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Miltefosine for Visceral and Cutaneous Leishmaniasis: Drug Characteristics and Evidence-Based Treatment Recommendations

Begoña Monge-Maillo and Rogelio López-Vélez

Tropical Medicine Centre, Infectious Diseases Department, Ramón y Cajal Hospital, Madrid, Spain

Miltefosine is the only recognized oral agent with potential to treat leishmaniasis. Miltefosine had demonstrated very good cure rates for visceral leishmaniasis (VL) in India, Nepal, and Bangladesh, but high rates of clinical failures have been recently reported. Moderate efficacy has been observed for VL in East Africa, whereas data from Mediterranean countries and Latin America are scarce. Results have not been very promising for patients coinfected with VL and human immunodeficiency virus. However, miltefosine's long half-life and its oral administration could make it a good option for maintenance prophylaxis. Good evidence of efficacy has been documented in Old World cutaneous leishmaniasis (CL), and different cure rates among New World CL have been obtained depending on the geographical areas and species involved. Appropriate regimens for New World mucocutaneous leishmaniasis need to be established, although longer treatment duration seems to confer better results. Strategies to prevent the development and spread of miltefosine resistance are urgently needed.

Keywords. leishmaniasis; visceral leishmaniasis; cutaneous leishmaniasis; therapy; miltefosine.

Leishmaniasis is considered a neglected tropical disease, despite being the world's second leading cause of death by a parasitic agent after malaria. Leishmaniasis occurs worldwide; approximately 0.2–0.4 million visceral leishmaniasis (VL) cases and 0.7–1.2 million cutaneous leishmaniasis (CL) cases are estimated to occur each year [1, 2].

The classic therapy for all forms of leishmaniasis uses pentavalent antimonials as sodium stibogluconate (SSG) and meglumine antimoniate (MA) administered intravenously or intramuscularly. Other systemic treatments used are amphotericin B deoxycholate (AB) and liposomal amphotericin (LAB), both intravenously, and intramuscular paromomycin. Local treatments based on intralesional pentavalent antimonials, topical paromomycin, thermotherapy, or cryotherapy are used for certain cases of cutaneous leishmaniasis. Miltefosine is the only oral agent with recognized efficacy for VL and is another oral option with azoles for CL [3, 4].

The objectives of this study were to review current data on miltefosine's drug characteristics and evidence-based treatment recommendations for visceral and cutaneous leishmaniasis.

METHODS

Medical literature was searched, using the databases Medline, Embase, Web of Science, and the Cochrane Library database. No limits were placed with respect to the date of publication nor language restrictions. Search terms were *leishmaniasis*, *visceral leishmaniasis*, *cutaneous leishmaniasis*, *mucocutaneous leishmaniasis*, *post–kala-azar dermal leishmaniasis*, *New World diffuse cutaneous leishmaniasis*, *New World leishmaniasis*, or *Old World leishmaniasis* AND *miltefosine* or *treatment*. Other search terms were *L. donovani*, *L. infantum*, *L. tropica*, *L. major*, *L. aethiopica*, *L.(viannia) braziliensis*, *L (V.) guyanensis*, *L.(V.) panamensis*, *L. (V.) peruviana*, *L. mexicana*, *L. amazonensis*, or *L. venezuelensis* AND

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Correspondence: Rogelio López-Vélez, MD, PhD, DTM&H, Tropical Medicine Centre. Infectious Diseases Department, Ramón y Cajal Hospital, Carretera de Colmenar km 9.1, Madrid 28034, Spain (rogelio.lopezvelez@salud.madrid.org).

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miltefosine or *treatment*. Bibliographical references from the included studies were reviewed. The reference sections of primary studies, narrative reviews, and systematic reviews were examined to search for additional primary studies that might have been missed during the electronic search.

Data regarding pharmacokinetics, dosage, toxicity, and resistance were collected. For therapeutic options, initially only clinical trials where miltefosine was evaluated were selected to obtain data with the highest-grade evidence. Later, other studies were included such as original articles where data on results and miltefosine regimens were shown, such as large case series and multicenter studies and also case reports when relevant results were reported. Based on the methodology and the results of the studies, miltefosine treatment recommendations were outlined for each leishmaniasis presentation form, country of origin, and *Leishmania* species. The strength of such recommendations was stratified based on the Infectious Diseases Society of America grade classification [5, 6].

