) will be prepared in the identical tubes which only labelled A, B, and C with no other information" Quote (from article): "in this randomised, controlled, double-blind clinical trial..." Comment: unclear if outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No intention-to-treat analysis but per protocol (52 of 60 = more than 80%)
Selective reporting (reporting bias)	Low risk	Trial registration found (IRCT201111266959N3), registered before publication; no major differences between trial registration and the study were found
Other bias	Low risk	Baseline comparison: no significant difference was observed between treatment groups with respect to disease severity at baseline as measured by HECSI and DLQI scores (P = 0.43; Welch's ANOVA; and P = 0.99; ANOVA, respectively) Diagnostic certainty: yes The study was completed

ALT: alanine aminotransferase.
ANOVA: analysis of variance.
AST: asparate aminotransferase.
BSI: brief symptom inventory.
CDLQI: Children's Dermatology Life Quality Index.
CI: confidence interval.
CPK: creatine phosphokinase.
DASI: Dyshidrotic eczema Area and Severity Index.
DLQI: Dermatology Life Quality Index.
DSCG: disodium cromoglycate.

EASI: Eczema Area and Severity Index.
EDI: Eczema Disability Index.
EQ-5D: standardised index for measuring quality of life by EuroQol in 5 dimensions.
FSH: follicle-stimulating hormone.
GLA: gamma linolenic acid.
HDL: high-density lipoprotein.
HEAS: Hand Eczema Area and Severity Score.
HEASI: adaptation of EASI for the hands: Hand Eczema Area and Severity Index.
HECSI: hand eczema severity index.
HEES: hand eczema extent score.
IGA: investigators' global assessment.
ISGA: investigators' static global assessment.
LDH: lactate dehydrogenase.
LDL: low-density lipoprotein.
MOP-8: 8-methoxypsoralene.
mTLSS: modified total lesion symptom score.
NB-UVB: narrow-band ultraviolet B.
PaGA: participants' global assessment.
PGA: physicians' global assessment.
PHQ: patient health questionnaire.
PSA: patient self-assessment.
PUVA: (topical and oral) psoralen combined with UVA.
QALY: quality-adjusted life-year.
RR: risk ratio.
SCORAD: Scoring Atopic Dermatitis tool.
SD: standard deviation.
SGA: subjects' global assessment.
TETDS: tetraethylthiuram disulfide.
TEWL: transepidermal water loss.
TLSS: total lesion symptom score.
UVA: ultraviolet A.
UVA-1: newer form of UV therapy that contains only long-wavelength UVA-1 radiation (340 to 400 nm) and thus reduces the risk of burning.
UVB: ultraviolet B.
VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aertgeerts 1985	The study included participants with different dermatoses on arms, hands, and legs. It was not clear for which participants the hands were involved and how the outcome was in the participants with hand eczema. This within-participant study was not randomised and therefore was excluded
Berndt 2001	Participants did not have hand eczema. The study examined slightly irritated hands in nurses. The study may be included in the Skin Group Review titled "Interventions for preventing occupational irritant hand dermatitis"
Chen 2015	Hand and foot eczema combined; no separate data available
Gergovska 2017	Study focusses on prevention instead of treatment for active disease
Grivcheva-Panovska 2013	Study on *Staphylococcus aureus* colonisation instead of hand eczema
Güler Özden 2004	Not clear whether participants were randomised to different treatment arms
HogenEsch 1998	Pilot study, in which it is unclear how many were allocated to each intervention. Not clear if the study was randomised

Study	Reason for exclusion
Petering 2004	Non-randomised study with a within-participant (left-right) design. It could be argued whether randomisation is important in this left-right study with bilateral hand eczema of similar severity. Observer of outcomes was blinded
Rosén 1987	Quasi-randomised
Zeichner 2018	Single-arm study without a comparator
Zimmerman 1967	It is unclear whether this within-participant study was randomised Study on 54 participants with "bilateral, symmetrical areas of dermatitis" and stating only the preference for betamethasone 17-valerate or fluocinolone acetonide ointment for 8 participants with hand eczema. No other outcomes for hand eczema specified. No information on frequency, dosage, and duration of treatment

Characteristics of studies awaiting assessment *[ordered by study ID]*

Beitner 1996

Methods	Randomised controlled trial This study was conducted at a single centre in Sweden The study probably was not blinded
Participants	30 consecutive participants with different dermatological hand dermatoses including pustulosis palmoplantaris (n = 5), psoriasis (n = 1), tylotic eczema (n = 4), atopic eczema (n = 3), dyshidrotic eczema (n = 1), allergic eczema (n = 7), and non-allergic eczema (n = 1), both allergic eczema and dyshidrotic (n = 2) Dropouts: 6 Inclusion and exclusion criteria were not stated
Interventions	**Intervention** • Clobetsaol propionate (Dermovate Glaxo) solution under occlusion with a hydrocolloid dressing twice a week for the first 2 weeks and once a week for the next 2 weeks • Clobetasol propionate ointment under occlusion with a hydrocolloid dressing twice a week for the first 2 weeks and once a week for the next 2 weeks Follow-up included a visit 12 weeks after the start of treatment
Outcomes	**Primary outcomes of the trial** Not stated **Other outcomes** • Symptom severity for itching, erythema, infiltration, and scaling, each graded on a 4-point scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe) • Participant-rated severity of itch on a visual analogue scale (VAS) • Vesicles/pustules: absent or present • Relapse within 12 weeks • Adverse events

Beitner 1996 *(Continued)*

Notes	Study results for hand eczema participants were not presented separately, and we were unable to obtain additional data from the study author This study was published as a very concise letter to the editor, and a lot was uncertain, for example, visits and outcome parameters

CTRI/2009/091/000212

Methods	Randomised parallel-group open-label study
Participants	60 participants with hand eczema **Inclusion criteria** • 18 years of age or older • Mild to moderate hand dermatitis, according to the Investigator Global Assessment (score 2 to 3) • Generally healthy, as determined by brief medical history • Capable of understanding and signing the consent form **Exclusion criteria** • Clinically relevant allergic or irritant contact dermatitis and inability to avoid exposure • Severe dermatitis according to the Investigator Global Assessment (score 4) • Severe vesiculation or bullae • History of psoriasis, contact urticaria, and/or pustular disease • Therapy with potent topical corticosteroids within 1 month before enrolment • Systemic treatment with oral retinoids, corticosteroids, or PUVA within the 8-week period before the beginning of the study • History or current evidence of a chronic or infectious skin disease • Pregnant or lactating, or women not using highly effective contraception • Current participation in any other interventional clinical trial • Received treatment with any non-marketed drug substance (i.e. an agent that has not yet been made available for clinical use) within 4 weeks before randomisation • Participant known or, in the opinion of the investigator, unlikely to comply with the Clinical Study Protocol (e.g. alcoholism, drug dependency, psychotic state)
Interventions	**Interventions** • Herbavate applied on affected area 3 times a day for 4 weeks • Betamethasone + Gentamycin applied on affected area 3 times a day for 4 weeks
Outcomes	**Primary outcome of the trial** • Investigators' Global Assessment (IGA) at baseline, week 2, and week 4 **Secondary outcomes of the trial** • Global assessment by patients (PaGA): at baseline and at the end of 2 and 4 weeks of treatment • Number of adverse events during 4 weeks of treatment • Number of participants with adverse events during 4 weeks of treatment • Adverse events reported during the study at baseline and at the end of 2 and 4 weeks of treatment • Total lesion symptom score (TLSS) at week 0, week 2, and week 4
Notes	Sponsor: Troikaa Pharmaceuticals Limited

CTRI/2009/091/000212 *(Continued)*	Study author was contacted on 20 February; however email was not-working: medicalservices@troikaapharma.com. Contact through LinkedIn revealed that study results have not been published and provided no further details

Draelos 2000

Methods	Randomised controlled trial with a within-participant design This study was conducted at a single centre in North Carolina, USA The study was double-blind; an intention-to-treat analysis was not carried out
Participants	80 participants between the ages of newborn and 80 years with the following dermatological conditions: household hand dermatitis (n = 21), occupational hand dermatitis (n = 18), latex glove irritant contact dermatitis (n = 9), diaper dermatitis (n = 5), cutaneous wounds (n = 17), and allergic contact dermatitis (n = 10) Dropouts: 7 **Exclusion criteria of the trial** • Use of any prescription skin medications or other treatments at the study site for a 2-week washout period before initiation of the study • Use of topical corticosteroid creams or oral corticosteroids
Interventions	**Intervention** • The study hydrogel barrier/repair cream (Hydron) for 4 weeks in 80 participants **Control** • Control moisturising cream (Eucerin, Beiersdorf, Germany) for 4 weeks in 80 participants
Outcomes	**Primary outcomes of the trial** Not stated **Other outcomes** • Participant-rated: overall skin appearance and feel based on a questionnaire in week 2 and week 4 • Investigator-rated improvement in erythema, roughness, desquamation, serum crusting (where appropriate), and inflammation on an ordinal rating system (–2, noticeably worse; –1, worse; 0, no change; 1, better; 2, noticeably better) • Photographs
Notes	RCT on different diseases, mostly on hand eczema. Number of participants with hand eczema and results for participants with this condition are impossible to reconstruct. We were unable to obtain separate data from the study investigator

English 1989

Methods	Randomised controlled parallel-group study This study was conducted at 2 dermatology departments in the United Kingdom

English 1989 *(Continued)*

Participants	97 outpatients with steroid-responsive dermatoses including 63 with endogenous eczema (38 with atopic dermatitis, 19 with hand eczema, and 6 with discoid eczema) and 34 with chronic plaque psoriasis Dropouts: 12 Inclusion and exclusion criteria were not stated
Interventions	**Intervention** • Betamethasone dipropionate cream 005% twice daily during 3 weeks • Betamethasone dipropionate cream 0.05% in the morning and base cream in the evening during 3 weeks
Outcomes	**Primary outcomes of the trial** Not stated **Other outcomes** • Physician-rated severity (absent, mild, moderate, severe): erythema, induration, scaling, crusting, pruritus, excoriation, and pain • Physician-rated overall evaluation of participants' responses: excellent (95% clear), good (50% to 95% clear), improvement (50% clear), poor (no response or exacerbation) • Participant-rated response on a 10-cm VAS line (visual analogue scale) • Participant-rated improvement: yes/no • Participant-rated acceptability of treatment • Adverse events
Notes	This study was part of a larger study on eczema and psoriasis. Analyses/outcomes among the 19 hand eczema participants were not given. We contacted the study author on 11 March 2014. This author responded 13 March 2014 that he was unable to provide additional data

EUCTR2004-002398-22-DE

Methods	Randomised placebo-controlled double-blind study

Participants	240 participants with different dermatoses, of which dyshidrotic hand eczema was one
	
	Inclusion criteria
	
	• One of the following dermal indications (mild to moderate):
	  ○ Atopic eczema in the crook of the arm or the hollow of the knee
	  ○ Dishidrotic hand eczema
	  ○ Plaque-type psoriasis (hyperkeratoses removed before treatment by urea or salicylic acid)
	  ○ Seborrhaeic eczema
	  ○ Acne vulgaris
	• Aged 18 to 80 years
	• Reliable method of contraception for women of child-bearing potentia
	
	Exclusion criteria
	
	• Systemic therapy for skin disease within 2 weeks before the start of treatment, except if maintained stable during the whole course of the study and approved by the safety officer
	• UV therapy for dermal indications within 4 weeks before the start of treatment

EUCTR2004-002398-22-DE *(Continued)*

	• Chronic or acute illness requiring systemic anti-inflammatory treatment except if maintained stable during the whole course of the study and approved by the safety officer • Skin cancer and precancerous skin lesions, except basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and actinic keratosis, if located outside the target area • History of peptic ulcers or gastric intolerance with NSAIDs • History of asthma bronchiale • History of chronic airway infection • History of renal insufficiency • Thrombocytopathia • Immunosuppressants (e.g. corticosteroids) within 2 weeks before the start of treatment • Known sensitisation to NSAIDs • Pregnancy or lactation • Mental disorder
Interventions	**Intervention** • IDEA-070 (ketoprofen in Transfersome) **Control intervention** • Placebo

Outcomes	**Primary outcomes of the trial**
	• Investigator Global Assessment score (IGA)
	Secondary outcomes of the trial
	• Clinical evaluation of the efficacy of IDEA-070 (ketoprofen in Transfersome) in participants with different dermatological diseases using the following scores:
	  ○ Patient Global Assessment score (PGA)
	  ○ Indication-specific scores which include the DASI for dyshidrotic hand eczema
	• Safety of IDEA-070 evaluated by
	  ○ Description of AE profile
	  ○ Changes in laboratory values
	  ○ Physical examination
	  ○ Vital signs including body weight and body temperature
	  ○ Ketoprofen plasma levels

Notes	Study conducted in Germany Sponsor: IDEA AG Current status: not recruiting

EUCTR2005-005793-75-DE

Methods	Double-blind randomised parallel-group design
Participants	40 patients with chronic hand dermatitis rated mild to moderate according to Investigator's global assessment (score, see page 20) that has persisted for longer than 6 month in spite of attempts to identify and remove the cause **Inclusion criteria** • Men and women 18 to 70 years of age

EUCTR2005-005793-75-DE *(Continued)*

- Chronic hand dermatitis rated mild to moderate according to investigator's global assessment (score, see page 20) that has persisted for longer than 6 months in spite of attempts to identify and remove the cause
- Physical examination must be without disease findings unless the investigator considers an abnormality to be irrelevant to the outcome of the study
- Danish sites: sexually active females of child-bearing potential should be surgically sterile (hysterectomy or tubal ligation), or should use a medically accepted contraceptive regimen: systemic contraceptive (oral, implant, vaginal or transdermal, injection) or intrauterine device (IUD) during the trial and at least 15 days after the end of the study
- German sites: sexually active females of child-bearing potential should be surgically sterile (hysterectomy or tubal ligation), or should use a medically accepted contraceptive regimen: systemic contraceptive (oral, implant, injection), diaphragm or cervical cap with intravaginal spermicide, intrauterine device (IUD), condom with intravaginal spermicide
- Danish sites: an epicutaneous test was performed within the previous 36 months before the first treatment and was documented in the participant record
- German sites: an epicutaneous test was performed within the previous 12 months before the first treatment and was documented in the participant record
- Written informed consent obtained

Exclusion criteria

- Primary hyperkeratotic forms of dermatitis, hand dermatosis other than eczematous dermatoses, or acute infection
- Allergic contact dermatitis if the allergen is identified and patient remained in contact with the allergen
- Metal-workers who are in permanent contact with cutting fluids
- Sun-tanned or hyperpigmentation or tattoos in the test fields
- Dark-skinned persons whose skin colour prevents ready assessment of skin reactions
- Treatment within 3 months before study day 1 with systemic medications (i.e. glucocorticoids or immune modulators), treatment within 2 weeks with topical glucocorticosteroids, or treatment with other systemic or locally acting medications that might counter or influence the trial aim within 2 weeks before study day 1 and during the study
- UV therapy within 4 weeks before study day 1 and during the study
- Medical history of skin cancer in the area of the hands or generalised skin cancer
- Known to be drug-resistant for this indication
- Evidence of drug or alcohol abuse
- Pregnancy or nursing
- Symptoms of a clinically significant illness that may influence the outcome of the study in the 4 weeks before study day 1 and during the study
- Participation in another clinical trial involving pharmaceutical products in the 4 weeks before study day 1
- Known allergic reactions to components of the study preparations
- German sites: known allergic reactions with symptoms such as asthma, allergic rhinitis, or urticaria to 2-acetoxy-benzoic acid (acetylsalicylic acid) or other non-steroidal antirheumatics (because of possible cross-allergic reactions)
- If in the opinion of the investigator or physician performing the initial examination, the patient should not participate in the study (e.g. due to probable non-compliance or inability to understand the study and give adequately informed consent)

Interventions	**Intervention** • ASF-1075 cream **Control intervention** • Placebo cream
Outcomes	**Primary outcomes of the trial**

EUCTR2005-005793-75-DE *(Continued)*

	• Clinical assessment of skin condition using the hand eczema severity index (HECSI)
Notes	Current status: not recruiting

EUCTR2008-006148-20-DE

Methods	Double-blind randomised parallel or within-participant design
Participants	Individuals with mild to moderate plaque-type psoriasis (PASI < 10) or hand and foot eczema with at least 2 symmetrical lesions
Interventions	**Intervention** • Mometasone furoate 0.1% ointment **Control intervention** • Placebo ointment
Outcomes	**Primary outcomes of the trial** • Tolerability and safety of Momegalen by assessment of AEs • Frequency, severity, and relationship to study medication are presented in frequencies, and percentages broken down by treatment group and visit **Secondary outcomes of the trial** • Evaluated safety assessed by vital signs and clinician's and participant's assessment of local skin reaction and irritability, as well as on a 4-point Likert scale, during a 3-week treatment. Efficacy assessed by PGA on a 5-point scale. Secondary objectives analysed descriptively
Notes	Not available

Goh 1999

Methods	Within-participant randomised controlled trial This study was conducted at a single centre in Singapore in a secondary setting This was an open-label, observer-blinded study; an intention-to-treat analysis was not done
Participants	60 consecutive patients with moderate to severe bilateral chronic eczema on the limbs for at least 6 months. Patients had different dermatological diseases such as hand and foot eczema, lichen simplex chronicus, discoid eczema, prurigo nodularis, and unclassifiable eczema. In 8 patients, the hands were treated Dropouts: 2 **Exclusion criteria of the trial** • Pregnancy • Known hypersensitivity to corticosteroids • Presence of skin atrophy • Use of systemic steroids within 28 days before the start of the study • Use of antihistamines 1 day before and during the study

Goh 1999 *(Continued)*

Interventions	**Intervention** • Mometasone furoate cream 0.1% once daily during 3 weeks • Clobetasol propionate cream 0.05% applied twice daily during 3 weeks No other medication was allowed during the study
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Physician-rated overall evaluation of severity of eczema • Physician-rated symptom scores for erythema, induration, crusting, scaling, excoriation, and pruritus using a severity scale from 0 (none) to 3 (severe) and the combination of these signs/symptoms • Percentages of improvement in the signs and symptoms score • Cosmetic acceptability • Adverse events
Notes	Study on different types of eczema in different body regions. Specific data on outcomes among the 8 hand eczema participants were not given. We contacted study authors on 11 March 2014; they responded 13 March 2014 that they were unable to obtain these data

Grundmann 1999

Methods	Randomised within-participant study This study probably was conducted at a single centre in Germany The study was not blinded, and all participants were included in the analyses
Participants	12 patients with severe plaque psoriasis (n = 4), severe atopic dermatitis (n = 4), or severe hyperkeratotic eczema (n = 4) Dropouts: none **Inclusion criteria** • Resistance to topical therapy • Severity score of at least 16 points in self-created scoring system (see outcomes)
Interventions	**Intervention** • PUVA cream therapy with 8-methoxypsoralen (8-MOP) 4 times a week • PUVA bath therapy 4 times a week Participants were followed up for an additional 8 weeks after the end of treatment. Exact duration of treatment and number of treatments were not clear
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes**

Grundmann 1999 *(Continued)*

	• Investigator-rated severity score for each item on each hand and/or foot for erythema, scaling, infiltration, pustulation, and hyperkeratosis from 0 to 4 (0 = no symptoms, 4 = maximum), resulting in a total score of 20 every week • Investigator-rated improvement in total score (0 to 4 excellent, 5 to 8 good) every week
Notes	RCT on different dermatoses among hand eczema. We were unable to reconstruct the results from the paper among participants with hand eczema, and we were unsuccessful in locating the study authors

Haddican 2014

Methods	Randomised double-blind vehicle-controlled parallel-group study
Participants	60 patients with hand and/or foot eczema **Inclusion criteria** • > 18 years of age • Written and informed consent • Clinical diagnosis of HFD affecting at least 1 hand or foot • Physician Global Assessment (PGA) of at least 3 (moderate) for HFD • Negative urine pregnancy test for females of child-bearing potential • Approved method of birth control for females of child-bearing potential **Exclusion criteria** • Pregnant or breastfeeding females • Known or suspected intolerance to retapamulin 1% ointment or clobetasol propionate 0.05% foam • Any overt signs of skin atrophy, telangiectasias, and/or striae in the treatment area • Any known history of active skin malignancy • Use of any topical corticosteroids, topical antibiotics, topical immunosuppressants, other topical therapies (tar, calcineurin inhibitors), or phototherapy within 8 weeks of the baseline visit • Use of any systemic corticosteroid, systemic antibiotic, or systemic immunosuppressant therapies within 8 weeks of baseline visit
Interventions	**Intervention** • Clobetasol propionate 0.05% foam twice-daily application to the hands or feet for 2 weeks and retapamulin 1% ointment twice-daily application to anterior nares and the hands or feet for 5 consecutive days • Clobetasol propionate 0.05% foam twice-daily application to the hands or feet for 2 weeks and vehicle (placebo) ointment application twice daily to anterior nares and the hands or feet for 5 consecutive days
Outcomes	**Primary outcomes of the trial** Proportion of participants with a PGA of clear or almost clear at day 6, day 15, and day 28 compared to baseline **Other outcomes** • Portion of participants with intranasal and hand/foot *S aureus* carriage rates • Portion of participants with methicillin resistance in S aureus isolates • Comparison of mean PGA score for participants with and without *S aureus* present in the target lesion, the proportion of participants in each treatment group who were culture-positive for *S*

Haddican 2014 *(Continued)*

	aureus on the skin, nares, or both at baseline, who were also culture-negative on both the skin and nares and clear/almost clear based on PGA at follow-up visits
Notes	RCT on hand and foot dermatitis combined. It was not possible to extract from the paper results of hand eczema participants

Handa 1988

Methods	Randomised parallel-group study
Participants	100 patients with moderate to severe eczema or other steroid-responsive dermatoses including eczema (n = 45), lichen simplex chronicus (n = 27), atopic dermatitis (n = 14), psoriasis (n = 4), contact dermatitis (n = 2), stasis dermatitis (n = 2), seborrhoeic dermatitis (n = 1), actinic dermatoses (n = 1), unclear (n = 4) Dropouts: 4 **Inclusion criteria** • Moderate to severe eczema or another steroid-responsive disorder • Over 12 years of age **Exclusion criteria** • Lesions associated with tuberculosis or viral infection • Requirement of another systemic or topical intervention for the primary diagnosis
Interventions	**Intervention** • Alclometasone dipropionate 0.05% ointment twice a day without occlusion for 3 weeks • Hydrocortisone 1.0% ointment twice a day without occlusion for 3 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Investigator-rated severity score for each item: erythema, induration, and pruritus from 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe) at baseline and at weeks 1, 2, and 3 • Investigator-rated overall severity score: clearing = 100% improvement; marked improvement = 75% to 99% improvement; moderate improvement = 50% to 74%; slight improvement = 25% to 49%; no change < 25% improvement • Adverse events
Notes	RCT on different dermatoses. It was impossible to extract from the paper the results of hand eczema participants, and we were unable to locate the study authors

IRCT201112018263N1

Methods	Double-blind randomised parallel-group design, placebo-controlled
Participants	70 patients with moderate to severe hand eczema, aged 12 to 70 years **Exclusion criteria**

IRCT201112018263N1 *(Continued)*

- Treatment with systemic steroid less than 1 month before the trial
- Treatment with topical steroid and antihistamines at the time of presentation
- Pregnancy
- Lactation
- Younger than 12 years

Interventions	**Intervention** • Doxepine 5% cream applied twice daily for 8 days and clobetasol 0.05% applied twice daily for 8 days **Control intervention** • Placebo and clobetasol 0.05% applied twice daily for 8 days
Outcomes	**Primary outcome of the trial** • Reduction or improvement in hand eczema before and 8 days after treatment measured with the hand eczema severity index (HECSI) **Secondary outcomes of the trial** • Adverse events 8 days after initiation of treatment
Notes	Recruitment completed Study authors contacted for additional information on 20 February 2014, but they remained unresponsive Sponsor: Shahid Sadoughi University of Medical Sciences, Yazd

IRCT201212303734N2

Methods	Randomised double-blind parallel-group study
Participants	108 patients with hand eczema confirmed by a dermatologist **Inclusion criteria** • 18 to 75 years of age • Eager to participate in the trial • With hand eczema confirmed by a dermatologist **Exclusion criteria** • Pregnancy and lactation • Application of topical drugs during previous 2 weeks • Systemic therapies such as corticosteroids • Immunosuppressive drugs and antibiotics during the past 4 weeks • Localised hand infection • History of allergic reaction to study medication
Interventions	**Intervention** • Anti Dry cream (contains Aloe Vera essence, Geranium essence, Lavander essence, respectively, with ratio of 50:1:15 in vanishing cream), 1 fingertip unit (0.5 grams) for 10 × 10 cm^2, twice daily for 2 weeks

IRCT201212303734N2 *(Continued)*

	• Fluocinolone acetonide cream 0.025%, twice daily, for 2 weeks
Outcomes	**Primary outcome of the trial** • Change in signs and symptoms of hand eczema on day 14 compared to day 0, measured by a questionnaire containing clinical signs and symptoms: erythema, scaling, lichenification/hyperkeratosis, oedema, vesicle, fissure, pruritus, and pain **Secondary outcomes of the trial** • Adverse events • Change in pruritus, erythema and scaling, bullae
Notes	Sponsor: Barij Essence Herbal Medicine Research Center Current status: recruiting

Lassus 1981

Methods	Randomised within-participant study Probably conducted at a single centre in Finland This study claims to be double-blind
Participants	80 patients with various symmetrical eczemas: allergic eczema (n = 27), atopic dermatitis (n = 21), toxic hand eczema (n = 10), chronic eczema (n = 7), stasis eczema (n = 5), nummular eczema (n = 4), neurodermatitis (n = 3), dyshidrotic eczema (n = 2), seborrhoeic eczema (n = 1) and 40 participants with psoriasis Dropouts: probably none Inclusion and exclusion criteria were not stated
Interventions	All participants were first treated with placebo for 1 week. Afterwards, they were randomised **Intervention** • Budesonide 0.025% ointment twice daily probably with occlusive dressing • Betamethasone-17-valerate 0.1% ointment twice daily probably with occlusive dressing Duration is not really clear from the article, but probably 2 weeks
Outcomes	**Primary outcomes of the trial** Not defined **Other outcomes** • Investigator-rated severity for itching, scaling, erythema, and induration from 0 to 4 (0 = absent, 4 = very severe) at baseline, week 1, and week 2 • Investigator-rated overall expression of response at baseline, week 1, and week 2 • Participant-rated overall expression of response at baseline, week 1, and week 2 • Adverse events
Notes	RCT on different forms of symmetrical eczema; this study is published alongside a study on psoriasis. We were unable to reconstruct the results in participants with hand eczema, and we were unsuccessful in locating study authors

NCT00404196

Methods	Double-blind randomised parallel-group design
Participants	75 patients with clinical diagnosis of hand eczema with or without atopic aetiology/background **Inclusion criteria** • Clinical diagnosis of hand eczema with or without atopic aetiology/background • Investigators Global Assessment of disease severity graded as at least mild at visit 1 • Caucasian males 18 years of age or older • Attending a hospital outpatient clinic or the private practice of a dermatologist • Following receipt of verbal and written information about the trial, the patient must provide signed and dated informed consent before any trial-related activity is carried out, including activities related to washout periods **Exclusion criteria** • Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporin, azathioprine) or corticosteroids within 4 weeks before randomisation (inhaled or intranasal steroids for asthma or rhinitis may be used) • PUVA or UVB therapy on the hands within 4 weeks before randomisation • Topical treatment with immunomodulators (pimecrolimus, tacrolimus) or corticosteroids from WHO groups III and IV on the hands within 2 weeks before randomisation • Other topical therapy on the hands (except for use of emollients) within 1 week before randomisation • Use of other treatment (drug, non-drug) on the hands during the study except for use of investigational product and emollient • Concurrent skin disease on the hands • Current diagnosis of exfoliative dermatitis • Significant clinical infection (impetiginised hand eczema) on the hands that requires antibiotic treatment • Known or suspected hypersensitivity to component(s) of the investigational product • Positive patch test as defined in Section 11.7.4.2 of the protocol • Known or suspected severe renal insufficiency or severe hepatic disorders • History/signs/symptoms suggestive of an abnormality of calcium homeostasis associated with clinically significant hypercalcaemia • History of cancer except for basal cell carcinoma • Current participation in any other interventional clinical trial • Received treatment with any non-marketed drug substance (i.e. an agent that has not yet been made available for clinical use following registration) within 4 weeks before randomisation • Previously randomised in this study • Patients known or, in the opinion of the investigator, unlikely to comply with the Clinical Study Protocol (e.g. alcoholism, drug dependency, psychotic state)
Interventions	**Intervention** • LEO19123 cream (calcipotriol 50 mcg/g and LEO80122 0.6 mg/g) for 3 weeks • LEO19123 cream (calcipotriol 15 mcg/g and LEO80122 0.2 mg/g) for 3 weeks • LEO19123 cream vehicle alone for 3 weeks
Outcomes	**Primary outcome of the trial** • Proof of concept **Secondary outcomes of the trial**

