A PHASE II DOSE-RANGING STUDY OF SITAMAQUINE FOR THE TREATMENT OF VISCERAL LEISHMANIASIS IN INDIA

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Abstract. This randomized, open label, multicenter study assessed the dose–response and safety profile for oral sitamaquine in 120 Indian subjects with visceral leishmaniasis (VL). Patients aged 5–64 years (mean age 21.2 years) received one of four sitamaquine doses (1.5, 1.75, 2.0, or 2.5 mg kg\(^{-1}\) day\(^{-1}\)) daily for 28 days. At Day 180 in the intent-to-treat population, final cure (primary efficacy outcome) was achieved in 92 of 106 (87%) patients overall and 25 of 31 (81%), 24 of 27 (89%), 23 of 23 (100%), and 20 of 25 (80%) patients at doses of 1.5, 1.75, 2.0, or 2.5 mg kg\(^{-1}\) day\(^{-1}\) sitamaquine, respectively. Sitamaquine was generally well tolerated. The most common adverse events during the active treatment phase were vomiting (8% [10 of 120]), dyspepsia (8% [9 of 120]) and cyanosis (3% [4 of 120]). Nephrotic syndrome (3% [3 of 120]) and glomerulonephritis (2% [2 of 120]) were also reported and require further investigation. Oral sitamaquine demonstrated efficacy in Indian VL and was well tolerated.

INTRODUCTION

Visceral leishmaniasis (VL), or kala-azar, is endemic in 47 countries, with an estimated annual incidence of 500,000 cases. Without treatment, symptomatic VL is almost always fatal. In India, 90% of infections occur in Bihar and neighboring states with an estimated annual incidence of 100,000–250,000 cases. In this region of India, the prevalence of resistance to the first-line drug for VL, sodium stibogluconate (Sb\(^{\text{A}}\)), has been rising; it has been reported that approximately 37–64% of patients now fail antimony treatment. Pentamidine was effective for a time but is now rarely used due to its toxicity and the emergence of resistance. Amphotericin B is being used effectively for Sb\(^{\text{A}}\)-refractory patients, but it is toxic and hospitalization is required to administer the infusion and to monitor and manage adverse events. Lipid-associated amphotericin has far fewer toxic adverse events, but it is prohibitively expensive, even when using single-dose therapy, which has been shown to be effective in VL in India.

Recently, oral miltefosine has become available for the treatment of VL in India. Oral therapy must be the way forward in the treatment of VL, and miltefosine is undoubtedly a breakthrough in this area. A 28-day course of miltefosine is highly effective in Indian VL, with 94–98% of adults and 90–94% of children achieving cure at 6 months in clinical studies. Miltefosine is also effective against antimony-resistant disease. However, the long half-life of miltefosine (approximately 8 days), may lead to sub-therapeutic levels and preliminary clinical studies in Kenya and Brazil have shown encouraging efficacy against various species of Leishmania. However, sitamaquine has not been tested in Indian VL. This study was conducted to determine the dose–response and safety profile for oral sitamaquine in Indian patients with VL caused by Leishmania donovani. A similar study was conducted in Kenya and is also published in this journal issue (see Wasunna and others).

PATIENTS AND METHODS

This was an open label, dose-ranging, randomized study conducted at three centers in Bihar, India. The study was conducted in accordance with Good Clinical Practice (ICH E6) and the Declaration of Helsinki. The protocol was approved by the ethical committees of the Kala-azar Medical Research Center, Rambag Road, Muzaffarpur, India and Balaji Uthan Sansthan, Patna, India. Informed, written or witnessed oral consent was obtained from all study subjects (or their parent/guardian for subjects less than 18 years of age).

