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Systemic Treatments of Leishmaniasis: A Narrative Review

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ABSTRACT

Cutaneous leishmaniasis is a prevalent parasitic infection in humans. According to the reports published in several localities across the world, leishmaniasis is an endemic disease in certain regions in Iran. Leishmaniasis is transmitted through sandfly bites and is often diagnosed through the smear examination of the affected area using a microscope. The treatments of choice for leishmaniasis involve the use of pentavalent antimony compounds, such as meglumine antimoniate and sodium stibogluconate. However, other medications have been proposed for the treatment of leishmaniasis, and there is ongoing research for effective, less harmful treatments. This narrative review aimed to summarize various systemic treatments for leishmaniasis.

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Introduction

Leishmaniasis is a prevalent disease of tropic and sub-tropic regions, affecting 15 million individuals across the globe. Based on tropism, leishmaniasis is categorized into four clinical syndromes, including cutaneous, mucocutaneous, diffuse cutaneous, and visceral leishmaniasis (1-5).

Cutaneous leishmaniasis is a chronic dermal condition, which is characterized by several clinical symptoms due to the variable immunity status of the host, affected area, and age of the patients. Leishmania major and L. tropica cause urban and rural leishmaniasis, respectively. The organism was transmitted to humans by Phlebotomus papatasi in the Old World and is transmitted by the Lutzomyia species in the New World (1, 4-8).

After the biting of the fly, lesions appear as erythematous papules, later developing into raised, ulcerated lesions (2,9,10). The lesions are painless and might heal within a few months, while they often cause impaired function, secondary infections or persistent wounds (5,9,10).

There are several influential factors in the spontaneous clearing of the wounds without interventions in the patients, including immunology and genetics, locality, number and species of the parasite, clinical symptoms, and severity of the lesions, and the outcome significantly affects the course of treatment. Considering the large variability of these factors, spontaneous recovery may prolong, thereby leading to the scars that care particularly problematic in various body parts that may be of cosmetic or functional importance. The leishmaniasis lesions in such areas require immediate treatment. Therefore, treatments are considered crucial to controlling the dissemination of leishmaniasis and its transmission between individu-

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als (especially in case of patients with immunodeficiency) and preventing recurrence. Some of the key objectives of leishmaniasis treatment include the treatment of all the patients, limiting the spread of the lesions, eradicating the reservoirs of the Leishmania species, controlling the spread of the disease, preventing the development of large scars (particularly facial scars), and preventing the associated complications and disease recurrence (11,12).

Various local and systemic treatments are available for leishmaniasis, including physical interventions (e.g., curettage, surgery, thermotherapy, cryotherapy, and laser therapy) and medications (e.g., derivatives of antimony and nanoparticle treatments). Since most of these treatments have not been thoroughly examined in the clinical setting, their dependability remains uncertain. Meanwhile, some of the main causes of unreliable treatment methods for leishmaniasis include the high costs, poor patient compliance due to the long-term need for intramuscular/intravenous injections, and risk of systemic toxicity (11,13).

One of the main challenges that limits the treatment options for leishmaniasis is the variable efficacy of the medications that are used against various Leishmania species (14,15). The present study aimed to summarize various systemic treatments for leishmaniasis.

Literature Review

Pentavalent Antimony Compounds

Antimony has been used in medicine for centuries, and its importance has long been recognized. In the past century, the most significant application of this element was the treatment of leishmaniasis. In the 20th century, Gaspar Vianna (a pioneer in the treatment of leishmaniasis) reported the effects of potassium antimony tartrate (a trivalent antimony compound) on mucocutaneous leishmaniasis. However, the widespread use of this compound in the following years revealed its adverse effects, which led to the cessation of its use. Since the 1940s, other less harmful trivalent antimony compounds have become widespread for the treatment of leishmaniasis, which are currently among the most common treatment options in this regard. However, their application is associated with specific limitations. For instance, the injection of these compounds and the associated complications affect patient compliance, thereby leading to the development of resistance in some endemic regions (16,17).

Currently, meglumine antimoniate (glucantime) and sodium stibogluconate (pentostam) are the most commonly prescribed pentavalent antimony derivatives for the treatment of cutaneous leishmaniasis. Glucantime is administered daily via intramuscular injection, while sodium stibogluconate is administered via slow intravenous injection. Glucantime is available in Iran. According to the guidelines of the World Health Organization (WHO), the prescribed dose of antimony for systemic treatment is 20 mg/kg of pentavalent antimony, which is equal to 75 mg/kg of glucantime. Since each five-milliliter shot of glucantime contains 425 milligrams of antimony (1.5 g of glucantime), 1-3 five-milliliter shots of glucantime could be prescribed per 20 kilograms of the body weight of patients. In general, the treatment period for rural and urban leishmaniasis is two and three weeks, respectively. If the signs of recovery are not observed within four weeks after the treatment, the treatment is considered a failure, and systemic treatment with the previous dosage is prescribed again (18). The most efficient approach to the use of glucantime involves the gradual increase of the dosage as one quarter, one half, and three quarters of the final dosage on the first, second, and third day, respectively, followed by the administration of the full dose on the fourth day and onwards (19).

