MAJOR ARTICLE

Efficacy and Tolerability of Miltefosine for Childhood Visceral Leishmaniasis in India

Sujit K. Bhattacharya,[1] T. K. Jha,[3] Shyam Sundar,[4] C. P. Thakur,[2] Juergen Engel,[5] Herbert Sindermann,[5] Klaus Junge,[5] Juntra Karbwang,[6] Anthony D. M. Bryceson,[7] and Jonathan D. Berman[8]

[1]Rajendra Memorial Research Institute of Medical Sciences, Agamkuan, and [2]Balaji Utthan Sanastan, Patna, and [3]Kala-azar Research Centre and [4]Kala-azar Medical Research Centre, Muzaffarpur, India; [5]Zentaris, Frankfurt am Main, Germany; [6]World Health Organization–Special Program for Research and Training in Tropical Diseases, Geneva, Switzerland; [7]The London School of Hygiene and Tropical Medicine, London, England; and [8]National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, Maryland

Miltefosine has previously been shown to cure 97% of cases of visceral leishmaniasis (VL) in Indian adults. Because approximately one-half of cases of VL occur in children, we evaluated use of the adult dosage of miltefosin (2.5 mg/kg per day for 28 days) in 80 Indian children (age, 2–11 years) with parasitologically confirmed infection in an open-label clinical trial. Clinical and parasitological parameters were reassessed at the end of treatment and 6 months later. One patient died of intercurrent pneumonia on day 6. The other 79 patients demonstrated no parasites after treatment, had marked clinical improvement, and were deemed initially cured. Three patients had relapse, and 1 patient was lost to follow-up. The final cure rate was 94% for all enrolled patients and 95% for evaluable patients. Side effects included mild-to-moderate vomiting or diarrhea (each in ~25% of patients) and mild-to-moderate, transient elevations in the aspartate aminotransferase level during the early treatment phase (in 55%). This trial indicates that miltefosine is as effective and well tolerated in Indian children with VL as in adults and that it can be recommended as the first choice for treatment of childhood VL in India.

Visceral leishmaniasis (VL) classically manifests as fever, hepatosplenomegaly, and pancytopenia. If untreated, it is almost always fatal, as a result of intercurrent infection. An estimated 500,000 cases of VL occur annually, 90% of which occur in India, Nepal, Bangladesh, Sudan, and Brazil [1, 2]. Many of the cases are in children. In India, 40% of patients are aged <13 years [2]; in Sudan, 65% are aged <15 years [3]; and in Brazil, 60% of patients are aged <5 years [4].

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Reprints: Dr. S. K. Bhattacharya, Rajendra Memorial Research Institute of Medical Sciences, Agamkuan, Patna 800 007, India. Correspondence: Dr. J. Berman, 6205 Poindexter Ln., Rockville, MD 20852 (JBe9320457@aol.com).

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The standard drug for the treatment of VL is a pentavalent antimonial that is given parenterally. The 2 usual second-line agents, pentamidine isethionate [5, 6] and amphotericin B desoxycholate [7], are also parenteral and are more toxic. Liposomal amphotericin B is effective and safe, but it is very expensive for developed countries [8] and prohibitively expensive for regions of endemicity. Miltefosine (hexadecylphosphocholine) is an oral agent that was originally studied as an antitumor agent and that did not have clinically relevant activity for that indication. Subsequent to the serendipitous laboratory finding that miltefosine was active against *Leishmania* in vitro and, after oral use, in animals [9], the drug was developed in a public-private partnership for the treatment of VL [10–13]. In a phase 3 trial involving Indian adults, miltefosine given at a dosage of 2.5 mg/kg per day for 28 days cured 282 (97%) of 291 evaluable patients with 6 months of follow-up [14].

In a pilot trial involving Indian children, Sundar et

al. [15] found that miltefosine given at 1.5 and 2.5 mg/kg per day for 28 days cured 19 (90%) of 21 and 15 (88%) of 17 evaluable patients, respectively, and that it was well tolerated. The lower cure rate in the pilot pediatric study, compared with the phase 3 adult study, suggested the possibility that miltefosine was less effective in children than in adults. To determine its efficacy and tolerability in children more precisely, we treated 80 Indian children who had VL with miltefosine. We chose the dosage of 2.5 mg/kg per day because a higher dose should lead to greater efficacy and because concordance of pediatric and adult dosing would facilitate treatment after registration.

