Review article

CED
Clinical and Experimental Dermatology

CPD

Treatment options for leishmaniasis

S. Pradhan,[1] R.A. Schwartz,[2] A. Patil,[3] S. Grabbe[4] and M. Goldust[4]

[1]Department of Dermatology and Venereology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India; [2]Department of Dermatology, Rutgers New Jersey Medical School, Newark, NJ, USA; [3]Department of Pharmacology, DY Patil Deemed, To Be University, Navi Mumbai, Maharashtra, India; and [4]Department of Dermatology, University Medical Center Mainz, Mainz, Germany

doi:10.1111/ced.14919

Summary

Leishmaniasis is broadly classified into three types: cutaneous, mucocutaneous and visceral. The visceral form is most dangerous and can result in death. Although leishmaniasis is an ancient disease, its treatment is still challenging. Several drugs, differing in their cost, toxicity, treatment duration and emergence of drug resistance, are used for different types of leishmaniasis. To overcome these limitations, the search for newer drugs and other treatments continues. In this article, we discuss conventional drugs, other treatments, including newer options such as immunotherapy and immunochemotherapy, and future prospects for leishmaniasis treatment.

Introduction

Leishmaniasis, caused by protozoan of the genus *Leishmania*, is classified into three types: visceral (VL), cutaneous (CL) and mucocutaneous. The CL form is the most common whereas VL, also known as kala-azar, is the most severe. The currently available treatment options are associated with several limitations including adverse effects (AEs), cost, poor efficacy and the need for multiple injections. Emergence of drug resistance is another concern. Recently, owing to a deeper understanding of the disease pathogenesis, newer therapies such as immunotherapy and immunochemotherapy are being tried. Similarly, various therapeutic targets in the metabolic pathways of *Leishmania* are being continuously explored. In this article, we discuss a number of options for the management of leishmaniasis.

Chemotherapeutic agents

Historically, pentavalent antimony was considered the first-line drug treatment for leishmaniasis; however, it is associated with cardiotoxicity,[1] cirrhosis, pancreatic toxicity[2] and risk of resistance.[3] Subsequently, amphotericin B (and lipid formulation) emerged as second-line therapies. Miltefosine has since been used in VL and CL; this has the advantages of being an oral drug with good efficacy and short course, but teratogenicity and drug resistance are its important limitations.

Existing drugs repurposed for leishmaniasis include amphotericin B, miltefosine, paromomycin and petamidine. Azole antifungals have also studied for leishmaniasis; itraconazole was found to be superior to ketoconazole and fluconazole for inhibiting growth of most *Leishmania* strains.[4] In a multicentre trial, paromomycin was found to be successful in Indian patients with VL, but was less efficacious in a Sudanese population.[5] Pentamidine is used intramuscularly/intravenously, but is not available in an oral formulation. It has the advantage of a short course, but its efficacy varies for different *Leishmania* species, and its use may be associated with dysglycaemia and other AEs.

All these therapies are shown in Table 1.

Combination chemotherapy

To prevent drug resistance, improve compliance, shorten the duration of treatment and thereby reduce the cost of therapy, combination chemotherapy has

Correspondence: Dr Mohamad Goldust, Department of Dermatology, University Medical Center Mainz, Station 1A, 1st floor. Langenbeckstr.1. Building 401. D-55101, Mainz, Germany Email: mgoldust@uni-mainz.de

Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 1 September 2021

Table 1 Chemotherapeutic agents for leishmaniasis.

Drug	Route of administration	Dose	AEs	Advantages	Disadvantages
Pentavalent antimonial	IM, IV or IL	20 mg/kg/day for 28–30 days	Cardiotoxicity, pancreatitis; nephrotoxicity; hepatotoxicity	Easy availability (in endemic areas); low cost	Prolonged treatment duration; pain during injection, toxic AEs; drug resistance
Amphotericin B	IV	0.75–1 mg/kg/day for 15–20 days, daily or alternate daily	Renal toxicity; injection-related reactions; hypokalaemia	Primary resistance is not common;	Requires hospitalization for administration; nephrotoxicity; heat; instability
Liposomal amphotericin B	IV	10–30 mg/kg total dose (single dose; 3–5 mg/kg/dose)	Chills and rigors during injection; mild nephrotoxicity	High efficacy; low toxicity	High cost; need for slow IV infusion
Miltefosine	Oral	100–150 mg/day for 28 days	GI AEs; renal and liver toxicity; teratogenicity	Effective	High cost; possibly teratogenic; drug resistance; poor compliance
Paromomycin	IM (VL) or topical (CL)	15 mg/day for 21 days or 20 mg/kg for 17 days	Renal, ear and liver toxicity	Effective; relatively cheap	Varied efficacy according to geographical area; potential for resistance
Pentamidine	IM	3 mg/kg/day IM alternate daily for 4 injections	Hyperglycaemia; hypotension; tachycardia; electrocardiographic changes	Short course needed	Varied efficacy depending on *Leishmania* species

