Efficacy and Safety of Amphotericin B Emulsion versus Liposomal Formulation in Indian Patients with Visceral Leishmaniasis: A Randomized, Open-Label Study

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Abstract

Background: India is home to 60% of the total global visceral leishmaniasis (VL) population. Use of long-term oral (e.g. miltefosine) and parenteral drugs, considered the mainstay for treatment of VL, is now faced with increased resistance, decreased efficacy, low compliance and safety issues. The authors evaluated the efficacy and safety of an alternate treatment option, i.e. single infusion of preformed amphotericin B (AmB) lipid emulsion (ABLE) in comparison with that of liposomal formulation (LAmB).

Methods: In this multicentric, open-label study, 500 patients with VL were randomly assigned in a 3:1 ratio to receive 15 mg/kg single infusion of either ABLE (N = 376) or LAmB (N = 124). Initial cure (Day 30/45), clinical improvement (Day 30) and long term definitive cure (Day 180) were assessed.

Findings: A total of 326 (86.7%) patients in the ABLE group and 122 (98.4%) patients in the LAmB group completed the study. Initial cure was achieved by 95.9% of patients in the ABLE group compared to 100% in the LAmB group (p = 0.028; 95% CI: −0.0663, −0.0150). Clinical improvement was comparable between treatments (ABLE: 98.9% vs. LAmB: 98.4%). Definitive cure was achieved in 85.9% with ABLE compared to 98.4% with LAmB. Infusion-related pyrexia (37.2% vs. 32.3%) and chills (18.4% vs. 18.5%) were comparable between ABLE and LAmB, respectively. Treatment-related serious adverse events were fewer in ABLE (0.3%) compared to LAmB (1.6%). Two deaths occurred in the ABLE group, of which one was probably related to the study drug. Nephrotoxicity and hepatotoxicity was not observed in either group.

Conclusions: ABLE 15 mg/kg single infusion had favorable efficacy and was well tolerated. Considering the demographic profile of the population in this region, a single dose treatment offers advantages in terms of compliance, cost and applicability.

Trial Registration: www.clinicaltrials.gov NCT00876824

Introduction

Visceral leishmaniasis (VL), also known as kala-azar, is a vector-borne disease transmitted to humans by the bite of an infected sandfly [1]. Globally, around 200,000–400,000 cases of VL occur each year of which 60% cases occur in India alone [2]. Kala-azar is a major public health problem in the areas of its prevalence,

principally India and its neighbors Bangladesh and Nepal. In India, the disease is highly prevalent in Bihar, Jharkhand, West Bengal and pockets of eastern Uttar Pradesh. Among these, Bihar is the most affected with >90% of cases [3], of which 10% are fatal [2].

Contrary to the severity, few drugs are available for its treatment and are further limited by safety, reduced effectiveness and challenges in administration. Use of pentavalent antimonials, the mainstay of

Author Summary

Visceral leishmaniasis (VL) is highly prevalent in northeastern India, particularly the state of Bihar and its bordering areas with Bangladesh and Nepal. The current standards of treatment, namely, miltefosine (oral) and pentavalent antimonials (parenteral) have long treatment durations and are faced with increasing resistance, decreased efficacy, low compliance and safety issues. In this regard, lipid formulations of amphotericin B (AmB) have become an attractive treatment option due to their high efficacy, shorter treatment regimens and favorable safety profiles. This Phase III study evaluated the efficacy and safety of preformed AmB lipid emulsion (ABLE) versus liposomal AmB (LAmB) (both 15 mg/kg single dose infusions) in the treatment of VL. ABLE showed favorable efficacy measured in terms of initial cure at Day 30/45, and overall clinical improvement. ABLE was well tolerated and its adverse event profile was consistent with previously documented findings. Based on the favorable efficacy and safety profile of ABLE, and considering the demographic profile of the population in the endemic region, a single dose treatment may offer advantages in terms of compliance, cost and applicability.

