Efficacy of Azithromycin versus Systemic Meglumine Antimoniate (Glucantime) in the Treatment of Cutaneous Leishmaniasis

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Abstract. Cutaneous leishmaniasis (CL) treatment is painful, and cosmetic results are often unsatisfying. Azithromycin has been reported to be effective in treatment of CL caused by *Leishmania viannia braziliensis*. The efficacy of azithromycin was compared with Glucantime in treatment of Old World leishmaniasis. Of 49 patients, 22 received 500 mg/day azithromycin for 5 days/month. Treatment cycles were repeated monthly to a maximum of 4 months; 27 patients received 60 mg/kg intramuscular meglumine antimoniate for 20 days. Both groups were followed up for 16 weeks. In the azithromycin group, 2 patients withdrew because of GI symptoms. The response rates of 20 patients (29 lesions) were as follows: full improvement, 10.3%; partial improvement, 27.6%; and 62.1%, no response. In the glucantime group with 27 patients (58 lesions), these rates were 34.4%, 13.8%, and 51.7%, respectively (*P* = 0.036). Azithromycin was determined to be not as effective as Glucantime in treatment of Old World CL.

INTRODUCTION

Treatment of leishmaniasis has classically been based on pentavalent antimonials, such as meglumine antimoniate (Glucantime) or sodium stibogluconate (Pentostam). Other therapeutic options of proven efficacy are amphotericin B, pentamidine, and aminosidine.¹⁻³ All of these drugs are administered through the parenteral route, but they present several side and toxic effects and must be used for several weeks. Oral medications, such as imidazole, triazole derivatives, and allopurinol, have been used, among others, with variable responses.³

The availability of an effective medication that could be administered by the oral route and which is effective against leishmaniasis would be highly relevant. Azithromycin is a macrolide derivative structurally related to erythromycin,⁵ and it has been used in clinical practice for the treatment of various infections.⁶ Its administration by the oral route, rapid passage into the intracellular compartments, slow release (a half-life of 2–6 days), and accumulation in various organs and tissues at high concentrations—especially in phagocytic cells—make this drug an attractive option for the treatment of microorganisms that cause intracellular infections.⁷ In addition, therapeutic levels of this medication are maintained up to 5 days after administration of the last dose.⁸⁹ Azithromycin shows good oral tolerance in both children and adults and has been successfully used in clinical practice administered as a single dose for the treatment of infections of the respiratory tract and skin and of sexually transmitted diseases, especially non-gonococcal urethritis, as well as of ocular infections, especially trachoma.¹⁰¹¹

The *in vitro* and *in vivo* activity against *Leishmania major* was reported by Krolewiecki and others.¹² Prata and others reported a cure rate of 85% in CL caused by *Leishmania viannia braziliensis* (LvB) in an open pilot study.¹³ These preliminary results encouraged us to perform this study, to assess the efficacy of azithromycin in the treatment of Old World CL and to compare its clinical effect with meglumine antimoniate.

MATERIALS AND METHODS

This prospective study was conducted from October 2004 through November 2005 at the dermatology department of Qaem University Hospital, Mashhad, Iran, where CL is endemic and *L. tropica* and, less commonly, *L. major* are the most prevalent species. Inclusion criteria were as follows:

- a) Patients older than 2 years with cutaneous leishmaniasis of <6-months’ duration;
- b) No treatment of the current infection during the last 3 months; and
- c) No history of a renal or liver disease.

Exclusion criteria were as follows:

- a) Pregnant women;
- b) History of intolerance or allergy to Glucantime or macrolides; and
- c) Simultaneous use of antacids containing Al and Mg, theophylline, phenytoin, barbiturates, carbamazepine, and cyclosporin.

Diagnosis of CL was confirmed by direct examination of the ulcer smear or slit–skin-smear stained by Giemsa, and all patients were submitted to clinical examination and photography of the lesions.

The 49 patients who met our criteria were randomly divided into two groups. The first group included 22 patients (35 lesions) who received a daily oral dose of 500 mg of azithromycin for 5 days/month in adults (according to the study by Prata and others¹³) and 10 mg/kg in children; treatment cycles were repeated monthly when no favorable response was achieved, up to a maximum duration of 4 months. The second group included 27 patients (58 lesions) who received 60 mg/kg of meglumine antimoniate for 20 days. Patients in the azithromycin group were evaluated monthly up to a maximum of 4 months, but patients in the Glucantime group were evaluated both at the end of the treatment period (day 20) and 45 days later. The patients’ evaluation and clinical response were determined on the basis of the lesions’ size, border, induration, and infiltration of papulonodular lesions; ulcerative lesions were evaluated on the basis of the ulcer depth, diameter, crusting, and the extent of epithelialization.

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At each visit, clinical response was determined on the basis of the following criteria:

a) Complete or significant improvement: decrease in the induration size >75% or full re-epithelialization of the lesions and a negative direct skin smear (absence of parasites in the lesion).

b) No improvement: decrease in induration size <30%.

c) Partial improvement: any changes between criteria a and b above.

It was decided that patients showing no favorable response after 4 months of azithromycin therapy would receive Glucantime at the same dose as the other group, at the end of the study.

Study goals were explained to the patients, and a signed consent form was obtained from the patients or their guardian before entering the study, which was also approved by the Ethics Committee of the Faculty of Medicine of Mashhad.

RESULTS

Forty-nine patients diagnosed with CL were enrolled in our study. Among them, two patients (6 lesions) from the azithromycin group were excluded because they experienced GI symptoms a few days after administration.