AD, adverse effect; CL, cutaneous leishmaniasis; GI, gastrointestinal; IL, intralesional; IM, intramuscular; IV, intravenous; VL, visceral leishmaniasis.

been developed. The various combinations include liposomal amphotericin B plus miltefosine, liposomal amphotericin B plus paromomycin, miltefosine plus paromomycin, and sodium stibogluconate/meglumine antimoniate plus paromomycin.[6–8]

Local therapies

Local therapies have been developed for limited CL as options to avoid toxicity with systemic use of drugs. Photodynamic therapy (PDT), cryotherapy and thermotherapy have all been tried in CL (Table 2).

Photodynamic therapy

PDT involves the use of aminolaevulinic acid (ALA) or methyl-aminolaevulinate applied topically to the skin, followed by irradiation with laser or intense pulsed light. A few mechanistic studies have addressed the principles underlying the use of PDT for the treatment

Table 2 Local therapies for cutaneous leishmaniasis.

Type	Mechanism	Advantages
PDT	Topical ALA/MAL, followed by laser or IPL; kills host cells and thus kills parasites	Rapid localized destruction of lesion
Cryotherapy	Reduces local tissue temperature, producing cryonecrosis	Usually not associated with secondary effects; short duration of therapy; potential for better compliance/adherence
Thermotherapy	Increases local tissue temperature by means of baths, infrared light, laser. Kills heat-sensitive parasites	Good efficacy, good safety profile

ALA, aminolaevulinic acid; IPL, intense pulsed light; MAL, methyl aminolaevulinate; PDT, photodynamic therapy.

of CL.[9–11] In mechanistic and *in vitro* studies, ALA-PDT did not demonstrate any antileishmanial effects.[9] However, *in vivo* studies showed that topical ALA-PDT resulted in extensive tissue destruction and significant reduction of parasite load. The macrophage number and interleukin-6 level decreased in the infected skin. The antileishmanial effects of ALA-PDT for CL are mediated through the killing of host cells. Owing to lack of sufficient data, topical ALA-PDT is not recommended in clinical practice.

Cryotherapy

Intracellular and extracellular ice-crystal formation and changes in cell membrane with cryotherapy ultimately result in damage to infected cells and destruction of amastigotes at temperatures below freezing. Cryonecrosis results in release of antigenic substances that induce immune response and result in healing of other lesions. Cryotherapy can be a good option for the treatment of CL, particularly given the various disadvantages of chemotherapy. It has shown excellent response in patients with skin lesions of 10–30 mm in size, those with fewer lesions and those with development of < 3 months.[12] Cryotherapy in combination with intralesional sodium stibogluconate was found to be very efficacious, resulting in 100% healing of CL lesions.[13] In another study, combination treatment with itraconazole and cryotherapy resulted in 80.9% improvement in CL lesions, and liver toxicity risk was also reduced as the itraconazole dose could be reduced.[14]

Thermotherapy

The species of *Leishmania* causing cutaneous disease are heat-sensitive, and cannot grow or survive in temperatures > 39°C.[15,16] Hence, thermotherapy has been considered as treatment option for CL lesions.

Radiofrequency (RF) therapy, a form of thermotherapy, has been tried in patients with CL. A study from Guatemala reported a cure rate of 73% in patients with CL, which were the same rates as obtained with a systemic pentavalent antimonial drug.[17] In RF, heat penetrates uniformly to a depth of 4 mm, heating and killing the amastigote forms of *Leishmania* residing in the upper dermis, without damaging the surrounding skin. In two randomized studies, RF thermotherapy had a lower cure rate than systemic pentavalent antimonial drugs, but RF was cost-effective and had fewer AEs.[18,19] Thermotherapy once every 3 weeks had a cure rate of 73%, whereas increasing the frequency to once weekly increased the cure rate to 81%.[20]

Newer options: immunotherapy

Modulation of the immune response for prophylactic and/or therapeutic purposes by using biological substances or molecules is the basic principle of immunotherapy.[21] Immunotherapy augments the natural host defences, restores impaired effectors functions and also decreases host excessive response, either directly or indirectly.[22] Immunotherapy in leishmaniasis constitutes vaccines, interferons (IFNs) and protein immunomodulators, or a combination of these.