Inclusion and exclusion criteria. Subjects eligible for inclusion had a clinical diagnosis of VL with symptomatic disease and diagnosis confirmed by the presence of amastigotes in spleenic aspirates. Subjects aged 5–65 years of either sex were included in the study. Females of child-bearing age had to have a negative pregnancy test and agree to practice effective contraception throughout the study. Exclusion criteria included known hypersensitivity to sitamaquine, receipt of an antileishmanial agent within 10 days or of an investigational compound within 30 days (or 5 half-lives) of study start, subjects with marked deviations in serum chemistry, patients with serious underlying disease, including HIV infection, malnutrition or severe kala-azar, pregnancy or lactation, G6PD deficiency, or previous inclusion in this study.

Investigations and assessments. Patients were randomized contemporaneously to receive sitamaquine daily for 28 days at one of four doses: 1.5 mg kg\(^{-1}\) day\(^{-1}\) (Cohort 1), 1.75 mg kg\(^{-1}\) day\(^{-1}\) (Cohort 2), 2.0 mg kg\(^{-1}\) day\(^{-1}\) (Cohort 3), or 2.5 mg kg\(^{-1}\) day\(^{-1}\) (Cohort 4). The randomization schedule provided for an equal number of subjects in all four cohorts (N = 30).

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However, to minimize the number of patients exposed to higher sitamaquine doses, the randomization schedule was not followed for the final block of 8 subjects (Subjects 113 to 120). These 8 subjects were entered into Cohorts 1 and 2.

Physical examination was performed at baseline, Days 1, 4, 7, 14, 21, 28, 42, 70, 90, and 180. Clinical response was assessed at Days 14, 21, 28, 42, 70, 90, and 180. Spleen size was determined by palpation and measurement below the costal margin. Parasite load was determined by examination of splenic aspirates by Giemsa and/or Leishmann stain and quantified using the Leishmania index by an investigator blinded to treatment group. Parasitological assessment was performed at screening and at Day 14, and at the follow-up visits if the previous assessment was positive (Leishmania index of +1 or more), or if clinical symptoms were suggestive of relapse.

**Determination of efficacy.** The primary efficacy outcome measure was final cure at Day 180 in the intent-to-treat (ITT) population. Final cure was defined as a Leishmania index of 0 at the last available parasitological assessment, with the patient remaining clinically well until Day 180, that is, a complete resolution of the clinical signs and symptoms of VL or clinical improvement (afebrile with regression of spleen size by 30% of pretreatment values and an increase in hemoglobin by 2.0 g/dL and of white blood cell count by 2.0 × 10^3/mm^3). Failure was defined as a Leishmania index of +1 or more at the last available parasitological assessment, not meeting the criteria for complete resolution of the clinical signs and symptoms of VL or for clinical improvement at Day 180, recurrence of the signs and symptoms of VL (fever and increase in spleen size) or relapse (positive splenic aspirate after a previous negative test) at Day 180 or withdrawal due to lack of efficacy at any time during the study, with failure carried forward to Day 180. Patients who withdrew due to adverse events were followed-up for the remainder of the study and their final outcome determined at Day 180. Observed data at Day 180 and failures due to a lack of efficacy were included in the efficacy analysis, with a sensitivity analysis performed to assess the impact of missing data.

**Safety assessment.** All adverse events, regardless of relationship to study medication were noted. Cause or relationship to drug treatment was recorded by the investigator, based on their clinical judgment, as not related, unlikely, suspected or probable. Clinical laboratory evaluations were conducted at baseline and on Days 7, 14, 21, 28, 42, 70, 90, and 180 of the study.

**Statistical analysis.** For the primary efficacy outcome, response rates were estimated and exact 95% confidence intervals calculated using the Clopper Pearson method. As the study was designed to estimate the dose–response and safety of sitamaquine and not to make any formal comparisons between cohorts, a sample size calculation was not performed. All other data were summarized using descriptive statistics only. The efficacy and safety analyses were carried out on the ITT and safety population, respectively. The ITT population was prospectively defined as those patients that had a valid baseline assessment, received at least one dose of study medication and had at least one on-study assessment after Day 21. However, during post hoc analysis, it was thought that this definition may result in censorship of early failures or withdrawals due to adverse events and would not represent a conservative analysis. The ITT population was, therefore, re-defined to include all patients that had at least one dose of study medication and was the same as the safety population.

