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Recent Trends in Leishmania Research: A Therapeutic Perspective

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Abstract

Leishmaniasis is a spectrum of disease caused by the infection of protozoan parasite *Leishmania* mainly affecting the antigen presenting cell of the host. The disease is although considered as neglected tropical disease still it is not completely eradicated. Majority of the issues related to the therapeutic approach is due to increased cytotoxicity of the drugs, less effectiveness, high cost and occurrence of drug resistance. Therefore, recent advancement in the field of parasitology has taken into consideration of the specific arms of immunity which can be triggered with the help of natural products, synthetic molecules or parasite specific ligands which helps in the restoration of host protective immunity and recovery from the infection. Therefore, in this review, we have highlighted the recent advancement in the field of *Leishmania* research taken into consideration of the therapeutic perspective. We have shown that apart from therapeutic potential of the available drugs and vaccination approach, the immune-therapy are emerging as the modern regime of treatment where the effectiveness of the therapy is significantly increased and making it safer and promising.

Introduction

Leishmaniasis is one of the world's oldest recorded protozoan infectious diseases dating back to the 7th century BC, which is caused by the bite of infected sandfly during the course of their blood meal[1]. As per the record, it has been estimated that the disease is prevalent in around 98 countries, around 4 to 12 million peoples across the globe with 2 million new cases registered each year and causing 20 to 50thousand death annually (WHO, Jan 2014). Unfortunately, regardless of its global prevalence and devastating impact on the lives of millions of individuals, the disease is still considered as neglected tropical disease, mainly affecting underprivileged communities, associated with poor economic conditions, inadequate access to shelter, healthcare and medication[2]. Sudden outbreak and the spread of the disease is associated with the changes in environmental conditions which is making more prone ambience for the growth of sand-fly vector, while the emigration of the people into the endemic areas are increasing the risk of mass individuals[3]. With passing time, the reservoir of the disease is increasing, and the major concern related to this disease is its co-occurrence with HIV[4]. Leishmaniasis is of three basic types cutaneous, muco-cutaneous and visceral form based on the involvement of different species of *Leishmania,* among which Visceral Leishmaniasis (VL) is considered as the most fatal one as it affects visceral organ and if left untreated it often leads to death of the mammalian host[1]. Although therapies are available for the cure of leishmaniasis including VL but most of these are associated with increased cyto-toxicity and showing

increased drug resistance problems which is a major area of concern[5]. Therefore, a serious concern is needed to find the way for the complete eradication of the disease which need government and private joint co-operation for the detail research in the field of leishmaniasis in order to find the effective solution for this problem. In this review we have highlighted the major therapeutic approach against leishmaniasis both past, present and the future strategies which is important to redefine the most safer, convenient and affordable way to fight against this deadly disease.

Major Treatments Regime Against Leishmaniasis

As far as treatment is concerned, drugs are available for the treatment of the VL, however; these drugs are either showing high toxicity or un-prescribed use can leads to development of drug resistance among parasite which ultimately result into more severe consequences. Since leishmaniasis is the disease of poor people therefore cost of drugs is one of the major concerns. Overall the available therapeutic regime can be classified into following categories which includes therapeutic approach which targeted drugs, vaccination and immunotherapy.

Therapeutic approach with targeted drugs

Currently the available therapies against leishmaniasis are based on the use of drugs belonging to the following categories i.e. antiprotozoan agents and antibiotics, pentavalent antimony compounds and systemic antifungal agents.

a. Antiprotozoan agents and antibiotics: These are the drugs which are efficient in killing many parasites by directly binding to one of its cellular components and inhibiting its functions. One of the most frequently used drugs among antiprotozoan agents is miltefosine which is sold under the commercial name of Miltex or Impavido and are used against all forms of leishmaniasis including visceral form. Miltefosine mainly works by interfering with the functions of membrane lipids affecting membrane integrity and destroy the activity of mitochondrial cytochrome c oxidase thereby causing apoptosis-like cell death[6]. Another drug pentamidine which come under antibiotics commercial sold by the name lomidin and inhibits the growth of *Leishmania* by blocking oxidative phosphorylation of inhibition of protein and phospholipids biosynthesis[7]. Fluconazole another important anti-fungal agent works by inhibiting the cytochrome 450 enzyme 14α-demethylase and blocks ergosterol synthesis also found to be effective against cutaneous leishmaniasis[8-9].

b. Pentavalent antimonials: Most commonly used antimonial drug is sodium stibogluconate sold under the commercial name of pentostam which act by inhibiting the nucleotide metabolism of the parasite and required for a long-term therapy[10]. Studies suggested that the combination of paromomycin and pentavalent antimonials remains treatment of choice when executed for a 17 days long trial in East Africa VL on the other hand studies from our lab reported that glycyrrhizic acid in combination with sodium antimony gluconate showed significant anti-leishmanial immune response[11]. These studies highlighted the increased effectiveness of the antimonials drug with lower chances of resistance and toxicity when used in combination with other drugs.

c. Systemic antifungal agents: In practical purpose the widely used drug against leishmaniasis is the amphotericin B which is a systemic antifungal agent and used in liposomal formulation with commercial name Ambisome. It mainly binds with the membrane sterols and causes lysis of the cells[12]. In a study it was found that lower doses of tamoxifen and amphotericin B showed increased efficacy against human cutaneous leishmaniasis where tamoxifen was found to prevent lipid peroxidation and thereby reduce the adverse effect of amphotericin B[13].

