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Amphotericin B Lipid Complex
In Visceral Leishmaniasis

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Abstract

▲ Amphotericin B lipid complex is a lipid formulation of amphotericin B, an antifungal drug with activity against *Leishmania* spp. Amphotericin B lipid complex appears to enhance uptake of amphotericin B by infected macrophages in patients with visceral leishmaniasis (VL).

▲ In randomised, open-label, dose-ranging studies, short-course treatment with once-daily amphotericin B lipid complex (5–15 mg/kg total cumulative dose over 5 days), administered by intravenous infusion, produced high rates of apparent (day 19) [93–100%] and definitive (6 months) [79–100%] cures in Indian patients with antimonial-resistant VL.

▲ Amphotericin B lipid complex appeared to be as effective as liposomal amphotericin B or the conventional deoxycholate formulation in a randomised, open-label study conducted in India in a mixed population of patients with previously untreated or antimonial-resistant VL.

▲ In patients with HIV infection and VL, amphotericin B lipid complex 3 mg/kg/day for 5 or 10 days appeared to be as effective as meglumine antimonate 20 mg/kg/day for 28 days in a small randomised pilot study in southern Europe.

▲ Amphotericin B lipid complex was generally well tolerated in patients with VL. Infusion-related reactions were the most common adverse events associated with amphotericin B lipid complex.

Features and properties of amphotericin B lipid complex (ABLC; Abelcet®)	
Indication	
Visceral leishmaniasis (VL)	
Mechanism of action	
Membrane permeability enhancer	
Dosage and administration of ABLC in randomised studies in immunocompetent patients with VL in India	
Route of administration	Intravenous infusion
Dosage	1–3 mg/kg once daily
Duration of treatment	5 days
Whole blood pharmacokinetic profile of ABLC 2.5 mg/kg/day in patients with mucocutaneous leishmaniasis	
Peak concentration	2.41 μg/mL
Area under the concentration-time curve	6.77 μg • h/mL
Volume of distribution	105.5 L/kg
Total clearance	349.6 mL/min
Elimination half-life	187.2h
Adverse events	
Most frequent	Infusion-related chills, fever and vomiting

Visceral leishmaniasis (VL; kala-azar) is a disseminated protozoal infection transmitted by sandflies.[1,2] Parasites of the *Leishmania* spp. multiply within cells of the reticulo-endothelial system producing clinical features of fever, hepatosplenomegaly and pancytopenia.[3] Other manifestations of infection with *Leishmania* spp. include cutaneous leishmaniasis and, rarely, mucocutaneous leishmaniasis.[1]

Of the estimated 500 000 new cases of symptomatic VL that occur annually worldwide, up to 50% occur in India (90% of these in Bihar state) as a result of infection with *L. donovani*.[2] Other endemic areas include parts of southern Europe (*L. infantum*) and South America (*L. chagasi*).[1] About 20–70% of the cases of VL in Mediterranean countries occur in patients co-infected with HIV[4] and often demonstrate atypical clinical features.[2] An estimated 2–9% of HIV-infected patients in this population develop new or reactivated VL.[4]

Drugs used to treat VL have traditionally been the pentavalent antimonial salts sodium stibogluconate and meglumine antimonate. Problems, however, with antimonial treatment include increasing resistance to these agents, particularly in India,[1] the long duration of therapy (several weeks)[5] and, in patients co-infected with HIV, a greater rate of relapse than in immunocompetent patients.[2] Treatment with the antifungal agent, amphotericin B deoxycholate, although an effective alternative agent, has been associated with adverse events, including infusion-related chills and fever, nephrotoxicity and hypokalaemia.[3]

Amphotericin B lipid complex (Abelcet®)[1], a lipid formulation of amphotericin B designed to improve its tolerability profile while preserving efficacy, is a well established treatment in patients with fungal infections.[6] This article summarises data on the pharmacology and clinical profile of intravenous amphotericin B lipid complex in patients with VL.

