The Treatment of Visceral Leishmaniasis: Safety and Efficacy

Rajesh Kumar Jha,[1] Ajit Kumar Sah,[1] Dev Kumar Shah,[2] Phoolgen Sah[1]

[1]Department of Pharmacology, [2] Department of Physiology , Chitwan Medical College, Bharatpur, Chitwan, Nepal.

ABSTRACT

Visceral leishmaniasis is the disease of poor; however availability of only expensive treatment of this disease impinges the socioeconomic condition of those affected. If untreated, almost all cases of visceral leishmaniasis are fatal. The demonstration of the leishmania donovani bodies from the tissue aspirates or serological tests confirms the diagnosis of the disease. Pentavalent antimony, amphotericin B, paromomycin, diamine pentamidine, miltefosine, sitamaquine and some new combinations are integrated in the limited therapeutic armoury for treatment of visceral leishmaniasis. The recommended first and second line therapy in the Indian sub-continent is miltefosine and amphotericin B respectively. Pentavalent antimonial, preceding first line therapy, has been replaced by miltefosine due to former increasing failure rate and toxicity. The problem of drug resistance, some of the serious drug toxicities along with high-priced drugs extends challenges equally to pharmaceutical companies and medical practitioners. More research on adverse drug events for the existing drugs and efforts to develop safer and effective drugs to counter resistance outbreaks for the successful management of visceral leishmaniasis are needed.

Keywords: *amphotericin; miltefosine; pentavalent antimony; paromomycin.*

INTRODUCTION

Leishmaniasis is a clinically heterogeneous group of diseases, caused by protozoa of the genus Leishmania. Disease can range from a solitary, spontaneous healing ulcer (Cutaneous leishmaniasis), to generalized involvement with visceral leishmaniasis.[1] Visceral Leishmaniasis (VL) also known as kala azar, is caused by Leishmania donovani (LD) in the Indian subcontinent, Asia and Africa,[2] L. infantum in Mediterranean regions, and L. chagasi in the New World.[3]

For past 70 years, therapeutic armoury for treatment of visceral leishmaniasis has been extremely limited.[4] While conventional therapies i.e. pentavalent antimonial and amphotericin B continue to play a major role, miltefosine, a first oral therapy, is recently approved for VL.[5] The recommended 1st and 2nd line therapy in the Indian sub-continent is miltefosine and Amphotericin B respectively.[6] Which has replaced Pentavalent antimonial due to its increasing failure rate [7] and toxicity.[8]

In this review, we describe current visceral leishmaniasis (VL) treatment options and their limitations.

EPIDEMIOLOGY

Despite the fact that infectious diseases have been identified as the third major cause of death in the world, many fall into the category of "neglected" diseases.[9] Leishmaniasis was selected by the World Health Organization for elimination by 2015, along with other neglected tropical diseases.[10] It is an ancient disease

Correspondence: Dr. Rajesh Kumar Jha, Department of Pharmacology, Chitwan Medical College (P) Ltd., Bharatpur-10, Chitwan, Nepal. Email: rkjhadr@gmail.com, Phone No : +977-9852049220.

affecting about 12 million people with 2 million new cases every year which constitute a serious public health problem. According to the World Health Organization (WHO), Leishmaniasis is now endemic in 88 countries, particularly in subtropical and tropical regions.[9] Annual incidence is estimated at 1-1.5 million cases of cutaneous leishmaniasis (CL) and 500,000 cases of VL. Of the annual estimated 500,000 cases of VL, 90% occur in 5 countries namely India, Bangladesh, Brazil, Nepal and Sudan. Leishmaniasis is associated with about 2.4 million Disability Adjusted Life Years (DALY) and around 70,000 deaths per year.[11]

