Eligibility for Local Therapies in Adolescents and Adults with Cutaneous Leishmaniasis from Southwestern Colombia: A Cross-Sectional Study

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Abstract. Local therapies have been proposed as safe and effective alternatives to systemic drugs in cutaneous leishmaniasis (CL), especially among less severe cases. However, they are not widely available and used in endemic places, including Colombia, which has a high burden of disease. Further complicating the uptake of local therapies is that different treatment guidelines have been established by the World Health Organization (WHO) and Pan American Health Organization (PAHO). Using data from a large referral center in Colombia, we determined the proportion of patients who would be eligible for and potentially benefit from local therapies according to both international guidelines. The sample included 1,891 confirmed cases of CL aged ≥ 12 years, mostly infected with *Leishmania Viannia pan-amensis* (91%, $n = 601/660$), between 2004 and 2014. Overall, 57% of the sample had one lesion, whereas another 31% had two to three lesions. For 74% of patients, all lesions were in an area other than head or neck. The maximum lesion size was ≤ 3 cm for 58% and < 5 cm for 88% of the sample. Based on our data, up to 56% of patients could have been eligible for local therapies according to the WHO criteria. By contrast, only 23% were eligible according to the more restrictive PAHO criteria. Regardless, these data suggest that a substantial proportion of CL patients in Colombia may benefit from local therapies given their relatively mild presentation of disease and low risk of complications. Individualized risk–benefit assessment and guideline adjustments may increase local therapy eligibility and benefit a large number of patients.

INTRODUCTION

Cutaneous leishmaniasis (CL) is the most common presentation of leishmaniasis (89.2% of reported cases),¹ a neglected tropical disease that occurs mostly in rural areas of developing countries. The disease often affects exposed, visible skin areas and might leave lifelong scars, or present complications such as mucosal lesions, associated with *Leishmania Viannia* species.^{2,3} The Americas region reports approximately 23% of the total global cases¹ and Colombia has the second highest number of cases in the region (6,870 cases for 2017).⁴ In addition, current systemic treatment options for CL have several disadvantages.⁵ Available treatments, except miltefosine, require parenteral administration and are invariably toxic to the patient.^{6,7} These drugs are the first-line option in the Americas [American CL (ACL)] and are commonly used based on the assumption of a risk of mucosal leishmaniasis.^{3,6}

To address these issues, in 2010 the World Health Organization (WHO) issued recommendations for the use of local therapies as alternatives for treating CL.⁸ These therapies include intralesional antileishmanials (antimony and pentamidine),^{9,10} physical therapies (cryotherapy and thermotherapy),¹¹ and topical drugs (e.g., paramomycin).⁵ The WHO recommendations aim to reduce toxicity and increase adherence, given the better risk–benefit ratio of local therapies compared with systemic drugs for CL, especially for mild clinical presentations.⁸ In addition, they are considered safer and the alternative for special populations for whom systemic treatments are contraindicated (e.g., pregnant women).¹² In 2013, the Pan American Health Organization (PAHO) recommended the use

of local therapies for ACL; considering that the benefit of having safer local treatments outweighs the risk of mucosal disease.⁶ Currently, both organizations recommend the use of local therapies for CL depending on the number, size, and location of lesions, the PAHO criteria⁶ being stricter than those of WHO.⁸

Available data on the feasibility of local therapies in the Americas is limited.^{9,11,13} A previous study in our center showed modest applicability of local therapies to pediatric populations (26% and 53% were eligible, based on PAHO and WHO criteria, respectively).¹⁴ Children constitute a population with special needs for therapy but represent only around 11% of Colombian cases.¹⁵ For the present study, we evaluated the feasibility of using local therapies for CL in patients aged ≥ 12 years. Clinical characteristics of patients from a referral center Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM) in southwest Colombia were used to assess eligibility by PAHO and WHO criteria.

MATERIALS AND METHODS

Study design and participants. We conducted a descriptive study using electronic databases of routinely collected data from patients who consulted at CIDEIM clinics in Cali and Tumaco (Colombia), between January of 2004 and December of 2014. Centro Internacional de Entrenamiento e Investigaciones Médicas is a WHO collaborating center for the diagnosis, treatment, surveillance, and control of leishmaniasis; CIDEIM's main area of influence is in southwest Colombia.

We included data from patients with parasitological confirmation of leishmaniasis¹⁶ categorized as adolescents (aged ≥ 12 and < 18 years) or adults (aged ≥ 18 years). Records from patients with missing data on eligibility for local therapies were excluded from the study. The study protocol was reviewed and approved by the CIDEIM's Institutional Ethics Committee on Human Research (approval number 08-2015). Eligibility

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criteria for local therapies, according to WHO and PAHO, are described in Table 1.

Data management. All records were available in digital format, and they included sociodemographic and clinical information (including lesion characteristics during follow-up), as well as laboratory and parasite identification data (identification of strains is not available for all patients). *Leishmania* species identification is performed using monoclonal antibodies and/or isoenzyme analysis.^{17,18}

We merged all available databases (clinical and laboratory data) using patient's identification (ID) as the common identifier between databases. This ID is a consecutive number assigned to all new patients at CIDEIM, and it is different to the Colombian ID number. A second investigator independently performed quality control, by reviewing the merging and coding of a sample of the final database.

