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Review Article

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Leishmaniasis: Standard Treatment and Recent Advances

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ABSTRACT

Leishmaniasis represents a significant impact to the world due to its high prevalence and distribution, especially with regard to the most affected areas located in the Tropical, Subtropical, and Mediterranean regions. There are several challenges which currently impair the control of this disease in endemic areas, which are a result of the lack of health and social investment associated with the scarce scientific support towards the optimization of leishmaniasis diagnosis and treatment. The currently available drugs for the treatment of leishamiasis have problems which limit their use, including toxicity, high cost, and resistant Leishmania strains. Therefore, leishmaniasis treatment research is currently focused on the possible substitution of conventional treatment through the discovery of new compounds or the employment of new therapeutic regimens provided they become safer alternatives to the established protocols. Another promising alternative is the use of drug combinations; however, little progress has effectively been made in this context. Despite the recent research advances, the combat of leishmaniasis still faces the results of decades of stagnation in terms of therapeutic possibilities.

Keywords: *Leishmania*; Leishmaniasis treatment; Leishmanicidal drugs; Advances in leishmaniasis treatment

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INTRODUCTION

Leishmaniasis is a neglected tropical disease caused by protozoan parasites of the genus *Leishmania*. This disease is endemic in 98 countries with approximately 1.3 million new cases occurring annually, 300.000 corresponding to the visceral form and 1 million corresponding to the cutaneous or mucosal forms of the disease. The exact global burden of the disease is, however, underestimated due to misdiagnosis in many cases and the fact that notification is only mandatory in 34% of the endemic countries [1,2]. There are approximately 53 *Leishmania* species described, of which 20 are responsible for human infections [3]. Leishmaniasis has a broad spectrum of clinical manifestations, varying from self-limiting cases with localised skin lesions to cases with disseminated lesions or visceral involvement, and may be grouped into three main forms; namely cutaneous (CL), mucosal (ML), and visceral (VL) leishmaniasis. There is also another condition known as post-kala-azar dermal leishmaniasis (PKDL) which is considered a complication of VL [4-6]. Among the currently available drugs for the treatment of leishmaniasis, pentavalent antimonials are the first-line therapy in most cases. Other available drugs include miltefosine, amphotericin B, pentamidine and paromomycin. Treatment with these drugs is, however, limited due to factors such as resistance; long treatment regimens associated with parenteral administration, with the exception of miltefosine which may be administered orally; and the occurrence of severe side effects. Therefore, the development of more effective and safer drugs for the treatment of leishmaniasis is still a necessity [7,8].

First-line Drugs for Leishmaniasis Treatment

The pentavalent antimonials (Sb(V)) used for the treatment of leishmaniasis are a result of modifications on trivalent antimonials (Sb(III)), which were the first drugs used to treat this disease in the early 20th century [9]. Currently, these antimonials are the first-choice drugs in many countries, including Brazil. Nonetheless, they have been progressively replaced in countries like India and Nepal due to drug resistance reaching rates as high as 60% [10,11]. The only currently available antimonials in the market are sodium stibogluconate (Pentostan®) and meglumine antimoniate (Glucantime®) [8].

The World Health Organization (WHO) states the doses of these drugs should not be higher than 20 mg/kg/day (intramuscular, intravenous or intralymphatic route) due to their high toxicity, causing side effects such as hepatic and cardiac disorders, myalgia, and abdominal pain [12]. As a result, these drugs are contraindicated in patients with cardiac disease, pregnant women, and patients with renal or hepatic insufficiency [13].

There are several hypotheses about the mode of action of Sb(V); the exact mechanisms are, however, not yet known. Chai and Demichele et al. proposed Sb(V) undergoes oxidation-reduction to generate Sb(III) [14,15]. In this context, thiol groups are important because they are present in biomolecules containing cysteine residues which have been associated with this conversion mechanism. Other studies showed Sb(III) is able to inhibit the trypanothione reductase and glutathione synthetase enzymes present in the parasites, consequently interfering with the trypanothione/trypanothione reductase system which is responsible for protecting the parasites against oxidative stress and the action of heavy metals [16]. Another reported mechanism is the inhibition of *Leishmania* topoisomerase I [17].