1. Pharmacodynamic Profile

- Amphotericin B enhances the membrane permeability of *Leishmania* spp. and fungi by binding to ergosterol, the predominant membrane sterol in these pathogens,[3] causing membrane damage, leakage and cell death.[7] In amphotericin B lipid complex, amphotericin B is complexed with phospholipids in a ribbon-like structure,[7] which appears to enhance uptake of amphotericin B by infected macrophages.[3,7]
- Data on the *in vitro* activity of amphotericin B lipid complex against *L. donovani* in murine macrophages, compared with that of amphotericin B deoxycholate, are inconsistent. In one study, the 50% inhibitory concentrations (IC_{50s}) of amphotericin B were 0.032 and 0.041 μg/mL with amphotericin B lipid complex or amphotericin B deoxycholate,[8] whereas in another study, the 50% effective doses were 2.6 and 0.013 μg/mL.[9]
- Amphotericin B lipid complex had greater *in vitro* activity than amphotericin B deoxycholate against different intracellular *L. infantum* strains from Spanish patients co-infected with HIV (IC_{50s} were 1.13–63.33 vs 13.50–471.07 μg/mL).[10]
- Similarly, *in vivo* comparisons between amphotericin B lipid complex and amphotericin B deoxycholate produced inconsistent results. Amphotericin B lipid complex demonstrated greater (*L. infantum*[11] and *L. donovani*[12]) or less (*L. donovani*)[9] activity than amphotericin B deoxycholate in various murine models of VL.

2. Pharmacokinetic Profile

The pharmacokinetic properties of amphotericin B lipid complex have been evaluated in healthy volunteers and in patients with a variety of conditions (but not VL) in phase I and II studies.[13,14] Data from the largest of these studies (n = 72), which compared the pharmacokinetic profiles of amphotericin B lipid complex and amphotericin B deoxycholate, both administered intravenously by infusion (duration of infusion not stated) in patients

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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with mucocutaneous leishmaniasis,[13] are briefly reviewed in this section.

- In animal studies, amphotericin B lipid complex appeared to be rapidly removed from the circulation and extensively distributed into tissues, particularly those of the reticulo-endothelial system, but not the kidney.[3] The lipid complex formulation appears to act as a depot for the drug in the tissues producing lower circulating concentrations of free amphotericin B than amphotericin B deoxycholate.[13,14]
- Although patients with mucocutaneous leishmaniasis receiving amphotericin B lipid complex or an equivalent dosage of amphotericin B deoxycholate (0.6 mg/kg once daily for 42 days; n = 8 and 5) had a similar peak concentration (C_{max}) of amphotericin B in whole blood (0.86 vs 1.06 μg/mL), the area under the concentration-time curve (AUC) was significantly lower in amphotericin B lipid complex recipients (4.45 vs 17.06 μg • h/mL; $p < 0.001$).[13] Patients receiving amphotericin B lipid complex had an almost 5-fold greater volume of distribution (Vd) [23.4 vs 5.1 L/kg; $p < 0.001$] and an almost 4-fold greater total clearance (CL) [132.7 vs 34.1 mL/min; $p < 0.001$].
- Amphotericin B lipid complex showed dose-dependent non-linear kinetics in patients with mucocutaneous leishmaniasis.[13] Increasing the daily amphotericin B lipid complex dosage from 0.6 mg/kg/day for 42 days to 2.5 mg/kg/day for 10 days (same total cumulative dose; n = 8 per group) produced numerically greater fold increases in CL (349.6 mL/min for the higher daily dose) and Vd (105.5 L/kg) than in C_{max} (2.41 μg/mL) and AUC (6.77 μg • h/mL).[13] The elimination half-lives were 113.1 and 187.2 hours with the 0.6 and 2.5 mg/kg/day regimens.[13]

3. Therapeutic Efficacy

This section summarises data from open-label, randomised studies evaluating the efficacy of intravenous amphotericin B lipid complex in VL.

Amphotericin B lipid complex has been compared with liposomal amphotericin B (another lipid formulation) or amphotericin B deoxycholate in children, adolescents and adults with VL (n = 153), the majority of whom were previously untreated, in a trial conducted in India (Bihar state).[15] Additionally, the efficacy of short- and ultra short-course amphotericin B lipid complex regimens in children, adolescents and adults with antimonial-resistant VL (n = 58–77) were evaluated in three dose-ranging studies[16-18] conducted in Bihar.

