

Short Report: Efficacy of Miltefosine for Bolivian Cutaneous Leishmaniasis

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Abstract. Oral miltefosine (2.5 mg/kg/d for 28 days) was compared with intramuscular antimony (20 mg/kg/d for 20 days) in the treatment of cutaneous leishmaniasis caused by *Leishmania braziliensis* in Palos Blancos, Bolivia. The cure rates with 6 months of follow-up were statistically similar: 36 of 41 evaluable miltefosine patients (88%) versus 15 of 16 (94%) evaluable antimony patients. However, antimony cured more rapidly, because, by 1 month after therapy, 31 of 44 miltefosine patients (70%) compared with 16 of 16 antimony patients (100%) had achieved cure. The two conclusions from this work are that oral miltefosine can be used for cutaneous disease in this part of Bolivia and that miltefosine was more effective for *L. braziliensis* in this region than for *L. braziliensis* in Guatemala. Chemotherapy needs to be evaluated in each endemic region, even if the “same” species of *Leishmania* causes disease in these locales.

Cutaneous leishmaniasis is typically treated with the parenteral product pentavalent antimony. Because the disease generally self-cures in 2–15 months depending on the endemic region in which it was obtained,¹ parenteral therapy is inherently unattractive, and the primary chemotherapeutic need is an effective oral or, if appropriate, topical regimen. Miltefosine is an oral agent, originally shown to be > 95% curative for Indian visceral leishmaniasis,² which underwent evaluation for cutaneous and mucosal disease of the New World. A 91% cure rate for *Leishmania panamensis* disease in Colombia compared with a 38% cure rate for placebo led to the registration of this drug in Colombia.³ However, miltefosine was not impressively effective in Guatemala, in which the infecting species are *L. braziliensis* and *L. mexicana*. In Guatemala, 50% of the miltefosine group were cured compared with 20% of the placebo group, and for patients with documented *L. braziliensis* disease, only 5 of 15 patients (33%) cured in the miltefosine group compared with 1 of 12 cases (8%) in the placebo group.³ In contrast, antimony routinely cures > 90% of patients in Guatemala, and it seemed as if miltefosine should not be recommended for *L. braziliensis* cutaneous disease.

The possibility that *L. braziliensis* in Guatemala is unusual in its low response to miltefosine led us to study miltefosine for Bolivian leishmaniasis, 94% of which is caused by *L. braziliensis*.⁴ We first studied mucosal leishmaniasis. In a single-group trial, the cure rate for miltefosine was similar to that of historic values for antimony.⁵ It could be argued, however, that antimony might have been superior had a randomized study been performed, and that at any rate, the mucosal data might not pertain to cutaneous leishmaniasis, which is by far the most prevalent presentation. To directly evaluate the relative efficacy of miltefosine to antimony for *L. braziliensis* cutaneous disease in this region of Bolivia, we compared the drugs in a randomized study of cutaneous leishmaniasis at the same site at which we had conducted the mucosal trial.

Our study patients lived in the same Bolivian provinces of Beni or La Paz from which we recruited mucosal patients⁵ and were treated at the community clinic of Palos Blancos. The inclusion/exclusion criteria for this cutaneous study were similar to that used in the Colombian/Guatemalan cutaneous study³: a skin ulcer confirmed to be caused by leishmania by visualization of parasites in lesion material by Giemsa stain-

ing; either sex; ≥ 12 years of age; without mucosal disease or anti-leishmanial therapy for at least 6 months; without significant concomitant disease by history, physical examination, or blood tests; without pregnancy or lactation. Eighty-one patients were seen at this facility during the time of the trial but not entered because they were too young or it seemed unlikely that they would comply with follow-up.

The number of patients and patient allocation (2 miltefosine:1 antimony) was chosen based on resource constraints and the desire to provide more patients for the experimental (miltefosine) group. The patients were randomized to open-label treatment with a standard course of oral miltefosine (2.5 mg/kg/d for 28 days; Impavido; Zentaris, Frankfurt-am-Main, Germany) or of intramuscular pentavalent antimony (20 mg/kg/d for 20 days; glucantime; Aventis, Paris, France) in a 2:1 allocation. Both treatments were observed. Drug-appropriate laboratory tests and symptoms were used to evaluate drug tolerance. For all patients, hemoglobin, white cell count, platelet count, serum glutamic oxaloacetic transaminase (SGOT), and blood urea nitrogen (BUN) were ascertained at the beginning and end of treatment. Miltefosine patients were queried daily during therapy for vomiting, diarrhea, nausea, anorexia, abdominal pain, headache, and motion sickness. Glucantime patients were queried daily for diarrhea, headache, arthralgia, and local pain. Efficacy was evaluated by measuring the size of the ulcer (maximum length and width) at baseline, at the end of therapy, and at 1, 3, and 6 months after the end of therapy. A lesion was defined as a failure if it enlarged by 50% at the end of therapy or at 1 month after therapy, did not diminish by 50% at 3 months after therapy, did not heal (completely re-epithelialize) by 6 months after the end of therapy, or relapsed (enlarged after previously diminishing in size). Lesion cure was the opposite of failure: complete healing of all lesions by 6 months after the end of therapy. For a patient to be cured, all lesions had to cure. “Cure rate at time X” means the percent of patients in whom all lesions had healed by time X.

