A Randomized Clinical Trial Comparing Oral Azithromycin and Meglumine Antimoniate for the Treatment of American Cutaneous Leishmaniasis Caused by Leishmania (Viannia) braziliensis

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Abstract. Azithromycin was compared with meglumine antimoniate for treatment of patients with cutaneous leishmaniasis. Patients were randomized to receive oral azithromycin, 500 mg/day (22 patients) or intramuscular meglumine antimoniate, 10 mg Sb/kg/day (23 patients), both for 28 days, with a second cycle of 15 days if necessary, and followed-up for one year after completion of treatment. Efficacy, defined as complete re-epithelization without relapse for 12 months after completing therapy, was 82.6% (95% confidence interval [CI] = 67–98%) for meglumine antimoniate and 45.5% (95% CI = 25–66%) for azithromycin. All patients who failed treatment with azithromycin were treated with meglumine antimoniate and clinically cured. Azithromycin was well tolerated; meglumine antimoniate caused arthralgias and local symptoms in 78% of the patients. In 17 cases, species identification was obtained; Leishmania (Viannia) braziliensis was identified in all of them. For the treatment of American cutaneous leishmaniasis caused by L. (V.) braziliensis, meglumine antimoniate is significantly more efficacious than azithromycin, which was clinically curative in almost half of the patients and well-tolerated.

INTRODUCTION

American cutaneous leishmaniasis (ACL) remains a serious tropical public health problem that affects 1.5 million predominantly poor people residing in rural areas. Clinical disease ranges from single cutaneous lesions to disfiguring mucosal disease caused by Leishmania (Viannia) braziliensis and less frequently by L. (V.) panamensis and L. (V.) guyanensis. Management of patients with ACL relies on the use of the pentavalent antimonials meglumine antimoniate (MA) and sodium stibogluconate, although there is a great need for alternative therapies. The disadvantages of pentavalent antimonials include the lack of oral formulations, high cost, the contraindication for use in pregnancy, with the main issue being its toxicity profile. This profile includes pancreatitis, arthralgias, injection site pain, and cardiotoxicity, which is an issue of significant clinical importance in areas where ACL and Chagas disease overlap.

In Argentina, and in the study area in particular, most cases of ACL are caused by L. (V.) braziliensis, with recent findings of human cases caused by L. (Leishmania) amazonensis and L. (V.) guyanensis. The disease has been reported as having an endemic nature with superimposed epidemic outbreaks and an expanding transmission area. The disease, which affects mostly rural populations, has a solitary ulcer as the most common clinical presentation. The simple cutaneous form is usually less problematic for the daily activities of the affected individuals than the complicated requirements of the therapy with antimonial drugs.

The search for alternative oral therapies for ACL has not yet been successful. Miltefosine, a drug shown to be efficacious against visceral leishmaniasis in India and against ACL caused by L. (V.) panamensis, had variable activity against ACL caused by L. (V.) braziliensis, with only partial activity in a clinical trial in Guatemala, but with good activity for mild mucosal disease in a trial in Bolivia. In vitro data showed a higher sensitivity to miltefosine in L. (L.) donovani than in L. (V.) braziliensis or L. (V.) guyanensis. Fluconazole has shown significant activity in shortening time to cure for human infections with L. (L.) major in a trial in Saudi Arabia, although it has not been evaluated for the treatment of ACL.

Azithromycin, an azalide antibiotic closely related to the macrolides clarithromycin and erythromycin, is a currently available drug widely used for the treatment of bacterial infections. In addition, it has demonstrated activity against Plasmodium falciparum, Toxoplasma gondii, and other intracellular microbes. Its main pharmacokinetic features are a peak concentration (Cmax) of 0.4 mg/L, a half-life of 14 to > 40 hours, an area under the curve of 6.48 mg.hour/L, an oral bioavailability of 37%, an average half-life in tissues of 2–4 days, and an elimination that is dependent mostly on biliary excretion; the last characteristic indicates that there is no dose adjustment required in renal impairment. The most common side effects are gastrointestinal (diarrhea, nausea, abdominal pain), and discontinuance of therapy is rarely required; reversible cholestatic hepatitis has been reported. This drug is approved for use in pediatric populations and during pregnancy (category B; Food and Drug Administration, Rockville, MD).

