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REVIEW ON PROTOZOAN PARASITE LEISHMANIA DONOVANI

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Abstract
Visceral leishmaniasis (VL) caused by the protozoan parasite *Leishmania donovani*is the most severe form of leishmaniasis. The WHO has classified the leishmaniasis as a major tropical disease. The current anti-leishmanial drugs have several limitations such as, their route of administration, toxicity and cost. Moreover no effective vaccines are available for the treatment of leishmaniasis. The need for safe and affordable anti-leishmanial therapies capable of overcoming the problems makes the identification of new drug candidates an urgent priority. This has sparked a renewed search for new types of drugs with novel targets. DNA minor groove has been an important therapeutic drug target for parasitic diseases including leishmaniasis.
Keywords: Visceral leishmaniasis, DNA minor groove, leishmaniasis, drug, parasite.

1. Introduction

Visceral leishmaniasis (VL) also known as kala-azar and black fever. VLis the most severe form of leishmaniasis.VL is the second largest parasitic killer in the world (after malaria) responsible for an estimated 500,000 cases each year worldwide[i-iii].Aheamoflagellate parasite of genus *Leishmania* is responsible for causing the disease leishmaniasis[iv-v].In 1903, "Willian Leishman and Charles Donovan" described the *Leishmania* parasites, but it has been observed in 1885, by "David D. Cuningham" and in 1989, by "Peter Borovsky".In 1903, "James Wright" proposed the genus *Leishmania*[v].There are more than 20 species and subspecies of *Leishmania* that have been identified as infective for humans. Thirty species of sand fly have been identified as vectors for the parasite[vi].The control of this disease remains a severe problem. At present, no successful drugs are available for the treatment of this disease. Existing drugs for the treatment of this disease are harmful, costly and resistant[vii-viii].

2.*Leishmaniasis* Distribution in the World

According to the WHO, leishmaniasis affects eighty eight countries, seventy two out of which are developing ones. There are half a million cases of VL and 1.5 million cases of cutaneous leishmaniasis (CL) found each year. Ninety percent of CL cases occur in Afghanistan, Iran, Brazil, Kingdom of Saudi Arabia and Syria. Over ninety percent of VL cases occur in India, Nepal, Bangladesh, Sudan and Northeast Brazil (WHO/TDR, 2005)[ix-x].

3. Transmission

Female sandflies are vectors of the leishmaniasis. Female sandflies are small (about 2-3mm long), hairy, yellow or gray colored with long antennae pointed upward-held wings. Wild animals (such as rodents) as well as domesticated animals (such as dogs) and humans themselves can act as reservoirs of infection. The sandfly vector is usually infected with one species of *Leishmania* by ingesting blood from infected reservoir hosts. Approximately 30 species/subspecies of sandfly are proven vectors and probably more than 40 additional species are involved intransmission[xi]. Old World forms of *Leishmania* are transmitted by sandflies of the genus *Phlebotomu*s (Europe, North Africa, Middle East and Asia) while New World forms are mainly transmitted by flies of the genus *Lutzomyia* (from Southern USA to Northern Argentina). Sandflies are relatively weak, noiseless fliers,they rest in dark, moist places and are typically more active during the evening[xii-xiii]. Most of well recognized *Leishmania* species known to infect humans are zoonotic, which include agents of visceral, cutaneous and mucocutaneous forms of the disease. However, for the anthroponotic forms (those transmitted from human to human through the sandfly vector, mainly associated with *L.tropica*) humans are the sole reservoir host[xiv]. A recent group of risk factors that also contribute to increased *Leishmania* transmission includes urbanization and deforestation, economic hardship, natural disasters, armed conflicts and tourism[xi,xv]. Other forms of *Leishmania* are congenital[xvi-xvii]and transmitted parenterally (through blood transfusion, needle sharing and laboratory accident)[xviii-xix].

4. Life Cycle of *Leishmania Donovani*Parasite

All *Leishmania* species are transmitted by the sandfly vector from the genus *Phlebotomus*or *Lutzomia* and itis generally accepted that they are obligated intracellular parasites in the macrophages from the mammal hosts[xx]. During the *L. donovani* parasite life cycle, *Leishmania* parasite comes in different morphological and biological phenotypes/forms, which include the promastigote appears as stage with variable morphology located inside the gutof the female sandfly (long flagellated parasite) and the amastigote stage (round form without free flagellum) inside the phagolysosome of the mammal host[xxi]. These phenotypes rely on variations in the expression of (specific) genes that allowthe parasite to survive in these two different environments. The more interesting parasiteforms in terms of virulence and pathogenicity are the metacyclic promastigotes, responsiblefor initiating the infection and the amastigotes forms, which are in charge of maintainingthe infection in the mammal host.