Vaccine Against Leishmaniasis

In the present situation there is no effective vaccine available against leishmaniasis regardless of effort in the field of leishmanial research. This is mainly because of the frequent change in the surface antigen of the parasite[14] thereby making it difficult to consider the antigenic determinant to be targeted against the disease. Still studies have shown the effectiveness of various forms of vaccination approach which includes the use of whole-killed parasite, live-attenuated parasite and recombinant surface antigen and ligands which can be promising against disease progression and onset.

a. Whole-killed parasite: Autoclaved whole organism and chemically killed organism have been used as vaccine candidates against leishmaniasis and have shown to provide increase Th-1 (T-helper type 1) responsiveness by elevating IFNγ (Interferon gamma) secretions in the host[15]. However, once the organism has been autoclaved, most of its antigens get denatured and therefore shows reduced efficacies with time.

b. Live-attenuated parasite: Treatment with non-hazardous chemicals and radiation can slightly alter the phenotype of the organism without completely killing them and this attenuated strain becomes avirulent which can be used against the infection as a vaccine candidate. In case of leishmaniasis several groups had reported the increased effectiveness of radio or chemical attenuated strain against leishmaniasis[16] in mice and hamster model however; there is always a major concern of the reversal of the strain to virulent form which can result in the serious consequences to the host.

c. Recombinant surface antigen and ligands: Surface

antigen of the virulent strain can be used against the disease as pre-immunization which makes the host immune system aware of the kind of antigens they can encounter during future challenges with the parasite. In studies with *Leishmania* several surface antigens have been implicated as an immunization approach which includes recombinant gp63, lipophosphoglycan, *Leishmania* Activated C Kinase (LACK)[17] etc. and have shown better efficacies against the disease. However, these approaches are still validated in the mice or hamster model but not established in case of human leishmaniasis since the degree of safety and post-immunization hazards are the major area of concern. In case of *L. major* infection, it was found that parasite surface protein component knows as hydrophilic acylated surface protein B1 (HASPB1) induced immunity against infection even without adjuvant supplementation. On the other hand, *Leishmania*- derived recombinant poly-protein also known as LEISH F1 has entered random clinical trial and veterinary testing[18]. Therefore, there still exists a way for the modern and safer therapeutics approaches and proved effectiveness of clinical trials of these antigens against leishmaniasis.

Immunotherapy Against Leishmaniasis: The Present and Future Treatment Regime

Modulation of immune system to mound protective immunity is the recent trends in therapeutic approach widely known as immunotherapy. The therapeutic strategies include modulation of any components of immune system through activation of receptors, transcription factors, cytokines and chemokines gradients or elevated antimicrobial molecules which ultimately give rise to protective host response either self-sufficient for the killing of the parasite or help to increase the efficacy of the anti-leishmanial drugs. Based on the recent advancement in the potential immunotherapeutic candidate, the strategies of immunotherapy can be classified into the following groups.

a. Activation of pattern recognition receptors: These are the protein receptors or the sensors of the innate immune cells which include dendritic cells, macrophages, neutrophil, NKT cells (Natural killer T cells) etc. responsible for sensing the pattern associated with molecules of the microbial origin and then sends signals for the activation of the immune response to execute the further encounter of the antigen[19]. It was reported that activation of the pattern recognition receptor TLR4 (Toll like receptor 4) during leishmanial antigen glycosphingophospholipid (GSPL) stimulation work synergistically with NKT cells activation and efficiently increase the expression of IFNγ which ultimately helps in the recovery of host immune response against pathogen[20]. In another study, it was found that treatment with GP29 (Glycoprotein 29), a leishmanial antigen causes stimulation of TLR4 and thereby increases the expression of IL-12 cytokines providing Th-1 protective and simultaneously decreasing the expression of IL-10 cytokines[21].

b. Induction of cytokines response: Cytokines are the small proteins secreted by the cells of the immune system and help in the maintenance of the immune function by activation transcription factors, by polarizing T cells subsets or by increasing the generation of anti-microbial molecules. It was revealed that application of recombinant LPG3 (Lipophosphoglycan 3) a leishmanial derived molecule helps in the elevated expression of IFNγ and TNFα from the NK cells and pave path for the successful eradication of the disease[22]. In another study it was found that direct IFNγ therapy increases the therapeutic effects of antimonial drugs against human VL[23] thereby making immunotherapy a successful attempt to increase the efficacies of anti-leishmanial conventional drugs. In a study it was highlighted that during inhibition of IL-10 cytokines by the administration of monoclonal antibody can elevate host NO (nitric oxide) generation with subsequent Th-1 cytokines induction during experimental VL[24]. Overall these studies have proven the importance of immune system modulation to fight against the disease in more natural way with more safer and promising response.

Conclusion

Leishmania although considered as major tropical neglected disease, but if continuously remain neglected can be a major threat to the developing nation due to continuous emigration and anthropogenic activities. Major concern is required in finding the way for the safety in administration of the drug, lower toxicity and high effectiveness and off course the affordability as it is affecting the underprivileged community. In the scenario of therapeutic and immunisation perspective it was found that although many different aspects have been considered for the safer mode of treatment but in some point of time it is causing huge distress to the effected people. Therefore, in line with current formulation it has been found that recent advancement in the therapeutic approach through monoclonal antibody-mediated selectivity in the target of leishmaniasis, and the use of immunotherapy parallel to the available conventional medicine for their better affectivity is proven to be worthy and a solution for the future encounter of the resistance. Altogether our study highlighted the past present and future advancement of the therapeutic approach in leishmaniasis which is also applicable to other similar neglected tropical diseases.

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