Immunotherapy, immunochemotherapy and chemotherapy for American cutaneous leishmaniasis treatment

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ABSTRACT

The first choice of treatment for American cutaneous leishmaniasis is the pentavalent antimonial drug. Although it has been shown that this treatment is mostly effective and indicated, some disadvantages should be taken into account such as side effects, long term treatment inconveniences and counter-indication for patients suffering from cardiopathy, nephropathy; yet, aging, pregnancy and other conditions. With the advent of the vaccine anti-American cutaneous leishmaniasis as a prophylactic measure, studies on therapy using the vaccine associated or not with other drugs have been performed by many investigators and it is currently among the alternative treatments and prevention measures for American cutaneous leishmaniasis. In conclusion, the association between antimony and vaccine (immunochemotherapy) showed the same cure rate when compared with the standard treatment (100%) and it was also able to reduce the salt volume in 17.9% and treatment length from 87 to 62 days, decreasing side effects.

Key-words: American cutaneous leishmaniasis. Treatment. Immunotherapy.

RESUMO

O tratamento de primeira escolha para leishmaniose tegumentar americana é o antimonial pentavalente. Embora este tratamento seja na maioria das vezes efetivo e indicado, devem ser consideradas as desvantagens tais como efeitos colaterais, longa duração do tratamento e contra-indicação para cardiopatas, nefropatas, idosos, grávidas e outras condições. Com o advento da vacina antileishmania tegumentar americana para fins profiláticos, muitas pesquisas têm sido desenvolvidas, sendo a vacina a principal entre os atuais recursos no tratamento e prevenção da leishmaniose tegumentar americana. Em conclusão, a associação de antimonio e vacina (immunoquimioterapia) apresentou o mesmo índice de cura em relação ao tratamento padrão (100%), e ainda reduziu o volume de sal em 17,9% e o tempo de cura significativamente, de 87 para 62 dias; conseqüentemente, reduzindo os efeitos colaterais.


† In memoriam.

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Leishmaniasis is a disease caused by several digenetic protozoan species of the genus Leishmania, which affect humans and different domestic and sylvatic animal species. The disease may arise in different forms and the most important are: American visceral leishmaniasis (AVL) or American kala-azar and American cutaneous leishmaniasis (ACL). The latter, is primarily a disease that affects sylvatic animals. Leishmaniasis is transmitted to humans through the female bite of female haematophagous insect vectors of the genus Lutzomyia, which are known, in Brazil, as ‘birigüi’, ‘mosquito-palha’ or ‘cangalhinha’.

ACL is a polymorphic disease of skin and mucous membranes with single or multiple ulcerative lesions (simple cutaneous form), nodular lesions (diffuse form) or mucocutaneous lesions (mucocutaneous form), affecting nasopharynx regions simultaneously with or just after an initial cutaneous infection. Such variation is closely related to the patient’s immunological status and the Leishmania species involved. ACL constitutes an important health problem mainly because of its difficult prevention. The World Health Organization (WHO) estimates around 1-2 million annual new cases annually8.

Up to 1912, leishmaniasis treatment had been unsatisfactory. Row62 reported results on the curative properties of promastigote forms, from Leishmania culture, used as a vaccine in the treatment for Oriental sore; this therapy was then abandoned due to a new systemic treatment with antimonial drugs introduced that year by the Brazilian physician Gaspar Vianna76. This investigator used emetic tartar at 1%, which proved to be more efficient than the vaccine.

Emetic tartar has been the only therapeutic alternative for leishmaniasis for many years and because of its toxicity, administration difficulties and unsatisfactory efficacy (frequent recurrences), it was, at last, replaced with pentavalent antimonial drugs21 25. Despite its counter-indications for elderly patients and other conditions, such as cardiopathy, nephropathy and pregnancy, the pentavalent antimonial drug represents the standard therapy for leishmaniasis nowadays.

Since the introduction of antimonial drugs for leishmaniasis therapy, which have also been shown to produce divergent results2 3 8 17 18 20 24 26 29 33 44 49 51 52 60 63 65 66 70 74, several studies have been carried out in order to establish the best therapeutic plan.

