The New England Journal of Medicine

VOLUME 347 NOVEMBER 28, 2002 NUMBER 22

ORAL MILTEFOSINE FOR INDIAN VISCERAL LEISHMANIASIS

SHYAM SUNDAR, M.D., T.K. JHA, M.D., C.P. THAKUR, M.D., JUERGEN ENGEL, PH.D., HERBERT SINDERMANN, PH.D., CHRISTINA FISCHER, KLAUS JUNGE, PH.D., ANTHONY BRYCESON, M.D., AND JONATHAN BERMAN, M.D., PH.D.

ABSTRACT

Background There are 500,000 cases per year of visceral leishmaniasis, which occurs primarily in the Indian subcontinent. Almost all untreated patients die, and all the effective agents have been parenteral. Miltefosine is an oral agent that has been shown in small numbers of patients to have a favorable therapeutic index for Indian visceral leishmaniasis. We performed a clinical trial in India comparing miltefosine with the most effective standard treatment, amphotericin B.

Methods The study was a randomized, open-label comparison, in which 299 patients 12 years of age or older received orally administered miltefosine (50 or 100 mg [approximately 2.5 mg per kilogram of body weight] daily for 28 days) and 99 patients received intravenously administered amphotericin B (1 mg per kilogram every other day for a total of 15 injections).

Results The groups were well matched in terms of age, weight, proportion with previous failure of treatment for leishmaniasis, parasitologic grade of splenic aspirate, and splenomegaly. At the end of treatment, splenic aspirates were obtained from 293 patients in the miltefosine group and 98 patients in the amphotericin B group. No parasites were identified, for an initial cure rate of 100 percent. By six months after the completion of treatment, 282 of the 299 patients in the miltefosine group (94 percent [95 percent confidence interval, 91 to 97]) and 96 of the 99 patients in the amphotericin B group (97 percent) had not had a relapse; these patients were classified as cured. Vomiting and diarrhea, generally lasting one to two days, occurred in 38 percent and 20 percent of the patients in the miltefosine group, respectively.

Conclusions Oral miltefosine is an effective and safe treatment for Indian visceral leishmaniasis. Miltefosine may be particularly advantageous because it can be administered orally. It may also be helpful in regions where parasites are resistant to current agents. (N Engl J Med 2002;347:1739-46.)

VISCERAL leishmaniasis is caused by infection of the visceral reticuloendothelial system by leishmania species acquired from sandfly bites. There are approximately 500,000 cases per year, with the majority in northeastern India, Nepal, and Bangladesh. Other areas where visceral leishmaniasis is endemic include East Africa, the littoral region of the Mediterranean, and Brazil.[1] The disease presents with fever, hepatosplenomegaly, and pancytopenia. Almost all untreated patients die, generally because of intercurrent infection.[2,3] Both standard treatment and secondary treatment are parenteral. Standard treatment consists of daily injections of pentavalent antimonial compounds for 28 days. In regions of India where there is a high frequency of resistance to antimony, amphotericin B in a dose of 15 to 20 mg per kilogram of body weight is administered intravenously over a period of 30 to 40 days.[4] In patients who can pay for liposomal amphotericin B, 5 mg per kilogram is administered intravenously over a period of five days.[5]

Miltefosine (hexadecylphosphocholine) is an alkylphosphocholine analogue that was originally developed as an antitumor agent but proved to be clinically ineffective. Although the antileishmanial biochemical mechanism remains unclear, miltefosine has good efficacy against leishmania in vitro[6] and, with oral administration, in animals.[7,8] Within the past five years, four phase 1–2 studies of the efficacy and tolerability of oral miltefosine for Indian visceral leishmaniasis have been reported.[9-12] In the largest of these studies,[11] 29 of 30 patients (97 percent) were cured with 100 mg

From the Institutes of Medical Sciences, Banaras Hindu University, Varanasi (S.S.); the Kala-azar Research Center, Brahmpura, Muzaffarpur (T.K.J.); and Balaji Utthan Sanastan, Patna (C.P.T.) — all in India; Zentaris–Asta Medica, Frankfurt am Main, Germany (J.E., H.S., C.F., K.J.); the London School of Hygiene and Tropical Medicine, London (A.B.); and the Walter Reed Army Institute of Research, Silver Spring, Md. (J.B.). Address reprint requests to Dr. Berman at the National Center for Complementary and Alternative Medicine, 6707 Democracy Blvd., Ste. 401, Bethesda, MD 20892, or at bermanjo@mail.nih.gov.

of miltefosine per day (a mean of 2.5 mg of miltefosine per kilogram per day) for 28 days.

