Treatment of American Cutaneous Leishmaniasis with Miltefosine, an Oral Agent

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There is no recognized oral treatment for American cutaneous leishmaniasis. A rising-dose, open-label phase I/II trial of the oral agent miltefosine against Colombian cutaneous leishmaniasis was conducted. Seventy-two male Colombian soldiers (mean weight, 67 kg) received miltefosine at 50–100 mg/day for 3 weeks (for 32 evaluable patients) or at 133–150 mg/day for 3–4 weeks (for 32 evaluable patients). The per-protocol cure rate for 50–100 mg/day was 21 (66%) of 32 patients. The per-protocol cure rate for 133–150 mg/day was 30 (94%) of 32 patients ($P = .01$, by use of Fisher's exact test). The historic per-protocol cure rate for standard injections of antimony is 93%. "Motion sickness" that did not interfere with normal duties was experienced by 40% of patients and was dose related. Vomiting and diarrhea were reported on ~2% of treatment days. In this uncontrolled study of oral miltefosine for treatment of patients with American cutaneous leishmaniasis, a dosage of ~2.25 mg/kg/day for 3–4 weeks was effective and tolerated.

The leishmaniases are cutaneous and visceral infections that are among the World Health Organization's 6 targeted tropical diseases, and interest in them is rising in the developed world in this era of facilitated international travel. Cutaneous leishmaniasis can be divided into New World disease, which is primarily caused by *Leishmania braziliensis* complex and *Leishmania mexicana* complex, and Old World disease, which is primarily caused by *Leishmania major* and *Leishmania tropica*. The organisms responsible for *L. braziliensis* complex cause ulcerative disease that frequently metastasizes to the draining lymph nodes [1, 2] and rarely metastasizes to the oronasal mucosa [3]. The natural cure rate is relatively slow: 22%–37% by 3–5 months in Guatemala [4] and in Colombia [3, 5].

Treatment is recommended for New World cutaneous disease to diminish the time to cure of the ulcer and to attempt to prevent metastasis. First-line treatment is pentavalent antimony in the form of meglumine antimonite or sodium stibogluconate for 20 days [6]; the second-line regimen is a short course of pentamidine [5]. These agents are parenteral and can be considerably toxic. Despite a 30-year search for an effective oral treatment, none has yet been identified [3, 5]. For example, the cure rate in Colombia for the promising agent allopurinol was 33% [3].

Miltefosine (hexadecylphosphocholine) interacts with cell signal transduction pathways and inhibits phospholipid and sterol biosynthesis [7]. Miltefosine is effective in vitro and in vivo against *Leishmania* species [8, 9], and Kuhlencord et al. [9] demonstrated efficacy in animals via the oral route. The first clinical test of miltefosine used dosages that ranged from 50 mg given every other day up to 250 mg/day in Indian patients with kala azar [10]. In a later large phase II trial, treatment with 100–150 mg for 28 days cured 86 (96%) of 90 viscerally infected Indian patients [11]. We investigated the efficacy

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Table 1. Characteristics of patients in trial of miltefosine for treatment of American cutaneous leishmaniasis.

Characteristic	Group 1 (n = 16)	Group 2 (n = 19)	Group 3 (n = 17)	Group 4 (n = 20)	P
Age, years	25 (19–34)	23 (19–53)	23 (19–29)	22 (18–27)	.28
Weight, kg	66 (52–84)	67 (57–90)	67 (56–80)	67 (55–81)	.98
No. of lesions	1.4 (1–3)	1.7 (1–4)	2.2 (1–6)	2.6 (1–6)	.04[a]
Lesion size, mm^2	172 (4–1680)	304 (4–1925)	307 (4–8000)	315 (4–6000)	.96
Duration of infection, months	4 (0–15)	2.5 (0–8)	4.4 (0–19)	1.1 (0–9)	.05[b]
Had previous treatment failure, no. (%)	6 (38)	7 (37)	12 (71)	4 (20)	.02[c]

NOTE. Data are mean values (range), except where otherwise indicated. P for difference in each entrance characteristic between treatment groups were calculated by analysis of variance or, when $P \leq .05$, by use of the Student-Newman-Keuls test.

