Visceral Leishmaniasis—Optimum Treatment Options in Children

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Abstract: Visceral leishmaniasis affects 200–400 thousand people annually worldwide. For last few decades, there has been a steady decline in the response to pentavalent antimonial (SbV), the drug that has been used for treating visceral leishmaniasis for almost a century. Oral miltefosine and amphotericin B are alternative drugs being used in the treatment of leishmaniasis in children. Liposomal amphotericin B has the advantage over conventional amphotericin B that is higher doses can be given with fewer adverse effects. Liposomal amphotericin B 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.

Key Words: visceral leishmaniasis, children, treatment, liposomal amphotericin B, combination therapy

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 and mucocutaneous leishmaniasis. It is a significant public health problem with incidence of VL amounting to 0.2–0.4 million cases and for cutaneous leishmaniasis 0.7–1.2 million cases each year. More than 90% of global VL cases occur in just 6 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. Among serologic tests, indirect fluorescent antibody and enzyme-linked immunosorbent assay are poorly adapted to field settings, whereas direct agglutination test and the rK39-based immunochromatographic test 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.

ANTILEISHMANIAL DRUGS

Sodium Stibogluconate

1. SbV is available as sodium stibogluconate (SSG) and meglumine antimoniate. It was introduced as cheap, effective and well-tolerated drug and has been in use for the treatment of leishmaniasis for more than 7 decades. Daily injection of 20mg/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 hospitalizations. Its major side effects are cardiac arrhythmias, prolonged QT interval, ventricular premature beats, ventricular tachycardia and ventricular fibrillation. Arthralgia and myalgia and elevated hepatic and pancreatic enzymes are other common adverse events. Antimonials are more toxic in HIV patients, and a significant proportion of them has chemical pancreatitis. Increasing refractoriness to SbV 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 the world—Africa, Americas, Middle East—SbV is used for the treatment of leishmaniasis.

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,

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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.

**Liposomal Drug Delivery System**

Conventional AmB 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, 3 formulations have been extensively tested in VL: liposomal AmB (L-AmB), AmB lipid complex and AmB colloidal dispersion. L-AmB is the only approved drug by the US Food and Drug Administration for clinical use. The total dose requirements of lipid formulations for the 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. In the Mediterranean region and South America, a total dose of 18–21 mg/kg has been recommended.

**Miltefosine**

Oral treatment for VL 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 and 50 mg capsules. The recommended dose for children between 2 and 11 years of age is 2.5 mg/kg for 28 days. For children 12 years of age 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 is given. 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 when compared with 2002. Its long half-life also makes it vulnerable to the development of drug resistance.

**Paromomycin**

Paromomycin (PM) (aminosidine) belongs to the class of aminocyclitol–aminoglycosides and possesses not only anti-bacterial 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 PM sulfate (11 mg base) for 21 days gave a cure rate of 95%. 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.

**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 intramuscularly (IM) PM, or 10 days each of miltefosine and PM (with similar daily dose as in monotherapy) had excellent cure rates (>97% in all arms). In East Africa, the combination of SSG at 20 mg/kg plus PM given at 15 mg/kg (11 mg base) for 17 days has shown excellent efficacy. Given the risk of development of resistance to established and new drugs, the Regional Strategic Framework for Elimination of Kala-azar from the Southeast Asia Region recommends that monotherapy other than L-AmB should be avoided in this region.

**TREATMENT IN HIV-INFECTED CHILDREN**

HIV infection increases the risk of developing VL by 100–2320 times in areas of endemcity, reduces the likelihood of a therapeutic response and greatly increases the probability of relapse. L-AmB is the drug of choice for HIV-VL coinfection. A dose of 3–5 mg/kg/d 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. Secondary prophylaxis with L-AmB (5 mg/kg) every 3 weeks has been found to be useful in decreasing relapses. If L-AmB is not available, AmB deoxycholate can be used. Antiretroviral therapy should be initiated immediately.

**INVESTIGATIONAL DRUGS**

Among all the investigational drugs, fexinidazole, a nitromidazole, has reached the stage of phase II clinical trial for VL. The oral advantage, comparable leishmanicidal activity to miltefosine and safety reiterates the potential of fexinidazole 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. Unfortunately, because of its low efficacy, development of this drug has been stopped for VL.

**CURRENT TREATMENT GUIDELINES**

Stibogluconate is considered as first-line treatment for VL in most parts of the 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 PM for 17 days is the treatment of choice in East Africa and Yemen. In Mediterranean basin, Middle East and Central Asia, L-AmB (18–20 mg/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.

**CONCLUSION**

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

**KEY HIGHLIGHTS**

- Increasing refractoriness have been reported to stibogluconate in Indian subcontinent and adjoining countries.
- L-AmB 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, L-AmB or multidrug therapy is preferred treatment for VL, whereas in East Africa, a 17-day combination therapy of pentavalent antimonials and PM is the best option.
- In HIV coinfection, L-AmB is used for treatment. Secondary prophylaxis may be considered for prevention of relapse.
REFERENCES


