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Efficacy of Miltefosine for the Treatment of American Cutaneous Leishmaniasis

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Abstract. Miltefosine is an oral agent used for cutaneous leishmaniasis treatment. An open-label, randomized, phase III clinical trial was carried out in the Colombian army population. Miltefosine, 50 mg capsule was taken orally three times per day for 28 days (N = 145) or meglumine antimoniate, 20 mg/kg body weight per day for 20 days by intramuscular injection (N = 143). The efficacy of miltefosine by protocol was 69.8% (85/122 patients) and 58.6% (85/145 patients) by intention to treat. For meglumine antimoniate, the efficacy by protocol was 85.1% (103/121 patients) and 72% (103/143 patients) by intention to treat. No association was found between drug efficacy and *L.* (*V.*) *braziliensis* or *L.* (*V.*) *panamensis* species of *Leishmania* responsible for infection. Adverse gastrointestinal events were associated with the use of miltefosine, the meglumine antimoniate treatment was associated with adverse effects on the skeletal musculature, fever, cephalea, and higher toxicity in kidney, liver, pancreas, and hematological system.

INTRODUCTION

Leishmaniases are zoonoses caused by parasites of the genus *Leishmania* and transmitted by female sand flies of the genera *Lutzomyia* (Americas) and *Phlebotomus* (Old World).[1] These diseases affect man and other wild and domestic mammals and are endemic in 88 countries, including 72 developing nations.[2,3] An estimated 12 million people worldwide are infected by *Leishmania* parasites, and between 1.5 and 2 million new cases occur annually, of which 1–1.5 million are of the cutaneous form (CL).[1,3,4]

Leishmaniasis has been a re-emerging disease in Colombia since 2005, and this country now ranks second in the number of reported cases in the Americas. Between 2005 and 2008, 61,120 cases were diagnosed, of which 34,262 (56.1%) were in military personnel.

The pentavalent antimonials meglumine antimoniate and sodium stibogluconate have been considered the first line treatment of leishmaniasis since the 1940s.[5] In Colombia, the national health authorities recommend a dose of 20 mg Sb^5/kg per day for 20 days for CL and 28 days for mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis (VL).

However, pentavalent antimonials are expensive (approximately US$200 per patient), toxic to the heart, liver (e.g., elevated levels of hepatic enzymes), kidney (e.g., elevated creatinine and uric nitrogen [BUN] levels), pancreas (e.g., pancreatitis), and the hematopoietic system (e.g., leucopenia and thrombocytopenia). These drugs can also cause arthralgias and myalgias. In addition, the lengthy duration of chemoprophylaxis can result in problems of adherence to the treatment regimen. Furthermore, the administration of antimonials is proscribed during pregnancy and lactation, in very small children, in individuals with hypersensitivity to the drugs, and in people suffering from certain chronic diseases. Reduced sensitivity of *Leishmania* parasites to antimonials has also been reported.[5–14] All of these factors have driven the search for therapeutic alternatives for the treatment of leishmaniasis.[2]

Various oral medications have been evaluated in the search for therapeutic alternatives to antimonials, including dapsone,[15] ketoconazol,[16,17] mefloquine,[18] allopurinol,[19] and others,[2] but none were shown to be effective. The analysis of the efficacy of different drugs is further complicated by methodological differences between the studies, as demonstrated by a recent meta-analysis of the literature that examined clinical trials of CL treatments, which failed to provide clear conclusions.[2,20]

Miltefosine (hexadecylphosphocholine) has been studied as an antitumoural agent[21] and was later showed to have *in vitro* and *in vivo* activity against *Leishmania* parasites.[22–26] Miltefosine has been used in India since 1998 for the treatment of VL,[27,28] and this success has driven its evaluation as a treatment of other forms of leishmaniasis.[29] In Colombia, two studies have been carried out to evaluate the efficacy of miltefosine in the treatment of CL. The first of these was a phase I–II study, which reported a cure rate per protocol of 66% in subjects who received a dose of 50–100 mg/day and 95% in those who received 133–150 mg/day.[30] The second was a multicenter study (Colombia and Guatemala) in which miltefosine was compared with a placebo. The cure rate per protocol was 91% and 53% for Colombia and Guatemala, respectively. Even when the sample size was reduced, the differences in the therapeutic response could be attributed to the *Leishmania* species predominant in each country: *L.* (*Viannia*) *panamensis* in Colombia and *L.* (*V.*) *braziliensis* and *L.* (*L.*) *mexicana* in Guatemala.[29] Nevertheless, recent studies carried out in Colombia have shown that *L.* (*V.*) *panamensis* predominates in the northeast region (Andean region), whereas in the southeast, the region responsible for most cases since 2005, 80% of lesions are caused by *L.* (*V.*) *braziliensis* (PECET, unpublished information).

