

## Oral Miltefosine Treatment in Children With Visceral Leishmaniasis: a Brief Review

Emilio Palumbo

Department of Pediatric, Hospital of Sondrio; Italy

Visceral leishmaniasis (VL) or kala-azar is an infectious disease caused by hemiflagellate protozoan parasites (*Leishmania donovani*) and transmitted to humans by the phlebotomine sandfly. Leishmaniasis is distributed worldwide and 13 million people are estimated to be infected, with about 1.8 million new cases each year. All antileishmanial drugs are toxic and most have to be used parenterally for prolonged period. The therapy has been further complicated by large number of infected children and declining effectiveness of pentavalent antimonial compounds. Although the lipid formulations of amphotericin B are an important advance in therapy, their high cost precludes their use. Miltefosine, a phosphocholine analogue originally developed as antimalignant drug, has been found to be highly active against *Leishmania in vitro* and in animal model. Based on these experiences this drug was tried against human visceral leishmaniasis and found to be highly effective in children. The aim of this review is to evidence the pharmacodynamic and pharmacokinetic characteristics and the safety, tolerance and efficacy of this drug for treatment of visceral leishmaniasis in children.

**Key-Words:** Miltefosine, treatment, children, Leishmaniasis.

Visceral leishmaniasis (VL) or kala-azar is an infectious disease caused by hemiflagellate protozoan parasites (*Leishmania donovani*) and transmitted to human by the phlebotomine sandfly. Leishmaniasis is distributed worldwide and 13 million people are estimated to be infected, with about 1.8 million new cases each year. Approximately 50% of these patients are children. Furthermore, *leishmania* has emerged as an opportunistic pathogen of HIV-infected children.

In recent years, the treatment of VL is far from satisfactory. All antileishmanial drugs are toxic and most have to be used parenterally for prolonged period. The therapy has been further complicated by large number of infected children and declining effectiveness of pentavalent antimonial compounds. Although the lipid formulations of amphotericin B are an important advance in therapy, their high cost precludes their use. Miltefosine, a phosphocholine analogue originally developed as antimalignant drug, has been found to be highly active against *Leishmania in vitro* and in animal model [1,2].

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### Mechanism of Action and Pharmacokinetics

Miltefosine primarily interferes with cellular membranes without interacting with DNA and modulates membrane permeability and fluidity, membrane lipid composition, metabolism of phospholipids and proliferation signal transduction. Miltefosine is well absorbed after oral

administration and is widely distributed. It has a long half-life of about eight days [3]. However, little pharmacokinetic data is available in human beings. In rats, miltefosine is rapidly taken up and accumulates in several internal organs, such as kidney, liver, lung, spleen and adrenal glands. On oral administration of miltefosine 30 mg/Kg of body weight twice per day, concentrations of 155 to 189 nmol/g of tissue are achieved [4]. Miltefosine is degraded slowly *in vivo*, with half-life of 96 hours in mice [5]. It is slowly metabolized by phospholipase to form products such as choline and long chain alcohols that are physiological metabolites and can be recycled into phospholipids [6,7]. The dose of miltefosine is 2.5 mg/Kg/day, preferably in two divided doses or single dose orally for 28 days. The drug is available as 50 mg and 10 mg capsules. *Leishmania* have high levels of ether-lipids and these are mainly found in the glycosylphosphatidylinositol anchored glycoprotein and glycolipids present on the surface of the parasites. Miltefosine acts on key enzymes involved in the metabolism of ether lipids. These enzymes include diethylacetonephosphate acetyltransferase, sn-1-acyl-2-lyso-glycero-phosphocholine and sn-1-alkyl-2-lyso-glycero-3-phosphocholine acetyltransferase. The initial steps in the ether-lipid metabolism occur in glycosomes. Miltefosine does not act on the enzymes involved in the initial steps in ether lipid metabolism in *Leishmania*. However, the metabolism of the latter phosphatidylcholine base intermediates, which are involved in the synthesis of acyl- and alkyl-glycerophospholipids, are associated with glycosomes. Miltefosine inhibits this glycosomal alkyl specific alkyl-specific-acyl CoA acetyltransferase in a dose dependent manner [8].

*In vitro* studies, it is demonstrated that miltefosine stimulates T cells and macrophages to secrete activating cytokines, including interferon gamma (IFN $\gamma$ ) and enhances macrophage production of microbicidal reactive nitrogen and oxygen intermediates. Genetically deficient mice were infected with *Leishmania donovani* to determine these effects *in vivo*.

