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Comparison between systemic and intralesional meglumine antimoniate therapy in a primary health care unit

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ABSTRACT

Cutaneous leishmaniasis (CL) is not a life-threatening condition. However, its treatment can cause serious adverse effects and may sometimes lead to death. Recently, safer local treatments have been included among therapies acceptable to New World CL cases, but the use of intralesional meglumine antimoniate (IL-MA) is recommended to be performed in reference centers, for patients with single cutaneous lesions < 3 cm in diameter at any location except the head and periarticular regions; the volume of injected MA should not exceed 5 mL. In this study we compared two groups of patients with CL treated with MA in a primary health care unit in Brazil. Patients were treated with systemic MA (n = 76) or IL-MA (n = 30). In the IL-MA group, 93% of patients had one or more of the following lesion characteristics: two or more lesions, lesions > 3 cm in diameter, lesions located in the head or in periarticular regions, or had been administered IL-MA volumes > 5 mL. Patients responded well (68.4% and 66.7% for the MA and IL-MA groups, respectively). When a second cycle of treatment was necessary, the responses were 72.4% and 90%, respectively. There were no significant differences between groups. In the IL-MA group, 43% had mild to moderate adverse effects, without needing treatment discontinuation. Results suggest that the treatment of CL lesions with IL-MA is simple, efficient, and safe.

1. Introduction

Cutaneous leishmaniasis is an endemic zoonosis transmitted through the bite of infected sandflies. Approximately two-thirds of the global incidence is concentrated in six countries, including Brazil (WHO, 2016).

Systemic antimonial therapy has been recommended by the World Health Organization for the treatment of cutaneous leishmaniasis for decades (WHO, 1990, 2010). Meglumine antimoniate (MA) is an antimonial drug available in Brazil for the treatment of both the cutaneous (CL) and mucosal (ML) clinical forms of American tegumentary leishmaniasis (ATL). The recommended dose for the treatment of ATL varies

Abbreviations: ATL, American tegumentary leishmaniasis; CL, cutaneous leishmaniasis; ML, mucosal leishmaniasis; IL, intralesional; MA, meglumine antimoniate; IL-MA, intralesional meglumine antimoniate; NIID, National Institute of Infectious Diseases; PAHO, Pan American Health Organization; WHO, World Health Organization

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from 10, to 20 mg Sb^{5+}/kg/day, for 20 to 30 days, via intramuscular or intravenous administration, with efficacy around 70% (Brasil MS - Ministério da Saúde et al., 2017; Tuon et al., 2008). This treatment often has to be temporarily or permanently discontinued due to serious adverse effects, and may occasionally lead to death. Electrocardiograms, and renal, hepatic, and pancreatic functions should be monitored (Brasil MS - Ministério da Saúde et al., 2017; Oliveira et al., 2011; WHO, 2010). When necessary, second-line drugs like amphotericin B or pentamidine isethionate are used via parenteral administration, however these are equally toxic (Brasil MS - Ministério da Saúde et al., 2017). In Brazil, 20,000 cases of ATL are reported annually, with lethality around 0.45% (Brahim et al., 2017; Brasil MS - Ministério da Saúde et al., 2017).

In 2010, the World Health Organization (WHO) acknowledged that CL is not a life-threatening condition and that serious complications are rare, proposing that the use of safer and less toxic local treatments should be evaluated (WHO, 2010). Intralesional (IL) pentavalent antimonials have been used for decades for the treatment of CL in the Old World, where ML is not common (WHO, 1990, 2010). However, in the Americas, the belief that local treatments would be a risk for the development of ML delayed its use (Blum et al., 2012; Monge-Maillo et al., 2013). Despite this, the intralesional treatment with meglumine antimoniate (IL-MA) was introduced in Rio de Janeiro in the 1980s (Oliveira-Neto et al., 1997). Subsequently, IL-MA was used in a group of patients with contraindications to the use of systemic MA (Vasconcellos et al., 2012). These patients were followed-up for up to 14 years without developing ML (Oliveira-Neto et al., 1997; Vasconcellos et al., 2012). The method of IL-MA treatment developed and used at the Evandro Chagas National Institute of Infectious Diseases (NIID) from the 1980′s onwards can be briefly described thusly: MA is injected subcutaneously with a volume necessary to infiltrate the base of the lesion, leaving it raised and swollen (generally 5–20 mL). There is no restriction for patients with more than one cutaneous lesion, of any size or location (de Oliveira Duque et al., 2016, 2017; Oliveira-Neto et al., 1997; Pimentel et al., 2017; Schubach and Conceição-Silva, 2014; Vasconcellos et al., 2012).

