Single-Dose Liposomal Amphotericin B for Visceral Leishmaniasis in India

Shyam Sundar, M.D., Jaya Chakravarty, M.D., Dipti Agarwal, M.D., Madhukar Rai, M.D., and Henry W. Murray, M.D.

ABSTRACT

BACKGROUND
Some 50% of patients with visceral leishmaniasis (kala-azar) worldwide live in the Indian state of Bihar. Liposomal amphotericin B is an effective treatment when administered in short courses. We wanted to determine whether the efficacy of a single infusion of liposomal amphotericin B was inferior to conventional parenteral therapy, consisting of 15 alternate-day infusions of amphotericin B deoxycholate.

METHODS
In this open-label study, we randomly assigned 412 patients in a 3:1 ratio to receive either liposomal amphotericin B (liposomal-therapy group) or amphotericin B deoxycholate (conventional-therapy group). Liposomal amphotericin B (at a dose of 10 mg per kilogram of body weight) was given once, and patients were discharged home 24 hours later. Amphotericin B deoxycholate, which was administered in 15 infusions of 1 mg per kilogram, was given every other day during a 29-day hospitalization. We determined the cure rate 6 months after treatment.

RESULTS
A total of 410 patients — 304 of 304 patients (100%) in the liposomal-therapy group and 106 of 108 patients (98%) in the conventional-therapy group — had apparent cure responses at day 30. Cure rates at 6 months were similar in the two groups: 95.7% (95% confidence interval [CI], 93.4 to 97.9) in the liposomal-therapy group and 96.3% (95% CI, 92.6 to 99.9) in the conventional-therapy group. Adverse events in the liposomal-therapy group were infusion-related fever or rigors (in 40%) and increased anemia or thrombocytopenia (in 2%); such events in the conventional-therapy group were fever or rigors (in 64%), increased anemia (in 19%), and hypokalemia (in 2%). Nephrotoxicity or hepatotoxicity developed in no more than 1% of patients in each group.

CONCLUSIONS
A single infusion of liposomal amphotericin B was not inferior to and was less expensive than conventional therapy with amphotericin B deoxycholate. (ClinicalTrials.gov number, NCT00628719.)
SOME 90% OF PATIENTS WITH VISCERAL leishmaniasis (kala-azar) in India and nearly 50% of patients worldwide live in the northeastern Indian state of Bihar. In Bihar, treatment with liposomal amphotericin B is effective in regimens as brief as 5 days, offering a remedy for the principal drawback of all other antileishmanial agents: a prolonged duration of treatment. However, when such a regimen of liposomal amphotericin B was abbreviated still further, to a single infusion of 5 or 7.5 mg per kilogram of body weight, the efficacy of the drug (90 to 91%) did not reach the desired cure-rate benchmark of at least 95%.

These single-dose trials were also carried out at a time when liposomal amphotericin B (AmBisome, Gilead Sciences) was priced at $200 per 50-mg vial. However, a new preferential price agreement for developing countries has reduced the cost to $20 per vial. This development, which has made it possible to use liposomal amphotericin B in countries such as India, where visceral leishmaniasis is endemic, prompted us to retest the single-dose approach. In this study, we aimed to determine whether increasing the dose of liposomal amphotericin B to 10 mg per kilogram would enhance the cure rate and whether the efficacy would be inferior to that of parenteral amphotericin B deoxycholate, which is considered the standard of care in the region.

METHODS

ELIGIBILITY CRITERIA

From February 2008 through March 2009, we enrolled patients in this open-label study at the field site (Muzaffarpur) of Kala-Azar Medical Research Center at Banaras Hindu University in Varanasi, after receiving approval from the center’s ethics committee. Patients between the ages of 2 and 65 years were eligible if they had symptoms and signs of leishmaniasis (e.g., fever, weight loss, and splenomegaly) and if parasites were shown on microscopy of a splenic aspirate smear. Patients who were seropositive for the human immunodeficiency virus (HIV) or who had a serious concurrent infection, such as tuberculosis or bacterial pneumonia, were excluded. Exclusion criteria also included a white-cell count of less than 750 per cubic millimeter, a hemoglobin level of less than 3.5 g per deciliter, and a platelet count under 40,000 per cubic millimeter; levels of hepatic aspartate aminotransferase or total bilirubin of more than five times the normal range; a serum creatinine level of more than 1.5 times the upper limit of the normal range; and a prothrombin time of more than 4 seconds above the control level.