With the advent of the ACL vaccine for prophylactic aims, idealized by Gomes73, Pessoa and Pestana75, modified by Mayrink et al35 56, and proved by Antunes et al4 and Armijos et al5, its therapeutic use has been under study, whether alone or associated with other drugs; and it has also been regarded as one of the current treatments, as well as one of the available prophylactic measures for ACL14 22 28 35 39 43.

Reports on the use of chemotherapy associated with immunotherapy have shown considerable efficacy in some cases of diffuse leishmaniasis37 71 72.

Immunotherapy combined with the use of BCG, first performed by Convit14, showed cure rates and treatment length comparable with those obtained through standard treatments with Glucantime®.

The present work was aimed at: 1) using immunotherapy in ACL patients for whom antimonial drugs are restricted and; 2) using immunotherapy combined with chemotherapy (immunochemotherapy), since we observed that an immunological stimulus associated with a chemotherapy treatment leads to a reduction in antimony volume and treatment period. This complex provides substantial benefits to the patient, reducing their visits to the outpatient facility, thus, diminishing ambulatory expenses, among many other advantages, when compared to the standard therapy. This process is described in detail in the present work.

The current work is aimed at evaluating the clinical effects among different therapeutic plans and not at assessing the immunological aspects involved in such responses, which has been widely studied by other investigators77 90 93 95.

**PATIENTS AND METHODS**

**Population studied.** A sample of 542 patients diagnosed with ACL, including males and females aged over five years old (Table 1), was randomly selected in a open assay from a group of subjects attending the Outpatient Facility Paulo Araújo de Magalhães in Caratinga, Minas Gerais. The present investigation and the protocols comply with the Research Ethics Committee of Instituto de Ciências Biológicas of Universidade Federal de Minas Gerais-ICB/UFMG.

**Diagnosis.** Individuals with typical cutaneous lesions were clinically diagnosed as being carriers of ACL. Clinical diagnosis was confirmed through positive parasitological examination and/or Montenegro skin test (MT).

**Parasitological examination.** Parasitological examination was confirmed by the presence of amastigote forms of the parasite in skin biopsies from the lesions. The examination was carried out by compressing the tissue from biopsy between two histological slides, after removing blood excess blood with filter paper. The material collected was fixed in methanol, Giemsa stained and, then, examined under light optical microscopy (magnification 1,000X).

**Montenegro test.** Montenegro antigen was produced under sterile conditions from cloned promastigote cultures of I-III-D Leishmania (Leishmania) amazonensis, which were killed, sonicated and kept in merthiolate solution at 1:10,00046. A volume of 0.1mL of the antigen with 40µg/mL of nitrogen30 41 was injected into intradermal layer in the inner side of the arm. Positivity was indicated after nodule formation, 48 hours post test, without considering erythematous areas.
Vaccine. The vaccine was prepared by the Laboratory of Leishmaniasis of the Department of Parasitology, ICB – UFMG, using dead promastigote forms of \textit{Leishmania (Leishmania)} \textit{amazonensis}, strain IFLA/BR/67/PH8, in accordance with the technique proposed by Mayrink et al$^{36}$ under quality control patterns of the Pharmacy School of UFMG.

**BCG.** BCG, used as coadjuvant (BCG, Calmette Bacillus - Guerin da Fundação Ataulfo Paiva, Rio de Janeiro, RJ), was reconstituted by dilution in 1mL solution (100µg/mL).

**Antimoniate N-methylglucamine.** The pentavalent antimonial (SbV) used here was N-methylglucamine (Glucantime®; Rhodia, São Paulo, Brazil), comprising 85mg pentavalent antimonial per mL.

**Therapy.** Group 1 (Standard treatment) Chemotherapy I (QT 1.0). This group consisted of 245 patients treated with Glucantime®. It was slowly administered through intramuscular route, at a daily dose of 1mL/5kg body weight, without exceeding 10mL/day, for 10 days. After a 10-day interval, this treatment was repeated. This period of 10 days without exceeding 10mL/day, for 10 days. After a 10-day intramuscular route, at a daily dose of 1mL/5kg body weight, as used for Group 1.

