

Miltefosine in the treatment of leishmaniasis: Clinical evidence for informed clinical risk management

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Abstract: Visceral leishmaniasis (VL) is a life-threatening disease. Traditional treatment with pentavalent antimony injections has become ineffective in the area with the world's highest prevalence of disease (North Bihar, India) and is becoming less effective elsewhere as well. A replacement is needed, best if it can be given to more patients outside the hospital. Miltefosine is the first oral drug registered for VL. Given daily under medical supervision for 4 weeks, it cures 94% of patients (both children and adults) and is reasonably safe. Miltefosine has great potential for improving access to treatment and overall control of VL and will be critical in the VL elimination campaign in the Indian subcontinent, but must be safeguarded or will be lost if misused. Its main limitations are adherence (and hence potential for selection of drug resistant parasites) and teratogenicity (pregnancy must be avoided during treatment and the following two months). This calls for responsible deployment, setting in place mechanisms to protect female patients in child-bearing age, monitoring effects and optimizing adherence in real-life conditions through directly observed therapy. One option to protect the useful life-span of miltefosine consists in shortening treatment duration by combining it with another drug.

Keywords: miltefosine, visceral leishmaniasis, kala-azar, India

Introduction

Of all forms of leishmaniasis, visceral leishmaniasis (VL, kala-azar) is the most severe, and can be fatal without treatment. VL occurs worldwide, but >90% of the cases are in five countries: north-eastern India, Bangladesh, and Nepal in the Indian subcontinent, Sudan in Africa and north-eastern Brazil in South America (WHO 2000). India alone shares almost 50% of the world's burden of disease. Here, pentavalent antimony has become ineffective in the 1990's in most of the high-burden areas of North Bihar except few eastern districts, and must be replaced. However, none of the traditional alternatives was satisfactory: pentamidine is no longer used; amphotericin B deoxycholate is impractical (hospitalization and several infusions required, risk of immediate and delayed toxicity) and severely dependent upon the availability of hospital beds; and liposomal amphotericin B is unaffordable. A replacement was needed urgently.

Oral drugs are very convenient as the need for hospitalization and related costs are eliminated, home treatment is possible, coverage and access is better. Past attempts to develop oral drugs have failed with allopurinol, ketoconazole, fluconazole, and atovaquone.

Miltefosine (hexadecylphosphocholine, HePC), an alkyl phospholipids compound, was originally intended for breast cancer and other solid tumors. However, it could not be developed as an oral agent because of dose-limiting gastro-intestinal toxicity, and only a topical formulation is approved for skin metastases (Verweij et al 1992; Dummer et al 1993). Then came the evidence of excellent antileishmanial activity

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both in vitro and in experimental animals (Croft et al 1987, 1996; Kuhlencord et al 1992). This, and the fact that the drug was already approved for human trials, prompted the clinical assessment of oral miltefosine in human visceral leishmaniasis in 1996. Clinical trials were aimed first at finding an effective and safe treatment schedule (phase I/II) and then confirming its properties in comparative Phase III studies. The initial evidence of clinical efficacy came from the collaborative efforts of Banaras Hindu University, Varanasi India, Cornell University, New York and Asta Medica, Frankfurt (the manufacturer of the drug). The results of these studies resulted in the involvement of WHO/TDR, Geneva and the Indian Council of Medical Research (ICMR), New Delhi along with Asta Medica, which by then had become Zentaris. The results of these clinical studies, along with chemistry, manufacturing and non-clinical data, were compiled in a dossier submitted by the manufacturer for licensure (Berman 2005; Sindermann and Engel 2006).

Mechanism of action

Miltefosine is effective in vitro against both promastigotes and amastigotes of various species of *Leishmania* (Croft et al 1987, 1996; Escobar et al 2002), and also other kinetoplastidae (*Trypanosoma cruzi*, *T. brucei*) and other protozoan parasites (*Entamoeba histolytica*, *Acanthamoeba*)

Like other alkyl-lysophospholipids the mechanism of action of miltefosine is only partly known; most data are in tumor cell lines as an anti-cancer agent where these compounds can trigger programmed cell death (apoptosis) (Wieder et al 1999; Rybczynska et al 2001; Wright et al 2004). Extension to *Leishmania* has come from similarities between metazoan and protozoan apoptosis, and work on drug-resistant parasites.