NCT00404196 *(Continued)*

	• Safety
Notes	Sponsor: LEO Pharma Study has been completed; john.english@nuh.nhs.uk was contacted on 20 February 2014. However, he was not at liberty to disclose information regarding the study. We therefore contacted LEO Pharma, which was unresponsive

NCT00614289

Methods	Double-blind randomised within-participant design
Participants	30 patients with hand eczema **Inclusion criteria** • 18 years of age or older • Mild to moderate hand dermatitis, according to Investigator Global Assessment • Generally healthy, as determined by brief medical history • Negative urine test for pregnancy if female, and use of highly effective method of birth control, such as condoms and spermicide, implants, injectables, combined oral contraceptives, intrauterine device (IUD), sexual abstinence, or a vasectomised partner. For those using a hormonal contraceptive method, the dose and type of contraception should stay constant 1 month before enrolment and throughout the study • Capable of understanding and signing the consent form **Exclusion criteria** • Clinically relevant allergic or irritant contact dermatitis and inability to avoid exposure • Severe and very severe hand dermatitis according to the Investigator Global Assessment • Severe vesiculation or bullae • History of psoriasis, contact urticaria, and/or pustular disease of the hands • Therapy for the hands with potent topical corticosteroids within 1 month of enrolment • Use of systemic treatment with oral retinoids, corticosteroids, or PUVA within 8 weeks before the beginning of the study • History of alcoholism or drug abuse • History or current evidence of a chronic or infectious skin disease • Pregnant or lactating females, or using method of birth control that does not comply with highly effective methods of birth control listed under inclusion criteria; pregnant or lactating females, or using method of birth control that does not comply with highly effective methods of birth control listed under inclusion criteria
Interventions	This study is designed as a prospective, randomised, double-blind right/left comparison of Epikeia coatings to improve hand dermatitis
Outcomes	**Primary outcomes of the trial** • Investigator Global Assessment after 85 days within participant (test versus control hands) • Hand Eczema Area and Severity Scores after 85 days (within-participant comparison) **Secondary outcomes of the trial** • Ordinal scales measuring subjective efficacy, pain, and itching during 85 days
Notes	Sponsor: Biomedical Development Corporation

NCT00614289 *(Continued)*

	Study has been completed; however we were unable to obtain data from the study authors, who were unresponsive

NCT00843466

Methods	Randomised open-label parallel-group study
Participants	46 patients who experience mild to moderate hand dermatitis induced by frequent cleansing **Inclusion criteria** • 18 to 65 years of age • General good health • Hands free of cuts and abrasions • Agrees to adhere to the requirements listed in the informed consent • Willing and able to use a mild, moisturising, non-antibacterial cleanser for all handwashing purposes for the duration of the test period • Willing to refrain from participating in any other clinical research trial for the duration of the study **Exclusion criteria** • Documented allergies to study product components, soaps, latex, or fragrances • History of the following conditions, which may affect response of the skin or interpretation of results: insulin-dependent diabetes, peripheral vascular disease • Participating in a concurrent clinical study involving treatment of the hands • Currently using a prescription medication for hand dermatitis
Interventions	**Intervention** • A test product (mild, moisturising hand cleanser) for all hand cleansing needs during the duration of the study. **Control intervention** • No Intervention: the control group will continue to use their current cleanser for handwashing
Outcomes	**Primary outcome of the trial** • Efficacy of mild, moisturising hand cleanser for improvement in hand dermatitis from frequent handwashing after 4 weeks
Notes	Sponsor: Wake Forest School of Medicine Study authors were contacted for additional information; they informed us that trial results were marginal and this exploratory study was the terminus of this line of investigation, but we were unable to obtain additional information

NCT00867607

Methods	Double-blind randomised cross-over design
Participants	80 patients 18 to 65 years of age with bilateral allergic contact dermatitis of the hands and forearms **Inclusion criteria**

NCT00867607 *(Continued)*

- Healthy adult men and women between 18 and 65 years old
- Male or non-pregnant female patients who agree to comply with applicable contraceptive requirements
- Satisfactory medical assessment with no clinically significant and relevant abnormalities (of medical history, physical examination, clinical or laboratory evaluation (haematology, biochemistry, urinalysis)) as determined by the Principal Investigator that might interfere with assessment of dermatitis or assessment of the safety or efficacy of the Study Drug
- Must understand and must be able, willing, and likely to fully comply with study procedures and restrictions
- Can understand and provide written informed consent to participate in the study, in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 and applicable regulations
- Mild to moderate bilateral allergic contact dermatitis on each hand, possibly extending to the forearm, according to Physicians Visual Assessment (PVA). Mild to moderate disease is considered a PVA score of 10 or greater, and there should be no more than a 1-point difference between hands
- Positive reaction to the Standard European Series patch testing kit (Chemotechnique Diagnostics Products, Malmo, Sweden) after application for 2 days

Exclusion criteria

- Current or recurrent disease that could affect the action, absorption, or disposition of the Study Drug, or clinical or laboratory assessments
- Used topical antihistamines in the past 2 weeks, topical corticosteroids, or received psoralen plus ultraviolet light therapy (PUVA) in the past 4 weeks, or have taken oral retinoids, corticosteroids in the past 8 weeks (inhaled or intranasal corticosteroids are allowed, if stable dose)
- Used any prescription or OTC medication (excluding hormonal contraceptive, hormonal replacement therapy, inhaled or intranasal corticosteroids, or oral NSAIDs) that, in the opinion of the Principal Investigator, could affect (improve or worsen) the condition being studied, or could affect the action, absorption, or disposition of the Study Drug, or clinical or laboratory assessments
- Must not have used another investigational product or taken part in a clinical trial within the last 30 days before enrolment
- Female patients who are pregnant or lactating, including those with a positive pregnancy test at screening
- Patient known to have a positive hepatitis virus test (hepatitis B virus surface antigen or hepatitis C virus antibody) or a positive human immunodeficiency virus (HIV) antibody test
- History of hypersensitivity to any of the Study Drugs or their excipients
- Any other significant dermatological condition that affects > 10% of the body surface area, or general medical condition that could interfere with the study evaluation
- Any significant medical condition that could compromise immune responsiveness
- History of alcoholism or drug abuse

Interventions

Intervention

• MRX-6 (2%) twice daily for 21 days

• MRX-6 (1%) twice daily for 21 days

• MRX-6 (0.2%) twice daily for 21 days

• Steroid twice daily for 21 days

Outcomes

Primary outcome of the trial

- Safety and tolerability of 3 dose levels of topical MRX-6 (0.2%, 1.0%, and 2% HyPE) when administered twice daily for 21 consecutive days

Secondary outcomes of the trial

NCT00867607 *(Continued)*

	• Difference in percentage change in each participant's total Physicians Visual Assessment (PVA) score from baseline to day 21 between vehicle- and MRX-6-treated hands/forearms
Notes	Sponsor: Hadassah Medical Organization

NCT00890968

Methods	Double-blind randomised parallel-group design
Participants	56 adults with chronic hand dermatitis **Inclusion criteria** • Clinical diagnosis of stable chronic hand dermatitis (greater than 6 weeks in duration) that is KOH-negative • Dermatitis of mild to moderate severity, as defined by an Investigator's Global Assessment (a score of 2 or 3 on the Target Hand) • Individual signs of hand dermatitis disease of at least mild scaling and mild erythema (a score of 2 or more on the Target Hand) • Written informed consent **Exclusion criteria** • Female and pregnant, lactating, or planning to become pregnant during the study • Spontaneously improving or rapidly deteriorating hand dermatitis at the time of enrolment; possible history of waxing and waning disease in the past • History of hand dermatitis that has been shown to be unresponsive to super-potent (Group 1) topical steroids • Concurrent flaring of inflammatory skin disease (e.g. atopic dermatitis, psoriasis) anywhere on the body outside the study areas • Bullous disorders or hand, foot, and mouth disease (HFMD); however, patients with dyshidrotic hand dermatitis or pompholyx are allowed to participate provided they meet all other Inclusion/Exclusion criteria • Known allergic mediated hand dermatitis (e.g. allergic to latex) • Concurrent skin disease in the study area that requires concomitant topical treatment (e.g. tinea manuum, scabies, infected eczema, paronychia) that could interfere with evaluation of his/her dermatitis • Pustular diseases of the hands (e.g. acrodermatitis perstans continua) • Used phototherapy, photochemotherapy, systemic immunomodulatory therapy (such as systemic corticosteroids, methotrexate, retinoids, or cyclosporin), or other therapy within 30 days before the first application of study medication that is known or suspected, in the opinion of the investigator, to have an effect on hand dermatitis • Prolonged exposure to natural or artificial sources (e.g. UVB, UVA) of ultraviolet radiation within 30 days before the first application of study medication or intending to have such exposure during the study • Received intralesional therapy to the hands (e.g. corticosteroids) within 30 days before first application of study medication • Treated with Grenz ray or soft X-ray therapy to the hands within 6 months of first application of study medication • Treated with topical hand therapy (e.g. tar, topical corticosteroids, topical retinoids, topical antimicrobials, topical calcineurin inhibitors, Burrow's solution soaks) within 7 days before first application of study medication that is known or suspected to have an effect on hand dermatitis • Received systemic antibiotic for infection of the hands within 7 days before the first application of study medication
Interventions	**Intervention**

NCT00890968 *(Continued)*

	• Triamcinolone acetonide (TAC) DuraPeel topical gel once daily (nightly) for total duration of 4 weeks **Control intervention** • Placebo: placebo DuraPeel topical gel once daily (nightly) for a total duration of 4 weeks
Outcomes	**Primary outcome of the trial** • Response as assessed by Investigator Global Assessment (IGA) at baseline, week 1, week 2, and week 4 **Secondary outcomes of the trial** • Subjects' Global Impression of Change (SGIC) at week 4 (end-of-treatment) • Individual primary parameters of hand dermatitis at baseline, week 1, week 2, and week 4 • Signs or symptoms of hand dermatitis at baseline, week 1, week 2, and week 4 • Participant's self-assessment of overall hand disease at baseline and week 4 • Study medication assessment at week 1, week 2, and week 4
Notes	Study has been completed; additional information was requested on 20 February 2014; however study authors were unresponsive Sponsor: ZARS Pharma Inc.

NCT01950494

Methods	A randomised double-blind placebo-controlled parallel-group study
Participants	20 patients with moderate to severe hand eczema **Inclusion criteria** • Informed consent must be signed and understood by patient • Symptoms and history consistent with hand dermatitis based on symptoms and clinical history • Male or female, 18 to 70 years of age, in generally good health, with no significant underlying systemic disease requiring ongoing medications • Hand eczema severity index (HECSI) with a score greater than 50 • Physician global assessment (PGA) of moderate to severe (PGA: severe, moderate, mild, almost clear, clear) **Exclusion criteria** • Topical corticosteroid or calcineurin inhibitor treatment of the hands and forearms during the last 7 days before enrolment • Systemic treatment with corticosteroids or other immunosuppressives during the last 14 days • Currently receiving (or received during the previous 4 weeks) other investigational drugs, treatments, or devices, or participating in another clinical study • Treatment with ultraviolet (UV) light (including tanning) during the previous 4 weeks • Acute dermatitis outbreak on the arms or hands • Unable to comply with protocol restrictions • Known to be unreliable or non-compliant with medical treatment, or unwilling to comply with multiple return visits • Any condition or prior/present treatment that in the opinion of investigators should render the participant ineligible for the study • Known allergy to benzalkonium chloride or other ingredients in the fiteBac vehicle

NCT01950494 *(Continued)*

Interventions	**Intervention** • FiteBac Hand Sanitizer **Control intervention** • Placebor: blinded emollient therapy
Outcomes	**Primary outcome of the trial** • Efficacy of fiteBac compared to emollient therapy after 1 month via standardised questionnaires, physical findings, and photography over a 1-month treatment period in adults with hand dermatitis **Other outcomes of the trial** • Bacterial counts after 1 month • Physician Global Assessment after 1 month, with excellent response defined as clear or almost clear hands • Number of adverse events • Number of flares during 1 month • Number of study discontinuations during 1 month • Patients Global Assessment score after 1 month
Notes	Both contact persons were emailed for additional information on 19 February 2014 but did not respond to our request for additional information Sponsor: National Jewish Health

8-MOP: 8-methoxypsoralene.
AEs: adverse events.
BCC: basal cell carcinoma.
DASI: Dyshidrotic eczema Area and Severity Index.
GCP: Good Clinical Practice.
HECSI: hand eczema severity index.
HFMD: hand foot and mouth disease.
ICH: International Conference on Harmonisation.
IGA: investigators' global assessment.
IUD: intrauterine device.
mTLSS: modified total lesion symptom score.
NSAIDs: non-steroidal anti-inflammatory drugs.
OTC: over-the-counter.
PaGA: participants' global assessment.
PASI: Psoriasis Area and Severity Index.
PGA: physicians' global assessment.
PUVA: (topical and oral) psoralen combined with UVA.
PVA: physicians visual assessment.
RCT: randomised controlled trial.
SCC: squamous cell carcinoma.
SGIC: subjects' global impression of change.
TAC: triamcinolone acetonide.
TLSS: total lesion symptom score.
UV: ultraviolet.
UVA: ultraviolet A.
UVB: ultraviolet B.
VAS: visual analogue scale.
WHO: World Health Organization.

Characteristics of ongoing studies *[ordered by study ID]*

IRCT2014012916412N1

Trial name or title	Effects of pumpkin (Moschata cucurbita) ointment on chronic hand eczema Official title: Effect of topical pumpkin, traditional medicine products, on the chronic hand eczema
Methods	Randomised double-blind parallel-group placebo-controlled study
Participants	60 patients with moderate chronic hand eczema **Inclusion criteria** • Interested in participating in the study • 18 to 60 years of age • Mild to moderate chronic hand eczema according to criteria HECSI (occupational dermatitis, atopic dermatitis, contact dermatitis irritant) • Non-use of oral corticosteroids during the last 2 months • Lack of local immunosuppressors within 4 weeks before treatment • Lack of pregnancy and lactation • No history of contact dermatitis to prescription drugs • Lack of local infection • No obsessive and excessive washing with water and detergent • Absence of immunosuppressive disease **Exclusion criteria** • History of allergy to drugs • Use of oral or topical corticosteroids during the 4 weeks before the study • Local infection at the site of the lesion eczema • Women during pregnancy or lactation • Severe obsessive washing • Physical or mental disorders that interfere with participation in the study
Interventions	**Intervention** • Betamethasone ointment twice a day for 1 month • Almond ointment twice a day for 1 month • Eucerin ointment twice a day for 1 month • Pumpkin ointment twice a day for 1 month
Outcomes	**Primary outcome of the trial** • Hand Eczema Severity Index • Dermatology Life Quality Index **Secondary outcomes of the trial** • Skin reactions • Recovery rates
Starting date	September 2014
Contact information	Alemeh Khademi Imam Khomeini Hospital

IRCT20140129164l2N1 *(Continued)*

	Islamic Republic of Iran Skin Clinic, Imam Khomeini Hospital, Keshavarz bulv Tehran 00982166595911 00989171132340 00 alemehkhadi@gmail.com
Notes	Sponsor: Vice Chancellor for Research at Tehran University School of Traditional Medicine

IRCT2017070922965N10

Trial name or title	Effect of topical atorvastatin on hand eczema Official title: Evaluating the effect of topical atorvastatin as adjuvant therapy in treatment of hand eczema
Methods	Randomised double-blind placebo-controlled parallel-group study
Participants	70 patients with moderate to severe eczema **Inclusion criteria** • 18 to 65 years old • Moderate to severe eczema • Less than 25% of the skin involved • Discontinuation of glucocorticoid agents 4 weeks before the investigation • Discontinuation of antipruritus agents 1 week before the investigation **Exclusion criteria** • Younger than 18 years of age • Inflammatory skin disease • Pregnant woman
Interventions	**Intervention** • Betamethasone ointment plus atorvastatin 5% cream 2 times per day for 10 days • Control group: betamethasone ointment plus placebo atorvastatin 5% cream 2 times per day for 10 days
Outcomes	**Primary outcome of the trial** • Hand eczema index for severity of eczema on day 5 and day 10
Starting date	2017-08-19
Contact information	Maryam Mehrpooya Hamedan University of Medical Sciences Shahid Fahmide Avenue Hamedan

IRCT2017070922965N10 *(Continued)*

	Iran (Islamic Republic of) +98 81 3838 1594 m_mehrpooya2003@yahoo.com
Notes	Sponsor: Vice Chancellor for Research, Hamadan University of Medical Sciences

ISRCTN80206075

Trial name or title	Comparison of alitretinoin with PUVA as the first line treatment in patients with severe chronic hand eczema: a randomised controlled trial
Methods	Randomised open-label parallel-group design

Participants	500 to 780 participants with severe chronic hand eczema
	Inclusion criteria
	• Aged ≥ 18 years at the time of signing the informed consent form
	• Uncontrolled, severe chronic hand eczema defined as the presence of both of the following criteria:
	  ○ PGA score of severe
	  ○ Resistance to treatment with potent topical corticosteroids for ≥ 4 weeks before the point of eligibility screening
	• Avoidance strategies for known contact allergens in place for at least a 2-week period before randomisation
	• Has provided written informed consent
	• Expected to comply with treatment and protocol schedule
	Exclusion criteria
	• An extensive list including skin-related, treatment-related, and general exclusion criteria

Interventions	**Intervention** • Alitretinoin 30 mg a day for 12 to 24 weeks • Immersion PUVA (twice weekly) for 12 to 24 weeks
Outcomes	**Primary outcome of the trial** • Disease activity of the index hand, quantified by the HECSI tool, at 12 weeks post planned start of treatment **Secondary outcomes of the trial** • Disease activity of the index hand, quantified by the HECSI tool, at 24 and 52 weeks post planned start of treatment • Disease activity of the index hand, quantified by the mTLSS tool, at 24 and 52 weeks post planned start of treatment • Disease activity of the index hand, quantified by the PGA tool at 24 and 52 weeks post planned start of treatment • Time to relapse of the index hand (HECSI score > 75% baseline HECSI score of the index hand) • Time in remission of the index hand (defined by the period when the participant is classed as clear/almost clear until the disease is scored as 'mild' or higher on the PGA scale, and participants have been using topical corticosteroids daily for the previous 7 or more days) • Patient-reported outcome using the DLQI tool, over the 52 weeks post planned start of treatment

ISRCTN80206075 *(Continued)*

	• Patient-reported outcome using the PBI-HE over the 52 weeks post planned start of treatment • PeDeSi over the 52 weeks post planned start of treatment • Cost-effectiveness over the 52 weeks post planned start of treatment
Starting date	01/01/2015
Contact information	Dr. Victoria Goss (Senior Trial Coordinator) ctru-alpha@leeds.ac.uk
Notes	The study protocol is published at http://www.nihr.ac.uk/__data/assets/pdf_file/0005/136994/PRO-12-186-01.pdf Sponsor: Unversity of Leeds (UK)

JPRN-UMIN000003326

Trial name or title	A clinical trial to determine the effect of olopatadine on itching in hand eczema
Methods	Randomised single-blind (participants are blinded) parallel-group placebo-controlled study
Participants	50 patients with hand eczema and itch **Inclusion criteria** • Outpatients • Hand eczema patients with itch • Able to provide their own written informed consent for taking part in the study • Male and female • Over 20 years of age **Exclusion criteria** • Treated with oral or injectable steroids • Under specific or aspecific modulation therapy • With severe hepatic or renal disorders • Pregnant or lactating women and women who may be pregnant
Interventions	**Intervention** • Olopatadine-treated group **Control intervention** • Placebo olopatadine non-treated group
Outcomes	**Primary outcome of the trial** • Visual analogue scale **Secondary outcomes of the trial** • Skin index
Starting date	1 March 2010
Contact information	Kaoru Takayama

JPRN-UMIN000003326 *(Continued)*

	Tokyo Medical and Dental University Dermatology Department Dermatology Bukyou-ku 1-5-45 Japan tkaoru.derm@tmd.ac.jp Telephone: +81-358035286
Notes	Sponsor: Department of Dermatology, Tokyo Medical and Dental University Current status: recruiting

NCT02664805

Trial name or title	Proof of concept, twice daily applications of LEO 124249 ointment in the treatment of chronic hand eczema Official title: A phase 2a, proof of concept trial, testing twice daily applications of LEO 124249 ointment in the treatment of chronic hand eczema
Methods	Randomised double-blind vehicle-controlled parallel-group study
Participants	91 patients with chronic hand eczema **Inclusion criteria** • Clinical diagnosis of chronic hand eczema with or without atopic aetiology/background with a history of not adequately controlled disease activity with cutaneously applied steroid • Physician's Global Assessment of disease severity graded as at least mild at visit 1 • In overall good health, including well-controlled disease **Exclusion criteria** • Systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine), retinoids (e.g. alitretinoin), or corticosteroids within 6 weeks before randomisation (inhaled or intranasal steroids corresponding to up to 1 mg prednisone for asthma or rhinitis may be used) • PUVA (psoralen ultraviolet A) or UVB (ultraviolet B) therapy on the hands within 4 weeks before randomisation • Cutaneously applied treatment with immunomodulators (pimecrolimus, tacrolimus) or corticosteroids on the hands within 2 weeks before randomisation • Use of systemic antibiotics or cutaneously applied antibiotics on the hands within 2 weeks before randomisation • Concurrent skin disease on the hands • Current diagnosis of exfoliative dermatitis • Significant clinical infection (impetiginised hand eczema) on the hands that requires antibiotic treatment • Markedly abnormal ECG at baseline • Known hepatic dysfunction or hepatic dysfunction tested at screening • Current participation in any other interventional clinical trial
Interventions	**Intervention** • LEO 124249 ointment twice-daily cutaneous application for 8 weeks

NCT02664805 *(Continued)*

	Control intervention • LEO 124249 ointment vehicle twice-daily cutaneous application for 8 weeks
Outcomes	**Primary outcome of the trial** • Treatment success according to Physician's Global Assessment (PGA) at end of treatment (8 weeks). Treatment success according to the PGA is defined as follows: subjects having mild disease at baseline must achieve clear. Subjects having moderate or severe disease at baseline must achieve clear or almost clear **Secondary outcomes of the trial** • Hand Eczema Severity Index (HECSI) at end of treatment (8 weeks) • Participants with treatment success according to the Patient's Global Assessment of disease severity (PaGA) at end of treatment (8 weeks). Treatment success according to the PaGA is defined as follows: Subjects having very mild or mild disease at baseline must achieve clear. Subjects having moderate or severe disease at baseline must achieve clear or very mild
Starting date	February 2016
Contact information	Prof. Dr. Margitta Worm, Allergie-Centrum-Charité Klinik für Dermatologie, Venerologie und Allergologie Berlin, Germany 10117
Notes	Sponsor: LEO Pharma

NCT03026907

Trial name or title	Efficacy of oral alitretinoin versus oral azathioprine in patients with severe chronic non-hyperkeratotic hand eczema. A randomized prospective open-label trial with blinded outcome assessment
Methods	Randomised observer-blind vehicle-controlled parallel-group study
Participants	116 patients with severe chronic non-hyperkeratotic hand eczema **Inclusion criteria** • ≥ 18 years and ≤ 75 years of age • Severe or very severe chronic non-hyperkeratotic hand eczema for a minimum duration of 3 months as defined by a Physician Global Assessment (PGA) using a validated Photoguide • Refractory to standard therapy, defined as follows: patients received treatment with topical corticosteroids of class II or higher for at least 8 weeks within 3 months before enrolment, with no response or a transient response. Patients had also received standard skin care, including emollients and barrier protection as appropriate, without significant improvement. Patients had avoided irritants and allergens, if identified, without significant improvement • Women of child-bearing potential are required to use at least 2 forms of contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after finishing treatment; these women are required to take monthly pregnancy tests • Able to provide written informed consent • Able to speak and read the Dutch language **Exclusion criteria** • Extensive list

NCT03026907 *(Continued)*

Interventions	**Intervention** • Oral alitretinoin capsule of 30 mg once daily for a total of 24 weeks • Oral azathioprine tablets twice daily at a dose of 1.5 or 2.5 mg/kg/d, depending on thiopurine methyltransferase (TPMT) activity
Outcomes	**Primary outcome of the trial** • Response to treatment/hand eczema severity (Photoguide) after 24 weeks (end of treatment) **Secondary outcomes of the trial** • Response to treatment/hand eczema severity (Photoguide) after 12 weeks • Response to treatment/hand eczema severity based on th Hand Eczema Severity Index (HECSI) at weeks 4, 8, 12, and 24 • Time to response at weeks 4, 8, 12, and 24 • Patient-reported improvement based on the Patient Global Assessment (PaGA) at weeks 12 and 24 • Adverse events up to 24 weeks • Cost utility. QALYs: registered direct/indirect costs, combined with EQ-5D outcome at weeks 12 and 24 • Cost-effectiveness: registered direct/indirect costs combined with primary and secondary effectiveness outcomes (Photoguide/HECSI) at weeks 12 and 24 • Quality of life: questionnaire at weeks 12 and 24
Starting date	May 2016
Contact information	Marie-Louise A. Schuttelaar, MD, PhD University Medical Center Groningen The Netherlands +31503612520 m.l.a.schuttelaar@umcg.nl
Notes	Sponsor: University Medical Center Groningen

NCT03026946

Trial name or title	Efficacy of oral alitretinoin versus oral cyclosporine in patients with severe recurrent vesicular hand eczema. A randomised prospective open-label trial with blinded outcome assessment
Methods	Randomised observer-blind vehicle-controlled parallel-group study
Participants	116 patients with severe or very severe recurrent vesicular hand eczema **Inclusion criteria** • Severe or very severe recurrent vesicular hand eczema for a minimum duration of 3 months as defined by a Physician Global Assessment (PGA) using a validated Photoguide • ≥ 18 years and ≤ 75 years of age • Severe or very severe chronic non-hyperkeratotic hand eczema for a minimum duration of 3 months as defined by a Physician Global Assessment (PGA) using a validated Photoguide

NCT03026946 *(Continued)*

	• Refractory to standard therapy, defined as follows: patients received treatment with topical corticosteroids of class II or higher for at least 8 weeks within 3 months before enrolment, with no response or a transient response. Patients had also received standard skin care, including emollients and barrier protection as appropriate, without significant improvement. Patients had avoided irritants and allergens, if identified, without significant improvement • Women of child-bearing potential are required to use at least 2 forms of contraception for at least 1 month before starting treatment, during treatment, and for at least 1 month after finishing treatment; these women are required to take monthly pregnancy tests • Able to provide written informed consent • Able to speak and read the Dutch language **Exclusion criteria** Extensive list
Interventions	**Intervention** • Oral alitretinoin capsule of 30 mg once daily for a total of 24 weeks • Oral cyclosporine A starting dose 5 mg/kg/d (split into 2 doses), with decreasing dose after 8 weeks to 3 to 3.5 mg/kg/d (split into 2 doses). The treatment period is 24 weeks
Outcomes	**Primary outcome of the trial** • Response to treatment/hand eczema severity (Photoguide) after 24 weeks (end of treatment) **Secondary outcomes of the trial** • Response to treatment/hand eczema severity (Photoguide) after 12 weeks • Response to treatment/hand eczema severity based on the Hand Eczema Severity Index (HECSI) at weeks 4, 8, 12, and 24 • Time to response at weeks 4, 8, 12, and 24 • Patient-reported improvement based on the Patient Global Assessment (PaGA) at weeks 12 and 24 • Adverse events up to 24 weeks • Cost-utility. QALYs: registered direct/indirect costs, combined with EQ-5D outcome at weeks 12 and 24 • Cost-effectiveness: registered direct/indirect costs combined with primary and secondary effectiveness outcomes (Photoguide/HECSI) at weeks 12 and 24 • Quality of Life: questionnaire at weeks 12 and 24
Starting date	1 March 2017
Contact information	Marie-Louise A Schuttelaar, MD, PhD University Medical Center Groningen The Netherlands +31503612520 m.l.a.schuttelaar@umcg.nl
Notes	Sponsor: University Medical Center Groningen ZonMw: The Netherlands Organisation for Health Research and Development

PACTR201704002194318

Trial name or title	Assessment of botulinum toxin type A in the treatment of hand eczema
Methods	Randomised double-blind placebo-controlled parallel-group study
Participants	60 patients with hand eczema **Inclusion criteria** • Active symptomatic palmar hand eczema • Bilateral involvement • 18 to 70 years of age **Exclusion criteria** • Skin infection at the site of injection • History of use of botulinum toxin in the last 4 months • Pregnancy, lactation in females • Any contraindication to botulinum toxin injection including associated disorder that may affect neuromuscular function, like myasthenia gravis and Lambert-Eaton disease • History of previous allergy to BTXA
Interventions	**Intervention:** • Intradermal palmar injection of a minimum of 50 units of botulinum toxin type A combined with topical corticosteroids • Topical betamethasone twice daily
Outcomes	**Primary outcome of the trial** • Visual linear analogue scale of pruritus at baseline at the third day, end of first week, fourth week, then monthly for a whole period of 6 months **Secondary outcomes of the trial** • Hand eczema severity index at baseline at third day, end of first week, fourth week, then monthly for a whole period of 6 months
Starting date	2017-04-15
Contact information	Carmen Amin El Areesh Street, No. 2, Smouha, 3rd floor #302 21646 Alexandria Egypt 002-01222966670 carmen271173@yahoo.com
Notes	Sponsor: Dermatology Department, Faculty of Medicine, University of Alexandria

BTXA: botulinum toxin A.
DLQI: Dermatology Life Quality Index.
ECG: electrocardiogram.
EQ-5D: standardised index for measuring quality of life by the EuroQol in 5 dimensions.