Group 2. Chemotherapy II (QT 0.5). This group comprised 29 patients under treatment with Glucantime®, at a daily dose of 0.5mL/5kg body weight. The administration was performed as described above and the maximum daily dose did not exceed 5mL/day.

Group 3. Serial immunotherapy (IT serial): in this group, 53 patients, underwent subcutaneous administration of the vaccine (nitrogen total concentration: 360µg/mL) administered to the top outer forearm, according to the method proposed by Mayrink$^{35}$ as follows: first day- 100µL; second day- 200µL; third day- 300µL; fourth day- 400µL and from the fifth to the tenth day- 500µL.

After a 10-day interval, daily doses of 500mL were administered.

**Group 4**. Immunochemotherapy I (IQT 1,0). In this group, 38 patients were administered anti-ACL vaccine through subcutaneous route, as described for Group 3, simultaneously with Glucantime® through intramuscular route at a dose of 1mL/kg body weight, as used for Group 1.

Group 5. Immunochemotherapy II (IQT 0.5). A group of 47 patients were given subcutaneous anti-ACL vaccine, as described for Group 3, simultaneously with Glucantime® through intramuscular route at a dose of 0.5mL/kg body weight, as used for Group 2.

Group 6. Colligation (BCG + Glucantime®). A group of 47 patients were administered 100µg intradermal BCG after 15 to 20 days of stimulation with the onset of colliquation, Glucantime® was used at a dose of 1mL/kg body weight, as described for Group 1.

Group 7. Monthly immunotherapy with BCG (100µg) (IT and BCG monthly). Fifty-eight patients were submitted to monthly intradermal doses of an association of 0.6mL of vaccine with 100µg BCG until clinical cure was achieved, without exceeding a period of five months under treatment.

Group 8. Monthly BCG. Thirteen patients were treated with monthly intradermal doses of 100µg of BCG, administered into the deltoid muscle.

Group 9. Monthly immunotherapy (IT monthly). In this group, 12 patients were treated with monthly doses of 0.6mL vaccine.

**Therapeutic failure.** It should be noted that each therapeutic plan was maintained until complete clinical cure was achieved; if cure was not effected after two series, the plan was, then, substituted for the standard therapy (serial chemotherapy with Glucantime®).

**Cure criterion.** The cure criterion was clinical, i.e., total healing of cutaneous lesions and epithelization of the skin.

**Statistical analysis.** Variance analysis for treatment period analysis, adjusted by age, disease period, and MT area was used$^{35}$. A significance level of 95% was taken into account.

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### Table 1 - Demographic and clinical characteristics of the treated American cutaneous leishmaniasis patients.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Therapeutic scheme</th>
<th>Number of cases</th>
<th>Male gender (%)</th>
<th>Age average (years)</th>
<th>Malnutrition (%)</th>
<th>Disease period (month)</th>
<th>Number of lesions</th>
<th>Lesion (cm)</th>
<th>MT</th>
<th>MT+ (%)</th>
<th>Positive parasitological exam (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>QT 1.0</td>
<td>29</td>
<td>58.6</td>
<td>25.4</td>
<td>13.8</td>
<td>2.1</td>
<td>1.1</td>
<td>2.6</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>2</td>
<td>QT 0.5</td>
<td>29</td>
<td>58.6</td>
<td>25.4</td>
<td>13.8</td>
<td>2.1</td>
<td>1.1</td>
<td>2.6</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>3</td>
<td>IT serial</td>
<td>53</td>
<td>64.2</td>
<td>33.2</td>
<td>9.6</td>
<td>5.9</td>
<td>1.2</td>
<td>3.3</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>4</td>
<td>IT 0.5</td>
<td>35</td>
<td>51.4</td>
<td>30.8</td>
<td>2.3</td>
<td>2.3</td>
<td>1.3</td>
<td>5.5</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>5</td>
<td>QT 1.0</td>
<td>38</td>
<td>50.0</td>
<td>21.5*</td>
<td>NR</td>
<td>2.4</td>
<td>1.4</td>
<td>3.5</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>6</td>
<td>QT 0.5</td>
<td>47</td>
<td>44.7</td>
<td>27.5</td>
<td>14.9</td>
<td>5.3</td>
<td>1.3</td>
<td>3.6</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>7</td>
<td>I QT Monthly</td>
<td>44</td>
<td>61.4</td>
<td>30.6</td>
<td>4.7</td>
<td>2.4</td>
<td>1.3</td>
<td>5.0</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>8</td>
<td>IT and BCG monthly</td>
<td>58</td>
<td>50.0</td>
<td>21.5*</td>
<td>NR</td>
<td>2.4</td>
<td>1.4</td>
<td>5.0</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>9</td>
<td>IT monthly</td>
<td>47</td>
<td>51.4</td>
<td>30.8</td>
<td>14.9</td>
<td>3.5</td>
<td>1.3</td>
<td>3.6</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
<tr>
<td>10</td>
<td>QT 1.0</td>
<td>47</td>
<td>61.4</td>
<td>30.6</td>
<td>4.7</td>
<td>2.4</td>
<td>1.3</td>
<td>5.0</td>
<td>7.8*</td>
<td>82.8</td>
<td>92.9</td>
</tr>
</tbody>
</table>

