

# Advances in the treatment of cutaneous leishmaniasis in the new world in the last ten years: a systematic literature review \*

Avanços no tratamento da leishmaniose tegumentar do novo mundo nos últimos dez anos: uma revisão sistemática da literatura

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**Abstract:** INTRODUCTION: The therapeutic arsenal against cutaneous leishmaniasis is very limited. Pentavalent antimonial compounds have been the drugs of choice for treatment of this disease for over 50 years. Despite their effectiveness, these drugs require daily injections, have many side effects and present prolonged healing time.

OBJECTIVE: To carry out a systematic literature review on the advances in the treatment of cutaneous leishmaniasis in the new world in the last ten years.

METHODS: We conducted an electronic search on the Pubmed and LILACS database as well as on the SciELO electronic library in June 2009. The search words in English were: "cutaneous", "leishmaniasis" and "treatment". We included only randomized, double-blind and placebo controlled trials. We used the Jadad scale to assess the quality of the selected studies.

RESULTS: According to the inclusion and exclusion criteria, only eight articles were selected. The drugs evaluated in the selected studies were glucantime®, miltefosine, immunotherapy, imiquimod, rhGM-CSF and pentoxifylline, and paramomycin.

CONCLUSION: Although cutaneous leishmaniasis is a major public health issue, the published data on the use of new drugs for the treatment of cutaneous leishmaniasis in Brazil are still quite limited.

Keywords: Leishmaniasis, cutaneous; Leishmaniasis, mucocutaneous; Treatment outcome

**Resumo:** INTRODUÇÃO: O arsenal terapêutico contra a leishmaniose tegumentar é muito restrito. Os antimoniais pentavalentes permanecem como as drogas de escolha para seu tratamento há mais de 50 anos. Apesar da sua eficácia, necessita de injeções diárias, apresenta muitos efeitos colaterais e tempo de cura prolongado.

OBJETIVO: Realizar uma revisão sistemática da literatura sobre os avanços no tratamento da leishmaniose tegumentar do novo mundo nos últimos dez anos.

METODOLOGIA: Realizou-se em junho de 2009 uma busca eletrônica nas bases de dados Pubmed, LILACS e na biblioteca eletrônica Scielo. As palavras de busca em inglês foram: "cutaneous", "leishmaniasis" e "treatment". Foram incluídos apenas ensaios clínicos randomizados, duplo-cegos, placebo controlados. Utilizou-se a escala de Jadad para avaliar a qualidade dos estudos selecionados.

RESULTADOS: Segundo os critérios de inclusão e exclusão, apenas 8 artigos foram selecionados. As drogas avaliadas nos estudos selecionados foram Glucantime®, miltefosine, imunoterapia, imiquimod, rhGM-CSF, pentoxifilina e paramomicina.

CONCLUSÃO: Apesar de a leishmaniose tegumentar ser um importante problema de saúde pública, os dados publicados sobre o uso de novas drogas para o tratamento da leishmaniose tegumentar em nosso meio ainda são bastante limitados.

Palavras-chave: Leishmaniose cutânea; Leishmaniose mucocutânea; Terapêutica

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## INTRODUCTION

Leishmaniasis is a chronic, non-contagious infection caused by several species of protozoa that belong to the genus *Leishmania*, which are transmitted from infected animals to humans through the bite of a sand fly.<sup>1</sup>

The worldwide incidence of leishmaniasis is two million cases. Of this, 1 to 1.5 million new cases correspond to cutaneous leishmaniasis (CL).<sup>2</sup> CL is a serious health problem in Brazil, with 388,155 cases reported in the last 15 years.<sup>1</sup>

The clinical spectrum of CL in humans include mucocutaneous leishmaniasis (MCL), cutaneous leishmaniasis (CL), disseminated cutaneous leishmaniasis and diffuse cutaneous leishmaniasis.<sup>3</sup> The clinical manifestations of the disease are determined by the characteristics of the host, the kind of leishmania involved and the immune response of the infected individual.<sup>2</sup>

The main defense mechanism against leishmaniasis is immune response associated with T cells. In CL, the immune response is complex and there is no relationship between the Th1 response and protection against the disease<sup>4</sup>, since patients with CL and MCL caused by *L. braziliensis* present an intense cellular response and still develop the disease.<sup>5</sup> One possible explanation for this fact is that an exacerbated production of IFN- $\gamma$  and TNF- $\alpha$  can be harmful to the tissue and the same cytokines involved in killing the parasite may be associated with the pathogenesis of CL and MCL.<sup>4</sup>