Promastigote parasites are injected into the mammalian host after sandfly takes a blood meal. In the vertebrate host, parasites are rapidly taken up via tissue phagocytes, monocytes and neutrophils, which are involved to the biting place due to the injury caused through the sandfly[xxii].Inside the macrophage, the parasite loses its flagellum and transforms into a non-motile amastigote shape. This amastigote is capable of surviving and replicating in the very acidic atmosphere of the phagolysosome[xxiii].In the case of VL, the expression of newly acquired infection varies from none (subclinical), to oligosymptomatic, to fully established (kala-azar), spreading to the organs of the mononuclear phagocytic system[xxiv].In other cases, amastigotes may also extend to additional cutaneous spot other than the inoculation site; this is called Diffuse cutaneousleishmaniasis. If they also migrate to the mucosa, mucocutaneous leishmaniasis appears. Once a sandfly takes a blood meal from an infected host, it release amastigotes or amastigote infected macrophages. Within the sandfly, amastigotes undergo several divisions and progressive metabolic and morphologic changes to long slender nectomonads (procyclic forms: short, ovoide, slightly motile). Non-infective promastigotes, change into harmful promastigote. These harmful promastigote forms will be injected into the mammalian host during the next blood meal[xxv-xxvi].

5. Clinical Manifestations of Leishmaniasis

According to the location of macrophage which harbors the parasite, four major clinical forms of leishmaniasiscan be observed (Cheesbrough, 1998)[xxvii].

5.1 Cutaneous Leishmaniasis (CL): Symptoms of CL have been first described in 1756 by Alexander Russell following an examination of a Turkish patient[xxviii].CL is characterized by lesions on the patient skin which ulcerates later to give a disfigurement scare after healing[xxvii,xxix]. In Saudi Arabia patients, lesion and ulceration occurs mainly in the uncovered areas of the body include limbs and face. CL lesions usually heal spontaneously within months. But in some patients complication may occur as the parasite metastasizes through the lymphatic system to the lymph node, leading to the formation of subcutaneous nodules or enlargement of the region lymph nodes[xxx-xxxi].Ulceration of the infection may be a consequence of the host immune response[xxxii-xxxiii]. CL is divided into two sections according to the geographical distribution and the parasite speciesOld World and New World CL[xxxiv]. However, the symptoms and the treatment of the disease are differing in reference to the species.

5.1.1 Old World CL: Several species of *Leishmania* cause CLin the Old World and the important one of which are *Leishmania major* (*L.major*) and *Leishmania tropica* (*L.tropica*)[xxvi-xxxv]*L. major*causes a boil of 5-10 mm in diameter which changes into a large uneven ulcer or moist type lesion characterized by reddish raised edge[xxvii, xxxvi]. Lesions may be multiple and differ in size[xxxvii]. *L. tropica*causes dry type lesion 25-70mm in diameter, the ulcer is characterized by crusted scab. Lesion formed by *L.major* infection requires 3-6 months for self-healing, while the lesion formed by *L. tropica*requires 1-2 years for self healing[xxvii, xxxv, xxxvi]. The incubation period of *L. major* and *L.tropica*varies from 1-2 weeks to several months[xxxvi]. It used to be thought that long lasting immunity against CLis acquired after cure of the infection[xxvii] but recent it has been reported that no lifelong immunity exist and re-infection may occurs[xxxvii].

5.1.2 New World CL: *Leishmania mexicana spp.* and *leishmania vianna spp.* are the primary species which cause New World CL. The lesion caused by *Leishmania mexicana*can be self healing but if the ears are infected, it may last for 30 years and destroy the pina of the ear. In the case of *leishmaniavianna spp.*infection ulcers formed might be self healing[xxxvii].

5.2 Diffuse Cutaneous Leishmaniasis (DCL): It occurs both in New World and Old World. Characterized by a wide, firm and smooth skin lesion which become scaly and rough later. DCL in the New world caused by *L .amazonensis*is resistant to treatment, while Old world DCL caused by *L .aethiopica* relapse after treatment[xxvii, xxxv].

