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 well 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), iOHW (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 I). 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 periternal 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 subcontinent. 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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Properties and administration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium stibogluconate</td>
<td>Organo-metal complexes in polymeric forms.</td>
<td>For VL and CL. There is extensive drug resistance in Bihar India. Variable response in different species that cause CL.</td>
</tr>
<tr>
<td>(Pentostam, SSG) and</td>
<td>Pentostam contains around 33% and</td>
<td>Generic sodium stibogluconate (SSG) has made treatment cheaper.</td>
</tr>
<tr>
<td>meglumine antimoniate (Glucantime)</td>
<td>Glucantime contains around 28% pentavalent antimony, intravenous or intramuscular</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B (Fungizone)</td>
<td>Polyene antibiotic, fermentation product of Streptomyces nodus, intravenous</td>
<td>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.</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>Unilamellar liposome, intravenous</td>
<td>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 (12%) with methyl benzylmethonium chloride available for CL. Topical with gentamicin and surfactants in Phase III trial. Other lipid formulations, including Abelcet, Amphiocid, Amphomul and multi-lamellar liposomes have been in clinical studies, mainly for VL. For specific forms of CL in South America only.</td>
</tr>
<tr>
<td>(AmBisome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miltefosine</td>
<td>Hexadecylphosphocholine, oral</td>
<td>First oral drug for VL. Also effective against some species that cause CL. Contraindicated in pregnancy as found to be teratogenic in rats. 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. Other lipid formulations, including Abelcet, Amphiocid, Amphomul and multi-lamellar liposomes have been in clinical studies, mainly for VL. For specific forms of CL in South America only.</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Aminoglycoside (also known as aminosidine or monomycin), fermentation product of Streptomyces rimosus. Supplied as sulphate. Intramuscular for VL and topical for CL.</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B formulations</td>
<td>Lipidic formulations, intravenous</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Diamidine, as isethionate salt, intramuscular</td>
<td></td>
</tr>
</tbody>
</table>

CL, cutaneous leishmaniasis; PKDL, post kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.
some\textsuperscript{\textregistered} + sequential 7 days oral miltefosine, (ii) single-dose intravenous AmBisome\textsuperscript{\textregistered} + sequential 10 days intramuscular paromomycin, and (iii) concomitant 10 days oral miltefosine + 10 days intramuscular paromomycin achieved a 98% cure rate [14]. The essential point of the study is the greatly reduced treatment time—from 30 days to potentially 8 days—important for both patient treatment and VL control. The advantages of this approach have been recently reviewed in relation to criteria for use [11] and cost [6]. The Indian studies did not include pentavalent antimonials within the co-administrations because of the extensive drug resistance in that region.

**Challenges and opportunities**

It is a major challenge to develop any new drug for the treatment of VL. An additional issue to be tackled is the regional, and perhaps strain, differences in response rates to drugs. A study over 10 years ago suggested that AmBisome\textsuperscript{\textregistered} was most effective in treating VL patients in India, less so in East Africa (L. donovani), and even less so against L. infantum (L. chagasi) in South America [15]. Clinical studies to confirm the worldwide efficacy of AmBisome\textsuperscript{\textregistered} for VL are required and are underway in East Africa (http://www.dndi.org) and Brazil. Clinical trials with paromomycin in East Africa using the same 15-mg/kg regimen for 21 days that was successful in India, showed much lower efficacy, particularly in Sudan where the cure rate was <50%. Even the increased dose of 20 mg/kg for 21 days gave only an 85% cure rate, insufficient for consideration as a monotherapy [16]. The reasons for these differences are not understood.

The dermal manifestation, post kala-azar dermal leishmaniasis (PKDL), which appears weeks to years after the end of treatment of visceral disease, remains poorly understood and whether this phenomenon is related to specific types of drug treatment is not clear [17]. There is no recommended treatment for PKDL and current practice is based upon long courses of antimonial treatment; small studies with miltefosine and AmBisome\textsuperscript{\textregistered} have been described [2,18]. The potential of an immunotherapeutic approach, using antimony plus vaccine plus bacillus Calmette–Guérin (BCG), showed higher cure rate than drug alone [19] and there are further opportunities for research in this area [20].

At the same time there are opportunities for improved use of drugs in treatment and control. For miltefosine, there is need for care in the use of this drug as both the 28-day course of oral therapy, with issues of compliance, and the long drug half-life favour the selection of resistant forms and use of a direct observed therapy system, as used for tuberculosis treatment, could be implemented [21,22]. For most drugs that have been recently introduced there is limited clinical pharmacokinetic and pharmacokinetic/pharmacodynamic information. However, an exemplary study was completed on sitamaquine, an oral 8-aminoquinoline, that had undergone extensive phase II trials in India and East Africa but is no longer in development (Glaxo Smith Kline, personal communication) because of <90% cure rates [23,24], which should provide a guide for studies on future anti-leishmanial drugs [25]. The importance of phase IV studies in the implementation of new drugs should not be underestimated and the information from trials in India on miltefosine [10] and paromomycin (a phase IV trial in 2008–2009 showed a cure rate of 94.2% at 6 months post-treatment, P. Desjeux, personal communication) helps to guide use. The next step in assessing the benefit and safety of new anti-leishmanials, pharmacovigilance, has been advocated and the steps required have been outlined [26].

