Medication options in the treatment of cutaneous american tegumentary leishmaniasis

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ABSTRACT

American cutaneous leishmaniasis is an infectious disease endemic in about 100 countries, with three predominant forms: cutaneous, mucosal and visceral. It is classically transmitted by the bite of the Lutzomyia mosquito and, after infection, occurs with the formation of a papular lesion, which evolves to the formation of a nodule, and may even be associated with regional adenopathy. Cutaneous leishmaniasis (CL) deserves special attention because it is the most recurrent presentation of ATL, subdivided into two forms: localized and disseminated. The diagnosis of ACL comprises the association of the clinical history with the local epidemiological profile, associated with laboratory tests that prove the presence of Leishmania. The complementary tests of choice are: histopathological, which reveals the presence of amastigote in tissue; the isolation of the parasite in an in vitro culture medium and the detection of parasite DNA by means of Polymerase Chain Reaction (PCR) examination. Regarding the treatment of this pathology, the main focus of this work, there are drugs under development and other drugs of already established use, such as: pentavalent antimonials, liposomal amphotericin B or deoxycholate, in addition to pentamidine, which belongs to aromatic diamines and is used for treatment in regions of the American, Asian and African continents. Therefore, when considering the impact that ACL can have on human quality of life, it is necessary to list the main drugs used in its treatment, in order to compare them and list the most effective and safe options. Therefore, a systematic literature review was carried out, in which research and scientific papers published in the last 10 years (January 2014 - January 2024) were evaluated in detail, in the PubMed bibliographic databases and in the Latin American and Caribbean Health Sciences Literature (LILACS). Thus, it will be possible to analyze which therapeutic options are available on the market, in addition to mentioning the new drugs under development, especially in order to minimize the side effects of the drugs in use.

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INTRODUCTION

Leishmaniasis is an infectious disease that occurs in all subtropical and tropical areas of planet Earth, being endemic in about 100 countries. It stands out as a condition that presents with three predominant clinical syndromes: cutaneous, mucosal, and visceral (MARIONA PINART et al., 2020). It is known that the infection occurs by the action of protozoa of the genus Leishmania, which cover more than 20 species, of which 7 are found in Brazil, with prevalence for 3: Leishmania (L.) amazonensis, L. guyanensis and L. braziliensis. Transmission occurs through the bite of a female mosquito of the genus Lutzomya. Within this spectrum, the subdivision into American Cutaneous Leishmaniasis is understood, which presents with cutaneous and mucosal forms (OLANDIM et al., 2022).

ACL has a variable clinical spectrum, which is related to immunological aspects and the type of species involved. Classically, after the mosquito bite, there is formation of a papular lesion, which evolves to the formation of a nodule, which may even be associated with regional adenopathy. After that, single or multiple lesions are formed that are characterized as painless ulcers with raised, regular borders and granulomatous background that can manifest itching, burning, and heat (OLANDIM et al., 2022)

Cutaneous leishmaniasis (CL) is the most recurrent presentation of ATL, with an incubation period of between 2 and 4 weeks, subdivided into two forms: localized and disseminated. In its localized form, there is the formation of a classic ulcerated lesion that can be single or multiple and that usually evolves well with treatment, tending to spontaneous cure (BRASIL, 2017). The disseminated form, on the other hand, is more uncommon, being observed in only 2% of cases. It is characterized by the formation of multiple lesions that begin as acneiform papules, mainly on the face and trunk, accompanied by primary ulcerated lesions. It is believed that hematogenous or lymphatic dissemination occurs, which would justify such a clinical presentation (BRASIL, 2017).

Mucosal leishmaniasis (SCI) is another presentation of ATL, which is commonly associated with CL progression. It mainly affects the nasal septum, but can also form lesions in the oropharyngeal region, laryngeal region, palate and trachea and bronchial tree. It is important to elucidate that although there is a higher incidence of SCI secondary to CL, there is a possibility of primary involvement in 15% of cases (BRASIL, 2017).

The diagnosis of ACL comprises the association of the clinical history with the local epidemiological profile, associated with laboratory tests that prove the presence of Leishmania. The complementary tests of choice are: histopathological, which reveals the presence of amastigote in tissue; the isolation of the parasite in an in vitro culture medium and the detection of parasite DNA by means of Polymerase Chain Reaction (PCR) examination. Montenegro Intradermal Disease (MRID)

used to be performed, which is in disuse, as it was not able to identify active and resolved infection (ARONSON et al., 2016).

