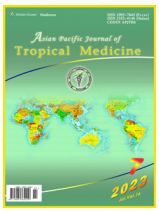

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Therapeutic response and safety of different treatments for cutaneous leishmaniasis in patients: A retrospective cross-sectional study

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ABSTRACT

Objective: To analyze the therapeutic response and safety of different treatments for cutaneous leishmaniasis, received by patients in the Program for the Study and Control of Tropical Diseases-PECET-Medellín-Colombia.

Methods: This is a retrospective cross-sectional study of patients attended at PECET Research Center during 2016-2021. Relevant information regarding sociodemographic characteristics, history of leishmaniasis, characterization of current infection, treatment received, follow-up of therapeutic response and safety was collected from the medical records. Data were analyzed with Pearson's *Chi*-square association tests and Mann-Whitney *U* test using statistical software.

Results: A total of 486 clinical records of patients were analyzed, and 356 received treatment. Eight different therapeutic alternatives (systemic, local and in combination) were analyzed. The therapeutic response of the different alternatives used (except thermotherapy) was higher than 50%. Most frequent adverse events were myalgias, arthralgias and headache, and vesicles for systemic and local treatment, respectively.

Conclusions: Safety profile and performance of local therapeutic alternatives and combined schemes for the treatment of uncomplicated cutaneous leishmaniasis are an interesting option for the management of the disease.

Keywords: Cutaneous leishmaniasis; Systemic treatment; Local treatment; Combined treatment; Tropical neglected disease; Safety; Therapeutic response

1. Introduction

Leishmaniasis is a parasitic disease caused by the protozoan of the family Trypanosomatidae of the genus *Leishmania*, of which about 22 pathogenic species are known to affect humans[1]. It is transmitted to mammals through the bite of female phlebotomine sandfly dipteran hematophagous insects, whose reservoirs are different wild and domestic animals[2,3], the disease is present in the five continents and is endemic in approximately 102 countries or territories, mainly affecting tropical areas[1].

The epidemiological and clinical features of the disease are variable

Significance

The available treatments for the management of cutaneous leishmaniasis have been limited primarily due to a lack of research. Additionally, these treatments have demonstrated certain health complications that significantly impact the quality of life of affected individuals. Therefore, there is a pressing need to explore new therapeutic options that offer improved safety profiles for patients. The objective of this research is to investigate the safety profiles of established treatment regimens as well as novel therapeutic interventions.

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due to the interaction of many factors such as parasites, vectors and hosts involved in the infection[4]. Although only a small proportion of people infected with the parasite eventually develop the disease[5], in cases where it occurs it can manifest in three clinical forms: cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML) and visceral leishmaniasis (VL), the last one associated with symptoms that include fever, weight loss, hepatosplenomegaly and anemia, and is the only lethal form of the disease[6].

In Colombia, the most frequent clinical form is CL (95% to 98% of cases), which is characterized by the presence of skin lesions ranging from papules to ulcers located at the site of the insect bite[3].

According to the World Health Organization (WHO), more than 350 million people live in areas endemic for leishmaniasis and are at risk of infection, and 1.3 million new cases are reported annually[1]. In the particular case of the Americas, CL is endemic in 18 of the 20 countries where it has been reported and during the last 20 years more than one million cases of CL and ML have been registered; by 2020, 6 161 cases were reported in Colombia, ranking second after Brazil where 16 432 cases had been reported[7].

Currently, there are no vaccines or prophylactic treatments for the control of the disease; therefore, its management is based on timely diagnosis and treatment[8]. For more than 70 years, pentavalent antimonials have been the main option in the treatment of the different clinical forms of leishmaniasis[9], however, the safety associated with their use can represent a risk for the patient, since frequent adverse reactions have been documented that range from mild to severe and even fatal; they are generally observed when high doses are administered and for prolonged periods, generating hepatic, renal, cardiac, pancreatic alterations in the patient and affectations in the musculoskeletal system[10].

