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Editorial

Miltefosine: a promising agent for leishmaniasis

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According to the World Health Organization leishmaniasis is one of the most serious diseases caused by protozoan parasites, with approximately 12 million cases reported in the world.[1] It is caused by more than 20 *Leishmania* species which are transmitted by hematophagous sandflies of the *Phlebotomus* genus in the Old World and the *Lutzomyia* genus in the New World, and more than 90 sandfly species are identified as probable vectors.[2] The disease occurs in varying presentations, from the self-limited and even self-healing cutaneous forms to fatal systemic disease.

Besides being an endemic healthcare problem, it is also increasingly being found in immunosuppressed patients like HIV-infected individuals, heart and kidney transplant patients and patients on long-term corticosteroid therapy.[3]

At present, leishmaniasis is treated with pentavalent antimony and/or pentamidine salts and amphotericin B, an antifungal drug. Although these drugs can be highly effective against the disease but because of their potential toxicity, administration difficulties, high cost, hospitalization and monitoring required along with emerging resistance and relapses, have greatly diminished their use in many areas.[1] Therefore, need for a safe and efficacious oral agent that does not require hospitalization always exists.

Miltefosine a new compound, derived from alkyl-phospholipids, has demonstrated its antileishmanial and antineoplastic efficacy.[4] Miltefosine is the first and still the only oral agent that is being used against all types of leishmaniasis since its registration in 2002.[4] Drug was approved in India first and has been used for the past decade in 14 countries for the treatment of leishmaniasis.[2]

The chemical name of miltefosine is hexadecylphosphocholine and the empirical formula is C21H46NO4P, yielding a molecular weight of 407.57 g/mol.[4] Miltefosine acts primarily on *Leishmania* by affecting the promastigote and amastigote stages of the species. Miltefosine exerts its antileishmanial

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activity by interacting with membrane lipids, inhibiting cytochrome C oxidase and causing apoptosis-like cell death, and thus affecting the membrane integrity and mitochondrial function of the parasite, and yet another mechanism of action described relates to the disruption of parasite Ca^{2+} homeostasis (**Figure 1**).[5]

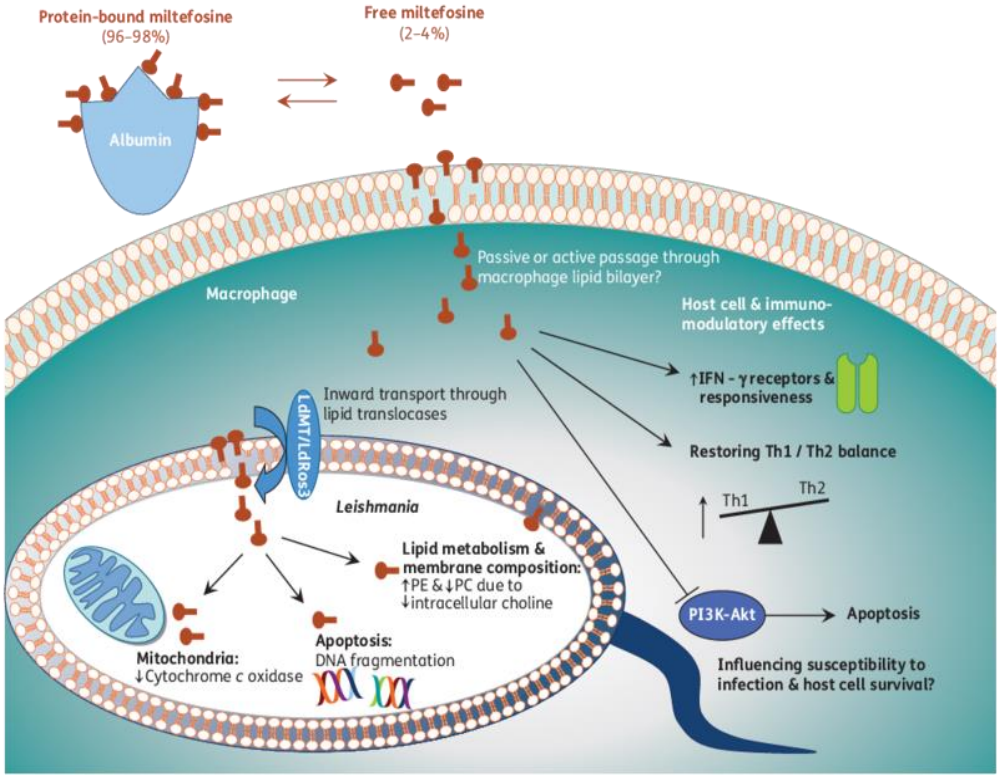

Figure 1 Antileishmanial mechanism of action of miltefosine: The various proposed mechanisms of action of miltefosine against the (intracellular) *Leishmania* parasite and the macrophage host cell during leishmaniasis infection [5].

not required.[6] The main safety concerns for miltefosine are related to its effect on the gastric mucosa and its potential teratogenicity.[4] The gastrointestinal side effects include loss of appetite, nausea, vomiting and diarrhea which can be overcome by taking the drug with meals. Transient elevation of transaminases or urea/ creatinine has been observed.[6] The drug is highly teratogenic, therefore, contraindicated for use during pregnancy and contraception is required for at least four months after the end of treatment in women of child-bearing age.[4,7]

Miltefosine is given at an oral dose of 2.5mg/kg/day for 28 days. The main advantage of miltefosine over other antileishmanial drugs is less side effects and oral administration route which is more convenient as hospitalization is

Miltefosine is also a good option in patients who are resistant to pentavalent antimony or exhibit cross-resistance to amphotericin B.[6]

The terminal half-life of miltefosine is long which ranges between 150 and 200 hours and about four half-lives (25-33 days) are needed to reach more than 90% of the peak levels, thereby a subtherapeutic level of miltefosine may remain for some weeks after a 4 week course.[8] This feature might encourage the emergence of resistance but it can be prevented by ensuring good compliance and adequate dosing for adequate duration or by using combination therapies.[8]

The drug has undergone various experimental and clinical trials, and is found more than 90% curative for visceral disease in India and cutaneous disease in Colombia, when given at a dose of 2.5mg/kg/day for 28 days.[9] Phase I, II and III clinical trials have been performed in visceral leishmaniasis in India; the overall response rate with miltefosine 100 mg/day over 4 weeks was 96%.[9,10] Another study conducted by Rubiano *et al.*[11] has shown superiority (demonstrated as fewer treatment failures) of oral miltefosine (28 days treatment) to intramuscular antimony and equivalent reepithelialization rates by 6 months compared with intravenous antimony in children.[11]

Nowadays, different combination therapy strategies including miltefosine, paromomycin and amphotericin B are being tested in multiple controlled clinical trials in various geographical areas of endemicity, both in South Asia and East Africa.[4] The Regional Technical Advisory Group (RTAG) for Kala-azar elimination has recommended miltefosine monotherapy as first-line therapy for treatment of visceral leishmaniasis in endemic countries like India, Nepal and Bangladesh.[4] In conclusion, miltefosine a well-tolerated oral drug, might play a fundamental role in the management of leishmaniasis patients.

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