treatment for over 70 years, has been limited by its resistance and toxicities [4]. In India, almost 65% of previously untreated cases fail to respond promptly or relapse after treatment with antimonials [5]. Efficacy of the first-line oral treatment, miltefosine (MF) has declined rapidly over the past decade (final cure rate: 96.7% in 1999, 94% in 2002, 82% in 2007, and 72% in 2011) and is also associated with gastrointestinal side effects [6–9]. In addition, owing to its teratogenic effects, treatment with MF may require strict medical monitoring for treating women of child bearing age, which considering current demographic outlook of India is a significant factor [10,11]. Paramomycin, an aminoglycoside, had shown 94% cure rate but is associated with systemic hepatic toxicity; the current regimen of 21 daily injections is also a major disadvantage for routine clinical use [12].

Amphotericin B (AmB), currently a second line drug used for treatment of VL, is highly effective with cure rates of 97%; however, the administration of 15 intravenous injections (i.v.) over 30 days of hospitalization, coupled with infusion- and drug-related adverse effects [13], has limited its wide-spread use. Liposomal formulations of AmB (LAmB) are better tolerated and thus preferable to conventional AmB [14,15]. Despite the WHO-negotiated price of LAmB, treatment with it still remains limited and unaffordable in India [16]. Educational, social and economic background of patients in endemic areas entails therapy that does not bother patients with cost, undue compliance issues and long treatment duration, making a simplified treatment regimen a need of the hour. Thus, an affordable premixed AmB deoxycholate with lipid emulsion (ABLE) was developed (licensed in India) [17] and can be a potential candidate for treatment and elimination in endemic countries. Previous Phase II studies have reported safety and efficacy with a single infusion of 15 mg/kg of ABLE [17,18] in the treatment of VL.

This Phase III study was conducted to evaluate the efficacy and safety of ABLE versus LAmB (both 15 mg/kg single dose infusions) in the treatment of VL.

Methods

Ethics statement

The protocol was approved by an Independent Ethics Committee or Institutional Review Board at each study site and the study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. All participants including guardians in case of minors provided written informed consent to participate in the study. This study was registered at ClinicalTrials.gov (NCT00876824).

Study design

This was a prospective, multicentric, randomized, open-label, comparative Phase III study.

Participants

Patients were enrolled from 4 centers in Bihar, India, between August 2009 and January 2011. Male and female, aged 5–65 years (both inclusive) diagnosed with VL (fever >2 weeks duration and splenomegaly), who had amastigotes (*Leishmania donovani* bodies) at prescreening (detected by recombinant K39 protein [rK39] dipstick test) and confirmed VL by splenic or bone marrow aspirate smear examination were included in the study. Other inclusion criteria were hemoglobin (Hb) ≥5 g/dL, white blood cells count ≥1000/cmm, platelet count ≥50000/cmm, prothrombin time ≤4 seconds above the control, and alkaline transaminase, aspartate transaminase, and alkaline phosphatase ≤2.5 times the upper limit of normal. Patients with past history of treatment with AmB or any other drug for VL within 30 days prior to screening, major surgery within 2 weeks prior to screening, concurrent malaria, alcoholism or illicit drug use/abuse or any condition associated with poor compliance, hypersensitivity to AmB, inactive ingredients of ABLE and LAmB formulations were excluded from the study. Patients who received any of the prohibited medications (any other investigational drugs, antileishmanial drugs other than study drug, corticosteroids, skeletal muscle relaxants, cyclosporine, digoxin, vancomycin, aminoglycosides, antifungal, immunosuppresive agents, and all potentially nephrotoxic drugs), who were positive for human immunodeficiency virus, hepatitis C virus and hepatitis B surface antigen infections and immune-compromised, were also excluded from the study.

