Visceral leishmaniasis (VL) is caused by infection of the visceral reticuloendothelial system by *Leishmania* spp. Of the estimated 500,000 cases of VL worldwide, 67% occur in the small part of the Indian subcontinent where northeast India borders Bangladesh and Nepal. Infection of macrophages of the liver, spleen, and bone marrow leads to fever, hepatosplenomegaly, and pancytopenia. Untreated VL is a fatal disease because of immunosuppression and intercurrent infections such as tuberculosis, pneumonia, or gastrointestinal.

The classic treatment for VL is with pentavalent antimony but this requires daily injections of antimony for four weeks. Other disadvantages of antimonial therapy are the frequent occurrence of hepatocellular toxicity and chemical pancreatitis, and occasional instances of thrombocytopenia and neutropenia. When the cure rate in Bihar, in the center of this disease-endemic region, decreased to 35% in the mid-1990s, the search for an alternative to antimony intensified.

In spite of leishmaniasis being a neglected disease, remarkable effort and progress has been made the past 10 years in finding new chemotherapies for Indian VL. Amphotericin B (AB) deoxycholate, liposomal amphotericin B, miltefosine, and paromomycin have all been registered and made available for treatment of Indian VL.

In this issue of the journal, Sundar and others report their experience with a new formulation of amphotericin B, AB pre- mixed with lipid emulsion (ABLE). To evaluate the role that this formulation might play in treatment for Indian VL, we need to compare ABLE with the theoretical ideal and with the properties of the four new agents.

Ideal therapy would be oral, 100% effective with one dose and not subject to resistance, extremely well-tolerated, and inexpensive. As would be expected, each agent fulfills some but not all of these criteria.

The strength of amphotericin B deoxycholate is efficacy: the drug has been shown in large numbers of patients to be essentially 100% curative and resistance is not recognized. The disadvantage of AB deoxycholate is toxicity. Fifteen intravenous injections over 30 days are required, and the drug has the well-known side effects of frequent and pronounced infusion-related fevers/chills, renal toxicity and potassium wasting, and occasional anemia and bone pain. Nonetheless, the availability of AB deoxycholate has set a high bar such that any other therapy has to cure ≥ 95% of patients.

Encapsulation of amphotericin B into liposomes has been shown, also in large numbers of patients, to have materially diminished amphotericin B toxicity. For liposomal amphotericin B, infusion-related rigors and fevers, kidney toxicity, and bone pain are generally mild. The problem has been preserving efficacy while simultaneously decreasing the number of intravenous injections and cost. One injection of 5 mg/kg or 7 mg/kg has been investigated but is not sufficiently effective. Virtually all patients initially cure by one-month post therapy, but after relapses are considered, the final six-month cure rate decreases to 90%. Because there is a good dose-response to liposomal amphotericin B, 5 injections totaling 15 mg/kg result a final cure rate of 97%, which is excellent.

Miltefosine represents a fundamental advance in antileishmanial chemotherapy because it is the first oral agent and it is a novel chemical entity. Miltefosine had a 95–97% final cure rate in large phase III and IV trials in India. On the other hand, with its half-life of one week, the drug is thought to be prone to generation of resistance, and “orally administered” does not automatically translate into “easy treatment.” Gastrointestinal side effects and mild-moderate elevations in liver enzyme levels are frequent, elevation in creatinine levels is less frequent, and the drug is contraindicated in pregnancy.

Paromomycin is an old aminoglycoside that for unknown reasons is active against protozoa especially *Leishmania* spp. A large phase III Indian trial showed 11 mg (base)/kg/day for 21 days to cure 95% of patients, with the only clinically meaningful systemic toxicity being hepatic. However, resistance to aminoglycosides is well known, at least in bacteria, and the present regimen of 21 daily injections, although intramuscular and not intravenous, is a major disadvantage for routine clinical use.

Cost has been a moving target, with the cost of higher-priced products decreasing as lower-priced competitors become available. For adults, the cost of a course of AB deoxycholate is approximately $100. The World Health Organization–negotiated preferential price of liposomal AB is approximately $250 per 15-mg/kg course. I estimate the price of miltefosine to have fallen to $100–$200 a course. The price of paromomycin is anticipated to be low, perhaps $20 per course.

In the present report by Sundar and others, four ABLE regimens, each containing a total of 15 mg of AB/kg, were evaluated in treatment groups of 15 patients each. For three regimens, the total dose was divided over one injection on day 1 and another injection on day 3: 7.5 mg/kg on days 1 and 3; 10 mg/kg on day 1 and 5 mg/kg on day 3; and 12.5 mg/kg on day 1 and 2.5 mg/kg on day 3. For the fourth regimen, all 15 mg/kg was administered on day 1. The cure rates of the first three regimens varied between not-quite-enough and unimpressive: 93%, 73%, and 80%, respectively. The fourth regimen, 15 mg/kg on day 1, cured 100% of patients.

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*Address correspondence to Jonathan Berman, Fast-Track Drugs and Biologics LLC, 5 Paramus Court, North Potomac, MD 20878. E-mail: jberman@fasttrackresearch.com*
The report concludes that “ABLE was safe and had excellent efficacy when given as a bolus of 15 mg/kg. More studies with larger number of patients and higher doses are needed to establish a safe and efficacious regimen.” The authors are to be complemented for finding a one-dose regimen that cures > 95% of patients in this initial study, and for their judicious statement that a database much greater than 15 is needed. The lack of a dose-response for this product—the regimen with the least drug on day 1 had the second-highest cure rate—suggests that the true efficacy of a 15-mg/kg bolus on day 1 could be lower than 95%. If efficacy is low when larger number of patients are investigated, more drug will needed to preserve efficacy, and the potential advantages of cost, tolerance, and single administration may be lost. We look forward to further reports with ABLE to see if this new formulation of amphotericin B is competitive in terms of efficacy, tolerance, cost, and feasibility of administration.

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Author’s address: Jonathan Berman, Fast-Track Drugs and Biologics LLC, 5 Paramus Court, North Potomac, MD 20878; E-mail: jberman@fastrackresearch.com.

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