
Research/Recherche

Efficacy and safety of liposomal amphotericin B (AmBisome) for visceral leishmaniasis in endemic developing countries*

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Reported are the results of a study to determine the efficacy and safety of liposomal amphotericin B (AmBisome) for treating visceral leishmaniasis (kala-azar) in several developing countries where the disease is endemic (Brazil, India, and Kenya).

At each study site, sequential cohorts of 10 patients each were treated with AmBisome at a dose of 2 mg·kg⁻¹·day⁻¹ (2 MKD). The first cohort received regimen 1: 2 MKD on days 1–6 and day 10 (total dose: 14 mg/kg). If the efficacy with this regimen was satisfactory, a second cohort received regimen 2: 2 MKD on days 1–4 and day 10 (total dose: 10 mg/kg); and a third cohort received regimen 3: 2 MKD on days 1, 5, and 10 (total dose: 6 mg/kg). In India, regimens 1, 2, and 3 (which were studied concurrently) each cured 100% of 10 patients. In Kenya, regimen 1 cured all 10 patients, regimen 2 cured 90% of 10 patients, but regimen 3 cured only 20% of 5 patients. In Brazil, regimen 1 was only partially curative: 5 of 13 patients (62%). Therefore, 15 patients were administered regimen 4 (2 MKD for 10 consecutive days; total dose, 20 mg/kg) and 13 patients were cured (83%).

These results suggest that for the treatment of kala-azar the following doses of AmBisome should be administered: in India and Kenya, 2 mg/kg on days 1–4 and day 10; and in Brazil, 2 mg/kg on days 1–10.

* Preamble by Dr Tore Godal, Director, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

AmBisome (liposomal amphotericin B) was originally developed to treat severe systemic and deep mycoses. Demonstration of its efficacy and safety in the treatment of visceral leishmaniasis is a significant achievement and was made possible through fruitful collaboration between UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), a pharmaceutical company, and clinicians from institutions in developing countries where the disease is endemic. The development of new chemotherapeutic agents for tropical diseases remains a high priority for TDR and attention is being focused on existing drugs intended to treat other infections as one approach in the strategy for drug development. Because of the high cost of some drugs, they are not reaching people in need of treatment. WHO will continue to negotiate preferential pricing for new therapeutic agents for tropical diseases, to make them affordable to developing countries where such diseases are endemic. Innovative research to develop less expensive alternatives is also supported by TDR.

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Introduction

Visceral leishmaniasis ("kala-azar") results from multiplication of *Leishmania* within the systemic reticuloendothelium. The disease is primarily caused by *Leishmania donovani* in the Indian subcontinent and Africa, by *L. infantum* in Mediterranean regions, and by *L. chagasi* in the New World; *L. infantum* and *L. chagasi* are closely related. Classic visceral leishmaniasis presents as fever, hepatosplenomegaly, and pancytopenia; visceral leishmaniasis is characteristically fatal if untreated, because of concomitant unrecognized infections such as pneumonia and tuberculosis, and can be fatal even if appropriately treated. In a large study of 3076 Sudanese patients, 336 (11%) died despite receiving appropriate therapy (1).

The classic treatment for visceral leishmaniasis is with pentavalent antimonials: stibogluconate (Pentostam) or meglumine antimonate (Glucantime) at a dose of 20 mg Sb⁵⁺ per kg per day for 28 days or 40 days for clinically resistant regions such as in India. These regimens routinely result in chemical pancreatitis, in one-third to two-thirds of instances produce abdominal complaints and musculoskeletal pain, and may give cytopenia (2–4).

Alternative therapy using formulations containing amphotericin B is biochemically rational, since the target of amphotericin B is ergosterol-like sterols, the major membrane sterols not only of fungi but also of *Leishmania* (5). Prior to 1990, amphotericin B was employed infrequently because of its known infusion-related (fever, chills, bone pain, rarely cardiac arrest) and delayed side-effects (decreased potassium and renal function) (6–8). Amphotericin B (desoxycholate) has recently been given to large numbers of kala-azar patients who were clinically resistant to stibogluconate and pentamidine. Thakur et al. have reported that for kala-azar patients amphotericin B could be administered daily so that 20 mg/kg could be given over 20 days with >95% efficacy and acceptable toxicity (6). Mishra et al. found that the daily dose could be diminished to 0.5 mg/kg instead of the normal 1 mg/kg; all naive or Sb⁵⁺-resistant patients given amphotericin B at 0.5 mg/kg every other day for 14 doses (total dose, 7 mg/kg) were cured (9,10).