Evidence of apoptosis-like death has been shown in *L. donovani* promastigotes treated with miltefosine (Paris et al 2004; Verma and Dey 2004). However, how this family of compounds induces apoptosis in either mammalian cells or parasites is not entirely clear. A prevalent though not yet fully established hypothesis is inhibition of the synthesis of phosphatidyl choline (PC), an essential element in the synthesis and integrity of cellular membranes and a source of signaling molecules (Arthur and Bittman 1998; Cui and Houweling 2002; Wright et al 2004).

In order for these effects to manifest with lysophosphatidylcholine analogues, intracellular accumulation is required (Gajate and Mollinedo 2002); resistant cell lines prove to accumulate less drug (Perez-Victoria, Castanys et al 2003). Drug accumulation is a three-step process which appears

to be common to eukaryotic cells, whereby the drug binds to the cell plasma membrane, enters the cell and reaches its target.

A current hypothesis is that phospholipids and phosphocholine derivatives such as edelfosine and presumably miltefosine move across membranes (from the outer to the inner layer) via inward translocation (also termed inward transbilayer movement, or flip), an energy-dependent, protein-mediated process.

For drug binding, the phospholipid composition of cell membranes seems critical: miltefosine resistant *L. donovani* have altered fatty acid elongation and unsaturation, and the C-24-alkylation of sterols (Rakotomanga et al 2005). For transport across the membrane, a putative transporter was recently identified; a *Leishmania* P-type ATPase gene, belonging to the aminophospholipid translocase (APT) sub-family termed LdMT (*L. donovani* Miltefosine Transporter) has been cloned. LdMT is expressed in the plasma membrane where it mediates the translocation of phospholipids across the plasma membrane in *Leishmania* parasites (Perez-Victoria, Gamarro et al 2003).

As *Leishmania* amastigotes reside inside macrophages, membrane binding and flip-flopping will have to occur multiple times across the various membranes until equilibrium is reached. *Leishmania* parasites do not seem to have the ability to metabolize miltefosine, but can extrude via either exocytosis or protein-dependent flop across the plasma membrane (possibly by proteins of the ABC transporters family, such as P-glycoprotein (mdr1) (Perez-Victoria et al 2001).

Clinical studies

Clinical studies for VL in adults

Phase I/II

The first clinical study was a phase I/II dose escalation trial in which miltefosine was used in a daily dose ranging from 50 mg on alternate days to 250 mg daily for 28 days. In this study only adult males (aged 14–65 years) were enrolled in six cohorts of five patients each. Those with hepatic, cardiac or retinal diseases or other serious concurrent disorders were excluded. Patients could be enrolled in the next dose level only after three patients in the previous group had completed 28 days of therapy without developing serious side effects. The maximum tolerated dose level was defined as one dose level below the dose not tolerated by at least three of the five patients. Initial cure was defined as absence of fever, reduction in spleen size and absence of parasites in splenic aspirate. For definite cure patients had to be asymptomatic with parasite free splenic/bone-marrow aspirate smear at

six month follow-up and absence of signs and symptoms of relapse two months later (eight months after treatment). In the later trials of miltefosine, final cure was defined as initial cure followed by absence of signs and symptoms of relapse at six month follow up.

Fourteen (47%) patients had received previous antileishmanial treatment, and either failed to respond or relapsed after treatment with antimonials (20 mg/kg/day for ≥ 28 days). Overall clinical and parasitological responses to miltefosine were rapid in all groups. On day 14, 28 of the 30 patients had parasite-free splenic aspirate, and the majority of patients had become afebrile by day 7.