There are other therapeutic options for the management of CL such as miltefosine, ketoconazole, pentamidine isethionate, liposomal amphotericin B, deoxycholate amphotericin B and thermotherapy, some of those options have better safety profiles, less traumatic routes of administration and/or acceptable reports of therapeutic response[11-14]; however, the lack of availability of these drugs, as well as the lack of quality scientific evidence to support their performance and allow their inclusion in the first line of treatment, have limited their use and most of the time they are employed as part of the second line of treatment in cases of failure with pentavalent antimonials[1].

In accordance with the above, and in response to the call of the Sixtieth World Health Assembly, which urges the scientific community to promote research on the control of leishmaniasis in order to find safe, effective and affordable alternative drugs, and to promote the dissemination of research findings[15], the results of the analysis of the therapeutic response and safety of different treatments for CL, received by patients treated in the Program for the Study and Control of Tropical Diseases-PECET-Medellín-Antioquia, during the years 2016 and 2021, are presented.

2. Subjects and methods

2.1. Study design

Location and population: This is a cross-sectional study enrolled patients attended at the Program for the Study and Control of Tropical Diseases-PECET-Medellín-Colombia, during the years 2016-2021.

Men and women of any age who had a confirmed diagnosis of CL by direct examination, PCR or culture and who had received treatment for this condition were included in the study. It was considered as exclusion criteria the report of serious concomitant diseases that may affect the performance of the therapeutic alternative.

Data collection: Relevant information regarding sociodemographic characteristics, history of leishmaniasis, characterization of current infection, treatment received, and follow-up of therapeutic response and safety was collected. Patient information was obtained from the medical records available at PECET.

For database construction, all the medical records of the participants who met the eligibility criteria were taken into account; the recording of the information was carried out independently by two researchers, validating discordance in the source document and making the respective corrections.

2.2. Ethical approval

This study was approved by the Bioethics Committee of the Sede de Investigación Universitaria (CIE-SIU) through approval act 21-05-944 of April 21, 2021.

2.3. Statistical analysis

Data were tabulated in Microsoft Excel and analyzed using SPSS (version 27, SPSS Inc. Chicago, IL) and Epi-dat (version 3.1) statistical software. Generally, for categorical variables, absolute and relative frequencies are presented; for quantitative variables, number of observations (n), medians and interquartile range are shown. Exploratory analyses using Pearson's *Chi*-square association tests and Mann-Whitney U test were carried out to outline a possible association between therapeutic response to treatments and variables of interest in the population and the health condition studied.

3. Results

A total of 486 clinical records of patients treated at PECET were analyzed. It should be noted that not all diagnosed patients are treated at the research center, therefore, the results of the analysis of socio-demographic information, clinical history and history of leishmaniasis were based on the 486 records, and the analyses related to therapeutic response and treatment safety were carried out on 356 patients who received treatment at PECET.

Table 1 shows the results of the description of the study population. Of the patients attended 73.3% were men, the age of 50% of the study population ranged between 20 and 44 years with a median of 28 years; students, military, farmers and housewives represented 50% of the population and the departments of Colombia where the patients attended most frequently came from were Antioquia and Chocó. In terms of clinical history, 90% of the population reported no comorbidities, however, it is important to highlight that hypertension was the most frequent comorbidity, with 24 patients (4.9%); in addition, some had this comorbidity accompanied by diabetes (*n*=9), anemia (*n*=1), asthma (*n*=1) and dyslipidemia (*n*=1); 69% of the study population reported no history of leishmaniasis (Table 1).

Analysis of the infection in the 356 patients treated at the research center revealed that the most frequent type of lesion was ulcer, present in 85.4% of the patients, and 62.9% presented only one lesion. A total of 72 patients (20.0%) had received treatment for the infection, and of these, 46 patients received systemic glucantime (Table 2). Regarding the treatment received at the research center, 8 different alternatives were found:

Table 1. Sociodemographic information, clinical history and history of leishmaniasis.

Variables		Frequency (%)
Sex	Male	356 (73.3)
	Female	128 (26.3)
	No data	2 (0.4)
Age, years*		28 (20-44)
Occupation	Farmer	52 (10.7)
	Housewife	46 (9.5)
	Student	76 (15.6)
	Military personnel	69 (14.2)
	Other	177 (36.4)
	No data	66 (13.6)
Department of origin	Antioquia	308 (63.4)
	Chocó	73 (15.0)
	Other	103 (21.2)
	No data	2 (0.4)
Comorbidities	Hypertension	24 (4.9)
	Negative	435 (89.5)
	Other	27 (5.6)
Previous infection with leishmaniasis	No	335 (68.9)
	Yes	88 (18.1)
	No data	63 (13.0)

*Data were expressed as median (range).