RESULTS

Development of Miltefosine

Originally, miltefosine was developed as an anticancer drug and was found to be highly active against *Leishmania* in vitro and in animal models in the 1980s [7]. In 1982, several studies concluded that ether lysophospholipids such as 1-O-alkylglycerophosphocholine, 1-O-alkylglycerophosphoethanolamine, and 1-O-hexadecyl-sn-glycerol were active against *Leishmania donovani* promastigotes [8]. Later on, miltefosine was administrated orally to BALB-c mice infected with *L. donovani* and *Leishmania infantum*, with high cure rates [9]. This motivated the creation of a phase 1/2 study in India where miltefosine was employed for VL [10]. In 2000 and 2001, miltefosine was demonstrated to be effective in immunodeficient infected mice [11]. This suggested that miltefosine could be a therapeutic option for leishmaniasis in patients coinfected with human immunodeficiency virus (HIV). Miltefosine was administrated topically on infected mice with *Leishmania mexicana* and *Leishmania major* CL, obtaining healing of the lesions in 2–5 weeks' time [12]. Several successful phase 2 and 3 clinical trails performed in India led to registered miltefosine as the first oral drug for VL in India in 2002. In addition, it is registered as an oral agent for VL and CL in Germany and several countries in South America.

Paladin Labs (Montreal, Canada) has been since 2008 the license holder for oral miltefosine for the indication leishmaniasis. Miltefosine was granted Orphan Drug Status by the European Medicines Agency in June 2002 and by the US Food and Drug Administration (FDA) in November 2006. Miltefosine was included in the World Health Organization essential medicines list as an antileishmaniasis medicine in March 2011 [13]. As of late 2013, the FDA endorses the use of miltefosine. In fact, the FDA's Anti-Infective Drugs Advisory Committee voted in favor of treating VL caused by *L. donovani*, CL caused by members of the *Leishmania viannia* subgenus (*Leishmania braziliensis*, *Leishmania guyanensis*, and *L. panamensis*) and mucocutaneous leishmaniasis caused by the 3 aforementioned *Leishmania viannia* subtypes with miltefosine [14]. Finally, in March 2014, the FDA approved oral miltefosine to treat visceral, cutaneous, and mucocutaneous leishmaniasis in patients aged ≥12 years [15].

Toxicity

The general side effects of miltefosine commonly affect the gastrointestinal tract; the most frequent symptoms are anorexia, nausea, vomiting, and diarrhea. Although these symptoms are usually mild, some studies have shown more severe gastrointestinal symptoms that interfered with activities of daily living [16]. Moreover, even a case of fatal acute pancreatitis secondary to miltefosine has been described [17]. Increases in serum aminotransferase and creatinine levels have also been described, which are usually mild, reversible, and dose dependent. Reproductive toxicity studies in rats during embryonic development and during organogenesis indicate an embryotoxic, fetotoxic, and teratogenic risk. Because of these findings, and as there are no controlled studies with miltefosine in pregnant women, its use is strictly contraindicated during pregnancy. Moreover, contraception use for 3 months once treatment has been finished is mandatory for women of childbearing age who are going to be treated with miltefosine [18]. There are no data on the risk of miltefosine during breastfeeding, so guidelines do not recommend its administration [19].

Treatment Failures

In vitro studies have postulated that there is a correlation between the accumulation of miltefosine within the parasite and its efficacy. Consequently, mechanisms that inhibit miltefosine intake or increase miltefosine efflux would lead to treatment failure [20–22]. It has been shown how the inactivation of 2 plasma membrane proteins (ie, LdMT and LdRos3) could produce a defect in the drug internalization into the parasite [23]. On the other hand, overexpression of multidrug exporter (as ATP-binding cassette P-glycoprotein/MDR1 and ATP-binding cassette subfamily G members) could increase the drug efflux from the parasite pumping miltefosine out [24].

It seems that a continuous drug exposure could lead to a miltefosine treatment failure. After a decade of use of miltefosine in the Indian subcontinent for VL, lower cure rates have recently been reported and the relapse rate has doubled; in India, Bangladesh, and Nepal, approximately 7%–10% of patients redevelop clinical relapse of VL within 6 months after miltefosine treatment, with relapse rates reaching 20% in Nepal after 12 months' follow-up [20, 25, 26]. In fact, higher ED_{90} values of miltefosine (the dose of miltefosine needed to eradicate 90% of

the pathogen) have been observed in endemic areas where there is wide use of miltefosine [27]. Further studies observed that although in vitro *Leishmania* pretreatment susceptibility was significantly higher than posttreatment susceptibility, such differences were not associated with the clinical outcome. However, these more tolerant parasites identified in vitro may be the first step toward the development of future complete resistance [20, 22].