HECSI: hand eczema severity index.
mTLSS: modified total lesion symptom score.
PaGA: participants' global assessment.
PBI-HE: patient benefit index for chronic hand eczema.
PeDeSi: Person-Centered Dermatology Self-Care Index.
PGA: physicians' global assessment.
PUVA: (topical and oral) psoralen combined with UVA.
QALY: quality-adjusted life-year.
TLSS: total lesion symptom score.
UVB: ultraviolet B.

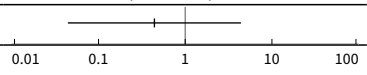
DATA AND ANALYSES

Comparison 1. Bland emollients: ceramide-containing emollient versus regular petrolatum-based emollient

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events: exacerbation resulting in dropout	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Bland emollients: ceramide-containing emollient versus regular petrolatum-based emollient, Outcome 1 Primary: adverse events: exacerbation resulting in dropout.

Study or subgroup	ceramide n/N	petrolatum-based n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kucharekova 2003	1/17	2/15		0.44[0.04,4.39]



Comparison 2. Bland emollients: emollient E-DO versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: percentage of participants with self-rated good/excellent control at week 4			Other data	No numeric data
2 Primary: percentage of participants with investigator-rated good/excellent control at week 4			Other data	No numeric data
3 Adverse events			Other data	No numeric data
3.1 At least 1 adverse event			Other data	No numeric data
3.2 Pruritus			Other data	No numeric data

Analysis 2.1. Comparison 2 Bland emollients: emollient E-DO versus vehicle, Outcome 1 Primary: percentage of participants with self-rated good/excellent control at week 4.

Primary: percentage of participants with self-rated good/excellent control at week 4			
Study	**Group - within-participant study**	**Total number of events**	**Total number of pairs of hands analysed**
Chu 2009	Emollient E-DO	22	67
Chu 2009	Vehicle	23	67

Analysis 2.2. Comparison 2 Bland emollients: emollient E-DO versus vehicle, Outcome 2 Primary: percentage of participants with investigator-rated good/excellent control at week 4.

Primary: percentage of participants with investigator-rated good/excellent control at week 4			
Study	**Group- within-participant study**	**Event number**	**Total number of pairs of hands randomised**
Chu 2009	Emollient E-DO	37	67
Chu 2009	Vehicle	36	67

Analysis 2.3. Comparison 2 Bland emollients: emollient E-DO versus vehicle, Outcome 3 Adverse events.

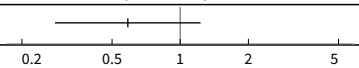
Adverse events			
Study	**Group - within-participant study**	**Event number**	**Total number of hands pairs of analysed**
At least 1 adverse event			
Chu 2009	Emollient E-DO	12	67
Chu 2009	Vehicle	8	67
Pruritus			
Chu 2009	Emollient E-DO	6	67
Chu 2009	Vehicle	2	67

Comparison 3. Corticosteroid creams/ointments: fluprednidene versus betamethasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms after 3 weeks of treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: number of participants with at least 1 adverse event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Secondary: investigator-rated improvement > 50% after 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

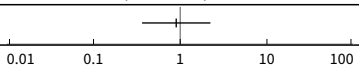
Analysis 3.1. Comparison 3 Corticosteroid creams/ointments: fluprednidene versus betamethasone, Outcome 1 Primary: investigator-rated good/excellent control of symptoms after 3 weeks of treatment.

Study or subgroup	Fluprednidene n/N	Betamethasone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bleeker 1989	8/37	14/38		0.59[0.28,1.23]



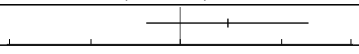
Analysis 3.2. Comparison 3 Corticosteroid creams/ointments: fluprednidene versus betamethasone, Outcome 2 Primary: number of participants with at least 1 adverse event.

Study or subgroup	Fluprednidene n/N	Betamethasone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bleeker 1989	7/37	8/38		0.9[0.36,2.23]



Analysis 3.3. Comparison 3 Corticosteroid creams/ointments: fluprednidene versus betamethasone, Outcome 3 Secondary: investigator-rated improvement > 50% after 3 weeks.

Study or subgroup	Fluprednidene n/N	Betamethasone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bleeker 1989	27/37	23/38		1.21[0.87,1.67]



Comparison 4. Corticosteroid creams/ointments: betamethasone-dipropionate film-forming lotion versus betamethasone-dipropionate thick lotion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms at day 7			Other data	No numeric data
2 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 At least 1 adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Application site reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Exacerbation eczema leading to withdrawal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

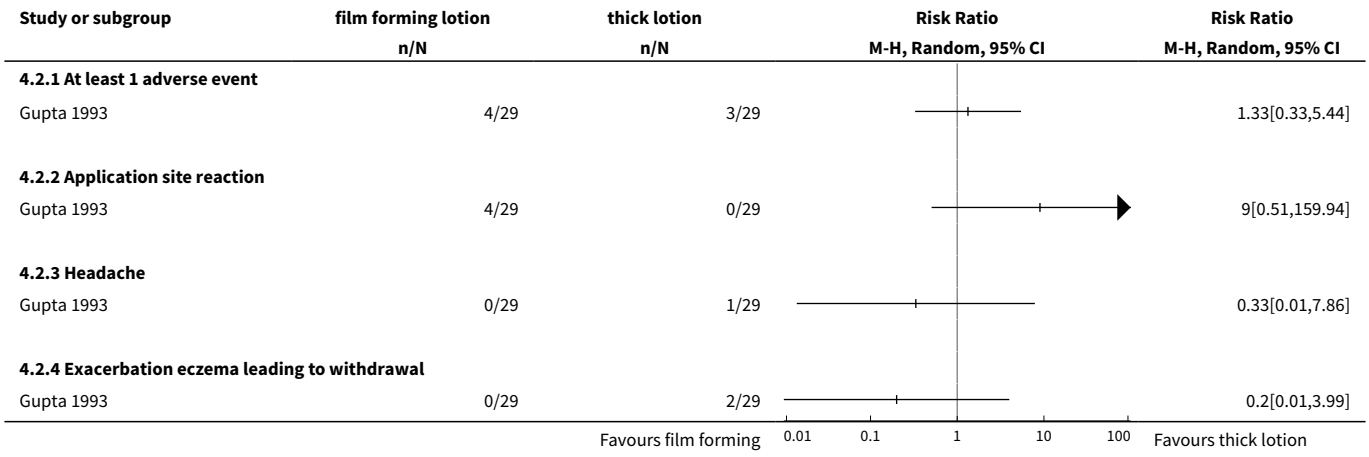
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Secondary: investigator-rated reduction (not specified) in severity at day 7	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Secondary: investigator-rated global improvement in eczema	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Corticosteroid creams/ointments: betamethasone-dipropionate film-forming lotion versus betamethasone-dipropionate thick lotion, Outcome 1 Primary: investigator-rated good/excellent control of symptoms at day 7.

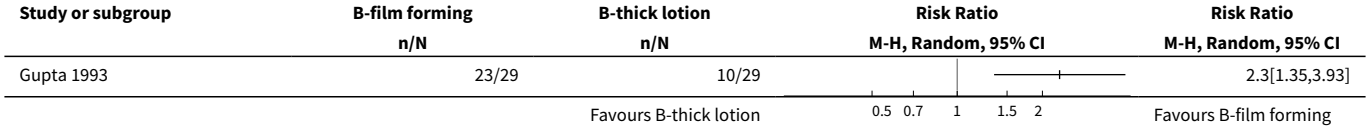
Primary: investigator-rated good/excellent control of symptoms at day 7

Study	Group	Number of participants with good/excellent control	Total number of participants
Gupta 1993	B-film forming lotion	5	28
Gupta 1993	B-thick lotion	0	26

Analysis 4.2. Comparison 4 Corticosteroid creams/ointments: betamethasone-dipropionate film-forming lotion versus betamethasone-dipropionate thick lotion, Outcome 2 Primary: adverse events.



Analysis 4.3. Comparison 4 Corticosteroid creams/ointments: betamethasone-dipropionate film-forming lotion versus betamethasone-dipropionate thick lotion, Outcome 3 Secondary: investigator-rated reduction (not specified) in severity at day 7.



Analysis 4.4. Comparison 4 Corticosteroid creams/ointments: betamethasone-dipropionate film-forming lotion versus betamethasone-dipropionate thick lotion, Outcome 4 Secondary: investigator-rated global improvement in eczema.

Study or subgroup	B-film forming lotion n/N	B-thick lotion n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gupta 1993	23/28	18/26		1.19[0.87,1.62]
		Favours B-thick lotion	1	Favours B-film forming

Comparison 5. Corticosteroids creams/ointments: clobetasol propionate versus flupredniden acetate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: percentage of participants with investigator-rated good/excellent control			Other data	No numeric data
2 Adverse events			Other data	No numeric data
2.1 At least 1 adverse event			Other data	No numeric data
2.2 Burning sensation			Other data	No numeric data
2.3 Reversible atrophy			Other data	No numeric data
2.4 Brittle skin			Other data	No numeric data

Analysis 5.1. Comparison 5 Corticosteroids creams/ointments: clobetasol propionate versus flupredniden acetate, Outcome 1 Primary: percentage of participants with investigator-rated good/excellent control.

Primary: percentage of participants with investigator-rated good/excellent control			
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Möller 1983	Clobetasol	32	46
Möller 1983	Flupredniden	14	46

Analysis 5.2. Comparison 5 Corticosteroids creams/ointments: clobetasol propionate versus flupredniden acetate, Outcome 2 Adverse events.

Adverse events			
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
At least 1 adverse event			
Möller 1983	Clobetasol	4	46
Möller 1983	Flupredniden	3	46
Burning sensation			
Möller 1983	Clobetasol	2	46
Möller 1983	Flupredniden	2	46
Reversible atrophy			
Möller 1983	Clobetasol	1	46
Möller 1983	Flupredniden	0	46

Study	Adverse events Group - within-participant study	Event number	Total number of pairs of hands analysed
	Brittle skin		
Möller 1983	Clobetasol	1	46
Möller 1983	Flupredniden	1	46

Comparison 6. Corticosteroids creams/ointments: clobetasol propionate foam 0.05% versus vehicle

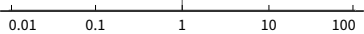
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: percentage of participants with investigator-rated good/excellent control at day 15	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: percentage of participants with self-rated good/excellent control at day 15	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Discontinuation due to adverse events (fissures)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 At least 1 adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Any adverse event treatment-related (application site pruritus)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Nasopharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Secondary: reduction in severity, participant-rated scoring at day 15	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Secondary: reduction in severity, investigator-rated scoring at day 15	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Improvement at least 2 grades	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Improvement at least 1 grade	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Corticosteroids creams/ointments: clobetasol propionate foam 0.05% versus vehicle, Outcome 1 Primary: percentage of participants with investigator-rated good/excellent control at day 15.

Study or subgroup	Clobetasol foam n/N	Vehicle foam n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kircik 2013	24/62	17/63		1.43[0.86,2.4]

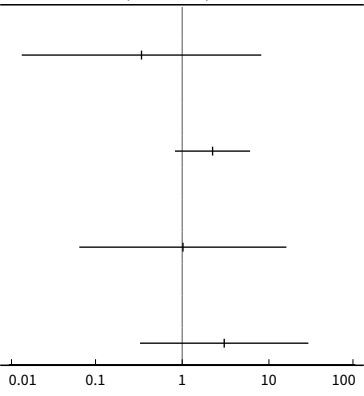
Analysis 6.2. Comparison 6 Corticosteroids creams/ointments: clobetasol propionate foam 0.05% versus vehicle, Outcome 2 Primary: percentage of participants with self-rated good/excellent control at day 15.

Study or subgroup	Clobetasol foam n/N	Vehicle foam n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kircik 2013	32/62	14/63		2.32[1.38,3.91]



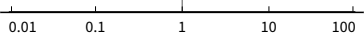
Analysis 6.3. Comparison 6 Corticosteroids creams/ointments: clobetasol propionate foam 0.05% versus vehicle, Outcome 3 Primary: adverse events.

Study or subgroup	Clobetasol foam n/N	Vehicle foam n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.3.1 Discontinuation due to adverse events (fissures)				
Kircik 2013	0/62	1/63		0.34[0.01,8.16]
6.3.2 At least 1 adverse event				
Kircik 2013	11/62	5/63		2.24[0.82,6.06]
6.3.3 Any adverse event treatment-related (application site pruritus)				
Kircik 2013	1/62	1/63		1.02[0.06,15.89]
6.3.4 Nasopharyngitis				
Kircik 2013	3/62	1/63		3.05[0.33,28.52]



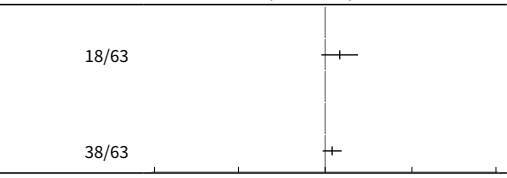
Analysis 6.4. Comparison 6 Corticosteroids creams/ointments: clobetasol propionate foam 0.05% versus vehicle, Outcome 4 Secondary: reduction in severity, participant-rated scoring at day 15.

Study or subgroup	Clobetasol foam n/N	Vehicle foam n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kircik 2013	51/62	33/63		1.57[1.21,2.04]



Analysis 6.5. Comparison 6 Corticosteroids creams/ointments: clobetasol propionate foam 0.05% versus vehicle, Outcome 5 Secondary: reduction in severity, investigator-rated scoring at day 15.

Study or subgroup	Clobetasol foam n/N	Vehicle foam n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.5.1 Improvement at least 2 grades				
Kircik 2013	26/62	18/63		1.47[0.9,2.39]
6.5.2 Improvement at least 1 grade				
Kircik 2013	45/62	38/63		1.2[0.94,1.55]



Comparison 7. Corticosteriods creams/ointments: desonide cream 0.1% versus desonide cream 0.05%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events			Other data	No numeric data

Analysis 7.1. Comparison 7 Corticosteriods creams/ointments: desonide cream 0.1% versus desonide cream 0.05%, Outcome 1 Adverse events.

Study	Adverse events Group - within-participant study	Event number	Total number of pairs of hands analysed
Uggeldahl 1986	Desonide cream 0.1%	0	50
Uggeldahl 1986	Desonide cream 0.05%	2	50

Comparison 8. Corticosteroid creams/ointments: mometasone furoate cream 3 times/week versus 2 times/week versus no steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Mometasone furoate 3 times/week vs mometasone furoate 2 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Primary: investigator-rated good/excellent control	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Mometasone furoate 3 times/week vs emollient and ointment only	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Mometasone furoate 2 times/week vs emollient and ointment only	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Mild atrophy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Corticosteroid creams/ointments: mometasone furoate cream 3 times/week versus 2 times/week versus no steroids, Outcome 1 Primary: investigator-rated good/excellent control.

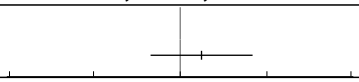
Study or subgroup	mometasone 3x a week n/N	mometasone 2x a week n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 Mometasone furoate 3 times/week vs mometasone furoate 2 times/week				
Veien 1999	29/35	25/37		1.23[0.94,1.61]

Analysis 8.2. Comparison 8 Corticosteroid creams/ointments: mometasone furoate cream 3 times/week versus 2 times/week versus no steroids, Outcome 2 Primary: investigator-rated good/excellent control.

Study or subgroup	mometasone n/N	emollient n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.2.1 Mometasone furoate 3 times/week vs emollient and ointment only				
Veien 1999	29/35	9/34		3.13[1.75,5.59]
8.2.2 Mometasone furoate 2 times/week vs emollient and ointment only				
Veien 1999	25/37	9/34		2.55[1.4,4.67]

Analysis 8.3. Comparison 8 Corticosteroid creams/ointments: mometasone furoate cream 3 times/week versus 2 times/week versus no steroids, Outcome 3 Primary: adverse events.

Study or subgroup	Mometasone 3x a week n/N	Mometasone 2x a week n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.3.1 Mild atrophy				
Veien 1999	5/35	3/37		1.76[0.45,6.83]



Comparison 9. Corticosteroid creams/ointments: clobetasol and zinc sulphate cream versus clobetasol cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome: percentage of participants with investigator-rated good/excellent control			Other data	No numeric data
1.1 Scaling			Other data	No numeric data
1.2 Redness			Other data	No numeric data
1.3 Lichenification			Other data	No numeric data

Analysis 9.1. Comparison 9 Corticosteroid creams/ointments: clobetasol and zinc sulphate cream versus clobetasol cream, Outcome 1 Primary outcome: percentage of participants with investigator-rated good/excellent control.

Primary outcome: percentage of participants with investigator-rated good/excellent control			
Study	**Group - within-participant study**	**Event number**	**Total number of pairs of hands analysed**
Scaling			
Faghihi 2008	Clobetasol cream	3	47
Faghihi 2008	Clobetasol cream Clobetasol & Zinc sulphate cream	25	47
Redness			
Faghihi 2008	Clobetasol cream	1	47
Faghihi 2008	Clobetasol cream Clobetasol & Zinc sulphate cream	41	47
Lichenification			
Faghihi 2008	Clobetasol cream	7	47
Faghihi 2008	Clobetasol cream Clobetasol & Zinc sulphate cream	24	47

Comparison 10. Corticosteroid creams/ointments: betamethasone-valerate 0.1% cream versus urea 5% cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Secondary: participant-rated reduction in severity (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Secondary: investigator-rated reduction in severity (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 Corticosteroid creams/ointments: betamethasone-valerate 0.1% cream versus urea 5% cream, Outcome 1 Primary: investigator-rated good/excellent control of symptoms.

Study or subgroup	BV n/N	BV + urea n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lodén 2012a	15/22	20/22		0.75[0.55,1.03]

Favours BV + urea 0.1 0.2 0.5 1 2 5 10 Favours BV

Analysis 10.2. Comparison 10 Corticosteroid creams/ointments: betamethasone-valerate 0.1% cream versus urea 5% cream, Outcome 2 Secondary: participant-rated reduction in severity (bigger reduction in severity = better outcome).

Study or subgroup	BV N	BV Mean(SD)	BV + urea N	BV + urea Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Lodén 2012a	22	36.3 (36)	22	54 (22.4)		-17.7[-35.42,0.02]

Favours BV -100 -50 0 50 100 Favours BV + urea

Analysis 10.3. Comparison 10 Corticosteroid creams/ointments: betamethasone-valerate 0.1% cream versus urea 5% cream, Outcome 3 Secondary: investigator-rated reduction in severity (bigger reduction in severity = better outcome).

Study or subgroup	BV N	BV Mean(SD)	BV + urea N	BV + urea Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Lodén 2012a	22	12.5 (13.9)	22	10.5 (9)		2[-4.92,8.92]

Favours BV -10 -5 0 5 10 Favours BV + urea

Comparison 11. Topical others: coal tar versus betamethasone-valerate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome: adverse events			Other data	No numeric data

Analysis 11.1. Comparison 11 Topical others: coal tar versus betamethasone-valerate, Outcome 1 Primary outcome: adverse events.

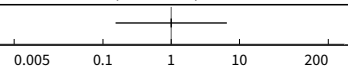
		Primary outcome: adverse events	
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Kemper 1998	Betamethasone valerate 0.1% cream	0	19
Kemper 1998	Coal tar paste	1	19

Comparison 12. Irradiation with UV light versus no UVB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events - exacerbation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 12.1. Comparison 12 Irradiation with UV light versus no UVB, Outcome 1 Primary: adverse events - exacerbation.

Study or subgroup	Irradiation with UV-light n/N	No UVB n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bayerl 1999	2/24	2/24		1[0.15,6.53]

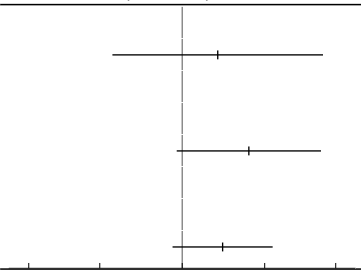


Comparison 13. Irradiation with UV light: whole-body UVB versus placebo or local UVB hands

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms by UVB hand vs whole-body UVB vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Local UVB hands alone vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Whole-body UVB + local UVB hands vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Whole body UVB + local UVB hands versus local UVB hands alone	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Secondary: time until relapse depicted in weeks of remission	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Local UVB hands alone vs placebo (high score = better outcome)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Whole-body UVB + local UVB hands vs placebo (high score = better outcome)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Whole-body UVB + local UVB hands vs local UVB hands alone (high score = better outcome)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

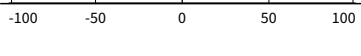
Analysis 13.1. Comparison 13 Irradiation with UV light: whole-body UVB versus placebo or local UVB hands, Outcome 1 Primary: investigator-rated good/ excellent control of symptoms by UVB hand vs whole-body UVB vs placebo.

Study or subgroup	UVB intervention n/N	Placebo / part UVB n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
13.1.1 Local UVB hands alone vs placebo				
Sjövall 1987	2/5	1/5		2[0.26,15.62]
13.1.2 Whole-body UVB + local UVB hands vs placebo				
Sjövall 1987	5/5	1/5		3.67[0.9,14.97]
13.1.3 Whole body UVB + local UVB hands versus local UVB hands alone				
Sjövall 1987	5/5	2/5		2.2[0.83,5.84]



Analysis 13.2. Comparison 13 Irradiation with UV light: whole-body UVB versus placebo or local UVB hands, Outcome 2 Secondary: time until relapse depicted in weeks of remission.

Study or subgroup	UVB intervention N	Mean(SD)	Placebo/part UVB N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
13.2.1 Local UVB hands alone vs placebo (high score = better outcome)						
Sjövall 1987	5	9.6 (6.3)	2	5.5 (3.5)		4.1[-3.25,11.45]
13.2.2 Whole-body UVB + local UVB hands vs placebo (high score = better outcome)						
Sjövall 1987	5	6 (2.9)	2	5.5 (3.5)		0.5[-4.98,5.98]
13.2.3 Whole-body UVB + local UVB hands vs local UVB hands alone (high score = better outcome)						
Sjövall 1987	5	6 (2.9)	5	9.6 (6.3)		-3.6[-9.68,2.48]

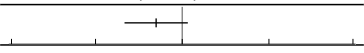


Comparison 14. Irradiation with UV light: local narrow-band UVB versus local PUVA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms in UVB vs PUVA	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Primary: adverse events - reported adverse event, mainly erythema	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 14.1. Comparison 14 Irradiation with UV light: local narrow-band UVB versus local PUVA, Outcome 1 Primary: investigator-rated good/excellent control of symptoms in UVB vs PUVA.

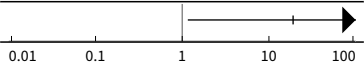
Study or subgroup	NB-UVB n/N	Local PUVA n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brass 2015	6/30	12/30		0.5[0.22,1.16]



Favours local PUVA | Favours NB-UVB

Analysis 14.2. Comparison 14 Irradiation with UV light: local narrow-band UVB versus local PUVA, Outcome 2 Primary: adverse events - reported adverse event, mainly erythema.

Study or subgroup	NB-UVB n/N	Local PUVA n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brass 2015	9/30	0/30		19[1.16,312.42]



Favours local PUVA | Favours NB-UVB

Comparison 15. Irradiation with UV light: local narrow-band UVB versus local PUVA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms in UVB vs PUVA			Other data	No numeric data
2 Primary: adverse events			Other data	No numeric data
2.1 Palmar hyperpigmentation			Other data	No numeric data
3 Secondary: investigator-rated improvement by local narrow-band UVB vs local PUVA			Other data	No numeric data

Analysis 15.1. Comparison 15 Irradiation with UV light: local narrow-band UVB versus local PUVA, Outcome 1 Primary: investigator-rated good/excellent control of symptoms in UVB vs PUVA.

Primary: investigator-rated good/excellent control of symptoms in UVB vs PUVA			
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Sezer 2007	NB-UVB	2	12
Sezer 2007	Local PUVA	1	12

Analysis 15.2. Comparison 15 Irradiation with UV light: local narrow-band UVB versus local PUVA, Outcome 2 Primary: adverse events.

Primary: adverse events			
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Palmar hyperpigmentation			
Sezer 2007	NB-UVB	0	12
Sezer 2007	Local PUVA	3	12

Analysis 15.3. Comparison 15 Irradiation with UV light: local narrow-band UVB versus local PUVA, Outcome 3 Secondary: investigator-rated improvement by local narrow-band UVB vs local PUVA.

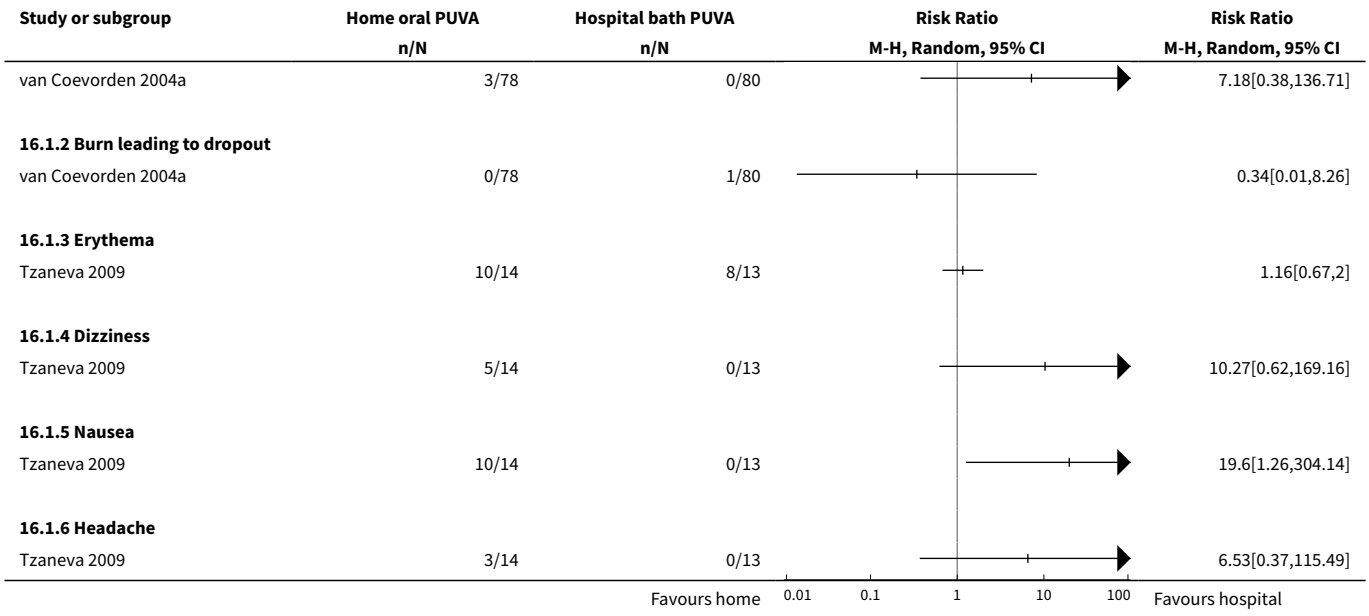
	Secondary: investigator-rated improvement by local narrow-band UVB vs local PUVA		
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Sezer 2007	NB-UVB	9	12
Sezer 2007	Local PUVA	9	12

Comparison 16. Irradiation with UV light: oral PUVA versus topical bath PUVA

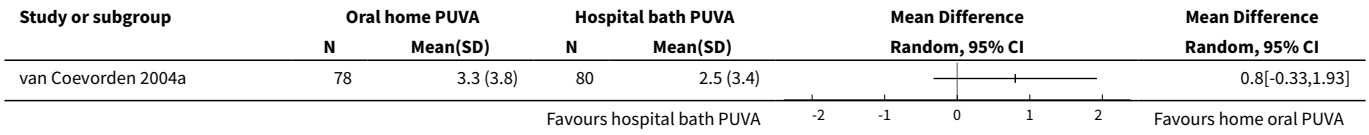
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Nausea leading to dropout	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Burn leading to dropout	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Secondary: investigator-rated reduction in severity at week 10 (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Secondary: investigator-rated reduction in severity at week 18 (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 16.1. Comparison 16 Irradiation with UV light: oral PUVA versus topical bath PUVA, Outcome 1 Primary: adverse events.

