Orally Effective Drugs for Kala-azar (Visceral Leishmaniasis): Focus on Miltefosine and Sitamaquine

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Abstract
Currently there are no effective orally administered drugs or visceral leishmaniasis or kala-azar, a parasitic disease affecting about 0.5 million people a year, majority of whom are in India and adjacent areas of Nepal. Symptoms of affected patients are fever, cachexia, hepatosplenomegaly and pancytopenia. The disease is usually fatal, if left untreated.

Traditionally kala-azar is treated with four weeks of injections of sodium stibogluconate, a pentavalent antimonial. However, this treatment has not only shown resistance in 37-64% patients of the current Indian epidemic in Bihar (the epicentre) but also life-threatening cardiotoxicity in 7-10% and treatment-related deaths in 5-10% cases, besides being unsuccessful at times. Parenteral amphotericin B is used as a secondary agent that shows 95% effectiveness but its toxicity and high cost of even the well tolerated liposomal complex precludes its wide use in the developing countries, where the disease is present in epidemic proportions.

Recently, miltefosine (hexadecylphosphocholine), a compound originally developed as an antitumour agent has been shown to be an orally effective drugs against kala-azar. All clinical trials with this drug are conducted in India in patients of visceral leishmaniasis. A regimen of 100 mg per day or 50 mg twice daily for 3-4 weeks was observed to produce a cure rate of 100%. Gastrointestinal side effects were frequent (62%) but no patient discontinued the therapy. A phase III trial involving 300 HIV-negative adults and adolescents is underway in India and the drug is hoped to be licensed in the next 2-3 years.

Few studies of phase II clinical trials mainly conducted in Kenya with another drug, sitamaquine or kalazaquine (WR 6026), an 8-aminoquinoline has also shown promise as an orally effective agent (in a dose of 1 mg/kg/day for two weeks) for visceral leishmaniasis.

These studies with two orally effective compounds, it appears, 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.

INTRODUCTION

Out of the three clinical manifestations of leishmaniasis-cutaneous, mucocutaneous and visceral, the latter is a potentially fatal form of the disease and has more severe public health consequences in several parts of the world. Cutaneous and mucocutaneous leishmaniases are caused respectively by *Leishmania braziliensis* and *L. tropica* (and also by over a dozen other species in different parts of the world), whereas visceral leishmaniasis is caused by *L. donovani*. Visceral leishmaniasis, although has been reported in 66 countries to affect 500,000 persons worldwide per year, 90% of these patients are in India, Nepal, Bangladesh, Brazil and Sudan.1,2 In the Indian subcontinent, the disease is called “kala-azar” a Hindi word for black fever or black sickness and has been endemic for many decades. However, it has re-emerged in the last three decades from near eradication and is a major health problem in Bihar, West Bengal, Eastern Uttar Pradesh and neighbouring areas of Nepal. The latest in the series of epidemics of kala-azar, centered in north-eastern India, flared up in 1970s, probably because of the discontinuation of insecticide spraying for malaria which also affects the ‘Phlebotomus’ sandfly that transmits the disease.
in this part of the world. The epidemic continues to generate as many as hundreds of thousands of cases annually. Globally, the disability-adjusted-life-years (DALYs) lost in 1999 due to kala-azar were estimated to be 1.20 million for men and 0.78 million for women. These epidemics underscore the need for therapy that not only is highly effective and safe even in patients who are critically ill from leishmaniasis and co-existing diseases, e.g. tuberculosis, dysentery or AIDS (where immunocompetence is very low) but also is easily administered and affordable for treating a large number of impoverished patients.

**NEW HOPE FOR ORAL AGENTS**

Few clinical trials, mainly conducted in the 1990s, have opened new vistas in the oral therapy of visceral leishmaniasis, which before 1994 was centered mainly on the drugs—sodium stibogluconate (a pentavalent antimonial), pentamidine isothionate and amphotericin B, all of which are highly toxic and need to be given for prolonged periods by parenteral route. In an attempt to improve the tolerability of IV infusion in 1997, liposome encapsulated amphotericin B was licenced for visceral leishmaniasis which had an added advantage of reduced toxicity and targeted delivery of the drug to the reticuloendothelial cells in the liver and spleen. In spite of the advantages of liposomal formulation, amphotericin B could not be successfully developed in the developing world due to its high cost and need for parenteral administration.

On the basis of the research into the host genetics that showed type-1 T helper (Th-1) response to be associated with the resistance and Th-2 response to susceptibility to leishmaniasis, recombinant interferon-gamma (IFNγ) and granulocyte-macrophage colony stimulating factor (GM-CSF) were administered parenterally (IM) with antimonial therapy to reduce its dose (and thus the toxicity) without compromising the effectiveness. Such a combined pharmacotherapy, although showed promising results, could not be recommended for routine use because of cost. In several studies paromomycin, an aminoglycoside, (aminosidine) administered parenterally alone or in combination with stibogluconate was found to give better results than the latter alone but again a long duration of treatment with a need for parenteral injections and variable effects in different species of *Leishmania* proved to be limiting factors in its use. Traditionally, therefore due to low cost, pentavalent antimonial agents have been the mainstay of treatment of visceral leishmaniasis until the end of the last century.

