Intralesional Infiltration with Meglumine Antimoniate for the Treatment of Leishmaniasis Recidiva Cutis in Ecuador

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Abstract. Meglumine Antimoniate (MA), administered intramuscularly for 21 continuous days is the recommended treatment of leishmaniasis in Ecuador. However, because of its toxicity and requirement for intramuscular injections, treatment is frequently abandoned before completion. In addition, therapeutic failure and reactivation are not uncommon. Here we evaluate the efficacy and safety of MA administered intralesionally (IL) in leishmaniasis recidiva cutis (LRC). LRC is a special clinical variant of cutaneous leishmaniasis, characterized by reactivation at the edges of a primary cured lesion, presenting with active papules around the scar. Twenty-one patients were included in the study. All were diagnosed parasitologically by one of three diagnostic methods (smear, culture, and Leishmanin skin test). Each patient received MA intralesionally weekly for 4 weeks. Each papule was infiltrated until complete saturation. On average, patients received 1 mL of MA per administration. The criterion of cure was the complete resolution of the papules. Follow up was performed at 30, 90, and 180 days after treatment. At day 30 after treatment, 19 (90.5%) of 21 patients were clinically cured. The two patients, who did not heal by the fourth application, were cured on the seventh and eighth dose, achieving a clinical cure of 100% without subsequent reactivation. Mild to moderate local pain during infiltration was the only adverse reaction experienced by 81% of patients. In one case, subsequent infiltrations were discontinued because of a local allergic reaction. Complete compliance of patients to treatment and the small volume of drug administered make this method of administering MA an effective, safe, and inexpensive alternative. Consequently, IL could replace intramuscular administration in the treatment of LRC in Ecuador.

INTRODUCTION

Leishmaniasis, which can clinically present as cutaneous (CL), mucosal (ML), and visceral, is caused by the protozoan parasite of the *Leishmania* genus. CL is considered one of the most severe infectious skin diseases acquired by humankind. In addition, WHO considers it to be one of the neglected tropical diseases in many developing countries, because of the lack of a treatment that is effective, available, inexpensive, and easy to administer.¹

Current recommendations for treatment of CL are insufficient and inadequate because of the lack of data supporting the use of various compounds.² In literature reviews, it has been shown that treatment by systemically administered antimonial derivatives is superior to that of other options available. In Ecuador, treatment of CL using MA (glucantime®), showed a low cure rate (80.6%), with a reactivation rate of 15.2%, along with systemic toxicity such as fever, weakness, palpitations, and headache.³ The need to investigate more effective drugs or new forms of administration with available drugs is evident. According to PAHO, clinical trials are necessary that prove new treatment modalities with reliable evidence of efficacy, safety, and tolerability.⁴

In Ecuador, the Ministry of Public Health (MSP) considers both CL and ML public health problems. From the years 2010 to 2014, an average of 1,321 cases have been diagnosed annually (Department of Epidemiology MSP, 2014). Human cases have been reported from 21 of the 24 provinces of Ecuador, mainly from the coastal and Amazon tropical and subtropical regions as well as from some inter-Andean valleys. The clinical form of CL with its clinical variants is predominant

in Ecuador.⁵ A recent study in the northwestern region of the province of Pichincha showed that all of the 524 cases reported were CL; no mucosal or visceral forms were found. Among the variants of the cutaneous form, three (0.6%) were described as leishmaniasis recidiva cutis (LRC), 20 (3.8%) as “chiclero ulcer,” and the rest (95.6%) ulcerous.⁶

