High-Dose Oral Fluconazole Therapy Effective for Cutaneous Leishmaniasis Due to *Leishmania (Vianna) braziliensis*

Anastácio Q. Sousa,1 Mércia S. Frutuoso,2,3 Elisabete A. Moraes,4 Richard D. Pearson,5 and Margarida M. L. Pompeu3

1Department of Internal Medicine, School of Medicine, 2Christus School of Medicine, and 3Department of Pathology, School of Medicine, 4Department of Physiology and Pharmacology, School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil, and 5Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia School of Medicine, Charlottesville

We report for the first time the successful use of fluconazole to treat cutaneous leishmaniasis due to *Leishmania braziliensis*. We used escalating doses from 5 to 8 mg/kg per day. At a dose of 5 mg/kg per day, 75% patients were cured, and at 8 mg/kg per day, the cure rate was 100%. Fluconazole was well tolerated.

Cutaneous leishmaniasis (CL) is a major public health problem in Brazil. Cases are reported from every state, and there are a total of 25 000 new cases each year [1]. In Ceará, in northeastern Brazil, which is one of the most heavily affected states, *Leishmania (Vianna) braziliensis* has been the only species identified from patients with CL in the past 20 years [2, 3]. The majority of cases occur in rural areas that are distant from medical facilities, which makes early diagnosis and treatment difficult. *L. braziliensis* is responsible for mucosal disease as well. The traditional treatment for CL has been pentavalent antimony given for ≥20 days or more by either the intramuscular or the intravenous route. It is logistically difficult to treat patients in remote areas with pentavalent antimonial drugs because of the requirement for parenteral administration. In addition, these drugs can cause important adverse effects on the heart, kidney, liver, and pancreas [4]. Alternative therapy using an orally administered drug with few adverse effects is needed.

Among the potential alternatives are the azoles, which are antifungal drugs with in vitro [5] and in vivo [6] activity against leishmania. Fluconazole, which is a triazole, has been used to treat CL caused by other *Leishmania* species at a dosage of 200 mg per day with variable results [7, 8]. Its safety profile and pharmacokinetic properties [9, 10] make it an attractive alternative for the treatment of CL. It has a long half-life, and the concentration is 10 times higher in the skin than in plasma [10]. Fluconazole impedes the growth of leishmania in culture by inhibiting cytochrome P-450–mediated 14-α-demethylation of lanosterol, blocking ergosterol synthesis, and causing accumulation of 14-α-4methyl sterols [9]. In this study, we evaluate the use of high-dose oral fluconazole for the treatment of CL due to *L. braziliensis*.

**METHODS**

Fluconazole treatment was used in individuals with contraindications to receive pentavalent antimonial drugs. They included the elderly population, those with diabetes mellitus, and persons with renal or cardiac disease. Also included were individuals who refused injectable medications as well as those who lived far from a health unit, for whom a 20-day course of injections would have been difficult to administer. Persons who had failed previous pentavalent antimony therapy were also included. Patients with liver disease, pregnant women, and breast feeding mothers were excluded. Only patients with a parasitologically confirmed diagnosis of CL were included in the analysis.

A history and physical examination were performed at the onset. Laboratory studies included a complete blood count, liver enzyme analysis, and renal profile. These studies were repeated at the first follow-up visit at 4 weeks and at the end of treatment. All skin lesions were measured, evaluated for secondary infection, photographed, and biopsied with a 2-mm punch for imprint smear and histology. In patients with satellite lymphadenopathy, lymph nodes were aspirated to obtain specimens for smears, and the specimens were inoculated in Novy-MacNeal-Nicolle culture medium. Escalating dosages of fluconazole of 5, 6.5, and 8 mg/kg per day were used. Patients were treated for 4 weeks and were then evaluated. In patients with no response, oral fluconazole was discontinued. For those patients who responded to treatment, evaluations were performed every 2 weeks, and fluconazole treatment was continued until the
lesions were completely healed. Distributions of continuous variables were described by median, minimum, and maximum values and were compared using the Kruskal-Wallis test. Proportions were compared by means of the $\chi^2$ test. The Research Ethics Committee at Hospital São José for Infectious Diseases approved the study, and all patients gave informed consent before the initiation of therapy.