In 2013, the Pan American Health Organization (PAHO) recommended to treat IL with 1–5 intradermal infiltrations of 1–5 mL every 3–7 days. The IL treatment was recommended for patients with single lesions, nursing mothers, and patients with contraindication to systemic treatment (nephropathies, hepatopathies, cardiopathies), and contraindicated for lesions larger than 3 cm in diameter, or those located in the head or periarticular areas, and for immunosuppressed patients (OPAS - Organización Panamericana de la Salud, 2013). For national control programs, it is necessary to include the evidence available in each country. Additionally, it was recommended that the IL treatment should be limited to reference centers to produce evidence based on clinical trial data (OPAS - Organización Panamericana de la Salud, 2013).

The Brazilian Ministry of Health (Brasil MS - Ministério da Saúde et al., 2017) added IL-MA treatment as a recommendation for CL, and adopted the technique as standardized at the NIID (de Oliveira Duque et al., 2016), with minor adaptations to the PAHO (2013) recommendations. Briefly, IL treatment should be administered by trained professionals, using 1–3 subcutaneous infiltrations of approximately 5 mL, at 15-day intervals. This technique is applicable in single lesions, up to 3 cm in the greatest diameter, at any location except the head and periarticular regions (Brasil MS - Ministério da Saúde et al., 2017).

Although the experience with this therapeutic modality is still limited to reference centers (Añez et al., 2018; Oliveira-Neto et al., 1997; Pimentel et al., 2017; Ramalho et al., 2018; da Silva et al., 2016; Soto et al., 2013, 2016; Vasconcellos et al., 2012), in the Americas (both in Bolivia), only two uncontrolled clinical trials using the standard treatment regimen (10–20 mg Sb^{5+}/kg/day) were published for *Leishmania braziliensis* (Soto et al., 2013, 2016). These trials (Soto et al., 2013, 2016) used the intradermal route, and included patients with a single lesion, with the major diameter $\leq$ 30 mm. The lesion area was calculated in mm^2 through multiplying the major diameter of the lesion by the minor diameter. The volume needed to infiltrate the lesions was standardized at 0.008 µL MA (650 µg Sb^{5+})/mm^2 of lesion area. Each intervention group comprised 30 patients. For comparison matters, the cure rates of 80–83% of Rio de Janeiro were used (Oliveira-Neto et al., 1997; Vasconcellos et al., 2012).

Restrictions relating to the number, size and location of the lesions may limit the use of IL-MA and second-choice drugs may be necessary (Brasil MS - Ministério da Saúde et al., 2017). Recently, we reported 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 (de Oliveira Duque et al., 2017). We highlight that, due to the characteristics of their cutaneous lesions, five of these six patients presented contraindications to IL-MA according to current recommendations (Brasil MS - Ministério da Saúde et al., 2017; OPAS - Organización Panamericana de la Salud, 2013). This led us to compare a larger number of CL patients treated with IL-MA, with a group of patients treated with systemic MA in the same primary care unit, in the previous contiguous period.

2. Methods

2.1. Study design

This is a comparative study between two groups of patients with CL, treated by the same physician, with IL or systemic MA, in consecutive periods from July 2006, to July 2016 in a primary health care unit in the city of Timóteo, in Minas Gerais state, Brazil. In all cases, the diagnosis was confirmed by finding amastigote forms in direct examination, or positivity in the intradermal Montenegro test.

The primary outcome was clinical cure at 360 days, of follow-up in the per-protocol populations, defined as: epithelialization within 120 days, scarring within 360 days, no clinical worsening or relapse of cutaneous lesions, and no appearance of mucosal lesions. Epithelialization was defined as complete wound closure without any erosion. Scarring was defined as the presence of the following criteria: complete epithelialization and absence of crusts, desquamation, infiltration, or erythema (Saheki et al., 2017).