Tolerability. As expected, gastrointestinal (GI) symptoms were the principal toxic effects: 26 (87%) patients had one or more episodes of both vomiting and diarrhea ($n = 15$; 50%), nausea and vomiting alone ($n = 9$; 30%) or diarrhea alone ($n = 2$; 7%). 72% episodes of vomiting lasted 1 day or less, and 53% involved a single episode during the entire treatment period; similarly 65% of the episodes of diarrhea lasted 1 day or less, and 33% involved a single episode. Severe vomiting or diarrhea (grade III) occurred in five patients (one on 200 mg and four on 250 mg miltefosine daily). In groups 1–4 (50 mg e.o.d., 100 mg e.o.d., 100 mg q.d., 150 mg q.d.) the GI side-effects were grade I and II (mild or moderate) only, and did not require treatment withdrawal. The maximum tolerated dose in this study was 200 mg q.d. One patient in group 6 (250 mg q.d.), aged 35 year, died on day 21. He was responding to miltefosine with decrease in fever, spleen size and splenic aspirate score and weight gain, however, his serum creatinine rose from 88.4 $\mu\text{mol/L}$ to 274.04 $\mu\text{mol/L}$ on day 14, and was removed from the study on day 19 because of profuse diarrhea. He died unexpectedly 2 days later despite supportive care (Sundar et al 1998).

Efficacy. Eight patients, who had completed 28 days of therapy, relapsed; seven were from lower dose alternate day regimen (3 and 4 from group 1 and 2 who received 50 and 100 mg of the drug on alternate days, respectively), and one from group 4. These were retreated successfully with amphotericin B (1 mg/kg \times 15 infusions e.o.d.). The remaining 21 were healthy without any sign or symptoms of the disease, and each had a parasite free smear bone marrow aspirate smear at 6 month follow-up. Two months later, all 21 patients were well, including 12 who had failed on a previous course with sodium stibogluconate (Sundar et al 1998).

This study though in a small number of patients clearly indicated that: (i) oral miltefosine was clearly and rapidly active against Indian VL; (ii) a daily dose up to 150 mg was well tolerated; (iii) 90% (9/10) on 100–150 mg/day group had

long term cures; (iv) as expected the main toxic effects were GI; no retinal toxicity was seen; however, (v) nephrotoxicity occurred in one patient on the high dose (250 mg/day).

This preliminary study allowed selecting a dose of 100–150 mg per day as reasonably effective and safe.

Phase II studies

Three phase two studies were done.

Phase II dose-finding study

First was a three arm comparative trial including both sexes; patients were randomized to receive 28 days of oral miltefosine treatment at 100, 150 or 200 mg per day. Women of childbearing age were required to use adequate contraception during and for two months after the treatment. While a sample size of 18 patients was estimated for each of the three treatment arms, the eighth, ninth and tenth subjects in the 200 mg per day group developed serious adverse reactions, and after an interim review, this arm was closed. All subsequently enrolled patients were randomized to receive 100 or 150 mg per day until the target number was reached in these dose groups. Seventeen (38%) of 45 enrolled patients had failed to respond to previous antileishmanial treatment.

Tolerability. Treatment was discontinued in five patients before day 14. One patient receiving 100 mg/day withdrew on day 5 and was lost to follow-up; four others (one receiving 150 mg/day and three on 200 mg/day) were removed from the study on days 7–11 because of grade III toxicity, one each because of vomiting (150 mg/day), diarrhea, hepatotoxicity and diarrhea, and nephrotoxicity; two additional patients (one each on 100 and 150 mg/day) were removed on day 15 and 17 because of grade III vomiting or diarrhea. However, these six continued to improve clinically and did not require rescue treatment.

As anticipated, the primary adverse reactions to miltefosine were gastrointestinal: vomiting alone ($n = 13$), diarrhea alone ($n = 5$) or both reactions ($n = 18$). Vomiting was mild in most subjects and there were only 1–2 episodes of vomiting during the entire duration of treatment for most subjects except two in whom it was severe. A similar pattern was observed with diarrhea with all but three patients having mild episodes.

Thirteen (29%) patients developed reversible nephrotoxicity, mild (grade I) in 11 and moderate (grade II) in one, returning to baseline values while treatment was continued. In one patient on 200 mg/day, creatinine and BUN concentration rose from 1.0 and 13 mg/dl to 8.0 and 62 mg/dl, respectively, on day 7 (grade III toxicity), and treatment was

stopped; 1 week later the levels returned to 1.2 and 17 mg/dl respectively. In 12 (27%) patients elevation of hepatic transaminases was seen, and in 11 it promptly returning back to normal. In one patient (on 200 mg/day miltefosine) severe rise in enzymes necessitated stoppage of treatment (Sundar et al 1999).

