Review

Therapy of cutaneous leishmaniasis
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There have been many treatment modalities used for the therapy of cutaneous leishmaniasis. Although treatment need not be given for cosmetically insignificant lesions, which are often self-limited, therapy is usually indicated for larger, cosmetically significant and disfiguring lesions, and lesions which progress. This review summarizes the published evidence in support of the numerous therapeutic options that have been employed for cutaneous leishmaniasis.


INTRODUCTION

Leishmania species are protozoal parasites of the order Kinetoplastida, which give rise to a number of distinct clinical syndromes, ranging from self-limited cutaneous lesions to progressive visceral disease and death. There have been more than 20 species identified, most of which cause zoonotic infections, but which can also cause disease in humans in endemic areas. Numerous rodent and canine species serve as reservoirs, and sandflies serve as vectors. Rare cases of congenital or transfusion-related transmission have also been reported. Cutaneous leishmaniasis is classified into two different clinical syndromes: New World if it is acquired in the Americas, and Old World if it is acquired in Africa, Asia, the Middle East, and northern Africa. This discussion will focus on reviewing the clinical evidence supporting various options for the treatment of cutaneous leishmaniasis (CL), particularly the Old World form.

Epidemiology

Over 350 million people live in endemic areas, and the WHO has estimated the prevalence of CL to be 12 million cases/year and that of CL to be 1.5–2.0 million cases/year, although the true prevalence and incidence may be considerably higher, due to underreporting.1 Old World CL is usually due to L. major, L. tropica, or L. aethiopica.2 New World CL is usually caused by members of the L. mexicana complex (L. mexicana mexicana, L. mexicana amazonensis, L. mexicana venezuelensis), and New World mucocutaneous leishmaniasis is usually caused by members of the L. braziliensis complex (L. braziliensis braziliensis, L. b. panamensis, and L. braziliensis guyanensis) (Table 1).

CL is usually sporadic in nature, but can occasionally occur in an epidemic pattern, e.g. when large groups of susceptible persons migrate to an endemic area (i.e. military personnel). Old World CL due to L. major is found in rural desert areas of central Asia, the Middle East, and northern Africa. It causes lesions that tend to be large and ‘wet’ in appearance. The primary reservoir consists of desert rodents. Old World CL due to L. tropica is endemic to urban areas of the Middle East, the Mediterranean, India, Pakistan, and central Asia. The lesions tend to be ‘dry’, with a central crust. Old World CL caused by L. aethiopica is found in the Ethiopian highlands and Kenya, where it causes both simple CL and diffuse CL.

Pathogenesis

Leishmanial infections are transmitted via the bite of infected female sandflies of the genera Phlebotomus, Lutzomyia, or Psychodopygus. The parasite lives as an extracellular, flagellated promastigote in the gut of the insect. After multiplication and differentiation in the sandfly gut, approximately 1 week later the infectious promastigotes migrate to the proboscis. Following inoculation into the skin of a mammalian host, the parasite exists within lysosomes of mononuclear phagocytes as an intracellular amastigote, characterized by a large eccentric nucleus and a mitochondrial structure called a kinetoplast. The clinical and histologic appearance of the CL skin lesions is related to an interaction between the host’s immune response and the virulence factors of the different Leishmania species. The clinical spectrum of CL ranges from an entity called diffuse CL, where there is a scarce immune response and heavily parasitized macrophages, to leishmaniasis recidivans, where there is a strong mononuclear cell response, with few amastigotes.

Clinical features

Thus, CL presents as a spectrum of disease ranging from single, chronic ulcerative lesions (‘oriental sores’) to
Table 1. Leishmaniasis: clinical syndromes and geographic distribution