With the goal of expanding information on the efficacy of miltefosine in Colombia, the *Ministerio de la Protección Social de Colombia* ordered a therapeutic trial to be performed in different endemic regions of the country, involving a greater number of clinical cases and identification of the *Leishmania* species causing the lesions.

MATERIALS AND METHODS

Study design. A randomized, open-label phase III clinical trial was carried out in which the efficacy and safety of miltefosine was compared with that of meglumine antimoniate. The protocol was approved by the bioethics committee for research on humans in the *Sede de Investigación Universitaria* (CBEIH-SIU) of the University of Antioquia and by the

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ethics committee of the General Health Directorate of the Colombian Army and carried out according to international norms of good clinical practice.

Population and study site. The study was carried out between June 2006 and April 2008. The subjects of the study were adult males serving in the Colombian Army. The study was carried out in five military health establishments located in central, northeast, and southern Colombia.

Inclusion criteria. The study included subjects who had 1) a confirmed parasitological diagnosis of leishmaniasis; 2) received no treatment of the current infection during the past 6 weeks; 3) normal renal, hepatic, pancreatic, and hematological functions; and 4) volunteered to participate in the study.

Exclusion criteria. Subjects with the following conditions were excluded from the study: 1) serious concomitant illnesses, 2) lesions with mucosal involvement, or 3) Disseminated cutaneous leishmaniasis (presence of 10 or more cutaneous lesions and a negative Montenegro skin test).

Study medications. One 50 mg capsule of miltefosine (Impávido®, Zentaris, Frankfurt, Germany) was administered orally three times per day for 28 days. Capsules were administered after each meal, for a daily dose of 150 mg and a total dose of 4,200 mg per patient. Meglumine antimoniate (Glucantime®, Aventis, Paris, France) was administered intramuscularly at a dose of 20 mg/kg body weight per day for 20 days. All patients remained in their military bases throughout the treatment, which was administered and supervised daily by the health personnel of the military units.

Collection of data and clinical samples. After the patients signed the informed consent form for participation, a clinical form containing demographic information, data on the lesions, and a summary of the inclusion/exclusion criteria was prepared for each patient. A photographic record was also made of each lesion. Clinical samples were taken from all subjects for the parasitological confirmation of leishmaniasis, lesion aspirate samples were taken from each of the patients and were processed as explained in other publications. In brief, the aspirates were cultured in NNN culture medium, incubated at 26°C, and from the fourth day on they were observed weekly for 1 month, in the inverted microscope in search of promastigotes.[31] The media cultures were labeled with the code of each participant and were stored on independent racks to avoid mixing. Each week positive cultures were mass cultured in 50 mL glass bottles with NNN modified medium, one part was frozen in liquid nitrogen and is now stored in the PECET Criobank, and the other was used for species identification and the identification of the *Leishmania* species involved using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), following established procedures.[32] In these procedures the good laboratory practice (GLP) standards were followed. The PECET is certified by Health Authorities and Quality Control is done by the DSA (Antioquia Local Health Department).

Assignment to treatment groups. Subjects were randomly assigned to the treatment groups. A list of treatments, generated randomly in blocks of eight (EpiInfo, version 3.1, CDC, Atlanta, GA), was used to assign each subject to a treatment group. Only the study coordinator had access to the list and was in charge of assigning the treatments.

Follow-up and outcomes. During the study, volunteers were evaluated at the start and the end of the treatment and at 6 weeks, 3 months, and 6 months after completion. Renal, hepatic, pancreatic, and hematological function was measured before the start of treatment, midway through treatment, and at the end of treatment. Adverse events were evaluated according to standard criteria used in therapy of cancer v.3 (CTCAE).[33]

The response to treatment was evaluated clinically. The following definitions were used for each lesion:

Initial cure: Complete re-epithelialization of all ulcers and complete disappearance of the induration up to 3 months after the end of treatment.

Definitive cure: Initial cure plus the absence of recurrences or MCL for 6 months after the end of treatment.

Clinical improvement: Re-epithelialization and at least 50% reduction of the area induration relative to previous observation. Lesions that presented clinical improvement 6 weeks after the end of treatment were monitored for an additional 3 months, after which time the lesion should have completely healed; if not, the case was classified as therapeutic failure.