Initial clinical manifestation of the disease is characterized by a single or multiple erythematous papules, usually located in the exposed region of the integument and which develop into ulcers with raised borders, regular contours and a bed of coarse granulation tissue, covered or not with sero-purulent exudate<sup>6</sup>. The involvement of the nasal mucosa, palate, pharynx, larynx and vocal cords may occur in up to 5% of the patients.<sup>7</sup>

Laboratory diagnosis can be done by direct smear of the lesion, *in vitro* or *in vivo* culture, histopathological examination, Montenegro skin test, serologic testing and PCR for detecting the parasite DNA.<sup>8</sup>

The therapeutic arsenal against leishmaniasis is still very restricted.<sup>9</sup> Pentavalent antimonial compounds have been the drugs of choice for the treatment of leishmaniasis for more than 50 years. The compounds available for use are N-methyl-glucamine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®).<sup>10</sup> The Brazilian Ministry of Health recommends 10 to 20 mg/kg/day of intravenous or intramuscular Glucantime® for a period of

20 days for the treatment of the localized and disseminated cutaneous forms. If there is no complete healing of the lesions three months after the end of the treatment, the scheme must be repeated for a period of 30 days. In case therapeutic failure persists, one of the second drugs of choice must be used.<sup>1</sup> Reported side effects include arthralgia, myalgia, loss of appetite, nausea, vomiting, feeling of fullness, heartburn, abdominal pain, pruritus, fever, weakness, headache, dizziness, insomnia, edema, hepatitis with increased transaminases and alkaline phosphatase, acute renal failure, pancreatitis and electrocardiographic dose-dependent changes, such as change in ventricular repolarization with inversion of the ST-segment, increased QT interval, ischemic changes, and bigeminal, polymorphous and polyfocal extrasystoles. Fatal arrhythmias are rare; there are few cases of sudden cardiac death, probably related to ventricular arrhythmias.<sup>11</sup> Amphotericin B is the second drug of choice when there is no response to treatment with antimonial or when it is not possible to use it. The efficacy of pentamidine, the third drug of choice, is less well known.<sup>9</sup> It should be noted that, even with appropriate treatment with antimonial, the occurrence of relapses and / or mucosal involvement is frequent; it corresponds to 2% of the treated cases and around 10% of the untreated cases.<sup>1</sup>

This study is justified by the importance of knowing well what has been done in an attempt to find new effective drugs with low toxicity and low cost for the treatment of new world cutaneous leishmaniasis.

## OBJECTIVE

To carry out a systematic review of the literature on the advances in the treatment of new world cutaneous leishmaniasis in the last ten years.

## METHODOLOGY

It is a systematic literature review on the advances in the treatment of new world CL in the last ten years. We conducted an electronic search on the Pubmed and LILACS database as well as on the SciELO electronic library in June 2009. The search on Pubmed was limited to clinical trials in humans published in English in the last ten years. The search words used in English were: "cutaneous", "leishmaniasis", and "treatment". We excluded open-label studies, reviews and case reports. We selected only randomized, double-blind, placebo-controlled trials in which new therapeutic regimens were used for the treatment of new world CL in the last ten years.

In order to minimize the controversies associat-

ed with the quality of the selected studies, we used the Jadad scale. The scores considered were the following: four and five = good quality, two and three = average quality, and one and zero = low quality. The articles selected should have a score equal to or greater than 4. This score comprises the following: one point if the study is randomized, one point if randomization is adequate, one point if the study is double-blind, one point if the double-blind method was described and appropriate, and one point if the dropouts were described.<sup>12</sup>

**RESULTS**

We found 281 studies, of which only eight were selected. Figure 1 shows a flow diagram showing the criteria for inclusion and exclusion of the articles found.

According to the criteria of Jadad *et al*<sup>12</sup>, six studies out of the selected ones had grade five and two had grade four. The results of the quality assessment of the selected studies, according to the Jadad scale, are described in Chart 1.

The drugs evaluated for the treatment of CL in the selected studies were glucantime®, miltefosine,

immunotherapy, imiquimod, rhGM-CSF, pentoxifylline and paromomycin. Table 1 summarizes the results of the selected studies and Table 2 describes the dropouts and side effects of the drugs evaluated.

