



A COMPARATIVE STUDY OF AMPHOTERICIN-B VERSUS MILTEFOSINE REGARDING EFFICACY AND SAFETY PROFILE IN PEDIATRIC CASES OF VISCERAL LEISHMANIASIS.

Dr. Akhilesh Kumar Ram*

Senior Resident, Department of paediatrics, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. *Corresponding Author

ABSTRACT From the treatment point of view many drugs have been tried with various efficacy in visceral leishmaniasis. **Objectives:** The study was undertaken to compare the efficacy of intravenous amphotericin B and oral miltefosine in the treatment of visceral leishmaniasis in children. **Materials And Methods:** In this study 60 consecutive diagnosed cases of kala-azar were studied in pediatric indoor ward of Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. All the cases included in study, randomly divided into two groups A and B with equal no. of patients (30 in each) in both groups. Patients of group A were given intravenous Amphotericin B in the dose schedule of 1mg/kg on alternate day for 15 doses. Patients of group B were given oral miltefosine in dose schedule of 2.5mg/kg daily for 28 days. During the therapy, clinical and parasitological response and safety profiles of the drugs in both groups were closely monitored. **Conclusion:** "Both the drugs i.e. Amphotericin B as well as Miltefosine had been observed as equally efficacious in causing clinical as well as parasitological cure in pediatric cases of visceral leishmaniasis and no sufficient toxicity developed in either group and so they are equally safe in children"

KEYWORDS :

INTRODUCTION:

Visceral leishmaniasis or Kala-azar is one of the major tropical disease which has been prevalent in India since time immemorial. It is the most severe form of infection among the spectrum of the disease caused by the protozoa "Leishmaniadonovani".

Kala-azar is one of the biggest health problem of North districts of Ganges. It has major medical, psychosocial and financial implication.. The leishmaniasis afflicts the poorest of the poor population.

Visceral Leishmaniasis, the disseminated intracellular protozoal infection is caused by hemoflagellate parasite of the genus *Leishmania* and the order kinetoplastida.

Visceral Leishmaniasis is characterized by an immunosuppressive state permitting dissemination and multiplication of amastigotes, despite very high level of antileishmanial antibodies in serum. Maximum burden of parasite is borne by macrophage rich organs viz, spleen, liver, bone marrow and lymph nodes. Spleen enlarges markedly, duodenal and jejunal RE cells show proliferation and bone marrow in infiltrated with LD bodies. This infiltration and hypersplenism contributes to pancytopenia, whereas chronic inflammatory response results in wasting, hypoalbuminemia and hypergammaglobulinemia. If untreated cachexia and debilitation are progressive.

From the treatment point of view many drugs have been tried with various efficacy. The currently drugs used are pentavalent antimony compound; sodium stibogluconate, meglumine antimony compounds; pentamidine and amphotericin B. Besides these some newer drugs have been developed with variable efficacies. e.g. oral miltefosine, amanosidine, sitamaquine, interferon γ .

Conventional drugs are administered under strict medical supervision, the treatment cost is high and therapeutic efficacy is limited.

The quest for an orally active, efficacious, cost effective and safe drug is on. Miltefosine is the first orally effective drug for the treatment of kala-azar.

The present study was undertaken to compare the efficacy as well as safety profiles of intravenous amphotericin B and oral miltefosine in the treatment of visceral leishmaniasis in children.

MATERIAL AND METHODS:

The present study was carried out in the pediatric indoor ward of Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi. Sixty diagnosed cases of kala-azar were selected and randomly grouped as group A and group B containing 30 patients in each group. Group A patients received intravenous amphotericin B in dose schedule of 1mg/kg body wt on alternate day, whereas group B patients received oral miltefosine in dose schedule of 2.5 mg/kg/day.

Inclusion Criteria:

1. A clinical diagnosis of active visceral Leishmaniasis with consistent sign and symptoms e.g. fever, splenomegaly.
2. Diagnosis confirmed by splenic aspirate / bone marrow smear showing characteristic amastigote.
3. Age 2-16 years
4. Completion of baseline screening studies – TLC, DLC, Hb% Blood smear for malarial parasite, splenic aspirate / bone marrow smear, Rk-39 strip test, serum bilirubin, SGPT, SGOT, Blood urea, serum creatinine, serum for HIV urine analysis, chest x-ray and ECG.

