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Miltefosine Combined with Intralesional Pentamidine for *Leishmania braziliensis* Cutaneous Leishmaniasis in Bolivia

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Abstract. Bolivian cutaneous leishmaniasis due to *Leishmania braziliensis* was treated with the combination of miltefosine (150 mg/day for 28 days) plus intralesional pentamidine (120 μg/mm^2 lesion area on days 1, 3, and 5). Ninety-two per cent of 50 patients cured. Comparison to historic controls at our site suggests that the efficacy of the two drugs was additive. Adverse effects and cost were also additive. This combination may be attractive when a prime consideration is efficacy (e.g., in rescue therapy), avoidance of parenteral therapy, or the desire to treat locally and also provide systemic protection against parasite dissemination.

INTRODUCTION

Cutaneous leishmaniasis (CL) in the New World generally presents as a papule that enlarges and ulcerates over 1–3 months and then self-cures, but the predominant species at our site in Bolivia, *Leishmania* (*Viannia*) *braziliensis* (*L. braziliensis*), infrequently disseminates to the mucous membranes of the nose and mouth, causing mucosal disease that does not self-cure.[1] The treatment aim is to cure the presenting skin lesion in a shorter time than the time for natural cure and, if possible, diminish the likelihood of dissemination.

Because the vast majority of CL self-cures, it might be considered a disease of modest severity, thus another aim is to avoid parenteral therapy, which means to obviate classic treatment with parenteral antimony, pentamidine, or amphotericin B. Because the only generally approved oral agent for leishmaniasis is miltefosine, we have been evaluating miltefosine and also the local interventions cryotherapy, intralesional (IL) antimony, and intralesional pentamidine. In 2016–2017, the cure rate at our site was 81% (47 of 58) for miltefosine (J. Soto, unpublished observations). In a 2013 publication, cure rates were 70% (21 of 30) for three intralesional injections of antimony, 20% (4 of 20) for cryotherapy, and 17% (5 of 30) for a placebo cream.[2] In a 2016 publication, cure rates were 57% (17 of 30) for three intralesional injections of antimony, 70% (42 of 60) for five intralesional injections of antimony, and 70% (43/60) for three intralesional injections of pentamidine.[3] At present, classic pentavalent antimony has a cure rate of 81% (116 of 144: J. Soto, unpublished observations).

From this experience, the most effective non-parenteral agents at our site are miltefosine at 81% and, because 70% cure was obtained with three, not five, IL injections, three intralesional injections of pentamidine. Although these 70–81% cure rates far exceed the 18–20% cure rate for placebo or cryotherapy pseudoplacebo, the cure rates are substantially less than an ideal cure rate in the middle or high 90%s. In the present experiment, we administered the combination of oral miltefosine plus intralesional pentamidine to try to achieve a cure rate greater than 90%.

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METHODS AND PATIENTS

Study design and treatments. This was an open-label evaluation of one intervention: standard treatment with oral miltefosine in combination with intralesional treatment with pentamidine. Miltefosine (Knight Therapeutics, Montreal, Canada) was administered orally 50 mg three times per day for 28 days, as recommended.[4] Pentamidine (30 mg/mL; Pentacarinat® Sanofi-Aventis, Bogota, Colombia) was administered intralesionally at a dose of 120 μg (4 μL)/mm^2 of lesion area on each of days 1, 3, and 5, as described.[3] Treatments were administered by the study staff, and the targeted number of administrations was achieved for all patients.

Patients. Patients acquired the disease in Nor Yungas, Departamento de La Paz, Bolivia. After signing the informed consent and meeting entrance criteria, the patients were treated at the Centro de Salud Integral La Asunta, Bolivia. Entrance requirements were as follows:[3] one ulcerative lesion ≤ 900 mm^2 in total area, ≥ 12 years of age, parasitologically diagnosed by visualization of amastigotes or culture of promastigotes from lesion material, no antileishmanial therapy in the last 3 months, no mucosal lesions, and no history of significant concomitant diseases including immunosuppression.

Outcome parameters and analysis. Efficacy was evaluated exactly as before.[3] The endpoint parameter was reduction in lesion size. Lesion size was defined as the area of the lesion ulcer computed as "maximum ulcer width" × "maximum ulcer length." Lesion size was measured at study entrance and then at 1 month, 3 months, and 6 months after the end of the therapy. The criteria for failure were the same as before: substantial enlargement (doubling) of lesion size by 1 month after therapy, non-substantial (< 50%) diminution in lesion size at 3 months after therapy, relapse (enlargement after previous diminution), and not being completely re-epithelialized ("re-epithelialized" = lesion size of "0" mm^2) at 6 months after therapy. Any lesion that did not fail was considered "cured."

Local adverse effects (erythema, edema, pruritis, and pain) were assessed on treatment days when intralesional treatments were applied by study personnel. Systemic effects focusing on gastrointestinal reactions were assessed for each day of miltefosine therapy. Blood was drawn for evaluation of aspartate transaminase (AST), creatinine, and glucose on days 14 and 28.

Ethical review. The study was approved by the Comité de Bioética de la Facultad de Medicina, Universidad Mayor de San Simón, Cochabamba, Bolivia (ClinicalTrials.gov identifier No. NCT03445897).

RESULTS

Patient characteristics: 78 patients were evaluated in the course of enrolling 50 patients into the study. The 28 who did not enter were rejected because of age (six patients), comorbidities (seven), and abnormal laboratory rests (six), and nine declined to participate. The 50 patients who were studied were aged 28 (8) (mean [standard deviation]) years and weighed 63 (8) kg. There were 45 men and five women. Lesion size at entrance was 337 (166) mm^2. With a mean weight of 63 kg, the average patient received 2.4 mg miltefosine/kg/day, very close to the recommended target of 2.5 mg/kg/day.[4] With a mean lesion size of 337 mm^2, the average patient received 40 mg pentamidine intralesionally on each of 3 days for a total of 120 mg over 5 days. This total dose is approximately one-quarter of that commonly used to parenterally treat cutaneous disease: 2 mg/kg/day × 4 days[5] = 8 mg/kg total dose or 504 mg for a 63-kg person.