2.2. Retrospective study

The medical records of all 76 patients with CL treated from July 2006 to November 2015 with MA 10–20 mg Sb^{5+}/kg/day for 20 days via intravenous or intramuscular were evaluated. Forty-six (60.5%) patients were diagnosed by direct positive exam for amastigotes and 30 (30.5%) by clinical-epidemiological criteria associated with a positive Montenegro skin test. In the cases with clinical worsening or without progression to scarring, the treatment followed the same therapeutic scheme. It was not possible to evaluate adverse effects based on the information in the medical records.

2.3. Prospective study

Between December 2015 and July 2016, all patients diagnosed with CL were invited to participate in the prospective study without restrictions on number, location, or size of the lesions. From the 36 patients diagnosed in the period, 30 agreed to participate in the study and signed the informed consent form. All the patients included in this group had positive direct examination for amastigote forms. The absence of mucosal lesions was confirmed by fibroscopic examination of the upper aerodigestive tract. Before treatment, baseline status was confirmed via clinical exams, electrocardiogram and laboratory tests (complete blood count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, lipase,

urea, creatinine, glucose and potassium levels in peripheral blood samples).

After local anesthesia with 1% lidocaine, MA was injected subcutaneously with either a 22 G or 23 G needle in syringes with threaded connection to the needle, with a volume necessary to infiltrate the base of the lesion, leaving it raised and swollen. Patients received three infiltrations with IL-MA in 15-day intervals (Brasil MS - Ministério da Saúde et al., 2017; de Oliveira Duque et al., 2016). In the cases either with clinical worsening, or without progression to scarring, the treatment included 1 or 2 additional IL-MA infiltrations (Brasil MS - Ministério da Saúde et al., 2017; de Oliveira Duque et al., 2016). After lesion epithelialization, the patients were followed up every 3 months for 1 year, when they underwent a dermatological examination and another fibroscopic examination of the upper aerodigestive tract mucosa.

After each IL-MA, patients were asked to rate the pain sensation (including the anesthesia procedure) according to the following scale: 0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Unbearable. The adapted Wong-Baker face scale was used for pediatric patients (Carvalho and Kowacs, 2006).

The patients were monitored for clinical adverse effects during treatment. Laboratory and electrocardiographic effects were monitored on day 30 after the third IL-MA infiltration. Adverse events were graded using a toxicity grading scale adapted from the Division of AIDS Table for Grading of Severity of Adult and Pediatric Adverse Events (Division of AIDS, 2004).

2.4. Ethics

This study was approved by the Research Ethics Committee of NIID (code CAAE 51187115.4.0000.5262) and it is in accordance with the Helsinki Declaration (1964, amended 2008). All prospective study patients signed the informed consent form.

2.5. Statistical analysis

Data were analyzed using Statistical Package for Social Science for Windows (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). The simple frequencies of the categorical variables were described, as well as the summary measures, mean ± standard deviation (SD), median, minimum, and maximum of the continuous variables. The association between categorical variables was verified by Pearson's chi-squared test. The normality of the continuous variables was verified by the Shapiro-Wilk test, at a 5% significance level. The Mann-Whitney test was used to compare the median of non-parametric variables, whereas the *t*-test was used to compare the means of the parametric variable. P-values < 0.05 indicated significant differences

3. Results

The comparison between the main clinical characteristics and the systemic or IL therapeutic response to MA for the 106 patients treated between July 2006 and July 2016 is shown in Table 1 and Fig. 1. Of the 30 patients diagnosed by clinical-epidemiological criteria associated with a positive Montenegro skin test in the retrospective group, 23 (76.7%) responded adequately to systemic treatment and 7 (23.3%) abandoned treatment and were excluded from the analysis. Three patients showed unfavorable therapeutic response after 1–5 IL-MA infiltrations. One responded to systemic treatment with MA 5 mg Sb^{5+}/kg/day in three series of 10 days, with 10-day intervals after each series; a 64-year-old patient responded to liposomal amphotericin B, and the other was lost to follow-up.

Seventeen (57%) patients treated with IL-MA did not present any adverse effects, while 13 (43%) showed one to three clinical, laboratory or electrocardiographic adverse effects, of mild to moderate intensity, without interrupting the treatment, and reversible after completing treatment (Table 2).

Twenty-seven patients responded well to IL-MA treatment; their lesions remained healed one year after the end of treatment. The 22 patients who underwent fibroscopic examination of the upper aerodigestive tract mucosa showed no mucosal lesions.