**DESCRIPTION OF THE DRUGS AND STUDIES INCLUDED**

**Pentavalent antimonial**

Pentavalent antimonials have been used in the treatment of CL since 1945.<sup>10</sup> Its mechanism of action remains unknown. *In vitro*, they have little effect on Leishmania, which contrasts with their clinical results. It is thought to have the ability to stimulate immune mechanisms in the infected individual.<sup>13</sup> A study by Wortmann *et al.*, which was<sup>14</sup> conducted with working military in Washington, U.S.A, included 36 patients infected by different species of Leishmania. The study evaluated the effectiveness of a 10-day treatment with Glucantime® compared to a 20-day treatment with Glucantime® to fight CL. At the end of the treatment, there was no difference between the efficacy of the treatment with Glucantime® for 10 or 20 days (p = 0.79). Only one patient in the group treated with Glucantime® for 20 days and infected with L.

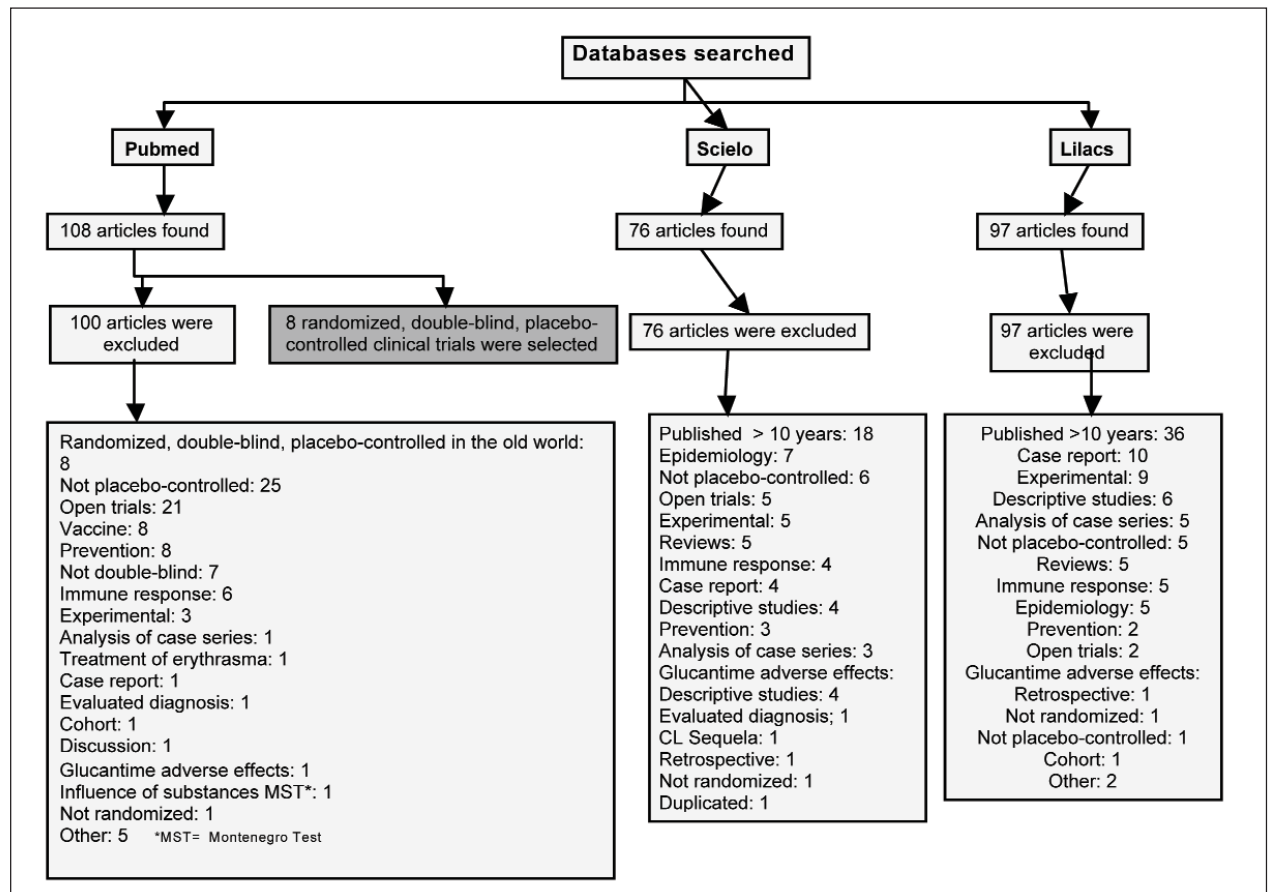


FIGURE 1: Inclusion and exclusion of the articles found

CHART 1: Quality assessment of the studies included according to the Jadad scale

Author / Year	Jadad scale					Total
	Randomization	Description of randomization	Masking	Description of masking	Description of dropouts	
ALMEIDA et al./1999	1	1	1	1	0	4
ARANA et al./2001	1	1	1	1	1	5
MACHADO-PINTO et al./2002	1	1	1	1	1	5
WORTMANN et al./2002	1	1	1	1	1	5
SOTO et al./2004	1	1	1	1	1	5
SANTOS et al./2004	1	1	1	1	1	5
MIRANDA-VERÁSTEGUI et al./2005	1	0	1	1	1	4
MACHADO et al./2007	1	1	1	1	1	5