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Most common species</th>
<th>Distribution</th>
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<tbody>
<tr>
<td>Cutaneous leishmaniasis</td>
<td></td>
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<tr>
<td>Old World</td>
<td><em>L. major</em></td>
<td>Rural desert areas of Asia, Middle East, and northern Africa</td>
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<td></td>
<td><em>L. tropica</em></td>
<td>Urban areas of Middle East, Mediterranean, India, Pakistan, and central Asia.</td>
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<tr>
<td></td>
<td><em>L. aethiopica</em></td>
<td>Ethiopian highlands, Yemen, and Kenya</td>
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<tr>
<td>New World</td>
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<td></td>
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<tr>
<td></td>
<td><em>L. mexicana</em></td>
<td>Central and South America</td>
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<tr>
<td></td>
<td><em>L. braziliensis</em></td>
<td>America</td>
</tr>
<tr>
<td></td>
<td><em>L. chagasi</em></td>
<td>Peru, Argentina</td>
</tr>
<tr>
<td></td>
<td><em>L. peruviana</em></td>
<td>Panama, Costa Rica, Colombia</td>
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<tr>
<td></td>
<td><em>L. panamensis</em></td>
<td>Venezuela</td>
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<tr>
<td></td>
<td><em>L. venezuelensis</em></td>
<td></td>
</tr>
<tr>
<td>Mucocutaneous leishmaniasis</td>
<td><em>L. braziliensis</em></td>
<td>Central and South America</td>
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<tr>
<td>(espundia)</td>
<td></td>
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<tr>
<td>Visceral leishmaniasis</td>
<td><em>L. donovani</em></td>
<td>India, China, Nepal, Pakistan, East Africa</td>
</tr>
<tr>
<td></td>
<td><em>L. chagasi</em></td>
<td>Latin America</td>
</tr>
<tr>
<td></td>
<td><em>L. amazonensis</em></td>
<td>Brazil</td>
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</tbody>
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Disseminated nodular lesions ('diffuse' CL). The typical lesion appears as an erythematous papule at the site of inoculation which increases in size and ulcerates. The lesions are round with a raised border. Wet lesions are covered with an exudate, and may become secondarily infected with bacteria or fungi. Other lesions are dry with central crusting. Old World CL is frequently self-limited, eventually resolving without treatment. However, scarring associated with the lesions is difficult to predict on initial presentation, and can be disfiguring, particularly in Old World CL.

There are two forms of chronic CL: diffuse CL and leishmaniasis recidivans. Diffuse CL is rare, and is associated with *L. aethiopica*, *L. amazonensis*, *L. mexicana*, and other minor species. In this condition, there is an absence of cellular immune responses, and heavily parasitized macrophages are abundant in the dermis. The cutaneous lesion begins as a non-ulcerative papule, followed by migration of the organisms to other sites, resulting in disseminated nodules. Areas of involvement can be extensive, and the lesions could be permanent. Leishmaniasis recidivans is a relapsing form of CL caused by *L. tropica*, and is seen mostly in Iran and central Asia. There is an intense cellular immune response to Leishmania antigen; on skin biopsy, a dense mononuclear infiltration with few amastigotes is seen. It usually affects the face, and it can last for several decades.

HIV co-infection with Leishmania species can alter the epidemiology, diagnosis, and response to therapy. Visceral leishmaniasis is an important opportunistic infection in patients with HIV/AIDS, and cutaneous leishmaniasis can present atypically with multiple cutaneous lesions and mucosal involvement.

Conventional therapy in patients with HIV/AIDS and leishmaniasis is associated with a higher relapse rate, and therefore secondary prophylaxis is recommended.

Diagnosis

The diagnosis of CL is confirmed by identification of amastigotes in tissue or culture of promastigotes. The two most common media utilized in culture are a modified Novy–MacNeal–Nicolle medium (NNN) and Schneider's Drosophila medium enriched with fetal calf serum. Growth of most organisms occurs within 1–2 weeks, although cultures should be maintained for 4 weeks. Demonstration of parasites in the skin can be accomplished by slit-incision along the ulcer edge, whereby exposed tissue and fluid are scraped onto a slide or culture medium. Skin biopsy by a standard punch biopsy can also be done at the most inflamed edge of a lesion. Giemsa staining allows the best visualization of the parasite.