The need to develop less toxic, perhaps more effective formulations of amphotericin B for systemic mycoses has led to three new clinical preparations in which desoxycholate has been replaced by other lipids: liposomal amphotericin B (AmBisome; NeXstar Pharmaceuticals Inc., San Dimas, CA, USA), amphotericin B colloidal dispersion (Amphocil; Sequus Pharmaceuticals, Menlo Park, CA, USA), and amphotericin B lipid complex

(Abelcet; Liposome Co., Princeton, NJ, USA). All three are available clinically in Western Europe and AmBisome has been specifically approved for treating visceral leishmaniasis in some European countries. In general, these formulations are well taken up by the reticuloendothelial system, where *Leishmania* reside, but poorly so by the kidney, the major target of organ toxicity (11); they should therefore be effective against visceral leishmaniasis, have minimal renal toxicity and, if amphotericin B remains bound to the lipid particles, have minimal infusion-related toxicity. Indeed, since *Leishmania* only multiply in and are almost exclusively found in phagocytic cells, in contrast to other amphotericin-B-sensitive pathogens which reside both in phagocytes and elsewhere, visceral leishmaniasis may be the disease for which the new lipid-associated amphotericin B formulations have the best therapeutic index.

The first report on the use of lipid-associated amphotericin B formulations to treat leishmaniasis was by Davidson et al. (12), who used AmBisome with a patient clinically resistant to Sb⁵⁺ and to pentamidine. This patient was cured using a regimen of 50 mg of the drug (ca. 1 mg/kg) daily for 21 days. Davidson et al. have also shown that a large dose of 3 mg·kg⁻¹·day⁻¹ for 10 days (30 mg/kg total dose) was 100% effective in European patients (13).

The significance of these results in terms of providing effective, well-tolerated therapy for visceral leishmaniasis led to an agreement between the pharmaceutical company NeXstar Pharmaceuticals Inc. and WHO to evaluate clinically AmBisome for the treatment of kala-azar. The objectives of this clinical development programme were as follows:

- to determine the minimal effective dose of AmBisome for kala-azar;
- to determine the safety of this dose;
- to perform these determinations in various developing, endemic countries, so that clinicians would have the information needed to treat patients; and
- to provide sufficient information for the registration of the drug for kala-azar.

Materials and methods

Study design

This study was an open label, phase II clinical trial of the efficacy and safety of AmBisome performed concomitantly at three study sites. At each site, sequential cohorts (10 kala-azar patients per cohort)

were treated with AmBisome at a dose of 2 mg·kg⁻¹·day⁻¹ (2MKD).

The first cohort was treated with regimen 1: 2MKD on days 1–6 and day 10 (total dose: 14mg/kg). This was chosen as the initial regimen because the total dose was less than 3MKD on days 1–10 (total dose, 30mg/kg), which has been reported to be 100% effective in Europe (13) and in a preliminary study in Kenya (K.M. Wasunna et al, unpublished data, 1997). If the efficacy was satisfactory in the first cohort, a second cohort was entered to receive regimen 2, which contained a lower total dose: 2MKD on days 1–4 and day 10 (total dose, 10mg/kg). If efficacy was satisfactory in the second cohort, a third cohort was entered to receive regimen 3, which contained a lower total dose: 2MKD on days 1, 5, and day 10 (total dose, 6mg/kg). In contrast, if the efficacy in the first cohort was unsatisfactory, a cohort was entered to receive regimen 4, which contained a higher total dose: 2MKD on days 1–10 (total dose, 20mg/kg). At one site (India), patients were initially randomized between regimens 1, 2, and 3, and the three regimens were investigated concurrently.

Study sites

There were three study sites; in India: Patna Medical College and Hospital, Patna, Bihar (Dr C.P. Thakur); in Africa: Kenya Medical Research Institute, Nairobi, Kenya (Dr K.M. Wasunna); and in the Americas: Hospital Universitario Professor Edgard Santos, Salvador, Bahia, Brazil (Dr R. Badaro). The trials were monitored by TDR (Dr K. Weerasuriya and Dr Pang).