4. Discussion

Historical comparative group study design has limitations. This study analyzed two groups of patients with CL treated by the same physician, in the same primary health care unit, in contiguous time periods, to compare therapeutic responses to systemic MA and IL-MA treatments. It is possible that, in 10 years, some changes have occurred in the characteristics of both the patients and the parasites. For example, the sensitivity of the parasite to MA may have changed over time. However, if such a change had occurred in the region, we should have found a decreased sensitivity to IL-MA compared to the systemic MA used in the previous period, which was not observed. The unexpected occurrence of a CL outbreak in the region in 2016 allowed the inclusion of a proportionally high number of patients in the IL-MA treated group.

Although clinical trials are recommended to provide evidence for IL-MA treatment (Olliaro et al., 2013, 2018; OPAS - Organización Panamericana de la Salud, 2013), we found only two open, uncontrolled clinical trials with the standard treatment (Soto et al., 2013, 2016).

Another question would be whether treatments performed for long periods could discourage patients from continuing treatments. Only one patient (3.3%) discontinued treatment in the IL-MA group, while 17 (22.4%) abandoned the 20 day standard MA treatment. Abandonment of the treatment by patients has not been a problem with treatments with IL-MA or 5 mg Sb^{5+}/kg/day of MA by systemic route (Brahim et al., 2017; Cataldo et al., 2018). A possible explanation for adherence to treatments with IL-MA or MA 5 mg Sb^{5+}/kg/day systemically would be its efficacy and the patients' good tolerance to treatment. In the case of IL-MA, we could add the reduced number of injections and attendances to the health service (for example, 3 visits over 30 days).

Recent evidence suggests that spontaneous healing is a relatively rare event in CL, mostly when caused by *L. (V.) braziliensis* (Cota et al., 2016; Oliveira-Ribeiro et al., 2017), which is predominant in Brazil outside the Amazon rainforest (Brasil MS - Ministério da Saúde et al., 2017). Clinical observations suggest that the risk of progression to the mucosal form is low (Blum et al., 2012; Oliveira-Ribeiro et al., 2017; WHO, 2010). IL-MA studies in Mérida and Trujillo (Venezuela) and in Rio de Janeiro (Brazil) included long patient follow-ups without developing ML (Añez et al., 2018; Oliveira-Neto et al., 1997; Vasconcellos et al., 2012). Between 2001 and 2013, 777 patients with ATL were treated at the NIID. Of these, 85.3% were treated with MA following alternative therapeutic regimens, 73.1% were treated with 5 mg Sb^{5+}/kg/day, and 12.2% were treated with IL-MA. Only two (0.25%) of 581 patients treated for CL progressed to ML (Brahim et al., 2017). Other authors suggest that the treatment of single and small lesions with IL-MA reduces the risk of dissemination to the mucosa by directly eliminating the parasites (Pimentel et al., 2017; Soto et al., 2016).

In the present study, 28 of the 30 patients treated did not follow the recommendations for treatment with IL-MA (Brasil MS - Ministério da Saúde et al., 2017; OPAS - Organización Panamericana de la Salud, 2013). Successful treatment with IL-MA in patients with similar characteristics that would contraindicate IL-MA treatment has been reported in other clinical series (Añez et al., 2018; Oliveira-Neto et al., 1997; Pimentel et al., 2017; Ramalho et al., 2018; da Silva et al., 2016; Soto et al., 2013; Vasconcellos et al., 2012). Restrictions relating to the number, size and location of the lesions may limit the use of IL-MA and second-choice drugs may be necessary. However, we found no reports of serious complications justifying such contraindications for treatment with IL-MA for cases of CL in the New World.

Table 1
Comparison of the main clinical characteristics and therapeutic response to systemic or IL-MA treatment in 106 patients treated in a primary health care unit in the city of Timóteo, Minas Gerais state, Brazil, between July 2006 and July 2016.