The treatment of ACL is important in several aspects, among them because it is a disease that promotes facial deformation and in other affected body regions, causing psychosocial impact, as well as because it has a high prevalence and is a neglected condition. The management of this disorder is especially with established drugs, such as pentavalent antimonials, liposomal amphotericin B or deoxycholate. In addition, there is also the participation of pentamidine, which belongs to aromatic diamines and is used for treatment in regions of the American, Asian and African continents. Another drug that has emerged in the treatment of ACL is pentoxifylline, which is classified as a peripheral vasodilator, and has been gaining ground as an adjuvant because it plays an immunomodulatory role, with a reduction in treatment time, when compared to conventional therapy (BRASIL, 2017).

With regard to CL, management should be directed according to the species of infecting Leishmania, but the absence of screening material in the services leads to an adaptation that is based on the prescription of the drug according to the epidemiological characteristics of each region. The management of patients with CL caused by L. braziliensis and other species, except L. guyanensis, has intravenous (IV) or intramuscular (IM) meglumine antimoniate as the first option, except for individuals with kidney, hepatic, and cardiac disease, or those over 50 years of age. In this profile, the use of liposomal amphotericin B is recommended. In the case of L. guyanensis infection, the first-line treatment is the use of pentamidine isethionate, except in patients with heart disease, nephropathy, liver disease and in individuals over 50 years of age, and in these cases the management also includes the use of liposomal amphotericin b. There is also an option for patients with a single lesion of up to 3 centimeters in diameter, who present a lesion in any location, except the head and periarticular regions, including the use of intralesional antimoniate (BRASIL, 2017).

In patients with SCI, it is preferable to undergo treatment in referral centers, with the aim of follow-up with an otorhinolaryngologist. The first management option is a combination of meglumine antimoniate and pentoxifylline, except for patients with cardiac, renal and hepatic comorbidities, as well as individuals over 50 years of age. If the individual is within any of the aforementioned profiles, he/she should start liposomal amphotericin b (BRASIL, 2017).

ACL is a condition that has a high prevalence worldwide and that has consolidated drugs for its treatment. However, some have liver, heart, and kidney damage, and are age-restricted for use. Thus, alternative management methods have been developed over time to circumvent this disease. The aim of this project is to evaluate the recent treatments developed and to analyze the comparison of several studies with the most established therapies.

METHODOLOGY

This is a systematic literature review, in which research and scientific papers published in the last 10 years (January 2014 - January 2024) were evaluated. The information was obtained through an active search performed in the electronic databases PubMed and LILACS. To this end, the descriptors in health sciences (DeCS) were used, namely: "American Cutaneous Leishmaniasis" and "Treatment".

The following inclusion criteria were approved in the production of the systematic review: studies carried out in the human species, of both sexes, in Portuguese, English and Spanish, all published in the last 10 years. In addition, only those whose abstracts presented the following terms were included: "American Cutaneous Leishmaniasis" and "Treatment".

As exclusion criteria, the withdrawal of outdated studies (more than 10 years and without relevant content for the research) and/or duplicates that did not address the drugs proposed for the treatment of cutaneous American cutaneous leishmaniasis was imposed. In addition, studies dealing with studies in children, in vitro studies, and studies in other species were excluded.

The search generated 267 results. All results were reviewed based on the abstracts, resulting in the exclusion of 143 of them because they did not meet the inclusion criteria. Of the remaining 124 studies after this stage, the selected articles and guidelines were thoroughly read, resulting in the choice of 10 studies that addressed the main objective of the review, reporting on cutaneous American cutaneous leishmaniasis and its treatment.

In this sense, during a research, the treatments used were examined, as well as the effectiveness of each one, and the drugs that demonstrate better results were identified, with efficacy being defined as the ability to promote hair growth in areas previously affected by cutaneous leishmaniasis. In addition, some variables (such as age, lifestyle, coexisting medical conditions, among others) were considered determinants of the stage of the disease and its impact on the body as a whole.

RESULTS

Table 1 lists the main drugs used to stabilize and reverse cutaneous American Cutaneous Leishmaniasis (ATL), as evidenced by scientific studies. Some of these have been in use for quite some time, while others show promising results, although they need further investigation to validate their effectiveness.