The findings for Patna have already been published (14), while those for Kenya and Brazil will appear later.

Parasitological diagnosis

Patients with clinical signs of kala-azar (fever, hepatosplenomegaly and weight loss) underwent splenic (or rarely, bone marrow) aspiration. In all cases, the parasitological diagnosis of kala-azar was made by visualization of *Leishmania* amastigotes in Giemsa-stained aspirates. A similar parasite quantification scale was used in Brazil and Kenya (15), but differed from the one used in India. Patients with parasitologically demonstrated leishmaniasis were enrolled in the study after giving their informed consent.

Study procedures

Haemoglobin levels, white blood cell counts, platelet counts, blood urea nitrogen levels, creatinine levels,

potassium and albumin levels were determined prior to and during therapy. Patients were monitored for fever and subjective adverse effects each day on which the drug was administered.

Determination of spleen size

Spleen size was determined with the patient in a supine position, breathing quietly, and was assigned a value equal to the distance between the costal margin and the tip of the spleen on a line at right angles to the costal margin.

Drug administration

AmBisome was supplied by NeXstar Pharmaceuticals Inc., readied for clinical use according to the manufacturer's instructions, and infused over 1 h in a 5% solution in dextrose into a peripheral vein.

Follow-up evaluation

Patients were seen for follow-up at 0.5-, 2-, and 6-months' post-therapy. Initial parasitological cure was established by reaspiration of the spleen at the 0.5-month follow-up, this period being chosen to permit delayed elimination of parasites. Clinical cure was assessed by improvement in physical examination and laboratory parameters at the 0.5-, 2-, and 6-month follow-up visits.

Definitions of cure, failure, and relapse

Initial cure (failure) was defined as the absence (presence) of parasites on repeat aspiration. Relapse was defined as reappearance of parasites after their initial disappearance.

Data analysis

Multivariate continuous data were compared by ANOVA and by a post-hoc test (Student–Neuman–Keuls). Bivariate nominal data were compared using Fischer's exact test.

Human use review

The protocols for these trials were approved by the ethical committees of the respective study countries and by the WHO Secretariat Committee for Research involving Human Subjects (SCRIHS). The free and informed consent of all subjects was obtained.

Table 1: Patient characteristics at entry to the study at each of the three sites

	Brazil (cohort):			Kenya (cohort):			India (cohort):		
	1	2	3	1	2	3	1	2	3
Regimen	1	2	4	1	2	3	1	2	3
No. of patients	13	4	15	10	10	5	10	10	10
Age (years)	7.6 ^a	7.5	10.1	13.3 ^a	13.5	16	28	23	23
Haemoglobin (g/dl)	8.2 (1.3) ^a	9 (1.1)	8.1 (1.3)	6.7 (0.8)	6.6 (1.1)	5.9 (0.9)	7.9 (2.1)	7.7 (1.1)	7.8 (1.7)
No. of platelets	171 (71)	223 (65)	155 (26)	122 (35)	99 (43)	124 (45)			
WBC ($\times 1000$) ^b	4.1* (2.1)	3.8 (0.9)	3.7 (1.5)	2.6* (0.7)	3.2 (1.2)	3 (1)	2.5** (0.4)	3.5* (0.7)	2.8* (1)
Albumin ^{c,d}	3.8** (0.67)	3.3 (0.38)	3* (0.6)	2.6** (0.5)	3.2* (0.6)	3 (0.3)	2.8** (0.3)	2.7* (0.4)	3.4* (0.3)
Spleen size (cm)	10.1* (4.5)	9.8 (3.6)	12.9 (5)	12.6* (4)	13.1 (4.1)	15* (6)	4.8** (3.2)	6.1 (2.9)	5* (2.4)
Spleen parasite grade	4.4* (1)	4.5 (0.6)	5.4* (0.55)	4.2 (1.2)	4.6 (1.2)	4.8 (0.4)	1.8	1.2	1.4

*: Significantly different from *cohort at the same study site.

†: Significantly different from *cohort at different study site.