Second-line Drugs for Leishmaniasis Treatment

Among the available second-line drugs against *Leishmania*, there are pentamidine, amphotericin B, and miltefosine. Pentamidine is an antimicrobial agent which has been used for decades against leishmaniasis. Its mode of action is not yet fully understood; however, studies demonstrate its activity on the parasite mitochondrion through inhibition of the S-adenosyl-L-methionine decarboxylase enzyme. Furthermore, it interferes with polyamine synthesis and topoisomerase I activity [9,18]. Pentamidine administration occurs via the parenteral route and the most significant adverse reactions reported after its use is: hipoglycemia, nausea, nefrotoxicity, abdominal pain, hypotension, diarrhoea, headache, and tachycardia. Therefore, nowadays, the study of pentamidine analogues has been performed with the aim of reducing toxicity and increasing efficacy [5,19]. Another drug used for the treatment of leishmaniasis is amphotericin B. In addition to its antifungal activity, this drug has selective activity against protozoan parasites such as *Trypanossoma cruzi* and *Leishmania* spp [7]. The mode of action of this drug is based on its binding to ergosterol, which causes an increase in the parasite plasma membrane permeability and consequent cell death [12]. Amphotericin B is used for the treatment of patients with pentamidine-resistant VL and for the cases in which there is no significant response to the treatment with pentavalent antimonials. Furthermore, amphotericin B is also efficacious against CL and ML [12,20,21]. Amphotericin B is administered intravenously and is associated with severe adverse effects, including cardiotoxicity, nephrotoxicity, and hepatotoxicity. With the aim of reducing its toxicity, a liposomal formulation of amphotericin B was developed (AmBisome®), which is preferentially uptaken by reticuloendothelial cells of organs like the liver and spleen with consequent decreased nefrotoxicity when compared to the conventional formulation [12,22,23].

Miltefosine (Impavido®) was registered for the treatment of VL in India in 2002 and was later used in other countries after clinical trials demonstrated satisfactory results in adults and children with the disease. Moreover, it was a relatively well-tolerated agent which could be administered orally. The main side effects observed after its use are headache, renal and gastrointestinal disorders, and its teratogenic potential [24]. Miltefosine is a fosfolipid analogue which is active against several *Leishmania* species, including those which cause the cutaneous form of the disease [25]. It is believed miltefosine has more than one molecular target, acting through interference with lipid-dependent cell signalling, induction of nitric oxide synthase 2 (iNOS2) expression with consequent production of NO, and free radical formation, which together lead to apoptosis-like parasite death [26]. Moreover, miltefosine is able to revert the cellular response back to Th1 in infected macrophages, activating functions which help to eliminate the parasites through induction of IFN-γ production [27]. Despite the fact that miltefosine is a simple and orally stable drug, its long half-life facilitates the development of parasite resistance and its efficacy relies on long treatment regimens, which could eventually lead to inadequate use [28]. Indeed, after 10 years of its use in clinical care, there was a significant increase in the number of cases of therapeutic failure [29]. Furthermore, the use of miltefosine to treat patients with PKDL was not shown to be successful, with patients relapsing before 18 months and persistent parasite load [30].

Recent Advances in Leishmaniasis Treatment

Many drugs have been studied for leishmaniasis treatment as isolated therapy or combined therapy to potentiate their effects and improve patient adhesion. Some orally administered agents such as alilamines (terbinafine) and imidazoles, including ketoconazole, itraconazole, and fluconazole demonstrated variable degrees of efficacy when used isolated or in combination [31]. In a study using 200 mg/kg of fluconazole for 6 weeks to treat patients infected with *L. major*, it was observed a cure rate of 79% [32]. However, in a randomised clinical trial conducted in Bahia (Brazil), fluconazole administered orally for 28 days was not efficacious for the treatment of CL caused by *L. braziliensis* [33].

One drug used as oral therapy for the treatment of VL in India and Africa is sitamaquine (WR6026). In India and Africa, phase II clinical trials were conducted in which this drug was efficacious against VL; however, renal adverse effects were reported after 21 days of treatment [34,35].

Combined chemotherapy using sodium stibogluconate and paromomycin was highly efficacious, with a cure rate of 95%, for the treatment of patients infected with *L. donovani* [36]. The combination of sodium stibogluconate and allopurinol or levamisole was considered more effective than sodium stibogluconate used as monotherapy. Furthermore, paromomycin in combination with methyl benzethonium was also efficacious. These combined therapies were recommended for the treatment of patients with HIV/AIDS suffering from VL [37]. Some studies indicate the use of pentoxifylline, a methylxanthine, for the treatment of CL and ML based on its inhibition of the nuclear factor kappa beta (NF-kβ), TNF-α, and intercellular adhesion molecule 1 (ICAM-1) as well as for its nefroprotective effect [38,39]. Recently, the Brazilian Health Ministry recommended the use of pentoxifylline at 400 mg orally as adjuvant therapy for the treatment of ML [40].

Evidences of lifelong immunity against leishmaniasis have also inspired the conduction of research to develop vaccines. Proteins have been investigated as vaccine candidates for CL. Recombinant proteins have also been studied as vaccines for VL with variable degrees of success depending on vaccine formulation, associated immunological adjuvants, and the animal model used. Moreover, parasite antigens from amastigotes and promastigotes are the most commonly tested vaccine candidates [41,42].

CONCLUSION

Leishmaniasis is a major public health problem worldwide; however, the current therapy for this disease remains expensive, besides requiring long treatment regimens and causing severe side effects or drug resistance. Therefore, the scientific support to the discovery and development of new drugs or prophylactic vaccines as efficient, cheap, and safe alternatives for the treatment and control of this disease is a priority.

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