LRC is clinically characterized as presenting with one or more papular lesions around a scar (healed primary lesion). After the cicatrization of the primary lesion, with or without pharmacological treatment, relapse along the edges of the scar can occur within months or years. These papular lesions can grow, leaving permanent scars. In addition, LRC is characterized by being non self-curing.^{7,8} In previous studies, using isoenzymes analysis, *Leishmania panamensis* was shown to be the causative species of LRC.^{9,10} *L. panamensis* is the dominant species of CL in the subtropical region of the Ecuador but is not incriminated in ML.^{5,11} LRC has been reported from several Latin American countries such as Brazil, Colombia, Perú, and Ecuador.⁹ In the Old World, LRC is known as leishmaniasis recidivans, whose occurrence is quite common and is usually caused by *Leishmania tropica*.¹

According to MSP, the management and treatment of all clinical forms of leishmaniasis in Ecuador, including LRC, is the systemic administration of MA (glucantime). However, in placebo studies, certain cutaneous forms were found to heal spontaneously¹² or with topical treatments with only paromomycin; with paromomycin plus methylbenzetonium; or MA plus merthiolate.^{3,8,13} The recommended treatment by the MSP is the intramuscular administration of glucantime for 21 continuous days. This regimen is difficult to administer with patients from rural areas. In addition, intramuscular administration is painful and can lead to the onset of adverse reactions that in many cases requires discontinuation of treatment or abandonment of treatment by the patient.^{3,14}

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Recommendations made by WHO (2010) and PAHO (2013) have led investigators to research alternative therapeutics such as the use of lotions or topical ointments, and in localized lesions, the use of intralesional antimonials. Studies have been published from Bolivia where CL ulcerative lesions caused by *Leishmania braziliensis* were treated intralesionally (IL) with Meglumine Antimoniate (MA) and pentamidine, reporting a cure rate of 70% and 73%, respectively.^{15,16} In Brazil, studies reported a cure rate of 80%, 83.3%, and 77.7% in patients with the ulcerative variant of CL.^{17–19}

Reported here are the results of a study conducted in the subtropical region of the province of Pichincha of Ecuador where 21 patients with LRC lesions were treated IL with MA.

METHODS AND PATIENTS

Design and place of study. This was a prospective open clinical-therapeutic study. It was carried out in the health centers of Los Bancos and Pedro Vicente Maldonado, in the northwest region of the province of Pichincha, Ecuador. Before informing the physicians and authorities of the MSP's health centers of the study, the authorization for the participation of the health personnel was obtained.

Patients. All patients were residents of rural communities surrounding the health centers. Patients were recruited as outpatients by MSP physicians, identified, performed anamnesis, and physical examination according to the norms and procedures, and reported in MSP statistics. If a patient met the eligibility criteria for the study, the objectives, scope, benefits, and probable discomfort related to the study were explained. After reading the informed consent and agreeing to participate in the study, all participants signed the consent form. Patients who did not enter the study received intramuscular glucantime treatment according to MSP recommendations.

Eligibility criteria. Both male and female above 6 years of age with lesions clinically suggestive of LRC were selected for the study. Each participant presented with one or two scars with as many as five nonulcerative papular lesions (Figure 1). Parasitological diagnosis was made by observing

amastigotes in smears or promastigotes of *Leishmania* in the cultures. If the parasitological diagnosis was negative, and other dermal pathology such as cutaneous tuberculosis was ruled out, the patient was considered for the present study if the leishmanin skin test (LST) was positive and presented with lesions suggestive of LRC.¹⁵ LST was provided by PECET, Universidad de Antioquia, Medellin, Colombia (Cat No. MSTA 90000 5 mL). Other criteria regarding participants included: they were not receiving or had received treatment in the last 3 months with anti-*Leishmania* drugs (antimonials, pentamidine, amphotericin B, miltefosine, imidazoles, or allopurinol); they did not present lesions of ML; they had not acquired the infection in the Amazonian region or in other country; and they did not have concomitant diseases such as diabetes or HIV infection.

Unique clinical history of leishmaniasis and follow up.

For each patient, in addition to the medical chart of the MSP, a special clinical history including demographic data, natural history and evolution of the lesion(s), treatments received, data on infiltrations, follow up, cure, and adverse reactions experienced during and after infiltrations was obtained. The lesions were documented with photographs at the beginning of treatment and during the controls at day 30, 90, and 180.