** Significantly different from + cohort at different study site.

^a Figures in parentheses are standard deviations.

^b WBC: white blood cell count. For WBC in India, cohort 2 was significantly different from cohorts 1 and 3; cohorts 1 and 3 were not significantly different.

^c For albumin in India, cohort 3 was significantly different from cohorts 1 and 2; cohorts 1 and 2 were not significantly different.

^d For albumin, cohort 1 in Brazil was significantly different from cohort 1 in Kenya and cohort 1 in India.

Results

Patients

Three cohorts of patients were treated at each of the three sites (Table 1). At each site, the patient's age and the extent of disease as determined by relevant parameters (haemoglobin, platelet count, white blood cell count, albumin level, spleen size, parasite count) were generally comparable in the three cohorts; significant differences are noted in Table 1. In Brazil, the patients who received regimen 4 were more seriously ill than those who received regimen 1 on the basis of their significantly higher parasite grades and lower albumin. In Kenya and India, in contrast, no cohort appeared more seriously ill than any other at the same site. Although in India, regimen 3 patients had significantly lower white cell counts than those in regimen 2, patients in regimen 3 had significantly higher albumin levels than either other cohort.

Efficacy

The efficacy of each regimen at each of the three study sites is summarized in Table 2.

In India, the initial cohort received regimen 1 (total dose, 14mg/kg), which proved to be 100% effective. The second cohort received regimen 2 (total dose, 10mg/kg), which was also 100% curative. The third cohort received regimen 3 (total dose, 6mg/kg), and this again was 100% effective.

In Kenya, the initial regimen was 100% effective and regimen 2, 90% effective. Regimen 3 was the least effective, with one cure, one relapse, and three initial failures, at which point entry into this

cohort was stopped. The difference in cure rate between regimens 3 and 2 in Kenya was statistically significant, as was that for regimen 3 in Kenya and India.

In Brazil, regimen 1 was not 100% effective, with only 8 of 13 patients (62%) being cured (because of side-reactions, one of the failures received 6 rather than the intended 7 doses of the drug). Inadvertently, however, four patients had been entered into a second group to receive the lower-dose regimen 2. Although these four patients were eventually cured, no more received this regimen, instead, a third group received regimen 4, which comprised a larger total dose (20mg/kg) than the initial regimen. This last group showed a high cure rate: 13 of 15 (87%).

Toxicity

In India and Kenya the observed adverse effects were few, with some instances of fever and chills associated with infusion and of irregular pulse. Quantification of the incidence of these events in the 32 Brazilian patients, 15 of whom received the high dose in regimen 4, revealed that 37% experienced fever with one or more infusions, 9% chills, and 6% back pain. In addition, three Brazilian patients (ca. 10%) exhibited respiratory distress and/or cardiac arrhythmia associated with infusion.

Discussion

In these phase II studies, a regimen of liposomal amphotericin B (AmBisome) was highly effective at all three sites: Brazil, India, and Kenya.

Table 2: Efficacy of the AmBisome regimens at each study site

	Brazil (regimen):			Kenya (regimen):			India (regimen):		
	1	2	4	1	2	3	1	2	3
WBC ^a (×1000 at 2 weeks)	6.8	8.7	7	4.8	5.1	3.8	5.4	7.7	6.3
Spleen (cm: 2 weeks)	4.1	3.8	6.9	5.8	8.1	13.8	2	2.9	2.8
Spleen (cm: 2 months)	3.4	2	1.1	6.3	5		1.1	2.1	1.4
Spleen (cm: 6 months)	1.1	0.25	2.4	2.6	0.9		0	1	0.1
<i>Outcome:</i>									
Cure	8	4	13	10	9	1	10	10	10
Failure	1	0	0	0	0	3	0	0	0
Relapse	4	0	2	0	1	1	0	0	0
% Cure ^b	62 ^a	100	87	100 ^a	90 ^a	20 ^{a*}	100 ^a	100	100 ^a

^a WBC: white blood cell count.

^b For % cure, regimen 1 in Brazil was significantly different from regimen 1 in Kenya and India.

* Significantly different from * cohort at same study site.

† Significantly different from * cohort at different study site.

‡ Significant different from † cohort at different study site.