[a] Groups 1 and 4 were significantly different.

[b] The groups did not significantly differ.

[c] Groups 1 and 2 together were not significantly different from groups 3 and 4 together ($P = .77$).

and toxicity of miltefosine against cutaneous leishmaniasis in patients in Colombia.

METHODS

Patients. Male Colombian soldiers acquired infection in the provinces of Uraba and Magdalena Medio and were evacuated to the Central Military Hospital in Bogota for diagnosis and treatment. Diagnosis was based on the findings of stain or culture of lesion scrapings, aspiration samples, or biopsy specimens. Parasites were speciated by isoenzyme electrophoresis [12].

Patients were admitted to the protocol if at least 1 lesion was ulcerative. If patients had received previous treatment with pentavalent antimony, antimony treatment had to have ended 4 weeks prior to the present study and lesion size had to be enlarging despite the prior treatment. Patients with mucosal lesions were excluded. In addition, screening laboratory values (complete blood counts, liver function tests, serum creatinine measurements) had to be, at most, 25% beyond normal limits.

Treatment with miltefosine. Patients were treated with miltefosine according to a rising-dose scheme. Group 1 received a low dosage, 50 mg (1 capsule)/day, for the time period during which standard therapy is given (20 days). Group 2 received 50 mg/day, on days 1–7, and then 100 mg/day (50 mg b.i.d.), on days 8–20. Group 3 received 100 mg/day, on days 1–7, and then 150 mg/day (50 mg t.i.d.), on days 8–20. Because the mean dosage was 133 mg/day, group 3 is referred to as the "133-mg/day group." Group 4 received 150 mg/day for 28 days. The drug was administered with the morning, midday, or evening meal.

Toxicity evaluation. Patients were interviewed daily during therapy for side effects. Laboratory values were determined weekly during treatment and at follow-up visits.

Efficacy evaluation. Ulcer size was measured in 2 perpendicular directions before therapy and at 2 weeks, 3 months, and 6 months after the beginning of therapy. On each of the posttherapy examination days, any lesion that had not 100% reepithelialized was reinvestigated for the presence of parasites.

After treatment with standard antimonials, lesions become parasite-negative, progressively heal up to 3 months after therapy, and rarely relapse thereafter [13]. To improve the comparison of the results of the present study with historic antimonial controls, for this study, "lesion cure" was prospectively defined as no parasites after therapy, complete reepithelialization by 3 months after the end of therapy, and no relapse by 6 months after the end of therapy. "Lesion failure" was defined as partial reepithelialization at 2 weeks or 3 months after therapy (if parasites remained at those times), no substantial improvement in lesion size at 3 months after therapy, relapse (enlargement of lesion size after previous complete epithelialization), or appearance of a new lesion. For a patient to be cured, all lesions had to be cured.

RESULTS

Presenting characteristics. The 72 patients who received treatment were young men with a mean age of 23 years and mean weight of 67 kg (table 1). Patients had a mean of 2.0 lesions, the mean size of which was 278 mm^2, and the mean duration of the disease before study entry was 2.9 months. Parasites were yielded on culture for 15 patients. *Leishmania amazonensis* was yielded on culture for 4 patients in group 1 and for 1 patient in group 2. *Leishmania panamensis* was yielded on culture for 1 patient in group 2, 6 patients in group 3, and 3 patients in group 4.

Efficacy. Of the 72 patients who received treatment, 64

(89%) were evaluable (table 2). No patient discontinued therapy for reasons of drug intolerance.

Efficacy was modest in group 1. Nine (64%) of 14 evaluable patients were cured. Three patients had lesion failure at 2 weeks with parasite-positive lesions, all of which were at least 50% of their original size. Two patients had failure at 3 months: 1 patient had a parasite-positive lesion that was markedly diminished (~10% of original size), but not completely epithelialized; 1 patient had 1 relapsed lesion and 1 new lesion.

