

Miltefosine for Mucosal and Complicated Cutaneous Old World Leishmaniasis: A Case Series and Review of the Literature

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Complicated Old World cutaneous leishmaniasis (OWCL) and Old World mucosal leishmaniasis (OWML) constitute an indication for systemic treatment. To date, there no controlled clinical studies that compare treatment options for these diseases. We compiled a case series of 24 cases successfully treated with miltefosine. We conclude that oral miltefosine is an effective treatment option for both OWCL and OWML.

Keywords. complicated cutaneous leishmaniasis; miltefosine; mucosal leishmaniasis; Old World leishmaniasis; systemic treatment.

Old World cutaneous leishmaniasis (OWCL) varies widely in its cutaneous presentation, ranging from a single limited skin lesion that may heal spontaneously to large and multiple locally destructive forms, as well as rare cases presenting with mucosal involvement (Old World mucosal leishmaniasis [OWML]). The kind of treatment depends on the clinical aspect of the lesion and the infecting species [1]. Antiparasitic treatment may be omitted in uncomplicated cases of OWCL caused by *Leishmania major*, because these infections are usually characterized by a benign, self-limiting course with spontaneous healing. In most other cases, local treatments such as intralesional pentavalent antimonials in combination with cryotherapy, topical paromomycin, or thermotherapy are indicated.

Systemic treatment is recommended in patients with complicated OWCL (defined as more than 3 lesions; lesions with diameters >30 mm; lesions in anatomic locations unsuitable for local treatment; and/or lesions refractory to local therapy) and in patients with OWML [1, 2].

The available drugs for systemic treatment are parenterally administered pentavalent antimonials (ie, meglumine antimoniate and sodium stibogluconate), parenterally administered (preferentially liposomal) amphotericin B and oral fluconazole, and miltefosine. In the absence of controlled clinical studies comparing the efficacy of these 4 compounds, preference for a specific treatment regimen is currently mainly guided by personal experience of the treating physician and practical considerations, such as drug availability and costs.

Miltefosine is the newest of the 4 drugs and is distinguished by 4 characteristics: (1) the often prohibitive cost of the drug; (2) the advantage of oral administration; (3) the teratogenic potential of the drug, demanding contraceptive measures during treatment; and (4) due to the more recent market introduction, a limited amount of clinical data. We describe 7 cases of complicated OWCL and OWML successfully treated with miltefosine at our institution and 17 cases published in the literature.

MATERIALS AND METHODS

We searched the internal medical records at the Swiss Tropical and Public Health Institute for cases of complicated OWCL and OWML that were treated with miltefosine, and we performed a systematic PubMed (MEDLINE) literature search using the key words “cutaneous leishmaniasis”, “mucosal leishmaniasis”, and “miltefosine”, including articles in English, French, German, and Spanish published before July 2015. In addition, the references of the identified case reports were screened for similar cases that may have been missed by the applied search approach.

RESULTS

By reviewing the internal medical records at the Swiss Tropical and Public Health Institute and systematically reviewing the available published literature, we identified 17 cases of OWCL and 7 cases of OWML that received miltefosine treatment. Table 1 depicts the parasitological and clinical characteristics of these 24 cases. Seven of the cases were treated at the Swiss Tropical and Public Health Institute between 2007 and 2015 (including 3 cases that have been described previously [3–5]), and 17 cases were identified by the performed literature search.

The indications for systemic treatment were either mucosal leishmaniasis (n = 7), an anatomic location unsuitable for local treatment (mostly in the face; n = 10), multiple lesions (n = 6), or large lesions (n = 5). The indication for systemic treatment remained unclear in 1 patient, and in 5 patients more than 1 indication for systemic treatment was present.

All 24 cases completed the treatment course and demonstrated healing on clinical evaluation. Follow-up data were available

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Table 1. Complicated OWCL and OWML Treated With Miltefosine

