

## Treatment of cutaneous leishmaniasis with intralesional meglumine antimoniate at a primary care unit in Brazil

*Tratamento da leishmaniose cutânea com antimoniato de meglumina intralesional em uma unidade básica de saúde*

Maria Cristina de Oliveira Duque<sup>1</sup>, José Jayme Quintão<sup>2</sup>, Luciene Fernandes Gonçalves<sup>3</sup>, Cléria Gomes<sup>4</sup>, Hugo Leonardo de Almeida<sup>5</sup>, Eunice Silva Silveira<sup>6</sup>, Adriene Paiva Araújo<sup>7</sup>, Marcelo Rosandiski Lyra<sup>8</sup>, Maria Inês Fernandes Pimentel<sup>9</sup>, Érica de Camargo Ferreira e Vasconcellos<sup>10</sup>, Maurício Naoto Sheki<sup>11</sup>, Mauro Celio de Almeida Marzochi<sup>12</sup>, Claudia Maria Valet-Rosalino<sup>13</sup>, Armando de Oliveira Schubach<sup>14</sup>

### Resumo

O antimoniato de meglumina (AM) intralesional (IL), por via subcutânea, é recomendado para o tratamento da leishmaniose cutânea (LC). A frequente falta de recursos nas unidades básicas de saúde costuma dificultar o monitoramento de efeitos adversos, o manuseio de comorbidades e o uso de medicamentos de segunda linha. São relatados seis casos de LC tratados com AM IL (devido a contraindicações ou efeitos adversos ao AM por via sistêmica) em uma unidade básica de saúde. As infiltrações com AM IL foram administradas quinzenalmente até a epitelização das lesões cutâneas, que ocorreu em todos os casos. Eczema local de intensidade moderada foi o único efeito adverso observado em um paciente. O AM IL se revelou um tratamento simples, eficiente e seguro para LC.

240

1. Médica Dermatologista, Mestre em Pesquisa Clínica. Instituto Nacional de Infectologia Evandro Chagas. Fiocruz
2. Médico Cardiologista. Secretaria Municipal de Saúde, Timóteo, Minas Gerais
3. Médica Otorrinolaringologista. Secretaria Municipal de Saúde, Timóteo, Minas Gerais
4. Bioquímica. Secretaria Municipal de Saúde, Timóteo, Minas Gerais
5. Farmacêutico. Secretaria Municipal de Saúde, Timóteo, Minas Gerais
6. Enfermeira. Secretaria Municipal de Saúde, Timóteo, Minas Gerais
7. Assistente Social. Secretaria Municipal de Saúde, Timóteo, Minas Gerais
8. Médico Dermatologista. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz
9. Médica Dermatologista. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz
10. Médica Dermatologista. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz
11. Médica Infectologista. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz
12. Médico, Parasitologista, PhD. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz
13. Médica Otorrinolaringologista. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz
14. Médico. Instituto Nacional de Infectologia Evandro Chagas. Laboratório de Pesquisa Clínica e Vigilância em Leishmanioses. Fiocruz

E-mail do primeiro autor: [dermato2@gmail.com](mailto:dermato2@gmail.com)

Recebido em 14/08/2017

Aceito em 16/08/2017

**Palavras-chaves:** Leishmaniose cutânea, tratamento farmacológico, antimônio

### **Abstract**

Intralesional (IL) meglumine antimoniate (MA) is recommended for cutaneous leishmaniasis (CL) treatment. The lack of resources in primary health care units usually hinders monitoring of adverse events, handling of comorbidities, and use of second-line drugs. We report six CL patients treated with subcutaneous IL MA (due to contraindication or adverse effects to systemic MA) in a primary health care unit. The procedure was repeated every two weeks up to the epithelialization of the lesion. All treated lesions epithelialized. The only adverse effect was moderate local eczema. IL MA treatment seems to be a simple, efficient and safe therapy for CL.