(1) Three with systemic route of administration: systemic glucantime (14.6%), miltefosine (5.6%) and pentamidine (2.8%);

(2) Four with local route of administration: intralesional glucantime (32.9%), thermotherapy using Thermomed® equipment (14.6%), device approved for CL treatment, topical under investigation (17.2%) and hydrogel thermotherapy (2.2%) these last two alternatives correspond to research center developments (alyeyuba and hydrogel);

(3) One combined treatment was used (10.1%), a scheme that included one thermotherapy session (Thermomed®) plus a 21-day course of miltefosine.

With the exception of thermotherapy treatment with hydrogel, the therapeutic response of the different alternatives used was higher than 50%, Combined treatment and thermotherapy (Thermomed®) treatments presented the best performance, reaching cure rates higher than 80% (Table 3).

Table 2. Description of infection and treatment received at the research center.

Variables		Frequency (%)
Types of lesions	Ulcer	304 (85.4)
	Nodule	10 (2.8)
	Crust	6 (1.7)
	Verrucous	6 (1.7)
	Papule	1 (0.3)
	Combined	18 (5.1)
	Not specified	11 (3.1)
Number of lesions	1	224 (62.9)
	2	65 (18.3)
	3	20 (5.6)
	4	19 (5.3)
	≥5	25 (7.0)
	Not reported	3 (0.8)
Anatomical location of lesions*	Head and neck	74 (20.8)
	Trunk	19 (5.3)
	Upper extremities	179 (50.3)
	Lower extremities	119 (33.4)
Previous treatment	None	284 (79.8)
	Systemic glucantime	46 (12.9)
	Intralesional glucantime	5 (1.4)
	Miltefosine	4 (1.1)
	Other/Combined	13 (3.7)
	Not specified	4 (1.1)
Treatment received for current infection	Thermotherapy (Thermomed®)	51 (14.3)
	Combined treatment	36 (10.1)
	Miltefosine	20 (5.6)
	Pentamidine	10 (2.8)
	Thermotherapy (Hydrogel)	9 (2.5)
	Topic under investigation	61 (17.1)
	Intralesional glucantime	117 (32.9)
	Systemic glucantime	52 (14.6)

*Patients may have lesions in several anatomical sites, therefore the number of lesions per anatomical area will not correspond to the value of the patients in the investigation.

Table 3. Therapeutic response of different treatments.

Treatment response	Treatment received							
	Intralesional glucantime (*n*=117)	Systemic Glucantime(*n*=52)	Miltefosine (*n*=20)	Pentamidine (*n*=10)	Thermotherapy (Thermomed®) (*n*=51)	Thermotherapy (Hydrogel)(*n*=9)	Topic under investigation (*n*=61)	Combined treatment (*n*=36)
Cure	75 (64.1)	33 (63.5)	11 (55.0)	6 (60.0)	41 (80.4)	4 (44.4)	31 (50.8)	32 (88.9)
Treatmetn failure	3 (2.6)	1 (1.9)	1 (5.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (3.3)	2 (5.6)
Improvement	29 (24.8)	17 (32.7)	5 (25.0)	1 (10.0)	7 (13.7)	4 (44.4)	16 (26.2)	1 (2.8)
Loss of follow-up	10 (8.5)	1 (1.9)	3 (15.0)	2 (20.0)	3 (5.9)	1 (11.1)	12 (19.7)	1 (2.8)