METHODS

Study design. The study was conducted as an open-label, multicenter trial involving 80 patients. Twenty patients were enrolled concurrently at 4 sites in Bihar, India. The first patient was enrolled on 19 February 2001, and the last visit for the last patient occurred on 9 January 2002. All of the authors participated in the study design, had access to study data, and took responsibility for data analysis. The authors who are not employees of Zentaris, the sponsoring company, had authority over the preparation of the manuscript.

Study drug. Miltefosine (10 mg capsules; Impavido [Zentaris]) was given orally at 2.5 mg/kg once per day for 28 days. All patients were hospitalized, and administration of medication was directly observed.

Patients. Potentially eligible patients were 2–11 years of age, were of either sex, and had VL suspected on the basis of clinical presentation (fever, splenomegaly determined by palpation, anemia, and cytopenia) and confirmed by the demonstration of amastigotes in splenic aspirate specimens. The parasite load was graded on a logarithmic scale [16], whereby 1+ equals 1–10 amastigotes per 1000 high-power fields (HPFs), and 6+ equals >100 amastigotes per HPF. Exclusion criteria were values for the formed elements of the blood suggesting a premorbid state and severe disease (platelet count, <50,000 platelets/μL; leukocyte count, <1000 leukocytes/μL; hemoglobin concentration, <6 g/dL; serum aspartate aminotransferase (ASAT) or alanine aminotransferase levels of >3 times the upper limit of normal; bilirubin level of more than twice the upper limit of normal; and serum creatinine or blood urea nitrogen levels of >1.5 times the upper limit of normal), documentation of other serious coincidental medical illnesses, HIV seropositivity, and, for patients capable of reproduction, pregnancy.

Study procedure. Informed written consent was obtained from the parents or guardians of eligible children. Patients were reevaluated weekly during treatment and 1 and 6 months after completion of treatment for hematological variables, serum chemistry findings, and spleen size, as on admission, and they were queried for subjectively experienced adverse events. Queries about gastrointestinal symptoms (vomiting and diarrhea) were also made daily during treatment. Subjective and objective adverse events were recorded and graded on the basis of the Common Toxicity Criteria (CTC) of the National Cancer Institute (Bethesda, MD) [17].

Splenic aspirate specimens were obtained on day 14 of treatment for all patients; on day 28 of treatment, if parasites had been present on day 14; and 4 weeks after the end of treatment, if there had been scanty (1+) parasites on day 28. An initial parasitologic cure was indicated by the absence of parasites on day 14 or 28; for patients with 1+ parasites on day 28, it was indicated by the absence of parasites 4 weeks after completion of therapy. During follow-up, splenic aspiration was performed for any patient with a palpable spleen or other signs or symptoms suggestive of VL. Relapse was defined as the presence of parasites in a splenic aspirate specimen after initial parasitological cure.

Efficacy end points. Patients were classified as having had "initial cure" if initial parasitological cure was accompanied by marked clinical improvement on day 28 (i.e., resolution of fever, regression of spleen size, and improvement in hematological and biochemical parameters). Patients who experienced initial cure were designated as having had "final cure" if they did not experience relapse during 6 months of follow-up. Failure was defined as the lack of initial cure or as relapse. Rescue treatment with liposomal amphotericin B [18] (5 mg/kg q.d. for 5 days) was administered to patients who relapsed.

Ethics. The ethics committees of each health care center separately approved the study protocol, the consent forms, and all amendments.

RESULTS

Characteristics of patients at enrollment. Clinical and laboratory characteristics of patients are summarized in table 1. The ratio of male patients to female patients was 1.3:1, and the mean age was 7.8 years. Nineteen patients (25%) had been treated previously for VL with antimonials. The mean parasite density was grade 2.2+ (range, 1+ to 5+). Mean diameter of splenomegaly was 6.8 cm.

Efficacy. One patient died (age, 4 years). The patient had not previously received antileishmanial therapy. The patient had presented with moderate VL (temperature, 39.5°C; parasite count, 2+; hemoglobin concentration, 8.1 g/dL; WBC count, 4300 cells/μL; and platelet count, 64,000 platelets/μL). The RBC count decreased on day 3 of treatment, however, and pneumonia developed on day 4 (temperature, 41.15°C). Cefotaxime therapy was started, and the patient's temperature decreased to 39.5°C on day 5, but the patient died on day 6.

Each of the other 79 patients received therapy past day 6 and had evidence of initial parasitological cure (table 2). Treat-

Table 1. Clinical and laboratory characteristics of 80 patients with visceral leishmaniasis (VL) at baseline.