Interventions

Eligible patients were randomized (3:1) to receive either ABLE or LAmB, as 15 mg/kg single dose infusions (Figure 1). Prior to administration of full-dose, patients received initial test doses (ABLE and LAmB) of 1 mg in 5% dextrose as an infusion over ~15–20 minutes for the ABLE treatment and over a period of 10 minutes for the LAmB treatment. Patients who experience any hypersensitivity or cardiopulmonary complications of hypersensitivity were withdrawn from the study. Full dose of ABLE and LAmB was diluted in 5% dextrose to a concentration of 1 mg/ml prior to administration. Patients received full doses of respective treatment in single intravenous infusion over 4–6 hours. Premedication was not allowed prior to the study drug administration. Patients were hospitalized for 7 days starting from day of first dose of the study drug for safety and efficacy evaluation.

Outcome measures

To assess parasitological cure, splenic aspirate (or bone marrow aspirate in whom splenic aspirates was not feasible) was performed on Day 30 post infusion. Parasite density was graded by microscopy using a conventional logarithmic scale of 0 (no amastigotes/1000 oil-immersion fields) to +6 (>100 amastigotes/1000 oil-immersion field). Patients with +1 score on Day 30 were re-evaluated on Day 45. Patients were considered to achieve initial
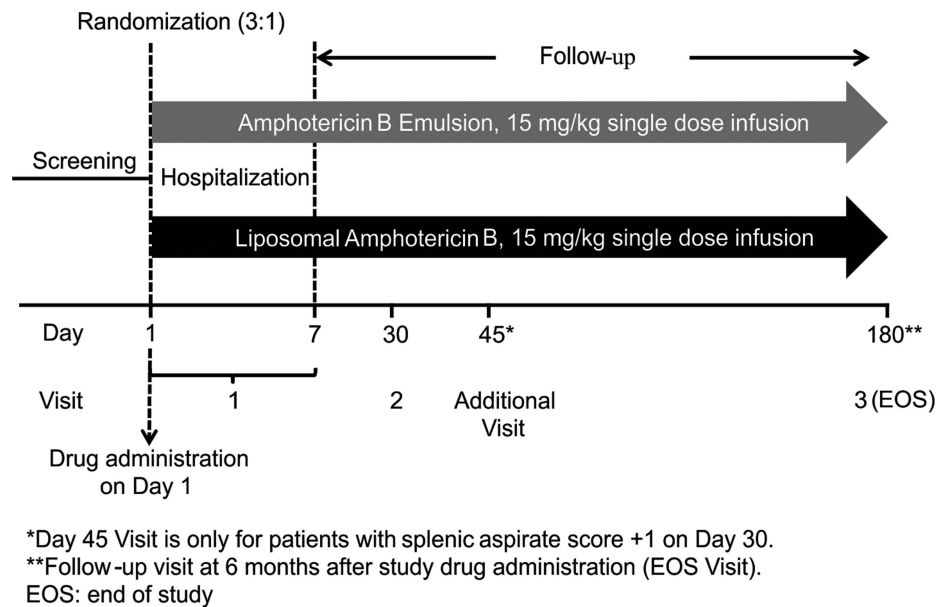
Figure 1. Study design.
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cure if the score was 0 on either Day 30 or 45. Patients with score >+1 on Day 30 and/or ≥1 on Day 45 were considered as treatment failures. They were withdrawn from the study and treated with rescue medication in appropriate doses as indicated in the protocol (LAmB 5 mg/kg i.v. on Days 1, 3, 5 and 7 or alternative antileishmanial drug in appropriate doses). Patients were further observed for clinical improvement presented as absence of fever and one or more of the following: increase in Hb concentration by ≥10%, weight gain, or decrease in spleen size by ≥33% (compared from baseline to Day 30). Patients who had achieved initial cure were followed-up for 6 months to study any sign/symptoms of relapse of VL. Patients with an initial cure and no signs or symptoms of VL at the last visit were considered to have achieved definitive cure.