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Address for correspondence: Dr. Emilio Palumbo. Via Dell'Arcangelo Michele, 71100 Foggia, Italy. Phone: + 39 0881 685023. E-mail: emipalu2003@yahoo.it.

Intracellular killing was retained in T cell deficient mice suggesting that miltefosine induced visceral leishmanicidal effect, which does not require host T cell-dependent or activated macrophage-mediated mechanisms [9].

### Efficacy and Tolerability

Singh U.K. et al. [10] have compared safety, tolerance and efficacy of miltefosine with available gold standard anti-leishmanial drug, amphotericin B, a parenteral formulation in children with VL. Patients were randomized into four groups. In groups 1 and 2, patients were given miltefosine in a dose of 2.5 mg/Kg/day orally to a maximum of 100 mg and groups 3 and 4 received amphotericin B at a dose of 1 mg/Kg/day (total: 15 mg/Kg). All patients were followed up at completion of therapy, at three and at six months after the end of the treatment for clinical response, splenic size and parasitologically. Out of 125 children, 44 were in group 1, 20 in group 2, 38 in group 3 and 23 in group 4; 124 patients had parasitological cure with relapse in one patient of group 1 during follow up. Final cure rate with miltefosine and amphotericin B was 93.2%, 95%, 92.1% and 91.3% in groups 1, 2, 3 and 4 respectively, which are statistically insignificant. Gastrointestinal side effects, as diarrhea and vomiting, were observed in 26 and 23 patients from group 1 and 2, respectively. Miltefosine is safe, well tolerated, and highly effective and has same efficacy as amphotericin B in newly diagnosed and SAG resistant children with visceral leishmaniasis [10].

In an other randomized, open-label study (Sundar S et al., 2006) 299 12 years-old patients or older received orally administered miltefosine [50 or 100 mg (approximately 2.5 mg per kilogram of body weight) daily for 28 days] and 99 patients received intravenously administered amphotericin B (1 mg per kilogram of body weight every other day for a total of 15 injections). In the end of treatment, splenic aspirates were obtained from 293 patients in the miltefosine group and 98 patients in the amphotericin B group. No parasites were identified, for an initial cure rate of 100%. At six months after the completion of treatment, 282 of the 299 patients in the miltefosine group [94% (CI 95%: 91-97)] and 96 of the 99 patients in the amphotericin B group (97%) had not had a relapse; these patients were classified as cured. Vomiting and diarrhea, generally lasting one to two days, occurred in 38% and in 20% of the patients in the miltefosine group, respectively. This study evidenced as miltefosine is an effective and safe treatment for visceral leishmaniasis and it may be particularly advantageous because it can be administered orally. It may also be helpful in regions where parasites are resistant to current agents [11].

Sundar et al. studied 39 children (defined as < 12 years of age) with visceral leishmaniasis, demonstrated by parasites in splenic aspirates, treating them with oral miltefosine daily for 28 days: 21 patients received 1.5 mg/Kg/day (group A); and 18 patients received 2.5 mg/Kg/day (group B). All patients were parasitologically negative and symptomatically improved by the end of therapy at day 28 of therapy; the initial

parasitologic cure rate was 100%. Two patients in each treatment group relapsed with fever, splenomegaly and parasite-positive splenic aspirates by the end of the 6-month follow-up. The protocol final clinical cure rate was 19 of 21 = 90% in group A and 15 of 17 = 88% in group B. Miltefosine was well-tolerated. As the adult experience, gastrointestinal adverse events were seen: 33 and 39% of children experienced vomiting and 5 and 17% experienced diarrhea in groups A and B, respectively, but all episodes were mild to moderate in severity and commonly lasted less than one day without symptomatic treatment. In this study, oral miltefosine was safe and had approximately 90% of effectiveness in this initial clinical trial of childhood visceral leishmaniasis [12].

Bhattacharya et al. evaluated the use of the adult dosage of miltefosine (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 at day 6. The other 79 patients demonstrated no parasites after treatment, had marked clinical improvement, and were deemed initially cured. Three patients had relapsed, and one patient was lost not found 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 approximately 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 [13].

### Conclusion

Miltefosine, a phosphocholine analogue originally developed as antimalignant drug, has been found to be highly active against *Leishmania in vitro* and animal model. Based on these experiences, this drug was tried against human visceral leishmaniasis and it was found to be highly effective in children. Studies in literature evidenced as miltefosine is an effective and safe treatment for visceral leishmaniasis (approximately 90% effective in childhood visceral leishmaniasis) and it may be particularly advantageous because it can be administered orally. It may also be helpful in regions where parasites are resistant to current agents.

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