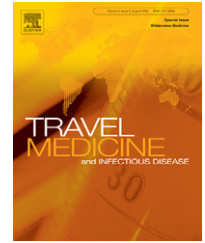




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REVIEW

Cutaneous leishmaniasis treatment

Philippe Minodier^{a,*}, Philippe Parola^b

^aPediatric Emergency Unit, CHU Nord, Chemin des Bourrelly, 13915 Marseille Cedex 20, France

^bInfectious Diseases Department, CHU Nord, Chemin des Bourrelly, 13915 Marseille Cedex 20, France

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Summary

The causative species of cutaneous leishmaniasis determines the clinical features and courses, and treatments. Intralesional or systemic antimonials are the gold standard for the treatment of these diseases. However, as for visceral leishmaniasis, other therapeutic options appear promising. Paromomycin ointments are effective in *Leishmania major*, *L. tropica*, *L. mexicana*, and *L. panamensis* lesions. In *L. braziliensis* localized leishmaniasis, both paromomycin and imiquimod may be topically applied. Oral fluconazole and zinc sulfate are useful in *L. major*. Oral azithromycin, effective in vitro and in mice, needs further investigation in human leishmaniasis. On the contrary, data with oral itraconazole are disappointing. Oral miltefosine, which is very effective in visceral leishmaniasis caused by *L. donovani*, appears ineffective in *L. major* and *L. braziliensis* infections. Intramuscular pentamidine is required for *L. guyanensis* cutaneous leishmaniasis, for which systemic antimony is not effective. Liposomal amphotericin B could be an alternative to antimony in south American cutaneous leishmaniasis with mucosal involvement (especially *L. braziliensis* and *L. guyanensis* infections).

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Introduction

Cutaneous leishmaniasis presents a broad spectrum of clinical features. It is caused by the same parasites belonging to the genus *Leishmania*, and is always trans-

mitted by the bite of tiny sand flies from the sub-family of *Phlebotominae* (more than 30 species known vectors of leishmaniasis).

Cutaneous leishmaniasis may be limited to a single part of the skin (localized cutaneous leishmaniasis) or may produce a large number of lesions (diffuse cutaneous leishmaniasis). Mucocutaneous leishmaniasis can lead to the destruction of mucous membranes of the nose, mouth and throat. Some *Leishmania* species isolated in cutaneous leishmaniasis (*Leishmania donovani*, *L. infantum*, *L. chagasi*) can also invade the viscera and cause life threatening visceral

*Corresponding author. Tel.: +33 491 96 87 50;
fax: +33 491 96 46 75.

E-mail addresses: philippe.minodier@ap-hm.fr (P. Minodier),
phparola@yahoo.fr (P. Parola).

leishmaniasis or kala-azar. In immunocompetent patients, clinical features of cutaneous leishmaniasis depend mainly on the causative *Leishmania* species [1–3].

In the Old World, localized cutaneous leishmaniasis is due frequently to *L. major* (zoonotic cutaneous leishmaniasis), and this leishmaniasis tends to resolve within 2–4 months [4]. *L. tropica* is restricted strictly to human beings (anthroponotic cutaneous leishmaniasis) and the lesions due to this species may persist for a longer time (6–15 months). *L. infantum* localized cutaneous leishmaniasis is observed less frequently. In the New World, localized cutaneous leishmaniasis is caused mainly by *L. peruviana*, *L. guyanensis*, *L. braziliensis* or *L. mexicana* species.

Diffuse cutaneous leishmaniasis is an infection caused by *L. aethiopica* in Africa, and *L. amazonensis* in South America. However, diffuse cutaneous leishmaniasis is also observed in immunosuppressed patients infected with species isolated commonly in localized forms. Mucosal dissemination is described in South America. It is caused by *L. braziliensis*, and, less frequently, by *L. panamensis* or *L. guyanensis*.

Finally, as the prognosis of the disease varies with the species, the choice of treatment also depends on the causative *Leishmania* [5]. Unfortunately, the species identification by culture and by isoenzymatic examination is fastidious and time consuming (several weeks), and new rapid tools, as genomic amplification by the polymerase chain reaction, are not available widely. This is the reason why clinicians encountering patients with leishmaniasis treat frequently patients without identification of the species, inferred from the geographical setting of the patient and the epidemiology of the disease in the area. Moreover, the distribution of *Leishmania* species may vary from region to region, and sometimes, especially in South America, several species with different clinical courses are endemic concurrently.