**RESULTS**

**Patient characteristics.** One hundred and twenty patients were enrolled, representing the safety population. Baseline demographic and clinical characteristics for the ITT population were broadly similar for the four cohorts, allowing for the small number of patients in each group (Table 1). All patients were of Indian ethnic origin.

**Efficacy.** Final cure at Day 180 in the ITT population (primary efficacy outcome) was achieved in 92 of 106 (87%) of patients overall (Table 2). For the individual cohorts, 25 of 31 (81%), 24 of 27 (89%), 23 of 23 (100%) and 20 of 25 (80%) patients receiving 1.5, 1.75, 2.0, or 2.5 mg kg^{-1} day^{-1} sitamaquine, respectively, were clinically cured at Day 180 (Table 2).

Of the 92 subjects with an outcome of final cure at Day 180, 84 (91%) had a complete absence of the signs and symptoms of VL and eight were clinically improved (three in Cohort 1, two in Cohort 2, two in Cohort 3, and one in Cohort 4). Eight patients (four in Cohort 3 and four in Cohort 4) who were withdrawn from the study due to adverse events, but subsequently followed up, had a Day 180 efficacy outcome of final cure.

Five patients (one in Cohort 1, two each in Cohorts 2 and 4) had a Day 180 assessment of failure with a Leishmania index of 2, 3, or 4. An additional eight patients (five in Cohort 1, one in Cohort 2, and two in Cohort 4) were withdrawn due to lack of efficacy and had their outcome of failure carried forward. One patient died during the study and was recorded as a failure for the efficacy analysis.

Fourteen patients had no Day 180 assessment (Table 2). In Cohort 1, one patient withdrew consent at Day 7. In Cohort 2, five subjects were lost to follow up; two of which had a complete absence of the signs and symptoms of VL at Day 90 and three met the criteria for clinical improvement at their final visit (one at Day 28, two at Day 90). In Cohort 3, four patients were lost to follow up, one at Day 70 and three at Day 90, all met the criteria for clinical improvement at their final visit; an additional patient attended the Day 180 assessment, but their outcome was unknown although they had met the criteria for clinical improvement at Day 90. In Cohort 4, one patient withdrew consent at Day 7 and two were lost to follow up at Day 90; VL was clinically resolved for one patient and one met the criteria for clinical improvement at this visit.

Clinical markers of VL (hematological variables, reduction in spleen size and increase in subject weight) showed improvements throughout the study that were maintained to Day 180 (Figure 1).

Mandatory splenic aspiration at Day 14 showed an early response to treatment, with a Leishmania index of 0 (absence of amastigotes in splenic aspirate) for 68% of patients in Cohort 1, 91% in Cohort 2, 93% in Cohort 3, and 77% in Cohort 4 (Figure 2). All but three patients experienced a reduction in parasite load by Day 14 (two in Cohort 1 and one in Cohort 3), and no patient had an increase in parasite load at this time compared with baseline.

**Safety and tolerability.** Overall, sitamaquine was well tolerated. During the active treatment phase, adverse events due to any cause were experienced by 35% (43 of 120) of patients.
Adverse events were more common in the two higher dose cohorts; 28% in Cohorts 1 and 2, 43% in Cohort 3, and 46% in Cohort 4. The most common adverse events during therapy were vomiting (8% [10 of 120]), dyspepsia (8% [9 of 120]) and cyanosis (3% [4 of 120]). Other gastrointestinal events included diarrhea (3% [3 of 120]), loose stools (3% [3 of 120]), and abdominal discomfort (2% [2 of 120]), but there was no consistent relationship to sitamaquine dose. A small number of patients experienced postprocedural pain (2% [2 of 120]) and decreased blood albumin (3% [3 of 120]). Nephrotic syndrome (3% [3 of 120]) and glomerulonephritis (2% [2 of 120]) were seen at the two higher sitamaquine doses: 4% [1 of 28] and 0% in Cohort 3 and 7% [2 of 28] and 7% [2 of 28] in Cohort 4, respectively (Table 3).