Reference	Age/Sex	Species (Most Likely Place of Infection)	Description	Indication	Miltefosine Regimen	Outcome (Follow up)
Patient 1	15/F	<i>Leishmania major</i> (Morocco)	Lesions on face, arms, and right leg	Location and number	50 mg TID for 28 d	Clinical cure (9 mo)
Patient 2	25/F	<i>L major</i> (Turmenistan)	5.5 × 6 cm lesion on the left thigh	Size	50 mg TID for 26 d	Clinical cure (1 y)
Patient 3	26/M	<i>L major</i> (Sudan)	Lesions on the penis, abdomen, and left elbow	Location and number	50 mg TID for 28 d	Clinical cure (9 mo)
Patient 4	24/M	<i>Leishmania donovani</i> (Spain/Italy)	5 × 5 cm lesion on the forehead	Location	50 mg TID for 28 d	Clinical cure (2 y)
Patient 5 [3]	64/F	<i>Leishmania infantum</i> (unknown)	Buccal lesions	ML	50 mg TID for 30 d	Clinical cure (1 y)
Patient 6 [5]	50/M	<i>Leishmania aethiopica</i> (Egypt?)	Multiple lesions at both auricles, underlying ankylosing spondylitis treated with etanercept	Location	50 mg TID for 28 d	Clinical cure (4 y)
Patient 7 [4]	76/M	<i>L infantum</i> (Italy)	Relapsing lesion on the tongue, underlying Good Syndrome	ML	50 mg TID for 28 d	5× clinical cure, 4× relapse ^a
Schraner 2005 [11]	43/M	<i>L major</i> (Burkina Faso)	Disseminated CL, underlying HIV-1 infection, CD4 cell count 10 cells/ μ L, HIV load 152 428 copies/mL	Number of lesions and failure to prior treatment	50 mg BID for 18 mo	Clinical cure (2 y)
Stojkovic 2007 [12]	26/M	<i>L major</i> (Tunisia)	Seven lesions on both arms (5 cm)	Size and number	50 mg TID for 28 d	Clinical cure (no data)
Neub 2008 [13]	1/F	<i>L infantum</i> (Mallorca)	Lesion on the nose	Location	10 mg OD for 28 d	Clinical cure (6 mo)
Mueller 2009 [14]	31/M	<i>L infantum</i> (Mallorca)	10 cm lesion on the right knee, underlying ankylosing spondylitis treated with infliximab	Size	50 mg BID for 6 wk	Clinical cure, 1 relapse after 1 y
Killingley 2009 [15]	12/M	<i>Leishmania tropica</i> (Afghanistan)	5 cm lesion, intolerance to local pentavalent antimony	Size	50 mg BID for 28 d	Clinical cure (5 mo)
Killingley 2009 [15]	19/M	<i>L tropica</i> (Afghanistan)	Multiple lesions including ear	Location	50 mg BID for 28 d	Clinical cure (3 mo)
Faber 2009 [16]	52/F	<i>L donovani</i> (Portugal)	Nodule on the left cheek with locoregional lymphadenopathy	Location	50 mg TID for 32 d	Clinical cure (6 mo)
Tappe 2010 [17]	?/F	<i>L tropica</i> (Afghanistan)	No data	No data	50 mg TID for 28 d	Clinical cure (4 mo)
Dorlo 2011 [18]	53/F	<i>L major</i> (Morocco)	15 lesions on the face and trunk	Number and location	50 mg TID for 28 d	Clinical cure (6 mo)
Dorlo 2011 [18]	54/M	<i>L infantum</i> (Spain)	Disfiguring lesion on the nose	Location	50 mg TID for 28 d	Clinical cure (7 mo)
Richter 2011 [19]	67/F	<i>L infantum</i> (Mallorca)	Buccal lesion, underlying systemic lupus erythematosus	ML	50 mg TID for 6 wk	Clinical cure (30 mo)
Poepl 2011 [20]	59/F	<i>L donovani/ infantum</i> (Cyprus)	5 × 7 cm swelling on the right cheek	Location and size	50 mg TID for 28 d	Clinical cure (2 y)
Ehlert 2013 [21]	50/M	<i>L donovani/ infantum</i> (Spain)	Buccal lesion, underlying HIV infection, CD4 cell count 276 cells/ μ L, HIV load 300 copies/mL	ML	50 mg TID for 21 d with AmphB	Clinical cure (no data)
Kassam 2013 [22]	66/M	<i>L donovani</i> (unknown)	Lingual lesion, use of corticosteroid inhaler for chronic obstructive airways disease	ML	50 mg TID for 28 d	Clinical cure (10 mo)
Salam 2013 [23]	40/M	<i>L donovani</i> (India)	Post-kala azar dermal leishmaniasis with mucosal involvement	ML	50 mg BID for 3 m	Clinical cure (no data)
Neumayr 2013 [24]	59/M	<i>L infantum</i> (Mallorca)	4 cm lesion, psoriatic arthritis treated with methotrexate	Size	50 mg BID for 28 d	Clinical cure (no data)
Neumayr 2013 [24]	53/M	<i>L infantum</i> (Mallorca)	Nasal lesion, psoriatic arthritis treated with adalimumab	ML	50 mg TID for 28 d	Clinical cure (no data)

