Treatment of cutaneous leishmaniasis: Review Article

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Abstract:

Cutaneous leishmaniasis(CL)is a prevalent parasitic infection , it has a wide distribution and is endemic in circumscribed areas in Northeastern Africa, Southern Europe, the Middle East, Mexico, and Central and South America. Twelve million people in over 90 countries are affected by leishmaniasis, with an annual incidence of 0.9 to 1.6 million, between 20,000 and 30,000 deaths per year, and 350 million people at risk of contracting the infection. Leishmaniasis is considered to be one of the six parasitic diseases with high priority, second only to malaria. Cutaneous leishmaniasis represent a socioeconomic burden on the affected communities. Old World cutaneous leishmaniasis (OWCL), mainly seen in the Eastern hemisphere, is caused by L. donovani, L. infantum, L. major, L. tropica and L. aethiopica, and New World cutaneous leishmaniasis (NWCL), which is more common in Central and South America, is predominantly caused by L.braziliensis, L.panamensis, L. guyanensis, L. amazonensis, L. mexicana and L. peruviana. Disseminated CL,mostly reported in north-eastern Brazil ,is comparatively more drug sensitive and manageable than diffuse CL which is more likely to be drug resistant. Moreover, the diffuse CL due to L. mexicana and L. amazonensis is considered a more difficult form to treat with contemporary treatment methods.CL causes skin lesions upon exposure to infection and leaves disfiguring scars and disabilities. Lesions caused by (CL) may be limited to a specific region on the skin (localized CL) or give rise to multiple lesions on a large area of the body (diffused CL and disseminated CL), which are notoriously difficult to treat. Moreover, the clinical presentation of CL lesions may vary depending on the host immunity and causative Leishmania species.

Although typical CL lesions are painless and tend to self-heal in 3–18 months, in some cases, particularly the ones caused by *L. tropica*, *L. major* and *L. aethiopica*, are associated with long-lasting multiple lesions and severe scarring**.** Although typical CL lesions are painless and tend to self-heal in 3–18 months, in some cases, particularly the ones caused by *L. tropica*, *L. major* and *L. aethiopica*, are associated with long-lasting multiple lesions and severe scarring. Available treatment options are expensive and associated with systemic toxicity. There are alarming reports of emerging resistance against the currently in use therapeutics. Comparative controlled trials for the effective and the least harmful treatment modalities are lacking. Leishmania major appears predominantly susceptible to most of the current treatment methods unlike other CL causing parasite species.

Keywords: cutaneous leishmaniasis, antimonials**.**

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Introduction:

Of note, the control of(CL) largely depends on early diagnosis, and expeditious treatment**.** In accordance with the priorities of World Health Organization(WHO)and world health developmental policies, there is a huge demand for studies focused on the proper use of drugs and treatment protocols for neglected tropical diseases including leishmaniasis.To date, a number of antileishmanial treatments have been introduced such as chemotherapy, cryotherapy, thermotherapy and several less frequently used alternative methods **(1).**

Commonly used leishmanicidal drugs include pentavalent antimonials, amphotericinB, miltefosine**,** paromomycin(PM)**,** Pentamidine, topical and systemic azoles and Doxycycline **(2).**

*Anti leishmanial Monotherapy

1- Antimony

Although several antileishmanial drugs have been used during the past few decades, unarguably, antimonials remain the first-line treatment for CL in most countries irrespective of the causative agent and clinical form of the lesions. Sodium stibogluconate (SSG) and meglumine antimoniate (MA) are the two major formulations of antimonials in use. The prominent antimonial dual mechanisms of action against CL are: firstly, antimonials activate the macrophages to kill the parasites; secondly, Sb(V), the prodrug, is reduced to active Sb(III) that inhibits trypanothione reductase which eventually leads to parasite killing. Accumulating evidence suggests that antimonials increase the expression of aquaglyceroporin (AQP1) and inhibit DNA topoisomerase,

glycolysis pathways, ATP/GTP synthesis and glucose catabolism resulting in decreased viability of Leishmania parasites **(3).**