Parasitological diagnosis. All clinically suspected LRC patients were classified as positive when one of three diagnostic techniques confirmed the diagnosis of leishmaniasis (visualization of amastigotes of *Leishmania* in direct smears, or promastigotes from culture medium, or a positive dermal leishmanin test). LST application, sampling for the smear, Diff Quik staining, aspiration of the lesion, inoculation, and culture in USMARU medium were done following the procedures of previous studies.³ The LST was measured at 48 hours with the pen-point method; patients were considered positive with the development of an induration > 10 mm.

Intervention. Meglumine antimoniate (glucantime, Aventis-Sanofi Pharma, São Paulo, Brazil, 81 mg/mL, 5 mL ampoules) was used for this study and was supplied by the MSP pharmacy that is regularly recommended in the treatment of all clinical forms of leishmaniasis in Ecuador. Intralesional infiltration was performed using an insulin syringe with #22 needle, without the use of any local anesthetic. The total volume of infiltration corresponded to the necessary amount required to achieve total saturation of the papules. Total saturation was obtained with one or two punctures. Each infiltration was measured and the volume used was recorded. The protocol consisted of infiltrating the lesions each week for four consecutive weeks. If there was no clinical resolution after 4 weeks, infiltration was continued until there was complete resolution of the papules.

Criterion of healing. The criterion of cure was clinical, based on the proposal made for the standardization of clinical research protocols in CL.² There had to be complete resolution of the papules, with no induration in the center or edges with complete flattening of the papules. There had to be no inflammation or edema at the site of the lesion. The evaluation of direct parasitological cure has ethical implications and is not considered safe.¹⁹

Ethics. This study was approved by the Human Research Ethics Committee of the Pontificia Universidad Católica del Ecuador (CEISH-057-2016) and the Ministerio de Salud Pública del Ecuador (MSP-DIS-2015-0011-O). The patient codes and information obtained were stored in the Unique

FIGURE 1. Patient 8 before treatment. A large scar (primary lesion) cured with intramuscular meglumine antimoniate 19 months prior. Nine months ago, three papules started developing around the edge of the scar that continued advancing along the periphery. This figure appears in color at www.ajtmh.org.

Clinical Record and could only be accessed by the principal investigator (MC).

RESULTS

In total, 25 patients were clinically and parasitologically diagnosed to have LRC. Twenty-one met the inclusion criteria and participated in the study held from September 2014 to July 2016. Gender consisted of 13 (62%) female and 8 (38%) male. Sixteen (76%) of the patients were diagnosed parasitologically by smear or by culture, whereas the remaining five (24%) patients were diagnosed by a positive LST plus the clinical and antecedent of having been infected in this endemic area. The relevant characteristics and clinical data for these 21 patients are summarized in Table 1. A total of 12 (57.1%) had previously received intramuscular glucantime, of which seven (33.3%) received complete treatment (20 mg/kg/day for 21 days) and the other five abandoned treatment of various reasons. One patient was treated with liquid nitrogen and another with mefloquine. Seven patients had not received any pharmacological treatment.

All 21 patients received four infiltrations at weekly intervals. However, two did not heal by control day 30. They received three and four additional weekly infiltrations. At control day 90, all lesions were healed and at control day 180 after treatment, there were no signs of reactivation. The average volume used per infiltration was 1 mL. Patients with three and four papules received up to 1.6 mL per infiltration whereas those with one small papule received as little as 0.4 mL (Table 2).

