Visceral leishmaniasis (VL), which is endemic in the Indian subcontinent (42,623 reported cases/year of which 34,918 were in India), the Mediterranean region (875 cases/year), East Africa (8,569 cases/year), and Brazil (3,481 cases/year) has undergone a revolution in chemotherapy in the last 15 years. Treatment had been with the classical agents pentavalent antimony and amphotericin B deoxycholate, but with >90% of Indian disease occurring in antimony-resistant regions, the sole effective drug in this key region of the world was amphotericin B deoxycholate. Amphotericin B deoxycholate is extraordinarily effective for Indian VL. In phase 3 studies using 1 mg/kg every other day for 15 intravenous injections, 259 of 260 (99.6%) of per-protocol patients were cured (Table 1 regimens 1 plus 2). Nevertheless, amphotericin B deoxycholate toxicity (infusion-related fever and chills, an infusion-related cardiovascular-respiratory syndrome, which can be mortal, renal and hematologic reactions), and the considerable inconvenience of 15 intravenous injections led to strenuous efforts in the 2000s, many by Dr. Sundar and associates in the Indian subcontinent, to find a replacement that is as effective and inexpensive (<$500 per course) but less toxic and less difficult to administer.

One approach is to use a different formulation of amphotericin B that might diminish toxicity, thereby permitting larger individual doses and a shorter total treatment period. Most reports concern liposomal amphotericin B (Ambisome), but there are a few reports on amphotericin B lipid complex (ABCL/Abelect), amphotericin B colloidal dispersion (ABCD/Amphocil), amphotericin B lipid emulsion (ABLE), and in this issue of the Journal, an Indian-formulated liposomal amphotericin B (Fungisome).

Ambisome: Although adverse reactions to Ambisome are qualitatively similar to those of amphotericin B deoxycholate, their frequency and severity are diminished. Improved tolerance led to higher daily doses, a trial of 7.5 mg/kg total dose over 5 days, and then a trial of 7.5 mg/kg in merely one injection, but both regimens were only 90–93% effective (Table 1 regimens 3 and 4). To bring efficacy up to amphotericin B deoxycholate levels, the total dose of Ambisome was increased to 10 mg/kg. Both 10 mg/kg over 5 days and finally 10 mg/kg administered once showed a high efficacy rate of 96% (Table 1 regimens 5 and 6).

ABCL/Abelect: In a head-to-head comparison, Abelect was inferior to Ambisome in efficacy (Table 1 regimen 7 versus regimen 5) and in tolerance (fever/chills were experienced by 76% of ABCL and 29% of Ambisome patients).

ABCDEFG/Amphocil: 97% efficacy was shown in a large trial using <1 week of therapy (Table 1 regimen 8).

ABLE: 15 mg/kg in one injection was only 85% effective (Table 1 regimen 9).

Fungisome: In this issue of the Journal, Sundar and others report the efficacy of one injection of 10 mg/kg or of 15 mg/kg in an early phase 2 study of 15 patients per cohort. One patient in each cohort relapsed therefore the cure rate was 14 of 15 (93%) for each regimen (Table 1 regimen 10). There was a 90% incidence of infusion-related fever and chills, and an ~25% incidence of diarrhea and vomiting. The 5 SAEs (2 nephrotoxicity, 2 thrombocytopenia, 1 pulmonary edema), even though reversible, may be considered frequent for a small 30-patient database.

In sum, systematic evaluation of Ambisome has led to a very high dose of 10 mg/kg administered in a very short period of time of 1 day, which in a large study showed 96% efficacy. This regimen is overall superior to the standard regimen of amphotericin B deoxycholate (1 mg/kg every other day for 15 infusions) on the basis of efficacy (almost equal), tolerance (superior), feasibility (far superior), and cost (~$200 for Ambisome at the developing-world favorable price). Ambisome 10 mg/kg once is now the treatment of choice for Indian subcontinent VL. ABCD/Amphocil showed excellent efficacy in a relatively short course; whether single dose Amphocil is competitive with single dose Ambisome is not known. Other amphotericin B formulations were either inferior in efficacy (ABCL/Abelect, ABE) or have not yet been evaluated in large trials (Fungisome).

Other approaches toward replacing amphotericin B deoxycholate for Indian subcontinent VL are a parenteral agent that can be administered intramuscularly (paromomycin) and an oral agent (miltefosine).

