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LOW EFFICACY OF AZITHROMYCIN TO TREAT CUTANEOUS LEISHMANIASIS IN MANAUS, AM, BRAZIL

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SUMMARY

An open trial to evaluate the azithromycin efficacy in cutaneous leishmaniasis patients was carried out in Manaus (AM), where *Leishmania (Viannia) guyanensis* is the main etiologic agent. Forty-one patients with skin lesions of less than 12 weeks duration, without specific treatment for the last three months and a positive imprint to *Leishmania* sp. were included. From these, 31 (75.6%) were male with median age of 30.2. All of them received a daily-single oral dose of 500 mg of azithromycin for ten days. At 25th day, 16 (39%) presented therapeutic failure and received intramuscular pentavalent antimonial, four were considered lost, 21, that had improved or were inaltered received another ten-day series of azithromycin and were monthly followed, but nine (21.9%) of them presented a poor clinical response and switched to intramuscular pentavalent antimonial on day 55. Of the 12 remaining cases evaluated on day 55, despite of clinical improvement, three asked for antimony therapy and 9 (21.9%) continued the follow-up but, only three were cured on 55th, 85th and 115th days, and six did not come back for final evaluation. The intention-treatment overall response rate was 22% and whole cure was seen in three (7.3%) of cases. Thus, azithromycin showed a low efficacy to treat cutaneous leishmaniasis in Manaus.

KEYWORDS: Azithromycin; Cutaneous leishmaniasis; Antimony; *Leishmania (Viannia) guyanensis.*

INTRODUCTION

During several decades, pentavalent antimonials have been the first choice to treat leishmaniasis in most places where it is endemic and other alternatives as amphotericin B and pentamidin have also been used with good results (MARSDEN, 1985; OLLIARO & BRYCESON, 1993; HEPBURN *et al*., 1994). These drugs must be administered by parenteral route, for three or four weeks, are toxic and sometimes patient hospitalization is required (HERWALDT, 1999; LLANOS-CUENTAS *et al*., 1984; ROMERO *et al*., 2001; ANTEZANA *et al*., 1992).

Attempts to find oral therapeutic options, ideally cheaper, with good tolerance and safe are highly desirable. In the last years, some trials using different oral medicaments with antileishmania effect were carried out with variable results, depending on clinical picture and leishmania sp. (JHA, 1983; GRIMALDI *et al*., 1989; DOGRA & SAXENA, 1996; ALRAJHI *et al*., 2002). Recently, miltefosine, an alkil fospholipid derivated cured 94% of patients with visceral leishmaniasis in India. Similar results for cutaneous leishmaniasis in Colombia were also reported (SUNDAR *et al*. 2002; SOTO *et al*., 2001).

Azithromycin, a macrolide antibiotic, has been used to treat several bacterial infections, mainly those caused by intracellular microbes, due to its good tissular concentration within phagocytes and its prolonged half life (PETERS, 1992; NEU, 1991; GIRARD *et al*., 1987; FOULDS & JOHNSON, 1993; FOULDS *et al*., 1990). After a single oral dose, azithromycin showed activity against atypical mycobacteria sp., *Toxoplasma gondii*, Cryptosporidium sp., and *Babesia microtii*, among others (WILDFEUER *et al*., 1996; KOLETAR *et al*., 1999; GIACOMETTI *et al*., 2000, PUKRITTAYAKAMEE *et al*., 2001; KRAUSE *et al*., 2000).

In experimental model *in vivo* and *in vitro*, using *Leishmania major* promastigotes in an acellular culture, azithromycin reduced the parasite number. Further, in bone marrow macrophages, infected with amastigotes and treated with different concentrations, also there was a dose dependent significant reduction of parasites. When BALB/cBYS rats were inoculated with the same microorganism, an inflammatory reaction on the site of inoculation and a decrease of parasite number following azithromycin administration were observed (KROLEWIECKI *et al*., 2002).

An open trial in an area, endemic for infections due to *Leishmania (Viannia) braziliensis*, was carried out to evaluate azithromycin efficacy in cutaneous leishmaniasis. Twenty-four patients received this drug in different doses and time and a whole scarring of lesions was observed

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in 85% of them (PRATA *et al*., 2003). Most recently, a report on three old chronic cardiopathy patients with mucosal involvement that hindered classical treatment, azithromycin dose was given with good results (SILVA-VERGARA *et al*., 2004).

The aim of this work was to evaluate the azithromycin efficacy in cutaneous leishmaniasis in Manaus, AM, Brazil, where infections due to *Leishmania (Viannia) guyanensis* are predominant.