DIAGNOSIS

Diagnosis is confirmed by parasitological demonstration of the LD bodies from the tissue aspirates or by serological tests. Diagnostic sensitivity by direct visualization of amastigotes for splenic, bone marrow and lymph node aspirate smears is >95%, 55-97% and 60% respectively.[12] This method is the diagnostic gold standard in regions where tissue aspiration is feasible and microscopy and technical skill are available. Elsewhere including epidemic settings serum antileishmanial IgG in high titre is the diagnostic standard primarily with Direct Agglutination Test (DAT) and other laboratory based serological assays. Freeze-dried antigen and rapid detection of anti-K39 antibody with fingerstick blood in an immunographic strip test have advanced field serodiagnosis. In symptomatic patients, anti-K39 strip test sensitivity is high (90-100%).[13]

TREATMENT

Visceral leishmaniasis is the disease of poor; however the cost of treatment of visceral leishmaniasis is high in those affected. Pentavalent antimonials, introduced in the 1940s, have been used for therapy of leishmaniasis and other protozoal infections, and include sodium stibogluconate and meglumine antimoniate. The discovery of amphotericin B in 1956 added a new option for the treatment of VL but its high cost has prevented its use in control programmes. Later on different lipid formulations of amphotericin B (i.e. liposomal amphotericin B) were developed with similar efficacy as that of conventional amphotericin but with fewer toxic effects. Amphotericin B was later joined by paromomycin, a cheap and effective parenteral drug with an acceptable toxicity profile that can easily be given by intramuscular injection.[14] Paromomycin was found to be effective in clinical trials with transient toxicity.[15] Miltefosine is the mainstay of the recently launched visceral leishmaniasis elimination plan in the Indian subcontinent,[16] and benefits from a preferential pricing scheme that puts it at the same price as generic pentavalent antimonials if large quantities are purchased.[17]

Studies found that the median total expenditure by the patient on visceral leishmaniasis treatment was 1.2 times the annual per capita income in Bangladesh,[18] 1.3 times in India,[19] and 1.1 times in Nepal.[20] They found that paromomycin was the cheapest option and liposomal amphotericin B was the most expensive. Private treatment with miltefosine is rather expensive than the WHO-negotiated preferential price but is cheaper than liposomal amphotericin B.[21] Although these formulations were initially prohibitively expensive, the preferential price now have been offered to government of countries with endemic disease of VL, WHO, and nongovernmental organizations. The newer compounds are also being developed and are likely to constitute the main therapeutic options for visceral leishmaniasis in the years to come.[7,22] These drugs belong to chemically unrelated classes and are thought to have distinct targets and disadvantages. As the drugs for the treatment of VL have diverse side effects, the confirmation of diagnosis is required before the start of treatment. If untreated, almost all cases of kala azar is fatal.[2]

The different drugs being used for the treatment of VL are discussed in following sections.

1. Pentavalent antimony

The pentavalent antimony drug still remains the therapeutic cornerstone in all regions except Bihar state (India) where the current approx. 35% cure response has ended the usefulness of antimony and in southern Europe. In regions other than Bihar and Southeastern Nepal, antimony is effective but has lengthy administration, high cost and adverse reactions.[12] Despite the spread of resistance and severe cardiac, hepatic, pancreatic and renal side effects of pentavalent antimonial compound, these drugs are the choice of treatment in most parts of the world.[23] Classically, it was thought that the antiparasitic effects of antimonials occurred through inhibition of glucose catabolism and fatty acid oxidation; however, recent studies suggest that the drugs operate by interfering with the trypanothione redox system. In drug-sensitive cell lines, antimonials induce a rapid efflux of trypanothione and glutathione from the cells, and also inhibit trypanothione reductase, thereby causing a significant loss of thiol reduction potential in the cells.[24]

Pentavalent antimonials are administered by intramuscular injections of 20 mg/kg/day up to a maximum for 30 days.[25] For these drugs, the cure rate is generally high (85–95%), except in Bihar-India where 60% of patients with VL are now unresponsive.[26]

Parenteral sodium stibogluconate administration has been associated with serious complications such as pancreatitis, cardiotoxicity manifested as T wave inversion, Q-T interval prolongation, S-T segment abnormalities in electrocardiogram.[27] With 20 mg/kg per day for 28 days, cardiotoxicity was reported in 8–17% of cases, with 5–7% proving to be fatal.[28]