During follow-up (post-active treatment), 21% (25 of 120) of patients experienced an adverse event due to any cause.
These included pyrexia (6% [7 of 120]), cough (5% [6 of 120]) abdominal pain (3% [3 of 120]), decreased blood albumin, diarrhea, dyspnea, nasopharyngitis, jaundice and pain (all 2% [2 of 120]). There was no consistent relationship to sitamaquine dose for these reports.

There was one fatality during the study in Cohort 4 due to cardiorespiratory failure, anemia and bone marrow depression. A possible relationship to study medication was noted by the investigator.

Table 3 shows the most common adverse events commencing during the active treatment phase that had a possible or probable relationship to study medication as recorded by the investigator. Drug-related adverse events were more frequent in the two higher sitamaquine dose cohorts. Cyanosis and dyspepsia were the most common drug-related adverse events. Two subjects had methemoglobinemia.

Drug-related adverse events leading to withdrawal occurred in the two higher sitamaquine dose cohorts. In Cohort 3, four patients were withdrawn, one each with proteinuria, nephrotic syndrome, elevated serum creatinine or edema. In Cohort 4, other than the patient who died, five patients were withdrawn because of drug-related adverse events: two with nephrotic syndrome, two with glomerulonephritis, and one with acute renal failure. All of these conditions resolved after withdrawal of therapy, apart from one subject in Cohort 3 who had proteinuria that was still present at Day 28. Although this patient was followed up clinically, no urinalysis data are available after their withdrawal.

Two patients had laboratory test abnormalities of National Cancer Institute Common Terminology Criteria for Adverse Events Grades 3 or 4, \( (> 3 \times \text{upper limit of normal}) \) after baseline for serum creatinine or urea. One subject in Cohort 1 had a Grade 3 urea result on Day 90 (6 days after starting amphotericin B after being classified as a treatment failure), and one subject in Cohort 4 had a creatinine result of Grade 3 at Day 21.

DISCUSSION

This was an open-label, descriptive study designed to determine an effective and appropriate dose of sitamaquine and the adverse event profile of sitamaquine in an Indian population with VL. Although this study was conducted as an open-label trial, parasitological and laboratory assessments were conducted blind to treatment cohort.

The overall efficacy of sitamaquine in Indian VL, based on final cure at Day 180 in the intent-to-treat population, was 87%, with 81%, 89%, 100%, and 80% of patients achieving final cure at sitamaquine doses of 1.5, 1.75, 2.0, or 2.5 mg kg\(^{-1}\) day\(^{-1}\), respectively. Although there does appear to be some dose-response relationship up to 2.0 mg kg\(^{-1}\) day\(^{-1}\) sitamaquine, the number of patients in this study and the high efficacy rates seen in all cohorts make it difficult to draw firm conclusions regarding the optimal sitamaquine dose.

In this study, there was no requirement for splenic aspirate at Day 180 in patients that were clinically well; only a Day 14 parasitological assessment was mandatory. The primary efficacy outcome measure in this study was defined prospectively as the derived parasitological outcome at Day 180, with a successful outcome defined as parasitological cure (Leishma-
nia index of 0). In the absence of a splenic aspirate at Day 180, this outcome could be carried forward from the last available parasitological assessment if the patient remained clinically well. Patients that showed any deterioration in their clinical condition, or did not continue to experience improvements in the signs and symptoms of VL had a repeat splenic aspirate performed. In fact, parasitological assessment was carried forward for all but 9% (10 of 106) of those patients who were evaluable at Day 180. As most of the efficacy outcomes were determined based on clinical outcome at Day 180, rather than parasitological assessment, we have used the term “final cure” in this paper for the primary efficacy outcome.

