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A STUDY ON EFFICACY AND TOLERABILITY OF MILTEFOSINE FOR CHILDHOOD VISCERAL LEISHMANIASIS IN A TERTIARY CARE CENTRE IN EASTERN BIHAR.

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ABSTRACT

Introduction: Leishmania donovani is an intracellular protozoan parasite of genus Leishmania. It causes Visceral leishmaniasis (VL), which is a disseminated and serious form of leishmaniasis. VL causes an estimated 500,000 new cases of disease and 60,000 deaths every year. VL is deadly and debilitating disease affecting children of Bihar and U.P. Antimony resistance is a serious problem, Amphotericin B and Pentamidine are effective by parenteral administration, associated with toxicities. Thus there is a need for an effective, orally administered, non-toxic and less expensive alternative drug like Miltefosine, to be used in children.

Aims and Objectives: The present study was designed to observe the efficacy of Miltefosine in VL, in Bihar by evaluating the usage of adult dosage of Miltefosine (2.5 mg/kg/d for 28 days) in 160 children (age, 2–11 years).

Materials and Methods: Our study is an open-label, clinical trial involving 160 patients admitted at JLNMCH, Bhagalpur, Bihar who were parasitologically proven cases of VL who received Miltefosine and were followed up for the following one year.

Results: Out of 160 children, 2 died of pneumonia, other 158 patients demonstrated no parasites after treatment and improved clinically. 6 patients relapsed, 2 patients lost follow-up. Cure rate was 94% .Side effects included vomiting or diarrhea (each 25%) and transient elevations in the AST level (55%).

Conclusions: The present study concludes that Miltefosine is effective, well tolerated, and easily administrable oral drug in the treatment of VL in Children in resource poor country like India.

KEYWORDS : Visceral leishmaniasis, Miltefosine, Children, Bihar.

INTRODUCTION:

Visceral leishmaniasis (VL) is caused by the protozoan parasite Leishmania donovani and transmitted by the bite of infected sandfly Phlebotomus argentipes. Nearly half of the VL cases occur in children (childhood or paediatric VL). The clinical manifestations of childhood VL are more or less same as in the adults The estimated annual global burden of VL is approximately half a million new cases and more than 50,000 deaths, of which 90% occur only in five countries; India, Bangladesh, Nepal, Sudan, and Brazil. [1] In India, leishmaniasis is prevalent in four states; Bihar, West Bengal, Jharkhand, and Uttar Pradesh, of which Bihar contributes half of VL cases that occur globally. [2] VL has been one of the major health problems in the State of Bihar in India, for the past three decades or more. At present, 28 of 37 districts are endemic. Ninety per cent of all the cases in India are reported from Bihar State alone. Visceral leishmaniasis (VL) classically manifests as fever, hepatosplenomegaly, and pancytopenia. If untreated, it is almost always fatal, as a result of intercurrent infection. 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].

For many years leishmaniasis has been treated with pentavalent antimonials, which are administered parenterally over 3 to 4 weeks. Antimony resistance is being increasingly recognized in India as well as in other geographic areas. Alternatively, amphotericin B deoxycholate and pentamidine isethionate have also been used. Sodium antimony gluconate (stibogluconate) has been the drug of choice for over past 50 years. 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].

Leishmaniasis has been identified by the World Health Organization (WHO) for elimination by 2015, along with other neglected tropical diseases. [15] In 2005, India, Nepal, and Bangladesh agreed to initiate a VL elimination program with the target of reducing annual VL incidence to 1/10,000 population by 2015. [16, 17]. In a pilot trial involving Indian children, Sundar et al. [18] 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 160 Indian children who had VL with miltefosine.

In the present study 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.

MATERIALS AND METHODS:

The study was conducted at Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar as an open-label, trial involving 160 patients from October 2016 to September 2018. The data was analysed using SPSS Software.

In the present study, Miltefosine was given orally at 2.5 mg/kg once per day for 28 days. All the patients were hospitalized, and administration of medication was directly observed by us. We included children, 2–11 years of age of both male and female 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 [19], 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.

Informed written consent was obtained from the parents or guardians of eligible children. Patients were re-evaluated 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. Gastrointestinal symptoms (vomiting and diarrhea) were asked 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) [20].

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 in our study.

In the present study 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 [21] (5 mg/kg q.d. for 5 days) was administered to patients who relapsed after treatment in this study.

RESULTS:

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. Thirty eight 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.

Table 1.

Clinical Characteristics	Value	Normal Range
Age, years Mean+- SD Range	7.8+_2.3 3-10	… …
Sex, no.(%) of patients Male Female	90 (56.3) 70 (43.8)	… …
Weight (in kg) Mean+_SD Range	18.1+_4.4 10-30	… … …
Previously treated for VL, no. (%) of patients	38(25.2)	…
Splenomegaly, cm below costal margin Mean+_SD Range	6.8+-3.4 1-16	… …
Laboratory values WBC count, cells/nl Mean+-SD Range Platelet count,platelets/nl Mean+-SD Range	4.4+-2 1.5-10.6 144+-70 50-390 7.6+-1.2	… 4.5-15 131-450
Haemoglobin conc. g/dl Mean+-SD Range	6-10.8 52+-17	11-14.5 …
Serum creatinine level, mmol/L Mean+-SD Range	18-97 11+-4.3	35-97 …
Blood urea nitrogen level, IU/L Mean+-SD Range	2-22 4.3+-22	4.7-23 …
Aspartate aminotransferase level, IU/L Mean+-SD Range	15-103	5-3

Clinical and laboratory characteristics of 160 patients with Visceral leishmaniasis (VL) at baseline.

