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Therapeutic Options of Cutaneous Leishmaniasis

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Introduction

Leishmaniasis is common in tropical and subtropical areas and more than 15 million people are infected by this disease. Depending on the tropism, leishmaniasis is divided into at least four clinical syndromes including visceral (VL), cutaneous (CL), muco-cutaneous (MCL), and mucosal leishmaniasis (ML) [1-5]. Cutaneous leishmaniasis (CL) is a chronic infectious skin disease which has diverse clinical manifestations due to chronocity of the disease, host immune system, anatomical area of infection and age of the patient. The etiological agent of cutaneous leishmaniasis is *Leishmania major* and is transmitted to humans via *Phlebotomus papatasi* flies in the Old World and the Lutzomyia genus in the New World [2,3,5-8]. After a bite, the lesions occur as inflammatory erythematous papules which further develop to nodules and crust in the center of the lesion [4,9,10]. The lesions are painless and heal spontaneously after several months or are characterized by function impairment, susceptibility to secondary infection, and development of disfiguring permanent scars [5,11,12]. In addition, the site, severity and extent of cutaneous disease as well as time to spontaneous resolution can affect on healing process. Hence treatment of cutaneous leishmaniasis is much more difficult and requires prolonged parenteral treatment. In addition, in many settings species identification is unavailable or impossible and local expertise is the only mode of therapy which is associated with significant toxicity and side effects. Therefore, the aim of therapy is to reduce the risk of dissemination and relapse, speed disease resolution and minimize scarring and on the other hand, improve re-epithelialization of the ulcerative lesions and resolution of popular or nodular lesions [11,12].

A wide variety of methods including physical methods such as curettage, surgical excision, thermotherapy, cryotherapy and laser therapy; topical treatments, systemic treatments and recently nanomedicines have been used in treatment of CL and since many of these agents have not undergone rigorous clinical trials could not always be reliable. From the other point of view, high cost, low adherence due to the prolonged use of intravenous or intramuscular injections, systemic toxicity, and in some cases, resistance are possible reasons for lack of a valid method [12,13]. One problem that limits treatment options in CL therapy is the variation in drug effectiveness for different *Leishmania* species [14,15].

A wide range of systemic drugs such as antimonials, pentamidine, amphotericin B, azoles, allopurinol and miltefosine have been used for treatment of CL. Pentavalent antimonials (sodium stibogluconate, Pentostam or meglumine antimoniate, Glucantime) are the first choice against all forms of leishmaniasis in most countries and due to their negligible toxic effects have been introduced in the therapeutics of leishmaniasis from the 1940s. Although antimonials are considered as the mainstay of treatment of CL, they are limited by systemic side effects, local pain during intramuscular injections, development of drug resistance, and high price in developing countries [12,15]. The alternative treatment regimens include miltefosine, pentamidine isethionate, amphotericin B, antifungal agents (e.g., ketoconazole, fluconazole, itraconazol), paromomycine, and granulocyte macrophage colony-stimulating factor [11]. Pentamidine is an alternative agent to antimonials in the management of CL and from the other side have adverse effects such as hypoglycemia, hypotension, nausea, vomiting, dizziness, myalgia, headache, syncope, transient hyperglycemia and pain at the injection site [12,16,17]. Although other drugs also are effective in the treatment of leishmaniasis, their side effects, toxicity and difficulty of intravenous administration limit the healing processes.

Antimony and amphotericin B have equivalent results in treatment of CL. However, because of considerably more serious side effects and related costs, amphotericin B has been considered as an alternative treatment [18,19]. However, topical application of drugs induces a more rapid healing due to a high drug concentration locally in the lesion and avoids the adverse effects of systemic therapies [12,20]. Local therapy usually is preferred in patients with less than five lesions. Also it has been shown that local therapy in combination within intralesional antimony and cryotherapy is more effective than antimony or cryotherapy alone. In the patients with multiple systemic or complicated Old World CL (*L. major*) lesions such as oral lesions, treatment by miltefosine is a proper treatment option. Another important finding is the fact that *L. mexicana* has been found resistance to miltefosine and antimony is preferred in systemic treatment [21,22]. Likewise in CL caused by *L. panamensis* or *L. amazonensis* which rarely cause MCL, combination of local therapy of antimony and cryotherapy is preferable than systemic therapy [11]. Moreover, since monotherapy causes a growing resistance of the parasite to antileishmanial drugs, multidrug therapy can lead to short duration of therapy, low dose requirement, reduce chances of toxic side effects and cost, and prevent the emergence of drug resistance. A combination therapy is a possible strategy in the recent years which has gained much attention in overcoming the side effects and toxicity drugs and may improve the efficacy of therapeutic schemes [17].

Physical treatment of CL has been successfully used in endemic countries and in spite of the low risk of associated adverse effects and low price; they are suitable for limited disease only of the Old World variant or *L. mexicana* species of the New World CL, which carry a very low risk of dissemination [12,20].

The use of drugs derived from natural sources is a valuable approach in treatment of leishmaniasis. Since the victims of leishmaniasis are generally poor, many patients pick out herbal therapy which is inexpensive and readily available [23,24]. The anti-leishmanial activity

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of some plants is related to the presence of the compounds such as alkaloids, chalcones, triterpenoids, naphthoquinones, quinones, terpenes, steroids, lignans, saponins, and flavonoids [24]. The Asteraceae family of native plants has the best anti-leishmania effect. The plants of Artemisia and marigold are effective against leishmania because of the bioactive compounds such as artemisinin, artemether, semen, sabinene, cineol, linalool, borneol, santonin, and farnezole [25]. A major challenge in the usage of traditional antileishmanial drugs is that they cannot penetrate inside the macrophages to kill the parasite. Recently, nanocarriers are considered as promising approach in the treatment of leishmaniasis. Nanoparticles such as liposomes, polymers, and nanospheres have proven for drug delivery as nanocarriers. Nanocarriers which penetrate into macrophages release the drug inside the cell and lead to a local high concentration of the therapeutic. In addition, the nanocarriers are able to reduce the drug toxicity and carry more than one drug and release directly in the target site. Although the nano-based delivery systems are certainly effective, high price could be the most serious disadvantage of this method [26,27]. It has been reported that despite anti-leishmanial property of the nanoparticles, they have the same cytotoxicity effects on macrophages. Therefore, administration of the nanoparticles for treatment of CL may have both positive and negative consequences [28]. For instance, liposomes display serious disadvantageous such as instability and large size [26,27]. Disfiguring scar is an unfavorable result of leishmaniasis and patients with these scars usually have psychosocial and cosmetic complains. A case report has showed that application of autologous fibroblasts and keratinocytes have been able to treat the atrophic cutaneous leishmaniasis scar.

Finally, finding a potential clinical therapy, cost-effective and with the lowest side effects is a suitable strategy in treatment of leishmaniasis. Today, due to the toxic consequence of systemic therapy a trend towards using of nanocarriers and combination of drugs is being preferred.

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