*braziliensis* showed lesion recurrence. Side effects occurred in both groups. Myalgia occurred in eight (42%) of the patients treated for ten days and thirteen (68%) of the patients in the group treated for 20 days and persisted longer in the group treated for 20 days ( $p = 0.037$ ). Therapy with 20 days of Glucantime® led to a significant increase in the levels of amylase ( $p = 0.028$ ), lipase ( $p = 0.003$ ), AST ( $p = 0.019$ ) and ALT ( $p = 0.018$ ) compared to therapy with ten days of Glucantime®. The decrease in the levels of leukocytes ( $p = 0.012$ ), hematocrit ( $p = 0.003$ ) and platelets ( $p = 0.006$ ) was greater in the group treated with Glucantime® for 20 days. Seven patients did not complete the treatment due to pancreatitis, four of them from the group treated for ten days and three from the group treated for 20 days.

### Miltefosine

Miltefosine is an alkyl phospholipid drug originally developed as an antineoplastic agent. It has a direct toxic effect on the promastigote forms of *Leishmania*. However, its action on amastigote forms is related to its effect on macrophages or on the immune response dependent on T-cell activation<sup>15</sup>. A

study by Soto *et al.*<sup>16</sup> included 133 patients infected by *L. panamensis*, *L. braziliensis* or *L. mexicana*. The study evaluated the efficacy of miltefosine compared to placebo in the treatment of CL in Colombia and Guatemala. In the areas of Colombia where *L. panamensis* is common, the cure rate was 91% in the group treated with miltefosine and 38% in the control group ( $p < 0.01$ ). In the areas of Guatemala where *L. braziliensis* and *L. mexicana* are frequent, the cure rate was 53% in the group treated with miltefosine and 21% in the control group ( $p = 0.023$ ). The cure rate for *L. braziliensis* was lower (33%) compared with the cure rate for *L. mexicana* (60%), but the difference was not statistically significant. The side effects reported included nausea, vomiting and elevated levels of creatinine. There was a difference between the frequency of these side effects in the study group and control group ( $p < 0.005$ ).

### Immunotherapy

A study by Machado-Pinto *et al.*,<sup>9</sup> conducted in an endemic area of Minas Gerais, Brazil, included 102 patients infected with leishmania to evaluate the efficacy of the combination of vaccine, containing extract

TABLE 1: Summary of the results of the studies included

Author / Year	Leishmania	Sample size	Experimental group	Control Group	Drug dose evaluated	Criteria for cure	Results
ALMEIDA et al./1999	<i>L. braziliensis</i>	20	GM-CSF + sodium stibogluconate	Placebo + sodium stibogluconate	Two local injections 200µg	Complete reepithelialization	GM-CSF > Placebo*
ARANA et al./ 2001	<i>L. braziliensis</i> (75%) e <i>L. Mexicana</i> (25%)	76	15% paromomycin + 12% <i>Methylbenzethonium chloride</i>	Placebo	2 topical applications daily for 20 days	Complete reepithelialization	15% Paromomycin + 12% <i>Methylbenzethoni chloride</i> > Placebo *
MACHADO-PINTO et al./ 2002	Não information	96	Vaccine + Glucantime	Placebo + Glucantime	1 SC injection of 0,5 ml of the vaccine for 10 days	Complete reepithelialization and no infiltration	Vaccine > Placebo *
WORTMANN et al./ 2002	<i>L. tropica</i> , <i>L. panamensis</i> , <i>L. major</i> , <i>L. braziliensis</i> , <i>L. naiffi</i> e <i>L. guyanensis</i>	38	Glucantime for 10 days Placebo for 10 days	Glucantime for 20 days	20mg/ Kg/day IV	Complete reepithelialization	Glucantime for 10 days = Glucantime for 20 days
SOTO et al./ 2004	<i>L. panamensis</i> , <i>L. braziliensis</i> e <i>L. mexicana</i>	133	Miltefosine	Placebo	2,5mg/Kg/day, orally for 28 days	Complete healing of all lesions within 6 months after the end of therapy	Miltefosine > Placebo *
SANTOS et al./2004	<i>L. braziliensis</i>	20	GM-CSF + Glucantime	Placebo + Glucantime	1 to 2 ml of tropical rhGM-CSF (10µg/ml of SF0,9%) 3x for week for 3 weeks	Complete reepithelialization	GM-CSF > Placebo*
MIRANDA-VERÁTEGUI et al./ 2005	<i>L. peruviana</i> e <i>L. braziliensis</i>	40	Imiquimod 5% + Glucantime	Placebo + Glucantime	125-250mg/day, topically, for 20 days	Complete reepithelialization without signs of inflammation	Imiquimod > Placebo *
MACHADO et al./ 2007	<i>L. braziliensis</i>	23	Pentoxifilina + Glucantime	Placebo + Glucantime	400mg orally 3x days for 30 days	Complete reepithelialization of the mucosa and absence of inflammatory activity 150 days after beginning the therapy	Pentoxifilina > Placebo *