A recently published study from Nepal has questioned miltefosine concentration at the end of treatment as the correct way of measuring the exposure of the parasite to the drug, proposing the total time of exposure to a high plasma concentration of the drug (>10 times the mean in vitro EC_{50}) mean half maximal effective concentration as more adequate. Most likely, miltefosine killing effect is time-dependent, so long-duration treatment regimens based on high miltefosine doses could be associated with better clinical success [26].

With respect to the host, being a child aged <12 years has been found to be a risk factor for treatment failure. This has been related to different child immune response or different pharmacokinetic characteristics, suggesting that the previously proposed miltefosine dosing regimen in children may need to be increased [26].

Therefore, the frequent premature treatment discontinuation due to the quick recovery obtained and the common gastrointestinal adverse events, added to miltefosine's long elimination half-life, could lead to tolerance and drug resistance due to the persistence of subtherapeutic levels. These, in anthroponotic foci such as the Indian subcontinent, could trigger an exponential rise of refractory parasites.

Miltefosine for Visceral Leishmaniasis

Miltefosine in Single Therapy

Several clinical trials performed in VL in India showed 94%–97% cure rates with miltefosine regimens of 2.5 mg/kg/day for 28 days [28–30] (Table 1). Other studies have observed that shorter regimens could also be effective; however, due to the scarce number of cases included and the absence of severe cases, these results cannot be generalized [31]. Also, 83%–94% cure rates have been obtained in clinical trials performed in India in children <12 years of age [32–34]. A trial performed in Bangladesh including both adults and children achieved 85% cure rates with the standard miltefosine regimen [35]. These initial results led to miltefosine being proposed as a first-line drug for VL in India, Nepal, and Bangladesh, but the lower cure rates recently reported may decrease the strength of recommendation for those countries [20, 26].

A clinical trial performed in Ethiopia in immunocompetent patients with VL registered a 75.6% cure rate with miltefosine [36]. Reliable data on the efficacy of miltefosine in VL in the Mediterranean region and Latin America have not been published.

Table 1. Miltefosine for Visceral and Cutaneous Leishmaniasis: Evidence-Based Recommendations

Treatment	Grade of Evidence
Miltefosine for visceral leishmaniasis	
Miltefosine (oral) 2.5 mg/kg/d for 28 d in children aged 2–11 y; 50 mg/d for 28 d in ages ≥12 y with weight <25 kg; 100 mg/d for 28 d in ages ≥12 y with body weight ≥25 kg; 150 mg/d for 28 d in ages ≥12 y with body weight >50 kg	BI[a]: VL in the Indian subcontinent, caused by *Leishmania donovani* BI: VL in East Africa caused by *L. donovani* CIII: VL in the Mediterranean basin and South America caused by *Leishmania infantum*
Combined therapy with miltefosine for VL	
Regimen 1: liposomal amphotericin B (IV) 5 mg/kg single dose + miltefosine (oral) for 7–14 d (doses as above); regimen 2: paromomycin (IM) 15 mg (11 mg base)/kg/d for 10 d + miltefosine (oral) for 10 d (doses as above)	AI (regimen 1 or regimen 2): VL in the Indian subcontinent, caused by *L. donovani*
Miltefosine for visceral leishmaniasis in HIV-infected patients	
Miltefosine (oral) 100 mg d + sodium stibogluconate (IM) 20 mg/kg/d for 30 d	CI: VL/HIV-coinfected patients in Ethiopia, caused by *L. donovani*
Miltefosine for Old World cutaneous leishmaniasis	
Miltefosine (oral) for 28 d (doses as above)	BI: Old World CL caused by *Leishmania major* in Iran CIII: Old World CL caused by *L. major* or *Leishmania tropica* or *L. infantum* in other geographical areas
Miltefosine for PKDL	
Miltefosine (oral) 100–150 mg/d for 60 d or 90 d	BI: PKDL caused by *L. donovani* in India
Miltefosine for New World cutaneous leishmaniasis	
Miltefosine (oral) for 20–28 d (doses as above)	BI: New world CL caused by *Leishmania panamensis* in Colombia, by *Leishmania braziliensis* in Brazil and Bolivia, and by *Leishmania guyanensis* in Brazil
Miltefosine for mucocutaneous leishmaniasis	
Miltefosine (oral) 2.5–3.3 mg/kg/d for 28–42 d	BII: New World moderate mucocutaneous leishmaniasis by *L. braziliensis* in Bolivia

Strength of recommendation: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation; D, moderate evidence to support a recommendation against use; E, good evidence to support a recommendation against use.