Genetically distinct populations of Leishmania are able to show varied responses to antimony with antimony-resistant phenotypes developing as result of genetic mutations of parasites. Also, the region of endemicity plays a pivotal role in differential antimonial responses. Cutaneous leishmaniasis caused by L. (V.) braziliensis in Peru, Brazil and Guatemala has shown 69.6%, 50.8% and 96.0% chemotherapeutic sensitivity, respectively, towards Sb(V) therapy (20 mg/kg/day for 20 days**) (4).**

Therefore, it could be hypothesised that either a genetic variation in the parasites of the same species or the differences in the genetic composition and immunity of the people within the regions have affected the therapeutic response. Cutaneous leishmaniasis caused by L.aethiopica has less sensitivity to SSG and appears slightly resistant to antimonial drugs in vitro, compared to the high SSG sensitivity that is reported in L. donovani**.** It has also been suggested that self-healing CL species such as L. major were fairly sensitive to increase oxidative stress and showed increased susceptibility to antimonial drugs than other species **(5).**

The cure rate (CR) of CL due to L. tropical treated with intralesional administration of SSG was higher and more efficient than intramuscular administration of SSG in a randomized controlled clinical trial**.** The use of intralesional therapy with antimonials aim to reducing adverse effects compared to their systemic administration**.** Furthermore, intrinsic differences were reported in Sb(III) sensitivities upon exposure to concentration series of potassium antimony tartrate whereas EC_{50} (effective concentration) data showed 2.6, 3 and 6 times more resistance to Sb in CL caused by L. braziliensis, L. tropical and L. panamensis, respectively, compared to L. major**.** With respect to the dosage, intravenous antimonial treatment at a daily dose of 20 mg/kg for 10 consecutive days could produce better cure rates against CL caused by L. panamensis and L. braziliensis. Furthermore, CL caused by L. major showed moderate CRs with the aforementioned treatment regimen. However, CL caused by L. (V.) panamensis cured 100% after 20 mg/kg/day for 20 days, compared to the lower CR (64%) with a dose of 10 mg/kg/day, during a course of 20 days of intravenously administered SSG**(6).**

In East Africa, SSG is commonly used but is potentially toxic, with daily painful injections, and treatment is long (30–60 days) leading to prolonged hospital stay **(7).**

SSG is administered by intramuscular injection,which is feasibly provided at primary health care level, as it does not require cold chain. However, systemic SSG is known to cause potentially serious toxicity (cardiotoxicity, nephrotoxicity, pancreatitis) and may even be fatal. Toxicity is dose-dependent, and therefore the risk of toxic adverse events increases with the

duration of treatment. The risk of SSG-induced toxicity is therefore lower with the combination therapy as with Paromomycin (PM) in the treatment regimen significantly reduces the number of systemic SSG doses required**.** In a systematic review of the efficacy of pentavalent antimoniate intralesional infiltration for CL, the efficacy rate in the Old World of 75% with intralesional pentavalent antimony (SbV) (higher when it was combined with cryotherapy), 83% with SSG, and 68% with MA. In the New World, the efficacy rate was 77% with intralesional infiltration SbV, 61% with SSG, and 82% with MA. We must consider that this therapy requires the infiltration of each lesion so is not for all cases of CL. The recommended dose is 1–5 mL (applied in five sites per lesion) every 3–7 days until healing; the only adverse events reported were local irritation, pain, edema, erythema, and pruritus **(8).**

2- Amphotericin B

Amphotericin B is commonly used as an alternative drug with a broad spectrum of antiparasitic or antifungal activities to treat patients with leishmaniasis with resistance to antimonials**.** There are two main types of amphotericin B: amphotericin B deoxycholate and liposomal amphotericin B(L-AmpB, trade name AmBisome)used intralesionally or intravenously as a second-line treatment for CL**.** Upon binding to ergosterol, the major sterol of the protozoal cell membrane, amphotericin B leads to cell death by promoting ion leakage, pore formation, changes in cell membrane permeability and sudden metabolic shock**.** Several studies have reported successful treatment of L. major and L. tropica-induced CL with intravenous (11 out of 13 patients cured) or intralesional injection of L-AmpB at a daily dose of 3 mg/kg for 5 days with an additional dose 10day. Initial infection was gradually re-epithelialized and then disappeared in 8 weeks without abnormalities **(8).**