of killed promastigotes of *L. amazonensis*, with low doses of pentavalent antimonial for the treatment of CL. The patients were divided into two groups. The first group received a daily dose of 0.5 ml of the vaccine administered subcutaneously with 8.5 mg/kg of intramuscular Glucantime® for ten days, followed by a period of ten more days of rest. The other group received daily doses of 0.5 ml of placebo administered subcutaneously with 8.5 mg/kg of intramuscular Glucantime® for ten days, followed by a period of ten more days of rest. The patients were re-evaluated every 20 days, and if there were no cure, a new cycle of treatment was started. After four treatment cycles, 100% of the patients treated with Glucantime® and antileishmania vaccine were cured, while only 8.2% of the patients treated with Glucantime® alone were cured ( $p < 0.0001$ ). The median number of cycles needed for cure was three in the study group and seven in the control group ( $p < 0.005$ ). Therapy with Glucantime® and antileishmania vaccine led the lesions to heal faster compared to the therapy with Glucantime® alone ( $p < 0.0001$ ). The only side effect reported was pain at the site of injection.

### Imiquimod

Imidazoquinoline, approved for the treatment of genital warts,<sup>17</sup> stimulates the Th1 response, thus increasing the production of TNF- $\alpha$ , IFN- $\gamma$  and IL-12.<sup>18</sup> *In vitro*, it shows antileishmania activity, since it stimulates the production of nitric oxide by macrophages, decreasing the number of parasites.<sup>19</sup> A study by Miranda-Verástegui *et al.*<sup>20</sup>, conducted in the endemic regions of the Peruvian Andes and the Peruvian jungle, included 40 patients infected by *L. peruviana* or *L. braziliensis*. The study evaluated the efficacy of the combination of 5% topical imiquimod and pentavalent antimonial compared with the use of antimonial alone for 20 days in the treatment of CL. The proportion of patients who achieved clinical cure in one, two and three months after the end of the treatment was higher in the group treated with imiquimod and antimonial ( $p < 0.02$ ,  $p < 0.03$  and  $p < 0.02$ , respectively). The most frequent side effect in the group treated with imiquimod was erythema ( $p = 0.02$ ). Edema, pruritus, burning and pain were also reported.

### rhGM-CSF

rhGM-CSF is a glycoprotein which induces the growth of granulocyte and/or macrophage colonies, stimulating their phagocytic and metabolic functions. For this reason, it has an important role in immune response against intracellular pathogens.<sup>21</sup> The role of rhGM-CSF as an adjuvant in the treatment of CL was evaluated in two studies. The studies by Adams *et al.*<sup>22</sup> and Santos *et al.*<sup>23</sup> conducted in the endemic area

of Corte de Pedra in the state of Bahia, Brazil, included 20 patients infected with *L. braziliensis*. In both studies, therapy with rhGM-CSF led to faster healing of lesions than therapy with the antimonial alone (49 + - 32.8 vs. 110 + - 61.6 days,  $p < 0.05$ ; 43 + - 14 vs. 104 + - 79 days,  $p = 0.043$ , respectively). In the study by Almeida *et al.*<sup>22</sup>, the rhGM-CSF was administered through intralesional injection, while in the study by Santos *et al.*<sup>23</sup>, it was administered through topical application. The drug was well tolerated, with no reports of relevant side effects.