RESULTS

From August 2007 through April 2010, 28 persons with a parasitologically confirmed diagnosis of CL were treated with oral fluconazole. All patients were seen at Hospital São José for Infectious Diseases in Fortaleza, Ceará. They contracted the disease in one of several areas of the state in which *L. braziliensis* infection was endemic. The age of patients ranged from 2 through 88 years, with a median age of 37.5 years. Fifteen (60%) patients were female (Table 1). Twenty-five patients (89%) were cured; the remaining 3 patients did not respond to fluconazole. The duration of therapy ranged from 4 through 12 weeks, with a median duration of 6 weeks. An analysis of time to cure showed a difference in duration of therapy when different doses were prescribed (Table 1). As the dose of fluconazole increased, the cure rate increased and the time to cure shortened. Individuals treated with 5 mg/kg per day had a cure rate of 75%, and healing of lesions took a mean of 7.5 weeks. Of those treated with 8 mg/kg per day, 100% were cured, and the time to healing was 4 weeks. Fluconazole was well tolerated in all patients. Only one patient complained of nausea, which was reported to be mild. Laboratory tests performed at the beginning and the end of therapy showed no significant hepatic or other abnormalities. Of the 25 patients cured with oral fluconazole, 23 had received no previous treatment for leishmaniasis, and 2 had been treated unsuccessfully with pentavalent antimony. One patient was a 2-year-old boy who had 3 skin lesions. He had received pentavalent antimony (Glucantime 20 mg/kg daily for 35 days) with no response. Fluconazole was given at 7 mg/kg per day for 8 weeks, and all lesions healed. The other patient who experienced failure of antimony therapy was a 64-year-old woman with 2 lesions (located on an arm and a leg) who had received Glucantime 1135 mg/day for 20 days, which was a higher dosage than that recommended by the World Health Organization. She healed while receiving fluconazole 6 mg/kg per day for 8 weeks. Fluconazole was not effective in 3 patients. One of these patients was a 79-year-old woman who had a skin ulcer on the right internal malleolus. She did not respond to fluconazole administered at a dosage of 5 mg/kg per day for 4 weeks. Another of these patients was a 63-year-old man with a cutaneous ulcer over the left Achilles tendon. He had severe coronary artery disease and had experienced 2 previous myocardial infarctions. He received fluconazole 4.7 mg/kg per day for 4 weeks with no improvement. These 2 patients were cured with liposomal amphotericin B. The third patient was a 60-year-old woman with diabetes mellitus. She had 2 skin lesions on the left cheek. She was treated with fluconazole 400 mg/day (4.5 mg/kg per day) for 4 weeks with no improvement. She was then switched to a triple-drug regimen that included oral fluconazole 450 mg/day (5 mg/kg per day), allopurinol (900 mg/day), and intralesional antimony (Glucantime 1.5 mL/week [127 mg/week]). After 8 weeks of triple therapy, her lesions were completely healed.

DISCUSSION

Since the discovery and marketing of pentavalent antimonials in the 1940s, individuals with leishmaniasis have been treated with these drugs. Undesirable side effects have been reported in a high percentage of recipients [4]. In addition to the untoward effects, these drugs have to be administered parenterally. The therapeu tic alternatives for CL caused by *L. braziliensis* have been amphotericin B deoxycholate and liposomal amphotericin B. The former is associated with fever, constitutional symptoms, renal toxicity, and other adverse effects. Although the adverse effects are less severe with liposomal amphotericin B, it is too expensive for use in poor areas, where the majority of cases occur. Fluconazole is available for oral administration and is well tolerated. *L. braziliensis* is the causative agent of CL in our region [2, 3]. To our knowledge, this is the first time fluconazole has been used successfully to treat *L. braziliensis* infection. In our series, the cure rate with fluconazole was very high. The dosages of fluconazole used in our study were higher than the ones used

Table 1. Characteristics of the Patients and Results of Treatment According to Fluconazole Dose

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5 mg/kg (n = 8)</th>
<th>6.5 mg/kg (n = 14)</th>
<th>8 mg/kg (n = 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>37.5 (8–88)</td>
<td>16.5 (2–64)</td>
<td>40.5 (10–58)</td>
<td>.271</td>
</tr>
<tr>
<td>Female sex, no. (%) of patients</td>
<td>3 (37.5)</td>
<td>7 (50)</td>
<td>5 (83.3)</td>
<td>.219</td>
</tr>
<tr>
<td>Duration of the disease, median weeks (range)</td>
<td>8 (4–64)</td>
<td>12 (2–64)</td>
<td>10 (4–24)</td>
<td>.662</td>
</tr>
<tr>
<td>Duration of treatment, median weeks (range), mean weeks</td>
<td>7.5 (4–12), 7.6</td>
<td>6 (4–10), 6.2</td>
<td>4 (4–5), 4.2</td>
<td>.012</td>
</tr>
<tr>
<td>Cure rate, no. (%) of patients</td>
<td>6 (75)</td>
<td>13 (92.8)</td>
<td>6 (100)</td>
<td>.272</td>
</tr>
</tbody>
</table>

Distributions of continuous variables were described by median values (range) and compared using the Kruskal-Wallis test. Proportions were compared using the $\chi^2$ test.
by others to treat CL [7, 11], but doses of this magnitude have been used to safely treat fungal diseases [12]. In our series, 28 patients were treated, and 25 patients (89%) were cured. Three patients did not respond to fluconazole treatment. They all received smaller doses and had potentially confounding factors. A 79-year-old woman had a malleolar ulcer. Lesions at this location are typically more difficult to treat and take much longer to heal than lesions at other locations. A similar potential confounding factor was present in the case involving the 63-year-old man who had an ulcer over the left Achilles tendon. He was overweight and had severe cardiovascular disease. The third patient was a 60-year-old diabetic and overweight woman. These 3 patients each received fluconazole 5 mg/kg per day. This dosage appeared to be the least efficacious dosage used. The best results were obtained with 8 mg/kg per day (Table 1). From our analysis, the dosage of fluconazole per kilogram of body weight is an important determinant of outcome. In the treatment of L. major infection, the cure rate was 79% in one study [7] and was 44.4% in another [8]. One possible explanation for the low cure rates may be the low dosage used in these studies (200 mg/day for adults) and the failure to take into account the weight of the patients. Emad et al [11] showed that the cure rate was dose dependent. If we compare the treatment cost of fluconazole with that of antimony, the cost of the former is 12 times lower than that of the latter. This makes fluconazole a better alternative from an economic standpoint. In summary, the data suggest that fluconazole administered at 8 mg/kg per day for the treatment of CL due to L. braziliensis is an effective, safe, and economically sound option. Additional studies are needed to test the efficacy of high-dose fluconazole against other Leishmania species.

**Notes**

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**