Outcomes: 46 patients (92%) cured and four failed. The entrance size of the lesions of those patients who ultimately cured was 330 (166) mm^2 compared with 410 (164) mm^2 in those who failed therapy, but this difference was not statistically significant ($P = 0.43$: *t*-test).

Lesions that were destined to cure responded rapidly to treatment. At 1 and 3 months after therapy, lesion sizes for ultimately cured patients were 28 (51) mm^2 and 0 (0) mm^2, respectively. At 3 months, four patients were declared failure because each had lesion sizes that were 50% or more of entrance size.

Adverse effects are summarized in Table 1. Local reactions to IL pentamidine were frequent. Erythema was mild-moderate in each of the 50 patients. Edema, pruritus, and pain were each present in 15–37 of the 50 patients. These incidences were higher than those in our previous experience of 60 patients, in which "irritation" (defined as any of erythema, edema, and pruritus) was mild-moderate in 10 patients and pain was present in eight patients. Gastrointestinal reactions and changes in creatinine characteristic of miltefosine treatment were seen in the present experience. Although AST elevations were predominately mild, their frequency surprised us because neither miltefosine[4] nor pentamidine[6] (even if absorbed from the intralesional injection) should cause such changes.

TABLE 1
Adverse effects in 50 patients

	Mild*	Moderate*	Severe*
Local reactions			
Erythema	45	5	0
Edema	37	0	0
Hard edema	27	2	0
Pruritus	11	4	0
Pain	20	3	0
Systemic reactions			
Nausea	25	3	0
Vomiting	14	1	0
Diarrhea	11	0	0
Hypotension	2	0	0
Laboratory parameters†			
Blood glucose change	3	0	0
AST	16	3	0
Creatinine	6	1	0

AST = aspartate transaminase.

* Number of patients with grade of adverse effect. Each local and systemic reaction other than pain was graded on a 0–3 scale defined as follows: 0 = absent, 1 = mild (present but treatment not required), 2 = moderate (present and needed specific treatment), and 3 = severe (present with such intensity that antileishmanial therapy had to be stopped). The 0–3 scale for pain was as follows: 0 = absent, 1 = mild (present but expected with injections, treatment not required), 2 = moderate (present and more than expected with injections, treatment not required), and 3 = severe (present with such intensity that analgesics were required).

† Laboratory parameters were graded according to the common toxicity criteria scale.[11] Of the three blood glucose abnormalities, two were first seen on day 14 and one on day 28. For AST, 14 were first seen on day 14 and 5 on day 28. For creatinine, four were first seen on day 14 and three on day 28. The mean (standard deviation) [range] for the laboratory abnormalities were as follows: glucose—104 (14) [88–114] mg/dL, AST—89 (33) [51–169] U/L, and creatinine—1.5 (2.0) [1.3–1.9] mg/dL. The upper limits of normal for our laboratory are as follows: glucose—100 mg/dL, AST—45 U/L, and creatinine—1.2 mg/dL.

DISCUSSION

We here report a cure rate of 92% (46 of 50 patients) for *L. braziliensis* CL in Bolivia treated with a combination of oral miltefosine and intralesional pentamidine.

This uncontrolled study was designed to test the principle that > 90% cure with some anti-CL regimen can be presently achieved at our site. It is difficult to choose a reasonable historical control against which our cure rate should be compared. Cure rates for a different *Leishmania* species would be a poor choice because cure rates for different species treated with the same drug differ widely. For azoles, for example, cure rates were 89% for *Leishmania mexicana*, 88% for *Leishmania infantum*, 80% for *Leishmania donovani*, 53% for *Leishmania major*, 49% for *L. braziliensis*, and 15% for *Leishmania tropica*.[7] Furthermore, cure rates for the same species treated with the same drug can differ between countries. The cure rate for miltefosine for primarily *L. braziliensis* in Guatemala (53%)[8] was much lower than the approximately 80% present cure rate for *L. braziliensis* in Bolivia. Cure rates for one species in one country treated with one drug can even differ between locations within that country. For *L. braziliensis* treated with parenteral antimony, the cure rate in Rio de Janeiro was 81%,[9] whereas the cure rate in Bahia was 45%.[10]

Given the remarkable variability of CL cure rate with *Leishmania* species and geographic location, we think the best historic controls for our present experience are data from the same species at our own site. In the last 5 years versus *L. braziliensis*, miltefosine has a cure rate of 81%; IL pentamidine had a cure rate of 70%. Comparison of the 92% efficacy of miltefosine plus IL pentamidine to the cure rates of the individual drugs suggests that the efficacy of these two agents is additive. It is unknown if systemic therapy will prevent mucosal dissemination, but if so, another advantage of the regimen tested in this report is the presence of one systemic agent.

One disadvantage of giving combinations of full treatment regimens is that side effects are likely to be the sum of the side effects of the individual drug regimens. Here, systemic and local side effects appear to be the sum of the systemic effects of miltefosine and the local adverse effects of pentamidine. Another disadvantage is additive cost. Nevertheless, we have not achieved > 90% with any other regimen in the last 5 years and propose that other sites might take advantage of the combination of miltefosine plus IL pentamidine when a prime consideration is efficacy (e.g., in rescue therapy), avoidance of parenteral therapy, or the desire to

not only treat locally but also provide systemic protection against parasite dissemination.

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