In 2004, Blum et al. [5] published an overview of the cutaneous leishmaniasis treatment options, but several drugs were still under investigation at the time. Recent trends for the treatment of visceral leishmaniasis are oral miltefosine (*L. donovani*) [6] or short-course regimens of liposomal amphotericin B (*L. infantum*, especially in children) [4,7,8].

In this paper, the available treatments for cutaneous leishmaniasis are discussed with regards to the causal *Leishmania* species. Noninvasive options and oral drugs are highlighted, when sufficient evidence is available.

Topical treatments and intralesional injections

Intralesional injections of pentavalent antimony

Several pentavalent antimonials are available currently: sodium stibogluconate (Pentostam[®], GSK, United Kingdom) and its generic forms, used in field conditions, and meglumine antimoniate (Glucantime[®], Aventis, France). Intramuscular or intravenous antimony has been used in VL for years: drugs regimens, adverse events, drug unresponsiveness are well known and discussed elsewhere [9].

The World Health Organization (WHO) [10] recommendations for the treatment of cutaneous leishmaniasis are intra-

lesional or systemic antimonials, according to the species and the clinical features. Local infiltration with pentavalent antimony has been used in Old World localized cutaneous leishmaniasis. WHO recommends an injection of 1–3 ml under the edges of the lesion and the entire lesion until the surface has blanched. The infiltration could be given every 5–7 days, for a total of 2–5 times [5]. In 1999, a systematic review of the reported series showed that intra-lesional antimonials partially or completely cured 72–97% of the lesions caused by *L. major* [11]. More recently, 106 pediatric cutaneous leishmaniasis cases have been published in Tunisia [12]. Species typing is not mentioned in the series. However, lesions are supposed to be due to *L. major*, which is endemic in Tunisia, or to *L. infantum* which is isolated sporadically in Northern Tunisia, where most of the children lived [13]. In the latter study, intra-lesional meglumine antimoniate (1 ml/cm²/week, until recovery) was used in children with fewer than five lesions, and/or without lesion on a cartilaginous area (ear, nose), or 63% of the subjects. The average number of injections for cure is 1.9, but some patients have been treated for one year. Pain during injection is reported frequently by the children. In another study in this country, including 272 children or adults treated with intra-lesional injections [14], adverse events were observed in 5%: bacterial super-infections (especially when cutaneous leishmaniasis was located on face or limbs), stibio-intolerance signs (in cephalic locations) or evolution to sporotrichoid lesions.

In *L. major* cutaneous leishmaniasis, intra-lesional injections of meglumine antimoniate (0.2–0.8 ml/lesion every other day for 30 days) have been compared to intramuscular injections (only 15 mg/kg/day, 6 days/week for 2 weeks) in a randomized study [15]. There was no statistically significant difference between the two groups on day 30.

Intra-lesional antimonials seem to be less effective in *L. tropica* cutaneous leishmaniasis. More than 3000 cases, presumed to be due to this species [16], have been reported in Turkey [17]. 66% of the patients were under 19 years. Intra-lesional injections of meglumine antimoniate (1 ml/cm²) were used in 76% of the patients regardless of the age. The average number of injections was 11. With a prolonged treatment however, relapses are reported less frequently than with short courses (4–6%) [18,19].

Other intra-lesional injections

Local injections of hypertonic sodium chloride solution or zinc sulphate have been reported to be as effective as local sodium stibogluconate in a few Iraqi patients [20,21].

Paromomycin (aminosidine) ointments

Paromomycin belongs to the aminoglycoside family of antibiotics. Its activity against parasites led to its use in amoebiasis, intestinal helminthiasis or visceral leishmaniasis [22]. Two topical preparations are available for cutaneous leishmaniasis: 15% paromomycin sulphate dissolved in a soft white paraffin base, either with 12% methyl-benzothonium chloride or with 10% urea.