2. Amphotericin-B

Another first line drug Amphotericin-B is highly effective despite being an arduous treatment option because of infusions, lengthy administration and adverse reactions. It binds to membrane ergosterol of leishmania leading to the formation of pores resulting in efflux of major constituent from protozoal cells and its lysis. Intravenous infusion (0.75–1mg/kg/day up to 20 days) of amphotericin B is an alternative treatment in all the regions where antimonials resistance has been reported.[29] Toxic effects of Amphotericin-B include fever and rigors during infusion, hypokalemia, renal failure with polyuria and metabolic acidosis. Hemolysis and bone marrow toxicity may induce anaemia.[30,31]

Lipid formulations of Amphotericin-B induce fewer side effects than free drug.[2] Lipid based formulations such as liposomal amphotericin B reduces the impairment of renal function by up to 50% with a therapeutic schedule.[32,33] Lipid formulations of amphotericin B improved highly the safety profile of this drug. Lipid formulations are taken selectively by the reticulo-endothelial system, and exhibit a highly localized enhanced antileishmanial action. There are three lipid formulations of amphotericin B: liposomal amphotericin B, amphotericin B lipid complex and amphotericin B cholesterol dispersion. Currently, liposomal formulations of amphotericin B are the first treatment choice in Southern Europe endemic countries as well as in other developed countries, because of their rapid and up to 100% cure rates with 3–5 days schemes, improved convenience for the patient and reduction of health-care costs.[34-36] However, in poor countries even short courses of liposomal formulations are unaffordable, and the selection of antileishmanial treatment turns more to a question of cost than of efficacy or toxicity.[37,38]

The use of nanoparticles and microspheres for the delivery of conventional amphotericin B also increased its efficacy against experimental VL.[39–41] Similar results have been reported with the heat-induced reformulation of amphotericin B.[42]

3. Paromomycin

Similarly, paromomycin is an aminoglycoside having antileishmanial activity. In a phase III study of VL in India, this drug was associated with 94.6% cure rates, similar to amphotericin B.[15] Since August 2006, paromomycin has been approved in India as a new alternative for visceral leishmaniasis treatment. It is administered intramuscularly 15 mg/kg daily for 21 days. The mechanism of action of the drug is still unclear. In Leishmania, paromomycin could interfere with RNA synthesis and membrane permeability.[43] Paromomycin inhibits protein synthesis and modifies membrane fluidity and permeability. An in vitro study showed that following a 72-hour exposure to L. donovani promastigotes and amastigotes to paromomycin, the mitochondrial potential was decreased, which indicates that mitochondria are the targets of the drug.[44] Paromomycin is equally effective as Amphotericin B (final cure rate, 94.6% vs. 98.8%). Mortality rates in the two groups were less than 1%. Adverse effects were more frequent in the paromomycin-treated group compared with the amphotericin B-treated group (6% versus 2%, resp.); paromomycin-related adverse effects included elevated hepatic transaminases, transient elevation of asparate aminotransferase (AST), transient reversible ototoxicity and pain at injection-site.[15] Currently, paromomycin is under phase IV clinical trials. Paromomycin is inexpensive but requires daily intramuscular injections for 21 days.[37]

In a retrospective study conducted among Sudanese patients with VL, it was found that combination of sodium stibogluconate and paromomycin administered for 17 days was associated with higher cure and survival rates compared to sodium stibogluconate monotherapy administered for 30 days (44%–86% lower odds of death in the combination group).[45]

4. Diamine pentamidine

Pentamidine isethionate given as four intramuscular doses of 3 mg/kg every other day has enjoyed some success in the treatment of cutaneous leishmaniasis (Oriental sore caused by L. tropica) but is not used routinely to treat this infection.[46] Pentamidine has been used to treat VL in courses of 15-20 intramuscular doses of 4 mg/kg every other day.[7] Antileishmanial activity is based on the inhibition of polyamine biosynthesis and the disruption of mitochondrial membrane potential.[47] Major side effects include hypotension, diabetes mellitus and renal impairment. A study in India (with Amphotericin-B and Pentamidine in antimony-unresponsive VL) showed 14 injections of 0.5mg/kg of Amphotericin-B on alternate days were more effective (100% initial and 98% definite cure rates) than 20 injections of pentamidine 4mg/kg on alternate days (80% initial 77% definite cure rates)[48] and at the same time Pentamidine is more toxic than Pentavalent antimony being both nephrotoxic and hepatotoxic and may produce hyperglycemia as a result of pancreatitis.[49]