Some toxic adverse effects are attributed to amphotericin B deoxycholate. However, liposomal amphotericin B has been less toxic.Toxic effects of amphotericin B include nephrotoxicity and infusion-related toxicity. The infusion-related-toxicity of liposomal amphotericin B is reliably lower than amphotericin B deoxycholate and other amphotericin B–lipid complexes.Also,flank/abdominal pain, chest pain/discomfort, and dyspnea that initiate in the first few minutes after infusion **(9).**

3- Miltefosine

The orally administered miltefosine (hexadecylphosphocholine) was first used as an anticancer agent Studies have proven antileishmanial properties with the ability to derange sterol and phospholipid biosynthesis, and cell signal transduction of parasites **(10).**

In instances when, antimony resistance became a challenge, miltefosine was used as the second-line drug and was effective on diffused Cutaneouse Leishmaniasis(CL) with80–90%

parasitological improvement within 2 months**.** Nonetheless, this regime resulted in high probability of relapsing with the development of new infection in the majority of cases**.** Miltefosine has been strongly effect CL due to L. guyanensis and L. panamensis, with robust decline against L. major and slow response against L. infantum**.** As a whole, a frequently recommended treatment regimen for miltefosine is 1.5–2.5 mg/kg/day (orally) for 28 days. Also effective and safe drug for treating CL caused by L. guyanensis, L. panamensis and L. donovani**.** Adverse events include gastrointestinal side effects and occasional hepatic and nephrotoxicity. Another miltefosine limitation is teratogenicity, and women of child-bearing age have to take contraceptives for the duration of treatment and for an additional 3 months afterward due to the long half-life of miltefosine **(11).**

4- Paromomycin

Paromomycin (PM), an aminoglycoside-aminocyclitol antibiotic, is used in some countries to treat Cutaneouse Leishmaniasis(CL)as a topical or parenteral drug. However, the systemic use of PM is less common. Act as an inhibitor of Leishmania parasite propagation by interfering with protein translation, with only a minute influence on human cell counterparts **(12).** According to the Pan American Health Organization (PAHO) guidelines, PM has not yet been recommended as a treatment for CL**(13)** In Ethiopia, as their health guidelines, the preferential first-line treatment for CL caused by L. aethiopica is intramuscular administration of PM **(14)**. In Colombia, CL therapy with PM doses of 18 mg/kg/day for 14 days or 14 mg/kg/day for 20 days regimens produced moderate CRs of 50% and 59%, respectively. Therefore, various PM formulations were introduced with increased efficacies. In particular, the formulation of PM comprising 15% PM sulfate with 12% methylbenzethonium chloride (MBCL) completely cured L. major-related CL in 6–10 days**(15).** The most common adverse event with paromomycin is injection site pain (55%); however, this typically does not lead to the discontinuation of therapy.Asmall fraction of patients experience reversible ototoxicity (2%) and a rise in hepatic transaminases (6%).**(11).**

5- Pentamidine

Pentamidine inhibits mitochondrial topoisomerase II, polyamine synthesis, calcium transport, lysine-arginine transport, and eventually impedes the active transport system and mitochondrial membrane potential that leads to parasite death. As per PAHO guidelines, pentamidine is recommended and included in the first line of drugs against CL due to L. guyanensis and L. panamensis. In a study on *L. guyanensis* CL, patients given pentamidine isethionate showed 78.8% CR for single injection (7 mg/kg), and 83.6% following two injections; hence,a single treatment at a high dose of 7 mg/kg has been recommended unless the lesions remain unhealed .Also, in an effort to minimize the number of treatment sessions, a Colombian study on CL revealed that four injections on alternate days of 2 mg pentamidine/kg and 3 mg

pentamidine/kg could give rise to 84% and 96% CRs, respectively, with even lesser side effects **(6).**