**Keywords:** Leishmaniasis, Cutaneous; meglumine antimoniate; injections, intralesional

### **Introduction**

For decades, World Health Organization (WHO) has recommended the use of systemic pentavalent antimonials for the treatment of CL. However, intralesional injections of meglumine antimoniate (IL MA) is a long-accepted modality for the treatment of cutaneous leishmaniasis (CL) in the Old World.<sup>1</sup> In 2010, a committee of experts on leishmaniasis recognized that CL is not a life-threatening condition, that severe complications are rare, and that the evolution to the mucosal form is limited to a few cases. WHO has therefore recommended that treatment for CL should not induce life-threatening complications, and local and safer treatments should be preferred.<sup>1</sup> In 2013, the Pan American Health Organization (PAHO) also recommended IL MA treatment for CL.<sup>2</sup> PAHO recommendations emphasize the need to incorporate scientific data presented by

each country into national control programs, and to consider variables such as the patient access to health services.<sup>2</sup>

In the New World, IL MA treatment was sometimes rejected in the past because of the possible risk of the development of mucosal leishmaniasis.<sup>1,3</sup> Despite that, based on successful reports of intralesional treatment in the Old World, IL MA treatment was introduced at the National Institute of Infectious Diseases (NIID), Oswaldo Cruz Foundation (Fiocruz), in Rio de Janeiro city, in the 1980s. We initially employed IL MA for the treatment of patients who could not receive systemic treatment with this medication. We subsequently extended its use to a greater number of patients who were followed up for a period up to 10 years without the development of mucosal lesions.<sup>4-6</sup>

Intralesional meglumine antimoniate – relato de caso

We recently demonstrated the standard method of IL MA treatment for CL developed in Rio de Janeiro.<sup>7</sup> Briefly, MA is injected subcutaneously with a volume necessary to infiltrate the base of the lesion, leaving it raised and swollen (generally 5-20mL). There is no restriction for patients with more than one cutaneous lesion, of any size or location. However, anatomical peculiarities such as the presence of vessels, nerves and noble structures must be considered. A favorable therapeutic response after 1-3 IL MA infiltrations is expected. If we do not achieve total epithelialization of the lesions approximately two weeks after the first IL MA infiltration, a second one is indicated. When total epithelialization is not observed approximately one month after the beginning of the treatment, a third and last infiltration is indicated. The patient is then reexamined every two weeks, and progression towards epithelialization is observed for as many as 120 days. In the months following epithelialization, we expect the successive disappearance of the crusts, scales, infiltration, and erythema to complete the cure process. Treatment is restarted using the same protocol if continuous progression to complete healing does not occur.<sup>6-7</sup>

The Brazilian Ministry of Health added in 2017 the IL MA treatment as a recommendation for CL and adopted the technique standardized at the NIID, with

minor adaptations to PAHO recommendations. Accordingly, the use of this technique was enabled in single lesions, up to 3 cm in the greatest diameter, and at any location except head and periarticular regions.<sup>2,7-8</sup>

In Brazil, meglumine antimoniate 1.5 g (Sanofi Aventis Farmacêutica Ltda, São Paulo, Brazil) is presented in ampoules of 5 mL containing 405 mg Sb<sup>5+</sup>, and distributed free of charge within the public health network. The effectiveness of systemic treatment with MA is usually around 70%.<sup>6</sup> Clinical, electrocardiographic, and laboratory adverse effects of varying intensities are common and require close monitoring during administration.<sup>1,6</sup> Occasionally, treatment should be discontinued due to electrocardiographic changes or renal, hepatic, or pancreatic toxicity. The second-choice drugs, amphotericin B and pentamidine, are indicated for patients over 50 years old, with poor response or contraindication to systemic MA. These drugs are also parenteral and similarly toxic.<sup>8</sup> Patients with CL are ordinarily treated at primary health care units where the lack of resources hinders the handling of comorbidities, the monitoring of adverse events, and the use of second-line drugs. In these field conditions, simpler and safer treatment schemes to CL, such as IL MA, are desirable. However, there is lack of reports of

treatments with IL MA in primary health care units.

We report the successful treatment with IL MA in six patients with CL, in a primary health care unit, due to contraindication or adverse effects to systemic treatment with MA.

### Case Report

Six patients (three men and three women), aged between 23 and 77 years, were treated with IL MA in a primary care unit in Timóteo municipality, Minas Gerais State, Brazil, between December, 2011 and October, 2015.

Patients presented with one or two cutaneous lesions (time of disease progression one to four months), measuring between 0.5 and 3.5 cm. In two patients, lesions were located in the head (**Table 1**). In all lesions, the direct smear examination was positive for *Leishmania* amastigotes. Five of the patients presented a positive result in Montenegro skin test, with a diameter equal or superior to 10 mm, and one presented a negative result.