In Europe, two randomised pilot studies in adults co-infected with HIV (n = 57[19] and 17[20]) have been reported; the first, comparing amphotericin B lipid complex with meglumine antimonate in the treatment of an initial episode of VL,[19] and the second, comparing amphotericin B lipid complex with no treatment as secondary prophylaxis in patients with at least one previous episode of parasitologically confirmed VL.[20]

Inclusion in the studies with active VL required microbiological evidence (e.g. from a splenic aspirate) of infection with *Leishmania* spp.[15-19] In the secondary prophylaxis study, a negative parasite culture from bone marrow aspirate was required.[20] Exclusion criteria in all studies included cardiac disease, pregnancy and various laboratory abnormalities.[15-20] Patients with serious concurrent infection were also excluded from the studies conducted in India.[15-18] The presence of HIV infection in the study populations in India was considered to be infrequent[15-18] and was a specific exclusion criterion in the largest trial.[15]

In the trials conducted in India, initial response to therapy with amphotericin B lipid complex (apparent cure) was determined clinically (absence of fever, clinical improvement and decrease in spleen size) and by a parasite-free splenic aspirate 19 days after the first infusion.[15-18] In patients receiving liposomal amphotericin B or amphotericin B deoxycholate, apparent cure was assessed at days 19 and 30, respectively.[15] Definitive cure in these studies was defined as an absence of signs or symptoms of relapse[15-18] and a parasite-free bone marrow aspirate[16-18] 6 months after treatment.

In the trial in patients with HIV infection and active VL, the primary endpoint was parasitological cure (generally bone marrow) 1–7 weeks after completion of treatment.[19] In both trials in patients with

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HIV infection, bone marrow aspirates[19,20] or tissue biopsy[19] were taken when relapse of VL was suspected clinically,[19,20] or 5[19] or 12[20] months after the beginning of treatment.

In Patients with Antimonial-Resistant Visceral Leishmaniasis

- Short-course treatment (5 days) with once-daily amphotericin B lipid complex (5–15 mg/kg total cumulative dose) produced high rates of apparent (93–100%) and definitive (79–100%) cure in two studies in Indian patients (n = 58 and 60) with active VL who had failed to respond to, or had relapsed after, a course (>30 days) of antimonial therapy.[16,17] For example, in one study,[16] all patients receiving once-daily amphotericin B lipid complex 1, 2 or 3 mg/kg for 5 days achieved an apparent cure, and ≥84% were free of disease 6 months after treatment (figure 1).
- In another study (n = 77),[18] once-daily amphotericin B lipid complex 5 mg/kg for 1 day or 2 consecutive days (5–10 mg/kg total cumulative dose) [ultra short-course treatment] produced apparent cure rates of 89% and 92% and definitive cure rates of ≥70% (figure 1). In the same trial, however, two doses of once-daily amphotericin B lipid complex 5 mg/kg administered 5 days apart, achieved a 100% initial response in all patients but did not appear to improve the definitive cure rate compared with treatment on 2 consecutive days (figure 1).[18]

Compared with Other Amphotericin B Formulations

- Amphotericin B lipid complex 2 mg/kg once daily for 5 days (n = 51) appeared to be as effective as intravenous liposomal amphotericin B 2 mg/kg once daily for 5 days (n = 51) or amphotericin B deoxycholate 1 mg/kg on alternate days for 30 days (i.e. 15 infusions) [n = 51] in producing apparent and definitive cure in a mixed population of patients with previously untreated (about two-thirds) or antimonial-resistant VL.[15] The study was insufficiently powered, however, to show statistical equivalence.[15]

