Short-Course of Oral Miltefosine for Treatment of Visceral Leishmaniasis

A total of 54 Indian patients with visceral leishmaniasis were treated with oral miltefosine, 50 mg given twice daily, for 14 days (18 patients; group A), 21 days (18; group B), or 28 days (18; group C). Cure was achieved in 89% of group A, 100% of group B, and 100% of group C. Adverse reactions were self-limited and primarily mild. The 21-day miltefosine regimen combines high-level efficacy, convenient dosing, and a relatively short duration.

Results from 2 recent phase I/II trials in Indian patients with visceral leishmaniasis (kala-azar) suggest that the synthetic phospholipid derivative hexadecylphosphocholine (miltefosine) is a promising oral treatment for this disseminated protozoal infection that occurs worldwide [1, 2]. These initial studies determined the safety, tolerance, and efficacy of 28 days of miltefosine therapy in a total of 75 patients who received doses that ranged from 50 to 100 mg on alternate days to 100–250 mg daily. By day 28, 73 subjects were considered to have apparent clinical and parasitologic cures. During the 6-month follow-up of these 73 patients, 8 (7 of whom received alternate-day treatment) relapsed, whereas 65 remained healthy and were designated as "definitive responders" (patients who were cured) [1, 2]. In another recently completed study, an additional 120 Indian patients were treated daily with varying doses of miltefosine for a total of 28–42 days; 114 (95%) of these subjects had long-term cure [3].

A 28-day duration of miltefosine treatment was selected for use in the 2 initial trials [1, 2] because it conformed to the length of conventional parenteral antimony therapy. However, 2 observations suggested that this duration might be shortened. First, miltefosine rapidly induced activity. On day 14 of treatment, 61 of the initial 75 subjects had parasite-free splenic aspirate smears and were considered to have an apparent cure. Second, 10 of the 65 patients with definitive cure at 6 months had actually received appreciably less than 28 days of therapy (range, 7–17 days) [1, 2]. For these 10 patients, who were receiving 100–250 mg of miltefosine per day, treatment was discontinued early because of adverse reactions (e.g., vomiting, diarrhea, or reversible nephrotoxicity). Nevertheless, all 10 patients continued to improve clinically after miltefosine treatment was stopped, and they fulfilled the criteria for apparent cure at day 28. At the 6-month evaluation and with no additional antileishmanial treatment, each of these 10 patients was also a definitive responder (was asymptomatic with no evidence of relapse) [1, 2].

In view of both the kinetics of the response to miltefosine and the experience in the 10 subjects who were cured after receiving abbreviated therapy, it seemed that courses of treatment of <28 days' duration might also prove to be active in the treatment of kala-azar. To test this hypothesis, we used a satisfactorily tolerated, effective dose of oral miltefosine (100 mg/day [1–3]) and randomized a group of Indian patients to receive treatment for either 14, 21, or 28 days.

The present study was performed at the Muzaffarpur (north Bihar) treatment site of the Kala-Azar Medical Research Center [1, 2], where kala-azar caused by *Leishmania donovani* is epidemic. All subjects were >12 years of age, since the effects of miltefosine on younger children had not yet been studied. Women of childbearing age were required to use adequate contraception both during and for 1 month after treatment.

Inclusion and exclusion criteria and baseline laboratory tests (as well as all trial procedures) were identical to those used in our prior studies of miltefosine and are described in detail elsewhere [1, 2]. In brief, patients were eligible if they had symptoms and signs of kala-azar (typically, fever, weakness, weight loss, and splenomegaly) and if they had characteristic amastigotes demonstrated microscopically in splenic aspirate smears. Patients were excluded from the study if they had another serious concurrent disease or infection or if they were <12 years of age or >65 years of age, were pregnant or breast-feeding, or were determined to be seropositive for HIV by means of ELISA testing (no screened subject was seropositive). Other exclusion criteria were a WBC count of <2000 cells/mm^3, a hemoglobin level of <6 g/dL, a platelet count of <50,000 cells/mm^3, levels of hepatic transaminases or total bilirubin >3 times the normal levels, a serum creatinine level of >2 mg/dL, and a prothrombin time >5 s above the control value.