TRIAL PROCEDURES AND TREATMENTS

A regimen of 15 alternate-day infusions of 1 mg of amphotericin B deoxycholate per kilogram is considered conventional parenteral therapy for leishmaniasis in Bihar, a region where pentavalent antimony is no longer effective and paromomycin is not yet available for distribution. To compare responses to liposomal amphotericin B versus amphotericin B deoxycholate, we used a 3:1 ratio for random assignment to treatment, aiming to assign 300 patients to receive liposomal amphotericin B (liposomal-therapy group) and 100 to receive amphotericin B deoxycholate (conventional-therapy group). We screened 449 patients and excluded 34 according to the preceding criteria; 3 patients elected not to participate. Thus, 412 patients were enrolled and underwent randomization (Fig. 1).

Patients completed baseline testing (standard biochemical and hematologic profiles, urinalysis, chest radiography, electrocardiography, rapid tests for anti-HIV antibody and malaria antigen, and blood smear for malaria). An independent statistician prepared sealed randomization envelopes, using a computer-based random-number generator. Within 1 to 3 days after diagnosis, patients were admitted to the treatment unit and assigned to receive either a single, 1-hour intravenous infusion of 10 mg of liposomal amphotericin B per kilogram or (after a 5-mg test dose) 15 alternate-day, 6-hour infusions of 1 mg of amphotericin B deoxycholate (Fungizone, Nicholas Piramal) per kilogram. All patients provided written informed consent, which was obtained from a parent or guardian for minors.

Patients in the liposomal-therapy group were sent home 24 hours after treatment unless it was deemed that additional observation or evaluation was warranted. Patients were advised to return if there was any deterioration in their condition. Patients in the conventional-therapy group remained in the unit for 30 days and were examined daily. Complete blood counts, serum chemical analysis, and urinalysis were repeated on day 2 in the liposomal-therapy group; on days 8, 15, and 22 or when clinically indicated in the...
conventional-therapy group; and on day 30 in both groups. In the conventional-therapy group, treatment was interrupted because of nephrotoxicity (which was defined as a creatinine level that doubled from baseline and exceeded 2.0 mg per deciliter or that was more than 2.5 mg per deciliter). Treatment was not restarted until the creatinine level decreased to 1.4 mg per deciliter, the upper limit of the normal range. Treatment was discontinued and patients were removed from the study if any adverse event of grade 3 or more (according to Common Terminology Criteria for Adverse Events) occurred, except for hematologic toxicity, for which the cutoff was a decrease of 33% or more from the baseline values for hemoglobin, total leukocyte count, and platelet count.

Splenic aspiration for evaluation of apparent cure was repeated on day 30, 29 days after the infusion of liposomal amphotericin B and 1 day after the administration of the final dose of amphotericin B deoxycholate. Parasite-density scores for aspirate smears before and after treatment were graded microscopically in a blinded fashion by two microbiologists, using a conventional logarithmic scale of 0 (indicating no parasites per 1000 oil-immersion fields) to 6 (indicating >100 amastigotes per 1000 fields). Apparent cure required the absence of fever, clinical improvement, a reduction in spleen size, and a splenic aspirate score of 0 (apparent parasitologic cure). Definitive cure, assessed 6 months later, required being healthy with no signs or symptoms of relapse.

**STUDY OVERSIGHT**

The study sponsors, the Sitaram Memorial Trust and the Varanasi Physicians Research and Education Foundation, had no role in the design of the trial or in the preparation of the manuscript. All authors vouch for the completeness and accuracy of the data presented. All study drugs were procured and donated by the Sitaram Memorial Trust.