Efficacy. Overall clinical and parasitologic responses to miltefosine were rapid. At six months, 44 patients (98%, CI 88%–100%) were complete responders (definitive cures) including the six treated for 7–17 days. The only subject considered as treatment failure was the one on 100 mg miltefosine/day who was lost to follow-up. These results reconfirmed that 100–150 mg/day of miltefosine for 28 days was likely to be an effective therapeutic option for VL, including antimony-unresponsive infections (Kumar et al 1999).

Phase II multicentre dose and schedule finding study

This trial was done in three centers testing four regimens, of which two with a lower dose during first week, followed by full doses in the next three weeks.

Tolerability. GI side effects were frequent (62% of patients) but mild to moderate in severity (grade I or II) and no patient had to discontinue therapy. There was a mean weight gain of 2.0 kg during therapy. Liver and kidney function tests were occasionally and rarely abnormal, respectively. In the two cases of premature termination of therapy due to elevated levels of SGOT and creatinine, respectively, values rapidly normalized after therapy had been stopped (Jha et al 1999).

Efficacy. All the 120 total patients enrolled were initially cured when tested 2 weeks after the end of therapy. The final cure rate was 93% (95% CI 78–99) in patients either receiving 50 mg/day for six weeks or 50 mg/day for the first week followed by 100 mg/day for the next three weeks, and was 97% (95% CI 83–100) in patients on 100 mg/day or 100 mg/day for the first week followed by 150 mg (Jha et al 1999).

Phase II duration ranging trial

In view of the kinetics of the response to miltefosine, which included parasitological cure being observed in most of the patients at day 14, and the experience in the 10 subjects cured after abbreviated therapy, courses of treatment shorter than 28 days were also considered. To test this hypothesis, we selected the best tolerated daily regimen (100 mg) and administered it for 2, 3 or 4 weeks to 18 patients each.

Except for one subject on the 2 week regimen, all 53 others improved and parasite were undetectable in splenic smears, and thus were labeled as apparent cure. During the

six months of follow up, one patient treated for two weeks relapsed, while the remaining 52 patients remained negative. The final cure rates were 16/18 (89%, CI 65%–99%) on the 2-week regimen, and 18/18 (100%, CI 85%–100%) in those treated for either 3 or 4 weeks. Although the sample size was small, this study indicated that miltefosine for 2 or 3 weeks would be able to cure $\geq 90\%$ patients (Sundar et al 2000).

Phase III pivotal study

The above mentioned studies allowed to select the optimal dose, which was compared, in a pivotal phase III study with the aim to obtaining regulatory approval for the indication, to the most effective standard treatment of VL ie, amphotericin B. This was a multicentric, randomized, open label study enrolling 299 VL patients (12 years and above) on miltefosine at the dose of 50 mg (if weighing ≤ 25 kg) or 100 mg (>25 kg) daily for 28 days, and 99 patients on amphotericin B at the dose of 1 mg/kg every other day for a total of 15 infusions.

Tolerability. Vomiting and diarrhea were the commonest adverse effect with Miltefosine (occurring in 38% and 20% patients respectively.) In most cases, the event was self limiting, lasting for 1–2 days and did not require withdrawal of treatment. Transient rise in transaminases occurred in 15% of the patients in the first two weeks of treatment, and then the levels started normalizing by the end of the 2nd week. Renal dysfunction with mild rise in blood urea and serum creatinine was observed in 10% of the patients but it did not lead to withdrawal of drug and normalized gradually during the course of treatment.