Two elderly patients had a contraindication to systemic treatment with MA. The other four patients were treated without success, up to 4 months before, with systemic MA 10 mg Sb<sup>5+</sup> / kg of body weight / day for 20 days intravenously. These four

patients had a moderate to severe increase in serum amylase or lipase. In addition, two of them were elderly and two refused to repeat treatment with systemic MA (**Table 1**).

The protocol adopted for treatment with IL MA was the same used in Rio de Janeiro.<sup>7</sup> Infiltration of IL MA was performed without anesthesia on five patients, who reported mild to moderate pain. One patient required local anesthesia with 1% lidocaine. Patients received one to four infiltrations with IL MA. No laboratory adverse effects (complete blood count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, lipase, urea, creatinine, glucose and potassium levels in peripheral blood samples) or electrocardiographic changes were observed. One patient presented moderate local eczema, which responded to topical corticotherapy. There was no worsening of baseline levels of amylase or serum lipase. No patient needed to discontinue treatment with IL MA. All six patients were followed from two up to six months after epithelialization of the lesions. All six patients were instructed to return to the primary health care unit in case of worsening of the lesions thereafter, but none returned.

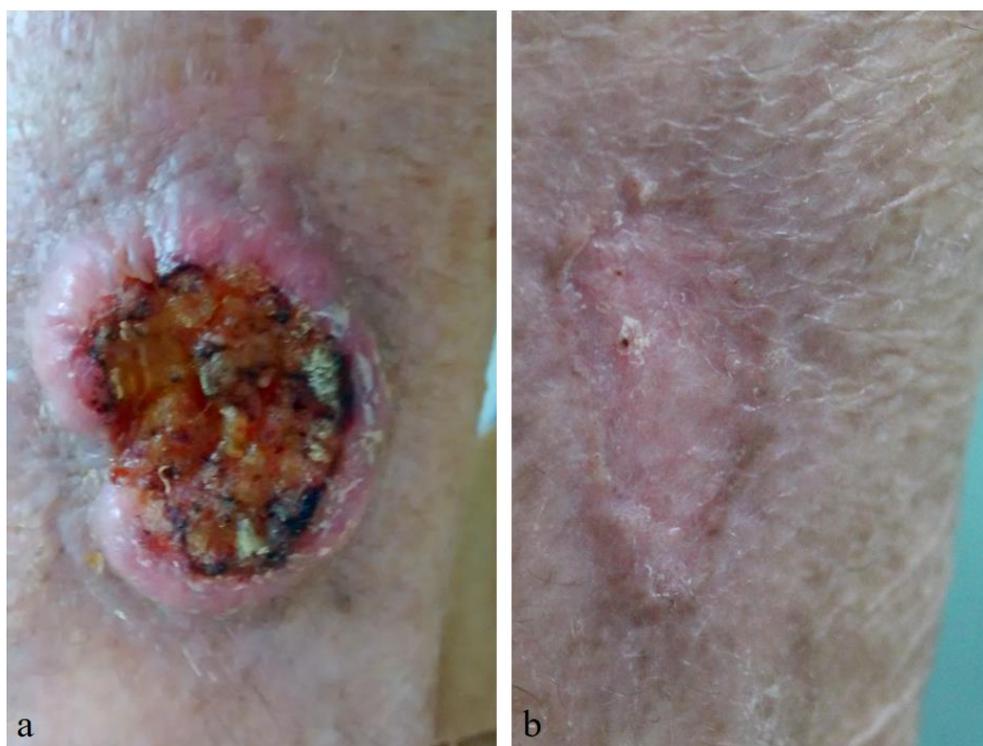
Intralesional meglumine antimoniate – relato de caso

**Table 1** - Demographic, clinical and treatment characteristics of six patients with cutaneous leishmaniasis treated with intralesional meglumine antimoniate at a primary health care unit in the municipality of Timóteo, Minas Gerais State, Brazil (2011-2015)