**STATISTICAL ANALYSIS**

Assuming a 99% cure rate for standard treatment with amphotericin B deoxycholate, we determined that we would need to enroll at least 400 patients in a 3:1 ratio to support a one-tailed noninferiority analysis without stratification and with a power of 90% to detect the probability of a type I error of 5%. The intention-to-treat analysis included all subjects who received at least one dose of a study drug. The per-protocol analysis included all patients who completed treatment and all protocol requirements. The exact one-tailed upper bound of the 97.5% confidence interval for the difference in success rates was compared with the use of a delta of 0.084 (the difference between the two study groups, the chosen margin of noninferiority).

Data were expressed as means (±SD) for continuous variables and percentages for categorical variables. An independent sample t-test was used to detect differences in clinical and laboratory results for the two study groups, except for differences in sex, previous treatment, and response rates, which were evaluated with a z-test for normal distribution. A paired-sample t-test was used to compare values before and after treatment in each group. Changes in clinical and laboratory measurements between the two groups were compared with the use of an independent sample t-test. We used the asymptotic normal approximation method for proportions to compute 95% confidence intervals for response rates. A P value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed with the use of SPSS software, version 16.0.
**RESULTS**

**Patients and Initial Responses**

At study entry (day 0), clinical and laboratory results were similar in the two groups (Table 1). Of the 412 patients, 80 had undergone previous treatment, including 38 who received treatment with sodium antimony gluconate elsewhere; in our unit, 13 had received treatment with amphotericin B deoxycholate, 10 with miltefosine, and 19 with paromomycin. Clinically severe disease (which was defined as a spleen size of >8 cm or a hemoglobin level of <7 g per deciliter⁹) was present in 27% of patients in each group.

Two patients in the conventional-therapy group were removed from the study because of severe diarrhea in one and presumed bacterial pneumonia in the other; both cases were considered treatment failures in the intention-to-treat analysis (Fig. 1). The remaining 410 patients completed their assigned treatment, and on day 30, all had parasite-free splenic aspirate smears and fulfilled the criteria for apparent cure (Table 2).

In the two study groups at day 30, patients had significant decreases in spleen size and increases in hemoglobin level and in white-cell and platelet counts (P<0.001). However, in the liposomal-therapy group, increases from baseline to day 30 in body weight, hemoglobin level, and white-cell count were significantly greater than in the conventional-therapy group (Table 3). The increases in levels of serum creatinine and blood urea nitrogen on day 30 were significantly greater in the conventional-therapy group than in the liposomal-therapy group (Table 3).

**Adverse Events**

No serious adverse events were reported in either group. Anticipated infusion-associated reactions (fever or rigors during drug administration⁹) occurred in 121 of 304 patients (40%) in the liposomal-therapy group and 69 of 108 patients (64%).

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**Table 1. Baseline Clinical and Laboratory Data.⁹**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Liposomal Amphotericin B (N=304)</th>
<th>Amphotericin B Deoxycholate (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean — yr</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Range — yr</td>
<td>2–60</td>
</tr>
<tr>
<td></td>
<td>≤12 yr — %</td>
<td>54</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>182 (60)</td>
<td>67 (62)</td>
</tr>
<tr>
<td>Patients who underwent previous therapy — no. (%)</td>
<td>54 (18)</td>
<td>26 (24)</td>
</tr>
<tr>
<td>Duration of illness — days</td>
<td>Mean</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>2–365</td>
</tr>
<tr>
<td>Splenic aspirate score†</td>
<td>2.0±1.0</td>
<td>2.1±1.1</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>30±15</td>
<td>28±14</td>
</tr>
<tr>
<td>Spleen size — cm below left costal margin</td>
<td>4.5±3.3</td>
<td>5.2±3.5</td>
</tr>
<tr>
<td>Hemoglobin — g/dl</td>
<td>8.0±2.0</td>
<td>7.8±1.6</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>3300±900</td>
<td>3300±1700</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>110,000±60,000</td>
<td>100,000±50,000</td>
</tr>
<tr>
<td>Creatinine — mg/dl</td>
<td>0.7±0.3</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Blood urea nitrogen — mg/dl</td>
<td>10±4</td>
<td>10±4</td>
</tr>
<tr>
<td>Aspartate aminotransferase — IU/ml</td>
<td>64±38</td>
<td>65±43</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences between the study groups for any variable. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for blood urea nitrogen to micromoles per liter, multiply by 0.357.