Speciation is usually only available from research laboratories, the Centers for Disease Control (Atlanta, USA), or the European reference center in Montpellier, France. Methods of speciation include isoenzyme analysis, kinetoplast DNA hybridization, and use of monoclonal antibody detection. Serologic testing is of limited utility in CL. Intradermal skin testing (Montenegro test) using killed Leishmania antigens can be of utility in some cases, and is available through the WHO. The sensitivity of Leishmania skin testing is high, but in endemic areas it lacks specificity, because it does not distinguish between current and past infections. Because of the difficulties with current diagnostic strategies, recent studies have focused on the develop-
ment of polymerase chain reaction (PCR) methods for the diagnosis of leishmaniasis by amplification and detection of ribosomal or kinetoplast target DNA. Weigle et al. compared a PCR method for detection of kinetoplast DNA in biopsy specimens with three conventional diagnostic methods, and found, in 255 patients with acute CL lesions, that the sensitivity of PCR (75.7%) was significantly better than that of Giemsa-stained lesion scrapings (46.7%), biopsy culture (55.3%), and aspirate culture (46.3%), and all three conventional methods combined (70.2%).

Overview of treatment modalities

The decision on whether to treat CL depends on the location and extent of the lesion, and whether mucosal leishmaniasis is a possibility. However, if the lesion is in a cosmetically unacceptable area or is not healing, specific treatment is indicated. An incredibly diverse array of therapeutic agents has been tried for the treatment of CL, in part due to the geographic and clinical diversity of leishmaniasis, the lack of a completely reliable mode of treatment, often with significant side effects, and a paucity of rigorous clinical trials studying these agents. The pentavalent antimony (Sb) compounds sodium stibogluconate (Pentostam, Glaxo-Wellcome, Research Triangle Park, North Carolina, USA) and meglumine antimoniate (Glucantime, Rhône-Poulenc, Paris, France) remain the mainstay of therapy for most forms of leishmaniasis. Other major treatments use physical modalities (heat, cryosurgery), local or intraleisional injections, various anti-infective agents (Dapsone, metronidazole, trimethoprim–sulfamethoxazole), amphotericin B, pentamidine, allopurinol, azoles, immunotherapy (i.e. interferon-γ), and a variety of miscellaneous agents.

Pentavalent antimony (Sb)

Sodium stibogluconate is available in the USA from the CDC (telephone: 404-639-36/0, business hours, 404-639-2888, non-business hours) through an investigational drug protocol. It is also available in Europe, Africa, and India. Meglumine antimoniate is used in Latin America and in French-speaking countries in Africa. There is extensive experience in the use of Sb in the treatment of leishmaniasis, although it is not clear how comparable in terms of efficacy and toxicity the different formulations are. In the only study to compare sodium stibogluconate and meglumine antimoniate for the treatment of CL, Deps et al. conducted a single-blind, randomized study of 63 patients with localized CL, and found that efficacy was similar but hepatic and pancreatic toxicity was higher in the sodium stibogluconate arm. However, the preparation of sodium stibogluconate used in this study may have been unusually toxic.

Sb has had variable success in the treatment of Old World CL, and because the disease is often self-limited, Sb can be avoided in many circumstances. Thus, few studies have been done specifically with Sb and Old World CL. Chulay et al. used high-dose Sb at 18–20 mg/kg twice daily for the treatment of three patients with CL caused by L. aethiopica in Kenya, which usually responds poorly to conventional dosing with Sb. All patients had a good long-term response. Belazzoug et al. treated approximately 400 school children in Algeria with Sb (given intramuscularly) or placebo, and found no significant differences in response rates (48% versus 55% respectively). Few details, however, were included in the publication. El-Safi et al. reported their experiences with the treatment of CL, giving approximately 110 patients Sb (600 mg/day for 21–30 days), and achieving clinical cure in all but two patients.

The recommended dose of Sb is 20 mg/kg per day for 20 days (for CL) or 28 days (for visceral leishmaniasis). Important side effects include cardio-toxicity (prolongation of QTc, ST-T wave changes), biochemical and, less commonly, clinical pancreatitis, arthralgias, myalgias, nausea/vomiting, liver transaminase abnormalities, pancytopenia, and, rarely, renal toxicity. Gasser et al. reported a small prospective study of 17 patients treated with Sb for CL, in which 16 patients developed an increase in pancreatic enzymes and 12 developed clinical pancreatitis, although pancreatitis resolved with discontinuation of therapy.