Quality of evidence: I, evidence from 1 or more randomized clinical trials; II, evidence from 1 or more well-designed clinical trials without randomization, from cohort or case-controlled analytic studies (preferably from >1 center), from multiple time series, or from dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Abbreviations: CL, cutaneous leishmaniasis; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

[a] Grade of evidence has been decreased with respect to initial outcomes due to the actual cure and relapse rates.

Miltefosine in Combination Therapy

The benefits of combination therapy for the treatment of VL are diverse: It could allow a reduction in the dose and duration of the regimens, decreasing toxicity and improving compliance; it could reduce costs, which is an important factor if we consider that VL mostly affects low-income countries; it could decrease the development of drug resistance and increase treatment efficacy; and it could be a good option in complicated cases and in HIV-coinfected patients.

A study performed in India showed that the combination of a single dose of LAB at 5 mg/kg followed by 7–14 days of miltefosine had slightly greater efficacy than LAB alone, with cure rates of 96%–98% vs 91%, respectively [37] (Table 1).

Another comparative study performed in India found that the combination of single-dose LAB plus miltefosine for 7 days or paromomycin plus miltefosine for 10 days was noninferior to the standard treatment based on AB for 30 days, with cure rates between 93% and 98.7%. However, patients in the combination groups had fewer adverse events than those assigned standard treatment [38]. Another recent study also carried out in India obtained a 91.9% cure rate with a combination of LAB at 5 mg/kg in single dose and miltefosine at 2.5 mg/kg/day for 14 days [39].

A clinical trial performed in East Africa pretended to assess whether a short combination of SSG plus a single dose of LAB, miltefosine plus a single dose of LAB, and miltefosine alone were effective in treating VL, but results are not yet available [40].

Miltefosine for Visceral Leishmaniasis in HIV-Infected Patients

Miltefosine has been used for the treatment of VL/HIV-coinfected patients, but published clinical information about efficacy, tolerance, and safety is scarce. Duration of treatment for primary infection or for secondary prophylaxis (maintenance treatment) has not yet been established.

Most of the data have been performed in southern Europe with *L. infantum*. In one of these published reports, miltefosine was used among HIV-infected patients where previous treatment for VL had failed, and although initial cure rates were 64%, almost all of them relapsed [41] (Table 1). In a report from Spain, 4 severely immunosuppressed, HIV-infected patients with recurrent VL after AB or MA treatment showed inefficacy of miltefosine despite an initial clinical response [42].

In Ethiopia, a randomized nonblinded clinical trial concluded that miltefosine (100 mg/day for 28 days) was safer but less effective than SSG (20 mg/kg/day for 30 days) for treating VL in a population with a high prevalence of HIV [36].

Regarding secondary prophylaxis for VL, 5 cases from a study performed in Portugal observed that the 3 patients who received miltefosine as maintenance treatment during 21, 14, and 12 months, respectively, remained disease free for a median period of 20 months. One case in Spain with miltefosine associated with itraconazole as maintenance treatment reported successful results [43]. Because of its long half-life and its oral administration, which allows ambulatory treatment, miltefosine could be a good option for secondary prophylaxis until improvement of immune function (ie, CD4 count >250 cells/μL) [44].

In addition to the antiparasitic effect, in vitro studies have demonstrated that miltefosine can reduce HIV type 1 replication in human dendritic and $CD4^+$ cells. This suggests that miltefosine may help in limiting HIV RNA load in VL/HIV-coinfected patients. However, the clinical relevance of these findings needs to be determined [45].

Miltefosine for Tegumentary Leishmaniasis

Miltefosine for Old World Cutaneous Leishmaniasis

Experience on the use of miltefosine for treating Old World cutaneous leishmaniasis (OWCL) is scarce. It has been used mainly for *L. major* infections, with cure rates between 87% and 100% [46, 47] (Table 1). There has been only 1 clinical trial performed for *L. major* OWCL in Iran, which showed that oral miltefosine was as effective as the intralesional antimonials [48]. The applicability of miltefosine for OWLC due to *Leishmania tropica* or *L. infantum* is only based on a few case reports [49, 50].

Miltefosine for Post–Kala-Azar Dermal Leishmaniasis

Several case reports have been published on the use of miltefosine on post–kala-azar dermal leishmaniasis (PKDL) in India, with high cure rates [51, 52] (Table 1). An open single-arm study from India with a large number of PKDL cases reported a 96% cure rate after 1 year of follow-up after treatment with miltefosine at 150 mg/day for 60 days (increasing 30 days more if response was not observed) [53]. Recently, a randomized clinical trial performed also in India with miltefosine 2.5 mg/kg/day for 8 or 12 weeks obtained cure rates of 76% and 78%, respectively [54].