† Splenic aspirate was graded on a conventional logarithmic scale of 0 (indicating no parasites per 1000 oil-immersion fields) to 6 (indicating >100 amastigotes per 1000 fields).
in the conventional-therapy group (Table 4). Of the 69 patients in the conventional-therapy group who had this reaction, 42 required subsequent oral pretreatment with an antipyretic (paracetamol) and an antihistamine (chlorpheniramine) with the use of standard pediatric or adult doses. None of these transient infusion reactions warranted the discontinuation of treatment. In the liposomal-therapy group, retesting before discharge on day 2 showed that increased anemia or thrombocytopenia or evidence of nephrotoxicity or hepatotoxicity had developed in no more than 2% of patients. Since anemia and thrombocytopenia regularly accompany leishmaniasis, it was difficult to distinguish at this early time point between the effects of liposomal amphotericin B and disease-induced effects. In the five subjects who had increased thrombocytopenia, platelet counts were low at baseline (47,000 to 56,000 per cubic millimeter) and decreased to 20,000 to 24,000 per cubic millimeter on day 2 with no evidence of bleeding. On day 30, platelet counts in these five subjects were 128,000 to 268,000 per cubic millimeter. In the conventional-therapy group, increased anemia developed in 21 patients (19%); other adverse events in this group are shown in Table 4.

**OUTCOME AND RETREATMENT**

No patient was lost to follow-up. Symptomatic relapse of infection (as confirmed by parasitologic analysis) occurred in 15 patients (Table 2). All other patients were healthy at the 6-month evaluation and were judged to have shown a definitive cure response. None of the 80 previously treated patients had a relapse, including the 13 subjects (6 in the liposomal-therapy group and 7 in the conventional-therapy group) who had received previous treatment with amphotericin B deoxycholate.

In the intention-to-treat analysis, overall cure rates were essentially the same in the two groups: 95.7% (95% confidence interval [CI], 93.4 to 97.9) in the liposomal-therapy group and 96.3% (95% CI, 92.6 to 99.9) in the conventional-therapy group. The observed difference between the cure rates (delta) was 0.58 percentage points, with 95% confidence intervals ranging from −0.036 to 0.048; the upper bound of the 95% confidence interval was 4.8 (P<0.001). Because the lower

<table>
<thead>
<tr>
<th>Variable</th>
<th>Liposomal Amphotericin B (N=304)</th>
<th>Amphotericin B Deoxycholate (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removed from study — no.</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Completed treatment — no.</td>
<td>304</td>
<td>106</td>
</tr>
<tr>
<td>Apparent cure at day 30 — no.</td>
<td>304</td>
<td>106</td>
</tr>
<tr>
<td>Relapse — no. (%)</td>
<td>13 (4.3)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Lost to follow-up — no.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Definitive cure at 6 mo†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Intention-to-treat population   |                                  |                                      |
| No. of patients                 | 291                              | 104                                  |
| Percent (95% CI)                | 95.7 (93.4–97.9)                 | 96.3 (92.6–99.9)                     |

| Per-protocol population‡        |                                  |                                      |
| No. of patients                 | 291                              | 104                                  |
| Percent (95% CI)                | 95.7 (93.4–97.9)                 | 98.1 (95.5–100.0)                    |

* Among 13 patients who received liposomal amphotericin B and had a relapse after an apparent cure response (4.3%), such relapses occurred in 2 patients at 2 months, in 2 patients at 3 months, in 2 patients at 4 months, in 2 patients at 5 months, and in 5 patients at 6 months; in 2 patients receiving amphotericin B deoxycholate who had such a relapse (1.9%), 1 occurred at 4 months and another at 6 months (P=0.37 for the comparison between relapse rates).
† The between-group difference in definitive cure rates in the intention-to-treat analysis was 0.6 percentage points, with an upper bound of the 95% confidence interval (CI) of 4.8 (P<0.001). The difference in the per-protocol analysis was 2.4 percentage points, with an upper bound of the 95% CI of 6.0 (P=0.02).
‡ The per-protocol population included 304 patients in the liposomal-therapy group and 106 in the conventional-therapy group.
limit of the difference (−0.036) was greater than −0.084 (assumed delta), we concluded that liposomal amphotericin B was noninferior to amphotericin B deoxycholate. The per-protocol analysis yielded the same conclusion (Table 2). The 15 subjects who had a relapse of infection were retreated with 15 mg of liposomal amphotericin B per kilogram (3 mg per kilogram per day for 5 days). Each of these patients had a response and was considered cured 6 months later.

