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Visceral Leishmaniasis – Optimum Treatment Options in Children

Shyam Sundar, MD, FRCP (London), FNA, FAMS, FASc, FNASc* and **Dipti Agarwal, MD****

*Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

**Department of Pediatrics, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India

Abstract

Visceral leishmaniasis (VL) affects 200-400 thousands people annually worldwide. For last few decades there has been a steady decline in the response to pentavalent antimonial (Sb^V), the drug that has been used for treating VL for almost a century. Oral miltefosine and amphotericin B are alternative drugs being used in the treatment of leishmaniasis in children. Liposomal amphotericin B (L-Amb) has the advantage over conventional amphotericin B is that higher doses can be given with fewer adverse effects. L-Amb in combination with other drugs is the preferred treatment option globally especially in Indian subcontinent. Combination therapy with multiple drugs should undergo larger clinical trials in children as these will shorten the duration of therapy, improve compliance, and decrease both toxicity and drug resistance.

Keywords

Visceral leishmaniasis; children; treatment; liposomal amphotericin B; combination therapy

Introduction

Leishmaniasis, a vector-borne tropical disease is caused by an obligate intracellular protozoa of the genus *Leishmania*. Clinical manifestations range from self-healing cutaneous ulcers to systemic multiorgan disease. It broadly manifests as visceral leishmaniasis (VL; also known as kala-azar), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL). It is a significant public health problem with incidence of VL amounting to 0.2 – 0.4 million cases and for CL 0.7–1.2 million cases each year. More than 90% of global VL cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia (1). Demonstration of the parasite from bone marrow, spleen or lymph node is the gold standard for the diagnosis of VL. Amongst serological tests, indirect fluorescence antibody (IFA), enzyme-linked immunosorbent assay (ELISA) are poorly adapted to field settings whereas direct agglutination test (DAT) and the rK39-based immunochromatographic test (ICT) have been developed for field use.

The treatment of VL has evolved significantly over time as a consequence of emerging resistance patterns and newer drug delivery systems. The currently available drugs for leishmaniasis have been discussed below to plan an optimal strategy for the treatment in pediatric population.

1. Antileishmanial Drugs

1.1 Sodium Stibogluconate

Sb^V is available as sodium stibogluconate (SSG) and meglumine antimoniate (MA). It was introduced as cheap, effective and well-tolerated drug and has been in use for the treatment of leishmaniasis for more than seven decades. Daily injection of 20 mg/kg body weight for 28 – 30 days has been the standard treatment for VL in most parts of the world.

Disadvantages of stibogluconate include the need for parenteral route of administration and lengthy hospitalisations. Its major side effects are cardiac arrhythmias, prolonged QT interval, ventricular premature beats, ventricular tachycardia, and ventricular fibrillation. Arthralgia and myalgia, elevated hepatic and pancreatic enzymes are other common adverse events. Antimonials are more toxic in HIV patients and a significant proportion of them have chemical pancreatitis. Increasing refractoriness to Sb^V in the state of Bihar (India), and to some extent in adjoining country, Nepal, have led to adoption of alternative treatment strategies in these regions. However, in other parts of world – Africa, Americas, Middle East, Sb^V is used for the treatment of leishmaniasis.

1.2 Amphotericin B

Amphotericin B (AmB) deoxycholate is a polyene antibiotic which is most commonly used for the treatment of refractory VL in India. It has excellent clinical response (~ 100%) at doses of 0.75 – 1.0 mg/kg for 15 – 20 intravenous infusions in this region. (2). However, this drug has many adverse effects including infusion reactions, nephrotoxicity, hypokalemia, hepatic dysfunction, bone marrow dysfunction and myocarditis. The drug is expensive, too. Therefore, for areas outside India this drug does not offer any obvious advantages over pentavalent antimonial agents.

1.3 Liposomal Drug Delivery System

Conventional amphotericin B requires prolonged administration and is associated with toxicities. To minimize the adverse events, various lipid formulations have been introduced. Lipid formulations of AmB are rapidly picked up by the reticuloendothelial tissues, thus the amount of free drugs available is low leading to significantly decreased toxicity. Globally three formulations have been extensively tested in VL: liposomal amphotericin B (L-AmB), amphotericin B lipid complex and amphotericin B colloidal dispersion. L-AmB is the only approved drug by the US FDA for clinical use. The total dose requirements of lipid formulations for treatment of VL vary from region to region. In India and Bangladesh, a single dose of 10 mg/kg results in a cure rate of more than 95%, and is currently one of the preferred treatments for VL in this region (3). In the Mediterranean region, and South America a total dose of 18–21 mg/kg has been recommended (4).

1.4 Miltefosine

Oral treatment for visceral leishmaniasis has only become a reality, with the introduction of miltefosine. It is an alkyl phospholipid (hexadecylphosphocholine) and registered for use in India since March 2002. It is the chosen drug for the VL elimination program in the Indian subcontinent (India, Nepal and Bangladesh). It is available as 10 mg and 50 mg capsules. The recommended dose for children between 2 years and 11 years is 2.5 mg/kg for 28 days. For children 12 years and above 50 mg daily for those weighing less than 25 kg and 50 mg twice daily for those more than 25 kg for 28 days. It is recommended that the drug be taken after meals to minimize gastrointestinal adverse events.