Miltefosine for New World Cutaneous Leishmaniasis

Miltefosine has been used in the treatment of several New World cutaneous leishmaniasis (NWCL) species, with variable efficacy. First, results were obtained in Colombia, where the most frequent species is *Leishmania panamensis* and where cure rates were >80% [55, 56] (Table 1). Another later clinical trial, also performed in Colombia, found a cure rate of <70%, probably due to the high proportion of isolated *L. braziliensis* cases [57]. In a study performed in Bolivia with NWCL presumably caused by *L. braziliensis,* miltefosine showed a cure rate up to 80%, with no difference with parenteral pentavalent antimonials [58]. In Brazil, the response rate with *L. braziliensis* was 75% [59], and slightly lower (71.4%) with *L. guyanensis* [60]. Data from Guatemala for *L. braziliensis* and *L. mexicana* obtained a low cure rate of 50% [56]. A recent report from Germany found a 63% cure rate in 8 imported cutaneous leishmaniasis

cases caused by *L. braziliensis* in travelers from Bolivia, Costa Rica, Peru, Ecuador, and Brazil [61].

A clinical trial comparing miltefosine with parenteral MA in pediatric NWCL was performed in Colombia. Children were aged 2–12 years, and *L. panamensis* and *L. guyanensis* predominate in the study locations. Results showed that miltefosine was not inferior (82.7%) to MA and that it had lower toxicity [62].

The disparity in cure rates obtained in the different clinical trials is probably due to a different geographical intrinsic sensitivity of *L. braziliensis* strains to miltefosine. In fact, it has been postulated that some strains of *L. braziliensis* may have a reduced capacity to internalize miltefosine from the extracellular medium [24].

Miltefosine for New World Mucocutaneous Leishmaniasis

Cure rates of 83% and 58% for moderate and severe New World mucocutaneous leishmaniasis (NWMCL) cases, respectively, were obtained in Bolivia in a nonrandomized clinical trial using miltefosine 2.5–3.3 mg/kg/day for 28 days [63] (Table 1), and further data suggested that prolonging treatment from 4 to 6 weeks increased the cure rate [64].

Miltefosine for New World Diffuse Cutaneous Leishmaniasis

Miltefosine has been used in the treatment of New World diffuse cutaneous leishmaniasis, obtaining varying cure rates, but in most cases did not seem to be effective [65, 66].

DISCUSSION

The advantages of miltefosine are its convenient oral administration route and its low toxicity. The main disadvantages of miltefosine are the high price, its potential fetotoxicity, and increasing treatment failures.

Miltefosine had demonstrated very good cure rates in adults and children in India, Nepal, and Bangladesh with VL by *L. donovani* [28–30, 32, 33, 36]. However, high rates of clinical failures are being reported [20, 25]. Moderate efficacy has been observed in East Africa [36], whereas more data from Mediterranean countries and Latin America are needed.

Results obtained for treating *Leishmania*/HIV-coinfected patients have not been very promising, with high relapse rates [41]. Probably the most beneficial use of miltefosine among those patients could be for secondary prophylaxis, and mostly in combination [43].

Good evidence of efficacy has only been documented in OWCL infections involving *L. major* in Iran. Different cure rates among NWCL depending on geographical areas and species involved have been obtained, so miltefosine recommendations should be on an individual basis [56, 57, 59, 60, 62]. The appropriate miltefosine regimen for New World mucocutaneous leishmaniasis needs to be established, although longer treatment duration seems to confer better results [63].

Strategies to prevent the development and spread of miltefosine resistance are needed, and several measures have been proposed: (1) implementation of medical education programs for those individuals at risk and for doctors and government agencies responsible for leishmaniasis control, as well as prevention focused on the diseases and the needs of effective and complete treatment; (2) treatment adherence ensured by directly observed therapy; (3) proper doses adequate to age and weight; (4) use of miltefosine in drug combinations; and (5) proper and effective management of HIV and leishmaniasis coinfection, especially in areas with anthroponotic transmission.

Miltefosine has great value; however, new pharmacokinetic and pharmacodynamic studies are needed. New clinical trials evaluating miltefosine mainly in combination with other anti-*Leishmania* drugs should be performed, and monitoring failure and relapse rates as well as the parasites' susceptibility from the strains circulating should be reported. Finally, follow-up periods for clinical trials should be prolonged up to 12 months to evaluate the long-term efficacy of the drug.

Note

Potential conflict of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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