Azithromycin has additional pharmacokinetic properties with respect to the other macrolides through the lack of significant drug-drug interactions, once daily posology, and fewer gastrointestinal side effects. The usual regimen is 500 mg orally for 3–7 days for the treatment of respiratory tract infections and 600 mg/day for over 24 months for Mycobacterium avium infections in patients infected with human immunodeficiency virus (HIV). The high intracellular concentration of this drug, which in macrophages is up to 200 times
the plasma levels, and its intracellular localization in the phagolysosomes makes azithromycin a potentially good candidate for treating leishmaniasis. Azithromycin has been shown to have activity against L. (L.) major in vitro and in BALB/cByJ mice. Furthermore, in uncontrolled non-randomized studies, the clinical efficacy of azithromycin at variable doses was observed for patients with cutaneous and mucosal lesions caused by ACL.

The objective of the current study was to evaluate the clinical efficacy and safety of oral azithromycin against cutaneous leishmaniasis and compare it to the standard therapy with parenteral MA in a leishmaniasis-endemic area in Salta, Argentina. This drug could thus potentially provide a safe oral alternative for the current standard therapy for ACL with either MA or sodium stibogluconate.

MATERIALS AND METHODS

Study design. The design of this study was a randomized open-label study of two treatment strategies for ACL, with the use of an experimental drug (azithromycin) versus the standard therapy in the study area (MA). Patients were randomized in a 1:1 fashion to either arm of treatment and patients within each group were stratified according to location of the lesion either above or below the knee. The rationale for this stratification was the likelihood of delayed healing in lesions below the knee. Forty-six patients were screened for the study between March 2003 and July 2004, and 45 patients fulfilled the entry criteria (Figure 1). The first patient was randomized on March 5, 2003, the last patient took his last dose on August 8, 2004, and the final month-12 follow-up was done on September 12, 2005.

The randomization sequence was obtained from a computer-generated random number table, the details of the series were unknown to the investigators and were contained in sealed envelopes sequentially numbered, each having on the outside only the name of the study, the strata, and the number. After acceptance of the patient to participate in the study and completion of the screening procedures, the appropriately numbered envelope was opened and the card indicated which treatment the patient would receive. All the authors participated in the design of the study, had access to all study data and take responsibility for data analysis. The study protocol and the informed consent form were reviewed and approved by an independent ethics committee and by Provincial, National and University authorities. The protocol was conducted in accordance to the Declaration of Helsinki as adopted by the 52nd World Medical Association (WMA) General Assembly, Edinburgh, Scotland, October 2000, and the note of clarification on paragraph 30 added by the WMA General Assembly, Tokyo 2004.

After the investigators verified fulfillment of all entry criteria, patients started their assigned treatment on the baseline visit. All treatments were done in an ambulatory setting. Azithromycin (Zitromax; Pfizer, New London, CT) was prescribed orally in 500-mg tablets at a dose of two tablets on the first day, followed by one tablet every 24 hours for another 27 days. A generic formulation of MA (5-mL vials containing 1.5 g of antimony, corresponding to 425 mg of pentavalent Sb) approved and distributed by the National Health Ministry of Argentina (Antimonio de meglumine Lazar; Dr. Lazar y CIA, Munro, Argentina) was prescribed at an intramuscular dose of 10 mg of Sb/kg/day, without a maximum dose, for 28 days (the intravenous route was used for patients intolerant to the intramuscular route). A second cycle at the same doses and lasting 15 days (so not to delay the administration of standard care to treatment failures) was indicated for patients with clinical improvement without resolution 14 days after completing the first cycle. Patients were evaluated at baseline visit and then at days 14 and 28 during treatment. The dosing regimen for MA was based on the standard therapy in the study area, which has demonstrated a short-term efficacy of > 95% in an observational study. The dosing regimen for azithromycin was chosen on the basis of a duration that would equal that of MA for better comparison, at a dose with predictable acceptable tolerance.

During all the visits, patients were clinically examined, side effects including serious adverse events (defined as adverse drug reactions that are fatal, life-threatening, and lead to or prolong a stay in hospital, are a congenital anomaly/birth defect or result in severe disability) were recorded and laboratory tests including complete blood count and clinical chemistries (creatinine, glucose, amylase, aspartate aminotransferase, and alanine aminotransferase) were performed. After completing therapy, visits were conducted every month for three months and then every three months until 12 months after completion of treatment. Electrocardiographic evaluation was performed at baseline for both groups and every two weeks during therapy for the MA group. Digital images of the lesions were recorded at each visit. Treatment adherence was supervised through pill counts at the clinical visits and house visits by sanitary agents.