In a large phase 3 study, 95% of Indian per-protocol patients were cured with a regimen of paromomycin 11 mg/kg/day for 21 days intramuscularly (Table 1 regimen 11). An attempt to shorten the inconvenient 21-day intramuscular treatment course to 14 days revealed low efficacy (84%) for the 2-week course (Table 1 regimen 12).

In a large phase 3 trial, 97% of Indian per-protocol patients were cured with a regimen of miltefosine 2.5 mg/kg/day for 28 days (Table 1 regimen 13) after which miltefosine was made the VL treatment of choice in India, but after 10 years of use, the efficacy rate has fallen to 90% (Table 1 regimen 14). Gastrointestinal side effects are frequent, and miltefosine is contraindicated in pregnancy.

Combining short courses of two drugs will decrease the length of parenteral therapy and should protect against resistance including that to miltefosine and the aminoglycoside paromomycin. When combinations of short courses of 2-drug combinations of Ambisome, miltefosine, and paromomycin were evaluated, each combination was 99% effective (Table 1 regimens 14-16).
Regimen no. | Drug and route | Regimen* | Per-protocol efficacy 6′m after RX† | Reference
--- | --- | --- | --- | ---
1 | Amphotericin B deoxycholate IV | 15 mg/kg over 30 days | 96/96 (100%) | 3
2 | Amphotericin B deoxycholate IV | 15 mg/kg over 30 days | 163/164 (99%) | 4
3 | Liposomal amphotericin B /Ambisome IV | 7.5 mg/kg over 5 days | 26/28 (93%) | 7
4 | Liposomal amphotericin B /Ambisome IV | 7.5 mg/kg once | 183/203 (90%) | 8
5 | Liposomal amphotericin B /Ambisome IV | 10 mg/kg over 5 days | 49/51 (96%) | 5
6 | Liposomal amphotericin B /Ambisome IV | 10 mg/kg once | 291/304 (96%) | 9
7 | ABLC/Abelec IV | 10 mg/kg over 5 days | 47/51 (92%) | 10
8 | ABCD/Amphocil IV | 7.5 mg/kg over 6 days | 131/135 (97%) | 11
9 | ABLE | 15 mg/kg once | 317/373 (85%) | 12
10 | India-formulated Liposomal Amphotericin B/Fungisome IV | 10 mg/kg or 15 mg/kg once | 14/15 (93%) | 13
11 | Paromomycin IM | 11 mg/kg/d × 21 days | 474/501 (95%) | 14
12 | Paromomycin IM | 11 mg/kg/d × 14 days | 183/217 (84%) | 15
13 | Miltefosine oral | 2.5 mg/kg/day × 28 days | 282/291 (97%) | 16
14 | Miltefosine oral | 2.5 mg/kg/day × 28 days | 512/567 (90%) | 17
15 | Ambisome IV + Miltefosine oral | 5 mg/kg once + 2.5 mg/kg/d for 7 days | 155/157 (99%) | 18
16 | Ambisome IV + Paromomycin IM | 5 mg/kg once + 11 mg/kg/d for 10 days | 153/155 (99%) | 19
17 | Miltefosine oral + Paromomycin IM | 2.5 mg/kg/day for 10 days + 11 mg/kg/d for 10 days | 156/158 (99%) | 20

*mg drug = mg active ingredient (amphotericin B, paromomycin base, miltefosine, antimony) in the formulation.
†Efficacy = no. cured/no. evaluable (%).
‡HIV-positive patients omitted from calculation.

Drugs for visceral leishmaniasis in otherwise immunocompetent patients in the Indian subcontinent

18 | Ambisome IV in East Africa | 7.5 mg/kg once | 8/20 (40%) | 17
19 | Ambisome IV in East Africa | 21 mg/kg over 21 days | 46/54 (85%) | 17
20 | Paromomycin in East Africa | 11 mg/kg/d × 21 days | 80/121 (66%)‡ | 16
21 | Ambisome IV in Mediterranean | 18 mg/kg over 10 days | 41/42 (98%) | 16
22 | Pentavalent Antimony in East Africa | 20 mg/kg/day × 30 days | 104/112 (93%)‡ | 16
23 | Pentavalent Antimony in Mediterranean | 20 mg/kg/day × 30 days | 47/52 (90%) | 16

**REFERENCES**