	Systemic MA (N = 76)	IL-MA (N = 30)	P-value
Period of inclusion	7/2006 to 11/2015	12/2015 to 7/2016	–
% Men/women	59 / 41	60 / 40	0.941
Age in years average (±SD)	34 (±18)	38 (±18)	0.396
Weight in kg median (min - max)	66 (14 - 120)	73 (27 - 100)	**0.032**
Time of lesion evolution in months median (min - max)	2.6 (0.3 - 18)	2.6 (0.5 - 9)	0.255
Number of lesions per patient median (min - max)	1 (1 - 5)	1 (1 - 5)	0.365
% Single lesions / two to five lesions	77 / 23	70 / 30	0.476
% Lower limb lesions[a]	39	55	0.063
% Favorable response after 1st trt	68.4[b]	66.7	0.255
% Favorable response after 2nd trt	72.4[c]	90	0.594
No. of MA doses 1st trt	20 - 30	3	–
No. of MA doses 1st + 2nd trt	40 - 50	4 - 5	–
mL of MA 1st trt median (min - max)	200 (40 - 300)	30 (13 - 89)	< **0.001**
mL of MA 1st + 2nd trt median (min - max)	400 (200 - 575)	42 (32 - 149)	< **0.001**
mg of Sb accumulated in 1st trt median (min - max)	16,200 (3240 - 24,300)	2430 (1053 - 7209)	< **0.001**
mg of Sb accumulated in 1st + 2nd trt median (min - max)	32,400 (16,200 - 46,575)	3402 (2592 - 12,069)	< **0.001**

MA = meglumine antimoniate, IL = intralesional, trt = treatment, SD = standard deviation.
[a] Total: 100 lesions in the Systemic MA group and 49 lesions in the IL-MA group.
[b] Nine cases of treatment abandonment (missing) excluded from the analysis.
[c] Four cases of abandonment and four cases treated with IL (total of 17 cases excluded from the analysis).

In Brazil, ATL treatment usually happens at primary health care units, which are known to have limited resources, and difficulty managing comorbidities and managing and monitoring adverse effects of medications such as amphotericin B and pentamidine isethionate. In addition, in municipalities throughout the country, secondary or tertiary care units are usually located far from patients' homes, and often in other cities, implying impaired access to second-choice treatments. Four patients treated with systemic AM in this study and who presented poor therapeutic response or adverse effects, were successfully treated with IL-MA in the same primary health unit (de Oliveira Duque et al., 2017). Alternatively, one of the failures in the IL-MA group was successfully treated with MA 5 mg Sb^{5+}/kg/day for 10 days in 3 sets at 10-day intervals in the same primary health unit (Cataldo et al., 2018; Vasconcellos et al., 2010). According to the Brazilian recommendations for patients over 50 years of age, the other failure in the IL-MA group was successfully treated with liposomal amphotericin B on hospitalization regimen (Brasil MS - Ministério da Saúde et al., 2017).

We did not use pentamidine isethionate in any patient in the primary healthcare unit where this study was performed. In Brazil, the experience with pentamidine isethionate is almost limited to the Amazon region where the main ATL-causing species is *L. (V.) guyanensis*, which usually responds poorly to MA treatment (Brasil MS - Ministério da Saúde et al., 2017). In a reference center in Rio de Janeiro, pentamidine isethionate is a third-choice drug, used only in cases of contraindication, intolerance or poor response to MA treatment and amphotericin B (deoxycholate or liposomal) (Pimentel et al., 2011; Terceiro et al., 2019). Between 2001 and 2013, pentamidine isethionate was used in only 12 (1.2%) of the 997 treatments performed at that center (Brahim et al., 2017). In Bolivia, IL pentamidine appears to be an attractive alternative for IL-MA in the treatment of CL caused by *L. braziliensis* (Soto et al., 2016).

In Brazil, therapeutic failure is defined as the absence of response to two regular treatment cycles (Brasil MS - Ministério da Saúde et al., 2017). The present study reports no significant difference in the therapeutic response to MA administration, either systemic or IL, considering both single and two treatment cycles. However, the number of sessions, volume of MA, and accumulated Sb dose were up to 10-fold lower with IL-MA (achieving the same result). A systematic review showed that the antimony infiltration efficacy rate is similar to that reported for systemic antimony administration (Brito et al., 2017). In Bolivia, an IL-MA study suggested that extending treatment from three to five injections may improve efficacy from 57% to 73% (Soto et al., 2016). Another study showed that the IL-MA cured 70% of the lesions, while the placebo cure rate was 17%. In that study, the mean intralesionally administered dose (503 mg Sb) was 2% of that which would have been administered intramuscularly (Soto et al., 2013).