In India, regimen 3, consisting of a very low dose (2 mg/kg on days 1, 5, and 10; total dose = 6 mg/kg) cured 100% of 10 patients. In Kenya, regimen 3 (6 mg/kg) cured only 20% of five patients, whereas regimen 2 (2 mg/kg on days 1–4 and day 10; total dose = 10 mg/kg) cured 90% of patients. Since in Kenya there was no significant difference in the entrance characteristics of the study groups, the failure of regimen 3 signifies that this dose was too low for Kenyan kala-azar. The reason for the greater efficacy of this regimen in India may be that the Indian patients, with smaller spleens, were less seriously ill. It is also possible that Indian *Leishmania* parasites are more sensitive to amphotericin B than are those in Kenya.

In Brazil, regimen 1 (2 mg/kg on days 1–6 and day 10; total dose = 14 mg/kg) was only partially curative (efficacy, 62%). Comparison of the degree of illness of the Brazilian and Kenyan patients who were administered regimen 1 is difficult. The spleen sizes of the Brazilian patients were smaller than those of the Kenyans, but the difference was not significant, and since the Brazilians were significantly younger, their spleens would be expected to be smaller. There was no difference in parasite grade between the regimen 1 patients in Brazil and Kenya. Since it is difficult to conclude that the disease in Brazilians administered regimen 1 was more severe than in Kenyans administered this regimen, the failure of regimen 1 in Brazil might have arisen because of diminished susceptibility of Brazilian *Leishmania* parasites. The lack of 100% cure with regimen 4 (total dose, 20 mg/kg) supports the hypothesis that Brazilian visceral parasites are relatively resistant to amphotericin B; alternatively, children may require a higher dose of the drug on a mg/kg basis than adults.

The results of the present study indicate that, for AmBisome to have a therapeutic margin, treatment for kala-azar in India and in Kenya should use a regimen of 2 mg/kg on days 1–4 and day 10 (total dose, 10 mg/kg). In Brazil, the regimen should be 2 mg/kg on days 1–10 (total dose, 20 mg/kg). It is important to remember that because these proposals derive from small phase II trials, the efficacy of the regimens should be verified in larger phase III trials. The results of trials against *L. infantum* in Europe indicate that a regimen of 3 mg/kg on days 1–5 and day 10 (total dose, 18 mg/kg) be recommended (16).

Patients who would benefit from AmBisome are those for whom standard agents are likely to fail, be toxic, or be difficult to administer. The above-mentioned regimens might therefore be used under the following circumstances:

— initial treatment of patients from antimony-/pentamidine-resistant regions and treatment of patients for whom standard agents have failed;

- treatment of patients with pre-existing organ dysfunction, for whom standard agents might be particularly toxic; and
- treatment of patients for whom the cost of hospitalization to receive standard agents would exceed that of AmBisome (US\$ 186 per 50-mg vial).

It is also important to note that for patients co-infected with human immunodeficiency virus (HIV) and visceral leishmaniasis, the latter initially responds to AmBisome treatment but that relapse is the rule. A total of nine evaluable patients received the high total dose of 40 mg/kg (10 injections of 4 mg/kg) between days 1 and 38. All nine exhibited clinical improvement and the bone marrow of eight of them was cleared of parasites; nevertheless, seven patients relapsed between 2 and 7 months later (17).

Fever and chills may be experienced after infusions of amphotericin B; rarely, a cardiorespiratory syndrome of respiratory distress and cardiac arrhythmia/enlargement occurs. The occurrence of pulmonary hypertension leading to ventilation-perfusion abnormalities, cyanosis, tachycardia, and fever in a patient administered a lipid-amphotericin B formulation other than AmBisome was attributed to the liposome component (18), and amphotericin B itself has caused similar symptoms in sheep (19). Although the adverse cardiorespiratory reaction rarely occurs, its possible severity indicates that treatment with AmBisome should be carried out in a hospitalized setting. Because only a few doses are needed, and trained individuals are required for this purpose, this recommendation should not result in added inconvenience. Some patients will experience a modest decrease in renal function, with a 25% increase in creatinine level from pre-therapy levels (13).