In *L. major* cutaneous leishmaniasis, the efficiency of two ointments per day for 10–30 days varies from 74% to 86%,

higher with repeated applications [23–25]. Paromomycin seems to be less effective in *L. tropica* lesions [26,27].

Paromomycin sulphate 15%+12% methyl-benzothonium chloride was very effective in *L. mexicana* infected mice [28], but it cured only 68% of 53 Belizean patients infected with this species [29]. In Guatemala, 76 patients, infected with *L. braziliensis* (75%) or *L. mexicana* (25%), have been treated with 20 days of 15% paromomycin sulphate plus 12% methyl-benzothonium chloride too [30]. Initial cure rate was 91%, but declined to 86% at the one year follow up (placebo, 39% and 39%, respectively). In the contrast, in Honduras [31], 15% paromomycin sulphate + 10% urea was identical to placebo to cure cutaneous leishmaniasis due to *L. mexicana* or *L. chagasi*. In the latter study, the intact skin (nonulcerative lesions) might hinder the absorption of paromomycin.

Recently, 15% paromomycin sulphate plus 12% methyl-benzothonium chloride and 15% paromomycin sulphate plus 10% urea (two applications per day for 30 days in each case) were compared to systemic meglumine antimoniate (20 mg/kg/d for 10 days) in *L. panamensis* cutaneous leishmaniasis [32]. At the 6 weeks follow-up, cure rates were 48.3%, 40% and 80.6%, respectively. However, by 12 weeks, clinically cured patients were 79.3%, 70% and 91.7% (not significantly different). Relapses during the first year after treatment were also identical in the three groups (17.4%, 10.5%, and 15.2%, respectively). Local side-effects were observed frequently with topical paromomycin ointments (20–40%).

Imiquimod

Imiquimod (Aldara[®]) is used in HPV-induced skin diseases, genital warts or premalignant conditions. This imidazoquinoline amine is an immune response modifier that targets preferentially monocytes and macrophages, and induces a T-helper 1 response with an increasing release of Interferon- α (IFN- α), Tumor necrosis factor- α (TNF- α) and Interleukins IL-1 β , IL-6 or IL-8. In an in vitro infection assay and in infected mice, imiquimod demonstrated a leishmanicidal activity by inducing the expression of the inducible nitric oxide synthase (iNOS) gene and the release of nitric oxide [33].

Imiquimod was first used in combination with antimony for *L. peruviana* cutaneous leishmaniasis [34]. In a recent randomized study [35], imiquimod 5% cream (application of a thin layer of cream every other day for 20 days) plus meglumine antimoniate (20 mg/kg/d for 20 days) cured patients more rapidly than meglumine antimoniate + vehicle control (50% versus 15% at 1 month, and 72% versus 35% at 3 months). In this study, patients may have been infected with *L. braziliensis* or *L. peruviana* and data were not analyzed according to the causative species. Residual scars seemed less prominent in the imiquimod group, but no standardized scale was used for the assessment of the quality of the scar.

In Old World leishmaniasis, imiquimod 5% (three times a week for 8 weeks) has been considered as ineffective in 12 patients [36].

Topical amphotericin B

In Israel, some *L. major* infected patients have been successfully treated with colloidal dispersion of amphotericin

B and cholesteryl sulphate (Amphocil[®]), dispersed in glucose-free 5% ethanol [37,38].

Cryotherapy

Cryotherapy has been only used in Old World cutaneous leishmaniasis. In Turkey for instance [17], 90% of 461 patients presumed to be infected with *L. tropica* have been cured by one session of cryotherapy with liquid nitrogen. Hypopigmentation after treatment was noted in 68%, but repigmentation occurred within 2–3 months. The optimal duration of each application and the intervals between applications cycles are not defined: two cycles of 10–30 s freezing time are sufficient for *L. tropica* lesions in Greece [39], whereas 1–3 sessions of two applications (15–20 s freezing time with a thaw of 1 min, each) are used in Jordan (*L. major* or *L. tropica*) [40].