We report the results of a phase 3 trial of miltefosine. The objectives of the trial were to investigate the efficacy and toxicity of miltefosine in larger numbers of patients and in comparison with the efficacy and toxicity of amphotericin B, the most potent clinical antileishmanial agent currently in use.

METHODS

Study Design

We undertook a randomized, open-label, phase 3 trial comparing oral miltefosine with the drug considered to represent the standard of care, intravenous amphotericin B. All authors participated fully in the design of the study, had access to all study data, and take responsibility for data analysis. The authors who are not employees of the sponsoring company had authority over the preparation of the manuscript. The study was conducted in parallel at three medical centers in Bihar, India. The ethics committees at the three clinical centers approved the study protocol, the consent forms, and all amendments. The initial visits of all study patients were completed between July 1999 and July 2000.

Study Drug

Miltefosine (Zentaris) was administered orally for 28 days in a dose as close to 2.5 mg per kilogram per day as was practicable. Patients weighing more than 25 kg received 100 mg daily (one 50-mg capsule in the morning and one capsule in the evening after meals); patients weighing 25 kg or less received 50 mg each morning. Amphotericin B (Fungizone, Bristol-Myers Squibb) was administered intravenously at a total dose of 15 mg per kilogram over a period of 30 days (1 mg per kilogram every other day for a total of 15 infusions). All patients were hospitalized during treatment, which was observed.

Study Patients

Potentially eligible patients were 12 years of age or older with visceral leishmaniasis suspected on the basis of clinical presentation (fever, splenomegaly, and cytopenia) and diagnosed by the presence of leishmania in splenic aspirates. Criteria for exclusion were a platelet count below 50,000 per cubic millimeter, a white-cell count below 1000 per cubic millimeter, a hemoglobin concentration of less than 6 g per deciliter, results on liver-function tests (serum aspartate aminotransferase and alanine aminotransferase concentrations) more than three times the upper limit of normal, a bilirubin concentration more than twice the upper limit of normal, serum creatinine or blood urea nitrogen values more than 1.5 times the upper limit of normal, other major medical illness including human immunodeficiency virus infection or severe malaria, pregnancy or lactation, inability to maintain use of contraception for the period of treatment plus two months, and previous therapy with amphotericin B.

Study Procedures

After written informed consent and data to evaluate eligibility had been obtained, patients were centrally registered and randomly assigned at each site to miltefosine or amphotericin therapy in a 3:1 ratio with the use of permuted blocks of four patients each. Treatment was administered as described above. Weekly during therapy, at the end of therapy (on day 28 for patients receiving miltefosine and on day 30 for those receiving amphotericin), and six months after the completion of therapy, patients were monitored for subjectively reported adverse events, hematologic variables, serum chemistry as on admission, and the size of the spleen as measured in centimeters below the left costal margin. Adverse events were graded according to the Common Toxicity Criteria of the National Cancer Institute.[13] Parasitologic analysis of splenic aspirates was performed at the end of therapy and was repeated at six-month follow-up in patients with signs and symptoms suggestive of visceral leishmaniasis. Male patients of reproductive age were queried a median of 23 months (range, 11 to 31) after the completion of therapy regarding the numbers and health of children born to their sexual partners.

Efficacy End Points

The density of parasites was graded on a log scale from 0 (no parasites per 1000 fields of 1000× power) to 6 (>100 parasites per field).[14] Cure was defined as an absence of parasites at the end of therapy or a parasite density of 1 with no parasites on repeated smear one month later (initial cure) plus no relapse during the six months of follow-up. Relapse was defined by signs or symptoms suggestive of leishmaniasis and appearing after an initial cure, followed by a positive test for leishmania in a splenic aspirate. Treatment failure was defined as either the lack of initial cure or relapse.