To evaluate the treatments received by patients in this population and considering that most of the records were not available in curated databases, we selected a sample of 10% of the study population ($n = 190$) by simple randomization. For this subset of patients, we reviewed the primary data sources (electronic and physical records) and recorded the treatment received when available.

Data analysis. First, we verified inclusion/exclusion criteria to the study; and then, we checked the eligibility for local treatment (at the moment of diagnosis) according to WHO and PAHO recommendations. Finally, we performed an exploratory analysis using Stata Statistical Software: Release 13 (StatCorp LP, College Station, TX) and R (V. 3.5.1) Foundation for Statistical Computing, Vienna, Austria. Descriptive statistics were used to summarize the demographic, clinical, and parasitological characteristics of the sample. Frequency of categorical variables was calculated, including the type of treatment received in a subset of the sample. We estimated measures of central tendency and dispersion of numerical variables according to their distribution.

RESULTS

Characteristics of study participants. We identified 1,903 records that were potentially eligible for the present study. Among them, 12 records were excluded because of missing data on eligibility for local therapies. In total, 1,891 adolescents and adults were analyzed for this study (Figure 1).

Patient age ranged from 12 to 85 years, with a median (Me) of 25 years. Fourteen percent of patients were adolescents ($n = 260$) and 86% adults ($n = 1,631$). Males predominated in both groups (80.8%). The most common self-appointed ethnicities were mestizo in adults (59.8%) and Afro-Colombian

FIGURE 1. Flowchart of included and excluded records.

in adolescents (50.4%). Most cases came from southwestern Colombia, especially from the Nariño department (65.8%). Agriculture was the predominant economic activity overall (52.4%) and in adults (54.8%); while less than half of adolescents were attending school (43.1%). *Leishmania* species isolation and identification was available in 34.9% of the cases, of which 91.1% were *L. (V.) panamensis* (Table 2).

Around half of the patients (56.7%) presented a single lesion. The time since onset of the first lesion at diagnosis was less than 3 months in 84.3% of patients. The most common clinical presentation of lesions was ulcerated (83.0%); most of the patients did not have the presence of either regional lymph nodes (82.1%) or palpable lymphatic tract (88.8%) at the physical examination.

In a random sample of 190 individuals, 62.6% of the clinical records did not include the treatment received by the participant. Among records with available information about treatment ($n = 71$), most of the patients received meglumine antimoniate ($n = 64$, 90.1%), and the remaining 10% received miltefosine ($n = 7$, 9.95%). None of these 71 patients received local therapies, but 54.9% ($n = 39$) of them were eligible according to the WHO criteria.

Eligibility for use of local therapies according to WHO and PAHO criteria. Fifty-six percent of patients were eligible for local therapies according to the WHO criteria (adolescents 55.0% and adults 56.5%). By contrast, only 23% were eligible for local therapies according to PAHO criteria (adolescents 16.0% and adults 24.0%) (Figure 2). Differences between the criteria were explained by the presence of < 4 lesions (WHO) versus single lesions (PAHO); whereas the proportion of patients with less than four lesions was 88%, only 56.7% of patients had a single lesion (Table 2).

DISCUSSION

We found a modest applicability of local therapies in patients aged ≥ 12 years in southwest Colombia. Estimates of the proportions of patients eligible for these therapies are 56.3% and 23% according to WHO and PAHO, respectively. These results are similar to those in children from the same Colombian population reported by Blanco et al.¹⁴ They also provide information about the feasibility of the future implementation of local therapies in the Colombian context, given the available treatment guidelines.

TABLE 1

Eligibility criteria for local therapies based on WHO and PAHO

WHO ^a	PAHO ^a
1. Less than 4 lesions	1. Single lesion
2. Lesions < 5 cm in diameter	2. Lesion area ≤ 900 mm ² (diameter up to 3 cm)
3. No potentially disfiguring or disabling lesions (face, joints, toes, and fingers)	3. Located elsewhere but head or near joints
4. No immunosuppression	4. Absence of immunosuppression
5. Possibility for follow-up	5. Possibility for follow-up

^aPAHO = Pan American Health Organization; WHO = World Health Organization.

FIGURE 2. Proportion of patients eligible for local therapies.

Considering the limited options for treating CL, the adoption of WHO criteria would benefit approximately half of the cases in this population. Although few data are available for CL, health economic analyses show that systemic therapies generate a considerable economic burden for patients, health system and society.¹⁹ In this context, the use of local therapies for around half of our population would alleviate the costs associated with the daily administration of treatment in health institutions and those represented by attention of adverse reactions.^{20,21} Implementation of local therapies could also have an added benefit for populations with contraindications to systemic therapy, which needs to be evaluated¹² and could facilitate access to treatment, especially in rural areas, by decreasing the number of contacts with the health-care facilities.