Clinical characteristics	Value	Normal range
Age, years		
Mean ± SD	7.8 ± 2.3	…
Range	3–10	…
Sex, no. (%) of patients		
Male	45 (56.3)	…
Female	35 (43.8)	…
Weight, kg		
Mean ± SD	18.1 ± 4.4	…
Range	10–30	…
Previously treated for VL, no. (%) of patients	19 (25.2)	…
Splenomegaly, cm below costal margin		
Mean ± SD	6.8 ± 3.4	…
Range	1–16	…
Laboratory values		
WBC count, cells/nL		
Mean ± SD	4.4 ± 2	…
Range	1.5–10.6	4.5–15.0
Platelet count, platelets/nL		
Mean ± SD	144 ± 70	…
Range	50–390	131–450
Hemoglobin concentration, g/dL		
Mean ± SD	7.6 ± 1.2	…
Range	6–10.8	11–14.5
Serum creatinine level, mmol/L		
Mean ± SD	52 ± 17	…
Range	18–97	35–97
Blood urea nitrogen level, mg/dL		
Mean ± SD	11 ± 4.3	…
Range	2–22	4.7–23
Aspartate aminotransferase level, IU/L		
Mean ± SD	43 ± 22	…
Range	15–103	5–35

ment was associated with marked clinical improvement of signs and symptoms suggestive of VL. In all 79 patients, the temperature was normal (i.e., <37.1°C) on day 6. The mean spleen size decreased steadily from 6.8 cm at enrollment to 4.0 cm after 2 weeks of treatment, 1.5 cm at the end of treatment, and 0.3 cm at 6 month follow-up in patients who did not have relapse. Mean values for formed elements of the blood (WBCs, platelets, and RBCs) were greater at week 1 and at the end of therapy (data not shown) than at baseline.

Three patients (4%), none of whom had experienced treatment failure with previous antileishmanial therapy, had relapse after initial parasitological cure. One patient (1%) was lost to follow-up. Thus, the final cure rate 6 months after completion of treatment was 94% (75 of 80 patients; lower limit of 95% CI, 87%), and the final cure rate for evaluable patients was 95% (75 of 79 patients; lower limit of 95% CI, 89%). Each of the 19 patients who had previously experienced antimonial therapy failure were cured with miltefosine.

Tolerability. Clinical adverse events were entirely gastrointestinal in nature and are listed in table 3. Twenty-one patients (26%) and 20 patients (25%) had episodes of vomiting or diarrhea, respectively. For 7 of these patients, the 2 symptoms (vomiting and diarrhea) occurred on the same day or within 1 day of each other. The durations of vomiting and diarrhea were short, and the intensity was mild (CTC grade 1) to moderate (CTC grade 2), except for a single instance of CTC grade 3 vomiting. Vomiting and diarrhea were treated with oral rehydration salt solution, as recommended by the World Health Organization (WHO)/United Nations Children's Fund (UNICEF) [19], and did not lead to discontinuation of therapy for any patient. Laboratory parameters determined by liver and kidney function tests that changed significantly are shown in table 4. Fifty-five percent of patients had a transient increase in ASAT levels, but only 1 patient had an increase to levels of CTC grade 3. Mean ASAT values were 19% higher at week 1 than at baseline, but, by week 2, had they decreased to less than the baseline values. Changes in kidney function were uncommon and mild (table 4).

DISCUSSION

VL, which is commonly known in India as "kala-azar," is endemic in more than 60 countries. Recurrent and at times unmanageable epidemics in India and Sudan account for most of the 500,000 new cases per year. Thus, kala-azar persists in poor, remote areas where people have limited access to drugs and preventive measures. It remains a neglected disease, especially with respect to new drug development, for which there seems little possibility of financial return. The partnership between the WHO and Zentaris provides an example of how this problem may be overcome. However, problems of drug delivery

Table 2. Efficacy of treatment in 80 patients with visceral leishmaniasis treated with miltefosine.

Parameter	No. (%) of patients
At completion of therapy	
Initial cure	79 (99)
Initial failure	1 (1)
Six months after completion of therapy	
Final cure	75 (94)
Failure due to lack of initial cure	1 (1.3)
Failure due to relapse	3 (3.8)
Lost to follow-up	1 (1.3)

Table 3. Gastrointestinal adverse reactions in 79 patients with visceral leishmaniasis treated with miltefosine.

Symptom	No. (%) of patients
Vomiting	
Total	21 (26)
Duration, days	
1–2	19 (24)
3–4	1 (1.3)
>4	1 (1.3)
Severity[a]	
CTC grade 1	13 (16)
CTC grade 2	8 (10)
Diarrhea	
Total	20 (25)
Duration, days	
1–2	19 (24)
3–4	1 (1.3)
Severity[a]	
CTC grade 1	17 (21)
CTC grade 2	2 (2.5)
CTC grade 3	1 (1.3)

NOTE. CTC, Common Toxicity Criteria of the National Cancer Institute (Bethesda, MD).