Vaccines

Various types of vaccines including whole-killed parasites, fractionated *Leishmania* antigen, live-attenuated pathogens and recombinant proteins (produced by genetically engineered cells) have been developed. Third-generation vaccines are under investigation.

Interferons

IFNs are naturally occurring cytokines and commercially produced by recombinant DNA technology. They produce various biological functions including immunosuppressive actions. The cytokine IFN-γ can induce macrophages to kill intracellular *Leishmania*.[23] IFN-γ-1b protein is administered with sodium antimony gluconate. It was found to be well tolerated and effective in patients with VLs refractory to monotherapy with pentavalent antimonial therapy.[24,25] Use of IFN-γ in untreated cases of VL led to accelerated parasitological control[26,27] along with increased clinical efficacy of pentavalent antimonial therapy.[27] In the study of Squires *et al.*, combination of IFN-γ and pentavalent antimonial therapy for 1 month produced a negative spleen culture more quickly among patients with VL.[26]

Immunomodulators

The immunomodulator protein aggregate magnesium–ammonium phospholinoleatepalmitoleate anhydride was found to improve clinical signs in canine VL and significantly reduce parasite load in the skin.[28]

Combination therapy

Immunotherapeutic and chemotherapeutic agents have been used to produce a synergistic action in activating the immune system and by the direct action of drugs on the infectious agent.[21]

Future prospects

Endochin-like quinolones are competitive inhibitors of the cytochrome bc_1 complex, which can affect the mitochondrial electron transport chain (ETC) in several species of *Leishmania*. Hydroxynaphthoquinone–buparvaquone acts by depleting adenosine triphosphate (ATP) levels and thereby producing inhibition of the ETC in amastigotes.[29]

New benzophenone-derived bisphosphonium salts are leishmanicidal and target complex II of the respiratory chain of the parasite, leading to death.[30] Artemisinin showed antileishmanial activity by triggering induction of cell cycle arrest and apoptosis.[31]

Tafenoquine impairs the bioenergetic metabolism of *Leishmania* promastigotes, causing a rapid drop in intracellular ATP levels, resulting in apoptosis and thereby leading to mitochondrial dysfunction.[32]

The major sterols essential for growth and viability in trypanosomatids are ergosterol and 24-methyl sterol, hence, the sterol and fatty acid metabolic pathway can be a potential drug target in leishmaniasis. In experimental studies, simvastatin and atorvastatin and resveratrol were found to inhibit the growth of *Leishmania donovani* promastigotes.[33] Other enzymes involved in sterol biosynthesis are also potential targets for antileishmanial drugs.

Alkylphospholipid analogues have recently been demonstrated as possible target drugs. In experimental studies, edelfosine killed both *Leishmania* promastigotes and amastigotes.[34]

Polyamines are strongly associated with cell survival, growth and proliferation. Various enzymes involved in polyamine metabolism and folate metabolism can also be used as targets for antileishmanial activity.

Conclusion

Chemotherapeutic regimens used for treatment of leishmaniasis are associated with several AEs. Advances in the understanding of the pathogenesis have resulted in development of various drugs targeting different biochemical pathways. Newer treatments such as immunotherapy and immunochemotherapy are gaining importance.

References

1 Sundar S, Sinha PR, Agrawal NK *et al*. A cluster of cases of severe cardiotoxicity among kala-azar patients treated with a high-osmolarity lot of sodium antimony gluconate. *Am J Trop Med Hyg* 1998; **59**: 139–43.

2 Gasser RA Jr, Magill AJ, Oster CN *et al*. Pancreatitis induced by pentavalent antimonial agents during treatment of leishmaniasis. *Clin Infect Dis* 1994; **18**: 83–90.