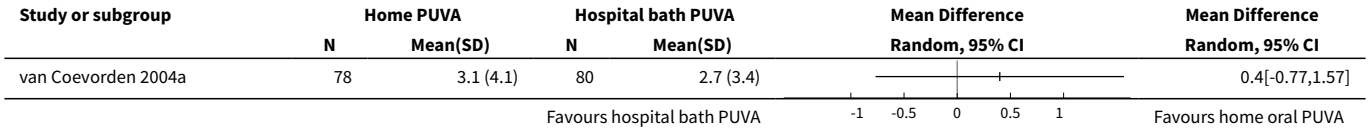
Study or subgroup	Home oral PUVA n/N	Hospital bath PUVA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
16.1.1 Nausea leading to dropout				



Analysis 16.2. Comparison 16 Irradiation with UV light: oral PUVA versus topical bath PUVA, Outcome 2 Secondary: investigator-rated reduction in severity at week 10 (bigger reduction in severity = better outcome).



Analysis 16.3. Comparison 16 Irradiation with UV light: oral PUVA versus topical bath PUVA, Outcome 3 Secondary: investigator-rated reduction in severity at week 18 (bigger reduction in severity = better outcome).



Comparison 17. Irradiation with UV light: topical PUVA versus UVA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events			Other data	No numeric data
1.1 Discontinuation due to adverse events			Other data	No numeric data
1.2 Burning			Other data	No numeric data
1.3 Exacerbation of eczema			Other data	No numeric data

Analysis 17.1. Comparison 17 Irradiation with UV light: topical PUVA versus UVA, Outcome 1 Primary: adverse events.

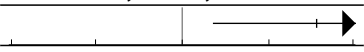
Study	Group - within-participant study	Primary: adverse events Event number	Total number of pairs of hands analysed
Discontinuation due to adverse events			
Grattan 1991	Topical PUVA	1	15
Grattan 1991	UVA	1	15
Burning			
Grattan 1991	Topical PUVA	1	15
Grattan 1991	UVA	0	15
Exacerbation of eczema			
Grattan 1991	Topical PUVA	1	15
Grattan 1991	UVA	0	15

Comparison 18. Irradiation with UV light: UVA-1 versus topical betamethasone valerate 0.1% cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events - hyperpigmentation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18 Irradiation with UV light: UVA-1 versus topical betamethasone valerate 0.1% cream, Outcome 1 Primary: adverse events - hyperpigmentation.

Study or subgroup	UVA-1 n/N	Betamethasone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Said 2010	18/24	0/23		35.52[2.26,557.08]



Comparison 19. Irradiation with UV light: UVA-1 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events - discontinuation because of exacerbation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Secondary: participant-rated reduction in severity on VAS for itch (week 3, bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Secondary: investigator-rated reduction in severity on dyshidrotic eczema area and severity index (DASI) (week 3, bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 19.1. Comparison 19 Irradiation with UV light: UVA-1 versus placebo, Outcome 1 Primary: adverse events - discontinuation because of exacerbation.

Study or subgroup	UVA-1 n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Polderman 2003	0/15	3/13		0.13[0.01,2.22]

Favours UVA-1 — 0.01 — 0.1 — 1 — 10 — 100 — Favours placebo

Analysis 19.2. Comparison 19 Irradiation with UV light: UVA-1 versus placebo, Outcome 2 Secondary: participant-rated reduction in severity on VAS for itch (week 3, bigger reduction in severity = better outcome).

Study or subgroup	UVA-1 N	UVA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Polderman 2003	15	2.3 (2)	13	-1.4 (4.1)		3.68[1.25,6.11]

Favours placebo — -5 — -2.5 — 0 — 2.5 — 5 — Favours UVA-1

Analysis 19.3. Comparison 19 Irradiation with UV light: UVA-1 versus placebo, Outcome 3 Secondary: investigator-rated reduction in severity on dyshidrotic eczema area and severity index (DASI) (week 3, bigger reduction in severity = better outcome).

Study or subgroup	UVA-1 N	UVA-1 Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Polderman 2003	15	8.7 (6.7)	13	-0.4 (8.9)		9.05[3.15,14.95]

Favours placebo — -10 — -5 — 0 — 5 — 10 — Favours UVA-1

Comparison 20. Irradiation with UV light: PUVA versus UVA-1

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events			Other data	No numeric data
1.1 Burning			Other data	No numeric data
1.2 Itching			Other data	No numeric data

Analysis 20.1. Comparison 20 Irradiation with UV light: PUVA versus UVA-1, Outcome 1 Primary: adverse events.

Study	Primary: adverse events Group - within-participant study	Event number	Total number of pairs of hands analysed
	Burning		
Adams 2007	PUVA	3	11
Adams 2007	UVA-1	1	11
	Itching		

Primary: adverse events			
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Adams 2007	PUVA	5	11
Adams 2007	UVA-1	3	11

Comparison 21. Irradiation with Grenz ray

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated improvement good/excellent control			Other data	No numeric data
1.1 after 1 month			Other data	No numeric data
1.2 after 3 months			Other data	No numeric data
1.3 after 6 months			Other data	No numeric data
1.4 Hyperkeratotic eczema after 6 months			Other data	No numeric data
1.5 Pompholyx after 6 months			Other data	No numeric data
1.6 Chronic palmar eczema after 6 months			Other data	No numeric data
2 Primary: adverse events - hyperpigmentation			Other data	No numeric data

Analysis 21.1. Comparison 21 Irradiation with Grenz ray, Outcome 1 Primary: investigator-rated improvement good/excellent control.

Primary: investigator-rated improvement good/excellent control			
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
after 1 month			
King 1984	Grenz Ray	7	15
King 1984	Placebo	0	15
after 3 months			
King 1984	Grenz Ray	10	15
King 1984	Placebo	6	15
after 6 months			
King 1984	Grenz Ray	11	15
King 1984	Placebo	8	15
Hyperkeratotic eczema after 6 months			
King 1984	Grenz Ray	4	8
King 1984	Placebo	2	6
Pompholyx after 6 months			
King 1984	Grenz Ray	7	7
King 1984	Placebo	6	7
Chronic palmar eczema after 6 months			
King 1984	Grenz Ray	11	15
King 1984	Placebo	0	15

Analysis 21.2. Comparison 21 Irradiation with Grenz ray, Outcome 2 Primary: adverse events - hyperpigmentation.

		Primary: adverse events - hyperpigmentation	
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Cartwright 1987	Grenz	1	30
Cartwright 1987	Placebo	0	30
Lindelöf 1987	Grenz	5	24
Lindelöf 1987	Placebo	0	24

Comparison 22. Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus mometasone furoate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary: reduction in investigator-rated severity - DASI			Other data	No numeric data

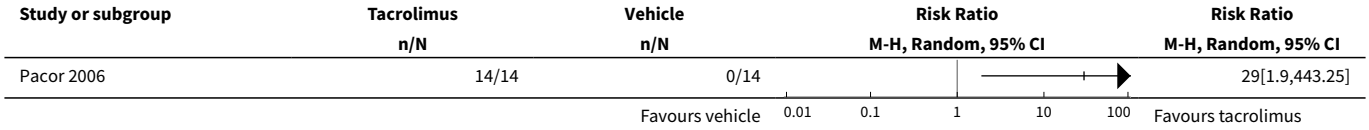
Analysis 22.1. Comparison 22 Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus mometasone furoate, Outcome 1 Secondary: reduction in investigator-rated severity - DASI.

		Secondary: reduction in investigator-rated severity - DASI		
Study	Group - within-participant study	Mean	SD	Total number of pairs of hands analysed
Schnopp 2002	Tacrolimus	6.6	6.18	8
Schnopp 2002	Mometasone	6.9	7.7	8

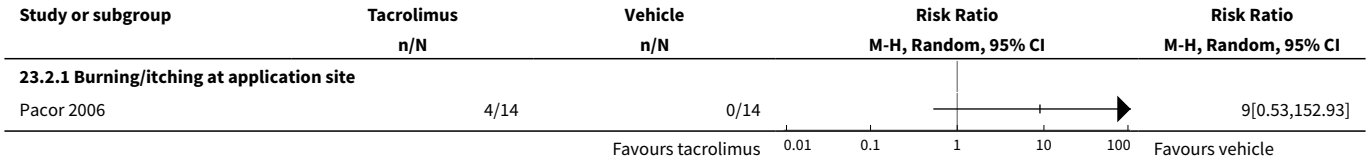
Comparison 23. Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: adverse events burning/itching at application site	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Burning/itching at application site	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 23.1. Comparison 23 Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus vehicle, Outcome 1 Primary: investigator-rated good/excellent control of symptoms.



Analysis 23.2. Comparison 23 Topical calcineurin inhibitors: tacrolimus 0.1% ointment versus vehicle, Outcome 2 Primary: adverse events burning/itching at application site.

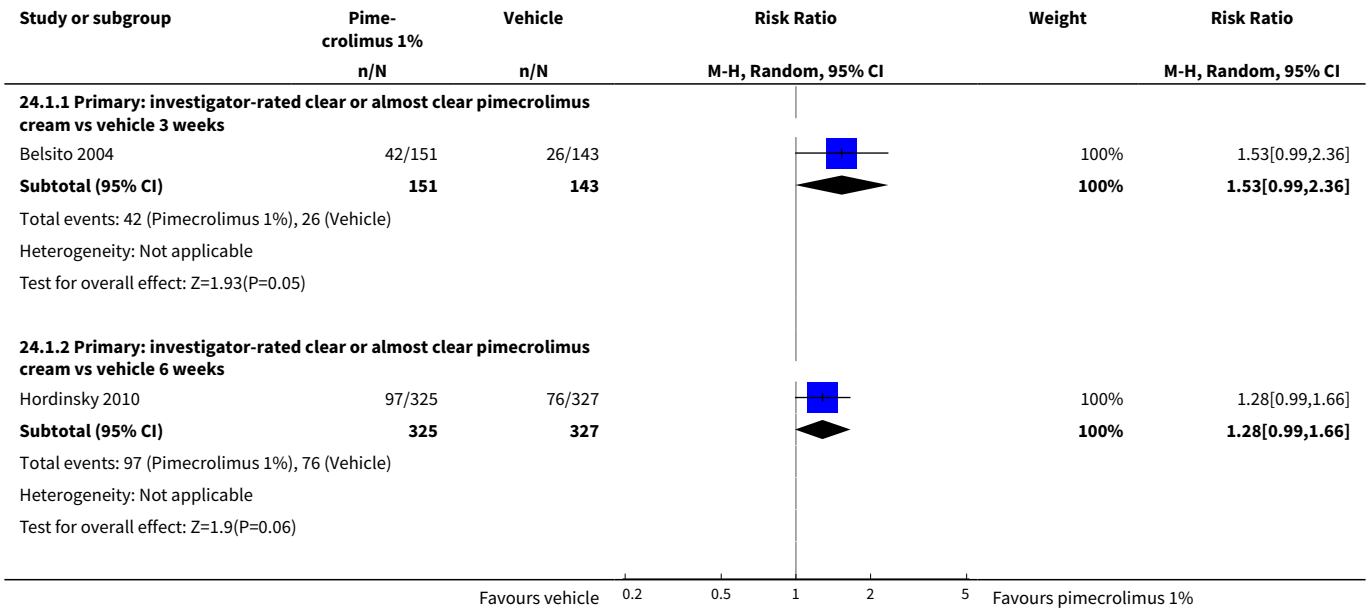


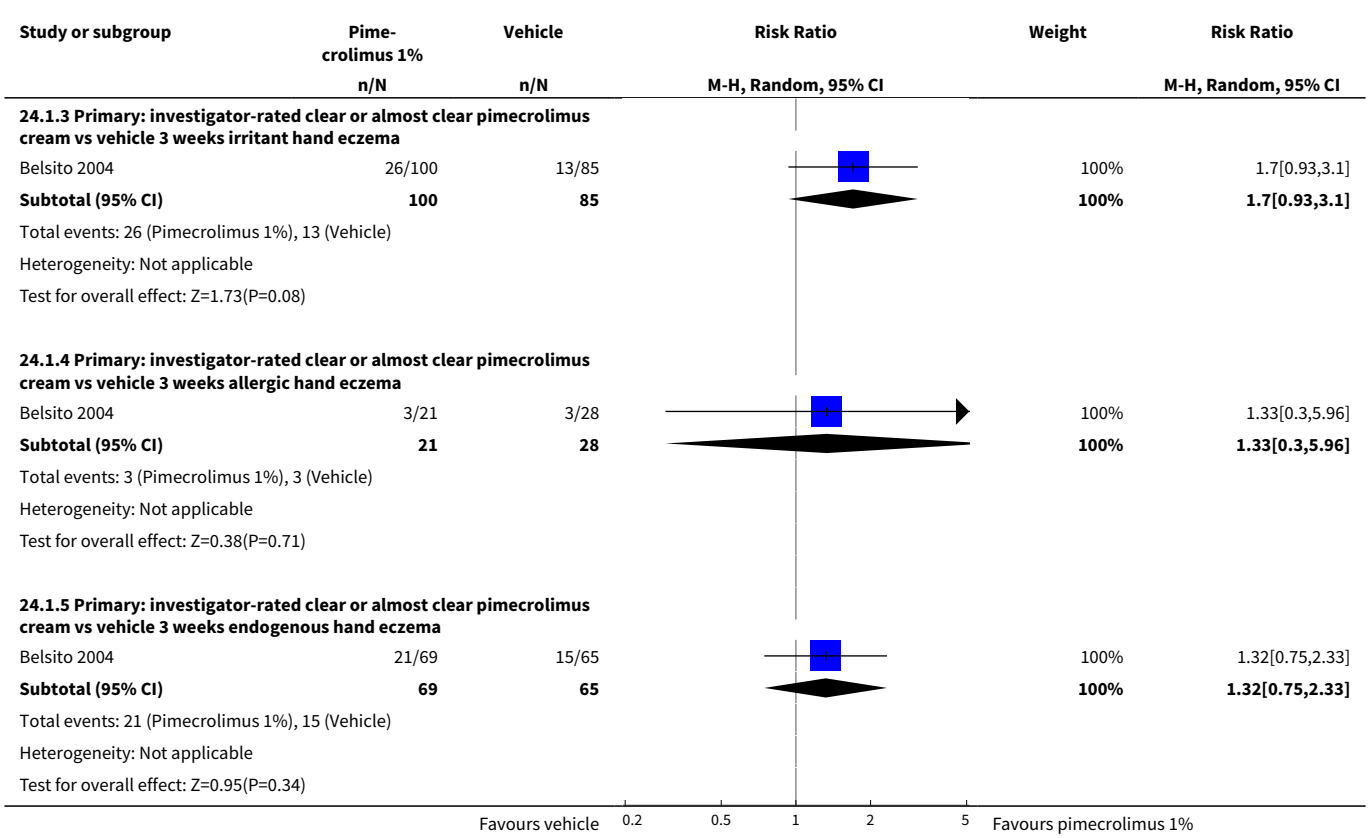
Comparison 24. Topical calcineurin inhibitors: pimecrolimus 1% cream versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms pimecrolimus cream vs vehicle	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Primary: investigator-rated clear or almost clear pimecrolimus cream vs vehicle 3 weeks	1	294	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.99, 2.36]
1.2 Primary: investigator-rated clear or almost clear pimecrolimus cream vs vehicle 6 weeks	1	652	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.99, 1.66]
1.3 Primary: investigator-rated clear or almost clear pimecrolimus cream vs vehicle 3 weeks irritant hand eczema	1	185	Risk Ratio (M-H, Random, 95% CI)	1.7 [0.93, 3.10]
1.4 Primary: investigator-rated clear or almost clear pimecrolimus cream vs vehicle 3 weeks allergic hand eczema	1	49	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.30, 5.96]
1.5 Primary: investigator-rated clear or almost clear pimecrolimus cream vs vehicle 3 weeks endogenous hand eczema	1	134	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.75, 2.33]
2 Primary: adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Discontinuation because of adverse event	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

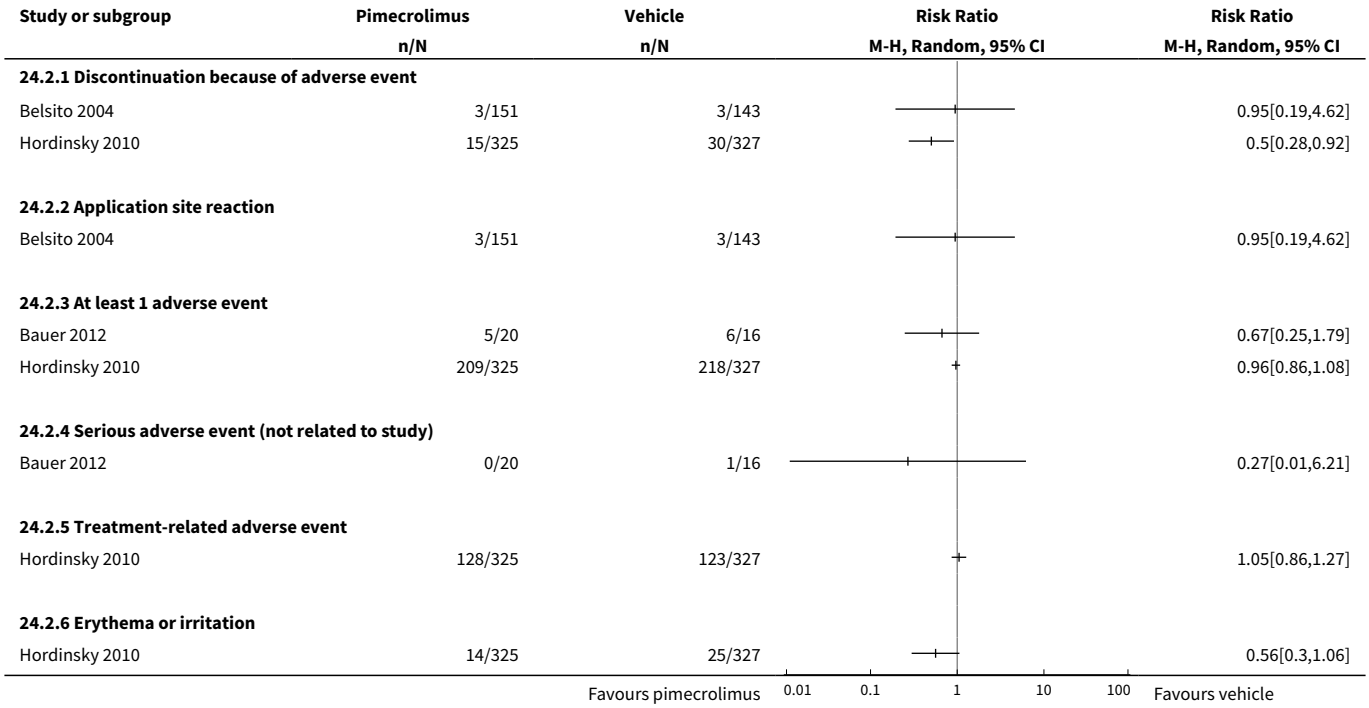
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Application site reaction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 At least 1 adverse event	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Serious adverse event (not related to study)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Treatment-related adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Erythema or irritation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.7 Itching	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.8 Warmth, stinging, burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.9 Herpes simplex virus infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Secondary: participant-rated reduction in severity pruritus relief between pimecrolimus 1% and vehicle	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 24.1. Comparison 24 Topical calcineurin inhibitors: pimecrolimus 1% cream versus vehicle, Outcome 1 Primary: investigator-rated good/excellent control of symptoms pimecrolimus cream vs vehicle.

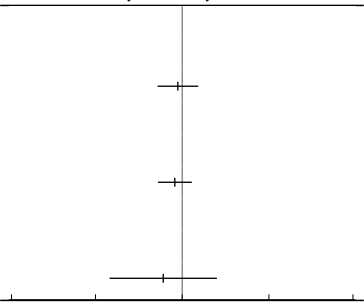




Analysis 24.2. Comparison 24 Topical calcineurin inhibitors: pimecrolimus 1% cream versus vehicle, Outcome 2 Primary: adverse events.

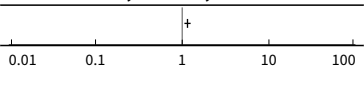


Study or subgroup	Pimecrolimus n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
24.2.7 Itching				
Hordinsky 2010	23/325	26/327		0.89[0.52,1.53]
24.2.8 Warmth, stinging, burning				
Hordinsky 2010	31/325	38/327		0.82[0.52,1.29]
24.2.9 Herpes simplex virus infection				
Hordinsky 2010	3/325	5/327		0.6[0.15,2.51]



Analysis 24.3. Comparison 24 Topical calcineurin inhibitors: pimecrolimus 1% cream versus vehicle, Outcome 3 Secondary: participant-rated reduction in severity pruritus relief between pimecrolimus 1% and vehicle.

Study or subgroup	Pimecrolimus 1% n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hordinsky 2010	272/325	238/327		1.15[1.06,1.25]



Comparison 25. Topical antibacterial agents: betamethasone-valerate/clioquinol cream versus betamethasone-valerate/fusidic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms (intention-to-treat)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 At least 1 adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Chest infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Irritation associated with application	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Deterioration of eczema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Eyes watering	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Hands coloured yellow	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.7 Hands felt thick	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.8 Vesicle on hand	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

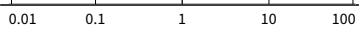
Analysis 25.1. Comparison 25 Topical antibacterial agents: betamethasone-valerate/clioquinol cream versus betamethasone-valerate/fusidic acid, Outcome 1 Primary: investigator-rated good/excellent control of symptoms (intention-to-treat).

Study or subgroup	Betam/Clioquinol n/N	Betam/Fusidic n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hill 1998	34/62	31/58		1.03[0.74,1.43]

Favours Betam/Fusidic | Favours Betam/Clioquinol

Analysis 25.2. Comparison 25 Topical antibacterial agents: betamethasone-valerate/clioquinol cream versus betamethasone-valerate/fusidic acid, Outcome 2 Primary: adverse events.

Study or subgroup	Betam/Clioquinol n/N	Betam/Fusidic n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
25.2.1 At least 1 adverse event				
Hill 1998	11/62	9/58		1.14[0.51,2.56]
25.2.2 Chest infection				
Hill 1998	1/62	0/58		2.81[0.12,67.62]
25.2.3 Irritation associated with application				
Hill 1998	5/62	5/58		0.94[0.29,3.07]
25.2.4 Deterioration of eczema				
Hill 1998	4/62	4/58		0.94[0.25,3.57]
25.2.5 Eyes watering				
Hill 1998	1/62	0/58		2.81[0.12,67.62]
25.2.6 Hands coloured yellow				
Hill 1998	1/62	0/58		2.81[0.12,67.62]
25.2.7 Hands felt thick				
Hill 1998	0/62	1/58		0.31[0.01,7.51]
25.2.8 Vesicle on hand				
Hill 1998	0/62	1/58		0.31[0.01,7.51]



Favours betam/clioquinol | Favours betam/ f.acid

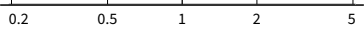
Comparison 26. Topical retinoids: bexarotene 1% gel versus bexarotene with corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms (> 90% clearance)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Bexarotene only (A) vs bexarotene + mometasone (B)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Bexarotene only (A) vs bexarotene + hydrocortisone (B)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Bexarotene + mometasone (A) vs bexarotene + hydrocortisone (B)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Primary: adverse events bexarotene vs bexarotene + mometasone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Irritation/rash	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Stinging/burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Exacerbation of dermatitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Primary: adverse events bexarotene vs bexarotene + hydrocortisone	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Irritation/rash	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Stinging/burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Exacerbation of dermatitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Secondary: investigator-rated reduction in severity (> 50% reduction in hand eczema area and severity index (HEASI))	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Bexarotene (A) only vs bexarotene + mometasone (B)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Bexarotene (A) only vs bexarotene + hydrocortisone (B)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Bexarotene + mometasone (A) vs bexarotene + hydrocortisone (B)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 26.1. Comparison 26 Topical retinoids: bexarotene 1% gel versus bexarotene with corticosteroids, Outcome 1 Primary: investigator-rated good/excellent control of symptoms (> 90% clearance).

Study or subgroup	A n/N	B n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.1.1 Bexarotene only (A) vs bexarotene + mometasone (B)				
Hanifin 2004	11/28	6/13		0.85[0.4,1.8]
26.1.2 Bexarotene only (A) vs bexarotene + hydrocortisone (B)				
Hanifin 2004	11/28	3/14		1.83[0.61,5.53]
26.1.3 Bexarotene + mometasone (A) vs bexarotene + hydrocortisone (B)				
Hanifin 2004	6/13	3/14		2.15[0.67,6.89]

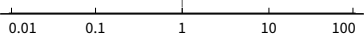


Analysis 26.2. Comparison 26 Topical retinoids: bexarotene 1% gel versus bexarotene with corticosteroids, Outcome 2 Primary: adverse events bexarotene vs bexarotene + mometasone.

Study or subgroup	Bexarotene n/N	Bexarotene+ mometason n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.2.1 Irritation/rash				
Hanifin 2004	8/28	4/13		0.93[0.34,2.53]
26.2.2 Stinging/burning				
Hanifin 2004	2/28	4/13		0.23[0.05,1.11]
26.2.3 Exacerbation of dermatitis				
Hanifin 2004	5/28	0/13		5.31[0.32,89.44]

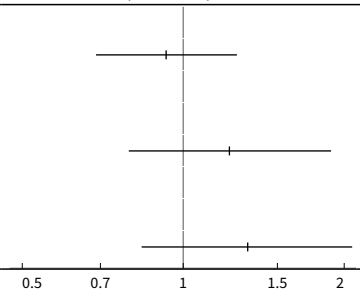
Analysis 26.3. Comparison 26 Topical retinoids: bexarotene 1% gel versus bexarotene with corticosteroids, Outcome 3 Primary: adverse events bexarotene vs bexarotene + hydrocortisone.

Study or subgroup	Bexarotene n/N	Bexarotene + hydrocortison n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.3.1 Irritation/rash				
Hanifin 2004	8/28	4/14		1[0.36,2.76]
26.3.2 Stinging/burning				
Hanifin 2004	2/28	2/14		0.5[0.08,3.19]
26.3.3 Exacerbation of dermatitis				
Hanifin 2004	5/28	4/14		0.63[0.2,1.97]



Analysis 26.4. Comparison 26 Topical retinoids: bexarotene 1% gel versus bexarotene with corticosteroids, Outcome 4 Secondary: investigator-rated reduction in severity (> 50% reduction in hand eczema area and severity index (HEASI)).

Study or subgroup	A n/N	B n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.4.1 Bexarotene (A) only vs bexarotene + mometasone (B)				
Hanifin 2004	22/28	11/13		0.93[0.69,1.26]
26.4.2 Bexarotene (A) only vs bexarotene + hydrocortisone (B)				
Hanifin 2004	22/28	9/14		1.22[0.79,1.89]
26.4.3 Bexarotene + mometasone (A) vs bexarotene + hydrocortisone (B)				
Hanifin 2004	11/13	9/14		1.32[0.84,2.07]



Comparison 27. Other topical agents: calmurid versus aquacare

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events: burning			Other data	No numeric data

Analysis 27.1. Comparison 27 Other topical agents: calmurid versus aquacare, Outcome 1 Primary: adverse events: burning.

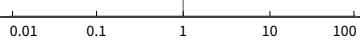
		Primary: adverse events: burning	
Study	Group - within-participant study	Event number	Total number of pairs of hands analysed
Fredriksson 1975	Aquacare	0	30
Fredriksson 1975	Calmurid	13	30

Comparison 28. Other topical agents: fumaric acid 5% cream verus triamcinolone 0.1% cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 28.1. Comparison 28 Other topical agents: fumaric acid 5% cream verus triamcinolone 0.1% cream, Outcome 1 Primary: adverse events.

Study or subgroup	Fumaric acid n/N	Triamcinolone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jowkar 2014	2/30	2/28		0.93[0.14,6.18]

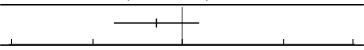


Comparison 29. Other topical agents: furpalmate 0.3% cream versus hydrocortisone acetate 0.5% cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 29.1. Comparison 29 Other topical agents: furpalmate 0.3% cream versus hydrocortisone acetate 0.5% cream, Outcome 1 Primary: investigator-rated good/excellent control of symptoms.

Study or subgroup	Furpalmate 0.3% n/N	Topical hydrocortisone acetate 0.5% n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lauriola 2011	18/20	20/20		0.9[0.76,1.07]



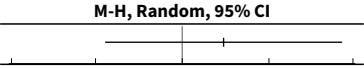
Favours Furpalmate 0.3% Favours topical hydrocortisone acetate 0.5% | Favours Furpalmate 0.3%

Comparison 30. Other topical agents: Fumaria parviflora versus vehicle cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: adverse events: discontinuation due to erythema and papules	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 30.1. Comparison 30 Other topical agents: Fumaria parviflora versus vehicle cream, Outcome 1 Primary: adverse events: discontinuation due to erythema and papules.