Local heat or cold therapy

Junaid reported his experience of treating 178 patients with CL in Iraq using a heat-generating device creating a temperature of 55°C for 5 min. One hundred and sixty-two patients responded well to a single application of heat. Aram and Leibovic used local hyperthermia to 42°C for 2–3 min induced by ultrasound to treat 18 patients with CL in Israel. Twenty-two lesions (78.5%) in 13 patients resolved completely over 5–10 weeks. Both of these uncontrolled studies reported minimal side effects. Navin et al. conducted a randomized trial of 66 patients in Guatemala with proven New World CL divided into three treatment arms: meglumine antimoniate (850 mg/day for 15 days), localized heat from a radiofrequency generator (50°C for 30 s, three weekly treatments), and placebo. Cure rates were 16 (73%), 16 (73%), and 6 (27%), respectively. Velasco-Castrejon et al. treated 201 patients with CL in Mexico with heat therapy. A localized current field-radio-frequency device was used to give a single application of heat at 50°C for 30 s. Of 191 patients evaluated at 8 weeks of follow-up, 172 (90%) were cured.

Bassiouny et al. used a CO2 cryomachine to treat 30 patients with histologically confirmed CL in Egypt in an uncontrolled trial, reporting that all patients were cured without scarring at 4–5 weeks. Applications generally lasted for 30–60 s, and most cases resolved with a single treatment. Serial biopsies confirmed killing
of the parasite. Leibovici and Aram treated 14 patients with confirmed CL in Israel with liquid nitrogen in an uncontrolled study. All lesions were cured clinically and parasitologically at 3–8 weeks, without scarring or relapse at 4 months. Despite these promising results, in a larger, unblinded trial, Al-Gindan et al treated 88 patients with cryosurgery but achieved a cure rate of only 27%, as compared to 41% with Sb and 30% with ketoconazole. Side effects included hypopigmentation, and some patients developed satellite lesions.

El Darouti and Rubaie compared cryotherapy, intralesional Sb and combined cryotherapy and intralesional Sb in a total of 44 patients in an unblinded study in the United Arab Emirates. The combination therapy group achieved a 100% cure rate at 6 weeks, compared to 68% in the cryotherapy group, and 44% in the intralesional Sb group.

Topical and intralesional therapies

Paromomycin ointment has been studied by several groups in the treatment of Old World CL, as a topical preparation of low toxicity. However, some paromomycin ointments are formulated with dimethylsulfoxide (DMSO), which is a potentially toxic irritant. El-Safi et al performed a double-blind study comparing 10-day courses of paromomycin (16 patients) and placebo (15 patients), and found no significant difference in the response rates, although when individual lesions were compared, a significant difference was found. El-On et al compared paromomycin and 15% methylbenzethonium chloride (MBCl), paromomycin and 12% MBCl, and placebo, in a randomized, double-blind, crossover study in 39 patients. Both treatment arms had a combined cure rate of 74.2% versus 26.6% in the placebo group. No difference was found between the two treatment arms. Two more recent randomized, placebo-controlled trials of paromomycin in Old World CL have not had similar success. In a study by Ben Salah et al, 115 patients with confirmed CL due to L. major in Tunisia were randomized to paromomycin ointment (57) or placebo (58) for 2 weeks. There was no difference in adverse effects. Although there was a trend for parasitologic improvement (negative smears) at day 15, this difference was not apparent at days 45 and 105.

In a study by Asilian et al, 251 patients with CL were randomized to paromomycin ointment (125) or placebo (125) for 2 weeks. Paromomycin ointment was well tolerated. Although at days 15 and 105 (but not at day 45) there was parasitologic improvement in the treatment group, no clear clinical benefit was observed.

Larbi et al performed a randomized, double-blind study of topical clotrimazole versus miconazole for 30 days for the treatment of CL in 54 patients (151 lesions) in Saudi Arabia. Of 89 lesions treated with clotrimazole, 15.7% healed fully, and 47.2% were reduced in size, versus 0.0% and 35.5% in the miconazole group. No significant side effects were observed.