Abbreviations: AmphB, amphotericin B; BID, twice a day; CL, cutaneous leishmaniasis; HIV, human immunodeficiency virus; ML, mucosal leishmaniasis; OD, once a day; TID, 3 times a day.
^a The relapses in 2007, 2010, and 2012 were treated with miltefosine.

for 19 of 24 patients (see Table 1). In 2 patients with persisting immunosuppression relapses occurred.

DISCUSSION

Systemic treatment is indicated in clearly defined cases of Old World tegumentary leishmaniasis ([1,2]). The advantages and

disadvantages of 4 possible drugs are as follows. (1) The first drug is pentavalent antimonials. In OWCL, the efficacy of systemic pentavalent antimony is poorly documented. Pentavalent antimonial (20 mg/kg for 10–14 days) achieved modest cure rates in *L major* cutaneous leishmaniasis (CL) ranging from only 52% to 87% at 3 weeks, and in 1 study it was not superior

to placebo [1]. For *Leishmania tropica* CL, the cure rates were even lower and ranged from 41% to 55% [1], but rates were not studied for *Leishmania infantum/Leishmania donovani* CL. Considering such low efficacy and high toxicity, pentavalent antimonials are no longer the first-line treatment for complicated OWCL and OWML. (2) The second drug, liposomal amphotericin B (3 mg/kg per day for 5 consecutive days and at day 10, with a total dose of 18 mg/kg), had a cure rate of 84% in 13 travelers and immigrants with *L. tropica* CL [6]. Considering such good efficacy, although data are scarce and the cost is high, it might be considered as a first-line treatment. (3) The third drug is fluconazole. Because previously described promising results of treatment with fluconazole (200 mg daily for 6 weeks) could not be reproduced, and higher doses of the drug led to significantly higher adverse events, fluconazole should only be considered as a third-line treatment of complicated OWCL [7]. (4) The fourth drug is miltefosine. In 3 treatment studies of *L. major* that included a total of 81 patients, CL cure rates of miltefosine (150 mg daily for 28 days) had a mean of 93% (range, 87%–100%) [8–10]. For *L. tropica* and *L. infantum/L. donovani* CL, experience with miltefosine is limited to a small number of case reports.

We compiled a case series of 24 cases of complicated OWCL (n = 17) and OWML that were treated with miltefosine. All 24 cases responded favorably to miltefosine treatment and showed clinical cure. The completion of the treatment course by all 24 patients reflects the overall good tolerability of miltefosine. Although relapses occurred in 2 patients with persistent immunosuppression, no relapses were observed among immunocompetent patients over a median follow-up time of 10 months (range, 3–48 months). Therefore, miltefosine seems to have excellent efficacy in immunocompetent patients suffering from complicated OWCL and OWML. Immunocompromised patients are at risk of sustaining relapse, irrespective of the specific treatment applied: 1 of the 2 relapsing patients suffered from “Good syndrome” (a rare cause of combined B- and T-cell immunodeficiency in adults) and even sustained multiple relapses irrespective of several rounds of treatment with different regimens. Because immunosuppression in this patient was persistent, the patient was finally put on indefinite secondary prophylaxis with monthly meglumine antimoniate and no further relapse was observed until his death, which was unrelated to leishmaniasis. In the other patient who relapsed, the infliximab therapy for ankylosing spondylitis had been resumed. The limitations of this study are its retrospective design, a possible publication bias of the reported cases, and the small number of patients included in the study.

CONCLUSIONS

Complicated Old World CL and OWML constitute an indication for systemic treatment. Systematic studies of systemic

treatment of OWCL and OWML are scarce, and conclusions for practical decisions are based on case reports and case series. Because pentavalent antimonials are relatively toxic and show limited cure rates and fluconazole has questionable efficacy, liposomal amphotericin B and miltefosine seem to be viable and promising treatment options for complicated OWCL and OWML. Because of easy oral administration, the overall good tolerability, and the promising results, miltefosine may be considered as a first-line treatment for complicated OWCL and OWML.

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