After completing initial diagnostic and baseline laboratory testing, 54 patients were randomized, by means of a computer-generated, sealed-envelope method, to receive one 50-mg capsule of miltefosine twice daily with meals for either 14 (group A), 21 (group B), or 28 days (group C). No more than 50 mg were given at one time to reduce anticipated nausea, vomiting, and diarrhea [1–5]. ASTA Medica AG (Frankfurt, Germany) provided miltefosine, advice on protocol development, funds for all trial-related expenses, and study monitoring. The company had no role in interpretation of the data or in deciding whether the study was to be submitted for publication. Treatment was given to patients free of charge.

All patients were hospitalized and examined daily. Urinalysis and hematologic and biochemistry testing were repeated weekly

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This study was approved by the Ethical Committee of Banaras Hindu University, Varanasi, India, and informed consent was obtained either from the patients or from their parents or guardians.

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S.S. participated in designing the study, collecting the data, and writing the paper and was the principal investigator. A.M., D.K.M., and G.A. were involved in the care and clinical assessment of patients and in the collection of data. A.V., C.F., and P.B. collaborated on the study design and monitored the trial procedures; H.W.M. collaborated on the design of the study, was responsible for data interpretation, and helped with the writing of the paper.

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during treatment, whenever clinically warranted, and at the 6-month evaluation. Splenic aspirate was repeated within 24 h of the final treatment. The parasite density score for pretreatment and posttreatment aspirate smears was graded by a microscopist who was blinded as to each patient's treatment; grading was done by use of a conventional logarithmic scale ranging from 0 (denoting no parasites per 1000 oil-immersion fields) to +6 (denoting >100 amastigotes per oil-immersion field) [1, 2]. The clinicians caring for the patients were not blinded as to treatment; facilities for the culture of tissue aspirates were not available.

For a patient to be designated as having apparent cure at the end of treatment, clinical improvement, the absence of fever, a reduction in spleen size, and a splenic aspirate score of 0 (denoting apparent parasitologic cure) were required [1, 2]. Six months after treatment, for a patient to be designated as having a complete response (definitive cure), the patient (a) had to be asymptomatic, with no signs or symptoms suggesting relapse, as in prior studies [1, 2], and (b) had to have a parasite-free bone-marrow aspirate smear examined in a blinded fashion.

Data were expressed as means ± SE. Analysis of variance (ANOVA) and the *t* test were used to detect, among the 3 patient groups, differences (table 1) between the clinical and laboratory results at baseline, with the exception of differences in sex and response rates, which were detected by use of the χ^2 test. Within each treatment group, the Wilcoxon signed rank test was used (table 2) to determine whether a given result had changed between baseline (day 0) and the day treatment ended. Exact binomial 95% CIs for the individual proportions of patients responding to each treatment regimen were computed. A P value of <.05 was considered significant.

The 3 treatment groups were similar at study entry, and there were no significant differences ($P > .05$) between the groups with regard to baseline clinical data or laboratory results (table 1). At enrollment, all 54 subjects received scores of 60 on the Karnofsky performance assessment (a score of 60 indicates that the patient requires occasional assistance but is able to care for most needs) [6]. Twenty-one patients either failed to have a response to or experienced relapse after previous treatment with amphotericin B (2 patients) or pentavalent antimony (19); the latter was given as sodium antimony gluconate, 20 mg/kg/day, for ⩾28 days [7].

Each of the 54 subjects completed their assigned miltefosine regimen. Fifty-one were afebrile by day 11; the duration of fever (mean ± SE) was 7.4 ± 0.5 days for patients in group A, 6.9 ± 0.9 days for those in group B, and 6.2 ± 1.2 days for those in group C. At the end of treatment, all patients were afebrile and showed clinical improvement and decreased spleen size. With the exception of 1 patient in group A, whose splenic aspirate smear showed a density score of 1+ (denoting scanty parasites), all other subjects had parasite-free splenic aspirate smears (density score, 0) at the end of treatment. Therefore, 17 of 18 patients in group A and 18 of 18 patients both in group B and in group C fulfilled the criteria for an apparent cure. The single nonresponder in group A was re-treated with and responded to amphotericin B. For each group, additional data obtained at the end of treatment (table 2) indicated significant improvement ($P < .001$) in Karnofsky performance score, spleen size, and the results of each of the 3 hematologic tests, compared with baseline results.