[a] For vomiting, CTC grades 1 and 2 signify 1 and 2–5 episodes per day, respectively. For diarrhea, CTC grades 1, 2, and 3 signify an increase of 2–3, 4–6, and 7–9 stools per day.

and access remain to be solved in countries where VL is endemic.

Approximately one-half of the patients with VL worldwide are children. The present trial of miltefosine involving 80 Indian children has shown that the drug is safe and effective for children aged 2–11 years. One patient died during the first week of therapy. The rate and timing of mortality in this study are compatible with historic data for kala-azar. In 1990, in Bihar, government records show that there were 589 deaths (1%) among 54,650 cases of kala azar [20], and, in smaller series of cases, deaths generally occurred close to the initiation of treatment [21].

The results of this trial are remarkably similar to those of the much larger phase 3 trial [14] in which an identical dosing regimen was used for patients aged ⩾12 years. In the present trial involving children, the efficacy was 94% for all patients and 95% for evaluable patients, compared with 94% and 97%, respectively, for the trial involving adults. Mild-to-moderate gastrointestinal side effects occurred in ~25% of patients in both trials. Reversible ASAT elevations during the early treatment phase were seen in 55% of children, which is comparable to the rate of 58% for adults. These 2 trials clearly document that miltefosine is highly effective and safe for treatment of kala-azar for patients in all age groups, including patients for whom treatment with pentavalent antimonials has failed.

One striking advantage of miltefosine over other antileishmanial drugs is that it is administered orally. Because of its efficacy, its tolerability, and the oral route of administration, we consider miltefosine to be the drug of first choice for most immunocompetent patients in all age groups in India. With respect to cost considerations, Sundar et al. (unpublished data and [22]) calculated that a course of miltefosine for a 30-kg person in Bihar, India, costs approximately US$170 (with a total medical cost of US$480). In comparison, the costs for

Table 4. Changes in laboratory parameters in 79 patients with visceral leishmaniasis treated with miltefosine.

Parameter	Value
ASAT level	
End of week 1	
Mean change from baseline, IU/L (% change)	7.8 (+19)
Range in absolute values, IU/L	17–200
End of week 2	
Mean change from baseline, IU/L (% change)	−1.0 (−2)
Range in absolute values, IU/L	11–131
At completion of therapy	
Mean change from baseline in IU (% change)	−2.3 (−5)
Range in absolute values, IU/L	13–135
At 6-month follow-up	
Mean change from baseline, IU (% change)	−8.3 (−20)
Range in absolute values, IU/L	8–117
Maximum severity, no. (%) of patients[a]	
CTC grade 1	35 (44)
CTC grade 2	8 (10)
CTC grade 3	1 (1)
Serum creatinine level	
End of week 1	
Mean change from baseline, mmol/L (% change)	−6.4 (−12)
Range in absolute values, mmol/L	9–115
End of week 2	
Mean change from baseline, mmol/L (% change)	−6.0 (−12)
Range in absolute values, mmol/L	16–88
At completion of therapy	
Mean change from baseline, mmol/L (% change)	−2.9 (−6)
Range in absolute values, mmol/L	14–80
At 6-month follow-up	
Mean change from baseline, mmol/L (% change)	+1.1 (+2)
Range in absolute values, mmol/L	14–106
Maximum severity of CTC grade 1,[b] no. (%) of patients	3 (4)

NOTE. ASAT, aspartate aminotransferase; CTC, Common Toxicity Criteria of the National Cancer Institute (Bethesda, MD).

[a] Grade 1, 2.5 times the upper limit of normal; grade 2, 2.6–5.0 times the upper limit of normal; grade 3, 5.1–20 times the upper limit of normal.

[b] Less than 1.5 times the upper limit of normal.

courses of generic sodium stibogluconate, amphotericin B, and liposomal amphotericin B are estimated to be US$21 (total medical cost, US$351), US$59 (total medical cost, US$426), and US$585 (total medical cost, US$607), respectively. Studies involving animals, however, have shown that miltefosine is abortifacient and teratogenic [23]. Thus it should not be given to women of child-bearing age, unless pregnancy has been excluded and rigorous contraceptive precautions are taken during treatment and for 8 weeks after completion of treatment. It must be kept in mind that this unique drug has a long half-life in humans [23]. Complete courses of therapy must be taken so that parasites do not remain, multiply in the presence of low drug concentrations, and generate drug resistance [24]. Patients coinfected with HIV and *Leishmania* species generally have relapse after initial treatment with miltefosine, as with other antileishmanial agents [25]. For the increasing number of patients coinfected with HIV and *Leishmania* species [26, 27], a combination of miltefosine and another antileishmanial agent may be needed to prevent the occurrence of resistance in the patient and then in the community. Finally, the very high cure rate among Indian patients (>95%) requires confirmation in other regions where VL is endemic.