Treatment failure was defined as the absence of cure of all lesions after 30 days of completion of treatment, new lesions after 48 hours of treatment, and mucosal lesions and/or relapse of cutaneous lesions within 12 months after treatment completion. Patients with lesions that were progressing after the first cycle were also considered treatment failures. Patients who failed therapy were treated with standard therapy consisting of a new full cycle of MA at standard doses (10 mg of Sb/kg/day until lesion resolution or up to 28 days) and/or second line drugs if necessary. The determination of the outcomes of treatment were performed by the trial physicians (A.J.K. and H.D.R.) and by the physicians at the local hospital, who were not involved with the study. Safety was assessed by the frequency and severity of adverse events and laboratory abnormalities.

Objectives. The primary objective of this study was to evaluate the clinical efficacy of oral azithromycin versus parenteral MA in the treatment of cutaneous leishmaniasis. For the efficacy endpoint, a lesion was considered cured when it had complete re-epithelization without signs of disease activity or inflammation, and remained so for 12 months after completing therapy. Time to clinical cure was a secondary outcome measure that was calculated as the time in days elapsing from baseline to the moment a lesion was considered cured according to the study definition.

Study population. The study was conducted at one site located in the Department Orán, Province of Salta in northwest Argentina, an area endemic for cutaneous and mucocutaneous leishmaniasis. The study population consisted of patients who came to the Instituto de Investigaciones en Enfermedades Tropicales at the Universidad Nacional de Salta in Orán. Patients with parasitologically proven cutaneous leish-
maniasis were eligible to participate in the study if they were ≥ 14 years of age, had lesions not longer than three months, and had stable residency in the area. Patients were excluded from participation in the study if they had received any drug with activity against *Leishmania* in the previous three months, if they had mucosal lesions, electrocardiographic abnormalities that would pose a risk for the use of antimonial drugs, were pregnant or breastfeeding, or had other diseases or laboratory abnormalities that would compromise the analysis, such as elevated levels of transaminases (> 3 times the upper normal limit), active tuberculosis or immunodeficiencies (patients infected with HIV were excluded if they had CD4 cell counts < 200 cells/μL). After providing written informed consent, a punch biopsy was performed on those patients with lesions in areas other than the face for parasite isolation and species identification. Serologic analysis for Chagas' Disease and HIV, and a urine pregnancy test (in females of childbearing age) were also performed at this time. Lesion size was measured at baseline, with width and breadth measured to the nearest millimeter. The area of the lesion was calculated assuming the lesions were rectangular by multiplying the length of both axes.

**Parasitology.** Lesions with clinical and epidemiologic features of ACL were investigated by scrapping the border of the lesion. The obtained sample was allowed to dry, was fixed, stained with 10% Giemsa, and examined for amastigotes. Bi-
opsy material from lesions was cultured in Novy-Nicolle-McNeal medium. For patients with more than one lesion, a representative lesion was chosen for sampling. In cultures with viable promastigotes, liquid samples of harvested parasites were collected with IsoCode I.D. Stix (Schleicher & Schuell, Keene, NH), and dried. Tips of IsoCode Stix were suspended with 200 µL of InstaGene Matrix (Bio-Rad, Hercules, CA). The solution was incubated for 1.5 hours at 56°C for separating genomic DNA, extracted with phenol/chloroform, and precipitated with ethanol. The purified DNA was then subjected to analysis by polymerase chain reaction for Leishmania species identification with the technique previously validated in the area and described elsewhere.28 A Montenegro skin test (produced at the Instituto de Investigaciones en Enfermedades Tropicales, Oran, Argentina) was applied by injecting intradermally 0.1 mL of Leishmanin (40 µg of protein nitrogen/mL) into the forearm. The reaction was recorded prior to initiation of treatment. Indurations > 5 mm were considered positive.

**Data analysis.** Calculations for sample size and confirmatory analysis were determined with an alpha of 0.05 and a power of 0.80, assuming a cure rate of 95% for MA and 65% for azithromycin according to the protocol definition of clinical cure and a 1:1 randomization between groups. The number of patients required overall was 38. Continuous variables were analyzed for statistical significance with the Mann-Whitney test or Student t-test according to underlying distribution. Toxicity analysis and differences in proportions of persons in each group in whom the assigned treatment was efficacious was assessed by the chi-square test. Differences were considered statistically significant if P values were < 0.05. Data analysis was performed with SPSS for Windows 12.0 (SPSS Inc., Chicago, IL).