POPULATION AND METHODS

This trial was carried out during 2002 in Manaus, Amazonas, Brazil where Leishmania transmission actively has occurred during several decades due to the enlargement of agricultural borders, new human settlement in the road-side and irregular urbanization, where native forest was previously found.

The Fundação de Medicina Tropical do Amazonas, a State Leishmaniasis Reference Center, receive most patients of the city to clinical evaluation, treatment and follow-up. Among them, 41 patients were selected for this trial. The inclusion criteria were: skin lesions with less than 12 weeks evolution-time; positive imprint to Leishmania sp.; age ranged from 14 to 70, both genders and no treatment history for the last three months. Patients with difficulty to attend to monthly clinical assessment; mucosal or diffuse involvement, fever, macrolide allergy, cardiac, hepatic or renal diseases, vasculopathies, diabetes mellitus, AIDS, use of corticosteroids or immunosuppressive drugs or engaged in another trial, were excluded.

All patients underwent a Montenegro intradermal test using UFMG® antigen, following the classical procedure described. Analysis of AST, ALT, blood urea nitrogen, serum creatinine, glycemia and other tests when indicated were carried out.

At the first day patients received 10 capsules of 500 mg of azithromycin and they were oriented to ingest a single-daily oral dose of 500 mg of azithromycin after meals for ten days and were asked for returning after 25 days for follow-up. If the patient had improved or his lesion remained unchanged, another cycle of azithromycim as above described was then offered. In case of worsening of lesions or on patient's demand, a daily intramuscular 20 mg/kg dose of antimony during 20 days was prescribed. The cure criteria was defined as whole lesion reepitelization and clinical failure was considered if on 25th day, the lesion had worsened, or lack of response on day 55, or worsening on day 85.

The study was approved by the Ethic Committee of the Fundação de Medicina Tropical do Amazonas and written informed consent was obtained from each patient.

RESULTS

From April to June 2002, 41 patients with cutaneous leishmaniasis were recruited. From these, 31 (75.6%) were male, median age 30.2, twenty five (61%) had two or more ulcers, that in 27 (70.7%) presented classic aspect and supraumbilically localized. Most patients had history of four or less weeks of lesion evolution and a Montenegro intradermal test evaluated after 48 hours was positive in 32 (78%) cases.

On 25th day, two patients refused to continue in the study and two did not come back for clinical evaluation. The other 37 individuals were divided in three subgroups according to their clinical outcome and further management.

Group I, nine (24.3%) patients received two cycles of azithromycin. On day 25, six (16.2) improved nearly 80% and three (8.1) 60%. Only three (8.1%) of them presented cure of lesions on 55th, 85th and 115th days. The other six patients, despite their clinical improvement, did not come back to final assessment.

Group II, 12 (32.4%) patients received two azithromycin cycles. Although in nine of them the lesion remained inaltered on day 25, they decided to stay in the trial until day 55 when all switched to antimony therapy. One of them developed mucosal lesions during the follow-up.

Group III, 16 (43.2%) patients received one azithromycin cycle. On day 25 were considered as therapeutic failure, because their lesions had worsened. Therefore, all of then received antimony therapy. Among them, one patient did not come for evaluation; other developed mucosal lesions and one third claimed of intolerance to azithromycin (Table 1).

In general, azithromycin was well tolerated and accepted by most patients, although, 24 (35%) of them referred symptoms such as: diarrhea, headache and nausea, occurring in seven (18.9%), six (16.2%) and four (10.8%) respectively, but these factors were not sufficiently to stop the treatment, except for one of them.

DISCUSSION

New therapeutic alternatives to treat leishmaniasis have been tested to find a cheap, safe, effective, well tolerated and orally administered.

Table 1
Evaluation of azithromycin therapy in 41 patients with cutaneous leishmaniasis in Manaus, AM, Brazil

Day	N	AZM10 days N	AZMCure N	Improving	No change	Worsening	Lost
0	41	41	-	-	-	-	-
25	37	21	-	12	9	16*	4
55	21	-	1	10	-	10**	-
85	9	-	2	1	-	-	6
115	3	-	3	-	-	-	-

N: Number of patients; AZM: Azithromycin; * switched to antimony on day 25; ** switched to antimony on day 55 (including two patients that were improving).

