Miltefosine Treatment of *Leishmania major* Infection: An Observational Study Involving Dutch Military Personnel Returning from Northern Afghanistan

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In a retrospective, observational study involving 34 patients with *Leishmania major* infection, 31 of whom had experienced unsuccessful treatment with intralesional antimony (ilSb^v), miltefosine proved effective. Thirty patients experienced cure after receipt of miltefosine, 3 after receipt of additional ilSb^v, and 1 after 28 daily intravenous injections of antimony. Temporary diminution of ejaculate volume was reported by 21 patients.

Miltefosine, an oral agent, has shown activity against *Leishmania* isolates in laboratory studies [1] and has proven to be effective in treating Indian patients with visceral leishmaniasis (VL) [2]. Data on miltefosine for the treatment of cutaneous leishmaniasis (CL) are limited [3–10].

In Afghanistan, CL is caused by *Leishmania major* and *Leishmania tropica;* in the northern province of Balkh, most infections are due to *L. major* [11]. *L. major* infection usually responds to cryotherapy and injections of intralesional antimony (ilSb^v). If these treatments fail, the next option is parenteral, relatively toxic antimony treatment [12]. An oral, less toxic treatment would be welcome. We report the results of miltefosine treatment of *L. major* infection acquired in Balkh province.

Patients and methods. Cutaneous leishmaniasis was diagnosed in 172 Dutch military personnel deployed near Mazar-e-Sharif, the capital of Balkh province, as well as in 3 visiting Dutch civilians. Details of this outbreak will be reported elsewhere. Miltefosine was offered to 31 patients who did not experience cure after treatment with ilSb^V alone or with cryotherapy (ilSb^V/cryo), to 2 patients with 22 and 31 lesions, and to 1 patient with lesions that were too large for local treatment.

Leishmaniasis was confirmed by microscopic examination of Giemsa-stained smear, Novy-MacNeal-Nicolle culture, polymerase chain reaction (PCR) [13], and quantitative nucleic acid sequence-based amplification (QT-NASBA) [14]. QT-NASBA was used during follow-up.

Patients were treated at the Academic Medical Center (Amsterdam, the Netherlands). Miltefosine (Impavido; Zentaris) was given as 50-mg oral capsules 3 times daily with meals for 28 days. Patients with concomitant diseases and pregnant or lactating women were not included; for female patients of child bearing age, use of effective contraception was required. Written informed consent was obtained from all patients.

Lesions were assessed weekly. Compliance and adverse effects were recorded. After 5 spontaneous reports of reduced ejaculate volume and 1 report of a complete absence of ejaculate, a questionnaire with questions about libido, ejaculate volume, and erectile function was developed and filled out by all participating patients. Full blood count, total bilirubin, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, alkaline phosphatase (AP) level, γ glutamyltransferase (γGT) level, amylase level, and creatinine level were assessed weekly.

Patients were seen at ~6 weeks (range, 5–9 weeks) and ~6 months (range, 5–12 months) after treatment. Parasitological investigations were repeated at the end of treatment and at 6 weeks and 6 months after treatment for those patients who did not have results negative for parasites. The pharmacokinetics of miltefosine in this group has been reported elsewhere [15].

Clinical improvement was defined as reduction in size, infiltration, induration, perilesional erythema, or crusting of the lesion or any combination thereof, without the appearance of new lesions or new manifestations. Unsatisfactory response was defined as extension of the lesion, development of satellite le-