Theoretically, glucantime acts by affecting the bioenergetic pathways of the amastigote form of Leishmania and disrupting oxidation and glycolysis processes, thereby reducing the cell levels of adenosine triphosphate (20). According to reports, the most significant clinical adverse effects of glucantime include musculoskeletal pain, nausea and vomiting, diarrhea, abdominal pain, headaches, cough, pneumonitis, loss of appetite, lethargy, fever, erythema, and hives. At the final stages of glucantime treatment, complications such as cardiac, hepatological, and nephrological disorders have also been reported. Among the other adverse effects of this compound are the elevation of pancreatic enzymes (observation of pancreatitis in some cases, particularly in patients with impaired renal function), dose-dependent changes in the electrocardiogram (most commonly T-wave and ST-segment changes and QT prolongation), and atrial and ventricular arrhythmia rarely (21).

The mechanism of action of sodium stibogluconate remains unclear. It is speculated that this drug functions through affecting the enzymes that are involved in DNA synthesis. Several side-effects have been documented for sodium stibogluconate, and reports have suggested the risk of sodium stibogluconate intolerance syndrome. Some of the associated symptoms include fever, arthralgia, myalgia, edema, and gastrointestinal complications, which may manifest at the initial stages of treatment. It is notable that these symptoms are not dose-dependent and do not justify

the cessation of treatment. On the other hand, the main symptoms of sodium stibogluconate toxicity include cardiotoxicity, pancreatitis, hepatological disorders, aplastic anemia, and nephrotoxicity on a few occasions. These symptoms are considered to be severe dose-dependent complications, which often occur during the second week of treatment (22).

Pentavalent antimony derivatives have variable degrees of success in the treatment of Old World cutaneous leishmaniasis. According to a review study by Masmoudi et al., which was conducted in Tunisia during 1999-2006, the success rate of the treatment with these compounds was reported to be 75% (22). Another study in this regard was performed by Belazzoug and Neal (1986) in Algeria, reporting no significant differences between the glucantime treatment group and controls (23). Furthermore, drug resistance has been recorded for pentavalent antimony derivatives, while the resistance may be merely an initial resistance or reflect the low-dose or short-term use of the medication (24).

Amphotericin B

Amphotericin B belongs to polyene macrolides and was first used as a highly effective antifungal drug in 1959. Despite the introduction of other medications (e.g., azoles), amphotericin B remains applicable as a potent medication for the treatment of systemic fungal infections. Amphotericin B acts through binding to membrane sterols (ergosterol in fungi) and changing membrane permeability, thereby causing the loss of small molecules and essential ions (e.g., potassium) (25-27). The most common side-effects of amphotericin B include anemia, low serum potassium, nausea and vomiting, fever and chills, arthralgia, myalgia, nephrotoxicity, neurological complications, rashes, and thrombophlebitis at the injection site. It is notable that renal function abnormality is considered to be the most significant side-effect of amphotericin B (28-31).

Amphotericin B is administered in the two forms of Fungizone (dosage: 1 mg/kg/day) via injection, along with intravenous dextrose solution every other day, and liposomal amphotericin B (dosage: 3 mg/kg/day dose), which is administered via intravenous injection for 10 days for a 21-day period (26, 32-35). Since liposomal amphotericin B is safer and causes fewer side-effects, it is more frequently prescribed. Moreover, liposomal amphotericin B is used as the secondary treatment for visceral leishmaniasis in the cases with resistance to pentavalent antimony (36).

In a study by Guery, which was conducted during 2008-2016 on 43 travelers with cutaneous leishmaniasis, 46% of the patients were reported to recover after receiving treatment with liposomal amphotericin B for 90 days (37). In another research by Mashayekhi et al. (2014), 93 patients with significant resistance to antimony compounds were administered with intralesional amphotericin B. After 12 weeks, 61.4% of the patients completely recovered from leishmaniasis. Similarly, another report by the same researchers was published on the treatment of ocular leishmaniasis, presenting amphotericin B as a promising treatment option for leishmaniasis, particularly in the cases with resistance to antimony derivatives (38,39).