### Pentoxifylline

Pentoxifylline is a vasodilator drug used to treat peripheral vascular disease.<sup>13</sup> It has been used experimentally to treat some inflammatory diseases, since it has an inhibitory effect on TNF- $\alpha$ .<sup>24</sup> A study by Machado *et al.*,<sup>25</sup> conducted in the endemic area of Corte de Pedra, Bahia, Brazil, included 23 patients with MCL infected with *L. braziliensis*. Therapy with pentoxifylline led the lesions to heal faster than therapy with the antimonial alone (83 + - 36 days vs. 145 + - 99 days,  $p = 0.047$ ). The proportion of patients who showed persistent disease was significantly higher in the group treated with the antimonial alone than in the group treated with pentoxifylline ( $p = 0.047$ ). The side effects reported were nausea (27%), arthralgia (9%), dizziness (9%), abdominal pain (9%) and diarrhea (9%).

### Paromomycin

Paromomycin is an antibiotic that inhibits the mitochondrial activity of Leishmania.<sup>10</sup> A study by Arana *et al.*,<sup>26</sup> conducted in Guatemala, included 76 patients infected with *L. braziliensis* (75%) and *L. mexicana* (25%). 15% paromomycin sulfate associated with 12% methylbenzethonium chloride was used twice a day for 20 days in comparison with placebo. Clinical response after twelve months of follow-up was 85.7% in the group treated with paromomycin and 39.4% in the placebo group ( $p = 0.000025$ ). Treatment failure and reactivation of the lesions clinically healed were more frequent in the placebo group.

### DISCUSSION

This study evaluated the progress achieved in the last ten years in the treatment of CL through a systematic literature review. Systematic reviews are research projects themselves, that is, they are original research in which search procedures are employed carefully to find eligible articles, which are selected according to criteria explicitly defined and classified based on their quality. They are the best way to start a primary-data research project, for they allow us to verify what is already known and, most importantly, what

**TABLE 2:** Description of dropouts and side effects of the drugs evaluated in the studies reviewed

Author / Year	Drugs studied	Dropouts	Side effects of the drugs studied
ALMEIDA et al./1999	GM-CSF	They were not described	They were not described
ARANA et al./2001	15 % paromomycin + 12% methyl benzethonium	8 patients, 3 of the study group and 5 of the placebo group	Local pruritus (46.7%), burning (30%), local pain (20%) and local edema (3.3%). There was no significant difference between the number of patients who reported adverse effects in the study group and the placebo group
MACHADO-PINTO et al./2002	Antileishmania vaccine	6 patients, 4 of the study group and 2 of the placebo group	Pain at the injection site
WORTMANN et al./2002	Glucantime for a period of 10 days	7 patients, 4 of the study group and 3 of the group treated with Glucantime for 20 days	Pancreatitis (21%), myalgia (42%), elevated levels of amylase, lipase, AST and ALT, and decreased levels of leukocytes, platelets and hematocrit. These changes were greater in the group treated with Glucantime for 20 days (p <0.05)
SOTO et al./2004	Miltefosine	6 patients, 4 of the study group and 2 of the placebo group	Nausea, vomiting and elevated levels of creatinine, with a significant difference between the frequency of these side effects in the study group and the placebo group (p <0.05)
SANTOS et al./2004	GM-CSF	There was no loss to follow-up	The drug was well tolerated with no reported side effects
MIRANDA-VERÁSTEGUI et al./2005	5% Imiquimod		Erythema was more frequent in the study group with a statistically significant difference between groups. Edema, pruritus, burning and pain were also reported
MACHADO et al./2007	Pentoxifylline	2 patients of the study group	Nausea, arthralgia, dizziness, abdominal pain and diarrhea

remains unclear. They help to identify methods and justify the sample size of new studies, but because they are retrospective observational studies, the presence of bias is inherent, especially that arising from the way the review is conducted and the studies included. Developing protocols to eliminate bias is a major challenge. Still, these protocols are an essential component for the advancement of knowledge for covering the gaps between past and future research and between research and clinical care.<sup>27</sup>

CL is widely distributed in the American continent and is endemic in some countries in Asia and North Africa. It is a global public health problem, being considered as the second most common parasitic infection worldwide by the World Health

Organization. It is an expanding disease in most affected countries, including Brazil. It has been documented in all Brazilian regions, thus constituting one of the dermatologic disorders that deserves more attention due to the magnitude of the disease, the risk of deformities, the increase in the upward trend of the disease in urban areas, the psychological damage caused to the patient and its reflections on the social and economic spheres.<sup>1</sup> CL, as most infectious diseases, is mostly a problem of developing countries and, therefore, offers little commercial incentive for pharmaceutical companies to develop cheap and effective drugs for its treatment.<sup>28</sup>