The case report developed by Olandim et al. describes the history of a patient treated with the therapeutic method homeopathy. The intervention was performed by an individualized medication at each visit and several homeopathic medications were administered progressively. Personalized treatment with homeopathy alone has shown efficacy in recovering from an ACL condition for a

period of months, free from the side effects of conventional therapy, maintaining its results over years of follow-up. Thus, the individualized approach with homeopathy can be contemplated in the management of ATL, providing patients with an alternative to the possible harmful effects of established medicines.

Martins et al., conducted a pilot, randomized, open-label clinical trial. A total of 384 patients with suspected ACL were approached in the pilot period of the RCT, 43 patients were included and randomized. Twenty-two were assigned to the M+P group (Miltefosine and Pentoxifylline) and 21 to the A+P group (pentavalent antimony and Pentoxifylline). There were 348 patients with a confirmed diagnosis of CL (Cutaneous Leishmaniasis), of which 18 were included, and there were 43 patients with SCI (Mucosal Leishmaniasis), of which 25 were included. It is concluded that, in this randomized pilot clinical trial, the M+P treatment and the A+P treatment produced similar cure rates, there was no difference in the chance of cure based on the treatment, and the first was associated with a lower risk of adverse effects. Therefore, further studies with more patients and longer follow-up are recommended.

A controlled, randomized, open-label clinical trial for a total number of 159 patients with cutaneous leishmaniasis, predominantly caused by Leishmaniasis guyanensis, was conducted by Gadelha et. al., In this study, from November 2013 to December 2015, a total of 159 patients were selected and divided into three groups to receive treatment with PI (Pentamidine Isethionate): I) 53 patients received a single intramuscular injection with a dose of 7 mg/kg body weight; II) 53 patients received two injections of 7 mg/kg, with an interval of seven days between them; and III) 53 patients underwent three injections of 7 mg/kg, with an interval of seven days between each dose. Of the 159 patients, 120 were detected with L. guyanensis, whose cure rates of 45%, 81.1% and 96.2% were observed in groups one, two and three, respectively. The cure rate in the group that received three doses of PI was significantly higher compared to the groups that received a single dose ($p<0.0001$) and two doses ($p = 0.03$). No serious adverse events were reported during the study. The current study demonstrates that PI is a safe drug, whose efficacy varies according to the number of doses administered. It should be noted that the administration of PI in patients with ATL, mainly caused by L. guyanensis, was more effective when performed in three or two doses of 7 mg/kg.

Añez N. et al., developed a study that addresses the treatment of ACL, mainly caused by Leishmania braziliensis, in which 122 lesions caused by Leishmania braziliensis in 92 patients were treated with weekly intralesional infiltrations (IL) of a generic pentavalent antimonial compound, combined with local anesthetics. The solution, consisting of a concentration of 90 mg/ml of Sb 5+ combined with 2% lidocaine in a 1:3 ratio, demonstrated efficacy in ulcer healing in all patients enrolled in the current protocol.

On the other hand, the study by Barroso et al., through a retrospective cohort study of an endemic area of Leishmania braziliensis, aimed to compare the results of the treatment of ACL with Meglumine Antimoniate (NMG) and liposomal amphotericin B (LAB). The NMG group had a higher cure rate than the LAB group (cure rate of 88% versus 55%, respectively) in the adjusted analysis (risk ratio (RR) = 1.55, 95% CI: 1.19 - 2.02) and after propensity score matching (RR = 1.63, 95% CI: 1.20 - 2.21). The NMG group also had a higher adverse event (AE) rate (52% versus 44% event rate) in the adjusted analysis (RR = 1.61, 95% CI: 1.06 - 2.43, p = 0.02), but this result was not observed after propensity score matching (RR = 0.87, 95% CI: 0.49 - 1.52, p = 0.61). Thus, it is observed that the NMG group demonstrated a higher cure rate than the LAB group.

Cataldo JI et al., conducted a retrospective review of medical records to analyze and compare the therapeutic response to meglumine antimoniate at low doses 5 mg/kg/day, especially when side effects are more feared, in patients who acquired ACL in Brazilian states other than Rio de Janeiro (OS group) and 72 patients from Rio de Janeiro. In this study, a course of 5 mg of Sbv/kg/day cured 72.8% of the 81 patients infected with cutaneous leishmaniasis (CL) and 66.6% of the 27 with mucosal leishmaniasis (ML): 70% in the CL/RJ group, 81% in the CL/OS group, 50% in the ML/RJ group, and 80% in the ML/OS group. After up to two additional treatment cycles at the same dose, 88.9% and 85.2% of patients with CL and SCI were cured, respectively.