Despite an approximate doubling of dosage, efficacy was also modest in group 2. Twelve (67%) of 18 evaluable patients were cured. Two patients had lesion failure at 2 weeks, with parasite-positive lesions that had not substantially changed size (1 patient) or a parasite-negative lesion that relapsed after healing during therapy (1 patient). Four patients had failure at 3 months because of a parasite-positive lesion that increased in size (1 patient), relapse (1 patient), or parasite-negative lesions that had not substantially changed in size (2 patients).

Group 3 was administered a larger dosage (mean dosage, 133 mg/day for 3 weeks). All 14 evaluable patients were cured. In group 4, who received 150 mg/day for 28 days, 89% of evaluable patients were cured. In groups 3 and 4, lesions that were destined to completely reepithelialize did so rapidly. By 2 weeks after therapy, lesions that eventually healed averaged 31 mm^2, 17% of their pretreatment size. The 2 patients in group 4 who had lesion failure demonstrated parasite-positive (1 patient) and parasite-negative (1 patient) relapsed lesions at 3 months.

There was a trend ($P = .05$, by use of the χ^2 test) between per-protocol cure rate and dosage group. In addition, there was a significant difference ($P = .01$, by use of Fisher's exact test) between the per-protocol cure rate for the lower-dosage groups (for groups 1 and 2 combined, 21 [66%] of 32 subjects) and the per-protocol cure rate for the higher-dosage groups (for groups 3 and 4 combined, 30 [94%] of 32 subjects).

There was an unequal distribution of species with respect to treatment group in that 4 of the 5 parasites found to be *L. amazonensis* were isolated from group 1 patients. However, it is unlikely that the low cure rate in group 1 can be attributed to the predominance of *L. amazonensis* in that group, because 3 of the 4 patients in group 1 who were infected with *L. amazonensis* were cured. There was no relationship between presenting lesion size and cure. The mean size ($\pm$SD) of 104 lesions destined to cure was 338 $\pm$ 1083 mm^2; the mean size ($\pm$SD) of the 20 lesions that did not cure was 264 $\pm$ 398 mm^2 ($P = .76$, by use of the t test).

Tolerance. The most common side effect was "motion sickness." Forty percent of patients reported motion sickness (defined as lack of balance plus gastrointestinal unease) at some time during therapy. The incidence increased significantly between groups 1 and 2 (1 [6%] of 16 and 4 [19%] of 19 subjects, respectively) and groups 3 and 4 (13 [77%] of 17 and 11 [55%] of 20 subjects, respectively; $P < .001$, by use of χ^2 test). Nevertheless, motion sickness lasted from 1 to 7 days (except for 1 patient in group 4) during the 3–4 weeks of treatment, and it did not prevent performance of normal duties. There was no correlation of motion sickness with the week of therapy. During weeks 1–4, 14%, 22%, 21%, and 11% of patients, respectively, reported this symptom.

Vomiting and diarrhea did not occur frequently and were not dose related ($P = 1.0$). These symptoms were experienced by 15 (21%) of 72 patients on no more than 5 days per patient.

One patient in group 4 reported a greater frequency of motion sickness and abdominal pain than did any other patient. This

Table 2. Efficacy of miltefosine for treatment of American cutaneous leishmaniasis.

	Group			
Parameter	1 ($n = 16$)	2 ($n = 19$)	3 ($n = 17$)	4 ($n = 20$)
No. nonevaluable	2	1	3	2
Lost to follow-up	2	1	3	0
Patient request to stop therapy	0	0	0	2
No. evaluable	14	18	14	18
Per-protocol analysis of evaluable patients				
No. (%) cured	9 (64)	12 (67)	14 (100)	16 (89)
No. with treatment failure	5	6	0	2
Intent-to-treat analysis of all entered patients				
No. (%) cured	9 (56)	12 (63)	14 (82)	16 (80)
No. with treatment failure[a]	7	7	3	4

[a] Includes patients lost to follow-up.

patient had motion sickness (grade 1), on days 4–5 and 10–28; abdominal pain (grade 1), on days 15–28; and headache (grade 1), on days 10–14 and 28; he also vomited once on day 4.