Pentavalent antimonials, pentamidine, paromomycin, and amphotericin B (desoxycholate) are useful agents for treating kala-azar. Because these drugs have either been on the market for some time or were originally intended for the treatment of other microbial diseases, clinicians have had access to them without a formal worldwide leishmaniasis drug development programme. Although AmBisome was also initially developed for other purposes, the collaboration between NeXstar, Inc., and TDR has resulted in the first formal worldwide drug development programme for an antileishmanial agent. The positive results generated by this work should facilitate regulatory approval in developing countries. This programme serves as an example of successful collaboration between a public sector agency and a pharmaceutical company, representing the interests of patients in disease-endemic countries, with the outcome of improving therapy for a parasitic disease in developing countries.

Résumé

Efficacité et innocuité de l'amphotéricine B incluse dans des liposomes (AmBisome) pour le traitement de la leishmaniose viscérale endémique dans les pays en développement

On utilise de plus en plus l'amphotéricine B (désoxycholate) pour traiter les cas de leishmaniose viscérale à cause du taux élevé de guérison qu'elle permet d'obtenir et de l'émergence de formes de la maladie résistantes aux anti-moniés. L'amphotéricine B incluse dans des liposomes (AmBisome) est une formulation moins toxique spécialement homologuée pour le traitement de la leishmaniose en Europe. Pour que les cliniciens et les autorités de réglementation puissent disposer des informations voulues concernant le traitement du kala-azar dans les pays en développement où cette maladie est endémique, un programme concerté entre le Programme spécial PNUD/Banque mondiale/OMS de recherche et de formation concernant les maladies tropicales et NeXstar Pharmaceuticals, Inc., a été institué afin d'évaluer l'efficacité et l'innocuité de l'AmBisome dans cette indication au Brésil, en Inde et au Kenya.

Dans deux des trois sites d'étude (Brésil et Kenya), on a traité des cohortes successives de 10 malades chacune, à raison de 2 mg/kg/jour d'AmBisome. La première cohorte a reçu cette dose aux jours 1–6 et 10 (dose totale: 14 mg/kg). Si l'efficacité s'avérait bonne, une seconde cohorte recevait le double de cette dose aux jours 1–4 et 10 (dose totale: 10 mg/kg); et une troisième cohorte a reçu 2 mg/kg/jour aux jours 1, 5 et 10 (dose totale: 6 mg/kg).

En Inde, où ces trois schémas ont été appliqués simultanément à 10 malades chacun, le taux de guérison a été de 100%. Au Kenya, le premier schéma a permis de guérir les 10 malades, mais le troisième n'a guéri que 20% des 5 malades. Au Brésil, le premier schéma n'a été que partiellement curatif: il a permis d'obtenir la guérison de 5 malades sur 13 (62%). Aussi, 15 malades se sont vu administrer un quatrième schéma posologique (à savoir, 2 mg/kg/jour pendant 10 jours consécutifs: dose totale = 20 mg/kg) et 13 d'entre eux ont guéri (83%).

Les principaux effets indésirables rencontrés l'ont été au cours des perfusions du médicament: fièvre et frissons, présents chez 10–40% des malades et, plus rarement, une détresse respiratoire et/ou des arythmies cardiaques. Il est à noter

que les cas de dysfonctionnement rénal ont été rares et bénins.

Ces résultats laissent à penser que pour avoir une marge de sécurité thérapeutique, il faut traiter le kala-azar en Inde et au Kenya à l'aide du deuxième schéma, à savoir 2 mg/kg/jour d'AmBisome aux jours 1–4 et 10 (dose totale, 20 mg/kg). Au Brésil, la posologie doit être de 2 mg/kg aux jours 1–10 (dose totale, 20 mg/kg). L'efficacité de ces posologies devra être vérifiée au moyen d'essais de phase III plus importants. Il est probable qu'on rencontrera souvent chez les malades des réactions de type fièvre et frissons au cours des perfusions d'AmBisome. Si les réactions cardio-respiratoires sont rares, leur gravité potentielle fait qu'un tel traitement doit être administré en milieu hospitalier.

Ainsi, ce programme de mise au point d'un médicament est un exemple de collaboration réussie entre le secteur privé, l'industrie pharmaceutique et un organisme du secteur public, l'OMS représentant les intérêts des malades des pays en développement.

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