Statistical Analysis

The end point of this trial designed to assess noninferiority was the proportion of patients with a final cure. The considerations for the sample size and the confirmatory analysis were determined on the basis of the restricted maximum-likelihood estimation of the variance of the test statistic,[15] with a one-sided alpha of 0.025, a power of 0.80, a margin of noninferiority of 15 percent, assumed cure rates for miltefosine of 88 to 92 percent and for amphotericin of 94 to 98 percent, and a ratio of 3:1 for the random assignment of patients to miltefosine and amphotericin. The number of patients required overall was 400.

RESULTS

Base-Line Characteristics of the Patients

Base-line characteristics of the patients are summarized in Table 1. Approximately 10 percent of screened patients with visceral leishmaniasis were excluded from the trial because they had severe disease (data not shown). Ultimately, 299 patients received miltefosine, and 99 patients received amphotericin.

Except for sex, the base-line characteristics were similar in the two treatment groups. The mean parasite density was approximately grade 3 (defined as 1 to 10 parasites per 10 fields); mean splenomegaly was 6.9 cm. Most patients had moderate pancytopenia. The serum aspartate aminotransferase and alanine aminotransferase concentrations were above the upper limit of normal in 82 percent of the patients in the miltefosine group and 77 percent of those in the amphotericin group. Twenty-eight percent of patients had previously been treated with pentavalent antimonial compounds.

Efficacy

The efficacy of the treatments is shown in Table 2. At the end of the course of treatment, splenic aspirates were obtained from 293 of the 299 patients in the miltefosine group and 98 of the 99 patients in the amphotericin group. All were parasitologically negative. Thus, for both treatment groups, the rate of initial cure was 100 percent among patients for whom parasitologic

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	MILTEFOSINE GROUP	AMPHOTERICIN GROUP	NORMAL VALUE
No. assigned to group	301	99	
No. who did not receive drug	1	1	
No. with randomization error†	1	0	
No. treated with drug	299	99	
Sex — no. (%)			
Male	211 (71)	58 (59)	
Female	88 (29)	41 (41)	
Age — yr	26±13	26±12	
Weight — kg	39±10	38±12	
No previous treatment prescribed for leishmania — no. (%)	214 (72)	71 (72)	
Parasite density‡	2.9±1.0	2.9±1.1	
Splenomegaly — cm below left costal margin	6.9±4.3	6.9±4.3	
Laboratory values			
White cells — no./mm³	3350±1670	3760±1880	>4,000
Platelets — no./mm³	122,000±68,000	117,000±50,000	>150,000
Hemoglobin — g/dl	8.0±1.5	8.4±1.7	>13.0
Serum aspartate aminotransferase — U/liter	58±25	58±26	<35
Serum alanine aminotransferase — U/liter	47±31	45±30	<56
Serum creatinine — μmol/liter	81±24	78±23	<124
Blood urea nitrogen — mg/dl	12±4	12±4	<21
Corrected QT interval — msec	348±40	341±38	<431

*Plus–minus values are means ±SD. To convert values for serum creatinine to milligrams per deciliter, divide by 88.4. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357.

†Data for this patient were analyzed with those for the amphotericin group.

‡Density ranges from 0 to 6, with higher scores indicating greater splenic parasite load.

TABLE 2. EFFICACY OF MILTEFOSINE AS COMPARED WITH THAT OF AMPHOTERICIN.*

EFFICACY	MILTEFOSINE GROUP (N=299)	AMPHOTERICIN GROUP (N=99)
At completion of therapy		
Parasitologic cure — no. (% [95% CI])	293 (98 [96–99])	98 (99 [95–100])
Difference between cure rate with miltefosine and cure rate with amphotericin — % (lower 95% confidence limit)	−1.0 (−3.5)	
Not assessed — no. (%)	6 (2)	1 (1)
At 6 mo		
Final cure — no. (% [95% CI])	282 (94 [91–97])	96 (97 [91–99])
Difference between cure rate with miltefosine and cure rate with amphotericin — % (lower 95% confidence limit)	−2.7 (−6.6)	
Treatment failure (relapse) — no. (%)	9 (3)	0
Not assessed — no. (%)	8 (3)	3 (3)

*CI denotes confidence interval.

analysis was performed. In both groups, at the end of therapy, the mean size of the spleen below the costal margin had decreased dramatically to 1.0 cm.