Other data collection

All the patients were monitored for incidence of infusion related toxicities, nephrotoxicity, hepatotoxicity, number of adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs), and laboratory values (normal; abnormal, not clinically significant; and abnormal, clinically significant) for different parameters. Any drug related Grade III or higher AEs recorded for abnormal clinically significant renal function tests or liver function tests were classified as nephrotoxicity or hepatotoxicity as per National Cancer Institute Common Terminology Criteria (NCI-CTC) AE, version 3.

Sample size calculation

A total of 500 patients in a 3:1 ratio (375 in ABLE and 125 in LAmB) were planned to be enrolled assuming a dropout rate of 20% and non-inferiority margin fixed at −0.10. This was expected to provide an estimated difference in proportions of patients achieving definitive cure for ABLE vs. LAmB equals to zero, with at least 80% power for the non-inferiority test.

Randomization

The permuted block randomization, with block size of 4, and ratio of 3:1 in the two groups (ABLE and LAmB) were generated for each center. Eligible patients were sequentially allotted to unique subject ID

and treatment (ABLE or LAmB) as per randomization schedule for that center. The screening and randomization log was maintained.

Statistical methods

Data were expressed as means (±SD) for continuous variables and percentages for categorical variables. Proportion of patients achieving all three-efficacy (initial cure, clinical improvement and definitive cure) endpoints were to be compared across the two treatment groups.

For initial cure and clinical improvement, the data was to be analyzed using chi-square test at 5% level of significance. But as the expected number of patients achieving or non achieving initial cure in any of the treatment group was found to be <5, a Fisher's exact test was used. P-value<0.05 was considered as statistically significant. For definitive cure, non-inferiority was assessed by looking at the lower end of a two-sided 95% confidence interval (CI) of the difference P_{test} - P_{ref} (the difference in the proportions of patients achieving definitive cure in ABLE (P_{test}) and LAmB (P_{ref}). Non-inferiority was only accepted if the lower limit of the two-sided 95% CI was greater than the non-inferiority margin of −0.10. For the three efficacy parameters, the 95% CI was calculated by using Wald's confidence interval with Yate's continuity correction formula.

For safety, the number and percentage of patients experiencing toxicities and AEs (including laboratory abnormalities) across two treatment groups were summarized. Percentages were based on total number of patients in ITT population in each treatment groups.

The efficacy analysis was performed on modified intent-to-treat (mITT) population, which includes all patients who received study drug as per the protocol specified duration and had at least one efficacy assessment throughout the study. Safety analysis was performed on intent-to-treat (ITT) population, which includes all patients who received the treatment of study drug.