Absence of response: An increase in the area of ulceration and induration relative to the previous examination, or less than 50% re-epithelialization of the ulcerated area and relative reduction of the indurated area. If there was no response at the end of treatment, the lesion was monitored for an additional 6 weeks. Absence of response at 6 weeks post-treatment was considered treatment failure.

Failure: At least 50% increase in lesion size at the end of treatment, absence of clinical response at 6 weeks, or any sign of lesion activity 3 months after the end of treatment.

Recurrence: Reactivation of the lesion at the original site after cure or mucosal compromise during follow-up.

Reinfection: Appearance of new lesions at anatomical sites different from the sites of the original lesions after the patient was evaluated as cured and returned to endemic areas.

Rescue therapy for all volunteers whose treatment failed involved the administration of 20 mg/Sb^5 (meglumine antimoniate)/kg body weight per day for 20 days as recommended by Colombian Ministry of Health guidelines. Those individuals who did not respond to rescue therapy were treated with amphotericin B.

Calculation of sample size. The sample size was calculated assuming an expected effectiveness of at least 78% for miltefosine and 90% for the pentavalent antimonials, 95% confidence interval (CI) and a power of 80%. An additional 20% was added to the calculated sample size to compensate for loss during the follow-up period. On the basis of these figures, the sample size was calculated as 144 subjects per group, for a total of 288 for both groups.

Statistical analyses. Data entry and analyses were performed using ACCESS and SPSS (version 15, SPSS Inc., Chicago, IL), respectively. The basal characteristics of the volunteers were tabulated and analyzed for each treatment group. The efficacy of the treatments was calculated by intention to treat and by protocol. The relative risk was calculated using 2×2 tables. The χ^2 test or Fisher's exact test was used for hypothesis testing of dichotomous variables. Taking into account the distribution of the variables, a Student's *t* test or Mann-Whitney *U* test was used for analyses of continuous data. Potential confounding factors and interactions were controlled with stratified analyses for the species of parasite responsible for the infection, lesions number, anatomic location of the lesion, type of lesion, and geographic location where the infection occurred. Statistical

methods of survival analysis (Kaplan-Meyer and Logrank test) were used to compare the cure times between the treatments. A statistical significance of $P < 0.05$ and 95% CIs were set for all analyses.

RESULTS

The 288 subjects included in the study were randomly assigned to groups receiving either miltefosine ($N = 145$) or meglumine antimoniate ($N = 143$). In the former group, two subjects (1.4%) did not complete the treatment because of secondary effects and 21 (14.7%) were lost during the 6-month follow-up, so that 122 (84.1%) completed the study according to the protocol. In the meglumine antimoniate group, 18 (12.6%) were lost during the 6-month follow-up, 2 (1.4%) left the army before completing the study, and two (1.4%) were killed in combat, so that 121 subjects (84.6%) completed the study according to the protocol.

Recurrences. Three (2.1%) and four (2.8%) patients treated with miltefosine and meglumine antimoniate, respectively, presented with recurrences. These patients received one cycle of meglumine antimoniate, and only one of the cases (a patient belonging to the group initially treated with meglumine antimoniate) required a third treatment cycle, this time with amphotericin B. All the recurrences appeared within 3 months after the end of treatment.

Basal analyses. As shown in Table 1, the demographic, clinical, and parasitological characteristics of the participants before treatment were similar in both study groups.

Therapeutic response. *Initial cure.* Three months after treatment ended, 67.6% (98/145) and 78.3% (112/143) of the subjects treated with miltefosine and meglumine antimoniate, respectively, were cured.

Definitive cure. Between the follow-ups at 3 months and 6 months post-treatment, 13 (9%) subjects were lost from the miltefosine group and seven (4.9%) were lost from the meglumine antimoniate group. The cure rate by protocol was 69.8% (85/122 patients) in the group treated with miltefosine and 85.1% (103/121 patients) in the group treated with meglumine antimoniate. By intention to treat, the cure rate in the group that received miltefosine was 58.6% (85/145 patients), whereas the cure rate in the group receiving meglumine antimoniate was 72% (103/143 patients) (Table 2).