Estimated Treatment Costs

In India, liposomal amphotericin B is available at $20 per 50-mg vial through the Gilead Sciences AmBisome Access Program. The retail cost of amphotericin B deoxycholate is approximately $6.50 per 50-mg vial. On the basis of previous calculations, the total cost of a single infusion of 10 mg of liposomal amphotericin B per kilogram for a 35-kg patient in Bihar would be $162 ($140 for the drug plus $22 for 1 day of in-hospital care); outpatient treatment would cost $148. For a similar patient, 15 alternate-day infusions of 1 mg of amphotericin B deoxycholate per kilogram during a 30-day hospital stay would cost $436 ($68 for the drug plus $368 for hospitalization and laboratory monitoring).

Discussion

This study extends the testing of single-dose liposomal amphotericin B in Indian patients with visceral leishmaniasis by addressing two questions: Does raising the administered dose to 10 mg per kilogram produce satisfactory efficacy, and is this treatment inferior to 15 infusions of amphotericin B deoxycholate, the conventional parenteral therapy in Bihar? Our results answer both questions by showing that a single-dose regimen of liposomal amphotericin B is effective and apparently noninferior to treatment with amphotericin B deoxycholate. In addition, the single 10-mg dose of liposomal amphotericin B per kilogram was not associated with any safety concerns in adults or children, and compliance was guaranteed.

It is important to point out that our study was conducted at an urban referral center in a well-controlled setting and that exclusion criteria precluded the enrollment of patients with certain conditions or markedly abnormal laboratory results. However, only 8% of patients were excluded on the latter basis, and criteria allowed for enrolling patients who were severely ill with visceral leishmaniasis. In addition, since visceral leishmaniasis is thought to be more treatment-responsive in India than in other endemic regions, our results may apply only to India. However, another abbreviated regimen of liposomal amphotericin B, consisting of two doses of 10 mg per kilogram per day on consecutive days, has also proved effective in Europe.

There are two practical concerns with the regimen of liposomal amphotericin B that we
used in this study: the requirement for intravenous administration (the same as for amphotericin B deoxycholate) and cost. In Bihar, however, it is now quite common to find government-designated health care personnel in most villages or nearby health centers who can administer infusions. In addition, the preferential pricing of the liposomal amphotericin B in India and other developing countries in which leishmaniasis is endemic (according to an agreement with the World Health Organization and Gilead Sciences on March 14, 2007), along with a single day of hospitalization, makes a single infusion of the liposomal preparation less expensive than 15 alternate-day doses of the deoxycholate preparation. A similar analysis that was applied to pentavalent antimony (a traditional therapy still active in India outside of Bihar, administered at 20 mg per kilogram per day for 30 days)1 yielded the same conclusion. Although generic pentavalent antimony in India is inexpensive ($32 per course for a 35-kg patient), the estimated total cost of parenteral treatment in a hospitalized patient is nevertheless high ($376).1

With any prolonged course of parenteral therapy, especially when clinically arduous (e.g., amphotericin B deoxycholate or antimony), satisfactory compliance and the possibility that incomplete treatment will induce drug resistance are major concerns.15 Moreover, 30 days of therapy with amphotericin B deoxycholate or antimony may produce prominent adverse reactions,1,9,10 as compared with the liposomal regimen. The use of a single-dose regimen removes any concern about compliance with treatment, and its simplicity makes it amenable for use at peripheral health facilities.