For evaluating the initial response (control at day 30 after treatment), four patients did not return. Fifteen patients had lesions that were completely healed, presenting no signs of activity or elevation of the papules (Figure 2). This gave an initial cure rate of 88.2% (15/17) excluding the four that were not evaluated. In the two patients with active and elevated papules, weekly infiltrations were reinstituted. For the intermediate response (control at day 90 after treatment), all the

TABLE 1

Characteristics of 21 patients with leishmaniasis recidiva cutis treated with intralesional meglumine antimoniate

Features	Media (range)
Age (years)	24.5 (8–67)
Gender	n (%)
Male	8 (38)
Female	13 (62)
Time of infection(s) before treatment (months)	20.4 (8–48)
Size of the papules (cm ²)	0.4 (0.2–0.8)
Number of lesions per patient	n (%)
1	6 (28.6)
2	6 (28.6)
3	6 (28.6)
> 4	3 (14.2)
Location of lesions	n (%)
Head/Neck	4 (19)
Upper limbs	10 (47.6)
Lower limbs	4 (19)
Trunk	3 (14.3)
Previous systemic treatment with MA	n (%)
Full (daily for 21 days MSP)	7 (33.3)
Incomplete	5 (23.8)
No treatment	7 (33.3)
Other drugs	2 (9.5)

MA = meglumine antimoniate; MSP = Ministry of Public Health.

TABLE 2

Intralesional treatment with meglumine antimoniate: details and results of 21 patients with cutaneous leishmaniasis, variant leishmaniasis recidiva cutis

	Media (range)
Volume of MA infiltrated per session (mL)	1.0 (0.4–1.6)
Number of infiltrations	n (%)
4	19 (90.5)
7	1 (4.7)
8	1 (4.7)
Response to treatment	n (%)
Initial response (30 days)	19/21 (90.5)
Intermediate response (90 days)	21/21 (100)
Definitive cure, no reactivations (180 days)	21/21 (100)
Adverse effects	n (%)
Mild local pain	8 (38)
Moderate local pain	10 (47.6)
Severe local pain	3 (14.3)
Local allergic reaction (pruritus, edema, vesicles)	1 (4.7)

MA = meglumine antimoniate.

lesions of the patients were cured. The four who did not report to the control day 30 had healed lesions without any activity, as did the two patients whose lesions were not cured by the first control but who had received a total of seven and eight infiltrations. For definitive cure (last control at day 180 after treatment), all 21 patients were evaluated, visiting them house to house, and all met the criterion of cure. No reactivation activity was found (Table 2). Ten patients were observed up to 360 days without any noted reactivation. Thus, after four intralesional infiltrations, at control day 30 after treatment, there was a cure rate of 90.5% (19/21 patients) and a definitive cure rate of 100% at day 90 and day 180 follow up. The two patients who did not heal with the four infiltrations included a 15-year-old boy who had LRC in the ear pinna with four reactivating lesions and a 67-year-old woman with LRC on both wrists with five medium-size papular lesions. During follow up, no patient reported or presented any mucosal lesions.

During infiltration, 17 patients reported a mild to moderate burning type pain at the puncture site. Three patients referred

FIGURE 2. Patient 8, at control day 30 after receiving four doses of intralesional meglumine antimoniate. This figure appears in color at www.ajtmh.org.

to the pain as intense: one with lesions on the ear pinna, another with five lesions on both wrists, and a girl with lesions on the back of her hand (Table 2). One lady presented a local allergic reaction 2 hours after the first infiltration with symptoms of pruritus, redness, edema, and vesicles that subsided in 24 hours with oral antihistamines and topical dexamethasone. This patient was seen on control day 30, 90, and 180 and complete healing was observed without subsequent reactivation at 360 days.

