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Leishmaniasis chemotherapy—challenges and opportunities

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Abstract

Although there have been significant advances in the treatment of visceral leishmaniasis (VL), there remain challenges to ensure that treatments effective in India are also effective in other regions of the world and to identify treatment for post kala-azar dermal leishmaniasis as well as the opportunity to develop a safe oral short-course treatment. At the same time, there have been few advances for the treatment of simple or complex forms of cutaneous leishmaniasis (CL), other than topical paromomycin formulations. The main challenge for CL is to ensure that this disease is on the research and development agenda, so that new drugs are evaluated or compounds are screened in appropriate models, and that the standardization of quality of clinical trials is guaranteed. Problems also remain in the treatment of HIV/leishmaniasis co-infected patients. We are some way from having the ideal treatments for VL and CL and drug research and development for these diseases must remain focused.

Keywords: Cutaneous leishmaniasis, drug sensitivity, HIV co-infection, standardization, visceral leishmaniasis
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Introduction

There have been significant differences in progress and approaches to drug development for visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL); these two manifestations will therefore be discussed separately. There are several underlying aspects of the biology of *Leishmania* parasites that affect drug development. For both forms of the disease this includes (i) the intracellular location of the target form of the pathogen, the amastigote, in the low pH phagolysosomal compartment of different macrophage populations and (ii) the varying sensitivities of strains and species compounded by their inter-relationship with the host immune response, which under some circumstances renders drugs ineffective. Where there might be differences in drug development between VL and CL relates mainly to the requirements of the different pharmacokinetic properties of compounds that distribute to the viscera (liver, spleen, bone marrow in VL) or skin (in CL) and to the pharmaceutical formulation of drugs that aid that distribution. Other more subtle differences relating to immunological responses include approaches to accelerate self-cure, especially in CL.

Visceral Leishmaniasis

Current status

As VL, caused by *L. donovani* (in Asia and Africa) and *L. infantum* (in southern Europe, as wells as South America where it used to be referred to as *L. chagasi*), is potentially fatal, it is included as a target disease by players in drug research and development (R&D), for example product development partnerships such as DNDi (Drugs for Neglected Diseases initiative), iOWH (Institute for One World Health), CPDD (Consortium for Parasitic Drug Development), funders such

as the Bill and Melinda Gates Foundation, and the pharmaceutical industry, for example Novartis.

Pentavalent antimonials, the standards drugs for 60 years, are now almost obsolete in the key endemic area in Bihar state, India because of parasite resistance [1], but are still useful in the rest of the world as sodium stibogluconate (Pentostam®), meglumine antimoniate (Glucantime®) [2] or a generic brand of sodium stibogluconate at reduced cost [3] (Table 1). Amphotericin B, normally considered a second-line drug, has been the first line in Bihar following the loss of effectiveness of antimonial drugs. Although a number of amphotericin B lipid formulations, developed during the 1980s for treatment of systemic mycoses in immunocompromised patients, have proved effective in the treatment of VL, only one of these, the liposomal formulation AmBisome®, has become a standard treatment. It is registered for the treatment of VL in various countries and its use is recommended by a WHO working group [4]. Recently, a single-course therapy of 10 mg/kg has been shown to cure 95% of patients in India [5]. The significant reduction in price negotiated by WHO with the producers (Gilead, Foster City, CA), currently $18/50 mg ampoule) is an important component in the impact of this drug. However, AmBisome® remains an expensive treatment as several ampoules will be required even for single-course treatment [6], administration is intravenous and there are adverse events [5], and temperature stability (manufacturer guarantee 25°C) is an issue. A parenteral formulation of the aminoglycoside paromomycin (aminosidine, monomycin), was first shown to have a curative effect in VL in the 1980s and moved slowly through clinical trials with WHO/Special Programme for Research & Training in Tropical Diseases (TDR) in the 1990s and iOWH in the 2000s. An extensive study by iOWH in India showed 94% efficacy (15 mg/kg for 21 days, intramuscularly) in phase III clinical trials in India [7], leading to registration for VL in India in 2006. The anti-leishmanial activity of the phospholipid derivative, miltefosine was first identified in the 1980s [8]; the drug was registered as the first oral treatment for treatment of VL in India in 2002 following clinical trials by WHO/TDR and Zentaris (Frankfurt, Germany) that showed 94% efficacy in adults and children [9]. It was also the first anti-leishmanial to undergo phase IV studies [10], and was incorporated into the VL elimination programme for the sub-continent. Issues around the drug have been (i) potential teratogenicity, requiring women of child-bearing age to take contraception, which they have to take for up to 3 months after treatment because of the long residence time of the drug in the patient organism, and (ii) the 28-day oral treatment, which leads to poor compliance. Drug combinations have proved to be a successful strategy to shorten the course of therapy, reduce toxicities through lower dosage and reduce the selection of resistant mutations for several infectious diseases, most notably malaria and tuberculosis [11]. Although the opportunity for co-formulation, with improved compliance, is not available for VL, a strategy of co-administration (either concomitant or sequential) of available anti-leishmanial drugs has been pursued by DNDi and others following on from experimental studies [12], pre-clinical toxicokinetic studies (DNDi, unpublished) and a pilot clinical study [13] to provide efficacy and safety data. A phase III study on three co-administration regimens showed that for Indian VL: (i) single-dose intravenous AmBi-

TABLE 1. Drugs in use for treatment of leishmaniasis, alone or co-administered

Drug	Properties and administration	Comment
Sodium stibogluconate (Pentostam, SSG) and meglumine antimoniate (Glucantime)	Organo-metal complexes in polymeric forms. Pentostam contains around 33% and Glucantime around 28% pentavalent antimony, intravenous or intramuscular	For VL and CL. There is extensive drug resistance in Bihar India. Variable response in different species that cause CL. Generic sodium stibogluconate (SSG) has made treatment cheaper.
Amphotericin B (Fungizone)	Polyene antibiotic, fermentation product of *Streptomyces nodus*, intravenous	For VL, CL and complex forms of CL, e.g. mucocutaneous leishmaniasis. Has been first-line drug for VL in India where there is antimonial resistance.
Liposomal amphotericin B (AmBisome)	Unilamellar liposome, intravenous	Proved to be most effective lipid formulation for VL and available at $18/50 mg ampoule via WHO. Also used for complex forms, such as PKDL and mucocutaneous leishmaniasis
Miltefosine	Hexadecylphosphocholine, oral	First oral drug for VL. Also effective against some species that cause CL. Contraindicated in pregnancy as found to be teratogenic in rats.
Paromomycin	Aminoglycoside (also known as aminosidine or monomycin), fermentation product of *Streptomyces rimosus*. Supplied as sulphate. Intramuscular for VL and topical for CL.	Registered for VL in India, completed phase III trials for VL in East Africa where less effective in Sudan. Topical formulation (12%) with methyl benzylmethonium chloride available for CL. Topical with gentamicin and surfactants in Phase III trial.
Amphotericin B formulations	Lipidic formulations, intravenous	Other lipid formulations, including Abelcet, Amphocil, Amphomul and multi-lamellar liposomes have been in clinical studies, mainly for VL.
Pentamidine	Diamidine, as isethionate salt, intramuscular	For specific forms of CL in South America only.

CL, cutaneous leishmaniasis; PKDL, post kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.