6- Azoles

The azole drugs, including fluconazole, ketoconazole and itraconazole, have been attractive candidates for the treatment of CL and have been authenticated in vitro, in vivo and also by clinical trials **(16).** Albeit with paradoxical outputs in their efficacies. The global efficacy rates of azoles for L. mexicana, L. infantum, L. donovani, L. major, L. braziliensis and L. tropica were 89%, 88%, 80%, 53%, 49% and 15%, respectively, which implicated a broader variation in species dependency of azole therapy **(17).**

Interestingly, the growth inhibition observed with itraconazole, fluconazole and ketoconazole against L. donovani and L. braziliensis strains was substantial as opposed to L. aethiopica, L. major, L. tropica or L. m. mexicana strains that had lower inhibition. Contradictory results are rife in azole treatment; hence, the dearth of data and the presence of discrepancies in the literature encourage extensive investigations on the antileishmanial activity of azoles, particularly species-specificities, to overcome the current confusions. In a study, excluded the possibility of using fluconazole (at a dose of 6.5–8 mg/kg/day for 28 days) as an effective regimen for CL due to L. braziliensis(Prates et al. 2017)and a non-randomized phase 2 trial in the Brazilian Amazon revealed that orally administered fluconazole has no potency in treating L. guyanensis CL. Nonetheless, in Saudi Arabia, 6-week administration of fluconazole was safe and efficient in treating CL due to L. major **(18).**

Treatment of CL due to L. braziliensis panamensis with ketoconazole showed comparable efficacy to parenteral antimonials, and has been suggested as an initial treatment for CL. Furthermore, L. braziliensis demonstrated substantial in vitro growth inhibition with ketoconazole. Ketoconazole is used to successfully treat L. major-related CL using 400 mg/day dose for 4 weeks. However, the topical treatment though considered more safe is found to be less effective. Even though many studies bear evidence for successful treatment of L. mexicana with ketoconazole, contradictory outcomes also have been reported with the occurrence of treatment failure **(8).**

However, it was proven that L. mexicana was predominantly sensitive to ketoconazole at a dose of 600 mg/day for 4 weeks. Currently, formulations like lipogel, cream and topical gel have been invented that contain different concentrations of ketoconazole; however, in vivo studies have implied meagre antileishmanial activities of these formulations in treating CL caused by L. (Viannia) braziliensis or L. (V.) panamensis **(19).**

As per the outcomes of in vitro studies and clinical trials that have been performed, ketoconazole can be taken as a reliable treatment against L. braziliensis, L. braziliensis panamensis, L. mexicana and L. mexicana. observed promising antileishmanial activity of itraconazole that was based on two studies that demonstrated its effects on patients with CL **(20)** and it was also effective in vivo by treating BALB/c mice subcutaneously inoculated with L. major **(21).**

Moreover, supportive evidence emphasizes that response following itraconazole therapy was comparable to that of a placebo in the treatment of L. major-associated CL. Therefore, the usefulness of itraconozole in the treatment of CL due to L. major remains doubtful because of inconsistent results shown in various studies. Apart from that, novel azoles, namely voriconazole, 3-imidazolylflavanones, and luliconazole, have brought about prominent repression of both promastigotes and amastigotes of L. major in CL treatment in vitro or in vivo **(22).**

7- Doxycycline

The effectiveness of doxycycline (71%) is quite competitive with pentavalent antimony, which has effectiveness from 60 t0 90% **(2).** However, the mechanism of action of doxycycline has not been determined yet. The most popular hypotheses of doxycycline effectiveness are as the following: (1) direct effect on the body of Leishmania due to good intracellular penetration**;** (2) doxycyclines affect protease–antiprotease imbalance inhibit collagenase activity, thus exerting anti-inflammatory activity**.** Doxycycline may possibly represent a therapeutic alternative in the treatment of CL, especially in endemic areas, providing better tolerance and lower cost **(23).**