At the six-month follow-up visit, 291 patients in the miltefosine group and 96 patients in the amphotericin group were evaluated. A total of 97 patients in the miltefosine group and 16 in the amphotericin group had symptoms that were potentially indicative of leishmaniasis. In 86 of these 113 patients, causes other than leishmaniasis were identified. The 27 patients in whom relapse of leishmaniasis could not be ruled out clinically were all in the miltefosine group. In most of these

TABLE 3. TOXIC EFFECTS.*

VARIABLE	MILTEFOSINE GROUP (N=299)	AMPHOTERICIN GROUP (N=99)
Symptoms		
Vomiting — no. (%)		
Total	113 (38)	20 (20)
Duration		
1–2 days	82 (27)	15 (15)
3–4 days	23 (8)	3 (3)
>4 days	8 (3)	2 (2)
Common Toxicity Criteria grade†		
1	79 (26)	16 (16)
2	34 (11)	4 (4)
Diarrhea — no. (%)		
Total	61 (20)	6 (6)
Duration		
1–2 days	46 (15)	4 (4)
3–4 days	14 (5)	1 (1)
>4 days	1 (<1)	1 (1)
Common Toxicity Criteria grade‡		
1	48 (16)	3 (3)
2	12 (4)	3 (3)
4	1 (<1)	0
Rigors — no. (%)		
Total	1 (<1)	90 (90)
Duration		
1–2 days	1 (<1)	13 (13)
3–4 days	0	14 (14)
5–16 days	0	63 (64)
Severity		
Mild or brief	1 (<1)	54 (54)
Pronounced or prolonged	0	36 (36)
Laboratory values§		
Serum aspartate aminotransferase		
Mean change from base line — U/liter (%)		
Wk 1	+10 (17)	+0.7 (1)
Wk 2	−1 (−2)	−13 (−22)
At completion of therapy	−5 (−9)	−19 (−33)
At 6 mo	−16 (−28)	−1 (−2)
Patients with increases — no. (%)¶		
Grade 1	91 (30)	28 (28)
Grade 2	70 (23)	16 (16)
Grade 3	16 (5)	3 (3)
Serum alanine aminotransferase		
Mean change from base line — U/liter (%)		
Wk 1	+0.7 (1)	+8 (18)
Wk 2	+5.5 (12)	−2 (−4)
At completion of therapy	+6 (13)	−10 (−22)
At 6 mo	−5 (−11)	−3 (−7)
Patients with increases — no. (%)¶		
Grade 1	133 (44)	26 (26)
Grade 2	21 (7)	2 (2)
Grade 3	1 (<1)	1 (1)

patients, the abnormality seen at that time was anemia. Splenic aspiration was performed in these 27 patients, and aspirates from 9 patients tested positive for leishmaniasis. Thus, there were nine patients in the miltefosine group (3 percent) and no patients in the amphotericin group with a relapse of visceral leishmaniasis after therapy. Spleens were not palpable in 262 of the 291 patients in the miltefosine group evaluated at six months (90 percent) or in 88 of the 96 patients in the amphotericin group evaluated at that time (92 percent). There were eight patients in the miltefosine group and three patients in the amphotericin group who could not be assessed at the six-month follow-up. The cure rate for miltefosine was therefore 282 of 299, or 94 percent, as compared with 96 of 99, or 97 percent, for amphotericin. Among the patients who

TABLE 3. CONTINUED.