Miltefosine

Miltefosine (hexadecyl phosphocholine) is an oral medication, which was discovered in 1980. It was initially used as an antitumor agent and abandoned immediately since it caused hemotoxicity. Miltefosine is an analogue of alkyl phosphocholine, which inhibits the biosynthesis of sterols and phospholipids, disrupting intercellular transduction pathways. Miltefosine was investigated as an anti-leishmaniasis medication in 1992, yielding acceptable outcomes against visceral leishmaniasis; therefore, it was prescribed for cutaneous leishmaniasis as well. Oral doses of 50-100 mg/kg are prescribed for 28 days for the treatment of cutaneous leishmaniasis. However, miltefosine may cause minor side-effects, such as gastrointestinal problems and elevated transaminase and creatinine levels. Since miltefosine is teratogenic, it must not be prescribed for pregnant women (40-44).

In 2007, Mohebali et al. used miltefosine for the treatment of Leishmania major infection, and the success rate was reported to be 90% (45). In a phase II/III randomized clinical trial, Chrusciak-Talhari et al. (2011) used miltefosine for the treatment of untreated leishmaniasis in Brazil. According to the findings, 71.4% of the patients receiving miltefosine therapy recovered as opposed to 53.6% of the patients administered with antimony derivatives. In the mentioned study, the safety of miltefosine was confirmed based on the high tolerance of the patients to the medication (46).

Miltefosine seems to be a superior alternative to antimony derivatives considering that it is orally administered and increases drug btolerance in patients, while causing fewer side-effects. In contrast, some reports have denoted the better performance of antimony in this regard. If further clinical trials confirm the efficacy of miltefosine in the treatment of leishmaniasis, this agent could be proposed as a viable option in the endemic areas.

Pentamidine

Pentamidine is an aromatic diamine molecule, which is used as an antifungal and antiprotozoal agent in the treatment of trypanosomiasis, pneumonia caused by Pneumocystis carinii, and some forms of leishmaniasis. Although the exact mechanism of action remains known, it is believed that the drug interferes with DNA, RNA, and protein synthesis through affecting folate.

Pentamidine is prescribed as a mesylate or isethionate salt. Pentamidine isethionate, which is the more common form of the drug, is often prescribed at the dosage of 4 mg/kg (equivalent to 2.3 mg/kg of pure pentamidine) and administered via intramuscular injection or intravenous infusion within a minimum of 60 minutes. Pentamidine isethionate is prescribed at various doses for the treatment of leishmaniasis, the most common of which are seven doses (2 mg/kg), which are injected intramuscularly/intravenously every other day, or four doses (3 mg/kg), which are injected intramuscularly every other day (47-49).

Pentamidine has also been used for the treatment of visceral leishmaniasis for several years. Considering its shorter course of treatment and length of hospital stay in the patients, as well as the low treatment costs, pentamidine is preferred over antimony derivatives. However, pentamidine has been reported to cause some adverse effects, the most prevalent of which are renal disorders. Renal disorders occur due to the reversible entry of creatinine and nitrogenous compounds into the bloodstream. Furthermore, pentamidine may cause acute renal failure and induce elevated liver enzyme levels or anomalies in blood cell counts. Acute pancreatitis has also been rarely observed. The quick intravenous injection of pentamidine should be avoided since it might cause an abrupt decline in blood pressure, as well as vertigo, headaches, vomiting, tachycardia, and syncope. In addition, gastrointestinal complications and dermatological side-effects, especially at the injection site, may restrict the application of pentamidine as the first drug of choice for the treatment of leishmaniasis (47-49).

Pentamidine seems to be a more viable treatment option for New World leishmaniasis. Non-responsiveness to this drug depends on the time of treatment and failure to complete the course of treatment before the complete resolution of leishmaniasis (19, 50-53). In a study by Esther et al. (2002), which was conducted in Surinam on patients with cutaneous leishmaniasis, 235 patients were administered with pentamidine mesylate, and 80 patients received treatment with pentamidine isethionate. According to the obtained results, 90% of the patients were successfully treated in both groups, and no recurrence was observed. On the other hand, 10% of the patients in both groups experienced infection recurrence (54).

Another research in this regard was performed by Robledo et al. (2006) in Columbia on 63 patients with cutaneous leishmaniasis, who were administered with 4 mg/kg of pentamidine four times. According to the obtained results, 43 patients were successfully followed-up for six months, and 86% were successfully treated after 1.5 months. However, treatment failure was reported in 11.6% of the patients, and only one patient experienced disease recurrence (55).

Azoles

Azoles have been widely used in the treatment of fungal infections since late 1970s. Their key mechanism of action is the inhibition and disruption of cytochrome P450 activity, which in turn leads to cell wall biosynthesis. Azoles are chiefly used as antifungals and have limited application in the treatment of leishmaniasis. Nevertheless, some azoles could be used in the treatment of Old World cutaneous leishmaniasis. Laboratory experiments have confirmed the effects of this drug category on Leishmania promastigotes (56-59).