Oral route of administration, 200 mg/day for1 month, lack of major adverse effects, low cost, and easy availability make doxycycline a good alternative option in the treatment of leishmaniasis **(24).**

Energy Base Therapy:

***Cryotherapy**

Cryotherapy involves exposing the lesions to extreme temperatures like − 196 °C, using cryogens like liquid N_2 or CO_2, which facilitates the destruction of infected tissues. Although painful, cryotherapy does not cause adverse systemic side effects compared to other drugs. It is a simple, inexpensive and rapid procedure that is devoid of the need for local anesthesia. A number of studies provide evidence for satisfactory cosmetic results and lower relapse rates associated with cryotherapy with only a minority of cases reporting burning and possibility of secondary

infections after treatment **(25).** Studies suggest thermos-sensitiveness of L. braziliensis, L. tropica, L. infantum and L. aethiopica, indicating cryotherapy as a promising option for CL treatment **(26).**

Cutaneous leishmaniasis due to L. major showed nearly 84% healing rate in 1–4 treatment sessions with liquid N_2 and the rest of the lesions were cured with an additional 1–3 sessions, leaving negligible scarring and no relapses. However, the physical location and the lesion size severely affected the treatment response (lesions smaller than 1 cm giving the better results) **(25).**

Cryotherapy given fortnightly was successful in treating CL caused by L. donovani in Sri Lanka, with ulceration, depigmentation and scarring post-treatment, and in Ethiopia, L. aethiopica was treated with an efficiency similar to **(27).**

***Thermotherapy**

Thermotherapy is a cost-effective and uncomplicated method that is used to treat CL in fewer treatment sessions with minimal side effects and scarring, and immensely useful for medically austere areas **(28).**

The few minor complications associated with this method are superficial burns (which heals without scarring) and the need for local anesthesia when thermotherapy is applied with certain devices **(1).** It was demonstrated that the potential for thermotherapy in hampering the multiplication of Leishmania parasites using temperatures greater than 39 °C. The underlying mechanism is believed to be both physical damage and immunological destruction of parasites **(29).**

***CO2 Laser and Er: YAG Laser:**

The first of use of laser for treatment of the CL goes back to 1981.used CO2 laser for 6 patients affected by CL in 1981 and achieved encouraging results **Babajev KB et al. (30)**. In this study, a CO2 laser and E:YAG were used in fractional mode for ablation of lesions of CL. The mechanism of action of carbon dioxide and Er: YAG lasers in cutaneous leishmaniasis is specific thermolysis of infected tissue without significant side effects in a normal tissue. The lesion heals within 4-5 weeks with quite acceptable cosmetic results. According to the therapy, the patients were divided into two groups: Group A; treated by CO2 laser (unixel RF, S. Korea) and (E. CO2, Korea) laser with articulated mirror arm and hand piece, wavelength is 10600 nm, fractional mode, 1-30 cm^2 spot size, and maximum power 30W. Group B; treated by Er:YAG laser (Action II, S. Korea) wavelength is 2940, fractional mode, 1-7 cm^2 spot size and 50W maximum power. Patients received single laser treatment session and observed every 2 weeks. Six weeks post-operatively, complete or very good improvement occurred in 39 of the 42 treated patients.

All the side effects that occurred postoperatively in this trial were transient and disappeared within few days after treatment. There was no serious symptoms reported, a part from mild pain that occur in many patients treated with CO2 laser but was tolerable. Hypopigmentation at site of lesion was noticed in one patient treated with Er:YAG laser .

Cutaneous Leishmaniasis can be treated effectively with CO2 laser and Er:YAG laser, excellent cosmetic outcome, and short duration of healing**.**

Conclusion: Leishmaniasis remains a major public health problem with a broad spectrum of clinical manifestations related to the immune response of the host. New drugs are proposed for treatment, but results are still unsatisfactory. Currently, pentavalent antimonials are effective and available, but research must be a cornerstone in the proposal of novel therapies.

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