In vitro experiments have demonstrated the parasidal activity of nitric oxide against Leishmania. Nitric oxide is synthesized in macrophages, and diffuses well into skin tissues. S-nitroso-N-acetylpenicillamine (SNAP) is a compound that generates the production of nitric oxide. Lopez-Jaramillo et al used SNAP cream every 4 h while the patients were awake for 10 days for the treatment of 16 patients with CL in Ecuador. At 30-day follow-up, all lesions were healed and new skin was observed. In contrast, Davidson et al treated 42 patients with CL with a topical cream that induces the generation of nitric oxide. In this approach, nitric oxide is generated non-enzymatically by the acidification of nitrite (KNO2) by ascorbic acid or salicylic acid. Only 11 (28%) patients showed clinical improvement, and only 5 (12%) were cured at 2 months.

Soto et al used a combined regimen of topical paromomycin (15%) and MBCl (12%) twice a day for 10 days plus intramuscular or intravenous meglumine antimoniate for 3 or 7 days in Colombian patients with CL. In the cohort of 20 patients who received the injectable meglumine, the cure rate was 90% versus 42% in those who received it for only 3 days.

Intralesional treatment of CL with Sb has been used to minimize the systemic effects of the medication. Faris et al conducted an uncontrolled study using intralesional Pentostam in 710 patients with confirmed CL in Saudi Arabia. Most lesions required eight injections for resolution, although some required up to 24 injections. Seventy-two per cent of lesions were cured, 23.9% improved, and 4.1% worsened. Side effects were limited to pain at the injection site and hyperpigmentation.

Tallab et al conducted a prospective dose-ranging study of 96 patients (129 lesions) with confirmed CL in Saudi Arabia with intralesional Sb. Their results suggest that alternate-day or weekly injections of Sb for a total of three injections was more effective than daily injection. The final complete cure rate was 99.2% after additional injections were given. Good results with intralesional Sb have also been obtained in New World CL.

Cohen and Livshin treated a total of 50 CL lesions in 31 patients with intralesional injections of emetine hydrochloride, and obtained a cure rate of 100%. The injections were administered weekly or bi-weekly, and the amount of emetine injected varied from 10 to 160 mg, depending on the size of the lesion.

Anti-infective agents

Several conventional anti-infective agents have been tried for the treatment of CL, including dapsone, rifampin with or without isoniazid, metronidazole, and trimethoprim–sulfamethoxazole (TMP–SMX). Dogra et al conducted the first study of dapsone (50 patients)
versus an untreated control group (15 patients) in India. Forty of 50 patients in the treatment group were clinically cured after 21 days of treatment, and no clinical improvement was seen in any members of the control group. The only side effect from the dapsone was nausea (14%). Following this, Dogra39 conducted a double-blind study of 120 patients, comparing oral dapsone (60 patients) or placebo (60 patients) for 6 weeks. Of the patients receiving dapsone, 49/60 (82%) were cured. Side effects included nausea (nine patients) and anemia (three patients). In the placebo group, 0/60 showed spontaneous healing in the 6-week study period.

Rifampin has shown some efficacy in the treatment of CL, with or without isoniazid. Livshin et al40 compared rifampin alone to rifampin with isoniazid in 39 patients with CL in Israel. The duration of therapy varied from 14 to 60 days. At both 1 and 2 months after beginning therapy, no major difference was found between the two groups (52.9% versus 55%, respectively). Other studies have shown variable success rates with rifampin, ranging from 0% to 80%.

There are various case reports and case series describing the use of metronidazole and TMP-SMX for the treatment of CL with variable success.10

Amphotericin B

Amphotericin has been used since its introduction into clinical medicine in 1955 as an alternative to Sb, with high cure rates, but significant toxicities.17 Although it is considered an effective alternative to Sb, there is a paucity of published trials regarding its use in CL. Liposomal formulations of amphotericin have demonstrated in vitro efficacy against experimental CL in mice,41 and several case reports have described its successful use in leishmaniasis.