During treatment, liver transaminase levels were elevated at up to 2.5 times the upper limit of normal in groups 1–4 in 38%, 42%, 35%, and 20% of patients, respectively. Elevations to 2.6–5.0 times the upper limit of normal were seen in 1 patient in each of groups 1, 2, and 4. All elevations were transient.

DISCUSSION

This first trial of oral miltefosine for cutaneous leishmaniasis was done according to standard rising-dose, open-label phase II design. Per-protocol efficacy of evaluable patients was 94% (30 of 32 subjects) for patients administered the highest dosages of drug (133–150 mg/day for 3–4 weeks). In contrast, the cure rate was 66% (21 of 32 subjects) for patients administered a dosage of 50–100 mg/day for 3 weeks. An intent-to-treat analysis, in which the criterion of failure is lack of cure, and in which lost patients are assumed to have had failure, is also presented in table 2. Efficacy on an intent-to-treat basis was 81% in the 2 highest-dosage groups and 60% in the 2 lowest-dosage groups. Published studies of antileishmanial chemotherapy, however, characteristically use per-protocol analysis of efficacy, and the 94% efficacy of 133–150 mg/day in this study can be compared with the per-protocol cure rate in historical controls. The efficacy of standard Glucantime treatment of *L. panamensis* in Colombia in 1997 was 93% (52 of 56 subjects), and the efficacy of placebo was 37% (17 of 46 subjects) [3]. While the present study was being performed in 1998–1999, the efficacy of a topical antileishmanial formulation and its placebo was determined at the same site [14]. Five (42%) of 12 patients who received placebo self-cured, as determined by use of the criteria of the present study. Miltefosine regimens of 133–150 mg/day (2.0–2.3 mg/kg/day) for 3–4 weeks seem to be about as effective as standard therapy and much more effective than placebo.

In cases of Indian visceral leishmaniasis treated with miltefosine, there was a slight dose response for patients treated with 100 mg/day (~2.5 mg/kg/day) for 4 weeks (cure rate, 97%) and 50 mg/day for 6 weeks (cure rate, 93%) [11]. Thus, for both cutaneous and visceral leishmaniasis, optimum cure rates in phase II trials occurred with dosages of 2.0–2.5 mg/kg/day for 3–4 weeks.

Feelings of motion sickness (lack of balance plus gastrointestinal uneasiness) were reported in this trial, but they were not reported by patients with visceral leishmaniasis. In contrast, gastrointestinal side effects were prominent in the visceral leishmaniasis trial but not in the present trial. Vomiting and diarrhea were reported by 62% of patients on an average of 4 days per patient in the study of visceral leishmaniasis, but by 21% of patients on an average of 2 days per patient in the present study of cutaneous leishmaniasis. We attribute the different side effect profile to the fact that patients with cutaneous leishmaniasis are systemically well, whereas viscerally infected patients are severely systemically ill. Motion sickness was recognized by patients with cutaneous leishmaniasis who were mobile and who performed normal duties throughout the treatment period, whereas vomiting and diarrhea were prominent in patients with visceral leishmaniasis whose gastrointestinal tracts were already compromised by disease.

The standard agents for leishmaniasis—pentavalent antimonials, pentamidine, and amphotericin B—have the disadvantages of repeated parenteral injection and of toxicity. After 30 years of disappointing data from clinical trials of new agents, favorable results are now being seen. A few injections of new formulations of amphotericin B have been successfully used for visceral disease from several regions of endemicity [15]; preliminary favorable data were reported with regard to treatment of visceral leishmaniasis in Kenya with orally administered WR 6026 [16]. Although both of these newer agents deal well with the problems of frequent parenteral injections and of toxicity for visceral leishmaniasis, there are no reports of efficacy of these agents against cutaneous leishmaniasis.

The present report is the first report of >90% efficacy of a nonparenteral agent for management of New World cutaneous leishmaniasis. Although this was the initial clinical trial of miltefosine, and it was by design uncontrolled, and although it requires confirmation in a controlled trial, the efficacy of ~2.25 mg of miltefosine per day for 3–4 weeks was striking.

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