Table 1. Clinical and laboratory results at baseline for 54 patients with kala-azar who were treated with a short course of oral miltefosine therapy.

Characteristic	Treatment group A (n = 18)	Treatment group B (n = 18)	Treatment group C (n = 18)
Age, years	25 ± 3	30 ± 3	25 ± 2
Male sex, %	50	78	83
Prior therapy, no.	7	6	8
Duration of illness, months	4.1 ± 0.5	3.7 ± 0.6	4.0 ± 0.8
Splenic aspirate score	2.0 ± 0.2	1.7 ± 0.1	2.3 ± 0.8
Weight, kg	34 ± 3	40 ± 2	41 ± 2
Karnofsky score	60 ± 0	60 ± 0	60 ± 0
Spleen size[a], cm	5.2 ± 0.8	7.0 ± 1.2	8.1 ± 0.2
Hemoglobin, g/dL	7.8 ± 0.4	8.1 ± 0.4	7.4 ± 0.4
WBC count, $\times 10^3$ cells/mm^3	3.7 ± 0.3	3.0 ± 0.2	2.8 ± 0.3
Platelet count, $\times 10^3$ cells/mm^3	128 ± 14	112 ± 11	113 ± 16

NOTE. Data are means ± SE, unless otherwise indicated. Duration of treatment: for group A, 14 days; group B, 21 days; and group C, 28 days.

[a] Spleen size was measured below the left costal margin in the anterior axillary line.

During treatment, no patient developed hematologic or renal toxicity, and none showed changes in visual acuity or signs suggesting retinal atrophy (which was detected in chronically treated animals [8]). Compared with the baseline results, the mean values for levels of blood urea nitrogen (BUN), creatinine, and serum glutamic oxaloacetic transaminase (SGOT) at the end of treatment either were unchanged or had improved for each group of patients (table 2); however, there were individual instances of hepatotoxicity. On the basis of the conventional World Health Organization (WHO) toxicity grading scale, 11 patients (20%; 2 in group A, 3 in group B, and 6 in group C) developed grade 1 (mild) or grade 2 (moderate) increases in the SGOT level, most often during the first week of treatment. This reaction was transient and resolved as treatment continued. Of these 11 subjects, 5 had peak SGOT values of <100 IU/mL (toxicity, grade 1), and 6 had SGOT values of 107–157 IU/mL (toxicity, grade 2). An SGOT value of 157 IU/mL developed in a man whose pretreatment result was 98 IU/mL.

As anticipated on the basis of results from other studies [1–5], the primary adverse reactions to miltefosine were gastrointestinal; vomiting occurred in 29 patients, diarrhea occurred in 1, and both vomiting *and* diarrhea occurred in 7. These side effects occurred in 12 patients in group A, 14 patients in group B, and 11 patients in groups C, usually during the first 7–14 days of therapy. Thirty-seven subjects (10–14 per group) had at least 1 episode of vomiting, which, in all instances, was moderate (WHO grade, 2) and transient (duration per episode, 1.3 ± 0.1 days [mean ± SE]) and resolved in the face of continued

Table 2. Clinical and laboratory results, before and after receiving oral miltefosine therapy (100 mg/day), for 54 patients with kala-azar.