In the present study, two patients died (age, 4 years). These two patients had not previously received antileishmanial therapy. The first 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 second patient also had almost similar presentation. 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 both the patients died on day 6 and day 7.

In this study, each of the other 158 patients received therapy past day 6 and had evidence of initial parasitological cure (table 2). Treatment was associated with marked clinical improvement of signs and symptoms suggestive of VL. In all 158 patients, the temperature was normal (i.e., <37.1°C) on day 6. The mean spleen size decreased steadily from 6.8 cm at enrolment 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 than at baseline in our study.

Table 2:

Parameter	No. (%) of Patients
At Completion of Therapy Initial cure Initial failure	158(99) 2(1)
Six Months after Completion of Therapy Final cure Failure due to lack of initial cure Failure due to relapse Lost to follow up	150(94) 2(1.3) 6(3.8) 2(1.3)

Efficacy of treatment in 160 patients with Visceral leishmaniasis treated with Miltefosine.

In the present study six patients (4%), none of whom had experienced treatment failure with previous antileishmanial therapy, had relapse after initial parasitological cure. Two patients (1%) lost to follow-up. Thus, the final cure rate 6 months after completion of treatment was 94% (150 of 160 patients; lower limit of 95% CI, 87%), and the final cure rate for evaluable patients was 95% (150 of 158 patients; lower limit of 95% CI, 89%). Each of the 38 patients who had previously experienced antimonial therapy failure were cured with Miltefosine in this study.

The clinical adverse events were entirely gastrointestinal in nature and are listed in table 3. 42 patients (26%) and 40 patients (25%) had episodes of vomiting or diarrhea, respectively. For 14 of these patients, the 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 solution, as recommended by the World Health Organization (WHO)/United Nations Children's Fund (UNICEF) [22], and did not lead to discontinuation of therapy for any patient.

In the present study, laboratory parameters were determined by liver

and kidney function tests that changed significantly are shown in table 4. 55% of patients had a transient increase in ASAT levels, but only 2 patients 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, as mentioned in table 4 in this study.

Table 3:

Symptom	No. (%) of Patients
Vomiting	42 (26)
Total	
Duration, days	38 (24)
1-2	2 (1.3)
3-4	2 (1.3)
>4	
Severity	26 (16)
CTC grade 1	16 (10)
CTC grade 2	
Diarrhoea	40 (25)
Total	
Duration, days	38 (24)
1-2	2 (1.3)
3-4	
Severity	34 (21)
CTC grade 1	4 (2.5)
CTC grade 2	2 (1.3)
CTC grade 3	

NOTE: CTC common Toxicity Criteria of the National Cancer Institute (Bethesda, MD)
#For vomiting CTC grades 1 and 2 signify 1 and 2-5 episodes per day, resp. For diarrhoea, CTC grades 1, 2 and 3 signify an increase of 2-3, 4-6, and 7-9 stools per day

Table 4:

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

NOTE: ASAT Aspartate aminotransferase, CTC Common Toxicity Criteria of the National Cancer Institute (Bethesda MD)
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.
@ Less than 1.5 times the upper limit of normal.

DISCUSSION:

Visceral leishmaniasis, commonly known as "kala-azar" in India, 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. However, problems of drug delivery and access remain to be solved in countries where VL is endemic.

The treatment of VL patients has improved over the past years, as the international scientific attention has increased and several not-for-profit organizations have made it a priority to develop new chemical entities, drugs, and combination treatments for this fatal neglected disease. Unfortunately, the currently available drugs for treatment of VL featured several lacunas during their development, which may have been in part due to the difficulty of performing clinical trials in the resource-limited settings where VL is present.

The present trial of Miltefosine involving 160 Indian children has shown that the drug is safe and effective for children aged 2–11 years. Two patients 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 [23], and, in smaller series of cases, deaths generally occurred close to the initiation of treatment [24].
In this study, results of 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 earlier.

The best 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 [25]) 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 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 [26]. 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 drug has a long half-life in humans [26]. 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 [27].

Patients coinfected with HIV and Leishmania species generally have relapse after initial treatment with Miltefosine, as with other antileishmanial agents [28]. For the increasing number of patients coinfected with HIV and Leishmania species [29, 30], 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. The final cure rate of 94% with miltefosine was also assessed during phase-III, on the basis of which NVBDCP introduced the drug in India. Similarly, a cure rate of 94% was observed among

pediatric patients also in Bihar. [31, 32] Finally, the very high cure rate among Indian patients (>95%) requires confirmation in other regions where VL is endemic which is highly fatal neglected disease in children.

CONCLUSION:

Miltefosine enjoys a superiority over other anti-leishmanial drugs perhaps due to better compliance as it is orally effective, hospitalization is not needed, and tolerance is good with few side effects. The present study concludes that Miltefosine is effective, well tolerated, and easily administrable oral drug in the treatment of VL in Children in resource poor country like India and the mortality and morbidity associated with this deadly disease in Indian children, especially of Eastern Bihar could be brought down.

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