Exclusion Criteria:

1. Patients with cardiac, renal or hepatic impairment, HIV positive cases.
2. Patient of below 2 years of age.

A total of sixty cases were selected according to criteria mentioned above. They were divided randomly in two groups of thirty each.

GROUP A:- (Patient receiving intravenous amphotericin B)

Each patient of this group was given intravenous amphotericin B in dose schedule of 1 mg/kg body wt. on alternate day for 15 doses.

The calculated amount was diluted in 250 ml of 5% Dextrose and infused over a period of 5-6 hours in the morning through pediatric scalp vein set.

GROUP B:- (patient receiving oral miltefosine) Miltefosine were given under following doses :-

1. Children (> 12 years & > 25 kg) : 100 mg / day, one capsule (50mg) in the morning and one capsule in the evening for 28 days.
2. Children (> 12 years & < 25 kg) : 50mg/day one capsule (50mg) daily for 28 days.
3. Children (2-11 years) : Miltefosine was given at 2.5 mg/kg body wt/day after meal in two divided doses for 28 days for this 10 mg capsules were used.

Clinical Assessment During Treatment And Follow Up:

At the beginning of treatment all of the patient were assessed clinically for abatement of fever, gain in weight, improvement in appetite, regression in spleen size and improvement of pallor. All clinical criteria were assessed at weekly intervals during treatment.

After cure patients were assessed clinically at monthly intervals for six months for any possible relapse.

Laboratory Investigations During Treatment And Follow Up:

At the start of therapy parasitological diagnosis was confirmed by bone marrow smear or splenic aspirate examination and graded according to number of LD bodies. During treatment weekly assessment of LD body was done to know the response of treatment in both the groups.

After completion of therapy of patients of both the groups Leishmania donovani mastigote form were again searched in the bone marrow smear or splenic aspirate and repeated at 6 months from the completion of therapy.

Other parameters were assessed weekly during treatment, viz, TLC, DLC, Hb%, routine urine analysis Blood urea nitrogen, serum creatinine, SGPT, serum potassium and ECG to assess the response to therapy and for evidence of toxicities, if any.

The Criteria For Clinical Cure In The Present Study Were:

1. Cessation of fever.
2. Significant regression in splenic size.
3. Definite improvement of hemoglobin concentration.
4. Increase in the leucocyte count to normalcy.

RESULTS:

Average weight gain was 2.5 kg by the end of therapy Group A patients which was statistically significant ($p < 0.05$) and this trend continued i.e. weight gain was maintained during follow up.

Whereas in Group B patients average weight gain by the end of therapy was 2.0kg which was significant ($P < 0.05$). Weight gain pattern in patients of both the study groups were similar and statistically insignificant ($t = 1.22$; $P > 0.05$).

Mean body temperature in patients of both the groups i.e. group A and group B touched the normal level by the beginning of second week i.e. 8th day of therapy and was maintained during follow up. There was no any significant ($t = 1.2$, $P > 0.05$) difference regarding pattern of normalization of body temperature among both groups. Therefore both the drug are equally efficacious in reducing body temperature in patients with visceral leishmaniasis.

Following therapy there was significant ($P < 0.05$) reduction in spleen size and spleen became non palpable by the end of 4 month in patients of both the groups and remained so during rest of the follow up period. Patients of both the group showed significant ($p < 0.05$) decrease in mean splenic size following therapy. Rate of regression of mean splenic size were similar ($t = 1.4$, $P > 0.05$) in both the study group. Therefore there is no any significant difference between two drugs i.e. Amphotericin B and Miltefosine in causing splenic regression following therapy in patients of visceral leishmaniasis.

There was significant ($p < 0.05$) rise in haemoglobin concentration in both the groups by the 15th day of treatment. Following therapy both the group showed similar ($t = 0.20$, $P > 0.05$) effect on haemoglobin concentration.

There was significant ($P < 0.05$) rise in total leucocyte count in group A patients by 2nd week of therapy whereas by 15th day of therapy in group B patients. The rate of rise in total leucocyte count was similar ($P > 0.05$) among both the study groups.