In turn, Lopes et al. analyzed the arsenal of the main medications available for the treatment of cutaneous ACL and concluded that, due to the high toxicity of current treatments, the uncomfortable parenteral administration and the increase in the rate of refractory cases, new pharmacologically active molecules effective against pathogens have become more intense, such as the secondary metabolites of the fungus of the genus Trichoderma. The effect of the ethanolic extract of Trichoderma asperelloides (Ext-Ta) and its fractions on promastigotes and amastigotes of Leishmania amazonensis was analyzed, and it was concluded that its pharmacological activity was attributed to the low molecular weight fraction (LMWF) of Ext-Ta. The results are promising, especially with regard to the creation of an easy-to-administer, accessible and simplified drug, however, a more detailed investigation of the active components of this fungus is needed, using improved identification techniques.

Finally, Carvalho et al., through a systematic review, expose the barriers to intramuscular/intravenous administration of meglumine antimoniate (MA; Glucantime) and studies the alternatives to this approach and the possibilities for developing cheap, accessible and non-toxic drugs or new delivery methods, with a main focus on nanotechnology. It is concluded that the chances of creating an innovative drug for ACL or a new way of administering AM are low. Although MA nanocarriers represent a promising prospect, this technology is still at an early stage. A more

immediate alternative would be to develop a bioequivalent of miltefosine, an efficient oral compound that is no longer subject to patents.

Table 1 – Main drugs used in stabilization and regression of cutaneous ACL

Authors	Type of study	N° of patients	Therapy used	Observation time	Results
Olandim, 2022	Case report	1 patient	Homeopathy	5 months	There was regression of all manifestations of the disease, with no side effects and no signs of relapse after 12 years of follow-up
Martins 2021	Pilot, randomized, open-label clinical trial.	43 patients	Oral Miltefosine and Pentoxifylline-Associated Pentavalent Antimonials	20-28 days	M+P treatment and A+P treatment produced similar cure rates, and the former was associated with a lower risk of AEs
Gadelha, 2018	Open-label, randomized, controlled clinical trial	159 patients	Isetionato de Pentagata	From November 2013 to December 2015	Administration of PI in patients with ATL, predominantly caused by L. guyanensis, was more effective at three or two doses of 7 mg/kg
Añez 2018	Case Series	92 patients	Generic pentavalent antimonial – intralesional	No information	Weekly intralesional infiltrations were effective enough to heal lesions in all patients included
Barroso, 2022	Retrospective cohort from Brazil	No information	Meglumine Antimoniate (NMG) and Liposomal Amphotericin B (LAB)	6 months	It is observed that the NMG group demonstrated a higher cure rate than the LAB group
Cataldo, 2018	Retrospective review of medical records	36 (other Brazilian states) 72 patients (Rio de Janeiro)	Meglumine antimoniate 5 mg Sbv/kg/day	No information.	Low doses of AM may be preferred when toxicity is the primary concern.

DISCUSSION

The treatment of ATL is based on the use of pentavalent antimonials, with emphasis on intravenous, intramuscular or intralesional meglumine antimoniate, as well as the use of liposomal amphotericin b and deoxycholate, pentoxifylline, pentamidine, miltefosine and adjuvant therapies. In addition, it was observed that the therapeutic approach is associated with the specific protozoan species for certain clinical forms of ATL.

Regarding local therapy with meglumine antimoniate, management benefit was observed in patients with single lesions that did not exceed 3 centimeters in diameter. According to Añez N. et al., there was a benefit in the associated use of antimoniate with 2% lidocaine, with a better response to wound healing.

With regard to systemic therapy, the association of pentoxifylline with antimoniate had similar results to management with pentoxifylline and miltefosine. According to Martins et al., in addition to the therapeutic similarity, there was a lower number of complications with the use of miltefosine when compared with the use of antimoniate. The profile of complications associated with pentavalent antimonials is reported to be prevalent, which is detrimental to patients, given the large number of patients with comorbidities. Therefore, miltefosine may be a good option for the management of patients with restrictions.