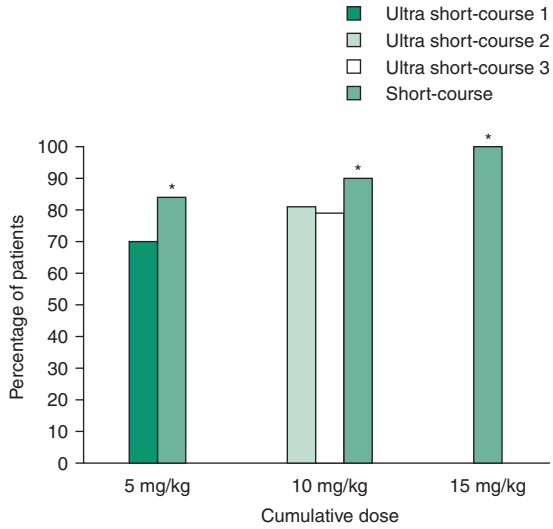

Fig. 1. Efficacy of intravenous amphotericin B lipid complex (ABLC) in two randomised, open-label, dose-ranging studies in Indian patients with visceral leishmaniasis.[16,18] Patients who had not responded to, or who had relapsed after receiving, treatment with sodium stibogluconate 20 mg/kg/day (for ≥28[18] or >30[16] days), received ABLC 5, 10 or 15 mg/kg (n = 19, 20 and 21) in divided doses over 5 consecutive days (short-course) in one study[16] and ABLC 5 mg/kg (single dose; n = 27) [ultra short-course 1], 10 mg/kg in divided doses on 2 consecutive days (ultra short-course 2; n = 26) or 10 mg/kg in two divided doses 5 days apart (ultra short-course 3; n = 24) in another study.[18] Bars show the proportion of patients with a clinical and parasitological cure (on bone marrow aspirate) [definitive cure] 6 months after treatment. * $p < 0.05$ for dose effect (Jonckheere-Terpstra test) in the study using short-course ABLC therapy.[16]

- Only one patient (receiving liposomal amphotericin B) in the study failed to initially respond to treatment.[15]
- Mean duration of fever was significantly longer in amphotericin B lipid complex recipients than in those receiving liposomal amphotericin B (6 and 3 days; $p < 0.05$), and significantly shorter in both groups compared with the amphotericin B deoxycholate group (23 days; $p < 0.05$).[15]
- Definitive cure rates after 6 months were 96% for both amphotericin B deoxycholate (two deaths during treatment) and liposomal amphotericin B (one relapse) recipients and 92% for amphotericin B lipid complex recipients (four relapses).[15]
- All six patients who failed to respond to treatment or who relapsed after an initial apparent cure

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were later successfully cured following treatment with the alternate-day amphotericin B deoxycholate regimen.[15]

In Patients Co-Infected with HIV

- Treatment with amphotericin B lipid complex 3 mg/kg/day for 5 or 10 days produced a similar rate of parasitological cure to that obtained with (parenteral) meglumine antimonate 20 mg/kg/day for 28 days (33% and 42% vs 37%; intention-to-treat analysis) in 57 Spanish adults with VL (first episode) and HIV infection (figure 2).[19] The cure rate with meglumine antimonate in an on-treatment analysis, however, was numerically higher than with either dosage of amphotericin B lipid complex (figure 2).[19]
- Five months after treatment, the proportions of patients with valid relapse data (n = 19) who received amphotericin B lipid complex (5- or 10-day course) or meglumine antimonate and who were VL-free were 50%, 38% and 57%, respectively.[19]
- Amphotericin B lipid complex appeared to be an effective treatment in the secondary prophylaxis of VL in patients with HIV in a study conducted in Spain and Portugal.[20] Patients with at least one previous episode of VL but currently free of disease were randomised to receive amphotericin B lipid complex 3 mg/kg every 3 weeks for 1 year (i.e. 17 administrations in total; n = 8) or no treatment (n = 9). After 1 year, 50% (95% CI 15.7%, 84.3%) of patients receiving amphotericin B lipid complex remained free of VL compared with 22.2% (95% CI 2.8%, 60.0%) of those who received no treatment. The non-relapse odds ratio was 3.5 (95% CI 0.3, 52.0) in favour of amphotericin B lipid complex.