Analysis by group. The *Leishmania* species responsible for infection was identified in 165 (57.3%) subjects. In the group treated with meglumine antimoniate, 32 (38.1%) subjects had lesions caused by *L.* (*V.*) *panamensis* and 52 (61.9%) had lesions caused by *L.* (*V.*) *brazililensis.* In the group treated with miltefosine, 30 (37%) subjects had lesions caused by *L.* (*V.*) *panamensis* and 51 (63%) had lesions caused by *L.* (*V.*) *brazililensis.*

The cure rate with meglumine antimoniate in patients with *L.* (*V.*) *panamensis* and *L.* (*V.*) *braziliensis* was 71.9% and 65.4%, respectively. In the group treated with miltefosine, the cure rate was 60% for *L.* (*V.*) *panamensis* and 49% for *L.* (*V.*) *braziliensis*. No association was found between the efficacy of the treatments (meglumine antimoniate $P = 0.5$ and miltefosine $P = 0.3$) and the species responsible for the infection.

No association was found between the efficacy of the treatments and characteristics such as lesions number, anatomic location of the lesion, type of lesion, and the geographic location where the infection occurred (Table 3).

Safety. The local and systemic adverse events found in the study are summarized in Table 4. With the exception of gastrointestinal problems, reports of adverse events were generally more frequent and serious in the group treated with meglumine antimoniate.

In evaluations carried out at the middle and end of treatment, the frequency of adverse events, such as fever, myalgia, arthralgia, and cephalea, was higher in the group that received meglumine antimoniate; furthermore, in the final treatment evaluation these adverse events were associated with the use of meglumine antimoniate ($P < 0.001$). In the group treated with miltefosine, an association with vomiting and nausea ($P < 0.001$) was found in the evaluations carried out during the treatment; however, miltefosine was associated with

TABLE 1
Baseline characteristics of the volunteers

Characteristic		Meglumine antimoniate $N = 143$	Miltefosine $N = 145$	P*
Age (years) (median [min – max])		23 (19–38)	23 (19–37)	0.4†
Race (%)	White	17 (11.9)	14 (9.7)	0.8
	Black	6 (4.2)	9 (6.2)	
	Mestizo	115 (80.4)	116 (80)	
	Mulatto	5 (3.5)	6 (4.1)	
Weight (kg) (median [min – max])		64 (47–90)	65 (50–96)	0.06†
Antecedents of leishmaniasis (%)	Yes	52 (36.4)	63 (43.4)	0.1
	No	91 (63.6)	82 (56.6)	
Geographical location of infection	NE	17 (11.9)	15 (10.3)	0.8
	SE	126 (88.1)	130 (89.7)	
Number of lesions (%)‡	1	97 (67.8)	101 (69.7)	0.7
	2 or more	46 (32.2)	44 (30.3)	
Type of lesion (%)	Nodule	7 (4)	9 (5.3)	0.6
	Ulcer	167 (96)	161 (94.7)	
Anatomical location of lesions	Upper part of the body	118 (82.5)	117 (80.7)	0.9
	Lower part of the body	17 (11.9)	20 (13.8)	
	Upper and lower parts	8 (5.6)	8 (5.5)	
Time of evolution (days) (median [min – max])		60 (6–210)	60 (15–1080)	0.1†
Species (%)	*L.*(*V.*) *panamensis*	32 (38.1)	30 (37)	0.9
	L. (*V.*) *braziliensis*	52 (61.9)	51 (63)	

*χ^2 test.
†Mann Whitney *U* test.
‡According to number of lesions.

TABLE 2
Efficacy of meglumine antimoniate and miltefosine by protocol and by intention to treat

Analysis	Meglumine antimoniate		Miltefosine		P*
	Cure/total	Efficacy (%) 95% CI	Cure/total	Efficacy (%) 95% CI	
By protocol	103/121	85.1 (77.4–91.9)	85/122	69.8 (61.1–78.2)	0.003
Intention to treat	103/143	72 (64.3–79.7)	85/145	58.6 (50.3–67)	0.02

* χ^2 test.

abdominal pain ($P < 0.05$) only in the final treatment evaluation (Table 4A).

Alterations in the renal, hepatic, pancreatic, or hematological function were more frequent in the group given meglumine antimoniate in all the evaluations carried out at the middle and end of the treatment. In both evaluations, an association was found between meglumine antimoniate and an increased amylase level ($P < 0.05$), which in some cases reached grade 3 (Table 4B).[33]

Serious adverse events. Four patients presented serious adverse events, three of which were unrelated to treatment (two deaths in combat and one a stab wound). One volunteer from the miltefosine group presented with hematemesis, which was treated medically until he recuperated.

Survival analyses. Patients who received meglumine antimoniate presented a significantly lower proportion of treatment failures (15%) than the group treated with miltefosine (30%) (Logrank = 8.8 $P = 0.002$).