Characteristic	Treatment group A (n = 18)		Treatment group B (n = 18)		Treatment group C (n = 18)	
	Day 0	Days 14–15[a]	Day 0	Days 21–22[a]	Day 0	Days 28–29[a]
Weight, kg	34 ± 3	34 ± 7	40 ± 2	41 ± 2	41 ± 2	43 ± 2
Karnofsky score	60 ± 0	99 ± 1	60 ± 0	100 ± 0	60 ± 0	100 ± 0
Spleen size, cm	5.2 ± 0.8	2.0 ± 0.5	7.0 ± 1.2	1.6 ± 0.7	8.1 ± 1.2	1.7 ± 0.6
Hemoglobin, g/dL	7.8 ± 0.4	9.0 ± 0.4	8.1 ± 0.4	9.6 ± 0.4	7.4 ± 0.5	10.0 ± 0.4
WBC count, $\times 10^3$ cells/mm^3	3.7 ± 0.3	7.7 ± 0.8	3.0 ± 0.2	7.1 ± 0.7	2.8 ± 0.3	7.4 ± 0.4
Platelet count, $\times 10^3$ cells/mm^3	128 ± 14	337 ± 33	112 ± 11	261 ± 21	113 ± 16	281 ± 24
Blood urea nitrogen, mg/dL	9 ±1	11 ± 1	10 ± 1	11 ± 1	10 ± 1	10 ± 1
Creatinine level, mg/dL	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.4	0.9 ± 0.1	0.8 ± 0.1
SGOT, IU/mL	55 ± 6	56 ± 7	63 ± 6	55 ± 5	54 ± 6	47 ± 3

NOTE. Data are means ± SE. Duration of treatment: for group A, 14 days; group B, 21 days; and group C, 28 days.
[a] Evaluation was performed within 1 day of the end of treatment.

treatment. The number of times that vomiting occurred per episode was 1.6 ± 0.1 (mean ± SE). Eight patients (15%; 2–3 per group) developed mild, grade 1 diarrhea (transient; no therapy required) that lasted for a duration of 1.1 ± 0.1 days (mean ± SE) and that resolved as miltefosine therapy was continued. The number of loose stools per episode was 2.6 ± 0.3 (mean ± SE).

During the 6-month follow-up, 1 of the 53 patients with an apparent cure, a patient in group A, had a relapse after 5 months; new fever, increased spleen size, and reappearance of amastigotes in the patient's splenic aspirate were noted. The patient responded to re-treatment with amphotericin B. At 6 months, the remaining 52 patients with apparent cure were healthy; 50 of these 52 patients had nonpalpable spleens, and all had parasite-free bone marrow aspirate smears. Therefore, overall, 16 (89%; 95% CI 65–99%) of 18 patients in group A, 18 (100%; 95% CI, 85%–100%) of 18 patients in group B, and 18 (100%; 95% CI 85%–100%) of 18 patients in group C were designated as "complete responders" (having definitive cure).

Identification of an effective oral treatment for visceral leishmaniasis has been a long-standing priority. The results of this study, in which 52 (96%; 95% CI, 87%–99%) of 54 patients treated with miltefosine for 2–4 weeks were considered to be cured, firmly support the efficacy of miltefosine that was demonstrated in our 2 initial trials [1, 2]. In a separate, recently completed study, which was cosponsored by the WHO and ASTA Medica and which was also performed in Bihar, 114 (95%) of 120 Indian patients had long-term cure after receiving treatment with various doses of miltefosine given for 4–6 weeks [3]. When considered together, the results of these 3 trials and of the current study (comprising results for a total of 249 patients [1–3]) clearly point to the promising use of this oral agent in the management of kala-azar.

As demonstrated in 19 patients in this trial and in 79 patients in the 3 previous studies [1–3], miltefosine is also fully active in patients with antimony-unresponsive infection. The timeliness of this observation, which further strengthens the usefulness of miltefosine, relates to the growing problem of antimony treatment failure in India. The state of Bihar, which is the epicenter of the decades-old epidemic of kala-azar in India, is thought, for example, to house as many as one-half of the estimated 500,000 new cases of visceral leishmaniasis that occur worldwide each year [9]. Currently, in Bihar, 37%–64% of previously untreated patients fail to respond to 28 days of full-dose parenteral antimony, 20 mg/kg/day [10–12], a treatment that must now be abandoned in Bihar.

