

Letter

Mucosal leishmaniasis: urgent need for more research

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Leishmaniasis is one of the most neglected tropical diseases and is strongly associated with poverty¹. Mucocutaneous or mucosal leishmaniasis (ML) is an important and devastating form of the disease that usually develops after the primary cutaneous lesion or as a primary manifestation. ML pathogenesis is related to parasite and host factors, in particular, the host's immunological response². ML may present many distinct manifestations, from lesions limited to the nasal and oral cavity (mild stage), involvement of the epiglottis (moderate stage), to the involvement of the vocal cords, subglottic region, trachea, and even bronchi (severe stage). In some cases, mucosal involvement may lead to the destruction of the face structure, and respiratory failure associated with death^{2,3}. The disfigurement related to ML often leads to economic losses, severe stigmatization, and may cause psychological disorders as well as restrict social participation of the individual⁴. Over 90% of ML cases occur in Bolivia, Brazil, Ethiopia, and Peru. In the American region, ML represents around 4% of tegumentary leishmaniasis cases⁵; however, in some countries this proportion can be even higher. In 2013, Paraguay and Argentina reported 37% and 14.4% of ML cases, respectively⁶. In 2014, 1,953 ML cases were reported in the American region, with 1,016 in Brazil alone⁵.

Current treatment recommendations for ML are: 1) pentavalent antimonials (Sb^v); 2) Sb^v in combination with oral pentoxifylline, as a first line treatment; 3) liposomal amphotericin B (L-AmB) in case of therapeutic failure or special situations; 4) amphotericin B deoxycholate (AB); 5) pentamidine isethionate (PT); or 6) miltefosine (MF)⁷. All of these drugs have limitations in terms of toxicity, variable efficacy, and inconvenient treatment schedules (e.g. long administration times and parenteral administration). Moreover, the treatment outcome also depends on the stage of the disease.

Higher cure rates are obtained when the lesions are limited to the nose and mouth (mild manifestation)⁸.

Cure rates of Sb^v range from 30-100%, depending on the geographical area and the severity of the disease⁸. It has been shown in a series of patients in Peru that the cure rate was 40.9% in the moderate stage and 7.1% in the severe stage³ indicating that Sb^v should not be recommended as a therapeutic option for these cases. Given the variable cure rates reported with antimonial drugs and its well-known toxicity, its use for the treatment of ML is limited.

Although the quality of the evidence is weak, the combination of oral pentoxifylline and Sb^v reduced the relapse rate and accelerated cure compared to Sb^v alone⁸. A recent study of 205 patients with ML in Lima, Peru has shown an increase in the cure rate of 61% in the group treated with Sb^v alone versus 79% (p=0.011) in the group treated with Sb^v plus pentoxifylline⁵.

Amphotericin B deoxycholate (very low quality of evidence) is effective in more than 90% of patients and it also cures cases refractory to Sb^v². However, the total required dose has not yet been established. In Brazil and Peru, most patients achieved cure with a cumulative dose of 25mg (approximately 42 doses). In addition, the toxicity of AB, mainly related to kidney failure, is a limiting factor for its use.

Limited data are available on the use of PT. It showed excellent results in 27 patients with moderate to high grade lesions in Brazil⁹. Nevertheless, the quality of evidence is very low, and its use is limited by its toxicity, mainly pancreatic, that requires careful monitoring.

The only oral option, MF was shown to be efficacious in one randomized clinical trial conducted in Bolivia¹⁰. However, therapeutic failure was observed in 17% of patients with a mild manifestation of the disease and 42% with a severe stage, characterized by the involvement of the palate, pharynx, and larynx¹¹. Despite the small number of patients, the Peruvian study was not very positive, with only one out of 10 patients cured³. In addition, MF may cause gastrointestinal side-effects and its teratogenicity is a limiting factor for women.

Some studies using L-AmB have been published; however, these studies were not controlled and included a limited number

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of patients, hence it is difficult to draw any conclusions regarding the most effective dose/regimen. According to the World Health Organization, a dose of 2-3mg/kg for at least 20 days provides a cure rate of 80-90%⁸. Three published case series conducted in Brazil, including a total of 15 patients with ML caused by *Leishmania braziliensis* who received L-AmB 2-3mg/kg/day until a total dose of 40-50mg/kg, achieved response rates of 83.3-100%¹². In a retrospective study conducted in Brazil, a 93.1% cure rate was achieved in 29 patients who received dose ranges of L-AmB of 18.2-55.2mg/kg². A recent unpublished clinical trial in Peru showed a cure rate of 90% in severe cases treated with 3mg/kg/day for 21 days³.

Current efforts to identify new treatments for leishmaniasis are largely focused on visceral leishmaniasis and to a lesser extent on cutaneous leishmaniasis; there are currently no efforts to identify new treatment options for patients with ML, despite the difficulties and limitations of using current treatment options and the severe complications of the disease, which include stigma, mutilation, and even death.

Even though progress has been made in the identification and preclinical development of compounds against *Leishmania* species, in a short period of time (5-7 years), currently available treatments will probably represent almost the entire therapeutic arsenal for the coming years. Hence, there is a great need to explore ways to optimize the use of existing tools and generate solid evidence in order to improve the treatment of ML.

Acknowledging these constraints, the 4th Leishmaniasis Research Network (redeLEISH) meeting proposed a special session on *Mucosal Leishmaniasis* which took place during the WorldLeish-6 Congress in Toledo on May 16, 2017.

The investigators present at the meeting agreed that there is an urgent need for:

- More incentives and funding to conduct well-structured clinical trials with L- AmB or other drugs and combinations of treatments in order to develop more effective and safer treatments for ML and to generate robust evidence for the adoption of new treatment recommendations.
- Encouraging investment to develop new rapid and non-invasive diagnostic tests.
- Raising awareness of the social problem of ML and engaging governments to support scientific research related to public health and ML.
- The promotion of better access to early diagnostic tools and treatment for patients with ML.

Thus, this proposal was launched during the ML session at the 4th meeting of redeLEISH at the WorldLeish-6 Congress and approved by the scientific community and social movements at the 53rd meeting of the Brazilian Society of Tropical Medicine. More people have embraced the cause and today we count 137 signatures. Virtual signatures are collected at the following link: <https://www.abaixoassinado.org/abaixoassinados/37330>.

In view of the current situation and the limited options available to treat ML, the participants of the meeting expressed their support to increase efforts to improve treatment of ML in line with the above statement.

Conflict of interest

The authors declare that they have no conflicts of interest.

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