A 28-day regimen of oral miltefosine and 21 days of once-daily intramuscular injections of paromomycin are also effective treatments in Bihar, producing cure rates of 94 to 95%, which are noninferior to rates for amphotericin B deoxycholate.10,16,17 The importance and practical usefulness of an oral agent in patients with leishmaniasis cannot be overemphasized. However, completing 28 days of treatment may be difficult, and miltefosine cannot be used in pregnant women (adequate birth control is also required in women of child-bearing age during and for 3 months after treatment), and initial gastrointestinal reactions (while self-limited) are common.16,17 Although not yet available for distribution in India, paromomycin has promise. In hospitalized patients, treatment produced a 95% cure rate and few adverse reactions.10 However, the efficacy of paromomycin outside a research setting has not yet been reported, and compliance with and the logistics of administering outpatient injections for 21 days are also under study.

<table>
<thead>
<tr>
<th>Event</th>
<th>Liposomal Amphotericin B (N = 304)</th>
<th>Amphotericin B Deoxycholate (N = 108)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion-related fever or rigors</td>
<td>121 (40)</td>
<td>69 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased anemia</td>
<td>6 (2)</td>
<td>21 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased thrombocytopenia</td>
<td>5 (2)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0</td>
<td>2 (2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* As compared with baseline values, adverse events were defined as a decrease in hemoglobin of more than 1 g per deciliter (increased anemia); a decrease of more than 50% in the platelet count (increased thrombocytopenia); a serum creatinine level that doubled from baseline and exceeded 2.0 mg per deciliter or that was more than 2.5 mg per deciliter (nephrotoxicity); a potassium level of less than 3.0 mmol per liter (hypokalemia); and an increase in the aspartate aminotransferase level by a factor of 5 or more (hepatotoxicity). Patients receiving amphotericin B deoxycholate were monitored more frequently for adverse events than were patients receiving liposomal amphotericin B. NS denotes not significant.
† P values are for the between-group comparisons at 30 days.
‡ A total of 106 patients were evaluated on day 30.
We hospitalized the patients in the liposomal-therapy group overnight for observation and repeated laboratory testing the day after the infusion. No unexpected clinical events occurred during this period, and retesting showed few adverse laboratory reactions. Thus, although not yet verified, it seems plausible that in many patients, an overnight stay may not be necessary and the 1-hour infusion of liposomal amphotericin B could be given in an outpatient clinic, as long as proper follow-up is available if needed before day 30.

Relapse of apparently cured infection occurred in the two study groups (Table 2). Relapse is well recognized in visceral leishmaniasis and most often develops in the first 6 months after treatment. In phase 3 trials in Bihar leading to drug approvals in India, relapse rates after treatment with miltefosine or paromomycin were 3.2% and 4.5%, respectively. In our study, the liposomal-therapy group had a relapse rate that was higher than that in the conventional-therapy group (4.3% vs. 1.9%), although the difference was not significant (P=0.37). All 15 patients who had a relapse were successfully retreated with a liposomal regimen of 15 mg per kilogram during a 5-day period.

Detecting and promptly treating patients who have a relapse is obviously important, especially for the National Kala-Azar Elimination Programme, since transmission of Leishmania donovani in the Indian subcontinent is anthropo- and zooonotic. This program's plan calls for patients to be treated near their homes, with government-assigned health care workers at the village and district level who are trained to recognize and report all infections, including relapses after treatment. The ability to treat a large number of patients effectively and efficiently is also essential to implementing this national program, and single-dose liposomal amphotericin B fulfills both criteria.

Oral miltefosine has been logically incorporated into the elimination program. However, concerns about compliance and resistance-engendering effects of partial treatment have already led to suggestions for directly observed therapy and for testing of miltefosine in combination with a second agent (e.g., single-dose liposomal amphotericin B at a dose of 5 mg per kilogram). The latter approach, which should shorten treatment to 7 to 15 days, is now being studied in additional trials in Bihar. The hope is that combination therapy will also diminish the future likelihood that drug resistance will develop. The particular pharmacokinetic properties of liposomal amphotericin B and its tissue macrophage-targeting formulation provide some assurance of high and persistent drug levels after a single infusion of 10 mg per kilogram. However, if this single-dose regimen becomes widespread in India, it will be critical to detect as early as possible any evidence suggesting that treatment failures are associated with drug resistance.

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