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TREATMENT OF VISCERAL LEISHMANIASIS IN INDIAN SUBCONTINENT

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ABSTRACT

The treatment of Visceral leishmaniasis has been challenging because of scarcity in treatment options. Long treatment regimens and associated adverse effects further makes its treatment arduous. The present treatment guidelines in Indian subcontinent includes a single dose of 10 mg/kg of liposomal amphotericin B (L-AmB) or combination therapy consisting of multidrug therapy (L-AmB + miltefosine, L-AmB + paromomycin (PM), or miltefosine + PM). With the emergence of drug resistance there is need of development of new drugs with anti-leishmanial activity to achieve the goal of VL Elimination programme in Indian subcontinent.

KEYWORD: kala-azar, liposomal amphotericin B, miltefosine, paromomycin.

Abbreviation

AmB: Amphotericin B
L-AmB: liposomal amphotericin B
VL: Visceral Leishmaniasis
PM: Paromomycin
MIL: Miltefosine
CR: Cure rate

INTRODUCTION

Visceral Leishmaniasis (VL) is the most severe form of leishmaniasis, caused by the Leishmania donovani complex. In the Indian subcontinent and Africa , VL is caused by *L. donovani* and in the Mediterranean basin, Central and South America it is caused by *Leishmania infantum* (*Leishmania chagasi*). Other milder forms of leishmaniasis include cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis.[1] It is transmitted as extracellular flagellated promastigotes by sand flies (*Phlebotomus* species) and replicate in mononuclear phagocytes of mammalian host as intracellular and aflagellated amastigotes. Globally, around 0.2 - 0.4 million VL cases occur each year, out of which 90% occurs in just six countries which includes India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia.[2] HIV-VL co-infection has been reported from more than 35 countries and is an emerging challenge in VL elimination. The co-infected patients were initially reported from south Western Europe, but slowly increasing in Ethiopia, Brazil and South Asia.[3,4] In India, HIV-VL co-infection was found in 1.8 - 4.5% patients in Bihar.[5]

VL is life threatening if left untreated and is characterized by prolonged fever, hepatomegaly, splenomegaly, pancytopenia, progressive anemia and weight loss.

The treatment of VL is challenging as the pool of antileishmanial drugs is scanty. Drugs which are available are pentavalent antimonials, Amphoterecin B(AmB) and its lipid formulations, miltefosine and Paramomycin(PM).

Review of Antileishmanial drugs

Pentavalent antimonials (Sb^v) have been used as the first line drug for several decades. It is administered in doses of 20 mg/kg body weight for 28 - 30 days. However, in North Bihar and adjoining areas of Nepal there are evidences of widespread resistance to this drug and alternative strategies of treatment has been advocated.[6,7] But, it remains efficacious in other part of world.[8] Its use is further limited by associated serious adverse effects like cardiac arrhythmias, prolonged QT interval (QTc), ventricular premature beats, ventricular tachycardia, ventricular fibrillation and torsades de pointes.

Amphotericin B deoxycholate (AmB) at doses of 0.75-1.0 mg/kg for 15-20 intravenous infusions has been used with excellent cure rates (CR ~ 100%) in this region. Side effects includes infusion related rigors, high fever, nephrotoxicity, hypokalemia, and myocarditis. Therefore treatment with AmB needs close monitoring and inpatient care for 4 - 5 weeks which indirectly increases the cost of treatment.[9] To overcome the side effects, various lipid formulations of AmB have been introduced. The lipid formulations which are used in VL are, liposomal amphotericin B (AmBisome; Gilead