With the continued efforts of the tropical disease research (TDR) program of the World Health Organization (WHO) which felt the need for new drugs for visceral leishmaniasis that would be effective orally, affordable and relatively free of severe side effects—miltefosine, a new compound has been discovered for oral treatment of kala-azar. Oral treatment for visceral leishmaniasis has been long sought, and hopes are high that miltefosine will be the first candidate in this respect. It is more so because decades of earlier work with azoles, such as ketoconazole and fluconazole and other assorted agents, like roxithromycin and allopurinol had so far failed to discover an effective agent that could be given orally for kala-azar and other forms of leishmaniasis.

**MILTEFOSINE, AN ALKYLPHOSPHONOID (ALKYLPHOSPHOCHOLINE)**

Based on the pioneering researches of Crofts *et al* in 1987, where several esters of alkylphosphorylcholines which were initially developed as antitumour agents, and shown to be active against *L. donovani* promastigotes, a group of four alkylphosphonoids were identified for further studies. They were ilmofosine, edelfosine, miltefosine and SR62-834. These compounds developed by different pharmaceutical companies, showed remarkable activity against intracellular amastigotes *in vitro*. Oral treatment of mice infected with *L. donovani* or *L. infantum* with miltefosine (chemical name: hexadecylphosphocholine, a phosphorylcholine ester of hexadecanol) was found to be superior to sodium stibogluconate in reducing parasite load in liver and spleen. In these studies, among all organs the maximum concentration of miltefosine was found to be in liver and spleen, the two destination organs for visceral leishmaniasis following an oral dose. Because of this reason, the drug was observed to exert 600 times better anti-amastigote effect in these organs than antimonial compounds.

**Results of Clinical trials of miltefosine in human visceral leishmaniasis**

Based on the previous preclinical work and availability of pharmacokinetic and safety data in humans, since the drug was already approved for clinical trials in patients of cancer, four Phase I/II clinical trials were conducted in India employing a total of 249 patients with miltefosine in visceral leishmaniasis. These trials have shown the drug to be orally effective and tolerated by majority of the leishmania-infected population. The third investigation in this series of clinical trials, a Phase II dose-finding study by Jha *et al* was conducted at three centres in India in 1998–1999 and is the largest trial published to date. The study was an open-label investigation employing a total of 120 patients, 71% of whom were males ranging in age from 12-50 years. All had anorexia, fever and splenomegaly with at least (2+) leishmania in a splenic aspirate. Miltefosine in the form of 50 mg capsule was administered orally in different dosages to sequentially enrolled four cohorts of 30 patients each with a snack of bread and butter. This was done to minimize the upper gastrointestinal (GI) side effects on the basis of prior knowledge that the presence of food does not limit GI absorption of the compound. Cohort 1 received 50 mg daily for six weeks (total dose: 2100 mg); cohort 2 received 50 mg daily for one week followed by 50 mg twice daily (100 mg/day) for three weeks (total dose: 2450 mg); cohort 3 received 100 mg daily for four weeks (total dose: 2800 mg); and cohort 4 received 100 mg daily for one week followed by 50 mg thrice a day (150 mg/day) for three weeks (total dose: 3850 mg). The parasitological cure was
defined by the absence of parasites in a splenic aspirate obtained after two weeks of completion of treatment. In all 120 patients there was an initial parasitological cure. Clinical and parasitological relapses were, however, observed in six patients. The remaining 114 patients did not show any relapse for the six months of observation period, thus registering a cure rate of 95% (95% confidence limits (CL): 89-98%). The final cure rate for all the cohorts was between 93 and 97%. The cure rate for patients who had never received the therapy with sodium stibogluconate was virtually identical to that for patients in whom previous therapy with antimonial compound had failed, i.e. miltefosine was as effective in those in whom an antimonial resistance had already been observed. In this study, miltefosine, at a dose of 100 mg daily for four weeks showed an effectiveness of 97% (95% CL: 83-100%) in a 30 patient cohort (29 of 30 patients in cohort 3) out of total 120 patients. Because the infection was cured in five of five and 16 of 16 patients in two previous trials by the same group of authors,25,26 the total cure rate with this dose (100 mg/d x 4 weeks) regimen was found to be 50 of 51 or 98% (95% CL: 90-100).27