Study or subgroup	Fumaria Parviflora n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jowkar 2011	1/22	0/22		3[0.13,69.87]



Favours fumariaparviflora | Favours vehicle

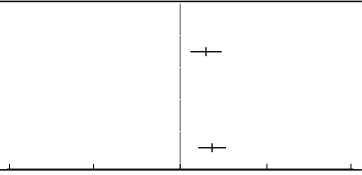
Comparison 31. Oral immunosuppressants: oral azathioprine with topical clobetasol propionate versus topical clobetasol propionate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: percentage of participants with investigator-rated good/excellent control	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Week 8	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Week 24	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Secondary: investigator-rated reduction in severity (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Week 4	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Week 8	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Week 12	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Week 24	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Secondary: participant-rated reduction in severity (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Week 4	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Week 8	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Week 12	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Week 24	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

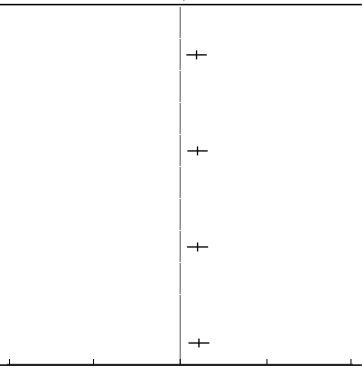
Analysis 31.1. Comparison 31 Oral immunosuppressants: oral azathioprine with topical clobetasol propionate versus topical clobetasol propionate, Outcome 1 Primary: percentage of participants with investigator-rated good/excellent control.

Study or subgroup	Azathioprine+Clobetasol n/N	Clobetasol only n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
31.1.1 Week 8				
Agarwal 2013	33/45	17/46		1.98[1.31,3.01]
31.1.2 Week 24				
Agarwal 2013	41/45	18/46		2.33[1.61,3.38]



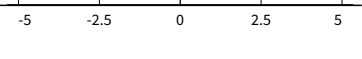
Analysis 31.2. Comparison 31 Oral immunosuppressants: oral azathioprine with topical clobetasol propionate versus topical clobetasol propionate, Outcome 2 Secondary: investigator-rated reduction in severity (bigger reduction in severity = better outcome).

Study or subgroup	Azathioprine+Clobetasol N	Azathioprine+Clobetasol Mean(SD)	Clobetasol only N	Clobetasol only Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
31.2.1 Week 4						
Agarwal 2013	45	19.9 (17.8)	46	10.5 (9.6)		9.41[3.52,15.3]
31.2.2 Week 8						
Agarwal 2013	45	20.7 (17.6)	46	10.7 (9.8)		9.97[4.11,15.83]
31.2.3 Week 12						
Agarwal 2013	45	21.5 (18.2)	46	11.5 (10.3)		10.01[3.92,16.1]
31.2.4 Week 24						
Agarwal 2013	45	22.2 (18.1)	46	11.5 (10)		10.79[4.77,16.81]



Analysis 31.3. Comparison 31 Oral immunosuppressants: oral azathioprine with topical clobetasol propionate versus topical clobetasol propionate, Outcome 3 Secondary: participant-rated reduction in severity (bigger reduction in severity = better outcome).

Study or subgroup	Azathioprine+Clobetasol N	Azathioprine+Clobetasol Mean(SD)	Clobetasol only N	Clobetasol only Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
31.3.1 Week 4						
Agarwal 2013	45	4.9 (2.3)	46	3.7 (2)		1.15[0.26,2.03]
31.3.2 Week 8						
Agarwal 2013	45	5.3 (2.7)	46	3.9 (2.1)		1.35[0.36,2.34]
31.3.3 Week 12						
Agarwal 2013	45	5.6 (2.5)	46	4.4 (2.2)		1.27[0.3,2.25]
31.3.4 Week 24						
Agarwal 2013	45	6 (2.4)	46	4.6 (2.3)		1.48[0.53,2.43]



Comparison 32. Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated very good or good efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: participant-rated very good or good efficacy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

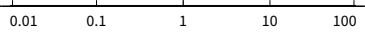
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 At least 1 adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Discontinuation due to dizziness, vomiting, and facial oedema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Discontinuation due to severe insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Increase in serum creatinine > 30%	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Secondary: investigator-rated reduction in severity in total disease activity score (6 weeks; bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 32.1. Comparison 32 Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate, Outcome 1 Primary: investigator-rated very good or good efficacy.

Study or subgroup	Cyclosporin n/N	Betamethasone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Granlund 1996	10/16	6/18		1.88[0.88,3.99]

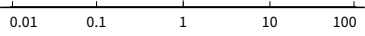
Analysis 32.2. Comparison 32 Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate, Outcome 2 Primary: participant-rated very good or good efficacy.

Study or subgroup	Cyclosporin n/N	Betamethasone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Granlund 1996	10/16	9/18		1.25[0.69,2.27]

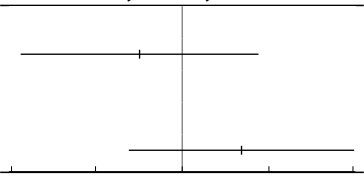


Analysis 32.3. Comparison 32 Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate, Outcome 3 Primary: adverse events.

Study or subgroup	Cyclosporin n/N	Betamethasone DP n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
32.3.1 At least 1 adverse event				
Granlund 1996	19/28	15/27		1.22[0.8,1.86]
32.3.2 Discontinuation due to dizziness, vomiting, and facial oedema				
Granlund 1996	1/28	0/27		2.9[0.12,68.15]

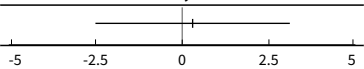


Study or subgroup	Cyclosporin n/N	Betamethasone DP n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
32.3.3 Discontinuation due to severe insomnia				
Granlund 1996	0/28	1/27		0.32[0.01,7.57]
32.3.4 Increase in serum creatinine > 30%				
Granlund 1996	2/28	0/27		4.83[0.24,96.16]



Analysis 32.4. Comparison 32 Oral immunosuppressants: oral cyclosporin versus topical betamethasone dipropionate, Outcome 4 Secondary: investigator-rated reduction in severity in total disease activity score (6 weeks; bigger reduction in severity = better outcome).

Study or subgroup	Cyclosporin N	Cyclosporin Mean(SD)	BetamethasoneDP N	BetamethasoneDP Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Granlund 1996	16	6 (4.3)	18	5.7 (4)		0.3[-2.5,3.1]

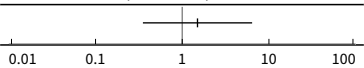


Comparison 33. Oral immunosuppressants: oral cyclosporin versus alitretinoin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control (IGA) after 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: participant-rated good/excellent control (PGA) after 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 33.1. Comparison 33 Oral immunosuppressants: oral cyclosporin versus alitretinoin, Outcome 1 Primary: investigator-rated good/excellent control (IGA) after 24 weeks.

Study or subgroup	Cyclosporin n/N	Alitretinoin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
NCT01231854	3/7	2/7		1.5[0.35,6.4]



Analysis 33.2. Comparison 33 Oral immunosuppressants: oral cyclosporin versus alitretinoin, Outcome 2 Primary: participant-rated good/excellent control (PGA) after 24 weeks.

Study or subgroup	Cyclosporin n/N	Alitretinoin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
NCT01231854	4/7	2/7		2[0.53,7.6]

Favours alitretinoin 0.01 0.1 1 10 100 Favours cyclosporin

Analysis 33.3. Comparison 33 Oral immunosuppressants: oral cyclosporin versus alitretinoin, Outcome 3 Primary: adverse events.

Study or subgroup	Cyclosporin n/N	Alitretinoin n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
NCT01231854	3/7	2/7		1.5[0.35,6.4]

Favours cyclosporin 0.01 0.1 1 10 100 Favours alitretinoin

Comparison 34. Oral retinoids: alitretinoin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Alitretinoin 40 mg vs placebo	1	159	Risk Ratio (M-H, Random, 95% CI)	1.97 [1.30, 3.00]
1.2 Alitretinoin 30 mg vs placebo	2	1210	Risk Ratio (M-H, Random, 95% CI)	2.75 [2.20, 3.43]
1.3 Alitretinoin 20 mg vs placebo	1	158	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.94, 2.34]
1.4 Alitretinoin 10 mg vs placebo	2	781	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.20, 2.07]
2 Primary: investigator-rated good/excellent control of symptoms hyperkeratotic eczema	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Alitretinoin 40 mg vs placebo hyperkeratotic eczema	1	131	Risk Ratio (M-H, Random, 95% CI)	2.61 [1.61, 4.23]
2.2 Alitretinoin 30 mg vs placebo hyperkeratotic eczema	1	519	Risk Ratio (M-H, Random, 95% CI)	3.94 [2.60, 5.97]
2.3 Alitretinoin 20 mg vs placebo hyperkeratotic eczema	1	136	Risk Ratio (M-H, Random, 95% CI)	1.72 [1.02, 2.90]
2.4 Alitretinoin 10 mg vs placebo hyperkeratotic eczema	2	662	Risk Ratio (M-H, Random, 95% CI)	2.05 [1.47, 2.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Primary: investigator-rated good/excellent control of symptoms pompholyx	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Alitretinoin 40 mg vs placebo pompholyx	1	37	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.58, 4.72]
3.2 Alitretinoin 30 mg vs placebo pompholyx	1	166	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.06, 3.91]
3.3 Alitretinoin 20 mg vs placebo pompholyx	1	38	Risk Ratio (M-H, Random, 95% CI)	0.9 [0.26, 3.08]
3.4 Alitretinoin 10 mg vs placebo pompholyx	2	197	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.70, 2.39]
4 Primary: investigator-rated good/excellent control of symptoms fingertip	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Alitretinoin 40 mg vs placebo fingertip	1	51	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.81, 3.86]
4.2 Alitretinoin 30 mg vs placebo fingertip	1	297	Risk Ratio (M-H, Random, 95% CI)	2.49 [1.59, 3.89]
4.3 Alitretinoin 20 mg vs placebo fingertip	1	53	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.50, 2.77]
4.4 Alitretinoin 10 mg vs placebo fingertip	2	330	Risk Ratio (M-H, Random, 95% CI)	1.51 [0.99, 2.29]
5 Primary: participant-rated investigator-rated good/excellent control of symptoms	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Alitretinoin 40 mg vs placebo	1	147	Risk Ratio (M-H, Random, 95% CI)	3.51 [1.80, 6.82]
5.2 Alitretinoin 30 mg vs placebo	2	1210	Risk Ratio (M-H, Random, 95% CI)	2.75 [2.18, 3.48]
5.3 Alitretinoin 20 mg vs placebo	1	147	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.37, 5.46]
5.4 Alitretinoin 10 mg vs placebo	2	765	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.25, 2.40]
6 Primary: adverse events alitretinoin 10 mg vs placebo	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 All adverse events	1	158	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.66, 1.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Headache	2	781	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.38, 3.19]
6.3 Dry lips	2	781	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 4.66]
6.4 Flushing	2	781	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.28, 4.70]
6.5 Dry mouth	2	781	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.53, 7.44]
6.6 Erythema	2	781	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.33, 3.71]
6.7 Eczema	2	781	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.38, 1.68]
6.8 Conjunctivitis	1	158	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.05, 5.27]
6.9 Eye pruritus	1	158	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.32]
6.10 Fatigue	1	158	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.12, 70.75]
6.11 Rigors	1	158	Risk Ratio (M-H, Random, 95% CI)	2.93 [0.12, 70.75]
6.12 Tonsilitis	2	781	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.15, 1.70]
6.13 Pharyngitis	2	781	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.44, 1.54]
6.14 Influenza	1	623	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.39, 3.86]
6.15 Nausea	1	623	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.45, 5.88]
6.16 Elevated blood creatinine kinase	2	781	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.73, 2.80]
6.17 Elevated blood triglycerides	2	781	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.56, 1.88]
7 Primary: adverse events alitretinoin 20 mg vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 All adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

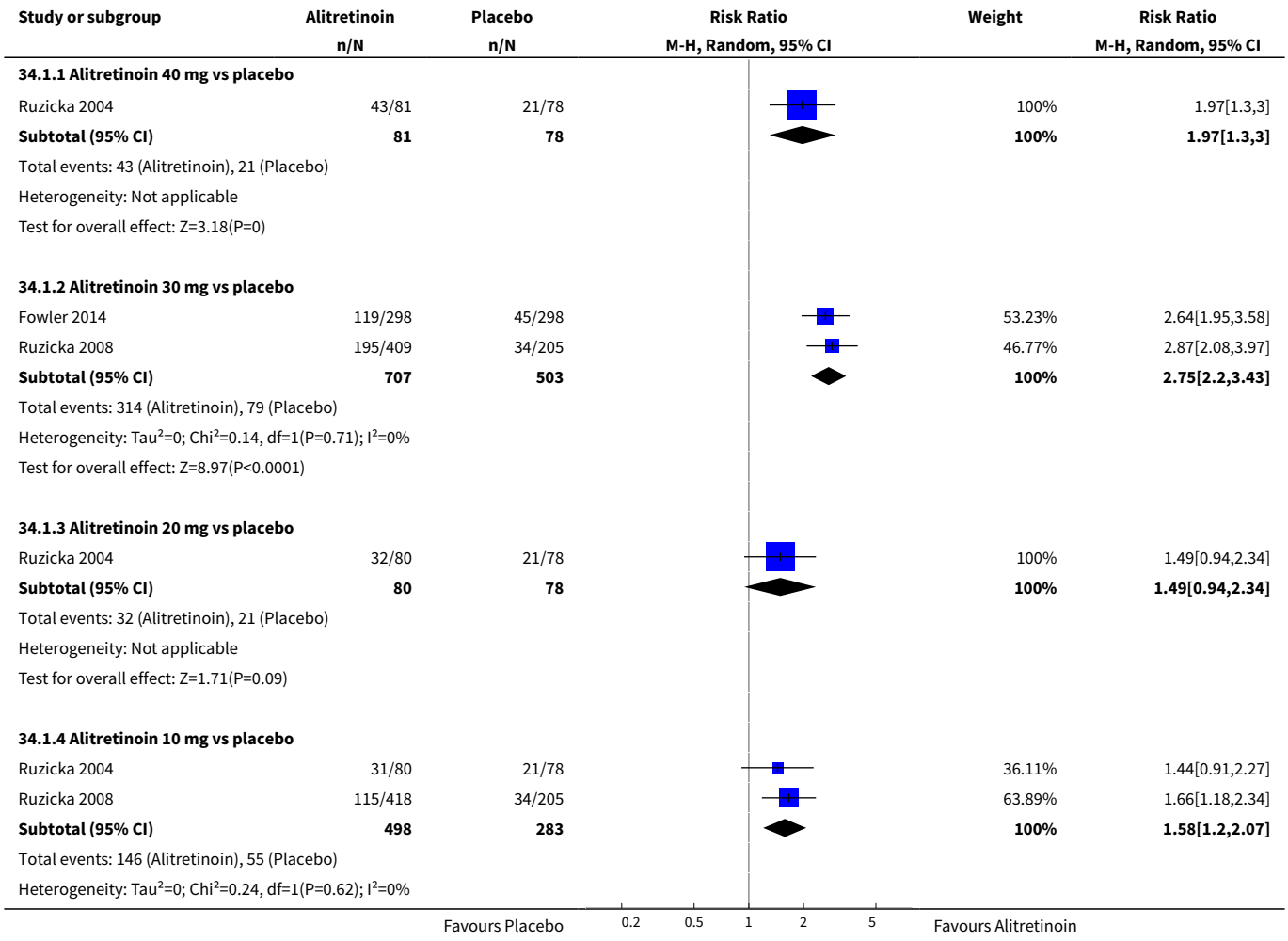
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Dry lips	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Flushing	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.5 Dry mouth	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.6 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.7 Eczema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.8 Conjunctivitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.9 Eye pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.10 Fatigue	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.11 Rigors	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.12 Tonsilitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.13 Pharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Primary: adverse events alitretinoin 30 mg vs placebo	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Headache	2	1210	Risk Ratio (M-H, Random, 95% CI)	3.43 [2.45, 4.81]
8.2 Dry lips	1	614	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.63, 5.59]
8.3 Flushing	2	1210	Risk Ratio (M-H, Random, 95% CI)	7.28 [2.05, 25.86]
8.4 Dry mouth	1	614	Risk Ratio (M-H, Random, 95% CI)	2.51 [0.55, 11.33]
8.5 Erythema	2	1210	Risk Ratio (M-H, Random, 95% CI)	5.79 [2.09, 16.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6 Eczema	1	614	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.29, 1.46]
8.7 Pharyngitis	2	1210	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.36]
8.8 Influenza	2	1210	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.45, 3.06]
8.9 Nausea	2	1210	Risk Ratio (M-H, Random, 95% CI)	3.82 [1.67, 8.76]
8.10 Elevated blood creatinine kinase	1	614	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.54, 4.93]
8.11 Elevated blood triglycerides	2	1210	Risk Ratio (M-H, Random, 95% CI)	7.05 [1.89, 26.28]
8.12 Dizziness	1	596	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.61, 6.57]
8.13 Upper respiratory tract infection	1	596	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.78, 3.04]
8.14 Sinusitis	1	596	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.35, 2.27]
8.15 Rash	1	596	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.54, 4.16]
8.16 Vomiting	1	596	Risk Ratio (M-H, Random, 95% CI)	8.00 [1.01, 63.57]
8.17 Arthralgia	1	596	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.37, 3.89]
8.18 Depression	1	596	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.61, 8.94]
8.19 Laceration	1	596	Risk Ratio (M-H, Random, 95% CI)	13.0 [0.74, 229.73]
8.20 Tinnitus	1	596	Risk Ratio (M-H, Random, 95% CI)	4.33 [1.25, 15.05]
8.21 Cough	1	596	Risk Ratio (M-H, Random, 95% CI)	2.25 [0.70, 7.23]
8.22 Hypertriglceridaemia	1	596	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.73, 49.53]
9 Primary: adverse events alitretinoin 40 mg vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 All adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Dry lips	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.4 Flushing	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.5 Dry mouth	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.6 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.7 Eczema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.8 Conjunctivitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.9 Eye pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.10 Fatigue	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.11 Rigors	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.12 Tonsilitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.13 Pharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Secondary: investigator-rated reduction in severity in total lesion symptom score			Other data	No numeric data
10.1 Alitretinoin 40 mg			Other data	No numeric data
10.2 Alitretinoin 30 mg			Other data	No numeric data
10.3 Alitretinoin 20 mg			Other data	No numeric data
10.4 Alitretinoin 10 mg			Other data	No numeric data
11 Secondary: investigator-rated reduction in severity in total lesion symptom score			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Alitretinoin 40 mg vs placebo			Other data	No numeric data
11.2 Alitretinoin 20 mg vs placebo			Other data	No numeric data
11.3 Alitretinoin 10 mg vs placebo			Other data	No numeric data
12 Secondary: reduction in severity, investigator-rated in modified total lesion symptom score (bigger reduction in severity scored negative = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

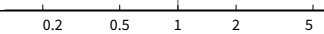
Analysis 34.1. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 1 Primary: investigator-rated good/excellent control of symptoms.



Study or subgroup	Alitretinoin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=3.24(P=0)					

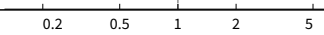
Analysis 34.2. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 2 Primary: investigator-rated good/excellent control of symptoms hyperkeratotic eczema.

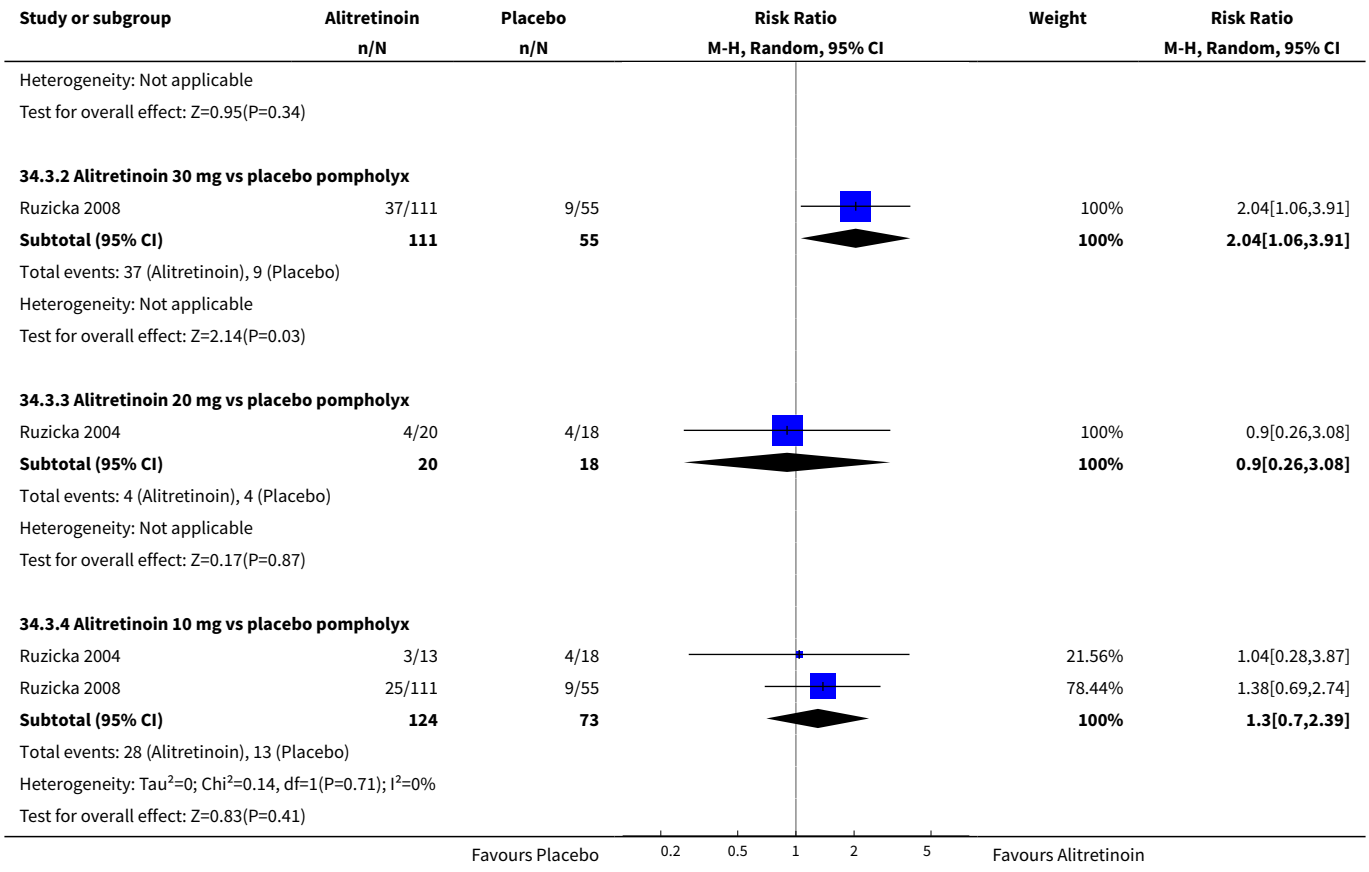
Study or subgroup	Alitretinoin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
34.2.1 Alitretinoin 40 mg vs placebo hyperkeratotic eczema					
Ruzicka 2004	41/67	15/64		100%	2.61[1.61,4.23]
Subtotal (95% CI)	**67**	**64**		**100%**	**2.61[1.61,4.23]**
Total events: 41 (Alitretinoin), 15 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.9(P<0.0001)					
34.2.2 Alitretinoin 30 mg vs placebo hyperkeratotic eczema					
Ruzicka 2008	170/349	21/170		100%	3.94[2.6,5.97]
Subtotal (95% CI)	**349**	**170**		**100%**	**3.94[2.6,5.97]**
Total events: 170 (Alitretinoin), 21 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.49(P<0.0001)					
34.2.3 Alitretinoin 20 mg vs placebo hyperkeratotic eczema					
Ruzicka 2004	29/72	15/64		100%	1.72[1.02,2.9]
Subtotal (95% CI)	**72**	**64**		**100%**	**1.72[1.02,2.9]**
Total events: 29 (Alitretinoin), 15 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					
34.2.4 Alitretinoin 10 mg vs placebo hyperkeratotic eczema					
Ruzicka 2004	27/66	15/64		40.08%	1.75[1.03,2.96]
Ruzicka 2008	102/362	21/170		59.92%	2.28[1.48,3.52]
Subtotal (95% CI)	**428**	**234**		**100%**	**2.05[1.47,2.86]**
Total events: 129 (Alitretinoin), 36 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=4.2(P<0.0001)					



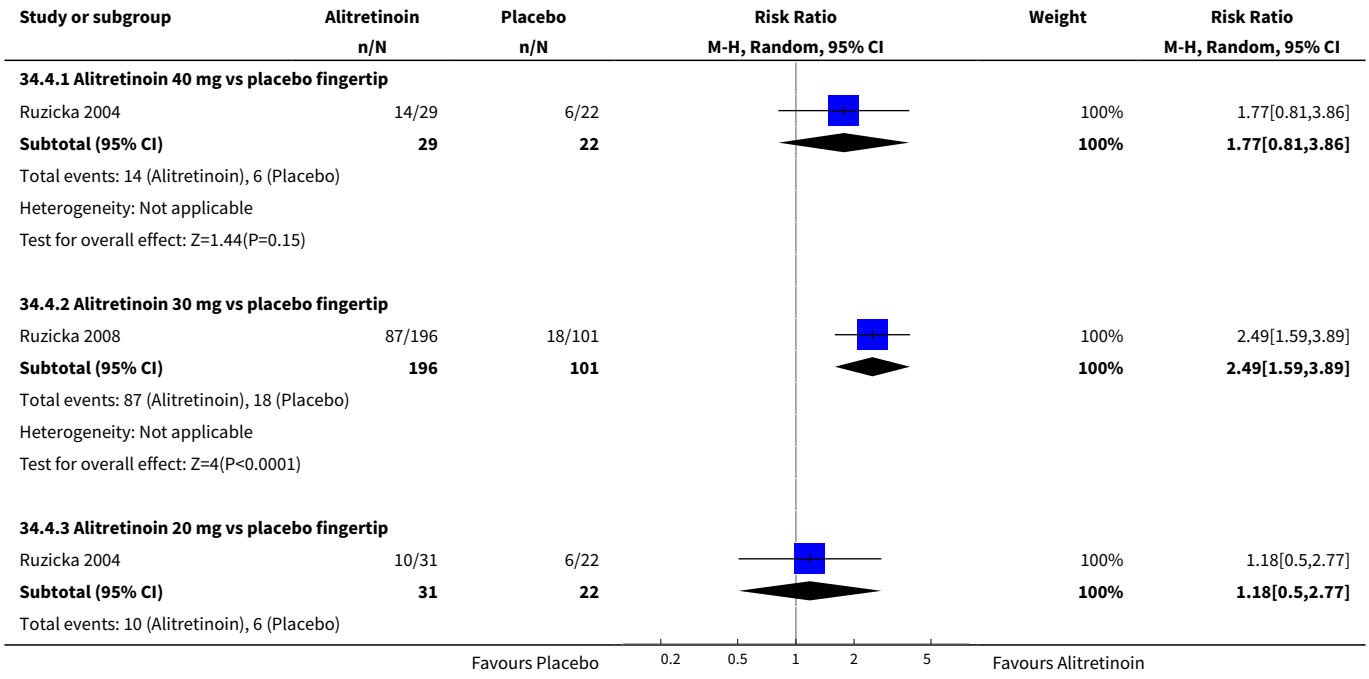
Analysis 34.3. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 3 Primary: investigator-rated good/excellent control of symptoms pompholyx.