5. Miltefosine

The most recently introduced drug in the armamentarium of treatment in VL is miltefosine, a hexadecylphosphocholine derived from cancer therapy.[50] Miltefosine was first approved in India (2002), Germany (2004) and Colombia (2005).[51-53] The availability of this oral anti-leishmaniasis drug may revolutionize treatment and control of VL in affected countries.[54] Miltefosine the first effective oral treatment for visceral leishmaniasis, including the antimony resistant infection, has opened the door to self administrative outpatient therapy. The exact antileishmanial mechanism of miltefosine remains largely unknown.[55] Miltefosine could alter glycosylphosphatidylinositol (GPI) anchor synthesis, ether-lipid metabolism, signal transduction and alkyl-specific acyl-coenzyme, acyl-transferase.[56,57] It has been found that miltefosine induces apoptosis as seen by nuclear DNA condensation and DNA fragmentation with ladder formation in L. donovani promastigotes[58] and in U937 cells, activates caspase-9, 3, and 8 through the intrinsic pathway involving the release of cytochrome C from the mitochondrion.[59]

With leishmaniasis, this oral drug treatment has enabled to attain high cure rates in Indian visceral leishmaniasis (95%) and Colombian cutaneous Leishmaniasis (91%) when used at 100-150 mg/day for 28 days.[60,61] Most of the patients respond with clinical improvement after 7-10 days.[62] Despite these encouraging reports, low cure rates observed in CL caused by L. braziliensis or L. major and transient cures followed by relapses in DCL or HIV/VL co-infected patients could minimize its extended use as a monotherapy. Miltefosine is well tolerated with considerably fewer adverse effects as compared to antimonials and amphotericin. The most commonly seen adverse effects are nausea and vomiting. There is an increase in aspartate aminotransferase and creatinine and/or blood urea nitrogen level, which is mild. Grade III hepatotoxicity and renal damage, has also been reported in some cases. However, these changes are reversible in the face of continued treatment or after discontinuation of treatment. Diarrhoea and hepatotoxicity is also reported and is common during first 2 weeks of treatment.[63-65]

Fortunately miltefosine is associated with high efficacy rates, including cases unresponsive to antimonials.[66,67] Miltefosine might be particularly vulnerable to the emergence of resistance, because of its narrow therapeutic index and long half-life, which has been estimated at around 7 days.[55,68] Resistance to miltefosine may emerge easily during treatment due to single point mutations.[69,70] Recent data from patients with cutaneous leishmaniasis suggested a terminal half-life of miltefosine 31 days, with still detectable 5–6 months after the end of treatment.[71] Resistant strains could be selected and amplified during this period because of subtherapeutic drug concentrations, either from relapsing patients, or from newly acquired infections.[55,68]

6. Miscellaneous

Another recently recognized drug for VL is Sitamaquine. The intracellular targets of the 4-methyl-6-methoxy-8-aminoquinoline, sitamaquine, are mitochondria and acidocalcisomes. This compound has been used in clinical trials against new and old-world VL with 67–92% cure rates after oral delivery (1.7–2mg/kg/day) for 28 days. A phase II trial is ongoing to study safety and tolerance.[72-74]

The problem of drug resistance in visceral leishmaniasis has been extensively reviewed.[75] L donovani has acquired resistance to several antileishmanial compounds. A recent study in Bihar indicates that a single dose of liposomal amphotericin B followed by 7–14 days of miltefosine is active against Indian VL.[76] The plant-derived immunostimulant agent picroliv has no antileishmanial activity, however when administered with half-dose miltefosine significantly increases the activity of the later.[77] An another combination of verapamil (a calcium channel blocker) and diperoxovanadate (a potent antileishmanial agent) with sodium antimony gluconate reversed the in vitro antimonials resistance among clinical L. donovani isolates.[78,79]

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