Although this study did not assess costs we can say that the amount of MA administered, as well as the need for syringes, needles and time of the patient and the health professionals related to the application of IL-MA, was up to 10 times lower than it would be required with systemic treatment with MA 20 mg Sb^{5+}/Kg/day for 20 days. In addition, with the reduction of adverse effects related to IL-MA treatment, we could also assume a reduction in costs related to the management of adverse effects. Other authors suggest a significantly better benefit / risk benefit with IL-MA compared to standard treatment with systemic MA (Añez et al., 2018; Vega et al., 2007).

We adopted as a cure criterion the continuous progression for epithelialization of the lesions up to 120 days after starting the treatment, with subsequent progression to scarring (Brasil MS - Ministério da Saúde et al., 2017; de Oliveira Duque et al., 2016; Saheki et al., 2017). Currently, it is accepted that final cure should be evaluated through lesion epithelialization and disinfiltration after 6 (Brasil MS - Ministério da Saúde et al., 2017; Olliaro et al., 2013, 2018) or 12 months (Saheki et al., 2017) after initiating treatment. The use of heterogeneous cure criteria made it impossible to compare across different studies (Brito et al., 2017; Oliveira-Neto et al., 1997; da Silva et al., 2016; Soto et al., 2013, 2016; Vasconcellos et al., 2012).

Reversible adverse events of mild to moderate intensity that did not interrupt the treatment were found in 43% of the patients treated with IL-MA. These findings corroborate previous findings (Añez et al., 2018; de Oliveira Duque et al., 2017; Ramalho et al., 2018; Vasconcellos et al., 2012). This study was developed in a primary health care unit where the patients underwent laboratory and electrocardiographic evaluation before and 30 days after treatment, which is corroborated by other authors (Francesconi et al., 2018). A thorough search for clinical, laboratory, and electrocardiographic adverse effects is not fully evident in other studies on IL-MA (Oliveira-Neto et al., 1997; Soto et al., 2013, 2016).

We used the previously described IL-MA treatment technique (de Oliveira Duque et al., 2016). However, there are variations in the IL treatment technique, namely: subcutaneous or intradermal route of administration, needle gauge, volume, daily dose limit, number of IL infiltrations, dose interval, infiltration technique, and use of anesthesia (Brasil MS - Ministério da Saúde et al., 2017; de Oliveira Duque et al.,

