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Oral miltefosine for the treatment of Indian visceral leishmaniasis

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Summary Large-scale antimony resistance in the treatment of visceral leishmaniasis (VL) in north Bihar, India, has led to the development of miltefosine as an alternative therapy. In a pilot study and later in three Phase II studies involving 249 patients, oral miltefosine, 100—150 mg/day for 28 days, was shown to cure ~90% patients with reasonable safety. In the pivotal Phase III trial, 299 patients were treated at three centres with amphotericin B as the comparator drug (99 patients). In this trial 38% and 20% patients had mild to moderate vomiting and diarrhoea respectively, similar to previous studies. Asymptomatic transient elevation of hepatic transaminases and mild renal dysfunction were observed in 15% and 10% patients respectively. The final cure rate was 94% with miltefosine and 97% with amphotericin B; based on these results, the drug was approved in India. Subsequently in two paediatric studies involving 119 patients in the age group of 2—11 years, the safety and efficacy of miltefosine (2.5 mg/kg daily for 28 days) was established with a cure rate (94%) similar to that seen in adults. Miltefosine is the first oral antileishmanial drug with a high degree of safety and efficacy for the treatment of VL.

1. Introduction

Visceral leishmaniasis (VL) is a disseminated intracellular protozoal infection caused by the *Leishmania donovani* complex. It is uniformly fatal unless treated, but the treatment options for VL are limited and consist essentially of parenteral drugs. Pentavalent antimonial (Sb^v) compounds have been the foundation of treatment for all forms of leishmaniasis in every endemic region for seven decades. Due to dwindling antimonial efficacy in the state of Bihar in India, the treatment regimen was periodically revised resulting in recommendation of a 10-fold higher total dose (Thakur et al., 1984, 1988, 1991a, 1991b). However, this elevation of dose resulted only in a temporary reprieve and the proportion of patients responding to Sb^v declined dramatically. In various reports, response to Sb^v was noted in only 35—47% of patients (Sundar et al., 2000a; Thakur and Narayan, 2004). Pentamidine, a diamidine compound, was used for a brief period of 10 years after which it was realized that its efficacy had decreased too, and it caused serious side-effects, such as insulin-dependent diabetes mellitus (Jha et al., 1991; Thakur et al., 1991). Pentamidine went out of favour and, thus, out of use in India for treatment of VL. Amphotericin B infusions remained the only treatment of VL for these

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patients coming from regions with high levels of Sb^v resistance (Mishra et al., 1994; Thakur et al., 1993), but this also required hospitalization for up to 5—6 weeks. Limited hospital beds in the region severely limit the capacity to treat all patients, and patients have to wait for weeks to months to be accommodated.

Oral medications have an obvious appeal with ease of administration, domiciliary treatment, no hospital costs, no limitation by bed capacity, etc. Thus, the quest for an effective oral antileishmanial drug has been ongoing for a long period. Drugs such as allopurinol, ketoconazole, triazoles (fluconazole), atovaquone, have been tested either alone or in combination for the treatment of VL; however, they had either no effect or only a partial effect (Berman, 1997).

Miltefosine, an alkyl-phospholipid (hexadecylphosphocholine) was developed as an oral anticancer drug against solid tumours, but due to treatment-limiting gastrointestinal adverse events, its development as a systemic antineoplastic agent was abandoned, although later it was approved as a topical formulation for treatment of cutaneous metastases of breast cancer (Dummer et al., 1993; Verweij et al., 1992). It was discovered in both in vitro and animal studies that miltefosine has excellent antileishmanial activity (Croft et al., 1987; Kuhlencord et al., 1992). With the backdrop of its oral antileishmanial activity in animal studies, the stage was set to initiate human trials to study the efficacy of miltefosine in VL. Between 1996 and 2004, eight clinical trials ranging from Phase I/II to Phase IV were done; five multicentre trials were spread over 2 to 15 centres. In this article, we provide an account of the studies leading to successful registration of this compound for the treatment of VL in India.

2. Pilot Phase I/II safety and efficacy dose escalation trial

The first clinical trial was an exploratory dose-ranging study, and was carried out at Banaras Hindu University, Varanasi, India, and its field site in Muzaffarpur, Bihar, in collaboration with Asta Medica (manufacturers of the drug) in Germany and Cornell University Medical College, New York, USA (Sundar et al., 1998).

2.1. Patients and methods

Patients were eligible if they had clinical features of VL (kala-azar) with positive parasites (amastigotes) in a splenic aspirate smear. All patients were males between 14 and 65 years of age, and had no cardiac or retinal disease. Since this drug is teratogenic and causes fetal absorption, malformations and abortions, only males were included in this preliminary study. Patients with serious concurrent infection or significant haematological or biochemical abnormalities were excluded.

The six treatment groups with five patients each are shown in Table 1. Each patient was treated for 4 weeks with total doses that ranged from 50 mg on alternate days to 250 mg daily.

In addition to daily clinical and weekly laboratory assessment, parasitological assessment by splenic aspiration was done on day 14, and if parasite-free at that time, not repeated on day 28. Splenic smears were graded for parasite density on a log scale. Since miltefosine produced retinopathy in animals as well as reversible abnormalities of retinal pigment in early human studies (Theischen et al., 1993), ophthalmological evaluation was done at baseline and at weekly intervals until the end of treatment. At day 28, after clinical and laboratory assessment, and if needed, parasitological assessment, the patients were sent home and were followed up.

2.2. Definitions of cure

Apparent cure (initial cure) was defined as resolution of fever, regression of spleen and clinical improvement with absence of parasites in splenic smears. Definitive cure (final cure) was defined as absence of signs and symptoms of kala-azar at the 6-month evaluation and parasite-free bone marrow aspirates. In this trial, an additional criterion of being free of signs and symptoms of relapse at 8 months after the end of treatment was also applied.

2.3. Efficacy

There was prompt response to the drug, and 53% patients became afebrile within 7 days. On day 14, 93% patients had no detectable parasites in repeat splenic smears. All patients were parasite-free on days 14 or 28, that is, they had achieved apparent cure by the end of treatment. However, in groups 1 and 2, in which the drug was used on alternate days, 7 (70%) of 10 patients relapsed. Except for one patient in the 150-mg group who relapsed, all remaining patients continued to be free of signs and symptoms and achieved definitive cure (Table 1).

Table 1 Pilot study: cure rates

Group (*n*)	Dose (mg/kg)	Frequency	Apparent cure on day 28	Definitive cure at 8 months
1 (5)	50	Alternate day	5	2
2 (5)	100	Alternate day	5	1
3 (5)	100	Daily	5	5
4 (5)	150	Daily	5	4
5 (5)	200	Daily	5	5
6 (4)	250	Daily	4	4