References

1. Guerin PJ, Olliaro P, Sundar S, et al. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and proposed research and development agenda. Lancet Infectious Diseases **2002**; 2:494–501.
2. Bora D. Epidemiology of visceral leishmaniasis in India. Natl Med J India **1999**; 12:62–8.
3. World Health Organization (WHO). Dramatic upsurge in visceral leishmaniasis cases in the Horn of Africa [press release]. Geneva: WHO, 13 February **1998**.
4. Desjeux P. Information on the epidemiology and control of the leishmaniasis by country or territory. WHO/LEISH/91.30. Geneva: World Health Organization, **1991**:36.
5. Jha SN, Singh NKP, Jha TK. Changing response to diamidine compounds in cases of kala-azar unresponsive to antimonials. J Assoc Physicians India **1991**; 39:314–6.
6. Jha TK. Evaluation of diamidine compound (pentamidine isethionate) in the treatment of resistant cases of kala-azar occurring in North Bihar, India. Trans R Soc Trop Med Hyg **1983**; 77:167–70.
7. Thakur CP, Sinha GP, Barat D, et al. Two hours versus six hours administration of amphotericin B in the treatment of kala-azar. Intl J Antimicrob Agents **1995**; 5:115–7.
8. Berman JD. Editorial response: US FDA approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis **1999**; 28:49–51.
9. Kuhlencord A, Maniera T, Eibl H, Unger C. Hexadecylphosphocholine: oral treatment of visceral leishmaniasis in mice. Antimicrob Agents Chemother **1992**; 36:1630–4.
10. Sundar S, Rosenkaimer F, Makharia MK, et al. Trial of oral miltefosine for visceral leishmaniasis. Lancet **1998**; 352:1821–3.
11. Sundar S, Gupta LB, Makharia MK, et al. Oral treatment of visceral leishmaniasis with miltefosine. Ann Trop Med Parasitol **1999**; 93: 589–97.
12. 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.
13. 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.
14. Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med **2002**; 347:1739–46.
15. Sundar S, Jha TK, Sindermann H, Junge K, Bachmann P, Berman J. Oral miltefosine treatment in children with Indian visceral leishmaniasis. Pediatr Infect Dis J **2003**; 22:434–8.
16. Chulay JD, Bryceson AD. 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.
17. Cancer Therapy Evaluation Program. Common toxicity criteria. Rockville, MD: National Cancer Institute, **2002**. Available at: http://ctep.cancer.gov/reporting/index.html. Accessed on 7 December 2003.
18. Meyerhoff A. US FDA approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis **1999**; 28: 42–8.
19. World Health Organization (WHO). The treatment of diarrhoea—a manual for physicians and other senior health workers. Diarrhoeal Diseases Control Programme (CDD). WHO/CDR/95.3. Geneva: WHO, **1995**.
20. Thakur CP, Sinha GP, Pandey AK, Barat D, Sinha PK. Amphotericin B in resistant kala-azar in Bihar. Natl Med J India **1993**; 6:57–60.
21. Hashim FA, Ali MS, Satti M, et al. An outbreak of acute kala-azar in a nomadic tribe in western Sudan: features of the disease in a previously non-immune population. Trans R Soc Trop Med Hyg **1994**; 88:431–2.
22. Sundar S, Jha TK, Thakur CP, Mishra M, Singh VP, Buffels R. Single-dose liposomal amphotericin B in the treatment of visceral leishmaniasis in India: a multicenter study. Clin Infect Dis **2003**; 37:800-4.
23. Zentaris AG. Impavido registration certificate for miltefosine capsules 10 mg and 50 mg. Issued by Drug Controller General India. 15 March **2002**.
24. Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug resistance. Trop Med Int Health **2001**; 6:928–34.
25. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. AIDS **1999**; 13:1063–9.
26. Thakur CP, Sinha PK, Singh RK, et al. Miltefosine in a case of visceral leishmaniasis with HIV co-infection, and rising incidence of this disease in India. Trans R Soc Trop Med Hyg **2000**; 94:696–7.
27. Sinha PK, Rabidas VN, Pandey K, et al. Visceral leishmaniasis and HIV coinfection in Bihar, India. J Acquir Immune Defic Syndr **2003**; 32: 115–6.