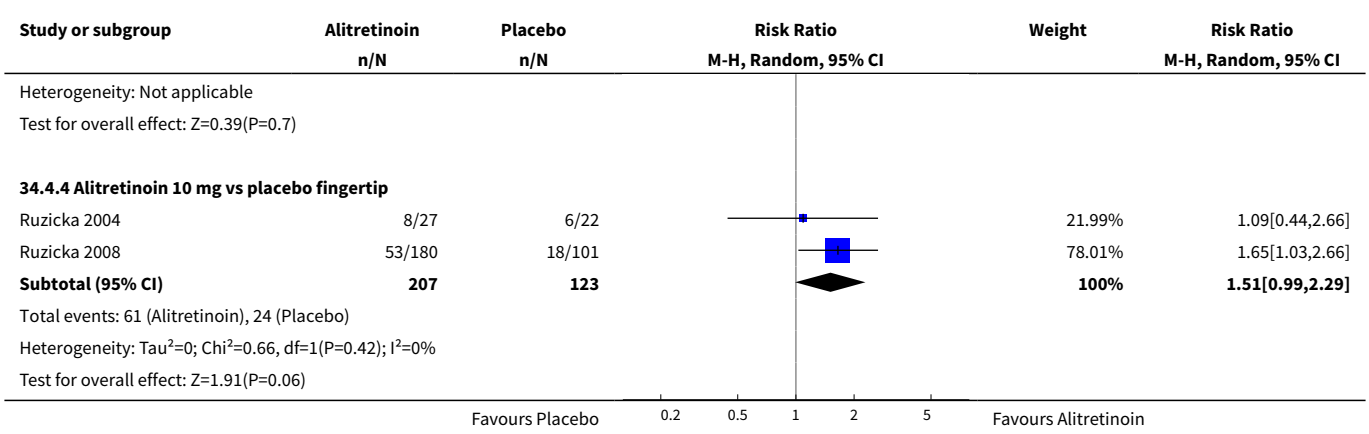
Study or subgroup	Alitretinoin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
34.3.1 Alitretinoin 40 mg vs placebo pompholyx					
Ruzicka 2004	7/19	4/18		100%	1.66[0.58,4.72]
Subtotal (95% CI)	**19**	**18**		**100%**	**1.66[0.58,4.72]**
Total events: 7 (Alitretinoin), 4 (Placebo)					



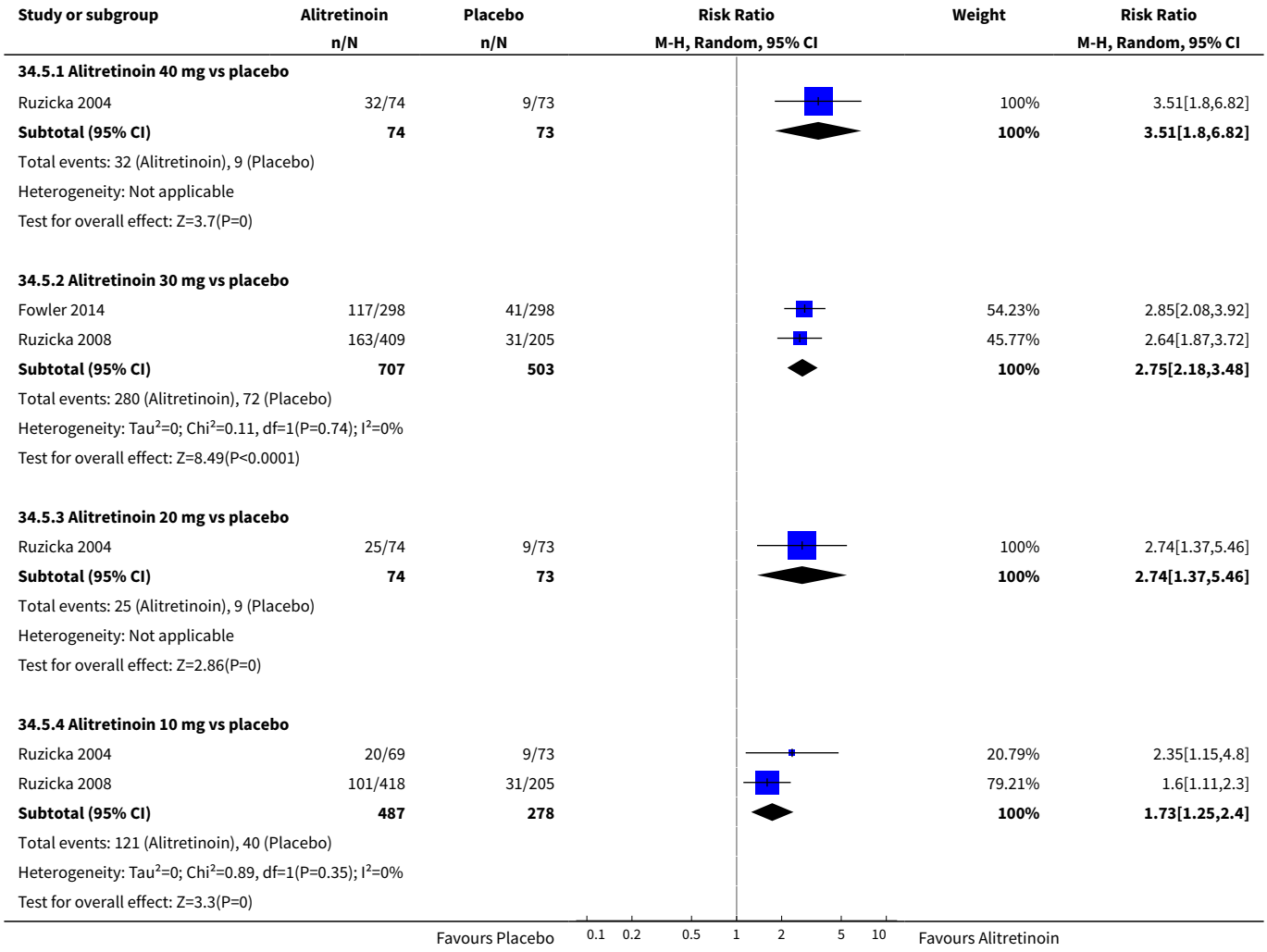


Analysis 34.4. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 4 Primary: investigator-rated good/excellent control of symptoms fingertip.



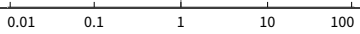


Analysis 34.5. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 5 Primary: participant-rated investigator-rated good/excellent control of symptoms.



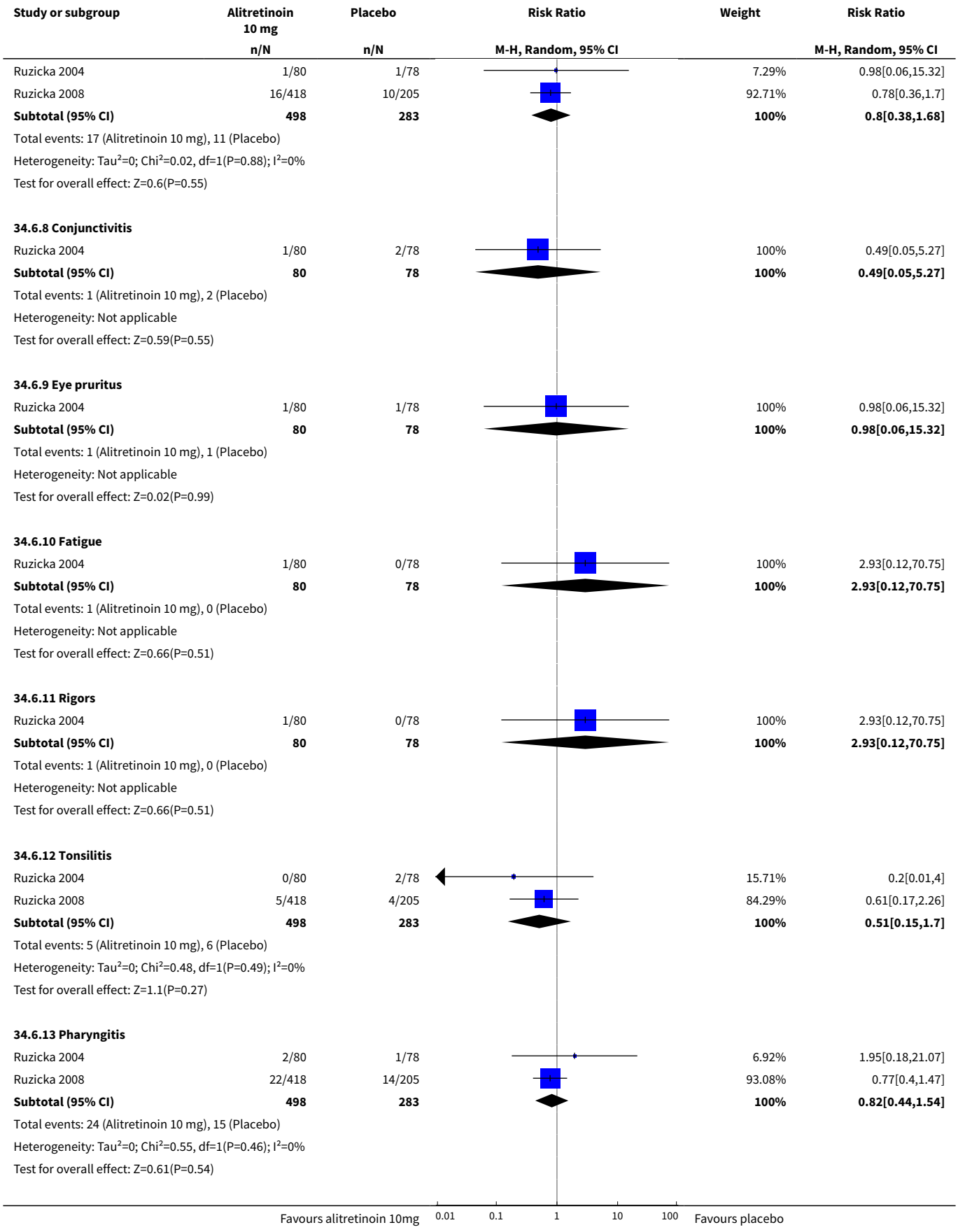
Analysis 34.6. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 6 Primary: adverse events alitretinoin 10 mg vs placebo.

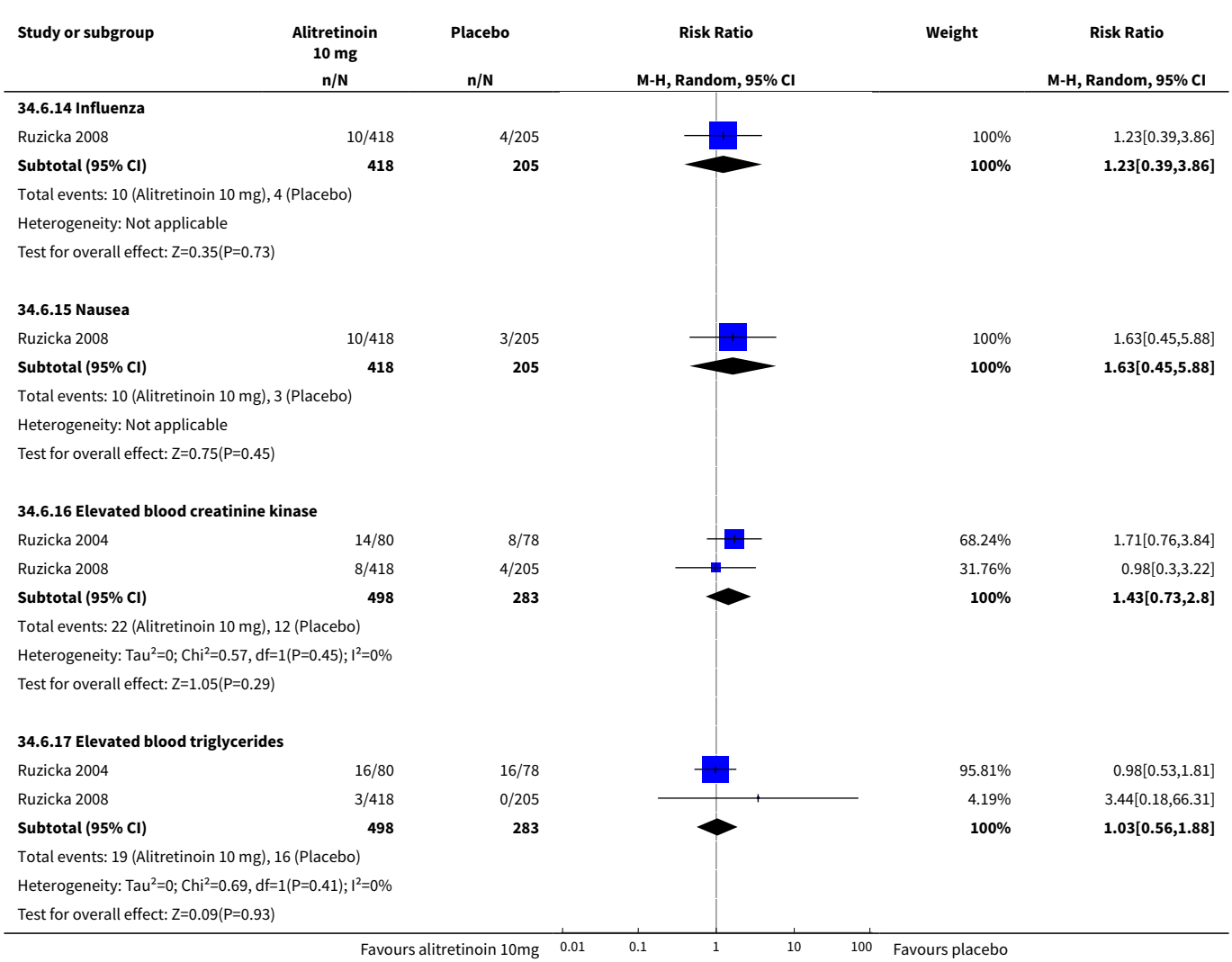
Study or subgroup	Alitretinoin 10 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
34.6.1 All adverse events					
Ruzicka 2004	28/80	27/78		100%	1.01[0.66,1.55]
Subtotal (95% CI)	**80**	**78**		**100%**	**1.01[0.66,1.55]**
Total events: 28 (Alitretinoin 10 mg), 27 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
34.6.2 Headache					
Ruzicka 2004	4/80	7/78		38.9%	0.56[0.17,1.83]
Ruzicka 2008	45/418	13/205		61.1%	1.7[0.94,3.08]
Subtotal (95% CI)	**498**	**283**		**100%**	**1.1[0.38,3.19]**
Total events: 49 (Alitretinoin 10 mg), 20 (Placebo)					
Heterogeneity: Tau^2=0.39; Chi^2=2.7, df=1(P=0.1); I^2=63%					
Test for overall effect: Z=0.18(P=0.86)					
34.6.3 Dry lips					
Ruzicka 2004	0/80	4/78		34.01%	0.11[0.01,1.98]
Ruzicka 2008	9/418	4/205		65.99%	1.1[0.34,3.54]
Subtotal (95% CI)	**498**	**283**		**100%**	**0.5[0.05,4.66]**
Total events: 9 (Alitretinoin 10 mg), 8 (Placebo)					
Heterogeneity: Tau^2=1.61; Chi^2=2.26, df=1(P=0.13); I^2=55.74%					
Test for overall effect: Z=0.61(P=0.54)					
34.6.4 Flushing					
Ruzicka 2004	1/80	1/78		25.97%	0.98[0.06,15.32]
Ruzicka 2008	5/418	2/205		74.03%	1.23[0.24,6.27]
Subtotal (95% CI)	**498**	**283**		**100%**	**1.16[0.28,4.7]**
Total events: 6 (Alitretinoin 10 mg), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					
34.6.5 Dry mouth					
Ruzicka 2004	1/80	1/78		23.09%	0.98[0.06,15.32]
Ruzicka 2008	10/418	2/205		76.91%	2.45[0.54,11.09]
Subtotal (95% CI)	**498**	**283**		**100%**	**1.98[0.53,7.44]**
Total events: 11 (Alitretinoin 10 mg), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					
34.6.6 Erythema					
Ruzicka 2004	1/80	1/78		19.19%	0.98[0.06,15.32]
Ruzicka 2008	7/418	3/205		80.81%	1.14[0.3,4.38]
Subtotal (95% CI)	**498**	**283**		**100%**	**1.11[0.33,3.71]**
Total events: 8 (Alitretinoin 10 mg), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.17(P=0.87)					
34.6.7 Eczema					



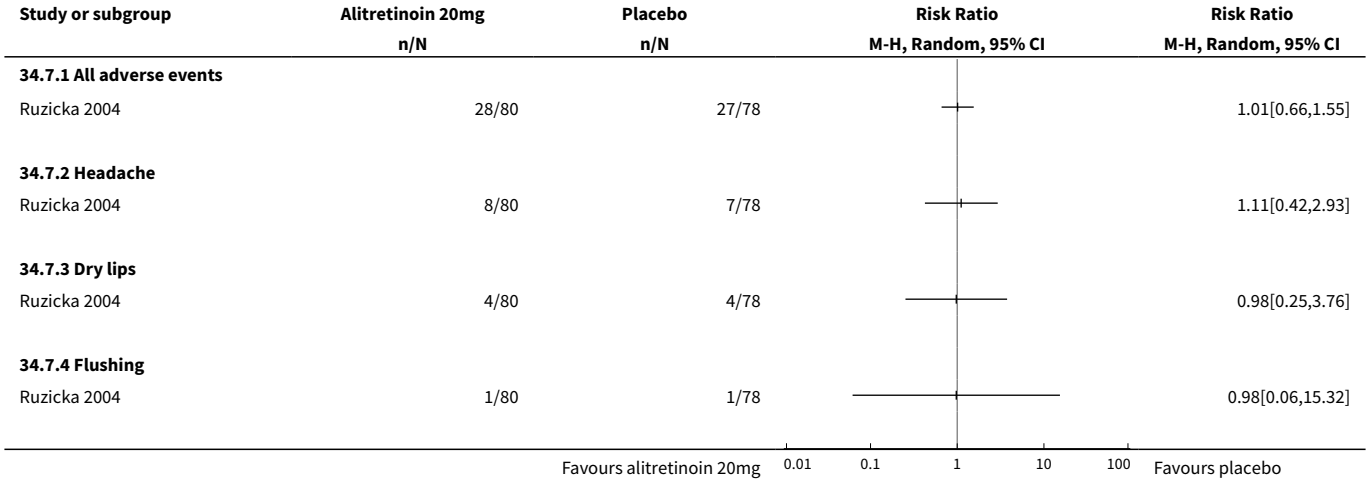
Favours alitretinoin 10mg

Favours placebo

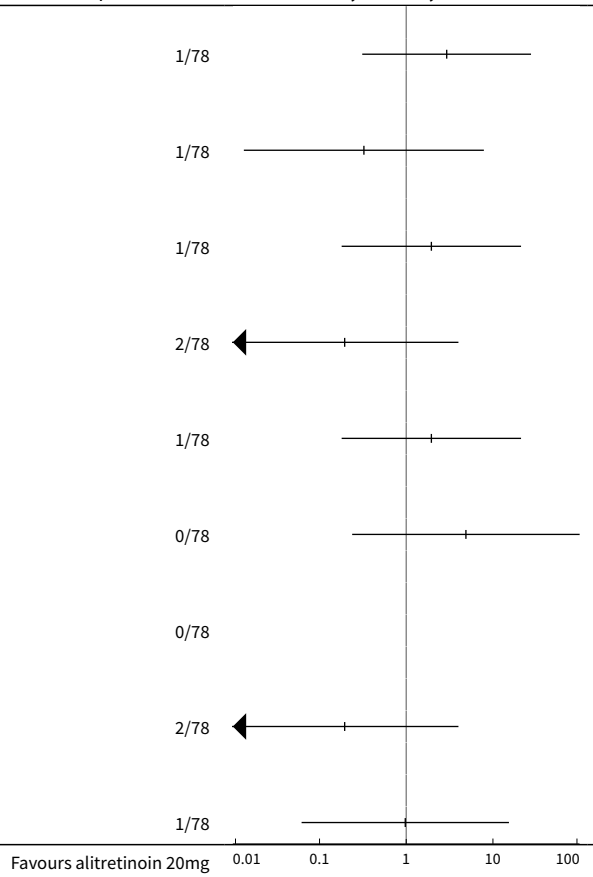




Analysis 34.7. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 7 Primary: adverse events alitretinoin 20 mg vs placebo.

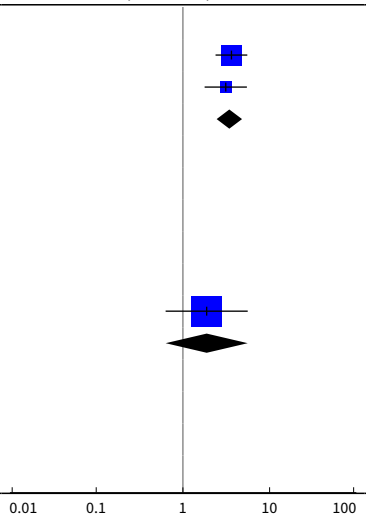


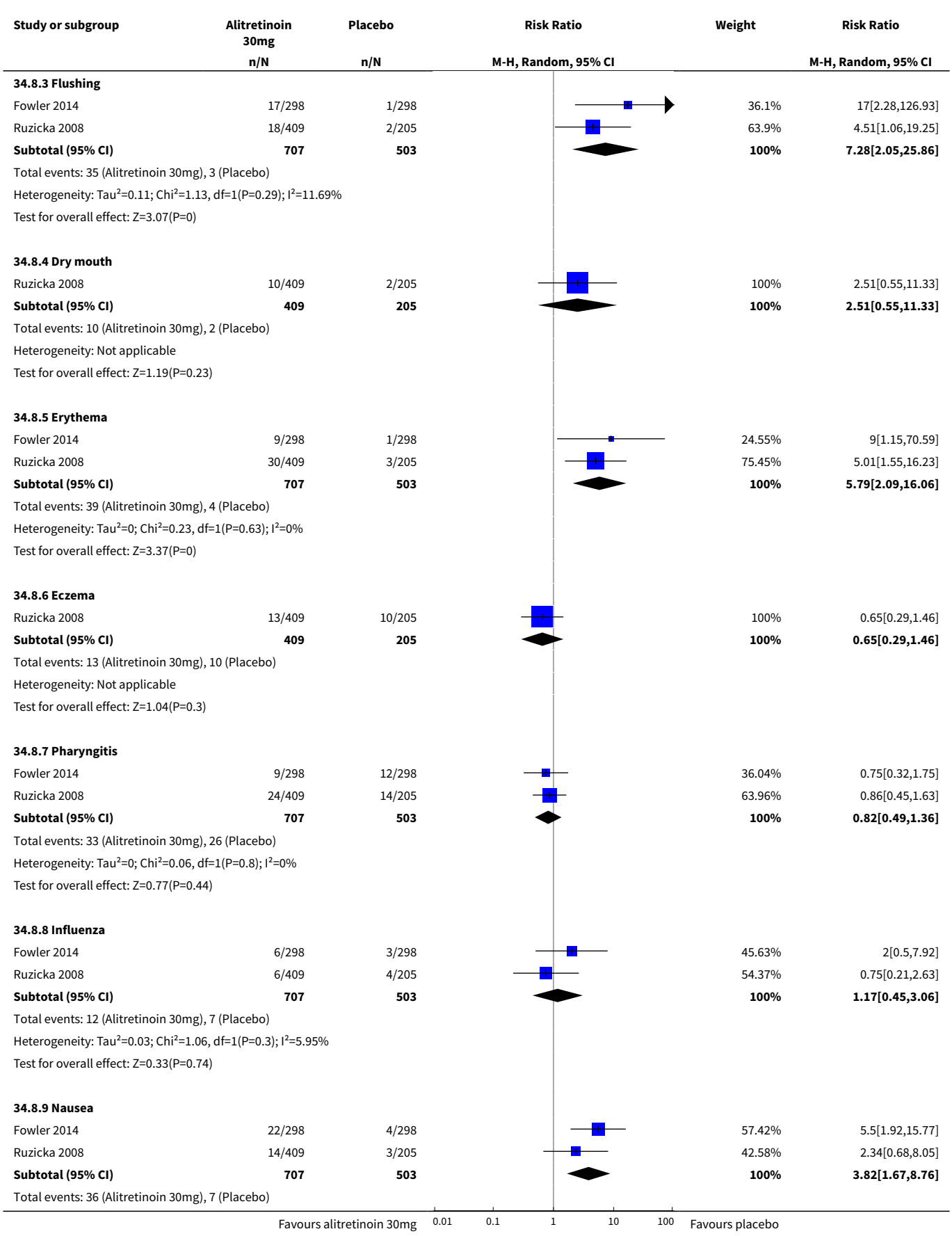
Study or subgroup	Alitretinoin 20mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
34.7.5 Dry mouth				
Ruzicka 2004	3/80	1/78		2.93[0.31,27.52]
34.7.6 Erythema				
Ruzicka 2004	0/80	1/78		0.33[0.01,7.86]
34.7.7 Eczema				
Ruzicka 2004	2/80	1/78		1.95[0.18,21.07]
34.7.8 Conjunctivitis				
Ruzicka 2004	0/80	2/78		0.2[0.01,4]
34.7.9 Eye pruritus				
Ruzicka 2004	2/80	1/78		1.95[0.18,21.07]
34.7.10 Fatigue				
Ruzicka 2004	2/80	0/78		4.88[0.24,99.98]
34.7.11 Rigors				
Ruzicka 2004	0/80	0/78		Not estimable
34.7.12 Tonsilitis				
Ruzicka 2004	0/80	2/78		0.2[0.01,4]
34.7.13 Pharyngitis				
Ruzicka 2004	1/80	1/78		0.98[0.06,15.32]

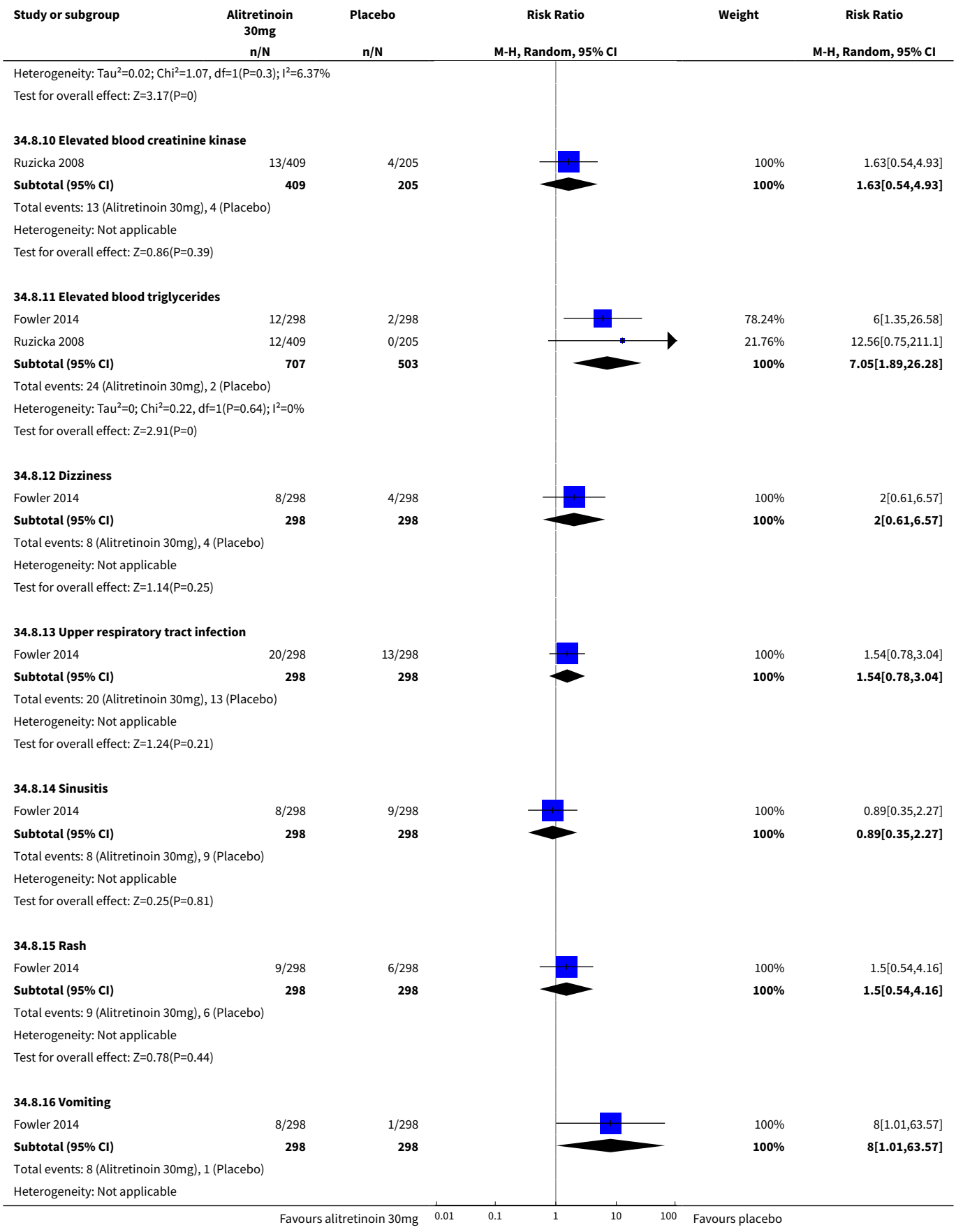


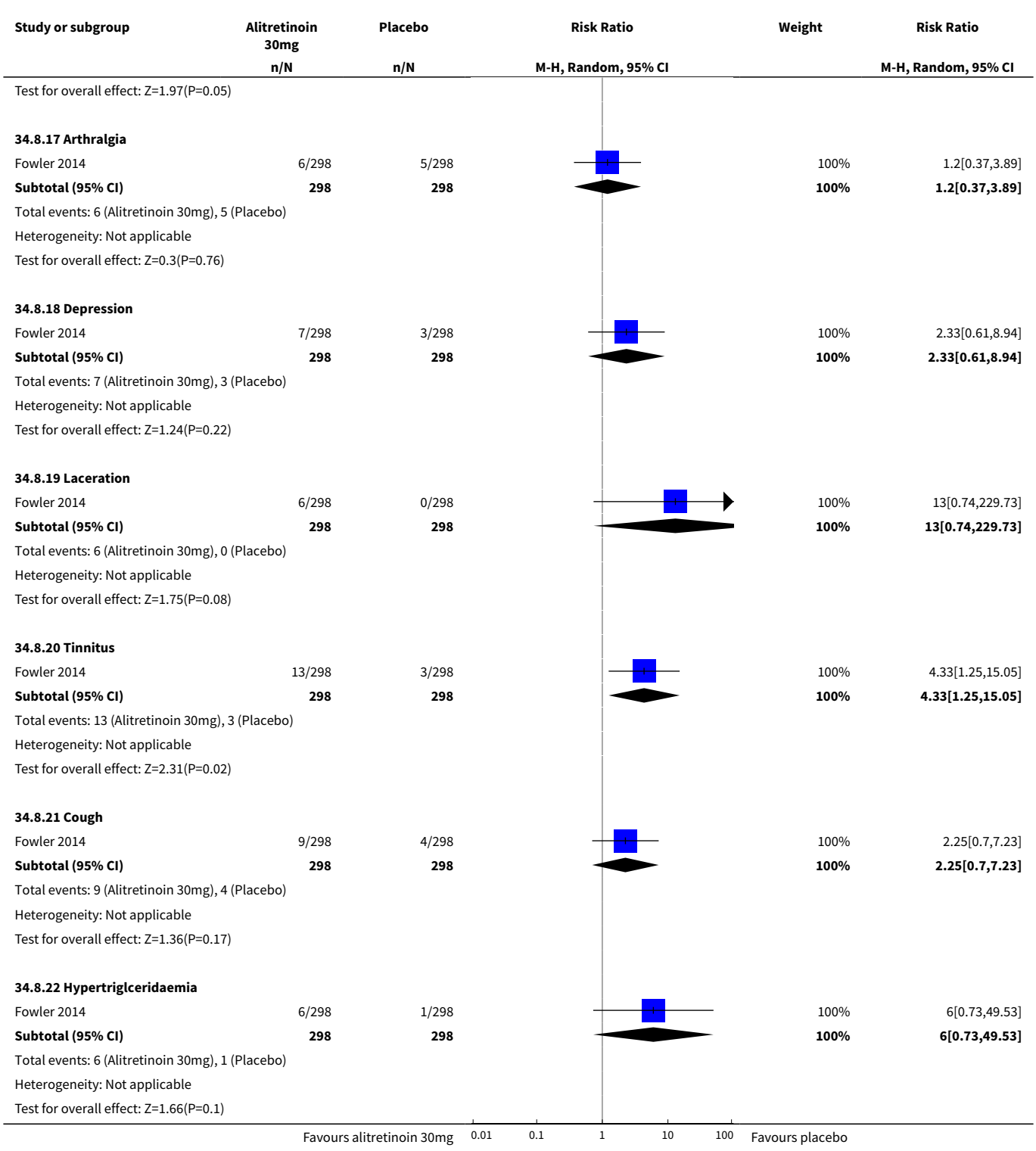
Analysis 34.8. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 8 Primary: adverse events alitretinoin 30 mg vs placebo.

