Topical Paromomycin/Methylbenzethonium Chloride Plus Parenteral Meglumine Antimonate as Treatment for American Cutaneous Leishmaniasis: Controlled Study

J. Soto, P. Fuya, R. Herrera, and J. Berman

We determined the efficacy of the combination of the topical formulation 15% paromomycin sulfate/12% methylbenzethonium chloride (MBCL) and a short course (7 days) of parenteral meglumine antimonate (pentavalent antimony [Sb]) as treatment of American cutaneous leishmaniasis in Colombian patients. Patients were randomly assigned in unequal allocation (2:1:1:1) to group 1 (topical paromomycin/MBCL plus injectable Sb for 7 days), group 2 (topical placebo plus injectable Sb for 7 days), group 3 (topical paromomycin/MBCL plus injectable Sb for 3 days), and group 4 (injectable Sb for 20 days). Cure was defined as complete reapithelialization of all lesions without relapse. Cure rates among groups were as follows: 58% (34 of 59), group 1; 53% (16 of 30), group 2; 20% (6 of 30), group 3; and 84% (26 of 31), group 4. Seventy-one percent of the organisms identified to the species level were *Leishmania braziliensis panamensis*. We conclude that 10 days of therapy with paromomycin/MBCL does not augment the response of cutaneous leishmaniasis (predominately due to *L. braziliensis panamensis*) to a short course of treatment with meglumine antimonate.

All effective therapies for New World cutaneous leishmaniasis are parenteral. For example, standard therapy with pentavalent antimony (Sb) consists of 20 daily injections of 20 mg of Sb/(kg·d). In a previous phase 2 trial [1], we showed that the combination of a topical regimen marketed in Israel for treatment of Old World cutaneous leishmaniasis—paromomycin sulfate/methylbenzethonium chloride (MBCL)—and a short course (7 days) of Sb as treatment of New World cutaneous leishmaniasis was 90% curative for 20 patients. Although concomitant control groups were not involved in that phase 2 trial, we did not think that either the topical regimen or the 7-day course of Sb alone would have been 90% efficacious. The cure rate among a group administered paromomycin/MBCL plus Sb for 3 days was 42%, and that among historical controls administered Sb for 10 days was 31%.

We report the results of a large, randomized, partially double-blind, controlled phase 3 trial of the efficacy of the combination of topical paromomycin/MBCL plus injectable meglumine antimonate (Sb) for 7 days as treatment of American cutaneous leishmaniasis.

Materials and Methods

Study Design

The study was a randomized, controlled phase 3 trial of four treatment regimens. Patients were randomly assigned in unequal allocation (2:1:1:1) to four groups: group 1 (experimental group), topical paromomycin/MBCL twice a day for 10 days plus injectable Sb for 7 days; group 2 (first negative control group), topical placebo twice a day for 10 days plus injectable Sb for 7 days; group 3 (second negative control group), topical paromomycin/MBCL twice a day for 10 days plus injectable Sb for 3 days; and group 4 (positive control group), injectable Sb for 20 days. Since both groups 1 and 2 received a topical cream for 10 days in addition to Sb for 7 days, the study was double-blinded for those two groups.

Study Population, Inclusion Criteria, and Exclusion Criteria

The inclusion and exclusion criteria, parasitological diagnosis, determination of clinical toxicity, and definitions of response were identical to those in our previous study [1]. In brief, patients were eligible for the study if they were 18–60 years old, had cutaneous leishmaniasis proven parasitologically by visualization or culture of organisms, and were otherwise healthy. The patients acquired their disease in the Colombian regions of Uraba, Magdalena Medio, and Llanos Orientales. As before, failure was defined as worsening of disease (>50% enlargement of any lesion at any time), inability to initially heal (<75% reapithelialization of any lesion by the first follow-up 1.5 months after the end of therapy), or relapse (enlargement...
of a lesion that had completely or partially healed) by the end of 9–12 months of follow-up. Cure was defined as an initial cure (complete healing of all lesions by the end of therapy or by the 1.5-month follow-up) with no relapse.

### Dosage and Administration of Drugs

**Topical formulation.** Fifteen percent paromomycin sulfate/12% MBCL (Leshcutan) or matching topical placebo was obtained from TEVA Pharmaceutical Industries, Jerusalem. Topical agents were administered as follows. The lesion was cleaned with soap and water, and then 0.001 mL of formulation per 1 mm² of lesion was applied by medical personnel twice a day for 10 days. Patients were instructed not to rub off the cream.

**Injectable formulation.** Meglumine antimonate (Glucantime) was obtained from Specia, Bogota, Colombia; this agent was administered intramuscularly at a dosage of 20 mg of Sb/(kg · d) for 3, 7, or 20 days.

### Ethical Review

The study was approved by the Ethical Review Committee of the Universidad Militar Nueva Granada, Bogata.

### Results

#### Patient Characteristics

Randomization was effective with respect to the mean number of lesions and the mean size of lesions (table 1). Because of a protocol error, one patient who was randomized to group 1 was instead treated with Sb for 20 days and was analyzed as a member of group 4. Before treatment, *Leishmania* amastigotes were demonstrated by direct examination of Giemsa or monoclonal antibody–stained smears or biopsy specimens of lesions in all 150 patients. Cultures of 69 of the 150 lesion biopsy specimens yielded *Leishmania*. Of the 69 cultured strains, 49 were identified by isoenzyme electrophoresis as *Leishmania braziliensis panamensis*, and 20 were identified as *Leishmania braziliensis braziliensis*.