**RESULTS**

Diagnosis of ACL was confirmed by the visualization of amastigotes in material obtained from scraping the lesions in all patients included in the study. All 45 randomized patients started their assigned therapy at the baseline visit. There were no patients lost to follow-up during treatment and during the first six months of follow-up. At 12 months of follow-up, a patient receiving MA moved away from the area and was lost to follow-up, although he had healed by the second month after completing therapy. This patient was removed from the 12-month analysis. Baseline characteristics of the study group are shown in Table 1. None of the patients was seropositive for HIV. Six patients were seropositive for Chagas Disease, 4 in the MA group and 2 in the azithromycin group. Most patients were male, weighed between 60 and 80 kg, and more than 90% of the patients in both groups had one or two lesions.

Efficacy analysis showed that MA had an efficacy of 82.6% (95% confidence interval [CI] = 67–98%). Nineteen of 23 patients had successfully treated lesions, according to the study definition, with their lesions resolved in a mean of 2.6 months after initiation of therapy. The four patients who were considered treatment failures had their lesions cured at six months post-randomization after a third cycle of MA in one case, at nine months with a course of pentamidine in the second case (this patient had no improvement after two cycles of MA; his isolate was identified as *L. (V.) braziliensis*), and after six months post-randomization without any extra cycles of medication in the third case. The fourth patient was considered a treatment failure because of relapse. At 12 months, the efficacy of MA was 81.8% (95% CI = 66–98%) after the patient lost to follow-up was removed from the analysis.

Azithromycin had a cure rate of 45.5% (95% CI = 25–66%) (10 of 22 patients). Among those failing therapy with azithromycin, 6 of 12 were defined as failures after 1 cycle because of worsening lesions (3 cases), no improvement (2 cases), and minor improvement (1 case). The patients successfully treated with azithromycin were cured at a mean of 3.7 months (P > 0.05 between groups), and of these patients, 4 were cured after 1 cycle and 6 were cured after 2 cycles of azithromycin (Table 2). The patients who did not respond to azithromycin according to the protocol definition were treated with MA with cures in all cases with one cycle of MA (Table 2).

The time to cure showed a statistically significant difference

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<th>No.</th>
<th>Meglumine antimoniate</th>
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**Table 1** Baseline characteristics of the study population according to treatment group

**Table 2** Efficacy of the assigned therapy in the two treatment groups according to the protocol definition of complete re-epithelization 30 days after completing therapy and remaining clinically healed for 12 months.*

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<th>No. randomized</th>
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*The first cycle of 28 days with either meglumine antimoniate, 10 mg/kg/day intramuscularly or azithromycin, 1,000 mg on day 1 and then 500 mg/day for another 27 days; the second cycle of 15 days at the same dosage prescribed for patient with improvement without resolution after the first cycle.

† One patient who had cured by month 2 was lost to follow-up after the month 6 visit (excluded from the analysis at month 12).

‡ A patient relapsed in this group after failing with azithromycin and curing with rescue therapy with meglumine antimoniate; his failure was classified as no healing with the assigned treatment.
between treatment groups \((P = 0.02)\), with a mean of 3.4 months for the MA group and 4.8 months in the azithromycin group (considering all randomized patients). There were two cases of relapse during the year of follow-up with one in each treatment group. The first occurred in a patient with 2 lesions located on the face who failed treatment with azithromycin because of progression of both lesions during the first cycle. After changing to MA, the patient received a 28-day course and cured both lesions by day 14 after completing therapy. However, the eyelid lesion had an active border six months after therapy was completed. This lesion healed after treatment with a new cycle of MA and remained healed after another year of follow-up. A second case of relapse was in a patient with four thoracic lesions that healed after treatment with MA but these lesions relapsed four months after therapy was completed. This patient was successfully re-treated with MA and remained healed after a year of follow-up.