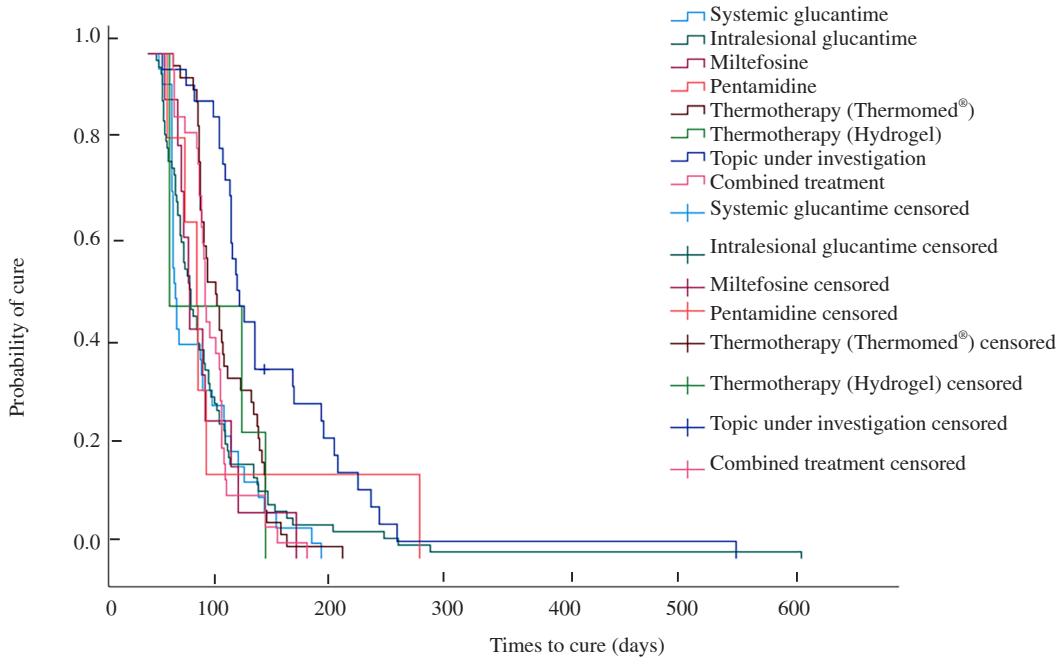

Figure 1. Healing time according to treatment received.

The overall median healing time was 48 days with an interquartile range between 28 and 78 days (data not shown). In the analysis of healing time discriminated by treatment, it can be seen that the treatments with the best healing rate were systemic glucantime, miltefosine and intralesional glucantime with a median (IQR) of 24 (18.4-29.6), 35 (17.7-52.2) and 36 (28.4-43.6) days, respectively (Figure 1). It should be noted that for the purposes of this analysis, the data from patients whose treatment was not completely followed up, such as those who presented improvement or loss of follow-up, were classified as therapeutic failures.

In exploratory analyses of the association between epidemiological and clinical variables that could be related to the performance of the different therapeutic alternatives, no correlation was found between these and the failure to cure the disease (Table 4).

Half of the patients who received treatment with systemic glucantime reported at least one adverse event, the most frequent being those related to discomfort of the musculoskeletal system (myalgia and arthralgias) and headache; on the other hand, vesicles in the lesion were the most frequent adverse event in those patients who received thermotherapy with the Thermomed® device; The most common adverse event with combined treatments were vesicles and vomiting (Table 5). Of the 356 patients who received treatment, 14.6% (*n*=52) received a second treatment at the center and 3.4% (*n*=5) received up to a third treatment (data not shown).

4. Discussion

The results of the study present a sociodemographic, epidemiological and clinical description of 486 patients diagnosed with CL who were attended at the research center during the last 6 years, as well as data on the therapeutic response and safety of the different treatments received by the patients at the center.

Table 4. Therapeutic response of the different treatments according to variables of interest in epidemiological and clinical terms.