Results

Patient population

Of the 500 patients randomized, 376 patients received ABLE and 124 patients received LAmB. The percentage of patients who
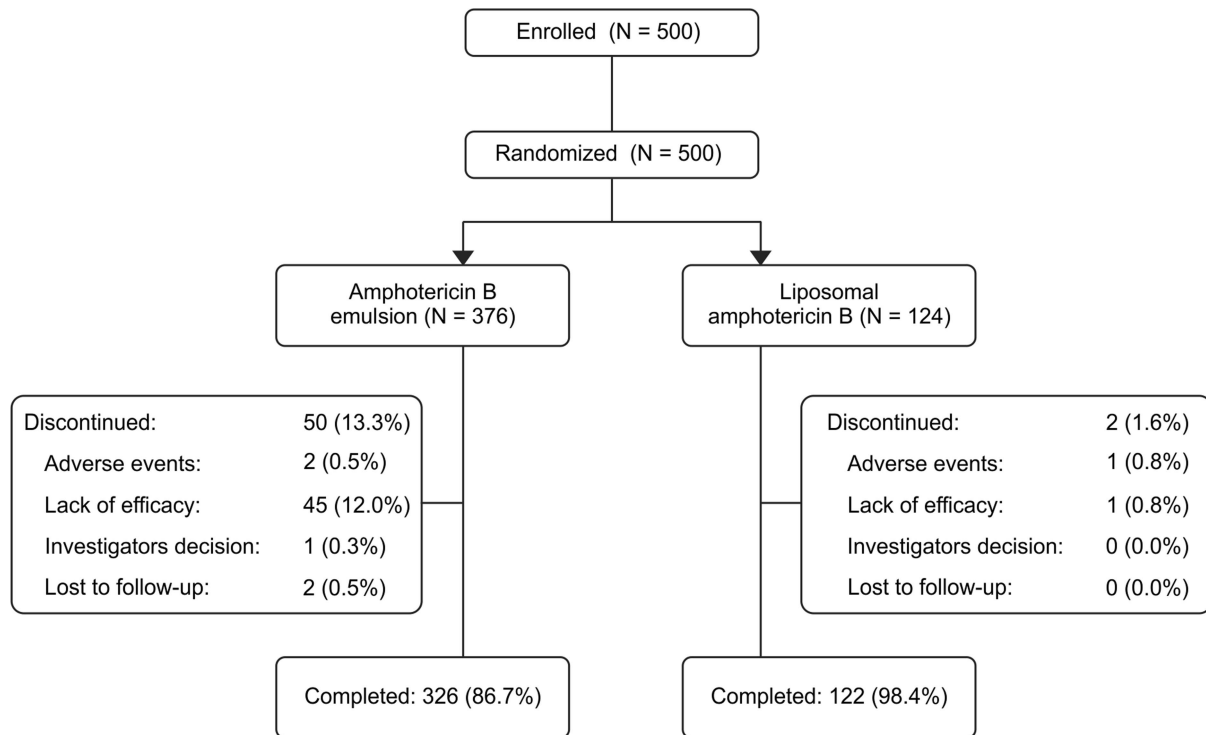
Figure 2. CONSORT patient flowchart.
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completed the study was lower in the ABLE group (86.7%) compared with the LAmB group (98.4%). A total of 50 (13.3%) patients discontinued the study in the ABLE group compared to 2 patients (1.6%) in the LAmB group (Figure 2). Patients were predominantly men (60.8%); mean age was 24.8 years (range: 5 to 62 years), and the rest of the baseline characteristics were similar for both groups (Table 1). In this study, all patients were qualified for treatment and included in the ITT population.

Table 1. Demographic and baseline characteristics (ITT population).

Characteristic		Amphotericin B		
		Lipid emulsion (N = 376)	Liposomal formulation (N = 124)	Overall (N = 500)
Age at onset, years		24.3±14.26	26.3±15.23	24.8±14.52
Sex, n (%)	Women	148 (39.4)	48 (38.7)	196 (39.2)
	Men	228 (60.6)	76 (61.3)	304 (60.8)
Height (cm)		144.51±19.45	145.75±19.08	144.81±19.35
Weight (kg)		37.10±14.71	39.09±15.26	37.59±14.86
Spleen size (cm)		6.06±3.92	6.31±3.94	6.13±3.92
Hemoglobin (g/dL)	Normal, n (%)	8 (2.1)	4 (3.2)	12 (2.4)
	Abnormal, NCS, n (%)	368 (97.9)	120 (96.8)	488 (97.6)
	Abnormal, CS, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
White blood cells (/µL)	Normal, n (%)	111 (29.5)	47 (37.9)	158 (31.6)
	Abnormal, NCS, n (%)	265 (70.5)	77 (62.1)	342 (68.4)
	Abnormal, CS, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Platelets (/µL)	Normal, n (%)	160 (42.6)	56 (45.2)	216 (43.2)
	Abnormal, NCS, n (%)	216 (57.4)	68 (54.8)	284 (56.8)
	Abnormal, CS, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine (mg/dL)		0.83±0.23	0.83±0.22	0.83±0.23

Data are mean ± standard deviation, unless stated; ITT = Intent-to-Treat; NCS = not clinically significant; CS = clinically significant.
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Table 2. Proportion of patients achieving initial and definitive cure after treatment with amphotericin B emulsion and liposomal amphotericin B (mITT population).