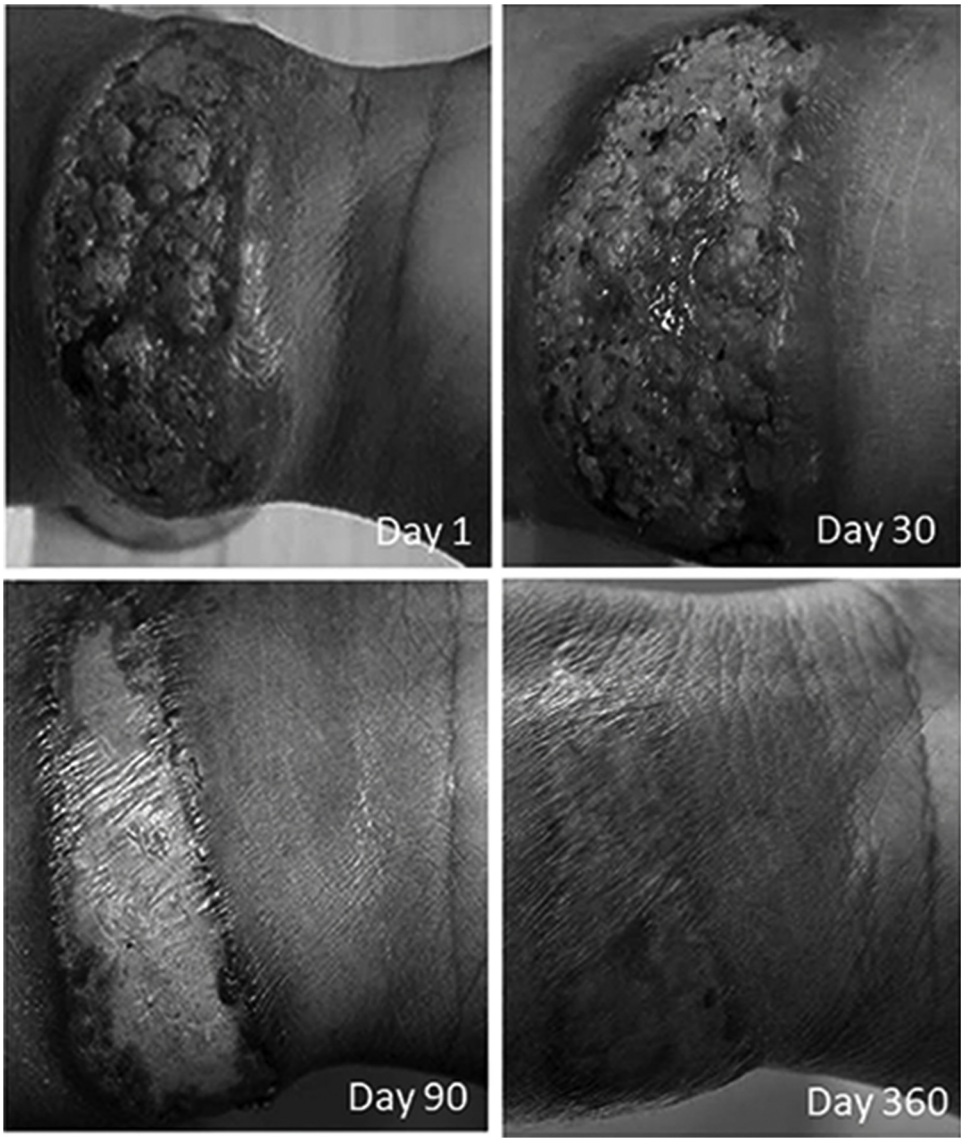

Fig. 1. Clinical evolution of an ulcerated lesion of localized cutaneous leishmaniasis in the wrist treated with three infiltrations of intralesional meglumine antimoniate. Ulcerated lesion before treatment (Day 1); partial improvement before the third infiltration (Day 30); total epithelization with infiltration of lesion edges, two months after the end of treatment (Day 90), scarring one year after starting treatment (Day 360).

2016; OPAS - Organización Panamericana de la Salud, 2013; da Silva et al., 2018). The evidence gathered thus far is insufficient to identify the ideal IL therapeutic regime (Brito et al., 2017).

In this study, IL-MA was injected subcutaneously (de Oliveira Duque et al., 2016; Oliveira-Neto et al., 1997; Vasconcellos et al., 2012), although other authors recommend the intradermal route (OPAS - Organización Panamericana de la Salud, 2013). However, the intradermal infiltration of more than 1.0 mL, as frequently required in intralesional treatment of CL, is difficult, if feasible at all (Pimentel et al., 2017; da Silva et al., 2018). Although the “intradermic” expression was frequently used, the tissues at the base of a CL ulcer are more probably deep dermis and hypodermis, so the infiltration under the base of such ulcer is rather “subcutaneous” (da Silva et al., 2018).

Different authors suggest that the volume of MA should be enough to infiltrate and swell the base of the lesion (Brasil MS - Ministério da Saúde et al., 2017; de Oliveira Duque et al., 2016; da Silva et al., 2018). Some authors standardized the injected volume at 0.008 µL MA/ mm^2 of lesion area (Soto et al., 2013, 2016). This volume is based on the mean amount of MA effectively infiltrated in lesions with different areas. In order to determine the area of the lesions, necessary for calculating the dose of IL-MA, these authors used the formula of the rectangle (larger diameter multiplied by the smaller diameter) easier to execute than the simplified ellipse formula (major diameter / 2 × minor diameter / 2 × π), as suggested by other authors (Ampuero-Vela et al., 2008; Oliveira-Neto et al., 1996). Curiously, although the ellipse formula is geometrically more adequate to calculate the area of CL lesions, the rectangle formula seems more appropriate for calculating the dose of IL-MA, since the calculated area includes both the ulcer and part of the infiltration around them. The use of formulas to calculate the area of CL lesions and the dosage of MA (both systemically and IL) are not so simple. It's easy to make mistakes. Therefore, we prefer to abolish the use of calculi to determine an exact dose for IL-MA infiltration, because it seems to us unnecessary. However, we believe that the use or not of a dose calculation is more a personal choice than a need for successful treatment with IL-MA.