In the original protocol, all subjects were supposed to have been followed to Day 180, even if they had withdrawn from the study. As a consequence, any subject who had no Day 180 data was considered as “missing” and was to be excluded from the efficacy analysis. However, when analyzing the data, it was realized that this approach risked ignoring those patients who were withdrawn due to lack of efficacy and who were not followed up for whatever reason. As a consequence, in the analysis presented in this paper, all patients that withdrew due to lack of efficacy had their outcomes carried forward to Day 180. This amendment did not materially affect the conclusions of the study but was considered to be a more representative interpretation of the protocol and findings.

The assessment of efficacy, based mainly on clinical outcome at Day 180 with negative splenic aspirate carried forward from Day 14, is a possible limitation of this study. However, in the Kenyan study reported in this journal issue, parasitological assessment was mandatory at Day 180, and cure was defined as an absence of amastigotes in tissue samples at this time point. Despite the differences in definitions, efficacy rates were similar between the two studies: 83% overall cure in Kenyan patients and 92%, 80%, 82%, and 91% cure for sitamaquine doses of 1.75, 2.0, 2.5, and 3.0 mg kg$^{-1}$ day$^{-1}$, respectively.

In the Kenyan study, there was no parasitological assessment performed during sitamaquine therapy. In this study in Indian patients, an early parasitological assessment at Day 14 was performed. This showed that, for the majority of patients (97 of 117 [83%]), parasites were no longer detectable in splenic aspirates after 14 days of sitamaquine therapy. In all patients, VL was confirmed by the presence of amastigotes in tissue samples at baseline. These results suggest that a course of sitamaquine shorter than 28 days may be possible in Indian VL.

In this study, data were missing at Day 180 for 14 of 120 (12%) patients. Only observed data and known failures due to lack of efficacy were included in the primary efficacy analysis. To test the effect of missing data, we performed a sensitivity analysis. Classifying all the “missings” as failures gives efficacies of 25 of 32 (78%), 24 of 32 (75%), 23 of 28 (82%), and 20 of 28 (71%) for Cohorts 1, 2, 3, and 4, respectively. Conversely, treating all the “missings” as cures gives efficacies of 26 of 32 (81%), 29 of 32 (91%), 28 of 28 (100%), and 24 of 28 (86%) for Cohorts 1, 2, 3, and 4, respectively. Details of the last available visit outcome for the patients with missing Day 180 data are provided in the results section. Excluding the two patients who had withdrawn consent early in the study, all of the remaining 12 patients that had missing data at Day 180 had a complete clinical resolution of VL or clinical improvement at their earlier visits (10 of 12 patients at Day 90, one at Day 70, and one at Day 28). All of these patients would have been assigned an outcome of final cure in the absence of a parasitological assessment. Therefore, many of “missings” in the primary analysis are likely to have remained final cures to Day 180. Indeed, of those subjects assessed at both Day 90 and Day 180, 92 of 98 (94%) of those who were cured at Day 90 remained cured at Day 180.

There was one fatality in this study. After six days of study treatment, this patient had elevated aspartate transaminase and alanine transaminase, alkaline phosphatase, sodium and methemoglobin levels with falling blood pressure, at which point study medication was stopped. The following day, cyanosis and dehydration were noted. Despite treatment, the subject died four days later. A review of this case indicated that this patient should not have been enrolled in the study as their baseline aspartate transaminase was elevated (197 IU/L) above the level stipulated in the protocol. An autopsy was not performed, however, bone marrow suppression and anemia are typical features of VL and overwhelming sepsis is not uncommon. The patient died despite supportive therapy and intravenous antibiotics. The investigator reported a possible association with study medication.