Overall, nine patients in Miltefosine group did not complete treatment: one patient withdrew from the study, while in the remaining eight treatments was discontinued prematurely due to lack of tolerance or intercurrent illness. Four out of these eight patients did not turn up for 6-month follow up visit while of the remaining four who were available, three achieved final cure while one relapsed. Three of these patients, who ultimately went on to achieve final cure despite not completing treatment, withdrew on the 6th day (Stevens Johnson syndrome), 14th day (elevated bilirubin) and 21st day (bleeding hemorrhoids), while the one who relapsed at 6 months discontinued the treatment on the 11th day because of arthritis and rashes (Sundar et al 2002).

Efficacy. At the end of treatment both groups achieved 100% parasitological cure in the patients available for evaluation (Miltefosine $n = 293$; amphotericin B $n = 96$). At 6 month follow up, 9 (3%) relapsed in the Miltefosine group while none relapsed in the amphotericin B group. In the former group,

at the end of the treatment parasitological evaluation could be done in 293 of the 299 patients and six month follow up could not be done in 8, while 9 patients relapsed. The final intent-to-treat cure rate was 94% for miltefosine (282 out of 299). In the amphotericin B group, all 96 patients achieved final cure and none of them relapsed. Since 3 patients had been withdrawn, the final cure rate with this drug was 97% (96 out of 99). If we consider only those patients who were available for evaluation at 6 months, then the cure rate was 282/291 (97%) for miltefosine and 96/96 (100%) for amphotericin B (Sundar et al 2002).

Conclusions. These clinical trials established the safety and efficacy of oral miltefosine in the treatment of VL in patients aged above 12 years. Treatment is associated with gastrointestinal adverse events (which are mild in most instances) and occasional severe complications like severe vomiting or diarrhea, nephro- or hepatotoxicity, which requires treatment discontinuation. In females of child bearing potential, contraception for the duration of treatment and further two months must be ensured because of the teratogenic potential of the drug.

Pediatric trials

Clinical trials with miltefosine involved patients above the age of 12 years. However, children under 12 constitute a large proportion of patients with VL not only in India, but also in other endemic regions. For the drug to be used in practice, its safety and efficacy was to be established in younger children. Two trials involving 119 children aged 2–11 years were conducted.

Phase I/II pediatric trial

It enrolled 21 and 18 patients at two sites treated with 1.5 and 2.5 mg/kg (10 mg capsules), respectively for 28 days. The entry criteria were similar to earlier studies, except that here they allowed for children with better hematological profile (hemoglobin ≥ 6 gm/dl; leucocyte count $\geq 2000/\mu\text{l}$; platelet count $\geq 50,000/\mu\text{l}$) since this was the first study in children. All patients achieved initial cure at the end of treatment, however, two patients in each group relapsed with clinical and parasitological features of VL. One patient in 2.5 mg group was lost to follow up. The final cure rates were by intention-to-treat analysis 90% and 83% in the 1.5 mg and 2.5 mg groups, respectively, and by per protocol analysis 19/21 (90%) and 15/17 (88%), respectively. There was no dose effect. While efficacy was similar in the two groups, the dose of 2.5 mg/kg was chosen for practical reasons (same dose as for adults) (Sundar 2003).

Phase II pediatric trial

Four centers enrolled 20 children (mean age 7.8 years) each ($n = 80$) who received 28 days of miltefosine at a dose of 2.5 mg/kg (including 19 (24%) patients who failed to respond to a previous course of antimony). One patient died of inter-current pneumonia during first week of treatment. In the remaining patients, treatment resulted in rapid improvement in clinical and laboratory parameters. They became afebrile by 6th day, spleen size regressed from a mean of 6.8 cm to 4.0 cm at 2 weeks of treatment and 1.5 cm at the end of treatment, and finally 0.3 cm at 6 month evaluation. All 79 children who completed treatment achieved initial cure; one patient was lost to follow up while three patients relapsed. The final cure rate was 94% (75/80; [95% CI-87–97]) on intention-to-treat basis and 96% (75/78; [95% CI-90–98]) on per-protocol analysis.

Similarly to other previous studies in adults and children, vomiting and diarrhea were the predominant adverse events, occurring in 21(26%) and 20(25%) of patients, respectively. Intensity was mild in most instances, with 1–2 episodes over the entire 28 days treatment duration. No nephrotoxicity was seen, though in a large proportion (55%) of children, asymptomatic elevation of hepatic enzymes was seen, with values returning to normal by the second week while treatment was continued (Bhattacharya et al 2004).