Gender / age (years)	Body weight (kg)	Number of cutaneous lesions	Larger diameter of lesions (cm)	Location of lesions	Indication for IL MA	Associated factors	Number of IL MA applications	Average volume (mL) per IL MA application	Epitelization time after start IL MA (weeks)
M / 61	77	2	1.5/0.5	head/shoulder	No response to systemic MA	Refused systemic MA retreatment	2	10*	3,5
M / 23	77	2	3.5/2	leg/head	No response to systemic MA	Hyperamylasemia 2,2x ULN	1	5*	2
M / 36	120	1	2	leg	No response to systemic MA	Refused systemic MA retreatment	2	7,5	6
F / 60	60	1	3	lower back	Systemic MA contraindicated	hyperamylasemia 1,5x ULN and hyperlipasemia 3,1x ULN	2	7,5	3
F / 65	58	1	3.5	leg	No response to systemic MA	hyperlipasemia 14,2x ULN + severe myalgia	4	10	5
F / 77	74	1	1.5	leg	Systemic MA contraindicated	hyperamylasemia 1,5x ULN + Refused systemic MA	2	5	4,5

Key: M = male; F = female; MA = meglumine antimoniate; IL = intralesional; Systemic MA = 10mg Sb<sup>5+</sup>/Kg body weight/day for 20 days by intravenous route; ULN = upper limit of normality

\* Average volume infiltrated in both lesions (total)



**Figure 1** - A 65-year-old woman with leg ulcer, 3.5 cm in diameter, with severe hyperlipasemia and myalgia after systemic MA: a) before and b) after 4 infiltrations of intralesional MA

## Discussion

We report six patients successfully treated with IL MA in a primary health care unit. Ordinarily, all of these patients should have been treated in a secondary or tertiary health care unit with second-line drugs (Amphotericin B or Pentamidine), which are difficult to administer and monitor in primary health care units. In addition, in the interior of Brazil, secondary or tertiary care units are usually located at long distances from patients' homes and often in other municipalities. We highlight that, due to the characteristics of their cutaneous lesions (more than one lesion, diameter > 3 cm or

head location), five of these six patients presented contraindications to IL MA according to OPAS or the Brazilian Ministry of Health recommendations.<sup>2,8</sup> However, such characteristics did not hinder epithelization nor did they result in treatment complications. Successful treatment with IL MA in patients with similar characteristics, that would contraindicate IL MA treatment, has been reported in other New World clinical series.<sup>4,5,9-11</sup> This suggests that there is no scientific evidence to support such contraindications for IL MA treatment for New World CL.

Hyperlipasemia and / or hyperamylasemia were involved in the indication of treatment with IL MA in four out of the six reported patients. We highlight that in none of these cases did serum amylase or lipase levels worsen with IL AM. In a clinical trial,<sup>12-13</sup> the pancreatic toxicity by systemic MA was more frequent with 20 mg Sb<sup>5+</sup> / kg of body weight / day compared to 5 mg mg Sb<sup>5+</sup> / kg of body weight / day.

Five out of the six patients treated with IL MA reported only mild to moderate discomfort without the need for local anesthesia. Other authors also reported mild to moderate local discomfort with IL AM.<sup>4,5,9-11,14</sup> However, it was reported that IL MA may cause relevant discomfort.<sup>1</sup>

We observed local eczema that progressed from mild to moderate after two infiltrations with IL MA in a patient who had not received previous treatment with systemic AM. Local eczema with varying levels of severity in patients subjected or not to prior systemic treatment with MA has been described.<sup>10,15</sup>

In the present study, it was not possible to follow the patients up longer than six months after the epithelialization of the lesions. It is common for patients with CL to abandon follow-up after wound healing, due to financial and transportation difficulties. However, we expected them to return if the lesions worsened, as it occurred after the

therapeutic failure with systemic MA. In previous studies conducted at NIID, IL MA treated patients were followed up to ten years, with no recurrence or development of mucosal lesions.<sup>4-5,11</sup>

## Conclusions

The series of cases here reported suggests that treatment of CL with IL MA is simple, efficient and safe, even if the lesions are larger than 3 cm, if the patient presents with more than one lesion, or if they are in the head. Furthermore, this treatment protocol may be used in primary health care units for the treatment of patients with contraindication or intolerance to systemic MA.

The here described series of cases have led to an ongoing study at this same primary health care unit, with a larger number of patients, and one year of follow-up, including the evaluation of mucous membranes, thereby contributing to the establishment of IL MA as a suitable treatment for CL in the New World.

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Intralesional meglumine antimoniate – relato de caso

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