VARIABLE	MILTEFOSINE GROUP (N=299)	AMPHOTERICIN GROUP (N=99)
Laboratory values§ (continued)		
Serum creatinine		
Mean change from base line — μmol/liter (%)		
Wk 1	−1 (−1)	+27 (35)
Wk 2	−3 (−4)	+21 (27)
At completion of therapy	−2 (−2)	+17 (22)
At 6 mo	+0.3 (0)	+4 (5)
Patients with increases — no. (%)‖		
Grade 1	20 (7)	33 (33)
Grade 2	6 (2)	9 (9)
Grade 3	2 (1)	0
Blood urea nitrogen		
Mean change from base line — mg/dl		
Wk 1	−0.6 (−5)	+5.0 (42)
At completion of therapy	0.9 (8)	+5.0 (42)
At 6 mo	−0.5 (−4)	+0.5 (4)
Patients with increases — no. (%)**		
Grade 1	20 (7)	30 (30)
Grade 2	6 (2)	10 (10)
Grade 3	4 (1)	3 (3)
Corrected QT interval on electrocardiography		
Mean change from base line — msec (%)		
Wk 1	+14 (4)	+39 (11)
At completion of therapy	+18 (5)	+31 (9)

*To convert values for serum creatinine to milligrams per deciliter, divide by 88.4. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357.

†For vomiting, a Common Toxicity Criteria grade of 1 signifies 1 episode per day, grade 2 signifies 2 to 5 episodes per day, grade 3 signifies 6 to 10 episodes per day, and grade 4 signifies more than 10 episodes per day.

‡For diarrhea, a Common Toxicity Criteria grade of 1 signifies an increase of 2 to 3 stools per day, grade 2 an increase of 4 to 6 stools per day, grade 3 an increase of 7 to 9 stools per day, and grade 4 an increase of 10 or more stools per day.

§Base-line values are shown in Table 1.

¶For aspartate aminotransferase and alanine aminotransferase, Common Toxicity Criteria grade 1 signifies values at least 2.5 times the upper limit of normal, grade 2 values 2.6 to 5.0 times the upper limit of normal, and grade 3 values 5.1 to 20 times the upper limit of normal.

‖For creatinine, Common Toxicity Criteria grade 1 signifies values less than 1.5 times the upper limit of normal, grade 2 values 1.5 to 3.0 times the upper limit of normal, and grade 3 values 3.1 to 6.0 times the upper limit of normal.

**For blood urea nitrogen, Common Toxicity Criteria grade 1 signifies values less than 1.5 times the upper limit of normal, grade 2 values 1.5 to 2.4 times the upper limit of normal, and grade 3 values more than 2.4 times the upper limit of normal.

were evaluated at six months, the cure rate was 282 of 291 (97 percent) for miltefosine and 96 of 96 (100 percent) for amphotericin B.

Patients with Relapses

The nine patients who had a relapse did not differ from the cured patients in terms of the following base-line characteristics. For the patients with relapse, the mean values were as follows: age, 36 years; extension of the spleen below the costal margin, 6.7 cm; parasite density, 2.1; proportion that had received previous treatment, 67 percent; and daily dose, 2.3 mg per kilogram.

Cure Rate among Patients with Premature Discontinuation of Drug Treatment

Of the nine patients in the miltefosine group in whom drug treatment was discontinued prematurely, one withdrew from the study and eight discontinued the drug because of a lack of tolerance or intercurrent disease. Of these eight patients, four did not return for the six-month follow-up. Of the other four patients, three had a final cure: one who discontinued treatment after 14 days because of a high bilirubin concentration, one who discontinued treatment after 6 days because of Stevens–Johnson syndrome, and one who discontinued treatment after day 21 because

of bleeding hemorrhoids. The fourth patient, who discontinued treatment after 11 days because of arthritis and rash, had a relapse.

Cure Rate among Patients with Previous Therapy for Leishmaniasis

In the miltefosine group, the cure rate among patients who had previously been treated was identical to the cure rate among patients who had not (94 percent).

Toxic Effects

Signs and symptoms of toxic effects are summarized in Table 3. The percentage of patients in the miltefosine group who had vomiting or diarrhea was higher than that in the amphotericin group. However, such effects were mild (grade 1 or 2) in almost all affected patients in both groups, and the number of patients taking antiemetic or antinausea agents was 3 to 4 percent in both groups. One patient in the miltefosine group discontinued treatment because of gastrointestinal intolerance. Ninety percent of the patients in the amphotericin group had rigors associated with fever, whereas only one patient in the miltefosine group had this symptom.