**Total** 542 59.3 28.6 10.8 5.3 1.3 4.1 5.2 82.4 89.0

QT 1.0: Standard Group. * Significant difference when compared with standard group. MT: Montenegro Test.
RESULTS

A total of 542 patients with positive ACL diagnosis were divided into 9 treatment groups. The demographic and clinical characteristics of the groups studied are shown in Table 1. The frequency of male gender was 59.3% and the mean age was 28.6 years old (ranging from 5 to 86 years old). No significant relationship regarding the gender and age of the patients was found among the groups tested, including the standard group. Malnutrition, defined by body mass index (BMI = weight/height²), was observed in 10.8% of the patients, which was shown to be similar for all the groups under study (Table 1).

The period of ACL disease, defined as the time taken between the initial observation of the lesion, reported by the patient, and clinical diagnosis, ranged from 10 days to 43.4 months with an average of 5.3 months. The number of lesions varied from 1 to 3, and their mean diameter was 4.1cm. The mean MT area, which was shown to be positive in 82.4% of patients, was 5.2cm. The parasitological exam was positive in 89% of patients. No relationship between the number of lesions, disease period, and area of ulcers was observed among patients (Table 1).

The treatment period of the groups under study and the volume of antimony necessary to achieve cure are shown in Table 2.

The therapy plans used in Groups 1, 4, 5, and 6 achieved clinical cure in 100% of the patients with varying periods (days) of 94, 64, 105 and 91 days, respectively.

Group 3, under immunotherapy, showed 98.1% of cured patients, despite its increased treatment length when compared with the standard group.