There was no volume restriction for IL-MA infiltration in this study. Previous studies described the use of up to 30 mL without significant adverse effects (de Oliveira Duque et al., 2016, 2017; Oliveira-Neto et al., 1997; Vasconcellos et al., 2012). Other authors suggest the limit of 5 (OPAS - Organización Panamericana de la Salud, 2013) or 15 mL

Table 2
Characteristics of lesions and adverse effects observed in 30 patients with CL treated with intralesional meglumine antimoniate (IL-MA) in a primary health care unit in the city of Timóteo, state of Minas Gerais, Brazil, between December 2015 and July 2016.

Number of patients (%) and lesion characteristics[a]	28 (93.5%) patients periarticular lesion: 13 patients lesion area > 900 mm^2: 5 patients two or more lesions: 9 patients in the head: 2 patients > 5 mL per infiltration[b]: 26 patients Lymphangitis: 3 patients
Intensity of pain related to the IL-MA treatment	Absent: 23.5% Mild: 43.5% Moderate: 26.5% Severe: 6.5%
Clinical adverse effects (n)	edema (4), local pain (2), pruritus (2), erythema (1), local eczema (1), cellulitis (1), headache (1)
Laboratory adverse effects (n)	increased AST/ALT[c] (1), neutropenia (1)
Electrocardiographic adverse effects (n)	extension of the corrected QT interval (1)

[a] not in agreement to the recommendations for treatment with IL-MA (Brasil MS - Ministério da Saúde et al., 2017; OPAS - Organización Panamericana de la Salud, 2013). Lymphangitis was included as a controversial marker of predictive risk for the development of mucosal leishmaniasis (Blum et al., 2012).
[b] volume of infiltrated IL-MA per session ranged from 3 to 33 mL (median 10 mL).
[c] AST/ALT = aspartate aminotransferase / alanine aminotransferase.

(da Silva et al., 2018) per IL-MA infiltration. However, the antimonial systemic toxicity is cumulative (Chulay et al., 1988; Lawn et al., 2006; Miekeley et al., 2002; Rees et al., 1980). A report showed that the accidental systemic administration of a dose ten times higher than recommended resulted in mild and reversible adverse effects (Herwaldt et al., 1992). Although the maximum daily limit of 15 mL used in some countries (Brasil MS - Ministério da Saúde et al., 2017; OPAS - Organización Panamericana de la Salud, 2013) may be considered prudent for systemic daily injections of MA for 20–30 days, we consider such a limit unnecessary for the administration of IL-MA over a fortnight.

All patients in this study underwent local anesthesia and responded to questions about their pain sensation after the procedure: 93.5% reported mild to moderate or absent pain. Other authors also reported mild to moderate local discomfort with IL-MA, with or without the use of local anesthesia (Añez et al., 2018; Oliveira-Neto et al., 1997; Pimentel et al., 2017; da Silva et al., 2016, 2018; Soto et al., 2013, 2016; Vasconcellos et al., 2012). Local anesthesia could be considered an individual choice for each patient (Brahim et al., 2017; de Oliveira Duque et al., 2016). Curiously, it was reported that IL-MA may cause relevant discomfort (WHO, 2010). This pain may be related to the use of intradermal injections and the short interval between administrations.

In Brazil, the IL-MA treatment administered by trained professionals is recommended (Brasil MS - Ministério da Saúde et al., 2017). One study suggested the use of a standard operational procedure for the IL-MA infiltration technique. IL-MA treatment even when performed by inexperienced professionals causes pain and bleeding at acceptable levels. In addition, the ability of previously experienced professionals improves with repetitions (da Silva et al., 2018).

5. Conclusion

The present results suggest that the treatment of CL with IL-MA subcutaneously in primary health care units is simple, efficient, and safe. The use of IL-MA may decrease the morbidity and lethality related to the treatment of CL.

5.1. Perspectives

A randomized, multicenter, and controlled clinical trial with the support of the Ministry of Health and the PAHO is being carried out to compare the conventional systemic treatment and the IL-MA treatment in different Brazilian states (Brazilian Registry of Clinical Trials – ReBEC – Nº RBR-6mk5n4).

Conflicts of interest

No competing interests have been declared by all authors.

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