Other challenges and opportunities are part of the drug R&D programmes, which given the recent progress in treatment with AmBisome\textsuperscript{\textregistered} and co-administrations, underline the need for a safe oral drug with >95% efficacy following a 10–14-day course.

**Cutaneous Leishmaniasis**

There are a limited number of proven treatment options for CL (Table 1). The issues of species variation, 15 Leishmania species can cause CL, and pharmacokinetics are major problems. Pentavalent antimonials have proved inconsistent in their effectiveness across the different Leishmania species, and pentamidine and amphotericin B are limited to specific types of CL [2]. Paromomycin has been tried in different topical formulations with variable clinical results [27,28]. A recent formulation of 12% paromomycin, containing also gentamicin and surfactants, showed efficacy in L. major CL in Tunisia [29], but the trial again exemplified the problems of design in a self-curing disease [30]. Oral miltefosine also has some variable, species-dependent effectiveness against CL [31,32]; it is registered for this indication in Colombia. A retrospective study also indicated that liposomal amphotericin B could have some use in the treatment of CL [33].

Two recent Cochrane analyses of clinical trials of CL in the New World (the Americas) and the Old World (everywhere else) concluded that most clinical studies were not worthy of inclusion in the analysis because they did not meet standards of randomized placebo-controlled trials. Of the Old World trials that were included, there was some evidence of the activity of antifungal azoles, fluconazole for L. major [34,35] and itraconazole for L. tropica [34], whereas in the New World, in addition to antimonials, miltefosine
L. braziliensis caused by antimonials are used for treatment of mucocutaneous disease. Topical approaches would be inappropriate. Long courses of therapy often involving lipid amphotericin B formulations. In the former category, a recently developed antifungal triazole, posaconazole, has shown activity against CL in experimental models [44] and also in one patient [45], supporting further investigation of this class of compounds. In the latter category, the topical approach offers advantages for simple CL (minimal systemic exposure, lesion protected from super-infections) but has limitations for complex CL (multiple lesions, lesions close to eye, potentially metastasizing forms); systemic treatments have disadvantages (high systemic exposure versus low skin concentrations). A recent example of the rational pharmaceutical approach is the performance of studies with the anti-protozoal agent, bu-paraquine, where topical formulations that can deliver drugs to the infected dermal layer in rodent models of infection have been designed [46,47].

Cutaneous leishmaniasis is not part of the R&D agenda of many foundations, partnerships or the industrial sector. The impact of this neglected disease and a road map to develop improved drugs, diagnostics and immunotherapeutics need to be raised on the international agenda. Some attempts have been made and target product profiles have been produced for key forms of CL caused by L. tropica and L. braziliensis [39].

**Leishmaniasis Co-infections—Challenges**

Co-infections of HIV and Leishmania have been reported for VL and CL. Since the first reported case of HIV–VL in 1985, 35 countries have reported co-infections with increasing numbers of cases in East Africa; recent reports are 23% of all VL cases in northeast Ethiopia. A range of treatment regimens with all standard drugs have been described to treat VL in co-infection cases, with relapse rates of 0–85% (39). The most recent review by Alvar et al.[48] highlights the major concerns around the increased risk of developing VL in HIV co-infected patients, by 320 times in areas of endemicity, the reduced likelihood of a therapeutic response and the greatly increased probability of relapse. Currently there is no successful current therapy for patients co-infected with HIV–VL. Countries have different policies; some have adopted a regimen of treatment with anti-retrovirals followed by treatment with anti-leishmanial drugs. Other countries have adopted a policy of maintenance therapy, for example in southern Europe, patients move to maintenance therapy often involving lipid amphotericin B formulations. This co-infection exemplifies the need for effective immune response and that drugs alone cannot clear parasites completely without concurrence by the immune system. The need to raise the importance of HIV–VL on the R&D agenda is crucial.

**Summary**

There have been significant advances in the treatment of VL but there have been few for the simple or complex forms CL, with only topical paromomycin in clinical trial for simple CL. The situation for HIV co-infected patients remains dire. Although we now have single-dose AmBisome® and short-course co-administrations for VL, the goal still remains a safe cheap oral drug requiring a 10–14-day course of treatment; this goal appears to be distant for both forms of the disease. However, there is potential for further development of topical formulations for simple CL. We are some way from hav-
ing the ideal treatments for VL and CL and drug R&D for these diseases needs to be kept high on the agenda.

**Transparency Declaration**

SLC is an advisor to GSK and GNF, Novartis on leishmaniasis.

**References**