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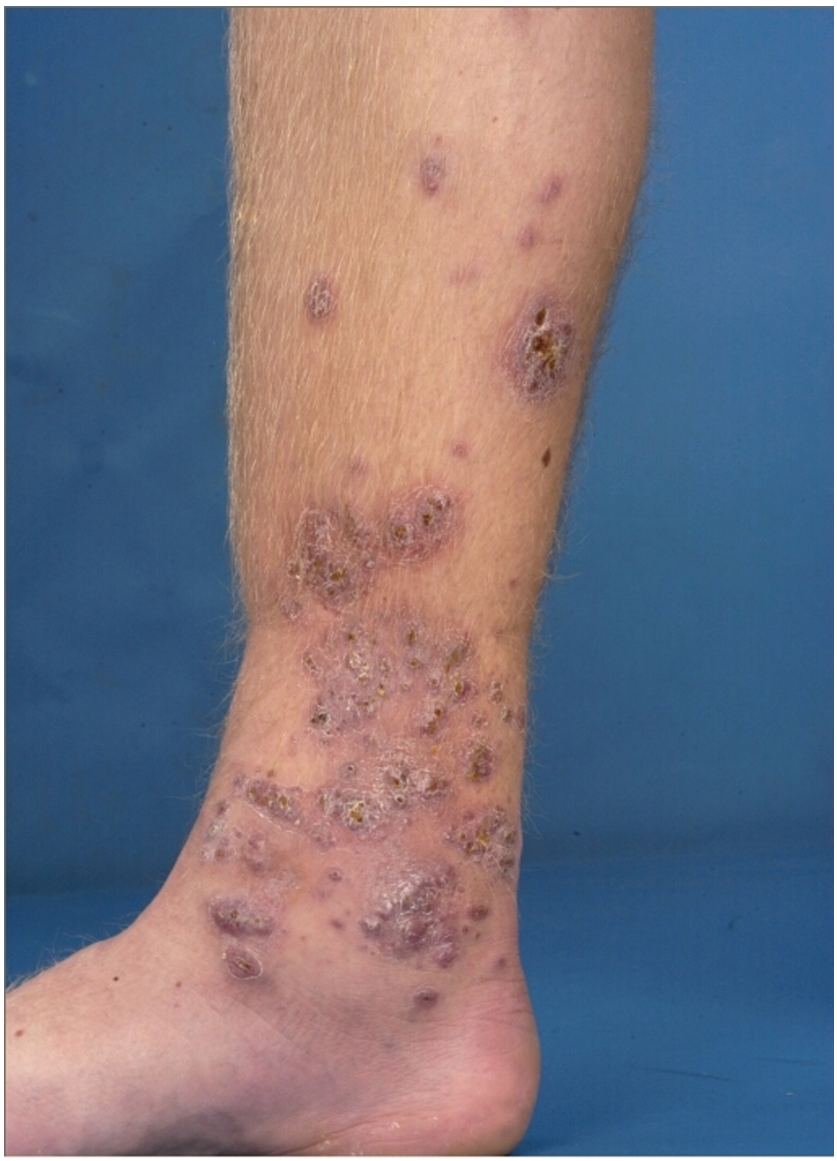

Figure 1. Patient with unsatisfactory response to miltefosine treatment before salvage treatment with intravenous antimony.

sions, lymphatic involvement (sporotrichoid spread, lymphangitis, lymphadenitis, or lymphnode enlargement) or any combination thereof during treatment or up to the first follow-up visit. Recurrence was defined as the appearance of new lesions at the original site after initial improvement or new manifestations of leishmaniasis at another site. Both unsatisfactory response and recurrence were based on clinical examination and demonstration of *Leishmania* parasites. Definite cure was defined as the complete re-epithelialization of all lesions without manifestation of active leishmaniasis at 6 months.

Results. The median age of the 34 patients (33 of whom were male) was 24 years (range, 19–49 years). Body weight ranged from 70 through 113 kg; thus, 2.1–1.3 mg of miltefosine per kg was administered daily.

The diagnosis was confirmed parasitologically in all patients except for 1 individual who was treated at a field site without proper facilities for parasitological confirmation and for whom diagnostic investigations were erroneously omitted in Amsterdam. PCR characterization, which was possible for 27 patients, showed identical *L. major* DNA sequences in all 27 cases [13].

At the end of treatment, all patients had experienced clinical improvement, but no patients had experienced cure, and QT-NASBA results were still positive in 13, negative in 18, inconclusive in 1, and not done in 2. At 6 months, 28 patients had experienced definite cure, confirmed by negative QT-NASBA results, and 2 patients, both with positive QT-NASBA results at the end of treatment, still showed nodules. They were cured without further treatment at 8 and 12 months, respectively.

Four patients showed unsatisfactory response or recurrence at 4, 9, 11, and 12 weeks after treatment, respectively. QT-NASBA results were positive at the end of treatment for 1 patient and negative for the other 3. Three patients received additional ilSb^v injections: 3 injections in 2 patients and 1 injection in 1 patient, with cryotherapy at the first injection. All 3 patients were cured 6 months later. In the fourth patient, extensive lesions developed, with lymphangitis and lymphadenitis on the lower right leg (Figure 1). Six months after additional treatment with intravenous Sb^v during 28 days, he was cured. All 4 patients had negative QT-NASBA results 6 months after treatment.