Sciences; L-AmB), amphotericin B lipid complex (ABLC; Abelcet, Enzon pharmaceuticals) and amphotericin B colloidal dispersion (ABCD); Amphotec, InterMune Corp.). L-AmB is the only approved drug by the US FDA. However cost has been the limiting factor, but due to negotiation with WHO, Gilead Sciences, Foster City, US agreed to decrease the price of its liposomal amphotericin B (AmBisome; L-AmB) and supply at 10% of the market cost (20 US$) to the developing countries . L-AmB has shown a cure rate of 91% and 90% when used in a single dose of 5 mg and 7.5 mg/kg respectively.[10,11] In a phase 3 study in India, a single dose of 10 mg/kg of body weight L-AmB was found to be non-inferior to the conventional amphotericin B deoxycholate administered in 15 infusions of 1 mg/kg (cure rate of >95%). The preferential pricing, along with a single day of hospitalization, makes a single infusion of the liposomal preparation an excellent option for this region.[12] Following this trial, WHO has recommended single dose (10mg/kg) L-AmB as the most preferred regimen for the treatment of VL in the Indian subcontinent.[1] L-AmB at a dose of 4 mg/kg for 10 doses (days 1 -- 5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg is recommended for treatment of HIV-VL co-infection.[1] In a retrospective study from Bihar, combination of 30 mg/kg body weight LAmB divided in 6 equal dose infusions given on alternate days, along with 14 days of oral miltefosine was given to HIV-VL coinfected patients (n=102) showed all-cause mortality and VL relapse at 6, 12, and 18 months to be 11.7%, 14.5%, 16.6% and 2.5%, 6.0%,13.9%, respectively.[13] Along with it patients should be started on Anti-retroviral therapy and secondary prophylaxis should be given till the CD4 counts are > 200/µl.[14]

Miltefosine is the first oral antileishmanial agent registered for use in India. This was as a result of a phase III trial in 2002 where 50 - 100 mg/ day dose of miltefosine given for 28 days showed a long-term CR of 94%.[15] It became the drug of choice of the elimination program in India, Nepal and Bangladesh because of its ease of use and administration. However, the relapse rate almost doubled and its efficacy has decreased after a decade of use of the drug in the Indian subcontinent.[16] In Bangladesh, CR was only 85% at 6 months and in Nepal, the relapse rate of 10.8% and of 20.0% was observed at 6 and 12 month respectively.[17,18] Also, the side effects of miltefosine further limits it use which includes gastrointestinal side effects , hepatotoxicity and nephrotoxicity which requires monitoring hence escalating the treatment cost. Women of child-bearing age have to follow contraception for the duration of treatment and for an additional 3 months as it is teratogenic. Its long half life(~1 week) also makes it susceptible to the development of resistance in parasites.

Paromomycin (PM) sulfate (11 mg base) in a dose of 15 mg/kg for 21 days demonstrated a CR of 95% and was approved by the Indian government in August 2006 for the treatment of patients with VL.[19] In a recent Phase III b, open-label, multi-center, single-arm trial assessed the efficacy and safety of PM administered at 11 mg/kg (paromomycin base) intramuscularly once daily for 21 consecutive days to children and adults with VL in a rural outpatient setting in Bangladesh showed final clinical response at 6 months was 94.2% after end of treatment.[20] Its efficacy is low however in countries like Ethopia, Sudan and Kenya.[21] Adverse effects include pain at the injection site, ototoxicity and mild self limiting hepatotoxicity. Its major limitation for being used in a control program is its parenteral administration. Also, the chances of developing resistance with monotherapy with PM might increase as its an aminoglycoside.

Combination therapy

The emergence of drug resistance has lead to development of combination therapy in VL with the intention to develop a shorter regime with drugs having additive effect, fewer side effects and to decrease the chance of resistance associated with monotherapy.

In a randomized, non-comparative, group-sequential, triangular design study combination therapy with LAmB and miltefosine was studied where 181 subjects were randomised to receive 5 mg/kg of L-AmB alone, 5 mg/kg of L-AmB followed by miltefosine for 10 days or 14 days or 3.75 mg/kg of L-AmB followed by miltefosine for 14 days. In all the groups the final CRs were similar (CR > 95%).[22] A Phase III study in the Indian subcontinent was conducted where three drug combinations of single injection of 5 mg/kg L AmB and 7-day 50 mg oral miltefosine or 10-day 11 mg/kg intramuscular PM; or 10 days each of miltefosine and PM showed an >97% CR.[23] In a other trail in India resulted in CR of 91.9 %(ITT) and 97.6 % by per protocol analysis when single dose of LAmB 5 mg/kg and miltefosine 2.5 mg/kg/day were given for 14 days.[24]

CONCLUSION

With the growing resistance in parasites and abatement in the efficacy of available antileishmanial drugs, it is high time that monotherapy should be put on hold. As treatment options are meagre, strategies to prevent drug resistance should be sorted out to accomplish VL elimination programme in Indian subcontinent. Strong political and Government support is essential for proper implementation of strategies. Newer drugs with antileishmanial activity are needed to be developed. Recently support from public--private partnerships (PPP) such as the Drug for Neglected Disease initiative (DNDi) has searched newer drug targets for various neglected tropical diseases. Such PPP are helpful in deciphering agents with antileishmanial activity and development of new drugs.

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