Treatment	Variable	Categories	Cure (%)	Failure (%)	*P* value
Systemic glucantime (*n*=52)	Time of evolution, weeks*		8 (4-13)	8 (6-17)	0.472
	Region of origin	Andean or Pacific	32 (96.9)	17 (89.5)	0.260
		Amazonic or Orinoco	1 (3.1)	2 (10.5)	
	History of leishmaniasis	Yes	1 (12.1)	4 (5.3)	0.070
		No	29 (87.9)	18 (94.7)	
	Number of lesions	1	10 (32.2)	6 (31.6)	0.930
		2-5	15 (48.4)	10 (52.6)	
		6 or more	6 (19.4)	3 (15.8)	
	Type of lesions	Ulcer	28 (93.3)	16 (84.2)	0.280
		Other	2 (6.7)	3 (15.8)	
Miltefosine (*n*=20)	Time of evolution, weeks*		8 (4-16)	8 (4-7)	0.322
	Region of origin	Andean or Pacific	11 (100)	8 (100)	NA
		Amazonic or Orinoco	0	0	
	History of leishmaniasis	Yes	2 (18.2)	1 (11.1)	0.570
		No	9 (81.8)	8 (88.9)	
	Number of lesions	1	5 (45.5)	2 (22.2)	0.540
		2-5	4 (36.3)	5 (55.6)	
		6 or more	2 (18.2)	2 (22.2)	
	Type of lesion	Ulcer	8 (72.7)	8 (100)	NA
		Otther	3 (27.3)	0	
Intralesional glucantime (*n*=117)	Time of evolution, weeks*		8 (4-17)	12 (6-17)	0.602
	Region of origin	Andean or Pacific	72 (96.0)	38 (92.7)	0.440
		Amazonic or Orinoco	3 (4.0)	3 (7.3)	
	History of leishmaniasis	Yes	20 (26.7)	8 (19)	0.350
		No	55 (73.3)	34 (81)	
	Number of lesions	1	54 (72.0)	28 (66.7)	0.550
		≥2	21 (28.0)	14 (33.6)	
	Type of lesion	Ulcer	67 (90.3)	33 (86.8)	0.280
		Other	5 (9.3)	5 (13.2)	
Thermotherapy (Thermomed®) (*n*=51)	Time of evolution, weeks*		8 (4-13)	9 (4-17)	0.772
	Region of origin	Andean or Pacific	8 (100.0)	41 (100.0)	NA
		Amazonic or Orinoco	0	0	
	History of leishmaniasis	Yes	15 (37.5)	1 (10.0)	0.110
		No	27 (64.3)	9 (90.0)	
	Number of lesions	1	33 (78.6)	8 (80.0)	0.920
		≥2	9 (21.4)	2 (20.0)	
	Type of lesion	Ulcer	39 (100.0)	10 (90.5)	NA
		Other	0	3 (9.5)	
Topic under investigation (*n*=61)	Time of evolution, weeks*		8 (8-17)	9 (6-13)	0.642
	Region of origin	Andean or Pacific	28 (100.0)	29 (96.7)	NA
		Amazonic or Orinoco	0	1(3.3)	
	History of leishmaniasis	Yes	2 (6.5)	4 (13.3)	0.320
		No	29 (93.5)	26 (86.7)	
	Number of lesions	1	22 (71.0)	24 (80.0)	0.310
		≥2	9 (29.0)	6 (20.0)	
	Type of lesion	Ulcer	28 (90.3)	27 (90.0)	0.970
		Other	3 (9.7)	3 (10)	
Combined treatment (*n*=36)	Time of evolution, weeks*		8 (6-13)	8 (6-8)	0.372
	Region of origin	Andean or Pacific	31	2	0.390
		Amazonic or Orinoco	1	1	
	History of leishmaniasis	Yes	28 (87.5)	4 (100.0)	NA
		No	4 (12.5)	0	
	Number of lesions	1	18 (56.3)	3 (75.0)	0.470
		≥2	14 (43.7)	1 (25.0)	
	Type of lesion	Ulcer	30 (93.8)	4 (100.0)	NA
		Other	2 (6.2)	0	

χ^2 test was used; *Data were expressed as median (IQR) and Mann Whitney *U* test was used. Not all data were found in the following categories: Systemic Glucantime: Number of lesions (*n*=2); Systemic glucantime: type of lesion (*n*=3); Miltefosine: type of lesion (*n*=1); Intralesional glucantime: Region of origin (*n*=1); Intralesional glucantime: type of lesion (*n*=7). Patients from abroad were excluded from the analysis of region of origin: miltefosine (*n*=1), thermotherapy (*n*=3), investigational topical (*n*=3), combination treatment (*n*=1). Note: due to the few records of patients treated with pentamidine and thermotherapy (hydrogel), these treatments were not included in this analysis.

Table 5. Reported adverse events with systemic, local and combined treatments [*n*(%)].