	Amphotericin B		P (95% CI)
	Lipid emulsion (N = 369)	Liposomal formulation (N = 122)	
Initial cure	354 (95.9)	122 (100.0)	0.0280 (−0.0663, −0.0150)
Clinical improvement	365 (98.9)	120 (98.4)	0.6414 (−0.0248, 0.0359)
Definitive cure	317 (85.9)	120 (98.4)	(−0.1720, −0.0770)

Data are n (%); mITT = modified Intent-to-Treat; CI = confidence interval.
doi:10.1371/journal.pntd.0003169.t002

Efficacy

Initial cure. Achievement of initial cure (on Day 30 and/or Day 45) was 95.9% in the ABLE group compared to 100% in the LAmB group (p = 0.028; 95% CI: −0.0663, −0.0150) (Table 2).

Clinical improvement. During evaluation of clinical improvement at Day 30, no patients in the ABLE and LAmB groups had fever. Hb concentration was increased by at least 10% from baseline in 293 (79.4%) patients treated with ABLE and 80 (65.6%) patients treated with LAmB (Figure 3a). Weight gain was observed in 318 (86.2%) patients in the ABLE group and 103 (84.4%) patients in the LAmB group (Figure 3b). Similarly spleen size had decreased by at least 33% compared to baseline in 348 (94.3%) patients in the ABLE and 117 (95.9%) patients in the LAmB group. Overall, clinical improvement was 98.9% in ABLE group compared to 98.4% in LAmB group (p = 0.6414; 95% CI: −0.0248, 0.0359) (Table 2).

Definitive cure. The proportion of patients with no clinical signs and symptoms of relapse of kala-azar for 6 months follow-up was 85.9% in the ABLE group compared to 98.4% in the LAmB group (95% CI [−0.1720, −0.0770]).

Safety

The proportion of patients with at least 1 AE was comparable in both the ABLE group and in the LAmB group (202 [53.7%] and 61 [49.2%]) (Table 3). The majority of AEs considered to be possibly related to the study drug was similar in both treatment groups (45.2%). Similarly, TEAEs in the ABLE (179 [47.6%]) and

LAmB (56 [45.2%]) were comparable. The most common TEAEs in both ABLE and LAmB were chills (18.4% and 18.5%) and pyrexia (37.2% and 32.3%), respectively (Table 3). The majority (>35%) of the patients (152 [40.4%] vs. 46 [37.1%]) experienced AEs of mild intensity.

Two patients in each group had at least one SAE (ABLE 0.5% vs. LAmB 1.6%). Of these SAEs, one patient (0.3%) in the ABLE and 2 (1.6%) patients in the LAmB group was considered treatment-related. The SAEs that occurred in ABLE were anemia, diarrhea, vomiting and sudden death; while in LAmB, pancytopenia and diarrhea (in one patient each). In total, two deaths occurred in the ABLE group due to AEs. One death occurred 2 days after drug administration due to severe diarrhea and was considered probably related to the drug. The other death occurred on Day 157 and was not related to the study drug. In the LAmB group, one patient (0.8%) was discontinued from the study due to urticaria (Table 3).

The incidence of infusion related toxicities on Day 1 was comparable between the groups (43.6% in ABLE and 41.9% in LAmB group). None of the patients in both the treatment groups had signs and symptoms of nephrotoxicity and hepatotoxicity.

Discussion

At present, VL remains one of the most neglected diseases globally [2]. To eliminate this endemic disease by 2015, a Tripartite Memorandum of Understanding agreement was signed