In Iran (*L. major* or *L. tropica*), cryotherapy was compared to intra-lesional meglumine antimoniate alone and to cryotherapy plus intra-lesional meglumine antimoniate [41]. In another study in this country, cryotherapy plus intra-lesional antimony was also compared to intra-lesional meglumine antimoniate alone [42]. In both studies, cure rates of cryotherapy plus local antimonials were close to 90%, whereas healing was obtained in only 50% with cryotherapy or antimony alone ($p < 0.05$).

Localized controlled heat

ThermoMed[®] (ThermoSurgery Technologies, Inc, Phoenix, Arizona) is an FDA-approved device that delivers localized radiofrequency-generated heat directly to a lesion through prongs placed onto it. Heat may be controlled locally and 50 °C for 30 s are used. The procedure is painful and requires local anesthetic. Localized controlled heat was found to be as effective as meglumine antimoniate in Guatemalan *L. mexicana* induced cutaneous leishmaniasis [43]. However, meglumine antimoniate was better for *L. braziliensis* infected patients in this study. The effectiveness against *L. mexicana* was substantiated in Mexico (90% healing at 2 months) [44].

In Old World cutaneous leishmaniasis, localized controlled heat has been used successfully in 26 soldiers returning from Operation Iraqi Freedom with *L. major* cutaneous leishmaniasis [45].

A randomized controlled trial was recently conducted in Kabul, Afghanistan too (*L. tropica* focus) [46]. The goal of the study was to compare thermotherapy using radiofrequency (≥ 1 consecutive application at 50 °C for 30 s), intralesional sodium stibogluconate (five injections of 2–5 ml every 5–7 days) and intramuscular sodium stibogluconate (20 mg/kg/d with a limited daily dose of 850 mg, for 21 days) for the treatment of single cutaneous leishmaniasis lesions. 259 of 401 patients > 5 years completed the 100 days follow up. The Odds ratio of cure were not significantly different in comparison of intralesional antimony (cure rate 75.3%) and localized controlled heat (cure rate 69.4%), whereas intramuscular antimony (with a daily limited dose) cured only 44.8% of the patients. Moreover the time of cure was significantly shorter in patients treated with thermotherapy than in these with intralesional or intramuscular sodium

stibogluconate (53 days, versus 75 days and >100 days, respectively).

CO₂ laser

Carbon dioxide laser has been used to vaporize cutaneous leishmaniasis lesions in Turmenistan [47] or Iran [48]. In the latter series (*L. major* infection presumed), a power of 30W (maximum 100W) and a pulse width of 0.5–5s, until the ulcer bed turned brown and the hemostasis was performed, provided 94% healing. Lesions were anesthetized previously by local injection of 1–2% lidocaine. The control patients were treated with meglumine antimoniate with 83% efficacy ($p < 0.0007$). Complications were observed in only 4.5% patients (24% in control group): hyperpigmentation, persistent redness, hypertrophic scarring. Moreover, healing was shorter in CO₂ laser treated patients (1 month versus 3 months with antimony). A recent report from Iran found that CO₂ laser cured $\frac{19}{21}$ patients with lupoid cutaneous leishmaniasis, which is a chronic form usually due to *L. tropica* [49].

Photodynamic therapy

Photodynamic therapy is used in malignant skin lesions and seems efficient against warts caused by Human Papilloma Virus. This treatment uses porphyrin compounds. A 10% δ -aminolevulinic acid emulsion is locally applied under occlusion for 4h. Then, irradiation was undertaken using broadband (570–670nm) red light (CureLight Broadband; PhotoCure ASA, Oslo, Norway), delivering 100J/cm² per treatment session at a light intensity of 150mW/cm². Treatment is repeated at weekly intervals [50].

In an in vitro assay [51], a combination of hematoporphyrin and menadione (a quinonoid compound) has been proved to be toxic against *L. donovani*, by producing reactive oxygen species, originating from cellular redox cycling of menadione and followed by decomposition of the formed hydrogen peroxide by hematoporphyrin. Following these in vitro data, photodynamic therapy has been used in a few *L. major* infected Israeli patients [50,52]. However, the good results observed might be related to self healing rather than photodynamic therapy, with regards to the duration of treatment [53].

Oral treatments

Azoles

As for amphotericin B, certain azole antifungal drugs inhibit the 14 α -demethylation of lanosterol, mediated by cytochrome 450. They cause an accumulation of 14 α -methyl sterols and block ergosterol synthesis of *Leishmania* parasites. The azoles can be given orally.

