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REVIEW PAPER

Kala-Azar- Treatment Update

Anup Singh

Associate Professor, Department of Medicine, Institute of Medical Sciences, BHU, Varanasi, INDIA

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Corresponding author

Dr. Anup Singh
Associate Professor
Medicine, IMS, BHU
Varanasi-221005, India

E-mail: dranupbhu@gmail.com

ABSTRACT

The sparse treatment options in Visceral Leishmaniasis (VL) makes its treatment very challenging. Long treatment duration and toxic adverse effect of anti-lesihmanial drugs further add to the problem of effective management. As still no effective vaccine is available, the sole treatment of VL is only based on anti-lesihmanial drugs. Also the increasing resistance to existing drugs also pose a hurdle to VL treatment. In Indian sub-continent, single dose of liposomal amphotericin B (L-AmB) and multidrug therapy (L-AmB + miltefosine, L-AmB + paromomycin (PM), or miltefosine + PM) are the treatment of choice for VL.

INTRODUCTION

Kala-Azar or Visceral Leishmaniasisis (VL) is a systemic disease characterized by prolonged fever, hepatosplenomegaly, weight loss, progressive anaemia, pancytopenia, and is complicated by serious infections. It is typically caused by obligate intracellular parasite, *Leishmania donovani* complex: *L. donovani* ,the causative organism of VL in the Indian subcontinent and Africa; *L. infantum* (*L. chagasi*) which causes VL in the Mediterranean basin, Central and South America.

An estimated 500,000 cases of VL occur every year worldwide. More than 90% of global VL cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia. The annual incidence of VL in India is approximately 100,000 cases with Bihar state accounting for more than 90% of these (1).

VL-HIV co-infection is a upcoming problem in Southern Europe, Brazil and Africa. The co-infection increases the risk of VL by 100- to 1000-fold in endemic area and has lower cure rates, with frequent relapses and high parasite load, making them a reservoir for the spread of the infection.

Treatment of VL

Treatment of VL is has been far from satisfactory as armory of antileishmanial drugs is spares. Drugs available are toxic and require prolong hospitalization. However, efficacy of newer drugs and combination therapy has revolutionized the conventional treatment of VL.

As the efficacy and required dosage of the antileishmanial agents vary in different areas the WHO recently published the treatment recommendation for VL based on these regional differences. The treatment recommendation for VL caused by *L. Donovani* is given in Table 1. Following is the review of the drug used:

Table 1: Recommended treatment regimens for visceral leishmaniasis, ranked by preference (Adopted from the Control of the Leishmaniases, WHO Technical Report Series 949, 2010)

Anthroponotic visceral leishmaniasis caused by L. donovani in Bangladesh, Bhutan, India and Nepal

1. Liposomal amphotericin B: 3–5 mg/kg per daily dose by infusion given over 3–5 days period up to a total dose of 15 mg/kg (A) by infusion or 10 mg/kg as a single dose by infusion (A)
2. Combinations (co-administered) (A)
   - liposomal amphotericin B (5 mg/kg by infusion, single dose) plus miltefosine (daily for 7 days, as below)
   - liposomal amphotericin B (5 mg/kg by infusion, single dose) plus paromomycin (daily for 10 days, as below)
   - miltefosine plus paromomycin, both daily for 10 days, as below
3. Amphotericin B deoxycholate: 0.75–1.0 mg/kg per day by infusion, daily or on alternate days for 15–20 doses (A)
4. Miltefosine: for children aged 2–11 years, 2.5 mg/kg per day; for people aged 12 years and < 25 kg body weight, 50 mg/day; 25–50 kg body weight, 100 mg/day; > 50 kg body weight, 150 mg/day; orally for 28 days (A)

   or

   Paromomycin: 15 mg (11 mg base) per kg body weight per day intramuscularly for 21 days (A)
5. Pentavalent antimonials: 20 mg Sb5+/kg per day intramuscularly or intravenously for 30 days in areas where they remain effective: Bangladesh, Nepal and the Indian states of Jharkhand, West Bengal and Uttar Pradesh (A)

Rescue treatment in case of non-response: conventional amphotericin B deoxycholate infusions or liposomal amphotericin B at higher doses.