DISCUSSION

In this study all of the patients were treated without any problem and the follow-up rate of patients at 6 months was 84.4%. In the meglumine antimoniate-treated group, the efficacy by protocol and intention to treat was 85.1% and 72%, respectively. In this study, the reduced efficacy of pentavalent antimonials at the same doses in Colombian patients was confirmed, where more than 90% effective in the 1990s did not exceed 85% efficacy in the present decade.[19,33,34] The reduced efficacy of antimonials could be due, among other factors, to the administration of incomplete, sub-optimal doses of the therapy, given the problems of adherence and inaccessibility of the total recommended dose for many patients. However, evidence of direct person-to-person transmission of American cutaneous leishmaniasis (ACL) may also explain this diminished efficacy.[34]

The efficacy of miltefosine in our study was 69.8% by protocol and 58.6% by intention to treat; in contrast, the multicenter study carried out in Colombia and Guatemala reported miltefosine efficacies of 91% and 53%, respectively, in the analysis by protocol. The difference between the two Colombian studies is statistically significant ($P < 0.001$).[29]

The results of this study show that the efficacy of meglumine antimoniate is statistically superior to that of miltefosine in the treatment of cutaneous leishmaniasis (CL) in Colombia ($P = 0.003$).

The differences in the therapeutic response between the studies carried out in Colombia and Guatemala were partially attributed to the *Leishmania* species predominant in each country.[29] The information from Colombia, however, is based principally on historical data: for the previous study, only seven isolates could be identified, all as *L.* (*V.*) *panamensis*. In this study, no differences were found in the response to treatment based on the species responsible for the infection. Furthermore, Soto and others[35] found miltefosine to be effective in 88% of cases in a study carried out in Palos Blancos, Bolivia, where the predominant species is *L. braziliensis*.

Interestingly, we found that even when there was no statistically significant difference between the groups, lesions caused by *L. braziliensis* responded poorly to meglumine antimoniate (65.4%) and miltefosine (49%) than the lesions caused by *L.* (*V.*) *panamensis* (71.9% and 60%, respectively). These results corroborate the results obtained by PECET in *in vitro* studies, which compared the sensitivity of *L.* (*V.*) *braziliensis*

TABLE 3
Efficacy of meglumine antimoniate and miltefosine according to the species of parasite, anatomic location, number and type of lesions and geographic location of infection

Characteristic	Efficacy/total volunteers (%) Meglumine antimoniate	P*	Efficacy/total volunteers (%) Miltefosine	P*
Overall efficacy	103/143 (72)	–	85/145 (58.6)	–
Species				
L. (*V.*) *panamensis*	23/32 (71.9)	0.5	18/30 (60)	0.3
L. (*V.*) *braziliensis*	34/52 (65.4)		25/51 (49)	
Number of lesions				
1	72/97 (74.2)	0.4	60/101 (59.4)	0.5
2 or more	31/46 (67.4)		24/44 (54.5)	
Anatomic location of the lesions				
upper part of the body	87/118 (73.7)	0.4	66/117 (56.4)	0.7
lower part of the body	10/17 (58.8)		13/20 (65)	
upper and lower body parts	6/8 (75)		5/8 (62.5)	
Type of lesion				
Nodule	6/7 (85.7)	1	5/9 (55.5)	1
Ulcerated	134/167 (80.2)		90/161 (55.9)	
Geographic location of infection				
NE	9/17 (52.9)	0.06	10/15 (66.6)	0.5
SE	94/126 (74.6)		74/130 (56.9)	

* χ^2 test.

TABLE 4
Incidence and relative risk of adverse local and systemic events present at the middle and end of treatment