Ketoconazole (600mg/d in adults and 10mg/kg/d in children, for a month) was tried during the 1980s [54]. Its efficacy varies with the species [54–56] and this drug is not used commonly.

Fluconazole has a long half-life, a high solubility in water and a concentration in skin that is ten times that in plasma

[57]. A randomized, double-blind, placebo-controlled trial was conducted in Saudi Arabia, in patients >12 years infected with *L. major* [57]. Its limitations have been emphasized elsewhere [58]. In an intention-to-treat analysis, fluconazole (200mg/d for 6 weeks) healed completely patients at the 3-month follow-up in 59%, versus 22% for placebo (relative risk, 2.76; 95% confidence interval, 1.84–4.12). The time to healing was also significantly shorter in the fluconazole group (median, 8.5 weeks). A pediatric case (fluconazole 100mg/d for 3 weeks) was published recently elsewhere [59].

Itraconazole (100–400mg/d) has been used with certain efficacy in small series, in India [60], Brazil [61], Argentina [62], Italy [63] or United Kingdom [64]. However, larger series in Iran (*L. major* cutaneous leishmaniasis) have found low response rates regardless of the duration of treatment (three [65] or eight weeks [66]). Finally, itraconazole (400mg/d for >3 months) cured only 23% of 13 patients with MCL from Ecuador (*L. braziliensis*) by 12 months, despite an improvement in all during the first month of treatment [67].

Azithromycin

Azithromycin is an azalide antibiotic (family of macrolide). It concentrates in tissues, especially in macrophages that are infected by *Leishmania* parasites, and can reach levels 100–200 times higher than in the serum [68]. Its oral administration, its long half-life, and its safety in children are advantages for the treatment of leishmaniasis. Azithromycin is effective for decreasing *L. major* promastigotes count in cell-free culture, and *L. major* amastigotes count in macrophages culture [68]. It proved to be effective in susceptible mice infected with *L. major* [68]. Two small series [69,70] of *L. braziliensis* infected patients have been described: azithromycine (500–1000mg/d, for 2–10 days per month, and a maximum of 4 months of treatment) cured 85% of them.

Miltefosine

Miltefosine (hexadecylphosphocholine) is an oral antitumor agent, that interferes with cell signal-transduction pathways and inhibits phospholipids and sterol biosynthesis. In India, miltefosine (2.5mg/kg/d for 28 days) is given in visceral leishmaniasis due to *L. donovani*. During a 6 months follow-up, 94% of children <12 years [71] and 97% of patients >12 years [72] are considered as cured. This drug has also been tried in South American cutaneous leishmaniasis [73]. In Colombia (*L. panamensis*), the efficacy rate was 91%, identical to meglumine antimoniate. However, miltefosine seemed to be less active in vivo against *L. mexicana* (60% efficacy) or *L. braziliensis* (33%) lesions. In the Old World, miltefosine was successfully used in an HIV-infected patient with a *L. major* diffuse cutaneous leishmaniasis [74].

The variation of sensitivity with the species is confirmed in vitro: in an amastigote-macrophage assay [75], the rank order of species sensitivity for miltefosine was *L. donovani* > *L. aethiopica* > *L. tropica* > *L. mexicana* > *L. panamensis* > *L. major*. Another recent study [76] demonstrates that

the sensitivity of *L. donovani* to miltefosine is greater than these of *L. braziliensis*, *L. guyanensis*, or *L. mexicana*.

Oral zinc sulfate

The in vitro sensitivities of *L. major* and *L. tropica* strains to zinc was reported to be higher than those to pentavalent antimony [77], and these data were confirmed in mice. Zinc sulphate was also delivered intralesionally with success in cutaneous leishmaniasis. The possible mechanisms of action of oral zinc are direct antileishmanial effect, immunomodulatory effect (including an effect on T-lymphocytes), effect on macrophages function, and/or wound-healing effect [78].