Cutaneous leishmaniasis

Cutaneous leishmaniasis is caused by various species of *Leishmania* and occurs both in the Old and New World; clinical manifestations, natural history and response to treatment vary. While various topical, oral and injectable therapies have been tried over time, in general antimony (parenteral or pre-lesional), remains the most common treatment. In the first dose-finding study of miltefosine for cutaneous leishmaniasis in Colombia (*L. amazonensis* and *L. panamensis*), the first two groups of patients received 50–100 mg for 21 days; of the 32 evaluable patients 21 (66%) were cured. The next group was treated with 100 mg daily for one week followed by 150 mg daily up to day 20: the cures rates were 82% and 100% on intention-to-treat and per-protocol analysis, respectively. The fourth group received 150 mg daily for 28 days, with success rates of 80% and 89% (intention-to-treat and per protocol). Only 21% of patients complained of GI side effects. The most common and unusual finding was a dose-related complaint of a feeling of “motion sickness” lasting for 1–7 days in 77 and 55% of the patients in the two higher dose groups (Soto et al 2001).

The next study was a double-blind placebo controlled multicenter trial conducted in Colombia and Guatemala. Patients were randomized to receive either placebo or miltefosine 150 mg daily in patients weighing ≥ 45 kg, and 100 mg to those with < 45 kg for 28 days. There was marked difference in the outcome between the two sites (and the species), and the final cure rate were 82 (intent-to-treat) and 91% (per-protocol) in Colombia (*L. v. panamensis*) compared to 50% and 53%, in Guatemala (*L. v. braziliensis*) respectively. These cure rates were significantly superior to the placebo groups (In Colombia 38% each both with ITT and PP analysis, whereas it was 20% and 21% in Guatemala, respectively), irrespective of the site. Though the drug was overall well-tolerated, nausea occurred in 36% of treatments, vomiting in 31%, motion sickness in 29%, headache 27%, and diarrhoea in 6%. Though 33% patients had an increase in serum creatinine, in all but one (1%) it was mild. Elevation of AST and ALT was seen in 8% and 10% patients, respectively. Thus, miltefosine may be used for cutaneous leishmaniasis due to *L. v. panamensis* in Colombia but not *L. v. braziliensis* in Guatemala (Soto et al 2004).

In a pilot study of 12 patients with diffuse cutaneous leishmaniasis failing multiple previous treatment, were treated with miltefosine 2.5 mg/kg for and 100% improvement was seen in 7 patients, and 90%–95% in the remaining five after two months of treatment (Soto and Soto 2006).

Treatment of HIV/VL co-infected patients

Treatment of VL in people with HIV is difficult and relapse is the rule. 39 HIV-coinfected patients were treated under a compassionate use program of miltefosine. Most of them had already had several courses of various treatments; 41% achieved initial cure, and 23% improved on the second course of treatment, n/22 (41%) were cured initially and 27% improved. Three (33%) of 9 and 1 (25%) of 4 patients had an initial cure after the third and fourth course, respectively. In those with initial response, the median disease-free interval was in the range of 4–5 months. Tolerance to drug was good; 26% had vomiting, 10% each had diarrhea and nausea. One patient received miltefosine as maintenance therapy for two years, and tolerated it well (Sindermann et al 2004). Ritmeijer et al (2006) in a recent study, the first done in Africa, randomized 580 patients, irrespective of the HIV status, to receive either oral miltefosine (100 mg per day for 28 days) or intramuscular SSG (20 mg/kg per day for 30 days). Considering all patients irrespective of HIV status the initial and final cure rate were similar (88% and 94% respectively for miltefosine and 88% and 89% for SSG) and

mortality was lower with miltefosine (6% vs 12% on SSG). Among HIV-coinfected patients, miltefosine was judged safer but less effective than SSG.