Pentavalent antimonials have been the treatment of choice for CL for over 50 years.<sup>29</sup> Although

they are effective, their intravenous use, prolonged healing time, side effects and high treatment cost<sup>7</sup> lead to the need of conducting research that evaluate therapeutic regimens different from what is currently recommended for the use of antimonials.<sup>30</sup> Wortmann *et al.*<sup>14</sup> suggested that treatment with Glucantime® for a period of ten days has similar efficacy and fewer side effects than treatment with the same drug for a period of 20 days, although results were not statistically significant. The study was limited by its small sample size and prevalence of patients infected by *L. panamensis*. It would be interesting to conduct a study using this same regimen and an adequate sample size in Brazil, where *L. braziliensis* is endemic, to evaluate the susceptibility of this species of leishmania to this new regimen.

A major challenge for studies that evaluate new drugs for the treatment of CL is to find a drug that is as effective as the antimonials, but of easy administration and low toxicity. Miltefosine appears to be promising for the treatment of CL, for it is administered orally and has few side effects. Treatment with miltefosine showed to be more effective in Colombia, where *L. panamensis* is endemic. In this region, the cure rates with antimonial and miltefosine were similar, around 90%. On the other hand, the use of miltefosine in Guatemala, where *L. braziliensis* and *L. mexicana* are common, showed cure rates of around 50% compared with historical cure rates of 90% with the use of antimonials. Soto *et al.*<sup>31</sup> compared the use of oral miltefosine with intramuscular antimonial in the treatment of CL caused by *L. braziliensis* in Bolivia and found statistically similar cure rates between the groups. Therefore, it becomes essential to conduct randomized, placebo-controlled trials evaluating the efficacy of miltefosine in endemic regions of *L. braziliensis* in Brazil, since Soto *et al.*<sup>31</sup> showed that miltefosine seems to be more effective against *L. braziliensis* in Bolivia than *L. braziliensis* in Guatemala.

The study of immunotherapy combined with antimony showed favorable results. The combination of low doses of Glucantime® and antileishmania vaccine led the lesions to heal faster than Glucantime® therapy alone in the treatment of CL. It is believed that its association with low doses of antimony, besides being effective, reduces the side effects associated with the use of the drug as well as the cost and duration of the treatment. The discovery of an effective antileishmania vaccine is the main expectation for the control of CL.<sup>32</sup> Although many studies have been made in this direction, the vaccine is not available in clinical practice yet and further studies to confirm its effectiveness in the prevention and treatment of CL are needed.

The combination of imiquimod and antimonial also proved to be effective in the treatment of CL, with decreased healing time and improvement of the quality of the scar. The fact that the study was conducted with patients infected with different species of leishmania has made it difficult to identify whether the observed treatment failures were related to infection by a particular species, thus limiting the results. The mechanism of action of imiquimod as an inducer of Th1-type immune response may be related to success in the treatment of patients cured with the combination of imiquimod and antimony; however, it is possible that the induction of a Th1 response is not the only target in the treatment of CL.<sup>22</sup>

The use of rhGM-CSF as an adjuvant in the treatment with pentavalent antimonial significantly decreased the cure time of CL. Santos<sup>33</sup> showed that patients treated with rhGM-CSF exhibit a significant increase in the production of IL-10 as well as higher levels of INF- $\gamma$  and TNF- $\alpha$  in comparison with the placebo group and suggested the hypothesis that the increased level of IL-10 in these patients may induce modulation of Th1-type immune response, partially blocking the effect of pro-inflammatory cytokines, with decreased inflammation and tissue damage. The author also indicated that modulation of the inflammatory immune response may also be an important target in the treatment of CL, increasing the possibility of reducing the duration of treatment with antimony. In addition, the study by Santos<sup>34</sup> showed that patients treated with rhGM-CSF have a lower probability of having to make repeated use of pentavalent antimonial, with reduction of the doses of antimony used and its toxicity. The topical use of rhGM-CSF in the study by Santos *et al.*<sup>25</sup> reduced the costs of its use; however, the topical preparation of rhGM-CSF is not commercially available and was only produced for that investigation. The high costs of this medication make its application in clinical practice difficult; however, these studies emphasize the need for further studies on drugs that have action and efficacy similar to the rhGM-CSF, but with a reduced cost.