In patients with a risk profile for antimoniate use, a better response to treatment was observed with a reduced daily dose and with cycles of pauses to avoid complications. According to Cataldo JI et al., there was cure in the group of patients, with a reduction in the incidence of complications.

Patients with ACL, whose etiologic agent is L. guyanensis, showed a better response to treatment with pentamidine isethionate. According to Gadelha et al., the profile with the best response was the one that had a longer period of treatment with pentamidine, consisting of 3 injections with application every 7 days of an injection. Therefore, there is a better response to treatment with more doses.

Finally, studies with homeopathy (OLANDIM et al., 2022), with secondary metabolites of the fungus of the genus Trichoderma (LOPES et al., 2020) and with a focus on nanotechnology (CARVALHO et al., 2019) are in early stages and need further research for clarification.

CONCLUSION

The obstacles related to conventional therapies for the treatment of ACL are evident, especially due to the toxicity of established treatments and the refractoriness associated with the use of some drugs. On the other hand, there are medications that have a curative effect similar to antimonials and amphotericin b deoxycholate, but with fewer established side effects. There is also an approach with the use of reduced doses of pentavalent antimoniate, with a good curative response, with minimization of adverse conditions.

In addition, there are prototypes of adjuvant therapies that may present a significant response in the fight against ACL, but are still in initial conditions. Therefore, it is important to encourage the production of studies that seek to compare the results of the treatment options, in order to evaluate which ones have the best performance in each class of individual, highlighting people over 50 years of age or who have comorbidities associated with cardiovascular, hepatic and renal conditions.

REFERENCES

1. Añez, N., et al. (2018). Successful treatment against American cutaneous leishmaniasis by intralesional infiltration of a generic antimonial compound-lidocaine combination. A follow-up study. *Acta Tropica, 185*, 261-266. doi:10.1016/j.actatropica.2018.06.001.

2. Aronson, N., et al. (2016). Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clinical Infectious Diseases, 63*(12), e202-e264. doi:10.1093/cid/ciw670.

3. Barroso, D. H., et al. (2022). Meglumine antimoniate was associated with a higher cure rate than liposomal amphotericin B in the treatment of American tegumentary leishmaniasis: A retrospective cohort study from a Leishmania braziliensis-endemic area. *Frontiers in Cellular and Infection Microbiology, 12*, 993338. doi:10.3389/fcimb.2022.993338.

4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. (2017). *Manual de vigilância da leishmaniose tegumentar*. Brasília: Ministério da Saúde. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/manual_vigilancia_leishmaniose_tegumentar.pdf.

5. Cataldo, J. I., et al. (2018). Favorable responses to treatment with 5 mg Sbv/kg/day meglumine antimoniate in patients with American tegumentary leishmaniasis acquired in different Brazilian regions. *Revista da Sociedade Brasileira de Medicina Tropical, 51*(6), 769-780. doi:10.1590/0037-8682-0464-2017.

6. Gadelha, E. P. N., et al. (2018). An open-label randomized clinical trial comparing the safety and effectiveness of one, two or three weekly pentamidine isethionate doses (seven milligrams per kilogram) in the treatment of cutaneous leishmaniasis in the Amazon Region. *PLOS Neglected Tropical Diseases, 12*(10), e0006850. doi:10.1371/journal.pntd.0006850.

7. Lopes, D. S., et al. (2020). Ethanolic Extract of the Fungus Trichoderma asperelloides Induces Ultrastructural Effects and Death on Leishmania amazonensis. *Frontiers in Cellular and Infection Microbiology, 10*, 306. doi:10.3389/fcimb.2020.00306.

8. Martins, S. S., et al. (2021). A Pilot Randomized Clinical Trial: Oral Miltefosine and Pentavalent Antimonials Associated With Pentoxifylline for the Treatment of American Tegumentary Leishmaniasis. *Frontiers in Cellular and Infection Microbiology, 11*, 700323. doi:10.3389/fcimb.2021.700323.

9. Olandim, A. A. C. C., et al. (2022). Leishmaniose Tegumentar Americana: relato de casos de sucesso com tratamento exclusivamente homeopático. *Revista Homeopatia (São Paulo),* 5–11. Disponível em: https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1381648.

10. Pinart, M., et al. (2020). Interventions for American cutaneous and mucocutaneous leishmaniasis. *The Cochrane Database of Systematic Reviews, 8*(8), CD004834. doi:10.1002/14651858.cd004834.pub3.