All patients completed treatment. Nausea (26 patients), vomiting (19), and abdominal discomfort (16) were common adverse effects, as has been previously reported [2, 8–10]. Twenty four patients felt unable to fulfil daily military exercises. Five patients spontaneously reported diminution of ejaculate volume, and subsequently 16 others reported the same after specific questioning. Two patients mentioned complete temporary absence of ejaculate. Five patients experienced diminished libido; erectile function and sexual performance were not affected. Four patients complained of scrotal tenderness, and epididymitis was diagnosed in 1 patient. Normalization occurred after treatment in all patients.

Hematological findings remained normal, with the exception of temporary, mild eosinophilia in 1 patient. Levels of AP, γGT, bilirubin, amylase, and glucose remained normal in all patients. Creatinine levels increased up to 20% above the upper limit of normal (ULN) in 1 patient; AST and ALT levels increased to <4 times the ULN in 2 patients and ALT increased to less than twice the ULN in 1 patient. All levels normalized after treatment.

Discussion. Miltefosine was effective treatment for *L. major* infection acquired in northern Afghanistan. Of 34 persons, 3 of whom were treatment-naive and 31 of whom had received previous treatment, 30 (88.2%) experienced cure, 3 (8.8%) received several additional intralesional injections of Sb^v, and 1 (3%) experienced cure after additional treatment with intravenous Sb^v for 28 days. Low plasma concentrations of miltefosine could not be blamed for the unsuccessful response, because concentrations in these 4 patients during the final week of treatment (>30 μg/mL) were comparable to levels found in the 22 patients in whom this could be measured (median concentration, 30.8 μg/mL; interquartile range, 25.2– 33.4 μg/mL) (T. P. C. Dorlo, personal communication) [15]. A "wait and see" approach would have been acceptable for the 3 patients who received additional ilSb^v injections, but because of pressure of duties, including training, incumbent overseas assignments, and career development, there was pressure to treat.

The contribution of natural evolution to the ultimately positive outcomes could not be assessed in this uncontrolled group. However, it may be emphasized that most patients had received previous treatment to which they had responded poorly.

Miltefosine is the first effective oral treatment for leishmaniasis. In laboratory studies, *L. major* was the least sensitive of all species tested [16], and the susceptibility of clinical isolates of *L. major* is not known [17]. In patients with VL in India who weighed <50 kg, 100 mg of miltefosine per day for 28 days was effective [2]. This schedule was adjusted for treatment of CL and mucocutaneous leishmaniasis (MCL), with patients weighing $\geqslant$50 kg receiving 3×50 mg per day. The optimal dosages and durations of treatment for the various parasites and regions may differ, but they have not been established. In Ethiopian patients with VL with or without human immunodeficiency virus coinfection, results were less satisfactory [18], and in Latin America, divergent results were observed in the treatment of CL and MCL [8–10]. Published results of miltefosine treatment of *L. major* infections are limited to reports on cases [3, 4] and a small uncontrolled study from Iran that reported a cure rate of 81.3% at 3 months of follow-up [5]. Because spontaneous cure rates may be 60%–70% at 3 months and 100% at 12 months [19], interpretation of uncontrolled studies remains difficult.

Common adverse effects of miltefosine treatment are nausea and abdominal discomfort, but few patients discontinue treatment as a result of adverse effects [2, 8–10]. Miltefosine is embryotoxic and teratogenic, prohibiting use during pregnancy and, because of its long residence time, requires effective contraception up to at least 5 months after treatment [15]. A remarkable observation in our patients was the reduction in ejaculate volume. Unfortunately, seminal fluid could not be examined for sperm count and quality. All complaints disappeared after treatment, and the partner of one of these patients gave birth to a healthy child within a year. This adverse effect has not been reported before and requires confirmation in prospective studies. Laboratory studies did not show significant abnormalities, as reported elsewhere [20].

The great advantage of miltefosine is its oral administration. Consistent efficacy of another oral agent, fluconazole, which has been shown to be effective in a study of *L. major* infection in Saudi Arabia [21], was questioned [22].

Thus, miltefosine was efficacious for treatment of *L. major* infection acquired in northern Afghanistan. The temporary diminution of ejaculate volume is a new finding that requires further investigation.

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