Ketoconazol, fluconazol, itraconazol, nifurtimox, dapsone and allopurinol, among other trials, showed variable efficacy depending on clinical picture and the Leishmania sp. involved (MARSDEN, 1985; GRIMALDI Jr. *et al*., 1989; ALRAJHI *et al*. 2002). Preliminary experimental and clinical reports have appointed azithromycin as a potential drug (PRATA *et al*. 2003; SILVA-VERGARA *et al*. 2004). For this reason, it was evaluated in patients with cutaneous leishmaniasis presumed to be caused by *L. (Viannia) guyanensis* in Manaus.

From 41 patients recruited, 37 performed at least two clinical evaluations, 16 (43%) switched to antimony on day 25 because of clinical worsening and only 21 (66.7%) completed two cycles of azithromycin. Of these, 12 received treatment with pentavalent antimonial on day 55. The analysis for the intention-treatment response rate was considered in eight (22%) and three (7.3%) of them presented whole clinical cure. Despite their good clinical evolution, six patients did not return for final assessment and can not be considered cured. These results are lower than those reported for antimony (30-40%) or pentamidine (100%) in Manaus (ROMERO *et al*., 2001; TALHARI *et al*., 1985).

Among patients that worsened during treatment, two developed mucosal lesions whose main etiological agent in Brazil is *L. (Viannia) braziliensis*. However its prevalence is very low compared with *L. (Viannia) guyanensis* (97.3%) that occasionally causes mucosal involvement (MARSDEN, 1985; LLANOS-CUENTAS *et al*., 1984; ROMERO *et al.* 2001).

Yet, leishmania culture was performed in all patients but contamination prevented species identification. Despite these results, the great number of parasites observed on the imprints and its high prevalence reported in Manaus, suggest that cutaneous lesions of these patients was caused by *Leishmania (Viannia) guyanensis.*

How azithromycin can act on *Leishmania* sp. is still unknown and some authors have suggested that it can stimulate phagocytosis, chemotaxis and cytotoxicity. Besides, it would act as immune stimulator (IANARO *et al*., 2000; XU *et al*., 1996). During the follow-up, patients with good clinical response presented an early and fast improvement of lesions appearance, followed by a very slow scarring process, what might suggest a leishmaniostatic effect of this drug.

At present, there is not evidence of ideal dose and treatment time with azithromycin in cutaneous leishmaniasis but preliminary clinical observations suggest that this medicament must be given for several weeks and other cycles may be repeated if necessary. The scheme proposed in this trial aimed to follow a classical treatment time of 20 days with antimony for this clinical picture and this can or not be divided in two cycles of 10 days with interval from 10 to 15 days between them (PRATA *et al.*, 2003; SILVA-VERGARA *et al.*, 2004). Most patients reported mild adverse effects related to the medicament but all except one underwent full treatment, confirming its good tolerance and safety in practice.

Several operational difficulties to accomplish follow-up, hindered the evaluation of more patients in this place. However a cure rate of 7% substantially differs from results with classical medicaments and clearly suggests a very low efficacy of azithromycin to treat leishmaniasis in a place where the main etiologic agent is *Leishmania (Viannia) guyanensis*.

RESUMO

Azitromicina para tratamento de leishmaniose cutânea em Manaus, AM, Brasil

Para avaliar a eficácia da azitromicina na leishmaniose cutânea, foi realizado ensaio clínico em Manaus, Amazonas, onde o agente etiológico predominante é a *Leishmania (Viannia) guyanensis*. Incluídos 41 pacientes com lesões de menos de 12 semanas, sem história de tratamento específico nos últimos três meses e com esfregaço positivo para *Leishmania* sp. Destes, 31 (75,6%) eram masculinos, idade média 30,2 anos. Todos receberam azitromicina 500 mg em dose única oral, diária, por 10 dias. No dia 25º, 16 (39%) pioraram e receberam antimonial pentavalente via intramuscular por 20 dias e, 21 (61%) que apresentaram melhora da lesão ou esta permanecia inalterada no 25º dia, receberam outro ciclo de 10 dias de azitromicina e foram acompanhados mensalmente. Destes, nove (21,9%) apresentaram piora das lesões na avaliação do dia 55 e iniciaram tratamento com antimonial neste dia. Dos 12 que permaneceram no estudo, porque tinham melhorado clinicamente, três optaram por tratamento com antimonial pentavalente no 55º dia e três apresentaram reepitelização completa das lesões nos dias 55º, 65º e 115º. Seis pacientes não retornaram para avaliação final. Análise por tentativa de tratamento foi 22% e cura confirmada em três (7,3%) casos. Estes resultados mostraram que azitromicina tem baixa eficácia para tratar leishmaniose em área onde a *Leishmania (Viannia) guyanensis* é o agente etiológico predominante.

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