Pentamidine

Pentamidine has also proven to be efficacious in the treatment of leishmaniasis, including Old World CL.8 Like amphotericin B, it is considered a traditional alternative to Sb, but its use is limited by its toxicities. Soto-Mancipe et al42 randomized 92 patients with New World CL to four treatment arms: intramuscular meglumine antimoniate (10 mg/kg b.i.d. for 20 days), intramuscular pentamidine (2 mg/kg q.o.d. in seven doses), oral itraconazole (200 mg b.i.d. for 28 days), or no treatment. Cure rates were as follows: meglumine antimoniate 21/23 (91%), pentamidine 23/24 (96%), itraconazole approximately 25%, and placebo 14/22 (36%, not including six patients lost to follow-up). A side arm of the study assessed intramuscular pentamidine at a lower dose (2 mg/kg q.o.d. in four doses), reporting cure in 14/19 patients (74%). The results of this study were difficult to interpret, due to a relatively high number of patients lost to follow-up or violating the treatment protocol.

Allopurinol

Allopurinol is metabolized to toxic nucleosides by the Leishmania parasite. Martinez and Marti43 conducted an open-label, randomized study of 110 patients, comparing allopurinol plus meglumine antimoniate versus meglumine alone in New World CL in Colombia. All patients had proven L. braziliensis panamensis infection. Allopurinol was given at 20 mg/kg per day in four divided doses for 15 days; meglumine was administered at 20 mg/kg for 15 days. Cure rates were as follows: meglumine alone 36%, allopurinol and meglumine 74%, allopurinol alone 80%, and untreated 0%. No major toxic effects were observed.

These results must be interpreted with caution, however, as there was an unusually low cure rate in the group treated with Sb alone.44 Velez et al45 conducted a randomized, partially double-blind, controlled trial using allopurinol alone to treat CL in Colombia, enrolling 187 patients. Patients were randomly assigned to receive either allopurinol (20 mg/kg q.d. for 28 days), placebo tablets (for 28 days), or intramuscular glucantime (20 mg/kg/day for 20 days). One hundred and fifty-seven patients (86%) were evaluated. Cure rates were as follows: allopurinol 18/55 (33%), placebo 17/46 (37%), and glucantime 52/56 (93%). No significant difference was found between the allopurinol and placebo groups.

The use of allopurinol in combination with Sb has also been specifically addressed. Momeni and Aminjavaheri46 conducted an uncontrolled trial of allopurinol and meglumine antimoniate in 25 patients with recurrent CL unresponsive to previous therapy, and a duration of disease greater than 2 years. Twenty-four of 25 patients responded well to treatment, and no relapse occurred at 1-year follow-up. No significant side effects were noted. Martinez et al47 conducted an open-label, randomized, controlled study in Colombia in 100 patients, comparing stibogluconate (49 patients) versus stibogluconate and allopurinol (51 patients) in the treatment of CL. Cure rates were 39% for Sb, and 71% for Sb and allopurinol, which was statistically significant.

Azoles

Azoles interfere with leishmanial cell membrane biosynthesis. Ketoconazole has been used in the treatment of Old World CL, with mixed results. Weinrauch et al48 report treating approximately 100 patients with CL in Israel, with a cure rate of approximately 70% in cases due to L. major after 4–6 weeks of treatment with 200–400 mg of ketoconazole. Results were poor in cases of CL due to L. tropica or L. aethiopica. Ketoconazole has been used with success in New World CL as well. Saenz et al49 obtained comparable cure rates in a small study comparing ketoconazole and Pentostam (16/21 versus 13/19, respectively). In a larger study, Navin et al50 randomized 120 patients to ketoconazole (600 mg q.d. for 28 days), Pentostam, and placebo. Treatment
outcome depended on the particular species involved. For *L. braziliensis*, response rates were 24/25 for Sb, and 7/23 for ketoconazole. For *L. mexicana*, response rates were 4/7 for Sb, and 8/9 for ketoconazole.