Study or subgroup	Alitretinoin 30mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
34.8.1 Headache					
Fowler 2014	87/298	24/298		63.82%	3.63[2.38,5.53]
Ruzicka 2008	81/409	13/205		36.18%	3.12[1.78,5.47]
Subtotal (95% CI)	**707**	**503**		**100%**	**3.43[2.45,4.81]**
Total events: 168 (Alitretinoin 30mg), 37 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=7.17(P<0.0001)					
34.8.2 Dry lips					
Ruzicka 2008	15/409	4/205		100%	1.88[0.63,5.59]
Subtotal (95% CI)	**409**	**205**		**100%**	**1.88[0.63,5.59]**
Total events: 15 (Alitretinoin 30mg), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.13(P=0.26)					



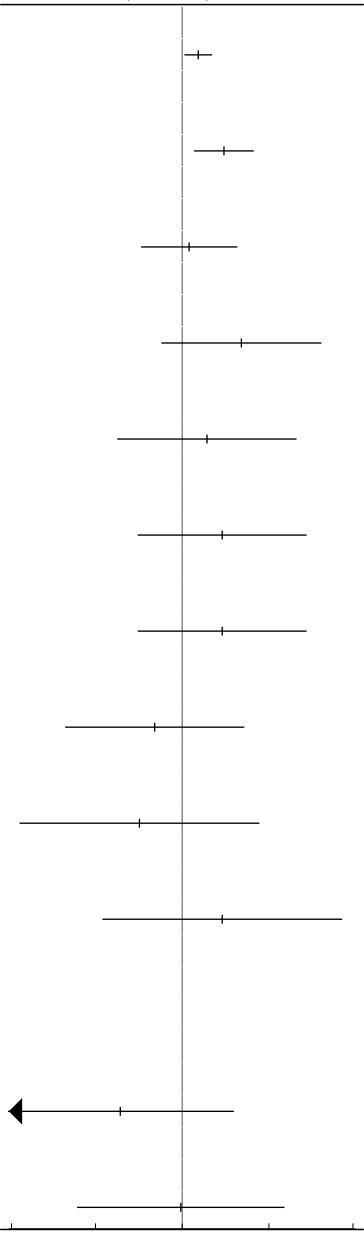






Analysis 34.9. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 9 Primary: adverse events alitretinoin 40 mg vs placebo.

Study or subgroup	Alitretinoin 40 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
34.9.1 All adverse events				
Ruzicka 2004	43/81	27/78		1.53[1.06,2.21]
34.9.2 Headache				
Ruzicka 2004	22/81	7/78		3.03[1.37,6.68]
34.9.3 Dry lips				
Ruzicka 2004	5/81	4/78		1.2[0.34,4.32]
34.9.4 Flushing				
Ruzicka 2004	5/81	1/78		4.81[0.58,40.29]
34.9.5 Dry mouth				
Ruzicka 2004	2/81	1/78		1.93[0.18,20.81]
34.9.6 Erythema				
Ruzicka 2004	3/81	1/78		2.89[0.31,27.18]
34.9.7 Eczema				
Ruzicka 2004	3/81	1/78		2.89[0.31,27.18]
34.9.8 Conjunctivitis				
Ruzicka 2004	1/81	2/78		0.48[0.04,5.2]
34.9.9 Eye pruritus				
Ruzicka 2004	0/81	1/78		0.32[0.01,7.77]
34.9.10 Fatigue				
Ruzicka 2004	1/81	0/78		2.89[0.12,69.9]
34.9.11 Rigors				
Ruzicka 2004	0/81	0/78		Not estimable
34.9.12 Tonsilitis				
Ruzicka 2004	0/81	2/78		0.19[0.01,3.95]
34.9.13 Pharyngitis				
Ruzicka 2004	1/81	1/78		0.96[0.06,15.13]



Analysis 34.10. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 10 Secondary: investigator-rated reduction in severity in total lesion symptom score.

Study	Secondary: investigator-rated reduction in severity in total lesion symptom score
Alitretinoin 40 mg	
Ruzicka 2004	Median of % change from baseline: -70.5% (95% CI -44 to -80).
Ruzicka 2004	Significant more reduction than placebo (P < 0.001; Kruskal-Wallis test).
Alitretinoin 30 mg	

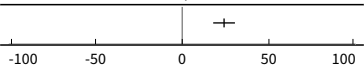
Secondary: investigator-rated reduction in severity in total lesion symptom score	
Study	
Ruzicka 2008	Median of % change from baseline: -75%
Ruzicka 2008	Significant more reduction than placebo (P < 0.001; Kruskal-Wallis test).
Alitretinoin 20 mg	
Ruzicka 2004	Median of % change from baseline: -52 (95% CI -42 to -73)
Ruzicka 2004	Significant more reduction than placebo (P < 0.01; Kruskal-Wallis test).
Alitretinoin 10 mg	
Ruzicka 2004	Median of % change from baseline: -25% (95% CI -14 to -42)
Ruzicka 2004	Significant more reduction than placebo (P < 0.01; Kruskal-Wallis test).
Ruzicka 2008	Median of % change from baseline: -56%
Ruzicka 2008	Significant more reduction than placebo (P < 0.01; Kruskal-Wallis test).

Analysis 34.11. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 11 Secondary: investigator-rated reduction in severity in total lesion symptom score.

Secondary: investigator-rated reduction in severity in total lesion symptom score				
Study	**Group**	**Median**	**SD**	**N**
		Alitretinoin 40 mg vs placebo		
Ruzicka 2004	Alitretinoin 40 mg	70.5	81.407	81
Ruzicka 2004	Placebo	25.0	62.13	78
		Alitretinoin 20 mg vs placebo		
Ruzicka 2004	Alitretinoin 20 mg	52.0	80.9	80
Ruzicka 2004	Placebo	25.0	62.13	78
		Alitretinoin 10 mg vs placebo		
Ruzicka 2004	Alitretinoin 10 mg	59.0	89.892	80
Ruzicka 2004	Placebo	25.0	62.13	78

Analysis 34.12. Comparison 34 Oral retinoids: alitretinoin versus placebo, Outcome 12 Secondary: reduction in severity, investigator-rated in modified total lesion symptom score (bigger reduction in severity scored negative = better outcome).

Study or subgroup	Alitretinoin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Fowler 2014	298	54 (40.2)	298	29.9 (37.8)		24.13[17.87,30.39]



Comparison 35. Oral retinoids: re-treatment alitretinoin versus placebo

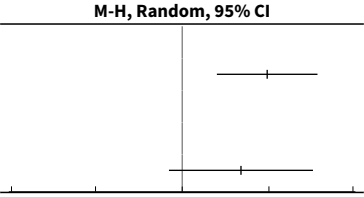
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Alitretinoin 30 mg vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Alitretinoin 10 mg vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Primary: adverse events 10 mg vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Any adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Treatment-related adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Nasopharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Influenza	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Eczema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.7 Dermatitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.8 Dry lips	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.9 Cheilitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.10 Dry mouth	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.11 Elevated triglycerides	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.12 High cholesterol	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.13 High triglycerides	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Primary: adverse events 30 mg vs placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Any adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Treatment-related adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Treatment-related serious adverse event	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Nasopharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.5 Rhinitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Bronchitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.7 Upper respiratory tract infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Influenza	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.9 Erythema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.10 Eczema	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.11 Dermatitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.12 Dry skin	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.13 Headache	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.14 Dry lips	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.15 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.16 Cheilitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.17 Dry mouth	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.18 Elevated creatinine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.19 TSH high	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.20 TSH low	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.21 High cholesterol	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.22 High triglycerides	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

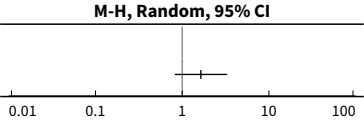
Analysis 35.1. Comparison 35 Oral retinoids: re-treatment alitretinoin versus placebo, Outcome 1 Primary: investigator-rated good/excellent control of symptoms.

Study or subgroup	Alitretinoin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
35.1.1 Alitretinoin 30 mg vs placebo				
Bissonnette 2010	39/49	2/24		9.55[2.51,36.27]
35.1.2 Alitretinoin 10 mg vs placebo				
Bissonnette 2010	10/21	1/10		4.76[0.7,32.25]

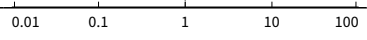


Analysis 35.2. Comparison 35 Oral retinoids: re-treatment alitretinoin versus placebo, Outcome 2 Primary: adverse events 10 mg vs placebo.

Study or subgroup	Alitretinoin 10 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
35.2.1 Any adverse event				
Bissonnette 2010	9/21	12/46		1.64[0.82,3.29]

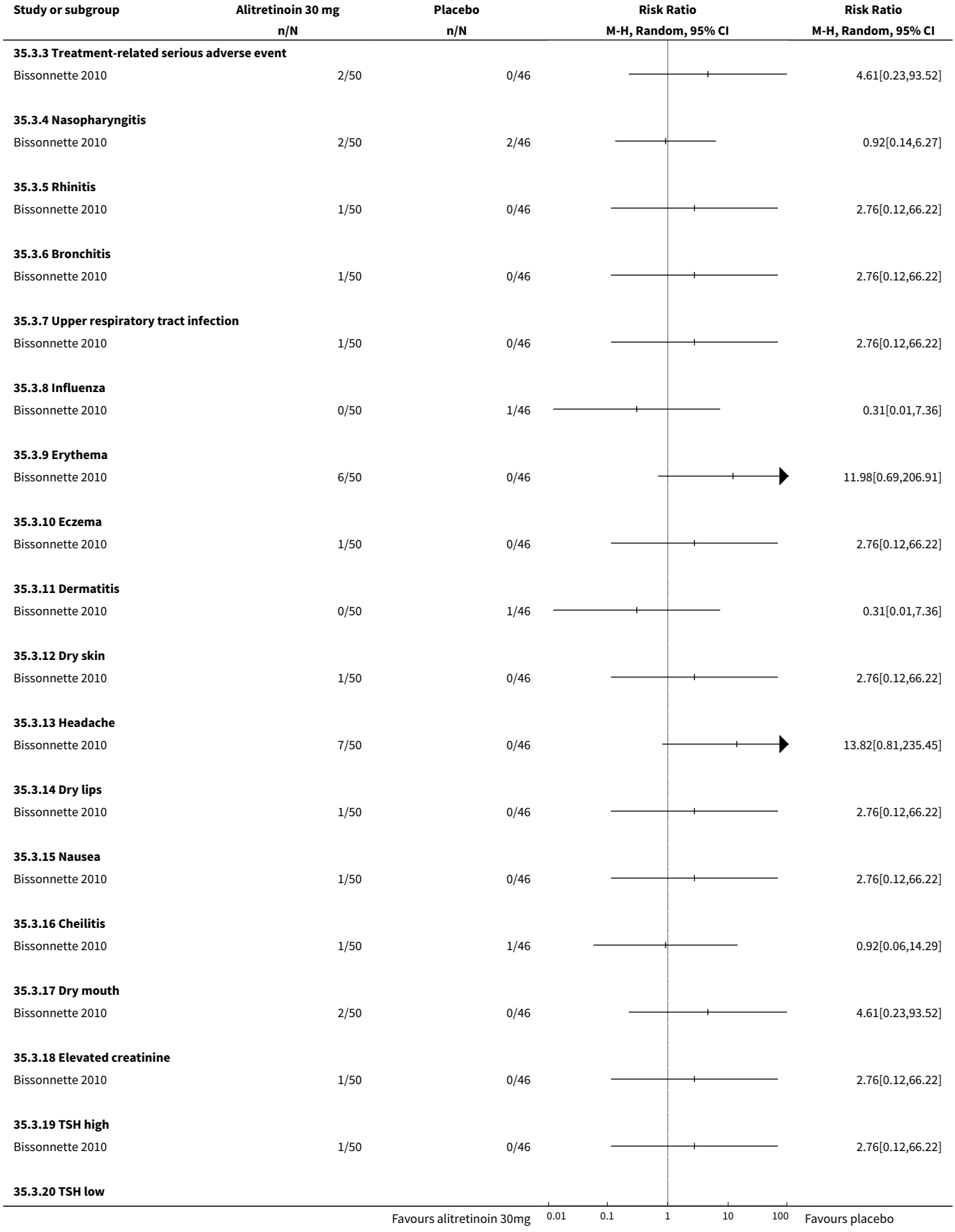


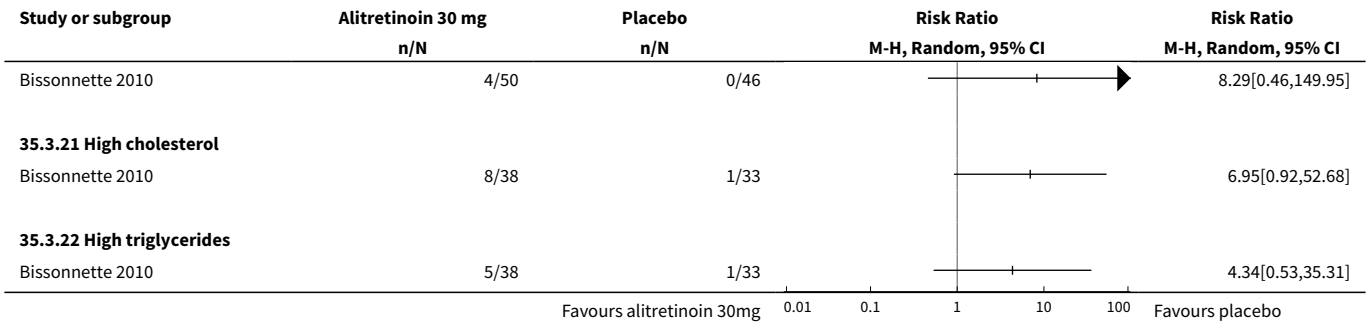
Study or subgroup	Alitretinoin 10 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
35.2.2 Treatment-related adverse event				
Bissonnette 2010	6/21	8/46		1.64[0.65,4.14]
35.2.3 Nasopharyngitis				
Bissonnette 2010	1/21	2/46		1.1[0.11,11.42]
35.2.4 Influenza				
Bissonnette 2010	0/21	1/46		0.71[0.03,16.79]
35.2.5 Erythema				
Bissonnette 2010	1/21	0/46		6.41[0.27,151.11]
35.2.6 Eczema				
Bissonnette 2010	0/21	1/46		0.71[0.03,16.79]
35.2.7 Dermatitis				
Bissonnette 2010	1/21	1/46		2.19[0.14,33.36]
35.2.8 Dry lips				
Bissonnette 2010	0/21	1/46		0.71[0.03,16.79]
35.2.9 Cheilitis				
Bissonnette 2010	0/21	1/46		0.71[0.03,16.79]
35.2.10 Dry mouth				
Bissonnette 2010	1/21	0/46		6.41[0.27,151.11]
35.2.11 Elevated triglycerides				
Bissonnette 2010	1/21	0/46		6.41[0.27,151.11]
35.2.12 High cholesterol				
Bissonnette 2010	0/21	1/46		0.71[0.03,16.79]
35.2.13 High triglycerides				
Bissonnette 2010	0/21	0/46		Not estimable



Analysis 35.3. Comparison 35 Oral retinoids: re-treatment alitretinoin versus placebo, Outcome 3 Primary: adverse events 30 mg vs placebo.

Study or subgroup	Alitretinoin 30 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
35.3.1 Any adverse event				
Bissonnette 2010	22/50	12/46		1.69[0.95,3.01]
35.3.2 Treatment-related adverse event				
Bissonnette 2010	16/50	8/46		1.84[0.87,3.89]





Comparison 36. Other oral interventions: oral triethylenetetramine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator- and/or participant-rated improvement			Other data	No numeric data

Analysis 36.1. Comparison 36 Other oral interventions: oral triethylenetetramine versus placebo, Outcome 1 Primary: investigator- and/or participant-rated improvement.

		Primary: investigator- and/or participant-rated improvement	
Study	Group - within-participant study	Event	Total number of participants analysed
Burrows 1986	Trientine	6	20
Burrows 1986	Placebo	10	20

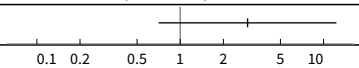
Comparison 37. Other oral interventions: oral tetraethylthiuram disulfide (TETDS) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms during treatment period	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Discontinuation due to depression	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Discontinuation due to dyspepsia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Hepatic toxicity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Headache requiring dose reduction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 37.1. Comparison 37 Other oral interventions: oral tetraethylthiuram disulfide (TETDS) versus placebo, Outcome 1 Primary: investigator-rated good/excellent control of symptoms during treatment period.

Study or subgroup	TETDS n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kaaber 1983	5/11	2/13		2.95[0.71,12.34]



Favours placebo — Favours TETDS

Analysis 37.2. Comparison 37 Other oral interventions: oral tetraethylthiuram disulfide (TETDS) versus placebo, Outcome 2 Primary: adverse events.

Study or subgroup	TETDS n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
37.2.1 Discontinuation due to depression				
Kaaber 1983	1/15	0/15		3[0.13,68.26]
37.2.2 Discontinuation due to dyspepsia				
Kaaber 1983	1/15	0/15		3[0.13,68.26]
37.2.3 Hepatic toxicity				
Kaaber 1983	2/15	0/15		5[0.26,96.13]
37.2.4 Headache requiring dose reduction				
Kaaber 1983	1/15	0/15		3[0.13,68.26]

Favours TETDS — Favours placebo

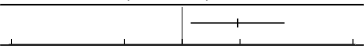
Comparison 38. Other oral interventions: low-nickel diet (LND) + disulphiram versus normal diet + placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: investigator-rated good/excellent control of symptoms after 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Primary: adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Metallic taste	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Drowsiness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Elevation of liver enzymes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 38.1. Comparison 38 Other oral interventions: low-nickel diet (LND) + disulphiram versus normal diet + placebo, Outcome 1 Primary: investigator-rated good/excellent control of symptoms after 4 weeks.

Study or subgroup	LND + disulphiram n/N	Normal diet + placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Sharma 2006	10/11	1/10		9.09[1.4,58.91]

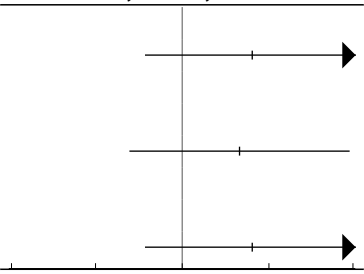


Favours norm diet+placebo

Favours LND + disulphiram

Analysis 38.2. Comparison 38 Other oral interventions: low-nickel diet (LND) + disulphiram versus normal diet + placebo, Outcome 2 Primary: adverse events.

Study or subgroup	LND + disulphiram n/N	Normal diet + placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
38.2.1 Metallic taste				
Sharma 2006	3/11	0/10		6.42[0.37,110.71]
38.2.2 Drowsiness				
Sharma 2006	2/11	0/10		4.58[0.25,85.33]
38.2.3 Elevation of liver enzymes				
Sharma 2006	3/11	0/10		6.42[0.37,110.71]



Favours LND + disulphiram

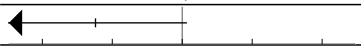
Favours norm diet+placebo

Comparison 39. Other oral interventions: oral evening primrose oil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Secondary: investigator-rated reduction in severity score at week 24 (bigger reduction in severity = better outcome)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 39.1. Comparison 39 Other oral interventions: oral evening primrose oil versus placebo, Outcome 1 Secondary: investigator-rated reduction in severity score at week 24 (bigger reduction in severity = better outcome).

Study or subgroup	Evening primrose oil		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Whitaker 1996	19	18 (12.4)	15	30.4 (23.4)		-12.4[-25.46,0.66]



Favours primrose oil — Favours placebo

Comparison 40. Other oral interventions: oral ranitidine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: participant- and investigator-rated good/excellent control of symptoms	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 40.1. Comparison 40 Other oral interventions: oral ranitidine versus placebo, Outcome 1 Primary: participant- and investigator-rated good/excellent control of symptoms.

Study or subgroup	Oral ranitidine	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Veien 1995	17/23	8/24		2.22[1.2,4.1]

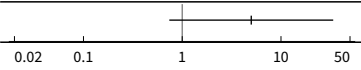
Favours placebo — Favours oral ranitidine

Comparison 41. Other oral interventions: disodium cromoglycate diet (DSCG) versus low-nickel diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary: participant-rated good/excellent control of symptoms (itch) after 3 months of itch in DSCG versus diet	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 41.1. Comparison 41 Other oral interventions: disodium cromoglycate diet (DSCG) versus low-nickel diet, Outcome 1 Primary: participant-rated good/excellent control of symptoms (itch) after 3 months of itch in DSCG versus diet.

Study or subgroup	DSCG	Low nickel diet	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Pigatto 1990	5/8	1/8		5[0.74,33.78]



Favours low nickel diet — Favours DSCG diet

ADDITIONAL TABLES

Table 1. Overview of studies on bland emollients: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comment
Kucharekova 2003	Ceramide-containing emollient versus regular petrolatum-based emollient	No data regarding the primary outcome investigator-rated good/excellent control	-
Chu 2009	E-DO lotion versus vehicle lotion	E-DO: 37 responders, 12 of whom responded to E-DO only (19%), and 25 to both (39.7%) Vehicle: 36 responders, 11 of whom responded to vehicle only (17.5%), and 25 to both (39.7%) Investigator-rated RR 1.06 (95% CI 0.54 to 2.10)	Within-patient study

E-DO is a trade/product name.

Table 2. Overview of studies on topical corticosteroids: investigator-rated good/excellent control

Study	Comparison of topical corticosteroids	Investigator-rated good/excellent control in RR (95% CI)	Comment
Möller 1983	Intermittent clobetasol versus fluprednidene	Clobetasol better since 32/46 versus 14/46 hands remained in remission; investigator-rated	Within-patient study
Uggeldahl 1986	Desonide 0.1% versus desonide 0.05%	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Bleeker 1989	Fluprednidene versus betamethasone	RR 0.59 (95% CI 0.28 to 1.23); investigator-rated	-
Gupta 1993	Betamethasone film versus betamethasone lotion	RR 10.24 (95% CI 0.59 to 176.56); investigator-rated	-
Veien 1999	Mometasone 3 times/week versus mometasone 2 times/week	RR 1.23 (95% CI 0.94 to 1.61); investigator-rated	-
Fowler 2005	Hydrocortisone butyrate versus fluticasone propionate twice daily Hydrocortisone butyrate versus prednicarbate emollient twice daily Hydrocortisone butyrate 0.1% cream versus mometasone furoate twice daily	No data regarding the primary outcome investigator-rated good/excellent control	Three parallel treatment groups Each group separately within-patient
Faghihi 2008	0.05% clobetasol cream versus 0.05% clobetasol + zinc sulphate cream	Clobetasol + zinc sulphate better in terms of respectively scaling (25/47 versus 3/47), redness (41/47 versus 1/41), and lichenification (24/47 versus 7/47); investigator-rated	Within-patient study
Lodén 2012a	Betamethasone-valerate 0.1% cream twice daily versus betamethasone-valerate 0.1%	RR 0.75 (0.55 to 1.03); investigator-rated	-

Table 2. Overview of studies on topical corticosteroids: investigator-rated good/excellent control *(Continued)*

	cream once daily + urea 5% cream once daily		
Kircik 2013	Clobetasol propionate 0.05% foam twice daily versus vehicle foam twice daily	RR 1.43 (0.86 to 2.40); investigator-rated	-

CI: confidence interval.
RR: risk ratio.

Table 3. Overview of studies on coal tar and derivatives: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comment
Kemper 1998	Coal tar paste versus betamethasone-valerate or zinc oxide once a week	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study

Table 4. Overview of studies on irradiation with UV light: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comment
Bayerl 1999	UVB versus no UVB	No data regarding the primary outcome investigator-rated good/excellent control	-
Sjövall 1987	Local UVB versus placebo	RR 2.0 (95% CI 0.26 to 15.6)	-
Sjövall 1987	Local UVB hand versus whole body + hand UVB	RR 2.2 (95% CI 0.83 to 5.8)	-
Sjövall 1987	Local UVB hand versus whole body versus placebo	RR 3.67 (95% CI 0.90 to 14.97)	-
van Coevorden 2004a	Oral PUVA versus topical bath PUVA	No data regarding the primary outcome investigator-rated good/excellent control	-
Grattan 1991	Topical PUVA versus UVA	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Polderman 2003	UVA-1 versus placebo	No data regarding the primary outcome investigator-rated good/excellent control	-
Brass 2015	Local NB-UVB versus topical PUVA	RR 0.50 (95% CI 0.22 to 1.16)	-
Sezer 2007	Local NB-UVB versus topical PUVA	NB-UVB was effective in 2/12 hands and topical PUVA was effective in 1/12 hands	Within-patient study
Tzaneva 2009	Oral PUVA versus bath PUVA	No data regarding the primary outcome investigator-rated good/excellent control	-
Adams 2007	UVA-1 versus topical cream PUVA	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study

Table 4. Overview of studies on irradiation with UV light: investigator-rated good/excellent control *(Continued)*

Said 2010	Local UVA-1 versus topical betamethasone-valerate cream	No data regarding the primary outcome investigator-rated good/excellent control	-

CI: confidence interval.
RR: risk ratio.
NB-UVB: narrow-band ultraviolet B.
PUVA: psoralen + ultraviolet A.
UVB: ultraviolet B.
UVA-1: a subtype of ultraviolet A.

Table 5. Overview of studies on X-rays (ionising radiation): investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comments
King 1984	X-rays 300 rad versus placebo	No difference after 6 months. Grenz ray effective in 11/15 hands versus 8/15 hands with placebo.	Within-patient study
Fairris 1984	X-rays 300 rad versus placebo	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Lindelöf 1987	Grenz rays 1800 rad versus placebo	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Cartwright 1987	Grenz rays 300 rad versus placebo	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Fairris 1985	X-rays 1 Gy versus Grenz rays 3 Gy	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Sheehan-Dare 1989	X-rays versus PUVA	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study

CI: confidence interval.
Grenz rays: a type of X-rays (ionising radiation).
Gy: Gray, a unit of radiation dose.
RR: risk ratio.