Pentavalent antimonials(Sb^V)

Sb^V is available in two forms: Sodium stibogluconate and meglumine antimoniate (MA). It is administered in doses of 20 mg/kg body weight for 28 - 30 days. Sb^V has been standard first-line therapy in India. However, misuse of this drug in Bihar in form of improper doses, splitting of daily dose, substandard batches of drugs lead to the emergence of widespread antimony resistance in this region (2). The failure rate is high as much as 60% in India, and adjoining Nepal. Due to the emergence of high level of resistance sodium stibogluconate has lost its utility in this region and no longer the recommended in this area. Serious toxicities like cardiac arrhythmias, prolonged QT interval (QTc), ventricular premature beats, ventricular tachycardia, ventricular fibrillation and torsades de pointes further add to limitation of its use. Other toxicities includes arthralgia, myalgia, elevated hepatic and pancreatic enzymes. Its also less efficacious in HIV-VL co-infection and associated with increase adverse effects.

Amphotericin B deoxycholate

Amphotericin B deoxycholate (AmpB) is most commonly used drug for treatment of VL in India. Amphotericin B has high cure rate (~100%) at a dose of 0.75 – 1 mg/kg for 15 – 20 intravenous infusions[3,4]. However, this drug has many adverse effects, which require close monitoring and hospitalisation for 4-5 weeks which eventually increase treatment cost.

To overcome the toxicity and to decrease the duration of treatment lipid formulations of amphotericin B have been developed. However, limiting factor of its use in endemic countries is its high cost. Among the lipid preparations, liposomal amphotericin B (Gilead Sciences, USA) has been tested most widely in all the leishmaniasis affected regions including India, and is the only antileishmanial drug approved by the Food and Drug Adminstration, USA. After a series of studies with multiple and single doses, it was established that L-AmB is highly effective in Indian VL. [5,6]

The total dose requirement for treatment of VL vary by geographical distribution. In India (*L. donovani*), a total dose of ≥10 mg/kg results in a cure rate of > 95% while a total dose of 18–21 mg/kg, has 90–100% efficacy in southern Europe.[7]

In a landmark study from India, 412 patients were randomly assigned in a 3:1 ratio to receive either liposomal amphotericin B (at a dose of 10 mg per kilogram of body weight) as a single dose or the conventional amphotericin B deoxycholate administered in 15 infusions of 1 mg per kilogram, given every other day during a 29-day hospitalization. Cure rates at 6 months were similar in the two groups: 95.7% (95% confidence interval [CI], 93.4 to 97.9) in the liposomal-therapy group and 96.3% (95% CI, 92.6 to 99.9) in the

conventional-therapy group. The single dose treatment along with a low pricing, makes single infusion of the liposomal preparation an excellent option for the Indian subcontinent. [8] WHO has recommended this as the treatment of choice in the Indian Subcontinent. In Bangladesh ,this regimen was further tested at primary health centers which showed 97% CR at 6 month.[9] A major hinderence is requirement of cold chain which demands infrastructure for it to be used at sub-district level.[10]

Miltefosine

Following a multicentre phase-3 study in 2002, it was first approved in India for the treatment of visceral leishmaniasis in same year. Its efficacy, ease of use and applicability in the control program made this drug the backbone of the elimination program in India, Nepal and Bangladesh.[11] Its limitations includes monitoring of gastrointestinal side effects, high cost, and occasional hepatic and kidney toxicity. As miltefosine is teratogenic, women of child-bearing potential have to observe contraception for the duration of treatment and for an additional three months. It has a long half-life of approximately one week, which also makes it vulnerable to the rapid development of drug resistance. The VL elimination program in India, Nepal and Bangladesh has recommended miltefosine as the first-line drug for treatment in this region because of its ease of use as it provides ambulatory care.[11] However, there is a decrease in the efficacy of this drug since its discovery a decade ago. In a recent study it was found that the cure rate has decreased to 90% and the relapse rate has almost doubled when compared to its cure rate of 94% and relapse rate of 3% in 1999-2000[12]. In Nepal, relapse rate of 10.8% at 6 and of 20.0% at 12 months was observed[13], and in Bangladesh the CR was only 85%[14]. In Ethopia, the final cure among non-HIV-infected patients was 75.6% at 6 months.[15] These findings suggest that monitoring miltefosine therapy is imperative to prevent emergence of resistance.

Paromomycin (aminosidine)

In the phase III trial of Paromomycin in the Indian subcontinent it has been shown to be noninferior to amphotericin B and was approved by the Indian government in August 2006 for the treatment of patients with visceral leishmaniasis.[16] 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.[17] The advantages of this agent is its cost, approximately US $10 per patient. The disadvantages are need for administering intramuscular injection, monitoring of serum transaminases and inadequate data regarding its use in pregnancy.