More recently, oral zinc sulphate was given to Iraqi patients suffering from parasitologically confirmed cutaneous leishmaniasis [78]. The species was not identified but it is known that only *L. major* and *L. tropica* are present in Iraq. Only patients with acute cutaneous leishmaniasis of 12 weeks or less duration and for whom systemic treatment was indicated, were included. Healing criteria were defined prior to treatment. One hundred and four patients completed the 45 days follow-up. At the end of the follow-up period, the cure rates were 83.9% in the patients receiving 2.5 mg/kg, 93.1% in the 5 mg/kg group, 96.9% in the 10 mg/kg group (not statistically significant), whereas none of the control patients without any treatment was cured or improved clinically. These encouraging results need to be confirmed in larger studies.

Intramuscular or intravenous drugs

Systemic antimonials

Systemic antimonials are generally required for the treatment of cutaneous leishmaniasis in the New World because of the risk of mucosal involvement (*L. mexicana* lesions excepted). WHO recommendations are 10–20 mg pentavalent antimony/kg/day with unlimited daily dose for 20 days, and for 30 days in patients with mucous involvement [10].

In a Colombian series (*L. panamensis* predominant), 136 patients were randomized to receive 10 or 20 days of meglumine antimoniate [79] with 63% of subjects below 15 years of age. Overall efficacies at the end of the first year of follow up in the two schedules were comparable: 61% in the 10 days group and 67% in the 20 days group. Antimonials efficacy was significantly reduced in children under 5 years (only 11–25%) regardless of the duration of treatment.

In a retrospective study in adults and children suspected to be infected with *L. braziliensis* [80], there was no statistically significant difference regarding the age, the dosage (<10 or >10 mg/kg/day), or the drug regimen (continuous or intermittent treatment). However, the long duration of treatment in the series has to be noticed. The patients that underwent continuous treatment were treated for 25–116 days. Intermittently treated patients received 2–5 courses of 10–25 days each, with intervals of 10–60 days between each series.

In fact, the efficacy of systemic antimony seems to vary with the species in South America. In a Brazilian series, 20 mg/kg/day for 20 days cure 51% of *L. braziliensis*

infections and only 26% of *L. guyanensis* infections, regardless of the age, the duration of the disease, the number or the location of the lesions [81].

In the Old World, parenteral antimonials are considered to be second-line treatment. In the Tunisian pediatric series [12], 20 mg/kg/d for 7–15 days were used successfully in children unresponsive to intralesional antimony treatment, in children with more than five lesions, or with lesions located close to cartilaginous areas.

Drugs combinations with antimonials

In order to enhance the efficacy of antimony, combinations with other drugs have been used. Most of the reports used antimony plus allopurinol, as proposed (then rejected) for visceral leishmaniasis treatment in the 1980s [82–85]. In Iranian patients infected with *L. major* [86], the addition of allopurinol reduced the antimonial dosage in half to achieve the same efficacy (close to 75–80%). In *L. tropica* infected patients [87], low doses (8 mg/kg/d) of intramuscular antimony combined to oral allopurinol seem to be more effective than allopurinol or antimony alone. More recently, the combination of antimony (20 mg/kg/d) and allopurinol (20 mg/kg/d) have been proposed in case of nonresponsiveness to antimony [88].

Pentoxifylline is a xanthine derivative that suppresses TNF- α gene transcription, potentiates the expression of iNOS leading to nitric oxide (NO) production and decreases leukocyte migration and adhesion [89,90]. As TNF- α seems to play a great role in the pathogenesis of mucosal leishmaniasis [89–91], pentoxifylline has been proposed in association with pentavalent antimony, in cutaneous leishmaniasis [89] and mucocutaneous leishmaniasis [90] due to *L. braziliensis*. For instance [90], oral pentoxifylline (400 mg \times 3/day) plus pentavalent antimony (15–20 mg/kg/d) for a month cure $\frac{9}{10}$ patients with mucosal and antimony-unresponsive lesions.

Pentamidine

Pentamidine was used in visceral leishmaniasis treatment for years. In France, the visceral leishmaniasis treatment schedule until 1980 was meglumine antimoniate (Glucantime[®]) for 15 days, then pentamidine mesylate (Lomidine[®]) for 15 days, then meglumine antimoniate again for 15 days [92]. In late 1980s, pentamidine mesylate was replaced by pentamidine isethionate (Pentacarinat[®]) in order to reduce side-effects.