a) Increase in Hb levels by ≥10% from Baseline

b) Increase in Body Weight
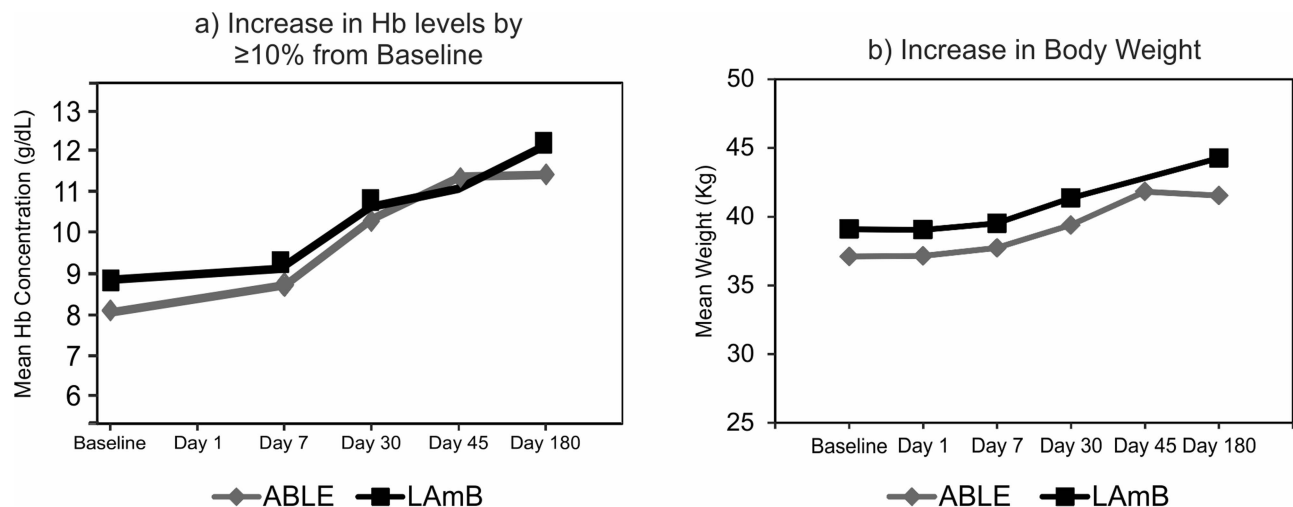
Figure 3. Increase in Hb levels (A) and body weight (B) from baseline after treatment with lipid and liposomal formulations of amphotericin B (mITT population).
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Table 3. Summary of adverse events (AEs) and treatment-emergent adverse events (TEAEs) (ITT population).

| | | Amphotericin B | | |
		Lipid Emulsion, N = 376	Liposomal Formulation, N = 124	Overall N = 500
Summary of AEs	Patients with ≥1 AE	202 (53.7)	61(49.2)	263(52.6)
	Patients with ≥1 SAE	2 (0.5)	2 (1.6)	4 (0.8)
	Patients with ≥1 TEAEs	179 (47.6)	56 (45.2)	235 (47.0)
	Patients with TESAEs	1 (0.3)	2 (1.6)	3 (0.6)
	AEs leading to death	2 (0.5)	0 (0.0)	2 (0.4)
	AEs leading to permanent interruption of study drug	0 (0.0)	1 (0.8)	1 (0.2)
TEAEs observed in ≥2% of patients	Pyrexia	125 (33.2)	37 (29.8)	162 (32.4)
	Chills	68 (18.1)	22 (17.7)	90 (18.0)
	Vomiting	5 (1.3)	3 (2.4)	8 (1.6)
	Diarrhea	1 (0.3)	3 (2.4)	4 (0.8)

Data are n (%); ITT = Intent-to-Treat; SAE = serious adverse events; TESAEs = treatment-emergent serious adverse events.
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in 2005 by the Governments of India, Nepal and Bangladesh wherein MF monotherapy was introduced as a first-line treatment [19]. However, of late, efficacy of MF has been declining steadily (96.7% to 72%) and its teratogenic potential remains a major concern in these areas where women are from low income groups and direct counseling is difficult, which limits its use in settings where the directly observed treatment is possible [10,11,20]. Other long-term treatment options, namely AmB (15 i.v injections over 30 days), pose a remarkable burden on the patient as well as health infrastructure [13]. Thus, short-course effective treatment regimens are greatly needed for the treatment of VL.