The demographic characteristics of our patients in both groups are shown in Table 1; 65% of the patients in the azithromycin and 44.4% of the Glucantime group were younger than 20 years of age. The most common lesion type was papulonodular, while ulceration and crust were noted in 4 lesions (8.6%). Results of the final evaluation of clinical response in both groups are shown in Table 2. Comparison of these results between the two groups showed a significant statistical difference ($\chi^2 = 6.636, P = 0.036$), in which systemic Glucantime was proved to have a higher efficacy in the treatment of Old World CL than azithromycin.

Three patients in the Glucantime group complained of myalgia, and one showed erythema at the injection site, but they all completed the treatment course. In the azithromycin group, 2 patients had complaints of nausea and vomiting a few days after administration and stopped the treatment course. After the 16-week follow-up period, none of the lesions with a complete response in either group showed any sign of recurrence.

DISCUSSION

Treatment regimens of CL in the Old World are scarce, fragmentary,\textsuperscript{14} and vary in dosage, total number of applications and intervals.\textsuperscript{15} Chronicity and resistance rates are increasing due to insufficient treatment, and the cosmetic results are often unsatisfying.\textsuperscript{14,15} Thus, new treatment protocols are required.

In experimental and clinical assays, azithromycin has shown efficacy in combined therapy for treatment and prophylaxis of infections caused by \textit{Mycoplasma avium intracellulare} in AIDS patients.\textsuperscript{5} The drug has also proved to be effective in vitro against \textit{Toxoplasma gondii} and in the prophylaxis of \textit{Plasmodium falciparum malaria}, among other infections.\textsuperscript{16,17}

The in vitro and in vivo activity against \textit{L. major} was reported by Krolewiecki and others.\textsuperscript{18} According to this study, the azithromycin mode of action against \textit{Leishmania} species is not yet known. It could be due to a direct drug effect on the parasite or modulated immune and inflammatory responses.\textsuperscript{18} Furthermore, other effects of this medication have been described, such as stimulation of phagocytosis, chemotaxis, and cytotoxic activity in addition to its immunomodulating action.\textsuperscript{19} Tanyukel and others showed that azithromycin is able to kill intracellular amastigotes and has anti-Leishmania activity.\textsuperscript{20}

Prata and others reported a cure rate of 85% in CL cases caused by LvB in an open pilot study that took place in Araguaí and Varzelandia (MG), where American tegumental leishmaniasis (ATL) is endemic and LvB is the most common species.\textsuperscript{13}

Silva-Vergara and others also reported on the efficacy of azithromycin in the treatment of mucosal leishmaniasis in three elderly Brazilian patients. The favorable response obtained in these cases again may support the anti-Leishmania activity of this macrolide on mucosal leishmaniasis.\textsuperscript{21}

The results of our study concerning the efficacy of azithromycin on Old World CL were not satisfactory, and disparities might be due to differences in the pathogenic species (especially \textit{L. tropica} and, less commonly, \textit{L. major}) in our area (Hajjaran and others, unpublished data).

However, partial improvement of the lesions in our study was higher in the azithromycin group than in the Glucantime group (27.6% vs. 13.8%, Table 2); moreover, we must indicate that these results cannot be due to spontaneous response because we elected patients who had a lesion appearance of <6-months’ duration. In our region, the usual spontaneous recovery is =1 year in CL with \textit{L. tropica} and <1 year with \textit{L. major}. Thus, modification in dosage or duration of the azithromycin regimen may be required to achieve a more effective response, or the drug could be administered in a

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**Table 1**

Demographic and CL characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>No. (%) treated with</th>
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<tbody>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Glucantime</td>
<td>$P$ value</td>
</tr>
<tr>
<td>No. of patients</td>
<td>22 (44.9)</td>
<td>27 (55.1)</td>
<td>0.192</td>
</tr>
<tr>
<td>Male</td>
<td>8 (36.4)</td>
<td>16 (59.26)</td>
<td>0.192</td>
</tr>
<tr>
<td>Female</td>
<td>14 (63.6)</td>
<td>11 (40.74)</td>
<td>0.192</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>21.77 ± 17.13</td>
<td>22.78 ± 13.17</td>
<td>0.563</td>
</tr>
<tr>
<td>Range</td>
<td>(5–70)</td>
<td>(4–70)</td>
<td></td>
</tr>
<tr>
<td>Number of lesions (±SD)</td>
<td>1.86 ± 1.52</td>
<td>2.15 ± 1.38</td>
<td>0.46</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Duration of lesion (months)</td>
<td>4.28 ± 1.39</td>
<td>3.22 ± 2.03</td>
<td>0.425</td>
</tr>
<tr>
<td>Type of lesions</td>
<td>Papule and plaque</td>
<td>27 (77.1)</td>
<td>49 (84.5)</td>
</tr>
<tr>
<td></td>
<td>Nodular</td>
<td>6 (17.1)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td></td>
<td>Ulcerative</td>
<td>2 (5.8)</td>
<td>2 (6.2)</td>
</tr>
</tbody>
</table>

**Table 2**

Improvement rate in CL lesions treated with azithromycin and Glucantime*<sup>6</sup>

<table>
<thead>
<tr>
<th>Improvement rate</th>
<th>No. (%) treated with</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Azithromycin</td>
<td>Glucantime</td>
<td>Total (%)</td>
</tr>
<tr>
<td>No response</td>
<td>18 (62.1)</td>
<td>30 (51.7)</td>
<td>48 (55.2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>8 (27.6)</td>
<td>8 (13.8)</td>
<td>16 (18.4)</td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (10.3)</td>
<td>20 (34.5)</td>
<td>23 (26.4)</td>
</tr>
</tbody>
</table>

* $\chi^2 = 6.636, P = 0.036$. 
combined therapy. Further in vitro studies are recommended to determine the intracellular efficacies of this drug against *L. tropica*.

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