3 Thakur CP, Sinha GP, Pandey AK *et al*. Do the diminishing efficacy and increasing toxicity of sodium stibogluconate in the treatment of visceral leishmaniasis in Bihar, India, justify its continued use as a first-line drug? An observational study of 80 cases. *An Trop Med Parasitol* 1998; **92**: 561–9.

4 Croft SL, Yardley V. Chemotherapy of leishmaniasis. *Curr Pharm Des* 2002; **8**: 319–42.

5 Sundar S, Jha TK, Thakur CP *et al*. Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med* 2007; **356**: 2571–81.

6 World Health Organisation. *Control of the Leishmaniases*. WHO Technical Report Series. Geneva: WHO, 2010.

7 Sundar S, Rai M, Chakravarty J *et al*. New treatment approach in Indian visceral leishmaniasis: single-dose liposomal amphotericin B followed by short-course oral miltefosine. *Clin Infect Dis* 2008; **47**: 1000–6.

8 Omollo R, Alexander N, Edwards T *et al*. Safety and efficacy of miltefosine alone and in combination with sodium stibogluconate and liposomal amphotericin B for the treatment of primary visceral leishmaniasis in East Africa: study protocol for a randomized controlled trial. *Trials* 2011; **12**: 166.

9 Akilov OE, Kosaka S, O'Riordan K, Hasan T. Parasiticidal effect of delta-aminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis is indirect and mediated through the killing of the host cells. *Exp Dermatol* 2007; **16**: 651–60.

10 Kosaka S, Akilov OE, O'Riordan K, Hasan T. A mechanistic study of delta-aminolevulinic acid-based photodynamic therapy for cutaneous leishmaniasis. *J Invest Dermatol* 2007; **127**: 1546–9.

11 Tsai JC, Chen IH, Wong TW, Lo YL. In vitro/in vivo correlations between transdermal delivery of 5-aminolaevulinic acid and cutaneous protoporphyrin IX accumulation and effect of formulation. *Br J Dermatol* 2002; **146**: 853–62.

12 Salmanpour R, Razmavar MR, Abtahi N. Comparison of intralesional meglumine antimoniate, cryotherapy and their combination in the treatment of cutaneous leishmaniasis. *Int J Dermatol* 2006; **45**: 1115–16.

13 el Darouti MA, al Rubaie SM. Cutaneous leishmaniasis. Treatment with combined cryotherapy and intralesional stibogluconate injection. *Int J Dermatol* 1990; **29**: 56–9.

14 Al-Mutairi N, Alshiltawy M, Khalawany M *et al*. Treatment of Old World cutaneous leishmaniasis with dapsone, itraconazole, cryotherapy, and imiquimod, alone and in combination. *Int J Dermatol* 2009; **48**: 862–9.

15 Berman JD, Neva FA. Effect of temperature on multiplication of Leishmania amastigotes within human monocyte-derived macrophages in vitro. *Am J Trop Med Hyg* 1981; **30**: 318–21.