In our study, eligibility by PAHO criteria is lower than using WHO recommendations. The most important criteria limiting eligibility for local therapies by PAHO are having a single lesion (56.7%) and diameter of lesions ≤ 3 cm (57.9%). These criteria are based on expert opinion and reports of risks factors for mucosal leishmaniasis (number, size, and localization of lesions, and concomitant conditions such as immunosuppression).^{22,23} Multiple studies have shown

parasite persistence after systemic treatment, showing the absence of sterile cure,^{24,25} and the exact risk of mucosal lesions among CL patients has not been clearly estimated,¹³ nor has the protection of systemic therapy against mucosal leishmaniasis been established.²⁶ Because of the limitations of assessing mucosal disease (e.g., low frequency), the quality of evidence for these associations is low and limits our understanding of the relationship between treatment options and development of mucosal lesions.¹³

Recent studies evaluating the use of local therapies in the Americas^{12,27–30} have used variable inclusion criteria. Lesion number varied from one to 10 lesions and lesion size from 3 to 10 cm. In addition, the quality of reporting also shows variability, ranging from incomplete to non-reporting of key criteria for local therapies, such as lesion size or location. To facilitate the implementation of local therapies in Colombia and the Americas, it is important to generate high quality evidence supporting their use and indications (number, size and location of lesions). Prospective studies and pharmacovigilance are needed to evaluate the long-term efficacy of local therapies.³¹ These data will allow adjustments of the current practice guidelines. In addition, individual case management with available local therapies should be adapted to the regional clinical and epidemiological profile of leishmaniasis, besides the risk-benefit ratio.¹³

One of the limitations of the present study was the use of routinely collected data to evaluate these criteria. However, as CIDEIM is a good clinical practices-compliant research center, clinical information is collected using standardized procedures, which is reflected in the small number of records with missing data. The main issue is the lack of information about presence of lesions on joints or fingers, which contraindicates the use of local therapies. Therefore, the proportion of eligible patients might have been overestimated. It is well known that clinical presentations of CL vary across geographic regions

TABLE 2
Sociodemographic and clinical characteristics by population group

	Adolescents, n = 260	Adults, n = 1,631	Total, n = 1,891
Age, median [range] (years)	15 [12–17]	27 [18–85]	25 [12–85]
Male, n (%)	189 (72.7)	1,339 (82.1)	1,528 (80.8)
Ethnicity, n (%)			
Mestizo	118 (45.4)	976 (59.8)	1,094 (57.9)
Afro-American	131 (50.4)	596 (36.5)	727 (38.4)
Others	2 (0.8)	19 (1.2)	21 (1.1)
Missing	9 (3.4)	40 (2.5)	49 (2.6)
Time in months since appearance of the oldest lesion, median [IQR]	1.5 [1–2]	2 [1–3]	2 [1–2.8]
Number of lesions, n (%)			
1	129 (49.6)	943 (57.8)	1,072 (56.7)
2–3	97 (37.3)	495 (30.4)	592 (31.3)
≥ 4	34 (13.1)	193 (11.8)	227 (12.0)
Maximum diameter of largest lesion in cm, n (%) [*]			
≤ 3	141 (54.2)	954 (58.5)	1,095 (57.9)
> 3 and < 5	85 (32.7)	478 (29.3)	563 (29.8)
≥ 5	34 (13.1)	199 (12.2)	233 (12.3)
Lesion localization, n (%)			
At least one on head and neck	66 (25.4)	422 (25.9)	488 (25.8)
All lesions in other locations	194 (74.6)	1,209 (74.1)	1,403 (74.2)
Leishmania species, n (%)			
n = 78		n = 582	n = 660
<i>L. (V.) panamensis</i>	77 (98.7)	524 (90.0)	601 (91.1)
<i>L. (V.) braziliensis</i>	1 (1.3)	30 (5.2)	31 (4.7)
Other	0	23 (4.0)	23 (3.5)
Undetermined	0	5 (0.8)	5 (0.7)

* Horizontal or vertical diameter.

and species,^{14,18,22,32} hence, generalization of these results should consider the local epidemiologic profile of CL, including the infecting *Leishmania* species. We highlight, however, that this study presents the clinical spectrum of CL, mainly caused by *L. panamensis* infection, within a large cohort of patients across a decade.

Availability of data regarding treatment administration and outcomes is still challenging, as evidenced by the high proportion of missing treatment data in a subset of this study sample. This situation has been reported in the Americas, where, according to PAHO, only 41% of reported cases have these data.³³ The low percentage of patients followed up by health facilities after diagnosis, mostly due to difficulties in access from their residence,³⁴ has been described as an explanation to this phenomenon. Among records with data about treatment, all patients received systemic drugs, mainly meglumine antimoniate (90%). However, 39 of these cases (54.9%) were eligible for local therapies, which highlight the limited use of local therapies for CL in Colombia, where national guidelines did not yet incorporate these treatment options.

In conclusion, our study shows the limited eligibility of patients for local therapies, according to current treatment guidelines. This finding is important to inform implementation of these treatment options. Standardization of reports and methodologies of clinical trials assessing local therapies will inform, and could allow adjustment of national and international treatment guidelines to allow wider use of these therapies.

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