Reported adverse events	Systemic			Local miltefosine		Combined
	Glucantime	Miltefosine	Pentamidine	Intralesional glucantime	Thermotherapy	Thermotherapy + Miltefosine
Arthralgias	11 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.7)	1 (2.8)
Myalgias	8 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	9 (17.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (9.6)	2 (5.6)
Diarrhea	2 (3.8)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)
Abdominal pain	4 (7.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)
Nausea	1 (1.9)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (11.2)
Vomiting	2 (3.8)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (36.1)
Fever	2 (3.8)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Anorexia	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Local pain	2 (3.8)	0 (0.0)	0 (0.0)	2 (1.7)	1 (1.9)	1 (2.8)
Edema at application site	2 (3.8)	0 (0.0)	0 (0.0)	4 (3.4)	5 (9.6)	3 (8.3)
Vesicles	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	37 (71.2)	31 (86.1)
Erythema	0 (0.0)	0 (0.0)	1 (10.0)	1 (0.9)	0 (0.0)	2 (5.6)

PECET is a research center recognized by the Colombian Ministry of Science and Technology, this center has research units in the areas of product development and clinical trials and has Good Clinical Practice (GCP) certification, a condition that allows it to access the different treatment options available and to carry out evaluations of new alternatives and/or schemes.

Regarding the frequencies reported in aspects of the study population such as age and sex distribution, history of leishmaniasis and clinical presentation of the disease with respect to type, number and location of lesions, this information coincides with a report from Colombia that suggests there have been no significant changes in the dynamics of the disease[16–18]. For this study, it was found that 78.4% of the patients reported that the area of origin, understood as the geographic place where the infection is believed to have taken place, was the departments of Antioquia and Chocó. Although this finding differs from that reported for the country, the location of PECET (city of Medellín) explains this result, since it is a nearby care center for the municipalities belonging to the departments mentioned.

With the exception of liposomal amphotericin B, the results of this manuscript reflect therapeutic response and safety data for all treatment options recommended by the Colombian Ministry of Health and Social Protection for the management of CL[3], as well as new developments[19,20] and combinations of treatments[21], in compliance with WHO recommendations for research on leishmaniasis therapeutics, which are based on the promotion of research on therapeutics for leishmaniasis in order to find new safe, effective and affordable alternative drugs, with shorter treatment cycles, as well as to evaluate new drug combinations defining appropriate doses and schedules for the patients, generate local evidence of the existing alternatives and promote the dissemination of the results of such research[8,15,22].

The performance of the different systemic and local therapeutic alternatives evaluated was variable, with cure rates ranging from 44.4% to 88.9% for hydrogel thermotherapy and combined treatment (thermotherapy plus a short course of oral miltefosine)[21]. Regarding antimonials, a drug recommended as first choice in Colombia, the results of this study showed a decrease in the proportion of cure when compared with local evidence and with evidence from scientific evidence synthesis studies such as meta-analyses[23,24]; on the other hand, thermotherapy as monotherapy or in combined use, were the options that presented the best performance, even superior to that reported in previous studies[21,24,25], findings of this type support the need to consider changes in national treatment guidelines, giving priority to less invasive treatments, with shorter schedules and better safety profiles, this last being mainly associated with local adverse events and mostly of mild intensity. However, it should be taken into account that the treatment that presented the shortest healing time was systemic glucantime; therefore, it is necessary to consider the treatment received when following up the evolution of the lesions, in order to avoid the underestimation of their performance.

In addition, no differences were found between the therapeutic response and epidemiological and clinical variables that could be related to the healing process. Although the recommendations for treatment of CL in the New World suggest taking into account the species of the parasite when choosing the drug or alternative to be used[8]. Unfortunately for this study there were no data available regarding the species of the parasite responsible for the infection; with the grouping of patient origin data by geographic region, we tried to infer this information, taking into account that

in the departments of the Andean and Pacific regions the species *L. panamensis* predominates and in the departments of the Amazon region and the Orinoco region the species *L. braziliensis* is the most frequent[25], but no significant differences were found in terms of treatment performance. These findings support the definition of patient management considering patient safety and availability rather than therapeutic response.