In amphotericin group there was significant ($P < 0.05$) reduction in LD bodies grading by the 15th day of treatment and all patients were free from LD bodies by 30th day i.e. at the completion of therapy. Whereas at 30th day i.e. completion of therapy all patients of miltefosine group were LD bodies negative except one patient in which even after completion LD bodies were present (+++). She was considered as unresponsive to miltefosine and later on treated with amphotericin infusion and finally cured.

Therefore in the present study parasitological cure rate in group A patient was found 100% where as it was found 96% in group B patient. Both the drug had statistically similar ($P > 0.05$) results in causing parasitological cure in patients of visceral leishmaniasis.

As far as renal toxicity are concerned neither of group recorded significant ($P > 0.05$) rise in serum creatinine at any point of time during therapy. The difference in rate of rise of serum creatinine between group A and group B was not significant ($P > 0.05$). As the serum creatinine to a better indicator of renal function in comparison to blood urea nitrogen, it is evident that intravenous amphotericin B in a dose of 1 mg/kg is not more nephrotoxic than oral miltefosine (2.5mg/kg body wt).

There was no any significant ($P > 0.05$) rise in ALT level was observed during treatment in amphotericin group. Whereas in miltefosine group

at the end of 2nd week of therapy there was a marked rise in mean ALT level. But after that it started declining and at the end of treatment it reached to almost pretreatment level. Therefore rise in ALT level is only transient. At the end of treatment there was no any significant ($P < 0.05$) rise in ALT level in either group.

DISCUSSION:

In this study 60 consecutive diagnosed cases of kala azar were studied in pediatric indoor ward of Vardhman Mahavir Medical College & Safdarjung Hospital New Delhi. All the cases included in study, randomly divided into two groups. Patients in one group were given intravenous Amphotericin B, whereas patients of group B were given oral miltefosine. During the therapy, clinical and parasitological response and safety profiles of the drugs in both groups were closely monitored. It was observed that clinical parameters viz. abatement of fever, spleen size regression, weight gain, as well as lab parameters e.g. rise in Hemoglobin & total leucocyte counts as well as parameters for parasitological cure were statistically significant in both the study group. As far as safety profile is concerned, elevation of serum transaminase was observed in more in miltefosine group which was only transient and started declining after 2nd week of therapy. Serum creatinine level was found raised in few patients of amphotericin group but there was not any frank case of azotemia. Gastrointestinal upset like nausea, vomiting and diarrhea were observed more in miltefosine group patients.

Various comparative studies of different drugs used for Leishmaniasis or different formulations of same drug or different regimen of same drug has been done by various workers time to time.

A prospective, multicentric cross-sectional study regarding miltefosine in children with visceral leishmaniasis was done by Singh UK, Prasad R, Mishra OP, Jaiswal BP. Safety, tolerance and efficacy of miltefosine were compared with amphotericin B. Patients were randomized into four groups. Group 1 and 2 patients were given miltefosine in dose of 2.5mg/day OD or bid per orally and group 3 and 4, amphotericin B at a dose of 1mg/kg/day. Final cure rate with miltefosine and amphotericin B was 93.2%, 95%, 92% and 91% in group 1,2,3, and 4 respectively. Raised BUN was observed more in patients who got amphotericin B i.e. 66.42% and 73.91% in group 3 and 4 respectively GI side effects i.e. diarrhea and vomiting were observed in 26% and 23% patient in miltefosine group. Conclusion: Miltefosine is safe, well tolerable and highly effective and has same efficacy as amphotericin B in newly diagnosed and SAG resistant children with visceral leishmaniasis. (Indian J Pediatr. 2006 Dec.).

It appears, further related study will open new vistas for orally effective affordable and acceptable drugs in the armamentarium for the treatment of kala-azar. It is expected that in future we would have effective ways to prevent and treat all forms of leishmaniasis without discomforting the patient.