Singh et al\(^1\) reported poor results in a small trial involving 16 patients with CL in India. Patients were given ketoconazole at 200 mg b.i.d. for 10 weeks. Of 14 patients completing the study, no patients showed any improvement. Alsaleh et al\(^2\) compared dosages of ketoconazole in the treatment of CL in Kuwait. Eighteen patients received 600 mg and 15 patients received 800 mg of ketoconazole daily, with cure rates of 12/15 (80%) and 9/11 (82%), respectively, inpatients completing the study, and minimal side effects. Ozgoztasi and Baydar\(^3\) compared topical paromomycin and oral ketoconazole in Turkey in an open-label, randomized study enrolling 72 patients. Cure rates were 15/40 (37.5%) in the paromomycin group and 0/32 (0.0%) in the ketoconazole group.

Itraconazole has shown promising results in several earlier case reports\(^4\) and small pilot studies.\(^5\) Momeni et al\(^6\) conducted a randomized, double-blind study comparing itraconazole (7 mg/kg/day) and placebo for 3 weeks in the treatment of CL in Iran. One hundred and forty patients were enrolled, and 131 patients completed treatment, from an area endemic for *L. major*. Cure rates were 59% in the itraconazole group, and 44.3% in the placebo group, although statistical significance was not achieved. No difference was found in adverse effects.

**Terbinafine**

Terbinafine is an antifungal agent of the allylamine group that inhibits ergosterol synthesis. Bahamdan et al\(^7\) administered terbinafine at a dose between 250 mg/day and 500 mg/day for 4 weeks to 27 patients with CL. Of the 14 patients who finished the study, 10 (71.5%) showed a clinical response (either partial or complete cure). No side effects were reported. Gonzalez-Ruperez et al\(^8\) have also reported the successful use of terbinafine in one HIV-positive patient with localized CL.

**Miltefosine**

Miltefosine (hexadecylphosphocholine), an agent that has been studied in oncologic clinical trials, has been used in the therapy of visceral and cutaneous leishmaniasis. Jha et al\(^9\) administered miltefosine 100–150 mg/day for 28 days to 90 Indian patients with visceral leishmaniasis, achieving a cure rate of 96%. Most recently, Soto et al\(^10\) enrolled 72 Colombian military personnel with CL in an open-label, rising-dose, phase II trial. The cure rate for patients receiving 133–150 mg/day miltefosine was 94%. Motion sickness was seen in 40% of the patients, but it did not interfere with their normal duties.

**Immunotherapy**

The roots of immunotherapy lie in the still used ancient practice of leishmanization, in which material from an active lesion of CL is inoculated into the arm or buttock to produce a self limited lesion in an inconspicuous site. Vaccines utilizing killed *Leishmania* antigens are still under investigation. Interferon-\(\gamma\) has shown promise when combined with Sb in the treatment of visceral, mucocutaneous or cutaneous leishmaniasis. Harms et al\(^11\) conducted a randomized, prospective trial comparing intralesional glucantime and intralesional interferon-\(\gamma\) in 40 patients in Syria. Interferon-\(\gamma\) alone showed mixed effectiveness. Arana et al\(^12\) conducted a randomized, double-blind trial of 66 patients in Guatemala, comparing meglumine for 20 days, meglumine for 10 days, and meglumine for 10 days plus interferon-\(\gamma\). Meglumine was given intravenously, and interferon or placebo was given subcutaneously (five injections in total). Cure rates were 19/21 (90%), 18/20 (90%), and 22/22 (100%), respectively. However, there was no statistically significant difference in response rates between the three groups.

**CONCLUSION**

The optimal approach to the treatment of CL remains a challenge, as systemic therapy is expensive and associated with significant toxicities. Definitive recommendations are hampered by the self-limited nature of many cases of CL, and a paucity of rigorously designed clinical trials. Sb remains the standard therapy for CL that requires treatment, despite its significant toxicities. In New World CL, the ability of *L. braziliensis* to progress to mucocutaneous disease necessitates systemic therapy. Pentamidine, amphotericin B and azoles are also effective as systemic therapy. Local and topical therapies, such as topical paromomycin or intralesional Sb, may be useful in cases where cosmetic aspects are of less concern, particularly in Old World CL, although specific therapeutic modalities may not be widely available. Immunotherapy and vaccine development represent a promising avenue of continued research.

**REFERENCES**

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