Sitamaquine was generally well tolerated in this study. Methemoglobinemia is a recognized side effect of 8-aminoquinolines and two subjects in this study had methemoglobinemia reported by the investigator as an adverse event. Based on laboratory findings, forty (33%) subjects had at least a 10% increase in methemoglobin recorded at any point during the study versus baseline. These typically peaked at Day 14. Only one patient had methemoglobin in excess of 20% (a value of 22.5%). A further four subjects had cyanosis recorded as an adverse event, three of whom had methemoglobin levels in

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### Table 3

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>1.5 mg kg$^{-1}$ day$^{-1}$</th>
<th>1.75 mg kg$^{-1}$ day$^{-1}$</th>
<th>2.0 mg kg$^{-1}$ day$^{-1}$</th>
<th>2.5 mg kg$^{-1}$ day$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>2 (6)</td>
<td>3 (9)</td>
<td>8 (29)</td>
<td>8 (29)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>0</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (3)</td>
<td>0</td>
<td>2 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>0</td>
<td>0</td>
<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Acquired methemoglobinemia</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (4)</td>
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excess of 10%. It is possible, therefore, that their cyanosis was in fact due to methemoglobinemia. Except for cyanosis, there were no symptoms relating to methemoglobinemia.

Renal adverse effects occurred in 10 of 120 (8%) subjects. One of these was an elevated creatinine in a subject who had failed therapy at Day 90 and was being treated with amphotericin B. Of the remaining nine subjects, two had glomerulonephritis, three nephrotic syndrome, two proteinuria, one elevated serum creatinine, and one acute renal failure. However, of these nine subjects, only two had creatinine values equal to or greater than twice the upper limit of normal, and the reporting of these adverse events was generally based on clinical signs and symptoms, rather than laboratory findings. In all cases, serum creatinine returned to normal after cessation of therapy. Urinalysis was not demanded by the protocol, but a subset of patients did have urinalysis performed. Of the 88 subjects who had at least one urinalysis, 30% had significant proteinuria (≥ 100 mg/dL). It is difficult to draw any definitive conclusions from these data as they were collected ad hoc, were not subject to quality control procedures, and it is not clear if the subjects were representative of the study population as a whole. Baseline urinalysis was not performed in any subject. In all cases that were followed-up, proteinuria was reversible on cessation of therapy.

In a previous study in 23 Brazilian subjects, reversible elevations in serum creatinine occurred in two subjects at a sitamaquine dose of 2.0 mg kg⁻¹ day⁻¹ and in one subject receiving 3.25 mg kg⁻¹ day⁻¹ sitamaquine. The two subjects receiving 2.0 mg kg⁻¹ day⁻¹ sitamaquine had concomitant varicella infection, which, it was suggested, may have contributed to this adverse event. In an earlier Kenyan study, formal renal monitoring was not conducted, but urinalysis in the 16 subjects included in the study revealed no significant abnormalities with sitamaquine doses of up to 1 mg kg⁻¹ day⁻¹. In the recent Kenyan study reported in this journal issue, two patients experienced glomerulonephritis and renal failure, one receiving sitamaquine 2.5 mg kg⁻¹ day⁻¹ and one 3.0 mg kg⁻¹ day⁻¹.

As no comparator or placebo arm was used in this study, it is impossible to be certain of the etiology of these renal adverse events. Of the nine patients with renal adverse events, one was on Cohort 1, three were in Cohort 2, and five were in Cohort 3. Although the numbers in this study were small, the possibility of a dose relationship is suggested, and a direct toxic effect of sitamaquine on the kidney cannot be ruled out. Preclinical studies are ongoing to further investigate renal toxicity and renal function will be closely monitored in future clinical studies.

To put these results into context, pathologic and epidemiologic studies show that renal impairment may be a consequence of VL or of its treatment. Glomerulonephritis and interstitial nephritis have been reported. Elevated serum creatinine is observed in 9–45%, and proteinuria in 18–91% of subjects. It has been suggested that circulating immune complexes may be responsible for these observations and during therapy, one might expect the levels of circulating immune complexes to rise sharply due to parasite lysis.

In conclusion, this study established that oral sitamaquine for 28 days is efficacious in treating VL at the doses explored and was generally well tolerated. The optimal dosing regimen has yet to be determined and effects on the kidney need to be better understood. Sitamaquine is a promising agent for the oral treatment of Indian VL, further preclinical studies are being conducted, and additional clinical studies are planned.

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