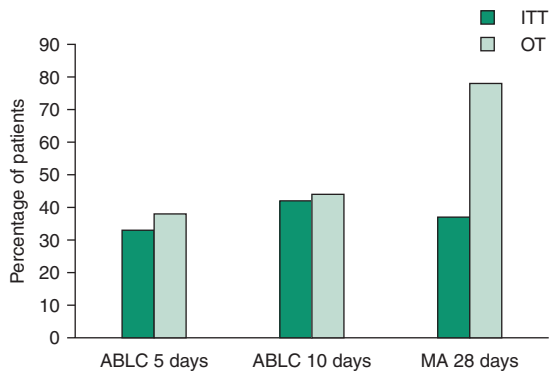

Fig. 2. Efficacy of intravenous amphotericin B lipid complex (ABLC) compared with parenteral meglumine antimonate (MA) in HIV-infected patients with visceral leishmaniasis in a multicentre, randomised, open-label study conducted in Spain.[19] Patients received ABLC 3 mg/kg/day for 5 (n = 18) or 10 (n = 20) days or MA 20 mg/kg/day for 28 days (n = 19). Bars show the proportion of patients with a parasitological cure (on bone marrow aspirate) 1–7 weeks after completion of treatment for both the intention-to-treat (ITT) [n = 56] and on-treatment (OT) [n = 43] populations.

4. Tolerability

- Amphotericin B lipid complex was generally well tolerated by patients with VL in the trials reported in section 3.[15-20] According to the manufacturer, adverse reactions in patients (with fungal infections) receiving treatment with amphotericin B lipid complex have usually been mild or moderate and were most frequent during the first 2 days of administration.[21]
- The most common adverse events in all studies were infusion-related chills, fever and vomiting.[15-20] For example, a 5-day course of either once-daily amphotericin B lipid complex 2 mg/kg (n = 51) or once-daily liposomal amphotericin B 2 mg/kg (n = 51) resulted in infusion-related reactions in 76% and 29% of patients in the largest Indian study compared with 98% of those receiving amphotericin B deoxycholate (plus premedication) [n = 51; no statistical analysis reported].[15]
- Tolerance to infusion reactions appears to develop rapidly with the lipid-based amphotericin B formulations.[15-17] Only one patient per group receiving either amphotericin B lipid complex or liposomal amphotericin B in the largest study had an infusion-related reaction after the fifth dose compared with 90% of amphotericin B deoxycholate recipients.[15] The incidence of infusion-related reactions did not appear to be dose-related.[16,17,19] For example, reactions occurred in 39% and 40% of patients (n = 18 and 20) co-infected with HIV receiving amphotericin B lipid complex 3 mg/kg/day (plus premedication) for 5 or 10 days.[19]
- No cases of nephrotoxicity were reported in patients receiving amphotericin B lipid complex in any of the Indian studies,[15-18] whereas three cases de-

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veloped in recipients of amphotericin B deoxycholate.[15] The renal effects of amphotericin B formulations, including amphotericin B lipid complex, has been assessed in greater numbers in patients with systemic fungal infections (reviewed by Barrett et al.[22]) rather than with VL. In a meta-analysis of seven randomised studies, the risk of doubling serum creatinine was significantly reduced (by an estimated 58%) with either amphotericin B lipid complex or liposomal amphotericin B compared with amphotericin B deoxycholate (odds ratio 0.42; 95% CI 0.33, 0.54).[22]

- Numerically fewer amphotericin B lipid complex recipients compared with liposomal amphotericin B or amphotericin B deoxycholate experienced a haemoglobin reduction (n = 0, 2 and 9) or hypokalaemia (n = 0, 3 and 9) in the largest study conducted in India.[15]
- In the comparative study in patients co-infected with HIV, the proportion of patients experiencing at least one treatment-related adverse event (including acute infusion-related reactions) was similar between groups receiving a 5- or 10-day course of amphotericin B lipid complex or meglumine antimonate for 28 days (61%, 75% and 74%).[19] Numerically fewer patients receiving either dosage of amphotericin B lipid complex than meglumine antimonate experienced adverse events not related to treatment infusion (22% and 35% vs 74%) [see figure 3 for the incidences of individual events]. Eight patients receiving meglumine antimonate stopped treatment prematurely as a result of serious adverse events compared with one amphotericin B lipid complex recipient ($p < 0.01$).