In line with what has been reported in previous studies, pentavalent antimonials (glucantime) present the greatest variety and frequency of systemic adverse events[25], which is of vital importance when defining the management of the disease. On the other hand, the local events reported by the patients who received thermotherapy with the Thermomed® device, such as the presence of vesicles at the site of heat application, although very frequent, were all mild, rapidly resolved and without consequences for the patients.

It is important to note that the patients who received the combined treatment option were part of a clinical trial[21], therefore, the careful collection of information for this type of study could reflect to a large extent the adverse events expected for the two therapeutic alternatives evaluated, which in this case were a single session of thermotherapy with the Thermomed® device and a 21-day course of miltefosine (oral).

Among the limitations of the study, we can highlight the lack of systematization in the reporting of adverse events and the non-adherence of patients to the follow-up of their treatments; these aspects result in a significant loss of information for the construction of safety profiles of the different treatments, as well as the possible underestimation of the cure rate of the different therapeutic alternatives, especially in those patients who had reported a clinical improvement but were unable to define the outcome of the therapy. Therefore, it is imperative to standardize guidelines and protocols for the care, management and follow-up of patients with CL in order to generate quality scientific evidence that allows evidence-based decision making and taking into account the particular characteristics of the patients.

In conclusion, the safety profile and performance of local therapeutic alternatives and combined schemes for the treatment of uncomplicated CL are an interesting option for the management of the disease.

Conflict of interest statement

All authors declare there is no conflict of interest.

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Authors' contributions

LLC participated in the development of the concept and design of the study. NRM and JQP participated in data collection. All authors participated data analysis, interpretation, writing of the manuscript and its critical revision.

References

[1] Organización Panamericana de la Salud. *Manual de procedimientos para vigilancia y control de las leishmaniasis en las Américas*. Washington, D.C.: OPS; 2019.

[2] Goto H, Lauletta Lindoso JA. Cutaneous and mucocutaneous leishmaniasis. *Infect Dis Clin North Am* 2012; **26**(2): 293–307.

[3] Ministerio de Salud de Colombia. *Lineamientos para la atención clínica de leishmaniasis en Colombia. Bogotá, 2018.* [Online]. Disponible en: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/PP/PAI/Lineamientos-leishmaniasis.pdf. [Accessed on 1 March 2021].

[4] Bailey MS, Lockwood DNJ. Cutaneous leishmaniasis. *Clin Dermatol* 2007; **25**(2): 203–211.

[5] World Health Organization. *Leishmaniasis*. [Online]. Available from: https://www.who.int/es/news-room/fact-sheets/detail/leishmaniasis. [Accessed on 1 March 2021].

[6] Pinart M, Rueda JR, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database Syst Rev* 2009; 2020; **8**: 14.

[7] Organización Panamericana de la Salud. Leishmaniasis: Informe epidemiológico de las Américas. Núm. 10, diciembre del 2021. Washington, D.C.: OPS; 2021. [Online]. Disponible en: https://iris.paho.org/handle/10665.2/51742.[Accessed on 1 March 2021].

[8] World Health Organization. Control de las leishmaniasis Informe. Control las leishmaniasis Inf una Reun del Com Expert la OMS sobre el Control las Leishmaniasis, Ginebra, 22-26 marzo 2010, 2010; p.186. [Online]. Disponible en: https://apps.who.int/iris/bitstream/handle/10665/82766/WHO_TRS_949_spa.pdf?sequence=1. [Accessed on 1 March 2021].

[9] Henao HH, Osorio Y, Saravia NG, Gómez A, Travi B. Eficacia y toxicidad de los antimoniales pentavalentes (Glucantime y Pentostam) en un modelo animal de leishmaniasis cutánea americana: Aplicación de la luminometría. *Biomédica* 2004; **24**(4): 393.

[10]Vásquez de Ricciardi Laura. Terapéutica antileishmania: revisando el pasado, el presente y el futuro. Gac Méd Caracas. 2009; 117(2): 93-111.

[Online]. Disponible en: http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S0367-47622009000200002. [Accessed on 1 March 2021].

[11]Limachi-Choque JW, Rojas-Cabrera E, Verduguez-Orellana A, Eid-Rodríguez D. El tratamiento intralesional de Leishmaniasis cutánea es seguro frente al riesgo de complicaciones mucosas? *Gac Medica Boliv* 2020; **43**(1):18-22.

