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Application of nanotechnology in treatment of leishmaniasis: A Review

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ABSTRACT

Leishmaniasis is a neglected tropical disease caused by a protozoan species of the genus *Leishmania* affecting mostly the developing countries. The disease with current mortality rate of 50,000 deaths per year threatens approximately 350 million people in more than 90 countries all over the world. Cutaneous, mucocutaneous and visceral leishmaniasis are the most frequent forms of the disease. Chemotherapy still relies on the use of pentavalent antimonials, amphotericin B, liposomal amphotericin B and miltefosin. Treatment of leishmaniasis has remained insufficient since the current antileishmanial agents have several limitations including low efficacy, toxicity, adverse side effects, drug-resistance, length of treatment and cost lines. Consequently, there is an immediate requirement to search for new antileishmanial compounds. New drug delivery devices transport antileishmanial drug to the target cell specifically with minimizing the toxic effects to normal cells. This study attempts to present a comprehensive overview of different approaches of nanotechnology in treatment of leishmaniasis.

1. Leishmaniasis

Leishmaniasis is one of the most important parasitic diseases, caused by protozoon kinetoplastid parasites found in *Leishmania* species (Oryan et al., 2007; Shirian et al., 2014). *Leishmania* are obligatory intracellular parasites that are transmitted to mammalian and infect them by the bites of female sandflies from the Phlebotomus and Lutzomyia genera via anthroponotic or zoonotic cycles (Murray et al., 2005; Oryan, 2015). Leishmaniasis is a non-contagious infectious vector-borne disease with extensive morbidity and mortality in more than 95 tropical and subtropical countries (Alvar et al., 2006). Leishmaniasis is a complex disease and has remarkable impact on global public health and it has been considered as one of the six main tropical diseases by the World Health Organization. However, after toxoplasmosis and cryptosporidiosis, leishmaniasis is the third most common parasitic disease (Shafiei et al., 2014). Moreover, leishmanial infection has become complicated with the co-infection of AIDS and it has obtained substantial importance in HIV-infected people as an opportunistic infection in regions where both infections are endemic (Alvar et al., 2008).

This parasitic infection manifests in several clinical forms including cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), diffuse cutaneous leishmaniasis (DCL), visceral leishmaniasis (VL), post kala-azar dermal leishmaniasis (PKDL) and leishmaniasis recidivans (LR) (Oryan and Akbari, 2016). The CL form is caused by two *Leishmania* species, including *Leishmania major* and *L. tropica* in the old World, whereas MCL and DCL are caused by *L. amazonensis* and *L. braziliensis* in the new World (Minodier and Parola, 2007; Souza et al., 2011; Oryan et al., 2013; Shirian et al., 2014). The VL is usually caused by several *Leishmania* species, such as *L. donovani* and *L. infantum* in the old World and *L. chagasi* in the new World (Yaghoobi-Ershadi et al., 2001; Oryan et al., 2008; Shirian et al., 2013). The cutaneous form of leishmaniasis may be localized in a single part of skin or produce diffuse lesions. Destruction of the mucous membranes of mouth, throat and nose are the main consequences of the MCL. The VL form is the most threatening leishmaniasis among different types of the disease. The VL is non-self-healing and usually mortal if left untreated. Leishmaniasis is included in the neglected tropical diseases especially in countries with poor socioeconomic conditions (Oryan and Akbari, 2016) and its strong link to poverty has previously been recognized (Alvar et al., 2006).

Nearly 350 million people live at risk of this parasitic disease all over the world (Oryan et al., 2008). The VL and CL form are the most important and also more popular clinical forms of the leishmaniasis and it has been estimated that about 1-1.5 million new cases of CL and 500,000 new cases of VL are infected, annually (Ardehali et al., 2000; Shirian et al., 2013). Moreover, according to the World Health Organization data, the *Leishmania* parasites affect approximately 12 million people worldwide among them about 60,000 deaths has been recorded in the world, annually (Tonui and Titus, 2007). Nevertheless, due to under reporting and misdiagnosis real cases are expected to be

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higher.

Leishmaniasis rapidly spreads and it is presently a major public health concern in the developing countries. Treatment of leishmaniasis is still a challenge because there are several problems such as high cost of drugs, high drug-dosage, incidence and prevalence of drug-resistance, side-effects and lack of affordable new antileishmanial drugs. Heretofore many attempts have been made to develop drugs with low cost and minimum adverse side-effects but still the morbidity and mortality from leishmaniasis is not decreasing. The need for an ideal agent to treat leishmaniasis is inevitable. An ideal drug should be effective in minimum doses, not induce drug resistance, be of low cost, should be free of adverse side effects, not be teratogenic and does not require hospitalization (Oryan, 2015). Improvements have been created in the treatment of leishmaniasis in the recent years. New drugs, new delivery systems and new treatment regimens have been designed and applied. This review examines the deployment and improvement of nanotechnologies in development of drug delivery for treatment of leishmaniasis.