Pentamidine isethionate is also used in South American cutaneous leishmaniasis, especially when caused by *L. guyanensis* which seem to be less sensitive to antimony. In French Guyana (*L. guyanensis* predominant), two intramuscular injections (days 1 and 4) of 4 mg/kg pentamidine-base (7 mg/kg Pentacarinat[®]) are used. The failure rate depends on the timeliness of the treatment: 5% if the drug is given in the first month of evolution, versus 25% if it is delivered later [93]. Elevated muscle enzymes are noted frequently with pentamidine.

In an area where *L. braziliensis*, *L. amazonensis*, *L. shawi* and *L. guyanensis* coexist in Brazil [94], a regimen of three intramuscular injections (days 1, 3 and 5 with 4 mg/kg

pentamidine-base; maximum dosage: 300 mg/d) has been compared to 20 days of antimony. The effectiveness was identical in the two groups: 70–75%. A lower dosage for a longer duration (2 mg/kg/injection and seven injections) is less effective than antimony on *L. braziliensis* infection (35% versus 78%). Most of the observed “failures” in the pentamidine group were attributed to the withdrawal of patients with persistent presence of parasites two weeks after therapy [95].

Amphotericin B

To date, liposomal amphotericin B (AmBisome®) seems to replace antimony in the treatment of pediatric VL due to *L. infantum* [9]. Other lipidic forms of amphotericin B (Amphocil®, Abelcet®) are available, especially in South America.

Some patients have been treated with lipidic amphotericin B for *L. guyanensis* [96], *L. braziliensis* [97], *L. infantum* [98] or *L. aethiopica* [99] cutaneous leishmaniasis. However, the use of amphotericin B in the cutaneous leishmaniasis treatment requires more extensive studies [100].

Other treatments

In vitro studies have identified new promising compounds [101]: biphosphonates that interact with isoprenoid biosynthesis, natural maesabalides or quinolines [102,103].

Conclusion

Cutaneous leishmaniasis is not a single disease, because different clinical features and courses of illness are observed. The prognosis is related frequently to the causative species in immunocompetent patients. Though, it is essential to isolate and characterize the species, or to infer the causative species from epidemiological data. The lack of comparative studies of treatment hinders consensual recommendations. Table 1 summarizes the drugs reported and their effectiveness according to the *Leishmania* species. However, the choice of the correct therapy often depends on the experience of the clinician, preferences of patients and the cost-effectiveness considerations for the patient and/or the health care system.

Table 1 Cutaneous leishmaniasis treatments according to the species and the route of administration (strength of recommendation and quality of evidence in brackets [104]).

Treatments	<i>L. major</i>	<i>L. tropica</i>	<i>L. mexicana</i>	<i>L. panamensis</i>	<i>L. braziliensis</i>	<i>L. guyanensis</i>
Topical	No treatment (A III)	Paromomycin (B I)	IL Sb (A III)	Paromomycin (B I)	Paromomycin (B I)	
	Paromomycin (A I)	LCH (B I)	Paromomycin (B II)		Imiquimod (C I)	
	IL Sb (A I)	IL Sb (B II)	LCH (C I)			
	Cryotherapy (B II)	Cryotherapy (B II)				
	LCH (B II)					
Laser (B II)						
Oral	Fluconazole (B I)	Zinc (C II)	Ketoconazole (C I)	Ketoconazole (C I)	Azithromycin (C III)	
	Zinc (C I)			Miltefosine (C II)		
	Azithromycin (C III)					
IM or IV injections	IM Sb (A I)	IM Sb (B III)		IM Sb (A I)	IM Sb (A I)	Pentamidine (A II)
					L AmB (C III)	L AmB (C III)
Ineffective	Itraconazole (E I)	Imiquimod (D II)			Miltefosine (D II)	IM Sb (E II)
	Imiquimod (D II)				Itraconazole (D II)	
	Miltefosine (D III)					

IL Sb: intralesional antimony; LCH: localized controlled heat; IM Sb: intramuscular antimony; L AmB: lipidic formulations of amphotericin B, especially liposomal amphotericin B.

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