[12]Soto J, Soto P. Oral miltefosine to treat leishmaniasis. *Biomedica* 2006; **26**(Suppl 1): 207-217.

[13]Robledo SM, Puerta JA, Muñoz DL, Guardo M, Vélez ID. Efficacy and tolerance of pentamidine for treatment of cutaneous leishmaniasis caused by por L. (V) panamensis in Colombia. *Biomedica* 2006; **26** (Suppl 1): 188–193.

[14]Medina-Morales DA, Machado-Duque ME, Machado-Alba JE. Epidemiology of cutaneous leishmaniasis in a colombian municipality. *Am J Trop Med Hyg* 2017; **97**(5): 1503-1507. doi: 10.4269/ajtmh.17-0233. Epub 2017 Aug 18. PMID: 28820714; PMCID: PMC5817762.

[15]Blanco VM, Cossio A, Martinez JD, Saravia NG. Clinical and epidemiologic profile of cutaneous leishmaniasis in Colombian children: Considerations for local treatment. *Am J Trop Med Hyg* 2013; **89**(2): 359-364. doi: 10.4269/ajtmh.12-0784. Epub 2013 Jun 24. PMID: 23798581; PMCID: PMC3741260

[16]López L, Robayo M, Vargas M, Vélez ID. Thermotherapy. An alternative for the treatment of American cutaneous leishmaniasis. *Trials* 2012; **13**: 58. Erratum in: *Trials* 2017; **18**(1): 408.

[17]Robledo Restrepo SM, Quintero J, Higuita J, Fernández M, Murillo J, Restrepo A, et al. *Caesalpinia spinosa* (Molina) Kuntze: Una nueva promesa para el tratamiento tópico de la leishmaniasis cutánea. *Rev Acad Colomb Cienc Exactas Fis Nat* 2020; **44**(173): 915-936.

[18]Robledo Restrepo S , Vélez Bernal I , Pantoja Sánchez H, Higuita Castro J. *Hidrogel que comprende acrilamida y ácido acrílico para el tratamiento de leishmaniasis cutánea*. NC2017/0004890 (patent) 2020.

[19]López L, Valencia B, Alvarez F, Ramos AP, Llanos-Cuentas A, Echevarria J, et al. A phase][multicenter randomized study to evaluate the safety and efficacy of combining thermotherapy and a short course of miltefosine for the treatment of uncomplicated cutaneous leishmaniasis in the New World. *PLoS Negl Trop Dis* 2022; **16**(3): e0010238.

[20]Pan American Health Organization. *Guideline for the treatment of leishmaniasis in the Americas*. 2nd edition [Online]. Washington, D.C.: Pan American Health Organization; 2022. [Online]. Available from: https://iris.paho.org/bitstream/handle/10665.2/56120/9789275125038_eng.pdf?sequence=13&isAllowed=y. [Accessed on 1 March 2023].

[21]World Health Organization. *Control of leishmaniasis, 2007*. [Online]. Available from: https://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_10-en.pdf. [Accessed on 1 March 2021].

[22]Vélez I, López L, Sánchez X, Mestra L, Rojas C, Rodríguez E. Efficacy of miltefosine for the treatment of American cutaneous leishmaniasis. *Am J Trop Med Hyg* 2010; **83**(2): 351-356.

[23]Cardona-Arias JA, Vélez ID, López-Carvajal L. Efficacy of thermotherapy to treat cutaneous leishmaniasis: A meta-analysis of controlled clinical trials. *PLoS One* 2015; **10**(5): e0122569.

[24]Vélez ID, Muskus C, Robledo SM. An updated geographical distribution of *Leishmania* species involved in human leishmaniasis in Colombia. 2021. [Online]. Available from: https://doi.org/10.21203/rs.3.rs-200484/v1. [Accessed on 1 March 2021].

[25]Vélez I, López L, Sánchez X, Mestra L, Rojas C, Rodríguez E. Efficacy of miltefosine for the treatment of American cutaneous leishmaniasis. *Am J Trop Med Hyg* 2010; **83**(2): 351-356.

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