At the same time and as previously reported [1–5], miltefosine also induces adverse reactions that are primarily gastrointestinal. Although, in the present trial, the side effects observed with the use of miltefosine, 100 mg/day, were largely graded as mild, such reactions have also been graded as moderate to severe in other patients receiving this dose or higher doses [1, 2]. Nausea, vomiting, and/or diarrhea are common during the first or second week of administration of miltefosine [1–5]; however, as shown in the present study, these reactions to a dose of 100 mg/day are brief and typically resolve as treatment continues [1–3]. Less frequently, asymptomatic increases in serum hepatic transaminases and serum levels of BUN and creatinine may develop [1, 2, 4, 5]. Although not observed in this study, reversible nephrotoxicity may accompany miltefosine therapy; however, such reactions are usually mild, and they most often abate as treatment proceeds [1, 2, 4, 5, 8].

Although they are derived from relatively small groups of patients who did not have severe visceral leishmaniasis, the results of the present study indicate that treatment courses that are shorter than the originally tested 28-day regimen [1, 2] are also effective. Our results suggest that 21 days of therapy may well be sufficient to induce high-level efficacy, although further testing of the 21-day regimen will be necessary before a more firm conclusion can be drawn. However, a regimen of miltefosine, 100 mg/day for 21 days, does appear to show promise as an oral alternative to traditional lengthy therapy with parenteral antimony or amphotericin B, and it offers both convenience (twice-daily dosing) and the potential for a shorter course of treatment.

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La Crosse Encephalitis Presenting Like Herpes Simplex Encephalitis in an Immunocompromised Adult

The diagnosis of the precise cause of viral encephalitis can be difficult, hampered by the nonspecific presentation, the number of etiologic viruses, and limited culture and serologic diagnostic methods. Because herpes simplex encephalitis (HSE) can be neurologically devastating and is treatable, timely diagnosis is important. We report an immunocompromised adult with encephalitis clinically consistent with HSE who had serology consistent with recent La Crosse encephalitis (LAC).

A 39-year-old man who underwent renal transplantation for idiopathic glomerulonephritis 5 years prior to presentation was admitted with a 40-h history of fever, confusion, and headache. From 14 days until 7 days before presentation, the patient vacationed in Tennessee and was bitten by numerous mosquitoes. Immunosuppressive medications included prednisone, mycophenolate mofetil, and cyclosporine. On physical examination, the patient's temperature was 39.4°C, and he was alert but distracted. A peripheral WBC count was 8.4 calls/mm^3, and his creatinine level was 1.9 mg/dL. A noninfused head CT scan was normal. A lumbar puncture yielded a sample with a WBC count of l44 cells/mm^3 (44% polymorphonuclear cells, 46% lymphocytes, and 10% monocytes), an RBC count of 113,500 cells/mm^3, a glucose level of 62 mg/dL (serum 104), and a protein level of 121 mg/dL. The patient started receiving ampicillin, ceftriaxone, doxycycline, and acyclovir empirically.

On the day following admission, the patient became less communicative. On neurologic examination, he was alert without spontaneous speech. He could not repeat phrases but could follow simple commands. He had a right pronator drift and mild weakness throughout the right upper extremity. MRI of the brain showed increased T2 signal abnormality in the left mesial temporal lobe (figure 1) without enhancement. An electroencephalogram (EEG) showed bilateral frontal slowing with occasional sharp waves. Bacterial, fungal, and viral cultures of CSF were negative. A CSF herpes simplex PCR was negative. Because of the clinical and MRI findings, the patient continued receiving iv acyclovir. Over the next several days, the patient began to speak and became more attentive but continued to have a predominantly expressive aphasia, mild weakness on the right, poor verbal memory, and dyscalculia. His symptoms and signs improved slowly over several months, although his verbal memory remained mildly impaired. A follow-up MRI, done 3 months after the initial presentation, showed resolution of the signal abnormality.

After the patient was hospitalized, an article in an infectious disease journal [1] reported cases of La Crosse encephalitis (LAC) in Tennessee, and a sample of the patient's blood was sent to the Tennessee Department of Health 4 months after his initial illness. By indirect immunofluorescent antibody testing, the patient's serum IgM to LAC was 1:80 and his IgG was 1:320.

Although most clinical cases of LAC are diagnosed in chil-

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