Laboratory Variables

The results of laboratory tests are summarized in Table 3. In the miltefosine group, the mean serum aspartate aminotransferase concentration increased by 17 percent during the first week of therapy, before falling to the pretreatment values during the second week and then decreasing further as disease resolved. The mean serum alanine aminotransferase concentration increased by 12 percent during the second week before regressing by the six-month follow-up visit. There was a grade 3 elevation in the serum aspartate aminotransferase concentration in 16 patients in the miltefosine group (5 percent), but therapy was not terminated prematurely in any patient because of liver-enzyme values. In the amphotericin group, 3 percent of patients had grade 3 elevations.

Mean values on renal-function tests did not change significantly in the miltefosine group. However, 16 percent of patients had grade 1, 2, or 3 increases in blood urea nitrogen values, serum creatinine concentrations, or both. There were five patients in the miltefosine group (2 percent) with grade 3 elevations: one patient had an elevated creatinine value of 1.63 mg per deciliter (144 μmol per liter) before treatment, which peaked at 5.00 mg per deciliter (442 μmol per liter) during therapy; three patients had concurrent administration of albendazole and diclofenac, concurrent malaria, or concurrent meningitis. The fifth patient had no explanation other than miltefosine treatment for a grade 2 increase in serum creatinine and a grade 3 increase in blood urea nitrogen on day 21. The creatinine and blood urea nitrogen concentrations partially regressed on day 28 despite continued therapy. In the amphotericin group, 60 percent of patients had elevated blood urea nitrogen or creatinine levels during therapy.

Hemoglobin, leukocytes, and platelets increased steadily in both treatment groups (data not shown), in accord with the resolution of disease. Electrocardiography (Table 3) and ophthalmologic examination in both treatment groups did not show clinically relevant abnormalities.

Reproductive Capacity

In rats, high-dose miltefosine impairs male reproductive capacity. In this study, we tracked the number of live and healthy infants born to sexual partners of male patients of reproductive age who did not use contraception. In the miltefosine group, there were 48 live infants with no known congenital abnormalities born to the partners of 80 such male patients (0.6 birth per patient). By comparison, in the amphotericin group, there were 12 live infants with no congenital abnormalities born to the partners of 20 such male patients (0.6 birth per patient).

Serious and Other Adverse Events

Six patients in the miltefosine group and one patient in the amphotericin group had serious adverse events. In the miltefosine group, these events included convulsion due to a cranial cyst (in two patients), abrupt anemia due to bleeding hemorrhoids (in one patient), *Plasmodium vivax* malaria (in one patient), gram-negative meningitis that resulted in death two days later (in one patient), and the Stevens–Johnson syndrome (in one patient). Only the Stevens–Johnson syndrome was thought to be attributable to drug treatment. The patient was a 12-year-old boy who received 50 mg of miltefosine (2.8 mg per kilogram) daily. On day 6 of therapy, rash was seen, and treatment was stopped. Bullae, necrosis, and peeling skin were apparent on day 7; dexamethasone therapy was started. Fever abated on day 8. The patient was afebrile on day 12, and lesions healed by approximately day 20. As noted above, this patient was cured.

Other Discontinuations Due to Adverse Events in the Miltefosine Group

The four patients in the miltefosine group (1 percent) who discontinued therapy because of probable drug intolerance were as follows. One patient had arthritis and an allergic skin rash on day 9 and stopped taking miltefosine the next day. One patient, who was receiving concomitant treatment with metronidazole for giardia cysts, had grade 4 diarrhea requiring parenteral fluids after two weeks of miltefosine therapy.

Miltefosine was stopped at that point. One patient had an increase in the bilirubin concentration on day 14 of miltefosine treatment, at which time miltefosine was stopped. The fourth patient had grade 4 thrombocytopenia, epistaxis, increases in aspartate aminotransferase, and an increase in blood urea nitrogen. Therapy was stopped on day 7.