16 Sacks DL, Barral A, Neva FA. Thermosensitivity patterns of Old vs. New World cutaneous strains of Leishmania growing within mouse peritoneal macrophages in vitro. *Am J Trop Med Hyg* 1983; **32**: 300–4.
17 Navin TR, Arana BA, Arana FE *et al*. Placebo-controlled clinical trial of meglumine antimonate (glucantime) vs. localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. *Am J Trop Med Hyg* 1990; **42**: 43–50.
18 Vega JC, Sanchez BF, Montero LM *et al*. The efficacy of thermotherapy to treat cutaneous leishmaniasis in Colombia: a comparative observational study in an operational setting. *Trans R Soc Trop Med Hyg* 2009; **103**: 703–6.
19 López L, Robayo M, Vargas M, Vélez ID. Thermotherapy: an alternative for the treatment of American cutaneous leishmaniasis. *Trials* 2012; **13**: 58–68.
20 Sadeghian G, Nilfroushzadeh MA, Iraji F. Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. *Clin Exp Dermatol* 2007; **32**: 371–4.
21 Roatt BM, de Oliveira Aguiar-Soares RD, Coura-Vital W *et al*. Immunotherapy and immunochemotherapy in visceral leishmaniasis: promising treatments for this neglected disease. *Front Immunol* 2014; **5**: 272.
22 Okwor I, Uzonna JE. Immunotherapy as a strategy for treatment of leishmaniasis: a review of the literature. *Immunotherapy* 2009; **1**: 765–76.
23 Murray HW, Rubin BY, Rothermel CD. Killing of intracellular Leishmania donovani by lymphokine-stimulated human mononuclear phagocytes. Evidence that interferon-gamma is the activating lymphokine. *J Clin Invest* 1983; **72**: 1506–10.
24 Sundar S, Rosenkaimer F, Murray HW. Successful treatment of refractory visceral leishmaniasis in India using antimony plus interferon-gamma. *J Infect Dis* 1994; **170**: 659–62.
25 Badaro R. The use of recombinant gamma interferon associated with pentavalent antimony in therapy for visceral leishmaniasis. *Mem Inst Oswaldo Cruz* 1988; **83** (Suppl): 376–7.
26 Squires KE, Rosenkaimer F, Sherwood JA *et al*. Immunochemotherapy for visceral leishmaniasis: a controlled pilot trial of antimony versus antimony plus interferon-gamma. *Am J Trop Med Hyg* 1993; **48**: 666–9.
27 Sundar S, Murray HW. Effect of treatment with interferon-gamma alone in visceral leishmaniasis. *J Infect Dis* 1995; **172**: 1627–9.
28 Santiago ME, Neto LS, Alexandre EC *et al*. Improvement in clinical signs and cellular immunity of dogs with visceral leishmaniasis using the immunomodulator P-MAPA. *Acta Trop* 2013; **127**: 174–80.
29 Ortiz D, Forquer I, Boitz J *et al*. Targeting the cytochrome bc1 complex of Leishmania parasites for discovery of novel drugs. *Antimicrob Agents Chemother* 2016; **60**: 4972–82.
30 Luque-Ortega JR, Reuther P, Rivas L, Dardonville C. New benzophenone-derived bisphosphonium salts as leishmanicidal leads targeting mitochondria through inhibition of respiratory complex II. *J Med Chem* 2010; **53**: 1788–98.
31 Sen R, Bandyopadhyay S, Dutta A *et al*. Artemisinin triggers induction of cell-cycle arrest and apoptosis in Leishmania donovani promastigotes. *J Med Microbiol* 2007; **56**: 1213–18.
32 Carvalho L, Lugue-Ortega JR, Manzano JI *et al*. Tafenoquine, an antiplasmodial 8-aminoquinoline, targets Leishmania respiratory complex III and induces apoptosis. *Antimicrob Agents Chemother* 2010; **54**: 5344–51.
33 Dinesh N, Pallerla SR, Kaur PK *et al*. Exploring Leishmania donovani 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR) as a potential drug target by biochemical, biophysical and inhibition studies. *Microb Pathog* 2014; **66**: 14–23.
34 Villa-Pulgarín JA, Gajate C, Botet J *et al*. Mitochondria and lipid raft-located FOF1-ATP synthase as major therapeutic targets in the antileishmanial and anticancer activities of ether lipid edelfosine. *PLoS Negl Trop Dis* 2017; **11**: e0005805.

CPD questions

Learning objective

To demonstrate up-to-date knowledge in the management of leishmaniasis.

Question 1

Which of the following forms of leishmaniasis is most severe?

(a) Visceral form.
(b) Cutaneous form.
(c) Mucocutaneous form.
(d) Cutaneous as well as mucocutaneous form.
(e) Mucocutaneous and visceral form.

Question 2

Which of the following drugs can be given by oral route in the treatment of leishmaniasis?

(a) Amphotericin B.
(b) Pentavalent antimonial.
(c) Liposomal amphotericin.
(d) Miltefosin.
(e) Paromomycin.

Question 3

What is the advantage of liposomal amphotericin B over conventional amphotericin B?

(a) Increase efficacy.
(b) Reduce toxicity.
(c) Increase efficacy and minimize toxicity.
(d) Reduce cost.
(e) Reduce plasma exposure.

Question 4

In which of the following types of aminolaevulinic acid is used as a part of therapy against leishmaniasis?

(a) Cryotherapy.
(b) Photodynamic therapy.
(c) Thermotherapy.
(d) Parenteral therapy.
(e) Preventive therapy.

Question 5

Which of the following routes are used for administration of pentavalent antimonials in the treatment of leishmaniasis?

(a) Oral.
(b) Topical application (e.g. cream).
(c) Oral and topical application.
(d) Intravenous.
(e) Intravenous, intramuscular and intralesional.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.