CONCLUSION:

1. Weight gain in patients of both the groups were significant at the completion of therapy, pattern of weight gain was also similar in both the study group.
2. Mean body temperature in patients of both the study group touched normal level by the 8th day of therapy. Thus both the drugs are equally effective in reducing fever in visceral leishmaniasis.
3. Splenic regression in both the groups were significant after completion of therapy. Overall pattern of splenic regression in both the study groups were also similar.
4. Both the study groups showed almost similar rise in total leucocyte count and hemoglobin concentration during therapy.
5. Parasitological cure at the end of therapy in group A patient (amphotericin B group) was 100 % whereas in group B (Miltefosine group) patient it was approximately 96%.
6. Serum cretinine level was found raised in few patients of group A, but there was no any frank case of azotemia, necessitating withdrawal of drug was observed.
7. Elevation of serum transaminases was observed more in group B patients. It was increased after 1st week of therapy which started declining after 2nd week of therapy and eventually decreased to the normal value after completion of therapy.
8. Acute reactions like chills, rigor, and fever was observed significantly more in group A patients which were gradually subsided in due course of treatment.
9. Gastrointestinal upset like nausea, vomiting and diarrhea were observed more in group B patients.

The final conclusion derived from this study was “ Both the drugs i.e. Amphotericin B as well as Miltefosine had been observed as equally efficacious in causing clinical as well as parasitological cure in pediatric cases of visceral leishmaniasis and no sufficient toxicity developed in either group and so they are equally safe in children”.

REFERENCES:

1. WHO (1996: World Health Report, 1996, Report of the Director General, WHO.
2. Eibi H. Hexadecylphosphocholine : a new selective antitumor drug. *Cancer treat. Rev.* 1990; 17 : 233-42.
3. Singh UK, et al. *Indian J Pediatr.* 2006 Dec;73(12):1077-80. Miltefosine in children with visceral leishmaniasis: a prospective, multicentric, cross-sectional study.
4. S.N. Jha et al : Changing response to diamidine compounds in case of kala-azar unresponsive to antimonials JAPI 1991, 39 : 314-16.
5. Goodman Gilman : *The Pharmacological basis of therapeutic*, 10th ed. 2001; 46 : 1295-99. Amphotericin B nephrotoxicity.
6. Sunder S et al. Liposomal Amphotericin B treatment efficacy – Treatment of Indian V.L. with single or multiple infusion of low dose liposomal amphotericin B. Randomised trial. *BMJ* 2001 : 419-22.
7. Bharat & Bhattacharya : Clinical profile of kala-azar in north Bihar 1986 : *J. Ind. M.A.* Vol. 84, No. –2, P. 367-9.
8. TK. Jha, et al : Miltefosine, an oral agent, for the treatment (Phase II), of Indian visceral leishmaniasis; 341 : 1975-1800.
9. S. Sunder et al : Trial of oral miltefosine for visceral leishmaniasis (phase I), 1998, *Lancet*, Vol. 352 : 1821-23.
10. S. Sunder et al : Oral miltefosine for V.L. (phase III) : *N. Engl. Med.* Vol. 342; 1739-46.
11. Manson's Tropical Text Book of tropical Diseases : 65 : 213-28.
12. Impavido Product Monograph 2003 : page 17.
13. Gangeux JP. Treatment of visceral leishmaniasis ; recent modalities. *Presse Med* 1999; 28 : 2057-66.
14. Hansjory E. Miltefosine for visceral leishmaniasis. *New Engl J Med* 2000; 342 : 894-5.
15. Massay HW – Kala-azar, progress against a neglected disease, *N. Engl. J. Med.* 2002; 347 : 1793-94.
16. Murray HW, Delp Etienne S, Visceral leishmanicidal activity of hexadecylphosphocholine (miltefosine) in mice deficient in T cells and activated macrophage microbicidal mechanisms. *J. Inf Dis* 2000; 181 : 795-9.
17. Nelson Text Book of pediatrics 19th edition; 2012: 1186-90.
18. Sundar S et al., Oral miltefosine treatment in children with mild to moderate Indian visceral leishmaniasis *Pediatr Infect Dis J.* 2003 May;22(5):434-8.
19. Bhattacharya SK et al. Efficacy and tolerability of miltefosine for childhood visceral leishmaniasis in India. *Clin Infect Dis.* 2004 Jan 15;38(2):217-21.