Treatment with miltefosine has been shown to be >90% effective and well-tolerated in studies conducted in India among newly diagnosed patients or patients unresponsive to pentavalent antimonial agents. Adverse events include vomiting and diarrhea in 40% and 20% patients, respectively, and there may be asymptomatic elevation of liver enzymes. Rarely nephrotoxicity may occur. As miltefosine is potentially teratogenic, it is contraindicated in pregnancy and in women of child-bearing age who do not use contraception. In a recent study from India, the efficacy of miltefosine appears to have declined and the relapse rate has doubled as compared to 2002. Its long half-life also makes it vulnerable to the development of drug resistance.

1.5 Paromomycin

Paromomycin (aminosidine) belongs to the class of aminocyclitol-aminoglycosides and possesses not only antibacterial but additional antiprotozoal activity effective against *Leishmania*, *Entamoeba*, and *Cryptosporidium*. Parenteral preparations have been developed and used in VL. Phase III trial showed that a dose of 15 mg/kg paromomycin (PM) sulfate (11 mg base) for 21 days gave a cure rate of 95% (5). Pain at the injection site was the commonest adverse event (55%), followed by reversible ototoxicity, rise in hepatic transaminases and nephrotoxicity is rare. The advantage of this agent is its extremely affordable cost.

2. Combination or multidrug therapy

Compounds with synergistic or additive activity acting at different sites shorten the duration of therapy and decrease dose requirement, thereby reducing chances of toxic side effects and cost, and preventing the emergence of drug resistance. In a recent phase III study from India, single infusion of 5 mg/kg of L-AmB with either 7-day oral miltefosine or 10-day IM paromomycin; or 10 days each of miltefosine and paromomycin (with similar daily dose as in monotherapy) had excellent cure rates (>97% in all arms) (6). In East Africa, the combination of sodium stibogluconate at 20 mg/kg plus paromomycin given at 15 mg/kg (11 mg base) for 17 days has shown excellent efficacy (7). Given the risk of development of resistance to established and new drugs, the Regional Strategic Framework for Elimination of Kala-azar from the South-East Asia Region recommends that monotherapy other than L-AmB should be avoided in this region (8).

3. Treatment in HIV infected children

HIV infection increases the risk of developing VL by 100–2,320 times in areas of endemicity, reduces the likelihood of a therapeutic response, and greatly increases the probability of relapse. Liposomal AmB is the drug of choice for HIV-VL co-infection. A dose of 3–5 mg/kg/day intermittently for 10 doses (days 1–5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg is recommended but relapse is common (9). Secondary prophylaxis with L-AmB (5 mg/kg) every 3 weeks has been found to be useful in decreasing relapses (10). If L-AmB is not available, amphotericin B deoxycholate can be used. Antiretroviral therapy should be initiated immediately.

4. Investigational drugs

Among all the investigational drugs, feximidazole, a nitroimidazole, has reached the stage of Phase II clinical trial for VL (11). The oral advantage, comparable leishmanicidal activity to miltefosine and safety reiterates the potential of feximidazole as a much-needed additional oral therapy for VL. Sitamaquine is the second orally active antileishmanial drug after miltefosine which has reached Phase II trials (12). Unfortunately, due to its low efficacy, development of this drug has been stopped for VL.

5. Current Treatment Guidelines

Stibogluconate is considered as first line treatment for VL in most parts of world except in Indian subcontinent and few more regions where high resistance has been reported. Single dose of L-Amb and combination therapy are preferred treatment options in the Indian subcontinent. The combination of SSG with paromomycin for 17 days is the treatment of choice in East Africa and Yemen. In Mediterranean basin, middle east, central Asia, L-Amb (18-20mg/kg) remains the treatment option, whereas in the New World, Sb and conventional AmB (20 mg/kg) are the recommended drugs for the treatment of VL.

6. Conclusion

Treatment of leishmaniasis in children should be based on appropriate selection of first-line drugs depending on efficacy, resistance and safety profile. HIV co-infection should also be taken into consideration. The emergence and spread of anti leishmanial resistance should be monitored and the combination regimens should be evaluated in larger clinical trials for children.

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7. Key highlights

- Increasing refractoriness have been reported to Stibogluconate in Indian subcontinent and adjoining countries.
- Liposomal Amphotericin B has reduced the duration of treatment and toxicities associated with conventional Amphotericin.
- Miltefosine has advantage of oral administration, but requires monitoring for gastrointestinal side effects.
- In Indian subcontinent liposomal amphotericin B or multidrug therapy are preferred treatment for visceral leishmaniasis; whereas in East Africa a 17-day combination therapy of pentavalent antimonials and paromomycin is the best option
- In HIV co-infection, L-Amb is used for treatment. Secondary prophylaxis may be considered for prevention of relapse