The average number of series, comprising all therapies, ranged from 3.3 to 11.3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Therapy</th>
<th>Number of patients/ Number of cured cases</th>
<th>Cure percentage</th>
<th>Mean number of series*</th>
<th>Reduction of SF volume (%)</th>
<th>Number of series of Glucantime in case resistance</th>
<th>Mean time of treatment until cure (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>QT 0.5</td>
<td>29/29</td>
<td>100.0</td>
<td>4.2</td>
<td>50.0</td>
<td>-</td>
<td>82.2</td>
</tr>
<tr>
<td>1</td>
<td>QT 1.0</td>
<td>39/39</td>
<td>100.0</td>
<td>4.6</td>
<td>100.0</td>
<td>-</td>
<td>94.6</td>
</tr>
<tr>
<td>3</td>
<td>Serial</td>
<td>53/52</td>
<td>98.1</td>
<td>8.7</td>
<td>17.9</td>
<td>7.0</td>
<td>172.8</td>
</tr>
<tr>
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<td>T 1.0</td>
<td>35/35</td>
<td>100.0</td>
<td>4.2</td>
<td>33.3</td>
<td>-</td>
<td>82.5</td>
</tr>
<tr>
<td>4</td>
<td>T 1.0</td>
<td>38/38</td>
<td>100.0</td>
<td>3.5*</td>
<td>7.7</td>
<td>-</td>
<td>64.7</td>
</tr>
<tr>
<td>1</td>
<td>T 1.0</td>
<td>49/49</td>
<td>100.0</td>
<td>4.8</td>
<td>100.0</td>
<td>-</td>
<td>94.8</td>
</tr>
<tr>
<td>5</td>
<td>T 0.5</td>
<td>47/47</td>
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<td>5.4</td>
<td>100.0</td>
<td>-</td>
<td>105.5</td>
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<td>4.8</td>
<td>100.0</td>
<td>-</td>
<td>94.6</td>
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<tr>
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<td>Colliquation</td>
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<td>-</td>
<td>-</td>
<td>91.0</td>
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<tr>
<td>7</td>
<td>IT and BCG monthly</td>
<td>58/27</td>
<td>46.6*</td>
<td>8.9*</td>
<td>3.6</td>
<td>177.2*</td>
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<tr>
<td>8</td>
<td>BCG monthly</td>
<td>13/4</td>
<td>38.8*</td>
<td>8.0*</td>
<td>4.2</td>
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<tr>
<td>9</td>
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<td>12/3</td>
<td>25.0</td>
<td>11.3*</td>
<td>4.5</td>
<td>226.7*</td>
<td></td>
</tr>
<tr>
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<td>100.0</td>
<td>4.4</td>
<td>-</td>
<td>86.5</td>
<td></td>
</tr>
</tbody>
</table>

Total 542 89.9 5.7 - 3.9 113.1

DISCUSSION

No individual aspect of the patients or possible correlations with age, gender, nutritional status and number of lesions was shown to have a significant difference through variance analysis among the groups under study.

Based on these results, immunotherapy (Group 3) may be an alternative treatment for those patients for whom Glucantime® is not indicated.

By associating the vaccine with the standard application of Glucantime® (Group 4), a reduction in the volume of antimony (17.9%) and treatment length for clinical cure (from 94.6 to 64.7 days) was observed, when compared with the standard treatment (Group 1).

In the case of immune-stimulation with vaccine, an enhancement in interferon γ and interleukin 2 (IL-2) production was observed potentializing the response type Th1 by activating macrophages through INF γ production, in agreement with that shown by other investigators. This leads to the destruction of parasites by increasing oxygen radical levels, mainly nitric oxide. Furthermore, interferon α induces macrophages to produce IL 12, which acts on lymphocytes and “Natural Killer” (NK) cells, potentializing the immune response. These are ongoing findings in our works (data not shown).

When meglumine antimoniate volume was diminished by 50% to treat Group 2 patients, treatment length was shown to be as short (81 days) as that for Group 1, and cure rates were the same in both groups.

Association between the antimonial drug and immunotherapy (Group 4) showed a significant reduction in treatment length and also approximately 18% decrease in antimony volume, when compared with Group 1.
Immunotherapy associated with half the dose of meglumine antimoniate (Group 5) increased treatment length, in contrast, antimony volume was decreased by 33.3%, consequently, minimizing the side effects caused by Glucantime®.

Group 6, receiving BCG for 15 to 20 days before chemotherapy, showed a reduction of 7.7% in antimony volume, with no statistical significance, and a slight increase in treatment length for clinical cure in relation to Group 1.

The therapy comprising BCG and monthly immunotherapy (Groups 8 and 9) did not contribute to a reduction in the treatment period when compared with the standard treatment.

Considering the fact that other investigators only achieved 50.8% of clinical cure at a dose of 20mg/kg/day, either through intramuscular or intravenous route, for 20 days40, it should be noted that our service achieved a cure rate of 100% with Glucantime® therapy (Group 1). Literature data has shown that treatment with meglumine antimoniate for 10 or 20 days, at a dose of 20mg/kg/day, achieves clinical cures of 61% and 67%, respectively41.

Similar results to those obtained here with the standard treatment here (Group 1) were also achieved by our research team in 200271 while treating 29 patients from the municipality of Araçuaí, State of Minas Gerais. These patients had no indication for treatment with the standard antimonial therapy; mainly due to the presence of electrocardiographic alterations (17), antimony allergy (4), pregnancy (6) and nephropathy (2). Among these patients, 10 underwent immunotherapy and another 19 immunotherapy. The cure rate proved to be 100% and the mean number of series up to clinical cure was 2.3 (ranging from 1 to 4 series), while for immunotherapy, this was 2.47 series, with similar variation for both therapies.