Table 6. Overview of studies on topical calcineurin inhibitors: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comments
Schnopp 2002	Tacrolimus ointment versus mometasone furoate	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Katsarou 2012	Tacrolimus ointment versus mometasone furoate	No data regarding the primary outcome investigator-rated good/excellent control	Improvement was reported separately for subcategories of clinical signs
Krejci-Manwaring 2008	Tacrolimus ointment versus vehicle	No data regarding the primary outcome investigator-rated good/excellent control	-

Table 6. Overview of studies on topical calcineurin inhibitors: investigator-rated good/excellent control *(Continued)*

Pacor 2006	Tacrolimus ointment versus vehicle	RR 29.0 (95% CI 1.9 to 443.25)	-
Belsito 2004	Pimecrolimus cream versus vehicle	RR 1.53 (95% CI 0.99 to 2.36)	-
Hordinsky 2010	Pimecrolimus cream versus vehicle	RR 1.28 (95% CI 0.99 to 1.66)	-
Bauer 2012	Pimecrolimus cream versus vehicle	No data regarding the primary outcome investigator-rated good/excellent control	-
Baskan 2005	Pimecrolimus cream versus vehicle	No data regarding the primary outcome investigator-rated good/excellent control	-
Cherill 2000	Pimecrolimus cream versus vehicle	No data regarding the primary outcome investigator-rated good/excellent control	-

CI: confidence interval.
RR: risk ratio.

Table 7. Overview of studies on other topical interventions: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comments
Hill 1998	Betamethasone-valerate + clioquinol versus betamethasone-valerate + fusidic acid	RR 1.03 (95% CI 0.74 to 1.43)	-
Fredriksson 1975	Aquacare HP cream versus calmurid cream containing betaine and lactic acid	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Odia 1996	Iontophoresis versus no iontophoresis	No data regarding the primary outcome investigator-rated good/excellent control	Within-patient study
Boroujeni 2017	Herbal cream containing fenugreek seeds 5%, marshmallow 5%, chamomile 5%, and walnut leaves 5% versus fluocinolone acetonide cream 2% twice daily	No data regarding the primary outcome investigator-rated good/excellent control	-
Hanifin 2004	Bexarotene 1% gel versus bexarotene with either mometasone furoate or hydrocortisone	RR 0.85 (95% CI 0.40 to 1.80) for bexarotene only versus B + MF; 1.83 (95% CI 0.61 to 5.53) for bexarotene only versus B + HC; and 2.15 (95% CI 0.67 to 6.89) for B + MF versus B + HC	-
Jowkar 2014	Fumaric acid 5% cream versus triamcinolone 0.1% cream	No data regarding the primary outcome investigator-rated good/excellent control	-
Lauriola 2011	Furpalmate versus hydrocortisone acetate cream	RR 0.90 (95% CI 0.76 to 1.07)	-
Jowkar 2011	4% Fumaria Parviflora Lam cream versus vehicle cream twice daily	No data regarding the primary outcome investigator-rated good/excellent control	-

Table 7. Overview of studies on other topical interventions: investigator-rated good/excellent control *(Continued)*

Yousefi 2012	Nigella sativa L. versus betamethasone ointment versus Eucerin	No data regarding the primary outcome investigator-rated good/excellent control	-

B: bexarotene 1% gel.
CI: confidence interval.
Fumaria Parviflora Lam: Fumaria Parviflora Lamarck.
HC: hydrocortisone.
MF: mometasone furoate.
Nigella sativa L: Nigella sativa Linne.
RR: risk ratio.

Table 8. Overview of studies on immunosuppressants: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comments
Granlund 1996	Oral cyclosporin versus topical betamethasone	RR 1.88 (95% CI 0.88 to 3.99)	-
Agarwal 2013	Oral azathioprine and clobetasol propionate 0.05% cream twice daily versus topical clobetasol propionate 0.05% cream twice daily	RR 2.33 (95% CI 1.61 to 3.38)	-
NCT01231854	Oral cyclosporin versus alitretinoin	RR 1.50 (95% CI 0.35 to 6.40)	Study terminated prematurely and included 15 participants only

CI: confidence interval.
RR: risk ratio.

Table 9. Overview of studies on oral retinoids: investigator-rated good/excellent control

Study	Comparison	Investigator- or participant-rated good/excellent control in RR (95% CI)	Comments
Thestrup-Pedersen 2001	Oral acitretin versus placebo	No data regarding the primary outcome investigator-rated good/excellent control	-
Ruzicka 2004	Oral alitretinoin (20 mg and 40 mg) versus placebo	**40 mg** Participant-rated RR 3.51 (95% CI 1.80 to 6.82) Investigator-rated RR 1.97 (95% CI 1.3 to 3.0) **20 mg** Participant rated RR 2.74 (95% CI 1.37 to 5.46) Investigator-rated RR 1.49 (95% CI 0.94 to 2.34)	-
Ruzicka 2008; Fowler 2014	Oral alitretinoin 30 mg versus placebo	**30 mg** Participant-rated RR 2.75 (95% CI 2.18 to 3.48) Investigator-rated RR 2.75 (95% CI 2.20 to 3.43)	-

Table 9. Overview of studies on oral retinoids: investigator-rated good/excellent control *(Continued)*

Ruzicka 2004; Ruzicka 2008	Oral alitretinoin 10 mg versus placebo	**10 mg** Participant-rated RR 1.73 (95% CI 1.25 to 2.40) Investigator-rated RR 1.58 (95% CI 1.20 to 2.07)	-
Bissonnette 2010	Re-treatment with oral alitretinoin (30 mg and 10 mg) versus placebo	**30 mg** Investigator-rated RR 9.55 (95% CI 2.51 to 36.27) **10 mg** Investigator-rated RR 4.76 (95% CI 0.70 to 32.25)	-

CI: confidence interval.
RR: risk ratio.

Table 10. Overview of other oral interventions: investigator-rated good/excellent control

Study	Comparison	Investigator-rated good/excellent control in RR (95% CI)	Comments
Burrows 1986	Oral triethylenetetramine versus placebo	Trientine was effective in 6/20 participants versus 10/20 in the placebo group	Unclear whether participant- or investigator-rated
Kaaber 1983	Oral tetraethylthiuram disulphide versus placebo	Investigator-rated RR 2.95 (95% CI 0.71 to 12.34)	-
Pigatto 1990	Oral disodium cromoglycate without dietary restriction versus a low-nickel diet	No data regarding the primary outcome investigator-rated good/excellent control	-
Sharma 2006	Low-nickel diet and disulphiram versus a normal diet and placebo	Investigator-rated RR 9.09 (95% CI 1.40 to 58.91)	-
Veien 1995	Ranitidine versus placebo	RR 2.22 (95% CI 1.20 to 4.10)	Unclear whether participant- or investigator-rated
Whitaker 1996	Oral gamma-linoleic acid (GLA; evening primrose oil) versus placebo	No data regarding the primary outcome investigator-rated good/excellent control	

CI: confidence interval.
RR: risk ratio.

APPENDICES

Appendix 1. Glossary of medical terms

Medical term	Explanation
Acrovesicular eczema	Form of vesicular hand eczema. (Large) vesicle eruptions on the palms that usually tend to recur. Also called dyshidrotic eczema or pompholyx
Betamethasone	Topical corticosteroid, high potency
Clobetasol propionate	Topical corticosteroid, very high potency
Desonide	Topical corticosteroid, low potency
Dyshidrotic hand eczema	Form of vesicular hand eczema. (Large) vesicle eruptions on the palms that usually tend to recur. Also called dyshidrotic eczema, pompholyx or acro vesicular eczema
Fluprednidene acetate	Topical corticosteroid, medium potency
Heterogeneity	Differences in which studies have been undertaken with regard to methods and/or materials
Hydrocortisone butyrate	Topical corticosteroid, low potency
Hyperkeratotic hand eczema	Form of hand eczema with areas of thick scaling on the palms, also called tylotic hand eczema
IGA	Investigator global assessment: global assessment of disease severity usually on a 5-point scale
Immunomodulator	Drug which changes the immune response such as tacrolimus
Immunosuppressor	Drug which suppresses the immune response such ad topical corticosteroids
Iontophoresis	Treatment by which the skin is soaked in (tap) water through which a weak electric current is passed
Mometasone furoate cream	Potent steroid cream
NB-UVB	Narrow-band ultraviolet B
Nummular hand eczema	Round ("coin sized") eczematous patches on the back of the hands
Palmar	Hand palms, the inside surface of the hands
Palmoplantar	Hand palms and foot soles
Phase I clinical trial	A clinical trial of a new drug or therapy. Phase I trials are conducted in small groups of participants
Phase II clinical trial	A clinical trial of a new drug or therapy. Phase II trials are conducted in larger groups of participants than phase I trials
Pimecrolimus	Topical calcineurin inhibitor, also known as "elidel"
Placebo	Simulated or otherwise medically ineffective treatment
Pompholyx	Form of vesicular hand eczema. (Large) vesicle eruptions on the palms that usually tend to recur. Also called dyshidrotic eczema, pompholyx or acro vesicular eczema
Potency	Strength

(Continued)

Prevalence	The proportion of a population having a particular condition or characteristic: e.g. the percentage of people in a city with hand eczema, or the proportion of people who smoke
Primary care	Health care provided at the principal point of consultation for patients within a healthcare system, e.g. GP
Pruritus	Itch
Psychosomatic disorder	A disorder in which physical symptoms originate from mental or emotional causes
Pulpitis	A dry, fissured, scaling dermatitis of the fingertips with occasional episodes of vesicles. Also known as fingertip dermatitis
PUVA	(Topical and oral) psoralen combined with UVA
Randomised control trials	A study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention. (National Institute for Health and Care Excellence)
RR	Relative risk
Secondary care	Health care provided by medical specialists and other health professionals, including dermatologists, who generally do not have first contact with patients. This contains hospital and out-patient care
Systemic treatment	Treatment which does not pertain to a certain surface area but might affect the entire body, usually taken by mouth or injection.
Tacrolimus	Topical calcineurin inhibitor, also known as "protopic"
Teratogenicity	Developmental abnormalities in the foetus
Therapy	A treatment that helps someone feel better, grow stronger, etc., especially after an illness (Cambridge dictionary)
Topical treatment	Treatment pertaining to a certain surface area (usually the skin) and only affecting the area to which it is applied
Transepidermal water loss (TEWL)	The amount of water that moves from inside the body to the surrounding atmosphere through the epidermal layer of the skin by means of diffusion and evaporation.
Tylotic hand eczema	Form of hand eczema with areas of thick scaling on the palms, also called hyperkeratotic hand eczema
UVA-1	Form of UV-phototherapy which only uses the longer UV wavelengths (340 to 400 nm) and reduces the risk of burning, which is associated with the shorter-wavelength UVA2 (320 to 340 nm) and UVB (290 to 320 nm).
UVB	Ultraviolet B
VAS (Visual Analogue Scale)	Continious scale to measure a (subjective) response
Vehicle	Something used to transport people or goods (Cambridge dictionary), in this case something to help the treatment get transport in/on the skin, but a vehicle alone (without the active substance) can be used as placebo.

Appendix 2. Cochrane Skin Specialised Register (CRSW)

pompholyx or cheiropompholyx or acrodermatitis or "hand eczema" or ((eczema or dermatitis) and (dyshidro* or dyshydro* or dishidro* or dishydro* or tylotic or hyperkeratotic or microbial or discoid or nummular or pulpitis or pulpite) and (hand* or finger* or palm*))

Appendix 3. CENTRAL (Cochrane Library) search strategy

#1 tylotic or hyperkeratotic or nummular or microbial or discoid
#2 MeSH descriptor: [Eczema] explode all trees
#3 MeSH descriptor: [Dermatitis] explode all trees
#4 eczema or dermatitis
#5 #2 or #3 or #4
#6 MeSH descriptor: [Hand Dermatoses] explode all trees
#7 MeSH descriptor: [Eczema, Dyshidrotic] explode all trees
#8 hand eczema
#9 MeSH descriptor: [Acrodermatitis] explode all trees
#10 pompholyx
#11 cheiropompholyx
#12 {or #6-#11}
#13 MeSH descriptor: [Hand] explode all trees
#14 (hand* or finger* palm*)
#15 #13 or #14
#16 #1 and #5 and #15
#17 pulpitis or pulpite
#18 #15 and #17
#19 dyshidro* or dyshydro* or dishidro* or dishydro*
#20 #5 and #19
#21 #12 or #16 or #18 or #20

Appendix 4. MEDLINE (Ovid) search strategy

1. exp *Hand Dermatoses/
2. exp Eczema, Dyshidrotic/
3. hand eczema.mp.
4. exp *Acrodermatitis/
5. pompholyx.mp.
6. cheiropompholyx.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Eczema/ or eczema.mp.
9. exp Dermatitis/ or dermatitis.mp.
10. 8 or 9
11. (tylotic or hyperkeratotic).mp.
12. (nummular or microbial or discoid).mp.
13. (pulpitis or pulpite).mp.
14. (dyshidro$ or dyshydro$ or dishidro$ or dishydro$).mp.
15. 11 or 12
16. exp Hand/
17. (hand$ or finger$ or palm$).mp.
18. 16 or 17
19. 13 and 18
20. 10 and 15 and 18
21. 10 and 14
22. 7 or 19 or 20 or 21
23. randomised controlled trial.pt.
24. controlled clinical trial.pt.
25. randomized.ab.
26. placebo.ab.
27. clinical trials as topic.sh.
28. randomly.ab.
29. trial.ti.
30. 23 or 24 or 25 or 26 or 27 or 28 or 29
31. exp animals/ not humans.sh.
32. 30 not 31

33. 22 and 32

[Lines 23-32: Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 5. Embase (Ovid) search strategy

1. exp *pompholyx/
2. hand eczema.mp.
3. exp *acrodermatitis/
4. cheiropompholyx.mp.
5. pompholyx.mp.
6. exp *hand eczema/
7. or/1-6
8. eczema.mp. or exp *eczema/
9. exp *dermatitis/ or dermatitis.mp.
10. 8 or 9
11. (tylotic or hyperkeratotic).mp.
12. (nummular or microbial or discoid).mp.
13. (pulpitis or pulpite).mp.
14. (dyshidro$ or dyshydro$ or dishidro$ or dishydro$).mp.
15. 11 or 12
16. exp hand/
17. (hand$ or finger$ or palm$).mp.
18. 16 or 17
19. 13 and 18
20. 10 and 15 and 18
21. 10 and 14
22. 7 or 19 or 20 or 21
23. crossover procedure.sh.
24. double-blind procedure.sh.
25. single-blind procedure.sh.
26. (crossover$ or cross over$).tw.
27. placebo$.tw.
28. (doubl$ adj blind$).tw.
29. allocat$.tw.
30. trial.ti.
31. randomized controlled trial.sh.
32. random$.tw.
33. or/23-32
34. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
35. human/ or normal human/
36. 34 and 35
37. 34 not 36
38. 33 not 37
39. 22 and 38

Appendix 6. AMED (Ovid) search strategy

1. random allocation/
2. double blind method/
3. single blind method.mp.
4. exp Clinical trials/
5. (clin$ adj25 trial$).mp.
6. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp.
7. (placebo$ or random$).mp.
8. research design/ or clinical trials/ or comparative study/ or double blind method/ or random allocation/
9. prospective studies.mp.
10. cross over studies.mp.
11. Follow up studies/
12. control$.mp.
13. (multicent$ or multi-cent$).mp.
14. ((stud or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).mp.

15. Randomized controlled trials/
16. or/1-15
17. hand eczema.mp.
18. hand dermatoses.mp.
19. acrodermatitis.mp.
20. pompholyx.mp.
21. or/17-20
22. exp Eczema/ or eczema.mp.
23. dermatitis.mp. or exp Dermatitis/
24. 22 or 23
25. exp Hand/ or hand.mp.
26. (hand$ or finger$ or palm$).mp.
27. 25 or 26
28. 24 and 27
29. (dyshidro$ or dyshydro$ or dishidro$ or dishydro$).mp.
30. 24 and 29
31. (tylotic or hyperkeratotic).mp.
32. (nummular or microbial or discoid).mp.
33. (pulpitis or pulpite).mp.
34. 27 and 33
35. 31 or 32
36. 24 and 27 and 35
37. 21 or 28 or 30 or 34 or 36
38. 16 and 37

Appendix 7. LILACS search strategy

(pompholyx or ponfolix or cheiropompholyx or acrodermatitis or ((eczema or eccema or dermatitis) and (hand$ or finger$ or palm$ or mano$)))

In LILACS we searched using the above terms and the Controlled clinical trials topic-specific query filter.

Appendix 8. Journals handsearched

1. Acta Dermato-Venereologica
2. Archives of Dermatological Research
3. Archives of Dermatology
4. British Journal of Dermatology
5. British Medical Journal
6. Clinical and Experimental Dermatology
7. Contact Dermatitis
8. Cutis
9. Dermatology (formerly Dermatologica)
10. Environmental Dermatology
11. Journal of Investigative Dermatology
12. Journal of the American Academy of Dermatology
13. Journal of the American Medical Association
14. Lancet
15. New England Journal of Medicine
16. Der Hautarzt
17. Giornale Italiano di Dermatologia e Venereologia
18. Nederlands Tijdschrift voor Dermatologie en Venereologie
19. H+G Zeitschrift für Hautkrankheiten
20. Annales de Dermatologie et Venerelogie
21 Journal of Dermatologic Treatment

CONTRIBUTIONS OF AUTHORS

The following contributions were made by the review authors.
Linking with editorial base and co-ordinating contributions from co-authors: PJC.
Drafting the protocol: HCW, PJC, with contributions from all.
Handsearching: PJC, TD, ÅS, with help from the EDEN steering committee members J.J. Grob and L. Naldi.
Performing other searches: PJC, JLB, WAC, with help from the Cochrane Information Specialist Liz Doney.

Identifying relevant titles and abstracts from searches (i.e. broad screen): JLB, PJC, WAC.
Obtaining copies of trials: JLB, WAC.
Selecting which trials to include: TD, PJC, ÅS, WAC.
Extracting data: PJC, TD, ÅS, WAC.
Entering data into RevMan: JLB, WAC.
Carrying out analyses: JLB, PJC, WAC, JX.
Interpreting analyses: PJC, ÅS, HCW.
Drafting the final review: JX, PJC, WAC, with contributions from all.
Updating the review: PJC, WAC, JX.

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DECLARATIONS OF INTEREST

Wietske Andrea Christoffers: nothing to declare.

Pieter-Jan Coenraads was involved in the included studies Ruzicka 2004, Ruzicka 2008, and van Coevorden 2004a.

Åke Svensson has been involved in educational events for Swedish dermatologists. Novartis has sponsored this event; however, the educational group have decided the content of the education, and no payment has been paid to Åke Svensson personally. Instead, payment has been made to his hospital for his time spent working outside hospital.

Thomas L Diepgen has received lecture and consultancy fees from Leo Pharma A/S and consultancy fees from Almirall Hermal GmbH, and he has co-authored the studies of Bauer 2012 and Ruzicka 2008.

Janine L Blok: nothing to declare.

Hywel Williams: nothing to declare.

Jun Xia: nothing to declare.

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- The National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was published in 2009. Since that time, methodological guidance has changed including development of the MECIR standards. Hence, many sections have been edited and some new sections have been added, including **Background** >**Description of the Intervention** and **Background** >**How the intervention might work**.

Moreover, we were also required to retrospectively select the most important comparisons for our **Summary of Findings (SoF) tables**, and we selected them based on clinical relevance and on our own experiences.

We have changed the review question slightly and made it more precise. The original protocol stated "To assess the effects of interventions for hand eczema", which was changed to "To assess the effects of topical and systemic interventions for hand eczema in adults and children" to make the review question a bit more concise, since this is already a very comprehensive review.

Methods >**Types of outcome measures:** in the original protocol, we stated primary (percentage of participants with self-rated good/excellent control of symptoms and percentage of participants with investigator-rated good/excellent control of symptoms), secondary (reduction in severity and time until relapse), and tertiary outcomes (adverse events and dose reduction). We adjusted the review to the most recent Cochrane guidelines and used only primary outcome measures (percentage of participants with self-rated good/excellent control of symptoms, percentage of participants with investigator-rated good/excellent control of symptoms, and adverse events) and

secondary outcome measures (reduction in severity, time until relapse and dose reduction).The 'Side effects' were changed into the primary outcome 'Adverse events'. Adverse effects were divided into short-term adverse events occurring during the treatment phase and long-term adverse events occurring after completion of treatment. We also removed from the primary outcomes the conditional element 'with adequate length of follow-up' because a substantial otherwise well-conducted number of studies did not include long-term follow-up, and there is no consensus regarding 'adequate' in this context. The secondary outcome time until relapse was not defined in the protocol. In the review, time until relapse was defined as the number of days/weeks until the participant reports worsening of symptoms after initial response.

We added a recommended time point for outcome measures of a minimum of three months, which is considered the most clinically important time point for decision-makers. Hand eczema is a chronic, relapsing condition that might improve due to the natural course. However, because of the tremendous impact of hand eczema on quality of life, we considered analyses after three months to be undesirable.

Methods > **Measures of treatment effect:** in the original protocol, we stated that results would be expressed as odds ratios (ORs with 95% confidence intervals (CIs)) and risk differences (RDs with 95% CIs) for dichotomous outcomes and weighted mean differences (WMDs and 95% CI) for continuous outcomes. However, during the review process, we decided that risk ratios should be used instead (RRs with 95% CIs), since these would give a more accurate estimation of relative differences between comparison groups, as in some studies the proportion of outcome events was close to one in one or both groups. In addition, risk difference is not a relative measure and is not recommended as the first choice for reporting pooled results; we decided to abandon the risk difference and include risk ratios instead. We also expressed results from analyses of continuous data as mean differences (MDs), including CIs and respective P values. If insufficient data were available for any of the two analyses, we summed up available data from the respective study including the stated P value. Subsequent to publication of the protocol, in studies where exclusively median values were presented for a particular outcome, we substituted the median for the mean, provided that data were not too skewed. Whenever standard deviations were not available from a paper, we tried to calculate them from other available data. When confidence intervals were provided, the formula given in Chapter 7.7.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* was used (Higgins 2011a). The results were also expressed as number needed to treat (NNT) where appropriate with different rates of baseline risk.

Methods >**Types of interventions:** we encountered different studies that reported on treatment during a remission- or clearance-induction phase for participants before they were randomised to a follow-up or maintenance phase. This problem was not addressed in the protocol. In the review, we considered only the latter (randomised) phase for these studies.

Methods >**Electronic searches:** we tried to obtain additional data regarding unpublished and ongoing trials, or grey literature, via correspondence with study authors and pharmaceutical companies. However, the results of contacting authors and pharmaceuticals were often disappointing. We did not search Pascal and JICT-EPLUS as planned in our protocol, as we did not have access to these databases by the time the review was written. In the review, we searched MEDLINE from 1946, rather than from 1957, as planned, and we did not use old MEDLINE, because a newer version was available and the old data were incorporated in the new database. We additionally searched LILACS and the Global Resource of EczemA Trials (GREAT) because these became available over the years. We also searched a number of trials registries, which were not part of our original plan, because over the years, the search strategy was updated, and newer ways to conduct searches became available.

Methods >**Searching other resources:** we contacted trial authors of articles published after 1999 for clarification of date issues. Older contact data were often obsolete, and we considered it unlikely that researchers would have saved study data longer than 15 years. We did not perform a separate search for adverse events. Although not planned in the protocol, we did examine data on adverse events from the included studies. We handsearched the following additional journals: H+G Zeitschrift für Hautkrankheiten, Annales de Dermatologie et Venerelogie, and Journal of Dermatologic Treatment, because these were expected to provide additional studies; however these journals were digitised during the time this review was compiled.

The original protocol stated that the review authors would also record methodological quality in the review. We performed a thorough assessment of risk of bias (authors PJC and AS).

The original protocol stipulated diagnosis of hand eczema by a physician. Although only one of the studies that we identified stated this explicitly, all studies were based on participants being outpatients at hospitals. Therefore, we assumed that the diagnosis was established by a physician for all participants.

The original protocol expressed the plan to conduct subgroup analyses on different classifications of hand eczema, such as recurrent vesicular hand eczema or hyperkeratotic hand eczema. However, in almost all studies, the different classifications of hand eczema were combined and we were unable to extract sufficient information to conduct subgroup analyses, or the subgroups were combined or were unclearly defined in general. This might be the topic of a future update.

Several studies reported scoring systems using un-named, non-validated, self-created, and combined objective and subjective scores; in these cases we provided a narrative account of study results and summarised statistical tests reported by study investigators; we did not attempt quantitative analyses.

Methods >**Types of participants:** in the review, we additionally included participants who had other parts of their body affected, in addition to having hand eczema, because patients with hand eczema often have comorbidities such as atopic dermatitis. In the protocol, we stated that we would consider other terms, such as 'pompholyx', 'dyshidrosis', and 'pulpitis', as acceptable if diagnosed by a physician. However, in the review, we did not apply the need for diagnosis by a physician because all participants were included from hospitals, and although it was almost never stated in the methods, we therefore believed that the diagnosis was confirmed by a physician. Subsequent to publication of the protocol, we decided to include participants with other diagnoses besides hand eczema in the review when we were able to obtain separate data for hand eczema participants, because otherwise some studies had to be excluded although they contained potentially valuable data. We also clarified in the methods that we included participants with all types of hand eczema.

Methods >**Types of participants:** in the protocol, we did not impose any age limits on the participants; however, we changed this because treatment requirements and ethics for children are considerably different from adults.

Methods >**Selection of studies:** specified authors that we assigned in the protocol to independently check titles and abstracts were different in the review because the composition of the review author team changed over the years. The specified authors that we assigned in the protocol to independently examine the trials retrieved as full text were also different in the review because of this. In the protocol, we planned to resolve discrepancies with a third review author (PE), but instead, differences between review authors were resolved in consensus meetings because we considered these discrepancies to be substantial for the review and therefore aimed for consensus between all review authors.

Methods >**Data extraction and management:** specified authors that we assigned in the protocol to independently extract data were different in the review because of an organisational change in the author team. In the protocol, we planned to resolve discrepancies with a third review author (ÅS), but instead, we resolved differences between review authors in consensus meetings because consensus is preferred over partial consensus. We planned for one review author to check and enter data into Review Manager; however, in the review, three review authors did this.

Methods >**Assessment of risk of bias in included studies:** we updated our process for assessing methodological quality in the review, following more up-to-date guidance than was planned in the protocol. We used the Cochrane risk of bias tool, described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Methods > **Unit of analysis issues:** we did not plan for cluster randomised trials or within-participant studies in the protocol, so the text in the Unit of analysis issues section regarding these types of trials was not envisioned at the time of development of the protocol.

Methods > **Dealing with missing data:** we did not state plans for dealing with missing data in the protocol, so the text in the Dealing with missing data section was not envisaged at the time of development of the protocol.

Methods > **Assessment of heterogeneity:** in the protocol, we did not define clinical heterogeneity as we did in the review because this was not an item at the time of writing the protocol. We did not specify in the protocol that we would investigate statistical heterogeneity using the I^2 test. Neither did we plan to explore reasons for heterogeneity in studies if the I^2 statistic was greater than 50%, because these were not issues at the time of writing the protocol.

Methods > **Assessment of reporting biases:** we did not state plans for assessing reporting biases in the protocol, so the text in the Assessment of reporting biases section was not envisaged at the time of development of the protocol.

Methods > **Subgroup analysis and investigation of heterogeneity:** had there been sufficient data, we would have examined the effects of studying or excluding study subgroups, for example, children versus adults, or recurrent vesicular versus hyperkeratotic hand eczema. This was different from the atopic versus allergic contact hand eczema analysis that we had planned in the protocol, because these subgroups often were not defined and data were not available, which were defined a priori, or those studies had high risk of bias. Future updates of this review will carry out these analyses if data permits.

Methods > **Sensitivity analysis:** in the protocol, we planned to undertake sensitivity analyses to examine the effects of excluding study subgroups (e.g. children versus adults, atopic versus allergic contact hand eczema) or studies with high risk of bias. But in the review, we stated, "had there been sufficient data, we had intended to perform sensitivity analyses for pooled data. Data on these subgroups were not sufficient for sensitivity analyses and often not available".

Methods > **Summary of findings:** we included Summary of findings for the main comparison to Summary of findings 8 for the clinically most relevant outcomes. "Summary of findings tables" were not included in the protocol but were recommended during an update of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Calcineurin Inhibitors [therapeutic use]; Eczema [*drug therapy]; Emollients [therapeutic use]; Immunosuppressive Agents [therapeutic use]; Odds Ratio; Pruritus [drug therapy]; Randomized Controlled Trials as Topic; Severity of Illness Index; Treatment Outcome

MeSH check words

Humans