2. Current drugs for treatment of leishmaniasis

2.1. Pentavalent antimonials

Pentavalent antimonials (Sb or Sb^V) have been used against leishmaniasis. In most areas of the world, the pentavalent antimonials, including sodium stibogluconate (Pentostam®, C12H38O26Sb) and meglumine antimoniate (Glucantime®, C14H29O10N2Sb) are considered the first line drugs and gold standard in treatment of leishmaniasis disease (Kedzierski et al., 2009). However, these drugs need long courses of administration (up to 30 days) and are very toxic to human (Herwaldt and Berman, 1992). Cardiotoxicity, hepatotoxicity, pancreatitis, reversible renal failure, anemia, leukopenia, thrombocytopenia, abdominal pain, nausea, vomiting, blood disorders and pain at the injection site when administered intramuscularly are several undesirable adverse side effects (Igbineweka et al., 2012). This treatment regimen has limitation for pregnant women and the elderly person and other disadvantages such as high cost, parenteral administration and so forth. Currently several reports have shown that the effectiveness of these drugs has significantly reduced (Sazgarnia et al., 2013). Moreover, large-scale drug resistance and treatment failures have been reported in recent years (Sundar and Chatterjee, 2006; Chakravarty and Sundar, 2010). Usually these drugs are used alone in systemic therapy of leishmaniasis and sometimes in combination with other agents (Roberts et al., 1998). However, when there is a limitation, such as treatment failure, in administration of pentavalent antimonials, alternative drugs such as amphotericin B, paromomycin and pentamidine should be used (Wiwanitkit, 2012).

2.2. Amphotericin B

Amphotericin B or fungizone (C47H73NO17) is an antibiotic and antifungal drug showing effective antileishmanial activity against different species of *Leishmania*. Amphotericin B is usually administered as the second line treatment for leishmaniasis and has often showed good clinical results. This drug has been used as the first choice treatment and resulted nearly 100% cure rates in India, where widespread resistance to pentavalent antimonials persists (Sundar et al., 2000; Kumara et al., 2014). However, adverse side effects are major limiting factors in administration of Amphotericin B. It is associated with common side effects such as fever, nausea, vomiting, anemia, hypokalemia, nephrotoxicity, hepatotoxicity, cardiotoxicity, hypersensitivity and anaphylaxis (Minodier and Parola, 2007; Lindoso et al., 2012; Gamboa-Leon et al., 2014). Although, amphotericin B has shown poor gastrointestinal absorption, it has usually been administered as intravenous infusion daily or on alternate days and required prolonged hospitalization (Sundar et al., 2000). Moreover, resistance may occur due to high frequency of its use.

2.3. Liposomal amphotericin B

Recent development of liposomal amphotericin B has reduced problems of amphotericin B. The World Health Organization has proposed administration of liposomal amphotericin B based on its high efficacy and safety (WHO, 2010). This form of amphotericin B is less toxic, more bioavailable and is better tolerated by patients (Muller et al., 2001). Additionally, the lipid form of amphotericin B is taken up selectively by macrophages and it is less nephrotoxic. In comparison with conventional amphotericin B, liposomal amphotericin B has generally mild adverse side effects such as urticarial rash and renal impairment which are resolved after treatment (Sundar and Chakravarty, 2013; Chávez-Fumagalli et al., 2015). However, the main limiting factor in application of liposomal amphotericin B is its high cost (Lindoso et al., 2012). Moreover, the lipid form of amphotericin B has short circulating half-life and quickly reaches its higher concentrations in liver and spleen (Lindoso et al., 2012; Oryan, 2015). Amphotericin B and its lipid form have effectively served as the therapeutic mainstay against leishmaniasis, but recent reports of limitations have necessitated evaluation of alternative therapeutic modalities. Paromomycin, pentamidine and sitamaquine are used in some instances, but each have restrictions such as affordability, resistance to the currently used drugs, toxicity and require parenteral administration (Sen et al., 2010). However, new therapeutic anti-*Leishmania* agents and novel treatment methods are required to combat this disease.

2.4. Miltefosine

Miltefosine (hexa decyl phosphocholine, Impavido®) is an alkyl phosphocholine compound used in treatment of microbial and fungal infection, cutaneous metastases of breast cancer, solid tumors, schistosomiasis and therapy of cutaneous and visceral leishmaniasis (Sundar and Olliaro, 2007; Eissa et al., 2015). The entry of miltefosine in treatment of leishmaniasis has been considered as a prominent event, because miltefosine is as the first non-parenteral drug and it can be administered orally and locally in treatment of leishmaniasis. Treatment with this drug does not need hospitalization and treatment in home is possible; therefore, the related costs of hospitalization and nursing are eliminated. In addition, efficacy of miltefosine has been reported in pentavalent antimonials resistant patients. Moreover, the cost of treatment with miltefosine is lower than pentavalent antimonials (Das et al., 2010). In general, clinical results using oral miltefosine have been satisfying but this drug supports development of resistance on extensive use.

Misuse of miltefosine, its long half-life of 7 days and inactivation of genes responsible in drug uptake are three reasons in development of resistance against miltefosine (Das et al., 2010; Oryan, 2015). However, several adverse side effects of miltefosine such as vomiting, diarrhea, toxicity in gastrointestinal, hepatic and renal systems are reported in literature (Sundar and Chatterjee, 2006; Sachdeva et al., 2013; Fernandez et al., 2014; Oryan, 2015). This compound should be administered through intravenous way in the patients with gastrointestinal disorders. But this route of prescription is limited, because of adverse side effects such as thrombophlebitis and hemolysis. Reports of failure in treatment and relapse in some cases treated with this drug have also been observed (Das et al., 2010). Additionally, miltefosine is teratogenic and should not be administered in pregnant women and person of child bearing age (Sundar and Chatterjee, 2006; Lindoso et al., 2012; Oryan, 2015).

3. New methods in treatment of leishmaniasis

The current chemotherapies have series of limitations such as high cost, parenteral prescription, high toxicity, development of resistance