Several azole compounds have been investigated for the treatment of leishmaniasis, including ketoconazole (200-600 mg/day for 28 days), fluconazole (200 mg/day for six weeks), and itraconazole (100-400 mg/day for 6-8 weeks). However, there are variable findings regarding the success rates of these compounds. In cases of hepatotoxicity, azoles have limited application. According to the literature, itraconazole has been effective in the treatment of 60-70% of the patients with lesions caused by Leishmania tropica (60).

In a recent study in this regard, a patient with sporotrichoid cutaneous leishmaniasis, who was unresponsive to pentavalent antimony treatment, was fully treated after the administration of oral itraconazole (61). Furthermore, the findings of Mohebali et al. (2002) indicated that the treatment of patients with L. major with fluconazole resulted in 79% recovery rate as opposed to only 34% in the placebo patients (45). However, some studies have reported no significant differences between azole fungicides and placebo in the treatment of leishmaniasis (62).

Metronidazole

Metronidazole is a narrow-spectrum antibiotic in the nitroimidazole class of antibiotics, which is used in the treatment of the infections caused by protozoa and most anaerobic bacteria. Following entry into anaerobic cells, metronidazole is di-

minished and metabolized. The toxic metabolites of metronidazole cause DNA damage, and some of the common side-effects of metronidazole include blood disorders (e.g., leukopenia and neutropenia), peripheral neuropathy, disulfiram-like reactions (e.g., nausea and vomiting, flushing, and tachycardia when taken with alcohol), metallic taste, dry mouth, and Stevens-Johnson syndrome in rare cases (63,64).

For several years, metronidazole has been prescribed for 15-30 days for the treatment of cutaneous leishmaniasis in children and adults (15 mg/kg/day for children and 25 mg/kg/day for adults). Retrospective studies in Tanzania have indicated that with the success rate of 66%, metronidazole could be a viable option for the treatment of Old World leishmaniasis (65-68). However, considering the self-limited nature of L. tropica and L. major infections, this rate may be statistically insignificant, and further controlled experiments may be required in order to confirm the effects of metronidazole on cutaneous leishmaniasis (69).

Similar results have been reported by the clinical trials comparing the effectiveness of metronidazole and glucantime in the treatment of leishmaniasis, indicating that metronidazole is not significantly superior to glucantime and could be viewed as an alternative only (70,71).

Other Systemic Treatments

Allopurinol is a xanthine oxidase inhibitor, which has been reported to be effective in the treatment of leishmaniasis with the success rate of 74% in Asia. Combined administration of allopurinol and antimony compounds to Iranian patients with L. major infection has also been shown to reduce the required effective dose of antimony by half (72-74).

Doxycycline is another effective therapeutic compound against leishmaniasis. In a study performed in Tunisia, daily doxycycline dose of 200 milligrams for 15-30 days could successfully treat 71% of the patients. Phototoxicity is considered to be the main side-effect associated with doxycycline (75).

Considering the high tolerance of patients with leishmaniasis, azithromycin is a feasible option for the treatment of children infected with the Leishmania species in the endemic areas. However, a study conducted in Iran in 2003 has undermined the relative effectiveness of this drug. In the mentioned research, 49 patients were assessed, 22 of whom received 500 milligrams of azithromycin five days per month for four months, and the other 27 patients received daily intramuscular injections of glucantime (60 mg/kg) for 20 days. According to the obtained results, azithromycin was not as effective as glucantime in the treatment of Old World cutaneous leishmaniasis (76,77).

Conflicting findings have been proposed regarding the effectiveness of rifampicin in the treatment of Old World leishmaniasis, with the values within the range of 0-80% (78). In addition, oral zinc sulfate has shown promising results in the treatment of cutaneous leishmaniasis in Iraqi patients although these findings have not been confirmed in the other studies in this regard (19).

Use of nanoparticles has been on the rise for the treatment of dermal conditions, and their new applications are constantly discovered. Cutaneous leishmaniasis has not been an exception, with several studies reporting the effectiveness of gold and silver nanoparticles in the treatment of leishmaniasis, especially in combination with phototherapy or electromagnetic radiation therapy (79,80).

The effectiveness of other compounds has also been investigated in the treatment of leishmaniasis, yielding controversial results. Such examples are antimalarial compounds, avlosulfon, sulfamethoxazole-trimethoprim, bleomycin terbinafine, and systemic paromomycin.

Conclusion

Given the importance of cutaneous leishmaniasis (especially the urban variety), all the patients should receive immediate treatment and definitive diagnosis. In Iran, which is considered to be an endemic area for leishmaniasis, the most effective treatment approach for the disease should be selected based on the associated advantages and risks of each treatment method, as well as the capabilities of the healthcare system, availability of the medications, and individual conditions of the patients. Combination therapy is considered to be the optimal treatment approach for leishmaniasis, along with the minimization of the associated complications and invasiveness, in order to prevent the development of resistance and improve patient compliance until complete recovery.

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Conflict of Interest

The authors declare no conflict of interest.

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