### Treatment Efficacy

Of the 150 patients in this study, 82 were cured or apparently cured (table 1): 76 patients were initially cured and did not relapse during 9–12 months of follow-up; 4 patients were initially cured without relapse at the 6-month follow-up; and 2 patients (both in group 1) were initially cured but were lost to follow-up after 1.5 and 3 months, respectively.

There were 68 treatment failures: treatment failed for 48 patients on the basis of >50% enlargement of a lesion by the end of treatment or by the 1.5-month follow-up; treatment failed for 9 patients because a lesion had diminished by <75% at 1.5 months; and treatment failed for 11 patients because an initially healed lesion subsequently enlarged (relapse).

The cure rate among group 1 was not different (P = .82) from that among group 2. The cure rate among group 4 was significantly higher (P < .025) than that among any of the other groups. The cure rate among group 3 was significantly lower (P < .02) than that among any of the other groups.

#### Discussion

In this phase 3 study of the efficacy of topical paromomycin/MBCL twice a day for 10 days plus a short course (7 days) of injectable meglumine antimonate as treatment of New World cutaneous leishmaniasis, the cure rate (58%) was no higher than that of injectable meglumine antimonate alone for 7 days (53%). Because standard treatment with meglumine antimonate for 20 days results in a high rate of cure (∼90%) in our previous study [1] and 84% in this study), it would be difficult to demonstrate that paromomycin/MBCL improves on the cure rate associated with the standard duration of meglumine antimonate. In

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>59</td>
<td>30</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Mean no. of lesions per patient</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean lesion size ± SD (mm²)</td>
<td>224 ± 210</td>
<td>202 ± 221</td>
<td>302 ± 423</td>
<td>267 ± 331</td>
</tr>
<tr>
<td>No. of cured patients</td>
<td>34</td>
<td>16</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>No. of patients for whom therapy failed</td>
<td>25</td>
<td>14</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Cure rate, % (95% CI)</td>
<td>58 (45–71)*</td>
<td>53 (35–71)*</td>
<td>20 (6–34)¹</td>
<td>84 (73–97)³</td>
</tr>
</tbody>
</table>

**NOTE.** Group 1 = patients who were treated with topical paromomycin/MBCL b.i.d. for 10 days plus injectable Sb for 7 days; group 2 = patients who were treated with topical placebo b.i.d. for 10 days plus injectable Sb for 7 days; group 3 = patients who were treated with topical paromomycin/MBCL b.i.d. for 10 days plus injectable Sb for 3 days; group 4 = patients who were treated with injectable Sb for 20 days; MBCL = methylbenzethonium chloride; Sb = antimony (meglumine antimonate).

* Not significantly different (P = .82).

¹ Significantly lower than those for each of the other three treatment groups (P < .02).

³ Significantly higher than those for each of the other three treatment groups (P < .025).
addition, the efficacy of paromomycin/MBCL combined with a very short course (3 days) of meglumine antimonate was only 20% efficacious in this study, and this finding may approximate the cure rate associated with placebo. Thus, this study indicates that for cutaneous disease in Colombia that is predominately due to L. braziliensis panamensis, paromomycin/MBCL either does not have or is unlikely to have additive efficacy when combined with the standard drug meglumine antimonate. Nevertheless, a very high cure rate was associated with paromomycin/MBCL alone in an uncontrolled study [2] in Ecuador, and it is possible that there are Leishmania species for which some regimens of paromomycin/MBCL might improve the efficacy of meglumine antimonate.

Since paromomycin/MBCL plus meglumine antimonate for 7 days was associated with a cure rate of 90% in our previous phase 2 study [1] and historically meglumine antimonate for 10 days was associated with a cure rate of ~35%, the low cure rate associated with paromomycin/MBCL plus meglumine antimonate for 7 days and the high cure rate associated with meglumine antimonate alone for 7 days in this study were surprising. For the previous study, paromomycin/MBCL was prepared locally, whereas for this study, paromomycin/MBCL was supplied by the manufacturer, who prepared it under good manufacturing practices. Nevertheless, the most likely explanation for the differing results is that phase 3 trials, which are larger and better controlled, inherently result in data more representative of the true situation than do phase 2 trials.

Paromomycin/MBCL is effective compared with placebo as treatment for Old World cutaneous leishmaniasis caused by Leishmania major [3, 4]. For example, L. major lesions treated with paromomycin/MBCL for 10 days cleared significantly more rapidly (100% cure at 21–30 days) than did untreated lesions (100% cure at 51–60 days) on the same patients [3]. In the present study, paromomycin/MBCL essentially by itself (i.e., paromomycin/MBCL plus meglumine antimonate for 3 days) was at most 20% curative and did not augment the efficacy of meglumine antimonate. Comparison of our results with L. braziliensis panamensis to those with L. major indicates that cutaneous syndromes with very different natural histories may also have very different responses to chemotherapy.

Acknowledgments

The authors appreciate the help in culture and identification of the Leishmania isolates by Dr. Santiago Nichols and LIC Martha Ayala of the Parasitology Department of the National Institute of Health, Bogota, Colombia.

References