The study was approved by the Comité de Ética, Colegio Médico, La Paz, Bolivia and had clinicaltrials.gov registry NCT00233545. All patients signed informed consent. Patients were studied between November 2005 and March 2007.

The patients were typical of patients with cutaneous leishmaniasis (Table 1): 25–30 years of age, with a median of one ulcer per patient with an average area of ~ 300 mm².

At the end of therapy, 26 of the 60 lesions (43%) on miltefosine patients had healed, and 34% of patients were cured.

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TABLE 1
Presenting characteristics and results

	Miltefosine patients	Glucantime patients
Presenting characteristics		
Number of patients	44	18
Age of patients [years; median (range)]	27 (12–57)	23 (12–51)
Male/Female	36/8	15/3
Weight of patients [kg; median (range)]	59 (39–78)	59 (38–80)
Number of ulcers	64	30
Number per patient [median (range)]	1 (1–3)	1 (1–3)
Area (mm ²) [median (range)]	181 (10–3,172)	150 (4–900)
Results		
End treatment		
No. of patients healed/failed/lost	15/0/0	9/0/1
Percent of patients healed/evaluable	15/44 = 34%	9/17 = 53%
1 month after treatment		
No. of patients healed/failed/lost	31/0/0	16/0/2
Percent of patients healed/evaluable	31/44 = 70%	16/16 = 100%
3 months after treatment		
No. of patients healed/failed/lost	39/4/1	15/1/2
Percent of patients healed/evaluable	39/43 = 91%	15/16 = 94%
6 months after treatment		
No. of patients healed/failed/lost	36/5/3	15/1/2
Percent of patients healed/evaluable	36/41 = 88%	15/16 = 94%

* $P = 0.01$ (Fisher exact test).

† $P = 0.67$ (Fisher exact test).

For the glucantime group, 17 of the 29 evaluable lesions had healed (59%; $P = 0.26$ versus miltefosine), and 53% of evaluable patients had cured ($P = 0.24$ versus miltefosine).

By 1 month after the end of therapy, 31 patients in the miltefosine group had cured, compared with all patients not lost to follow-up in the glucantime group. The difference in cure rate was statistically significant.

By 3 months, one miltefosine patient was lost and four patients had failed. Three of the failed patients had lesions that were larger than before (relapse), and one patient had a lesion that had not sufficiently diminished in size. Two of the relapses were parasite positive. In the glucantime group, one patient relapsed.

By 6 months, one further miltefosine patient relapsed with a parasite-positive lesion, and two patients, both of whom had been cured at 3 months, were lost. The per-protocol cure rate for miltefosine (36 of 41 = 88%) was not statistically different from the per-protocol cure rate for glucantime (16 of 17 = 94%).

The five patients that failed their initial drug were re-treated, successfully, with the other drug.

Three of the miltefosine patients had previously failed glucantime, and one of the glucantime patients had previously failed miltefosine. All four of these patients cured in this trial.

During therapy, the primary adverse event for the miltefosine group was gastrointestinal symptoms, which were experienced by 27 of 44 patients (61%) for a median of 3 days (range, 1–10 days). For the glucantime group, 13 of 18 patients (72%) reported arthralgias and/or local pain at the injection site for a median of 7 days (range, 5–14 days).

In this study of oral miltefosine versus parenteral pentavalent antimony for Bolivian cutaneous leishmaniasis in an *L. braziliensis* region, the cure rate at 6 months after therapy for miltefosine (88%) was statistically indistinguishable from that of standard therapy with glucantime (94%). Nevertheless, the glucantime cure rate was statistically superior at 1 month after therapy, and it may be that, in this region, antimony is more rapidly active.

The practical importance of this finding is that miltefosine can be administered for cutaneous leishmaniasis in this region of Bolivia, with the understanding that the oral agent will be approximately as active as standard injections of antimony. Because this was the first study of miltefosine for Bolivian cutaneous leishmaniasis, it was confined to subjects > 11 years of age. A limitation of the study is that the data might not hold for younger patients. As per the Product Brochure,⁶ patients and physicians need to be conscientious in making sure that female miltefosine patients of reproductive age use reproductive contraception for the period of treatment and for 3 months thereafter.

The theoretical importance of this data is that the relative efficacy of miltefosine to antimony for *L. braziliensis* in Palos Blanco, Bolivia is far superior to the relative efficacy in Guatemala. The general conclusion is that efficacy in one endemic region cannot be relied on to pertain to other endemic regions, even if the apparently “same” species of *Leishmania* is present in both regions. For example, it is not clear if *L. braziliensis* in Brazil will follow the Guatemalan pattern or the Bolivian pattern. We would broaden this conclusion and suggest that as any new anti-leishmanial agent or combination of agents is evaluated, the evaluation needs to be undertaken in many endemic regions to have confidence in the general use of the intervention.

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