With this dose regimen, the adverse effects associated with the miltefosine have usually been tolerable and reversible. Based on the frequency of GI side effects, however the therapeutic window of the drug appears to be narrow. GI symptoms, such as vomiting and diarrhea although common, were seen in 62% of patients (range 20-100%) and occurred 30 min to two hours following the drug administration. These symptoms were observed 13% of days on which patients received the drug, i.e. on an average of four of the 28 days of their therapy and the symptoms were seen in patients of all cohorts irrespective of the quantum of administered dose. No patient, however either lost weight during or discontinued the therapy because of GI episodes. In some patients, hepatotoxicity and nephrotoxicity were observed but these were reversible and treatment could be continued in most of them. In the two patients in whom treatment had to be discontinued, the serum activity of aspartate aminotransferase and creatinine level rapidly returned to normal. Although the toxicity associated with miltefosine appeared to be milder than that seen with some parenteral therapies, GI symptoms could be of more consequence in severely ill patients, such as those who are malnourished or dehydrated than they were in patients included in the clinical trials. As miltefosine has been shown to be teratogenic in animals, it should not be used in pregnancy.27

Because of the propensity of GI side effects which have no bearing to the administered dose, the fourth trial was undertaken to see whether the dose of 100 mg/day can be given in two divided doses and the duration of therapy can further be reduced.28 The treatment was initiated in three groups of 18 patients each (total 54), given 50 mg twice daily for 14 days (Group A), 21 days (Group B) and 28 days (Group C). Cure was achieved in 89% of patients in Group A and in 100% of both Group B and Group C. Adverse effects were primarily mild and self-limited. Authors concluded that a 21-day, 50 mg twice daily miltefosine regimen combines high level efficacy, convenient dosing and a relatively short duration.28

On the basis of the overall results of four clinical trials of miltefosine in kala-azar by the same group of workers and in view of the observations of few relapses, effectiveness and side effects vis-a-vis different dose regimens used, the authors have recommended a dose of 50 mg twice daily or 100 mg per day (approximately 2-2.5 mg/kg/day) for 3-4 weeks27-28 for the subsequent Phase III trials and eventual regulatory approval.29 It was suggested that the dose should be adjusted to the patient’s weight so that a dose of 4 mg/kg/day is not exceeded.29 The hopes from miltefosine are high and a clinical trial involving 300 HIV-negative adult and adolescent patients of Indian visceral leishmaniasis is already underway.30 However, the future and ongoing clinical trials have to address the following questions: a) Will the drug continue to be highly effective and acceptably tolerated when more and a large variety of patients are treated?, b) To what extent will the miltefosine therapy be effective against syndromes caused by 21 leishmanial species in 88 countries?, c) Will miltefosine become one more option for treating a particular subgroup of patients, or will it become the drug of choice for most patients who require systemic antileishmanial therapy?, d) How will it fare in HIV-infected patients?

Results of miltefosine in experimental cutaneous leishmaniasis

Studies on the effectiveness of topical miltefosine in other leishmanial syndromes, including American cutaneous leishmaniasis, are in progress and the results of one recently published experimental study in mice has shown the drug to reduce the parasite burden in cutaneous leishmaniasis induced by L. mexicana and L. major.30 The treated mice healed their lesions much faster than the untreated infected controls. On the basis of the encouraging results of this study, the authors have suggested that the clinical application of miltefosine (miltex: liquid preparation for local use) for the treatment of cutaneous leishmaniasis may be highly efficient because humans do not show a relapse once the cutaneous lesions are healed.

Sitamaquine (Kalazaquine; WR6026), an 8-Aminoquinoline

A Phase II clinical trial conducted in Kenya in 1994 showed the effectiveness of oral sitamaquine (kalazaquin) in visceral leishmaniasis.31,32 In this trial, one of the eight patients treated with the drug at dose of 0.75-1 mg/kg/day for two weeks was cured and 4 of 8 patients treated with a dose of 1 mg/kg/day were cured. This drug is still being evaluated as an orally effective drug for visceral leishmaniasis and to date 42 patients have been treated with various daily doses in excess of 1 mg/kg/day.33 However, the data on the safety and effectiveness of different regimens have not been made public. It is however, hoped that sitamaquine will be an alternative drug to miltefosine to be used in those, where the
latter cannot be used due to GI intolerance or, where it does not show a cure, or resistance develops to it. Further experimental tests are needed to determine whether the two drugs in combination would have a synergistic effect, since miltefosine, being an antitumour agent acts by impairing the integrity of cell membranes and this would increase the availability of sitamaquine as it needs to cross the cell membrane to reach its site of action in the chromosome. 

If a synergy is shown, it may be possible to reduce the doses and potential toxicity of these two orally effective antileishmanial medications. There is also a need to study the effect of both of these drugs in patients with AIDS.

**CONCLUSION**

The study of success in achieving a cure in patients of kala-azar by miltefosine and sitamaquine, the fruits of careful observations of basic and clinical scientists, have not only paved the way for the long-awaited orally administered drugs but also have opened a path for many more to come. Phase III clinical trials with miltefosine are already on under the aegis of TDR programme of WHO. It is hoped that in the next 2-3 years, miltefosine will be a licensed antileishmanial agent and will be affordable to those who need it most. With the availability of more data on its safety in large and varied population of patients and mechanism of action, the days are not far where there will be a fundamental change in the approach to the treatment of visceral leishmaniasis and perhaps other leishmanial syndromes. With these developments, one can envisage a future scenario where parenteral therapy for kala-azar would rarely be needed.

**REFERENCES**


