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# Short Report: Efficacy of Extended (Six Weeks) Treatment with Miltefosine for Mucosal Leishmaniasis in Bolivia

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*Abstract.* We investigated whether increasing the period of follow-up or increasing the duration of therapy would markedly alter the 71% cure rate of mucosal leishmaniasis in Bolivia consequent to treatment with miltefosine for 4 weeks. Increasing the follow-up from 12 months to 24 months demonstrated additional relapse in only 2 of 41 patients. Increasing the period of therapy from 4 weeks to 6 weeks only increased the cure rate to 75%. The cure rate of mucosal leishmaniasis in Bolivia, whether 4 or 6 weeks of therapy is used and whether 12 month or 24 months follow up is conducted, is approximately 70%.

We have recently reported that mucosal leishmaniasis in Bolivia is responsive to treatment with a standard regimen of the oral agent miltefosine (2.5 mg/kg/day for 4 weeks). A total of 51 (71%) of 72 evaluable patients cured after 12 months of follow-up, with 21 of the 72 patients failing treatment.[1] The 71% cure rate with 4 weeks of oral miltefosine was comparable to that with classic therapy with 4 weeks of parenteral antimonial therapy.[2,3] Nevertheless, a higher cure rate is desirable.

Two issues with respect to the cure rate in this study have been raised. The first issue is would the 71% cure rate diminish if follow up were two-years as has been used, for example, in Brazilian mucosal leishmaniasis?[4] The second issue is could the 71% cure rate be increased by increasing the dose of miltefosine? Because miltefosine has a small therapeutic index, the daily dose of 2.5 mg/kg should not be exceeded. However, this drug has a half-life of approximately 1 week,[5] steady state is barely reached at the end of the standard 4-week treatment period, and a higher total dose could be achieved by increasing the duration of therapy (e.g., to 6 weeks).

To address the first issue, we extended the follow-up period of the 51 initially cured patients to 24 months (patient group A). To provide observational data relevant to the second issue, we re-treated the 21 patients who initially failed treatment with 6 weeks of therapy (patient group B), and treated 21 new patients with 6 weeks of therapy (patient group C). Informed consent was obtained from the Comité de Etica del Colegio Médico de La Paz (La Paz, Bolivia).

As per the original investigation, each potential site of disease (nasal skin, nasal mucosa, palate, pharynx, and larynx) was evaluated for erythema, edema, infiltration, and erosion. Each of these signs of disease was graded for severity on a four-point scale (0 = none; 1 = mild; 2 = moderate; and 3 = severe). The mucosal severity score was defined as the sum of the severity grades for all lesion sites, and had a maximum value of 60: 3 severity points for each of 4 signs at each of 5 sites.

In the original investigation, we assumed that slight remaining signs of disease at 12 months might spontaneously remit. Thus, cure was defined as a 12-month severity score being 0–10% of the entrance severity score. In the present investigation, we thought that although disease might not have completely resolved by 12 months after therapy, disease should have reached a final state by 24 months after therapy. Thus, for patient group A, who underwent 24 months of follow-up, cure was defined as a severity score of 0 at that time point. For patient groups B and C who underwent 12 months of follow-up, cure was defined as before as a 12-month severity score of 0–10% of the entrance severity score.

In patient group A, forty-one of the 51 patients treated with miltefosine for 4 weeks and apparently cured at 12 months of follow-up were located and evaluated 12 months later by the same ear, nose, and throat (ENT) specialist who had initially evaluated the patients. Thirty-nine of the 41 patients were considered cured because they had no objective ENT findings, although most patients reported nasal dryness, itching, and/or rhinorrhea. Two of the 41 patients relapsed with infiltration of the palate or of the vocal cords, respectively.

Four of the 10 patients who were not personally seen were contacted by telephone. Three reported no symptoms and likely represent cures; one reported bleeding, pain, and obstruction and likely represents a relapse. The per-protocol failure rate between 12 and 24 months of follow-up was 5% (2 of 41). If the four patients reached by telephone are included, the failure rate was 7% (3 of 45).

Of the original 21 patients in patient group B who were not cured with 4 weeks of miltefosine, 17 were located and re-treated with miltefosine for 6 weeks. For 14 of the patients, the ENT specialist who had initially evaluated the patients performed the evaluation of re-treatment. For 3 patients who moved after re-treatment, the 12-month follow-up was performed by the nurse-coordinator who has assisted the ENT specialist for the 2 years of these trials.

With 12-months follow-up after re-treatment, there were 11 cures and 6 failures (cure rate = 65%). The entrance severity scores of the cures (mean [SD] = 7.7 [4.2], range = 2–19) was similar to the entrance scores of the treatment failures (8.2 [4.6], range = 2–15). Nine of the 11 cured patients had final severity scores of 0 at 12 months. One of the 11 cured patients entered with disease at three sites (nasal mucosa, palate, pharynx) and at 12 months had only erythema of the nasal mucosa. The ratio of the final severity score to entrance severity score was 1:19 (0.05). Another of the 11 cured patients entered with severe erythema, edema, infiltration, and erosion of the nasal mucosa and at 12 months had only mild infiltration. The ratio of severity scores was 1:12 (0.08).