Perspectives for use in practice

Miltefosine is the first oral drug licensed for the treatment of leishmaniasis. As such, it is a major advance in that it makes home treatment possible, with the advantage of large-scale use. However, oral bioavailability exposes also the drug to misuse and untoward effects (toxicity, premature discontinuation of therapy, failure, and development of resistance). The key questions are therefore how this drug performs in real-life and what the best conditions to deploy it are.

Though formally the results of a large phase IV study in India are not available, preliminary results (unpublished observations) indicate that the cure rate with a partly supervised regimen (adherence assessed based on weekly pill count) may be somewhat lower than in Phase II and III trials (where treatment was fully supervised). Sub-optimal compliance may be the cause. Miltefosine is still available freely in the private sector in India at a price which cannot be afforded by the typical cash starved patient in this area. Quick recovery (within 10 days most patients feel better) coupled with the high cost of the drug will likely motivate these patients to prematurely discontinue treatment (Sundar and Murray 2005). Miltefosine is now becoming publicly available at pilot scale at no cost to patients, but compliance post-improvement will remain an important problem. A further problem if compliance is sub-optimal is the likelihood of the development of parasite resistance. Parasite resistance can be induced experimentally, and the long clinical half life (~170 hrs) makes miltefosine vulnerable to the development of resistance in endemic regions in which, like India, transmission is anthroponotic. The effects of the recent introduction of miltefosine for the treatment of canine leishmaniasis by Virbac in Southern Europe on the development of resistance in areas on zoonotic transmission are unknown.

For these reasons, the drug should be delivered to the patients under directly observed therapy either free or at a heavily subsidized cost to make it affordable.

A second important aspect is serious toxicity occurring in about 3% patients, which can generate sizeable numbers of casualties if hundreds of thousand of patients are to be treated. Every physician needs to be made aware of these toxicities, in order to be able to recognize them and stop treatment at once as these events manifest. In about 2% of these patients, severe vomiting and diarrhea or both can occur leading to rapid dehydration and its consequences.

Renal and liver toxicity may develop before they become clinically manifest, and can be detected only by laboratory investigations.

A third precaution involves the teratogenic potential of this drug; females of child bearing potential constitute a significant proportion of the patients and must avoid getting pregnant during treatment and for a further two months in view of the drug's long half life. In the developing world this is a challenging task; a contraceptive effective for three months (eg, depot progesterone), should be mandatory for these patients, and in case of non-acceptance an alternative therapy should be considered for VL.

The first country to grant marketing authorization to miltefosine for VL was India in 2002, followed by Germany and Colombia; approval will be sought in Nepal and Bangladesh. It is not registered elsewhere, and for the time being is not on the WHO list of essential drugs.

The three countries in the Indian sub-continent, India, Nepal and Bangladesh have joined hands in an elimination program for VL, and hope to eliminate the disease by 2015; in this endeavor miltefosine is going to be an important tool. However, a 28 day twice daily regimen and frequent gastrointestinal adverse events makes it imperative that the dispensing physicians are educated as to how counseling every patient before the drug is dispensed. Teratogenic effect of the drug and largely illiterate female population puts this drug in a vulnerable position. It is therefore important to devise strategies to monitor the effects of miltefosine (both in terms of real-life efficacy and toxicity) during large-scale deployment.

Miltefosine, being an oral drug with long half-life has great potential to be one component of combination chemotherapy. Unfortunately not many antileishmanial drugs are available for use in combination as conventional amphotericin B deoxycholate can not be used as the country does not have the capacity to treat many patients. Current options for combination treatment are miltefosine, liposomal amphotericin B (AmBisome®) and paromomycin (recently granted marketing authorization in India). A large dose of AmBisome® can be given as a bolus in single dose (ca. 90% effective on its own) (Sundar et al 2001, 2003), followed by eg, two weeks of miltefosine (ca. 89% effective on its own) (Sundar et al 2000). The biggest limitation of this approach is the cost of drugs, even at the prices recently announced for AmBisome® (now \$20 per vial) and miltefosine (conditional to the size of the order: WHO recently obtained an average of \$64/treatment for ~20,000 treatments).

This is the time to launch studies to test the combination to make the treatment of VL more effective, attractive and

available to all sections of the society. This will also improve compliance and prolong the useful therapeutic life-span of the drugs.

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