Considering that antimony may produce side effects, a concentration reduction in ACL treatments is quite important. However, appropriate therapy should be carried out in order to diminish likely recurrences of the mucous form61 as well as other kinds of recurrences that have been frequently reported42 46 48 49 54 57 67 77.

Considering the broad range of therapies for ACL, there is no consensus among those aimed at seeking a reduction in the side effects of pentavalent antimonial drugs, there is no consensus. Azevedo-Coutinho and Mendonça44 compared two therapies: a continuous plan, as recommended by WHO49, and a serial one. These investigators concluded that the cure rate obtained with the intermittent treatment (serial) proved to be significantly higher than that with the continuous plan. The cure criterion was defined by complete skin epithelization observed up to three months after the end of treatment. Surprisingly, the follow-up of the patients was greatly superior when they were submitted to the serial treatment. Most of the patients under continuous treatment did not attend the Outpatient Facility throughout the complete period of treatment. Such data corroborate our findings34 concerning serial treatment, although there are divergences regarding clinical cure criteria. In the present study serial treatment was maintained until complete healing of the cutaneous lesions and the use of only three series was not followed.

Despite Machado-Coelho’s31 reports on resistance, have been quite rare cases of resistance to Glucantime in chemotherapy treatment have been quite rare in the municipality of Caratinga. Patients from other regions usually seek this Out Patient Facility due to previous failed treatments, performed in other localities.

In the case of ACL recurrence, patients attended at our service are recommended to return to the Outpatient Facility of Caratinga, as well as those from other regions, who are addressed by different health units due to the popular knowledge on treatments of cutaneous lesions provided by this ambulatory in Caratinga. Some patients from different regions, who underwent the treatment, indicated by the WHO50 (15mgSb/kg/day for 20 days and maximum daily dose of 15mL/day), sought our services due to disease recurrence or intolerance to the salt. Based on the WHO therapy, cure criterion is the complete healing of cutaneous lesions observed up to 3 months after the treatment end, which lasts 20 days with or without complete epithelization. Eight, from among these patients, sought our ambulatory and underwent further treatment with the antimony in a serial plan (a 10-day treatment + a 10-day rest) associated with the vaccine (0,5mL/day), simultaneously administered with Glucantime®. The Glucantime® daily dose was 1mL/5kg body weight without exceeding 10mL/day. This treatment varied from 2 to 4 series, which was only interrupted with clinical cure.

Several investigators have reported the side effects of Glucantime® used in different therapy plans27 28 32 45 51 64 66. Considering the therapy plans of the current work, side effects such as nausea, asthenia, myalgia, arthralgia and abdominal discomfort were not observed throughout the follow-up every 20 days along with treatment until clinical cure. This might be due to the serial plan with 10-day intervals between administrations of N-methylglucamine antimoniate.

Due to the complexity involved in vector-host-parasite interactions, investigators have been faced with different therapeutic choices. No clear consensus exists among the various therapies available in literature31 35 25 72 and those presented here. One of the most serious problems is the lack of information regarding daily doses of antimony50 45 56 69. Our therapy plans are in accordance with maximum daily dose of antimony (10mL - 850mg/Sb/day); thus, an intravenous treatment using 20mg/kg/day would take 1,400mg/Sb/day, or 16.47mL, for a patient weighing 70kg, though most investigators do not mention such information.

The results from the patients under study and those from a casuistic of 6,900 cases, since 1965, provide strong evidence regarding the efficacy of the therapy used here. We have only observed 5 recurrence cases, which is frequently reported when the classic therapy recommended by the WHO49 45 50 51 67 68 77 is used.

The current work shows the possibility of decreasing antimony volume for ACL treatment, with minimal occurrence of the most likely side effects. It also offers an alternative immunotherapy with promising results for patients, for whom antimony use is not indicated.
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