Efficacy analysis based on the stratification of the groups between lesions above or below the knee did not show differences in any of the treatment groups. The time to cure was not different among strata in any group although there was a trend towards significance in the MA group, where the upper strata healed at 2.8 ± 1.6 months and the lower strata healed at 4.6 ± 2.6 months \((P = 0.06)\). The area of the lesion at baseline was not a statistically significant predictor of failure, with lesions among patients who failed treatment not showing any significant difference compared with patients successfully treated. Lesions with a mean ± SD area of 338 ± 246 mm² were seen in patients healed with azithromycin compared with lesions 673 ± 685 mm² in patients who failed to be cured by azithromycin. Lesions 356 ± 331 mm² were seen in patients healed by MA and lesions 935 ± 1,102 mm² were seen in patients who failed to be cured by MA. However, none of these differences were statistically significant.

There were no severe adverse events or treatment interruptions due to drug toxicity with azithromycin, and laboratory analyses showed no alterations in hematologic values or liver transaminases throughout the course of therapy. The main side effects in this group were mild-to-moderate gastrointestinal complaints in 6 patients (27%) and mild rash in 1 case that resolved with oral antihistamines. There were significant differences in tolerance between drugs, with 18 (78%) of 23 patients treated with MA reporting moderate or severe musculoskeletal symptoms (local and general myalgias, arthralgias and/or injection site pain), with 11 patients (47.8%) requiring a change to the intravenous route to complete therapy. The intravenous route was administered through slow infusion in an ambulatory setting and no complications were registered. There was no evidence of differences in drug efficacy between those who required intravenous injections versus those who did not. However, the number of patients was small and the study was not designed to evaluate efficacy on the basis of route of administration. In the MA group, there were significant increases in levels of alanine aminotransferase at day 28 of therapy compared with baseline with mean values of 58 versus 44 IU/L \((P < 0.01)\). These differences were not seen after treatment was completed and all values returned to baseline. There were no abnormalities in either group in amylase, creatinine, and hematologic values. Electrocardiographic evaluations did not show any significant changes that would require treatment interruption or dose modification.

**Leishmania (V.) braziliensis** was identified in all 17 patients (38% of the study population) in whom species identification was obtained. These 17 cases were evenly distributed among groups (8 in the azithromycin group and 9 in the MA group). Among patients with species identification, the efficacy of both treatments did not differ compared with the entire study population (50% for azithromycin and 89% for MA). Identification was not attained in other cases because of a variety of reasons including facial location of the lesions that precluded biopsy sampling, inability to obtain positive cultures, culture contamination, and inability to amplify cultured sample.

**DISCUSSION**

To our knowledge, this study is the first randomized controlled study evaluating azithromycin for the treatment of ACL. Azithromycin had clinically significant activity in the treatment of ACL caused by *L. (V.) braziliensis*, and an efficacy rate statistically significantly lower than the standard therapy (MA), but of clinical relevance, considering the scarcity of oral options, the various toxicities of antimonials, and the ethical impossibility of performing a placebo-control trial for ACL given the risk of mucosal involvement. Treatment with azithromycin had an efficacy of 45.5% in achieving complete lesion healing during a period of up to three months after starting therapy and resulting in patients remaining free of disease for 12 months after resolution. This stringent definition was developed to prevent the persistence of active lesions caused by *L. (V.) braziliensis* for long periods of time, an issue that has been considered a potential risk factor for development of mucosal lesions. Despite the advantages of such oral therapies, length of the regimen, which in most cases required two cycles, might be a factor in adherence to therapy.

Compared with other uncontrolled studies on the use of azithromycin for treatment of cutaneous leishmaniasis, our results show lower efficacy than one study that achieved 85% efficacy using a variety of regimens in Brazil, compared with no efficacy against *L. (L.) major* in Syria after a 10-day course of treatment. The potential role of alternative drugs such as azithromycin for treatment of patients with contraindications for standard therapy is emphasized by the report of three patients with mucosal leishmaniasis successfully treated with azithromycin in Brazil.

Among other oral drugs evaluated against leishmaniasis, miltefosine, which showed good activity against Indian visceral leishmaniasis and ACL caused by *L. (V.) panamensis*, was only 33% effective against ACL caused by *L. (V.) braziliensis*, in contrast to an efficacy of 83% for mild mucosal leishmaniasis caused by *L. (V.) braziliensis* in Bolivia. In another study, 30% of lesions caused by *L. (V.) braziliensis* were cured by ketoconazole compared with 89% of lesions caused by *L. (L.) mexicana*. These studies demonstrate the discrepant responses to therapy among different species of *Leishmania* and highlight the need for species-specific studies and treatment recommendations.