5. Dosage and Administration

- There is no formal recommended treatment regimen for amphotericin B lipid complex in patients with VL. Following several dose-ranging studies in India,[16-18] designed in part to determine the most affordable amphotericin B lipid complex regimen without compromising efficacy,[18] the dosage used in a comparative study[15] with other amphotericin B formulations was 2 mg/kg once daily for 5 days (total cumulative dose of 10 mg/kg). In contrast, total cumulative doses of up to 30 mg/kg (3 mg/kg/day for 5 or 10 days) were administered to patients co-infected with HIV in a Spanish study.[19]
- Amphotericin B lipid complex should be administered intravenously by infusion at a rate of 2.5 mg/kg/h.[21] A 1mg test dose should be administered prior to the first administration in case of hypersensitivity.[21] Because amphotericin B is a potentially nephrotoxic drug, renal function should be monitored in patients with pre-existing renal disease and in those receiving other concomitant potentially nephrotoxic drugs.[21] Monitoring of liver function

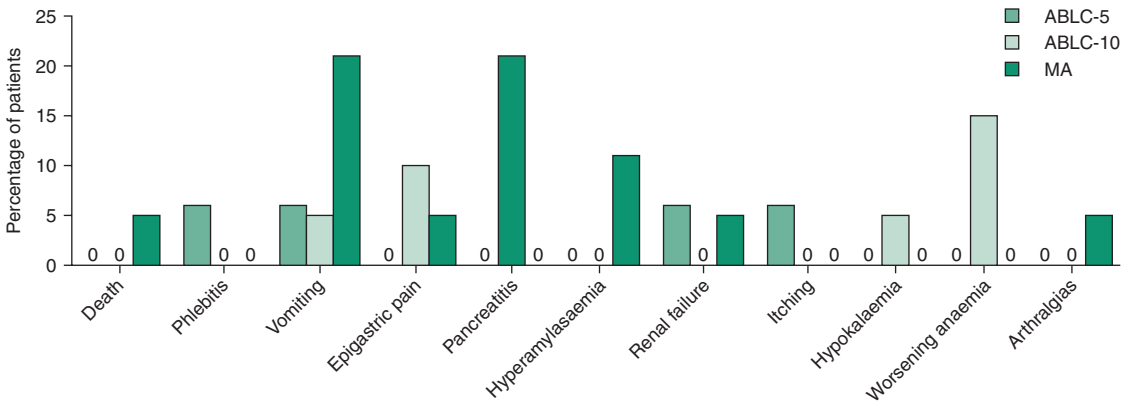

Fig. 3. Tolerability of intravenous amphotericin B lipid complex (ABLC) compared with parenteral meglumine antimonate (MA) in patients with an HIV-related first infection with visceral leishmaniasis in a multicentre, open-label, randomised pilot study conducted in Spain.[19] Patients received ABLC 3 mg/kg/day for 5 (ABLC-5) or 10 (ABLC-10) days (n = 18 and 20) or MA 20 mg/kg/day for 28 days (n = 19). Bars show the proportion of patients with treatment-related adverse events; acute infusion-related reactions are excluded.

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in patients with abnormal liver function tests is also recommended.[21] No studies on the interaction of amphotericin B lipid complex with other drugs have been reported.

6. Amphotericin B Lipid Complex: Current Status in Visceral Leishmaniasis

Amphotericin B lipid complex, administered once daily for 5 days, is an effective treatment for immunocompetent children, adolescents and adults with previously untreated or antimonial-resistant VL, according to the results of studies conducted in India. In addition, amphotericin B lipid complex has shown efficacy in the treatment of VL in adults co-infected with HIV in a pilot study in southern Europe. Treatment with amphotericin B lipid complex is generally well tolerated and appears to be associated with fewer infusion-related reactions than conventional amphotericin B.

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