DISCUSSION

This controlled trial shows that oral miltefosine is an effective and safe treatment for Indian visceral leishmaniasis in immunocompetent patients 12 years of age or older. To our knowledge, this is the largest chemotherapy study performed according to the Good Clinical Practice guidelines[16] for any form of leishmaniasis. Of the 398 patients who presented with moderate visceral leishmaniasis (kala-azar), 299 were treated with oral miltefosine for 28 days at a dose of approximately 2.5 mg per kilogram per day. At the end of therapy, none of the 293 patients in whom parasitologic analysis was performed had evidence of parasites, and all were considered to be cured. At the six-month follow-up, 291 patients were evaluated; 9 had parasites on splenic aspiration. Thus, the six-month cure rate was 282 of 299 (94 percent).

Vomiting and diarrhea occurred in 38 percent and 20 percent, respectively, of patients receiving miltefosine. Approximately three quarters of the gastrointestinal events lasted one to two days per patient and occurred once on each of these days. The mean serum aspartate aminotransferase and alanine aminotransferase concentrations increased by approximately 15 percent during the first and second weeks, respectively, before normalizing by the end of week 2 and by the six-month follow-up visit, respectively. The transient elevation in liver enzymes during treatment is attributed to a moderate effect of miltefosine on hepatocytes. Mean results on renal-function tests were not substantially altered by miltefosine, although 16 percent of individual patients had mild-to-moderate elevations of serum creatinine, blood urea nitrogen, or both. Results on electrocardiography and ophthalmic examination and male reproductive capacity were not significantly altered.

Therapeutic agents may be compared with respect to efficacy, tolerance, and feasibility and cost of administration. Standard therapy for visceral leishmaniasis is pentavalent antimony or, in regions with a high prevalence of antimony resistance such as the one where this study was conducted, amphotericin B. Antimonial compounds have the disadvantages of both toxicity and clinical resistance in at least 40 percent of cases in certain regions where they have been in use for a long time.[17] Common adverse effects are myalgia, arthralgia, anorexia, hyperamylasemia, and increases in liver enzymes. Uncommon adverse effects are substantial decreases in the numbers of leukocytes and platelets and death due to arrhythmia.[2]

For comparison with miltefosine, amphotericin B was tested in 99 patients in this phase 3 study. A total of 97 percent of patients who received amphotericin were cured, but the well-known adverse effects of fever or chills and elevations on renal-function tests occurred in 90 percent and 60 percent of patients, respectively. Liposomal amphotericin B is highly effective and well tolerated, but its cost is a barrier to widespread use even in developed countries. Pentamidine has been used in antimony-resistant cases, but tolerance is problematic, and resistance is now evident.[18,19] Paromomycin is still being evaluated.[20]

Given our demonstration of a cure rate of 94 percent in a large number of patients 12 years of age or older, the efficacy of miltefosine compares well with that of all other agents, including amphotericin B and liposomal amphotericin B. The side effects of miltefosine are generally tolerable and compare favorably with those of all agents other than liposomal amphotericin B. Miltefosine has toxic effects on reproductive capacity in female animals, and strict contraception must be practiced by female patients during the period of treatment and for two months after therapy. The risk of fetal abnormalities means that the distribution of drugs must be carefully controlled in countries where leishmaniasis is endemic.

The striking advantage of miltefosine is that it is administered orally. Miltefosine is now registered in India (under the trade name Impavido [Zentaris]) for patients 2 years of age or older on the basis of other studies in patients in India 2 to 11 years of age that have been completed but not reported. However, because the heaviest patient in Indian studies weighed only 67 kg, dose recommendations for patients with higher weights have not yet been specified. Future trials should show whether this drug will be useful against visceral leishmaniasis in other regions and in populations for which parenteral agents are not attractive.

Supported by grants from Zentaris (to Dr. Sundar) and the Special Program for Research and Training in Tropical Diseases of the United Nations Development Program, the World Bank, and the World Health Organization (to Drs. Jha and Thakur).