It is known that the involvement of the mucous membranes may occur in CL,<sup>35</sup> and it is believed that MCL is triggered by an exacerbation of the inflammatory response.<sup>25</sup> Evidence of the role of the immune response in the pathogenesis of MCL includes the presence of inflammatory infiltrate despite the small number of parasites in samples of culture or biopsy,<sup>36</sup> high levels of INF- $\gamma$  and TNF- $\alpha$ <sup>4</sup> with an increase in the expression of these mediators in the tissue,<sup>37</sup> and a decreased ability of the immunomodulator IL-10 to the exacerbated inflammatory response.<sup>38</sup> MCL, which is mainly caused by *L. braziliensis*, is treated with pentavalent antimonial and presents high rates of treat-



ment failure and relapse. The combination of pentoxifylline with antimony significantly reduced the healing time of lesions, with no recurrences documented during the two years of patient follow-up, suggesting that the antiinflammatory action of pentoxifylline is effective in the treatment of the disease. Pentoxifylline acts by inhibiting the synthesis of TNF- $\alpha$ , IL-2, IL-12 and INF- $\gamma$  and influencing the production of other cytokines such as IL-4, IL-6 and IL-10.<sup>39</sup> The efficacy of pentoxifylline, therefore, appears to be due to its ability to modulate the immune response extrinsically.<sup>40</sup> Its use associated with pentavalent antimonial is interesting for the treatment of patients with MCL that is severe and refractory to conventional treatment.

The use of paromomycin showed promising results; however, despite the advantage of its topical administration, more studies with adequate methodology are needed to prove its efficacy in the treatment of the new world CL.

Amphotericin B is the second drug of choice when antimonials fail or cannot be used. However, it is a toxic and expensive drug, which often requires hospitalization for its administration.<sup>9</sup> An alternative to the treatment with conventional amphotericin B is the use of liposomal amphotericin B, which has higher peak plasma levels and lower toxicity.<sup>7</sup> Despite the importance of the use of liposomal amphotericin B in the treatment of CL that is refractory to treatment with antimony, this review emphasizes the lack of randomized, double-blind, placebo-controlled trials evaluating the use of this drug for the treatment of CL in the past ten years.

Pentavalent antimonials remain the drug of choice for the treatment of cutaneous and mucocutaneous leishmaniasis. Despite its availability in health facilities, its high toxicity and its parenteral use are limiting factors for the proper treatment of cases of CL. It should be noted that most of these cases occur in areas of difficult access, in rural areas, which complicates the parenteral application of the drug and monitoring of its side effects.<sup>32</sup> Treatment of CL with the drugs currently available represents an obstacle to proper clinical handling of the cases of leishmaniasis, and efforts should be made in order to add the promising drugs discussed in this review to clinical trials and investigate the use of new alternative drugs.

The heterogeneity of the studies reviewed, evi-

denced mainly by the different species of leishmania involved and the variety of the sample sizes, makes it clear that there is lack of proper standard methodology for evaluating new drugs for the treatment of CL.

Randomized and placebo-controlled clinical trials are described as the gold standard in the evaluation of therapeutic issues in health for reducing the likelihood of obtaining biased data in research.<sup>41</sup> Although effective, this type of study has practical limitations. The difficulty in finding a sufficient number of patients with the disease in a particular time and place and the high cost to conduct a scientifically sound clinical trial of large size are its main limitations.<sup>42</sup> Multicenter clinical trials and increased investment in medical research from the part of the government may be the solution to minimize these difficulties.

During the process of selecting articles for this review, many open trials that were not placebo-controlled were found and they evidenced the use of promising drugs for the treatment of CL. These studies could not be included for not allowing a proper comparative analysis of their results. However, they are important and serve as pilot studies for conducting randomized, double-blind, placebo-controlled trials, with an adequate sample size. The correct calculation of the sample size of a study is extremely important for obtaining more reliable results and reduced costs.<sup>41</sup> In this review, most of the studies included have a small sample size that restricts extrapolation of their results. It should be noticed that, if the studies had the same standard methodology, even with small samples, a meta-analysis would be possible in the future, expanding the results obtained.

## CONCLUSION

Although CL is a major public health problem in Brazil and the Americas, published data on the use of new drugs for the treatment of CL in our country are still quite limited. It is extremely important to carry out more randomized, double-blind, placebo-controlled clinical trials with adequate samples in order to evaluate new drug regimens for the treatment of CL. These studies should aim at finding effective drugs with low toxicity, easy administration and reduced cost and treatment time, thus facilitating the treatment of the disease in endemic regions. □

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