The high prevalence of *L. (V.) braziliensis* in the study area was confirmed by identification of this species in all isolates in which specimen identification was determined. The impact of the spontaneous healing, which has not been investigated in
In the case of pentavalent antimonials, which parasites is unknown and might be related to *L. (L.) mexicana*. There is limited information on the rate of spontaneous cures in ACL caused by *L. (V.) braziliensis*, with cure rates at 12 months in a placebo-controlled trial of 0% for infections caused by *L. (V.) braziliensis* and more than 70% for those caused by *L. (L.) Mexicana*. In other studies, the cure rate of patients with infections caused by *L. (V.) braziliensis* and treated with placebo ranged from 0% to 8% compared with 45.5% efficacy with azithromycin in this study. For patients successfully treated with azithromycin in this study, most had lesions for less than six months prior to cure and all patients successfully treated with azithromycin resolved lesions within eight months after lesion appearance.

The efficacy of MA in this trial (82.6 ± 15.4%) was expected on the basis of reported rates of 79–96% in other studies, despite the lower doses of pentavalent antimonials used. Standard treatment with MA at the study site is 10 mg of Sb/kg/day for 21–28 days because of poor tolerance to the standard dose of 20 mg of Sb/kg. The efficacy observed in this study was similar to the 84% efficacy rate obtained in a study where only 5 mg of Sb/kg of MA were used for 30 days for the treatment of ACL; lesions in both studies were uncomplicated, mostly single, and of 2–3-months duration. For MA, the only significant adverse events were related to musculoskeletal symptoms in 78% of the patients. This finding resulted in a change to the intravenous route in a significant number of patients, an issue that further complicates its administration. The similar efficacy between those requiring MA through the intravenous route versus those who did not should be evaluated with caution because numbers were small without statistical power to demonstrate differences. Laboratory abnormalities were all mild in both groups, lacked clinical significance, and did not require treatment interruptions. We were not able to confirm in this study the pancreatic and electrocardiographic abnormalities described in patients using antimonials. The results of this study confirm the good tolerance of azithromycin for periods of time longer than those usually prescribed. These marked differences in adverse events between MA and azithromycin and the route of administration should be weighted against their efficacy and relapse rate (whether cutaneous or mucosal) to search for the most beneficial risk:benefit ratio in the treatment of leishmaniasis in each particular region.

Analysis of drug efficacy based on lesion size and localization did not demonstrate any significant statistical difference in this study that could help in the definition of variables that serve in the prediction of responses to any of the study drugs. A trend toward significance in the time to faster resolution for lesions above the knee among patients in the MA group might justify the use of this variable in stratifying groups in further studies. However, this concept is supported by evidence-based data. A limitation of this study was the lack of blinding to the study arms, which included patients, investigators, and hospital physicians not participating in the trial.

The mechanism of action of azithromycin against *Leishmania* parasites is unknown and might be related to antimicrobial mechanisms, immune activation, or a combination of both. Azithromycin has been shown to have immunomodulatory effects in bronchiolitis obliterans. Treatment of macrophages with azithromycin enhanced the elimination of fungal pathogens. In the case of pentavalent antimonials, which have been used for more than 50 years in the treatment of leishmaniasis, their mechanisms of action are uncertain, with direct and immune-mediated mechanisms being implicated.

Longer follow-up periods will provide information about recurrence rates after treatment with azithromycin. These results could potentially demonstrate that MA should be used for patients who fail oral treatment with azithromycin. This untested strategy could obviate the use of the parenteral route in a significant proportion of patients, who would be able to reduce side effects and improve compliance because of limited disruption of their daily activities. This issue could be of importance in areas such as our study region where the incidence of mucosal leishmaniasis is low (1.5%), but should be considered cautiously in areas with higher incidences of mucosal lesions.

In conclusion, the moderate activity of azithromycin against ACL caused by *L. (V.) braziliensis* precludes its recommendation as a first-line agent for this infection. Our findings support results of preclinical studies of its activity and provide evidence about the safety of this oral therapy for ACL, which in this study produced a clinical cure in almost half of the patients. Defining the subsets of patients that could benefit from this therapeutic option and evaluation of azithromycin in combination therapy should be the subject of further studies.

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