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Twenty-one patients who satisfied the inclusion/exclusion criteria of the original 72 patients[1] were treated with six weeks of therapy (patient group C). For the 21 new patients, the mean age (36 years), mean weight (54 kg), and percent that were males (71%) were comparable with the values for the original 72 patients. However, the duration of mucosal disease for the new patients (mean = 14 months, range = 4–20 months) was much shorter than the mean duration of 5 years[1] for the previous patients. This difference reflects the fact that the original patients included many who had waited years for treatment, whereas the present patient population consisted of persons whose disease appeared in the time between the previous study and our present study.

Nineteen patients were followed-up at 12 months by the ENT specialist. Two patients who had relocated to another city were followed-up at 12 months by the nurse-coordinator. With 12 months of follow-up, 15 patients cured and 5 failed (one was lost to follow-up) for a per protocol cure rate of 75%. Fourteen of the 15 cures had final severity scores of 0. One cured patient entered with a severity score of 24 and had a final severity score of 2.

The cured patients had entrance mucosal severity scores with a mean value of 8.7 (range = 3–24). These scores reflect the fact that 12 patients had disease limited to the nasal mucosa, 1 patient had disease of the nasal mucosa and one other anatomic site (palate), 2 patients had disease of the nasal mucosa and 2 other sites (palate, pharynx and/or larynx).

The patients who failed to respond to therapy had entrance severity scores with a mean of 6 (range = 5–9). These low scores reflect the fact that all patients destined to fail therapy had disease at only one anatomic site: 4 had disease of the nasal mucosa and 1 had disease of the palate.

The 42 patients had a mean ± SD age of 38 ± 16 years and a mean ± SD weight of 58 ± 11 kg. The entrance mean ± SD aspartate aminotransferase (AST) level was 24 ± 7 U/L and the entrance mean ± SD creatinine level was 0.49 ± 0.34 mg/dL. No patient had liver or kidney toxicity. Mean ± SD values at the end of therapy on day 42 were 24 ± 7 U/L for AST and 0.43 ± 0.30 mg/dL for creatinine. In terms of individual values on day 42, all AST values were < 38 U/L and all creatinine values were < 1.2 mg/dL.

Thirty-one of the 42 patients reported gastrointestinal symptoms of common toxicity criteria (CTC) severity grade 1 that lasted for a mean of 4 days (range = 1–10 days). The CTC grade 1 signifies vomiting once, 2–3 episodes of excess stools, or a mild degree of anorexia, nausea, or abdominal pain. Two additional patients had 9 and 10 days of gastrointestinal symptoms for which CTC grade 2 vomiting (2–5 episodes) or diarrhea (4–6 excess stools) occurred on at least one day.

Overall, six weeks of therapy was well tolerated. There were no instances of systemic intolerance although the gastrointestinal discomfort previously reported in this patient population[1] was evident.

Extending follow-up to 24 months or treating patients with miltefosine for 6 additional weeks did not dramatically change the conclusions from the original report on patients followed-up for 12 months after treatment with miltefosine for 4 weeks.

In patient group A, 12 months of additional follow-up resulted in only 5–7% additional relapses. In patient group C increasing the duration of therapy to 6 weeks resulted in cure of 75% of new patients. Although the new patients in the present study were of necessity not randomized with the patients from the previous study, and the two groups of patients differed in the important entrance characteristic of duration of disease, the 75% cure rate with 6 weeks of treatment in the present study is comparable in absolute value to the 71% cure rate after 4 weeks of therapy in the prior study.[1] In patient group B, re-treatment of initial miltefosine treatment failures with six weeks of additional therapy did not lead to a remarkably high or low cure rate. Although either a high cure rate caused by the large amount of additional drug or a low cure rate caused by possible resistance in response to the initial course of therapy might have been predicted, the 65% re-treatment cure rate was not markedly different from the initial cure rate of 71% in these patients.

We note that the observation in the original report[1] linking entrance disease severity scores with treatment outcome (persons who had high severity scores were more likely to fail therapy) was not confirmed in the present study. In patient group B, the entrance severity scores of cured patients and failed patients were similar in absolute value. In patient group C, the entrance scores of patients who cured were higher in absolute value than those of patients who failed.

In neighboring Peru, Franke and others attempted to increase the response of mucosal leishmaniasis to classic antimonial therapy by extending the treatment period from the 4-week standard to 6 weeks. The cure rate was 63% in both groups: 10 cures of 16 patients in the 4-week group and 12 cures of 19 patients in the 6-week group.[2] Llanos-Cuentas and others attempted to improve the antimony cure rate by co-administration of allopurinol.[3] Four weeks of antimony alone cured 75% (21 of 28) of the patients whereas 4 weeks of antimony plus allopurinol cured 63% (14 of 22) of the patients.[3] In contrast, mucosal leishmaniasis in Brazil may be more responsive to antimony[6] or to antimony plus adjunctive therapy.[7] We conclude that the cure rate of Andean mucosal leishmaniasis using presently licensed agents (miltefosine or antimony) is approximately 70%, whether 4 weeks or 6 weeks of initial therapy is administered.

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