Combination therapy

Combination therapy is expected to prolong the useful therapeutic lifespan of the existing drugs by reducing the probability of development of resistant parasites. The idea behind multi drug therapy is increased activity through use of compounds with synergistic or additive activity, preventing the emergence of drug resistance, lower dose requirement thereby reducing chances of toxic side effects and cost, and increased spectrum of activity.

Single infusion of L-AmB followed by a brief self-administered course of miltefosine has shown to be an excellent option against Indian kala-azar.[18]

In a phase 3 trial, three drug combinations (single injection of 5 mg/kg L AmB and 7-day 50 mg oral miltefosine or single 10-day 11 mg/kg intramuscular paromomycin; or 10 days each of miltefosine and paromomycin) were tested in the Indian subcontinent and it was found that all the combinations showed an excellent cure rates (>97% in all arms).[19]

Post Kala-Azar Dermal Leishmaniasis (PKDL)

Post Kala-azar Dermal Leishmaniasis (PKDL) is a dermal manifestation of *L donovani* infection, and often follows resolution of VL. PKDL is characterized by macular, papular or nodular lesions or a mixture of them. It is quite common in Sudan (occurring in > 50% patients with VL), where it may occur concurrently or follows immediately after an episode of VL and heals spontaneously in majority of patients. Whereas, in the Indian subcontinent it occurs in 2-20% of patients, 6 months to several years after an episode of VL.[20] In a recent trial the prevalence of confirmed PKDL cases was 4.4 per 10 000 individuals and 7.8 if probable cases were also considered.[21] Diagnosis is confirmed by demonstration of parasite in split skin smear. It has been found in studies that smears are more likely to show amastigotes if taken from a larger lesion or from nodular (67–100%) lesions compared with papular (36–69%) and macular lesions (7–33%). Cultures may offer higher yield than smears but are likely to be contaminated. Newer techniques like Monoclonal

antibodies and PCR increase the diagnostic yield considerably to 88% and 83–94%, respectively, but these are restricted to research laboratories.[20] Several treatment regimens have been recommended for the treatment of PKDL in India but has a long course and associated with various adverse effect. WHO has recommended treatment of PKDL for the Indian subcontinent. (Table 2)

Table 2: Post-kala-azar dermal leishmaniasis (Adopted from the Control of the Leishmaniases, WHO Technical Report Series 949, 2010)

East Africa

1. Pentavalent antimonials: 20 mg Sb5+/kg per day intramuscularly or intravenously for 30–60 days, when indicated (C)
2. Liposomal amphotericin B: 2.5 mg/kg per day by infusion for 20 days, when indicated (C)

Bangladesh, India, Nepal

1. Amphotericin B deoxycholate: 1 mg/kg per day by infusion, up to 60–80 doses over 4 months (C)
2. Miltefosine orally for 12 weeks at dosage as above (A)

Vaccine

Leishmaniasis is unique among parasitic diseases because a single vaccine has the potential to protect against mo re than one species and be successful at both treating and preventing disease. Unfortunately there is no vaccine approved for VL, though several vaccine development programmes are underway.

Treatment of HIV/VL Co-infection

These patients respond poor to treatment and have high relapse rate due to high parasite burden, and a weak immune response. Pentavalent antimonials are more toxic to HIV patients, who require close monitoring for pancreatitis and cardiotoxicity.[22] The best option for these patients are L AmB at 4 mg/kg given on day 1-5, 10, 17, 24, 31 and 38.[23] Secondary prophylaxis to prevent relapses has been reported in several publications, but more evidence from clinical trials is needed to establish a beneficial effect Initiation of HAART dramatically decreases the incidence of VL co-infection and also increases the interval between relapses. Therefore; HAART in combination with antileishmanials should be advocated strictly in these patients.

CONCLUSION

Single dose L-AmB and combination therapy has revolutionized the treatment of VL. However, the emergence of drug resistance is further complicating the control of leishmaniasis. As newer antileishmanial drugs are still in development phase, combination therapy by reducing the duration of therapy and decreasing the chances of developing resistance should be encouraged. The use of vaccines and immunomodulators for prophylaxis as well as treatment are also areas which are being explored for control of the disease.

Therefore, for the success of VL elimination programme effective implementation of tools for early diagnosis and treatment of cases, integrated vector management, effective disease surveillance through passive and active case detection, social mobilization and partnership building at all levels and clinical and operational research is needed.

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