In this study, in the mITT population, efficacy of single day infusions of ABLE 15 mg/kg/day was satisfactory with an initial cure rate of 95.9% compared with 100% for LAmB. The difference in the initial cure rate was statistically significant between the groups (p = 0.028). However, this should be interpreted with caution, as in field settings LAmB is used as a single bolus dose of 10 mg/kg/day, compared to 15 mg/kg/day as was used in this study. This might have caused differences in the intended exposure to the treatment drug between groups. These results are in line with the results observed in a previous Phase II ABLE study [17].

Weight gain and decrease in spleen size were similar in both groups. The ABLE group showed greater increase in Hb concentration (79.4%) compared to the LAmB group (65.6%). Overall, clinical improvement (Day 30) was comparable (p = 0.6414) between the ABLE (98.9%) and LAmB groups (98.4%). Furthermore, the proportion of patients with no symptoms of relapse or showing no clinical signs of disease (definitive cure) was 85.9% in the ABLE group and 98.4% in the LAmB group.

The safety and tolerability of ABLE observed over 6 months duration was consistent with the earlier Phase II ABLE studies [17,18]. Infusion related pyrexia and chills were the most common drug-related adverse events in both groups. These were mainly attributed to non-administration of premedication. However, in the field and in most studies, the patients are given premedication to prevent infusion related reactions [21]. No patient showed signs and symptoms of nephrotoxicity and hepatotoxicity, which was consistent with results from previous Phase II studies [17,18]. Thus, the efficacy and safety results indicate that the treatment with ABLE is efficacious and safe.

Apart from efficacy and safety, which are important aspects of any drug or formulation, secondary aspects such as cost-effectiveness, affordability, better compliance and ease of availability must also be considered to assess the feasibility of its use. The necessity to assess secondary aspects of drug become even more important as VL mainly affects poor and neglected populations in East Africa and the Indian sub-continent [22]. It is estimated that illness due to VL may result in loss of income for up to 60% of the total household cost [23]. Thus, single-dose treatment regimens will not only reduce the hospital cost, but also drastically reduce the economic burden on the family [15]. Additionally, it has been proposed that extensive use of AmB and its formulations for treatment of VL may aid in decreasing the incidence of post-kala-azar dermal leishmaniasis, a potential reservoir of disease [24]. However, it is necessary to closely monitor and counsel patients about infrequent cases of post-kala-azar dermal leishmaniasis that tend to occur post-treatment with novel AmB formulations [25,26].

In addition to poor economic conditions, co-infection with human immunodeficiency virus has changed the classical picture of VL in India, particularly in Bihar [27,28]. Co-infected patients generally have poor response to the treatment, which leads to frequent relapses and high mortality [29]. In this context, it is imperative that such patients are diagnosed and treated appropriately through active case detection approaches as co-infected patients tend to transmit more virulent strains of VL.

In summary, novel formulations of AmB due to its high therapeutic index, short treatment courses and favorable safety profile have become an attractive treatment option [20]. However, in India, which bears the highest burden of VL, LAmB is not yet registered and is imported under special license, which can be a limiting factor in its availability. Also, India is not a recipient of the LAmB donation initiative, which may further impact its availability to poorer patients [16]. In addition, in India, LAmB is available at a preferential price only in limited quantities through specific treatment channels, thereby limiting its access to several patients infected with the disease. On the other hand, the ABLE formulation has been registered in India and can be supplied in liberal quantities, locally. Thus, favorable efficacy and safety profile, treatment compliance, affordability and availability of

ABLE formulation make it a strong candidate for treatment of VL and for inclusion into the VL elimination program.

Conclusions

In this study, ABLE 15 mg/kg single bolus was found to be efficacious, safe and well tolerated in patients with VL. In addition, its ancillary properties such as favorable applicability and compliance (due to single dose administration), low cost and unrestricted supply, make it a suitable option for VL treatment in endemic countries.

Supporting Information

Supporting Information S1 CONSORT checklist.
(DOC)

Supporting Information S2 Protocol.
(DOCX)

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