We are indebted to Drs. Win Gutteridge and Juntra Karbwang of the Special Program for Research and Training in Tropical Diseases, World Health Organization; to Drs. Andreas Voss and Peter Bachman of Zentaris; and to the clinicians and support staffs at the involved medical centers for their contributions.

REFERENCES

1. Desjeux P. Leishmaniasis: public health aspects and control. Clin Dermatol 1996;14:417-23.
2. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis 1997;24:684-703.
3. Herwaldt BL. Leishmaniasis. Lancet 1999;354:1191-9.

4. Thakur CP, Sinha GP, Pandey AK, Barat D, Singh RK. Daily versus alternate-day regimen of amphotericin B in the treatment of kala-azar: a randomized comparison. Bull World Health Organ 1994;72:931-6.
5. Sundar S, Agrawal G, Rai M, Makharia MK, Murray HW. Treatment of Indian visceral leishmaniasis with single or daily infusions of low dose liposomal amphotericin B: randomised trial. BMJ 2001;323:419-22.
6. Lux H, Heise N, Klenner T, Hart D, Opperdoes FD. Ether-lipid (alkylphospholipid) metabolism and the mechanism of action of ether-lipid analogues in Leishmania. Mol Biochem Parasitol 2000;111:1-14.
7. Croft SL, Neal RA, Pendergast W, Chan JH. The activity of alkyl phosphorylcholines and related derivatives against Leishmania donovani. Biochem Pharmacol 1987;36:2633-6.
8. Kuhlencord A, Maniera T, Eibl H, Unger C. Hexadecylphosphocholine: oral treatment of visceral leishmaniasis in mice. Antimicrob Agents Chemother 1992;36:1630-4.
9. Sundar S, Rosenkaimer F, Makharia MK, et al. Trial of oral miltefosine for visceral leishmaniasis. Lancet 1998;352:1821-3.
10. Sundar S, Gupta LB, Makharia MK, et al. Oral treatment of visceral leishmaniasis with miltefosine. Ann Trop Med Parasitol 1999;93:589-97.
11. Jha TK, Sundar S, Thakur CP, et al. Miltefosine, an oral agent, for the treatment of Indian visceral leishmaniasis. N Engl J Med 1999;341:1795-800.
12. Sundar S, Makharia A, More DK, et al. Short-course of oral miltefosine for treatment of visceral leishmaniasis. Clin Infect Dis 2000;31:1110-3.
13. Cancer Therapy Evaluation Program. Common Toxicity Criteria. Rockville, Md.: National Cancer Institute, 2002. (Accessed October 7, 2002, at http://ctep.cancer.gov/reporting/index.html.)
14. Chulay JD, Bryceson ADM. Quantitation of amastigotes of Leishmania donovani in smears of splenic aspirates from patients with visceral leishmaniasis. Am J Trop Med Hyg 1983;32:475-9.
15. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypotheses of non-zero risk difference or non-unity relative risk. Stat Med 1990;9:1447-54.
16. Center for Drug Evaluation and Research. Guidance for industry: E6 good clinical practice: consolidated guidance. Rockville, Md.: Food and Drug Administration, April 1996. (Accessed October 7, 2002, at http://www.fda.gov/cder/guidance/959fnl.pdf.)
17. Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug resistance. Trop Med Int Health 2001;6:928-34.
18. Jha SN, Singh NKP, Jha TK. Changing response to diamidine compounds in cases of kala-azar unresponsive to antimonial. J Assoc Physicians India 1991;39:314-6.
19. Thakur CP, Kumar M, Pandey AK. Comparison of regimes of treatment of antimony-resistant kala-azar patients: a randomized study. Am J Trop Med Hyg 1991;45:435-41.
20. Jha TK, Olliaro P, Thakur CP, et al. Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India. BMJ 1998;316:1200-5.

POSTING PRESENTATIONS AT MEDICAL MEETINGS ON THE INTERNET

Posting an audio recording of an oral presentation at a medical meeting on the Internet, with selected slides from the presentation, will not be considered prior publication. This will allow students and physicians who are unable to attend the meeting to hear the presentation and view the slides. If there are any questions about this policy, authors should feel free to call the *Journal*'s Editorial Offices.