DISCUSSION

This study demonstrates the high efficacy and low toxicity of MA in the intralesional therapy (IL) of LRC in Ecuador. With the small volume of drug used in each IL, no systemic adverse reaction was seen in any patient, and the weekly dosing scheme improved patient's adherence to protocol. The occurrence of LRC is not uncommon, being reported from Brazil, Colombia, Perú, and Ecuador. In Ecuador, it has been diagnosed in patients from the tropical, subtropical, and Andean regions.⁵⁻⁸ Currently, MA is the recommended treatment administered systemically (intramuscular or intravenous) at 20 mg/kg body weight for 21 continuous days (Ministerio de Salud Pública del Ecuador). This dose and form of administration invokes serious systemic adverse reactions and abandonments of treatment are frequent.^{3,14} In addition, it cannot be administered to pregnant women, children younger than 2 years, the elderly, those with allergies, and patients with cardiac, renal, and hepatic disorders.^{18,20}

Because of the high efficacy and low toxicity of intralesional MA seen in the present study, this technique could be recommended as an excellent alternative in the management of this clinical form of CL in Ecuador. With four IL sessions, a cure rate of 90.5% was achieved, and with subsequent infiltrations, a cure rate of 100% was reached. The study also demonstrated that it is necessary to continue infiltrations until healing is achieved. In a previous study performed in the same region, after administering MA intramuscularly in all clinical forms of CL, a much lower efficacy (80.6%) was obtained.³ Also, systemic adverse reactions such as fever, weakness, palpitations, and headaches were not uncommon whereas in the present study, no systemic adverse reactions were experienced, only local puncture pain during infiltration that subsided in a few minutes.

These encouraging results are in agreement and increase the evidence of the high efficacy and safety of IL administration in treating CL. Studies in neighboring countries such as Bolivia and Brazil obtained cure rates ranging from 70%, 77.7%, 80% to 83.3%.^{15,17-19} Using pentamidine IL, a cure rate of 73% was achieved.¹⁶ The present study was superior in effectiveness probably because it was applied to papular lesions of the clinical LRC variant, whereas in the aforementioned studies, it was performed in the ulcerous form. In LRC, the lesions are small circumscribed papules and are easily infiltrated completely with the drug, conditions that can favor the cure. An essential element in the IL technique is to fully infiltrate the active lesion. In the study of Silva (2016), a cure rate of 100% was achieved by the 12-month follow up after treatment. This indicates that patient follow up should be prolonged or, as in our case, should continue with IL injections until healing is achieved.

Of interest is the efficacy of MA administered in patients who had previously been treated with the drug. This is in agreement with other studies where previous administration of the drug did not affect its ability to cure.¹⁹ However, in other studies, there was an apparent resistance if MA was reapplied, resulting in no cure.¹⁵ We believe that with infiltration, the microorganisms are killed by direct contact of the toxic antimony (Sb) metal.

The local, mild, and self-limiting adverse reactions seen in our study were similar to those observed in other studies.^{15,17-19} One patient developed a local allergic reaction to the medication similar to the two cases who presented with eczema in the intralesional MA treatment of localized CL in Brazil.¹⁹ Of interest is that this patient had been previously treated systemically with MA and that upon retreatment, the lesions were cured with a single dose, similar to the case reported in a 42-year-old female in Rio de Janeiro, Brazil.²¹

Advantages shown by this study of infiltrating MA intralesionally are 1) the use of low doses of the drug (average 1 mL per infiltration) regardless of patient weight; 2) the weekly treatment regimen, which increases patient's adherence; 3) no need for costly laboratory examinations or electrocardiographs, which reduces costs; 4) the few local and nonsystemic adverse reactions, not requiring hospitalization or close medical supervision; and 5) the reduced cost of treatment to both the patient and the medical provider. In Ecuador, the cost of one ampoule of glucantime is about US \$5.00. In addition, the easy and risk-free IL administration can potentially be performed by a trained health promoter in rural endemic areas, eliminating the use of hospital facilities thus reducing patient's costs for transportation and food. However, there was some limitation related to this study: 1) it was limited only to the treatment of CL, variant recidiva cutis (LRC); 2) it was limited geographically with treated patients coming from only one subtropical region on the Pacific coast; 3) there was no definite identification of the *Leishmania* causing species; and 4) the study did not compare the efficacy in a randomized placebo-controlled trial or a comparative study using the standard treatment with MA. Further studies are needed to address these issues.

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