Test/event		Middle of treatment: Event or test/total volunteers (%)			End of treatment: Event or test/total volunteers (%)		
		Meglumine antimoniate	Miltefosine	RR (95% CI)	Meglumine antimoniate	Miltefosine	RR (95% CI)
A Clinical symptoms							
Clinical symptoms	Fever	11/119 (9.2)	8/130 (6.2)	1.5 (0.6–3.6)	29/131 (22.1)	8/129 (6.2)	3.6 (1.7–7.5)**
	Myalgia	12/119 (10)	9/130 (6.9)	1.5 (0.6–3.3)	67/131 (51.1)	16/129 (12.4)	4.1 (2.5–6.7)**
	Arthralgia	17/119 (14.2)	9/130 (6.9)	2.6 (1–4.5)	65/131 (49.6)	13/129 (10.1)	4.9 (2.8–8.5)**
	Cephalea	17/119 (14.2)	23/130 (17.7)	0.95 (0.5–1.7)	52/131 (39.7)	30/129 (23.3)	1.7 (1.2–2.5)**
	Vomiting	3/119 (2.5)	29/130 (22.3)	0.1 (0.04–0.4)**	16/131 (12.2)	44/129 (34,1)	0.4 (0.2–0.6)**
	Nausea	4/119 (3.4)	38/130 (29.2)	0.1 (0.04–0.3)**	27/131 (20.6)	59/129 (45.7)	0.5 (0.3–0.7)**
	Anorexia	8/119 (6.7)	19/130 (14.6)	0.5 (0.2–1)*	45/131 (34.4)	37/129 (28.7)	1.2 (0.8–1.7)
	Diarrhea	–	–	–	2/131 (1.5)	6/129 (4.7)	0.3 (0.1–1.6)
	Abdominal pain	–	–	–	2/131 (1.5)	9/129 (7)	0.2 (0.05–1.0)*
B Biochemistry and hematological effects							
Blood chemistry	↑ Creatinine	–	–	–	–	1/103 (0.9)	–
	↑ BUN	4/108 (3.7)	–	–	1/116 (0.9)	3/103 (2.9)	0.3 (0.03–2.8)
	↑ AST	1/107 (0.9)	1/113 (0.9)	1.1 (0.07–16.8)	10/11 1 (9)	5/103 (4.9)	1.9 (0.7–5.3)
	↑ ALT	3/110 (2.7)	1/114 (0.9)	3.1 (0.3–29.4)	20/112 (17.9)	10/104 (9.6)	1.9 (0.9–3.8)
	↑ Amylase	29/105 (27.6)	15/111 (13.5)	2.04 (1.2–4)*	24/109 (22)	11/102 (10.8)	2.04 (1.1–4)*
Hematology	↓Hemoglobin	–	–	–	5/111 (4.5)	1/102 (0.9)	4.5 (0.55–38.8)
	↓ Erythrocytes	14/100 (14)	1/105 (0.9)	14,7 (2–109.7)**	7/107 (6.5)	1/102 (0.9)	6.7 (0.8–53.3)
	↓ Leukocytes	5/110 (4.5)	2/115 (1.7)	2.6 (0.5–13.2)	2/115 (1.7)	1/105 (0.9)	1.8 (0.2–20)
	↓ Platelets	1/110 (0.9)	–	–	1/114 (0.9)	–	–

* < 0.05; ** < 0.001.

and *L.* (*V.*) *panamensis* parasites isolated in Colombia to miltefosine (PECET, unpublished data).

Treatment with meglumine antimoniate has been associated with adverse effects on the skeletal musculature (myalgia and arthralgia) as well as fever and cephalea in different studies.[2] The higher toxicity of meglumine antimoniate to organs such as the kidney, liver, pancreas, and hematological system has also been demonstrated. The previously reported association between miltefosine and adverse gastrointestinal events such as nausea, vomiting, anorexia, abdominal pain, and diarrhea[27,29,30] was confirmed during this study. However, these complications were not considered to be sufficient cause for the suspension of treatment.

Although miltefosine is the first oral agent to have showed efficacy against VL in the Old World, it has limited potential for the treatment of ACL. Among its constraints are cost, which is currently as high as that of antimonials, and the duration of treatment (28 days), which represents a serious barrier to ensuring that patients receive the full recommended dose (adherence) and may lead to the appearance of resistant strains. Its administration to women of childbearing age is inadvisable given the teratogenic risk, meaning that contraception should be guaranteed during treatment and for up to 3 months after treatment. Additionally, more than 30% of patients treated develop nausea, vomiting, and diarrhea as secondary effects. Finally, and most importantly, in light of this study, the cure rate of miltefosine for the treatment of CL in Colombia is only 69.8%, a percentage that falls to 49% when administered to patients with lesions caused by *L. braziliensis,* which comprise more than 60% of CL cases in Colombia.

On the basis of the previous evidence and given that no relationship was found between the efficacy of miltefosine and clinical or epidemiological characteristics, this drug is not recommended as a first choice treatment of ACL. Nevertheless, miltefosine has proved efficacious in the treatment of MCL cases that do not respond to treatment with antimonials[36] (PECET, unpublished data) and cases of diffuse CL (DCL).[36,37] Therefore, it can be considered as a second treatment option in certain cases. Overall, the findings of this study reinforce the need to find new therapeutic alternatives for the treatment of CL.

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