5.3 Visceral Leishmaniasis (VL): It is caused by *L. donovani* as well as *L. infantum*. Symptoms of this form of leishmaniasis include fever, hepatomegaly (greatly enlarged liver), splenomegaly (greatly enlarged spleen), diarrhea[xxvii, xxix, xxxviii, xxxix]weight loss, anemia, skin darkening[xxxiv] and death if patient remain untreated[xxvii, xxxiii, xxxviii].Twenty percent of Indian patients, who cured from previous *L. donovani*, individuals suffer the symptoms of Post Kala Azar Dermal *Leishmaniasis* (PKDL). Symptoms of PKDL include rashes occurs around mouth, hypo pigmented face, limbs or body trunk[xl-xli].

5.4 Mucocutaneous Leishmaniasis (MCL): Although, it is usually caused by *L. Panamensi s*and *L. guyanensis*,[xxix]immune compromised patients also can show MCL symptoms byother *Leishmania* species including *L. major*, *L. infantum* and *L. donovani*. MCL begins as lesions that ulcerate and become large and long-lasting that involve of human mucousal system[xxix, xxxvi]. The parasite attacks the nasal (nasopharynx) or the buccal cavity and slowly degenerate the cartilaginous and soft tissues to cause disfiguration and destruction of the nasalseptum, lips and larynx[xxiii, xxviii, xxix, xxxiii, xlii].

6. Diagnosis of Leishmaniasis

The "golden standard" method for diagnosing leishmaniasis is the microscopic examination of Giemsa-stained slides prepared from biopsies, scrapings or impression smears. The aim of this method is to identify amastigotes according to their characteristics including size (2-4 μm), shape (round-oval), inner organelles, nucleus and kinetoplast[xii]. Other traditional methods are the *in-vitro* culture of infected tissues or lesion aspirates or *in-vivo* infections using animal models. As it is sometimes difficult to obtain tissue samples in patients suffering from VL, the following serological methods are mainly used. The freeze-dried agglutination test (DAT) to detect antibodies. DNA based methods like PCR usually have high sensitivity and specificity but require sophisticated equipment and highly trained personnel that are not currently available in peripheral laboratories of most developing countries. As a result additional assessment of its field applicability is still needed.

7. Chemotherapy of Leishmaniasis

7.1 Pentavalent Antimonial: Pentavalent antimonials (Sb^V) are used for the treatment of every types of leishmaniasis[xliii].Long course treatment of Sb^V shows the accumulation in the tissues mainly in liver and spleen. Treatment with Sb^V has been caused many side effects including nausea, abdominal pain and pancreatic inflammation leading to the reduction of treatment[xliv].Currently several limitations have decreased the use of pentavalent antimonials. The recommendations have replaced the pentavalent antimonials by amphotericin B in refractory zones[xlv].

7.2 Amphotericin B: A polyene antibiotic, amphotericin B showed its anti-leishmanial activity in early 1960s[xlvi-xlvii].Amphotericin B causes several side effects such as fever with rigor and chills. Its use requires prolonged hospitalization and close monitoring[xlviii]. Three lipid formulations of amphotericin B: liposomal amphotericin B (AmBisome), amphotericin B lipid complex (Abelcet) and amphotericin B colloidal dispersion (Amphocil) are available. These formulations have been considered as the most striking advancement in leishmaniasis therapy[xlviii-xlix].Among the lipid formulations, AmBisome is the best tested and some studies demonstrated the success in patients with CL and VL, specifically in areas where antimonials resistance has been detected[li-lii].

7.3 Pentamidine: Aromatic diamidine, pentamidine is used as first line drug for certain forms of CL. In VL it is used as second line treatment only, due to toxicity[xlviii]. Pentamidine preferentially bind to kinetoplast DNA[li].Pentamidine causes several side effects such as nausea, headache, hypotension and a burning sensation. It also causes diabetes mellitus and death[lii]. Low dose of pentamidine given for a short period, makes it an attractive alternative for CL in antimonies treatment failure cases. Use of pentamidine has declined due to their low efficiency and toxicity[lii].

7.4 Miltefosine: In March 2002, miltefosine was registered for oral treatment of VL[liii-lv]. Adverse effects of miltefosine consist of gastrointestinal turbulence and renal toxicity. Fortunately, these symptoms are not a major cause for concern[lvi-lvii].

7.5 Paromomycin: Paromomycin is also known as aminosidine. In 1960s its anti-leishmanial activity was described by Neal *et al*[lviii]. Paromomycin has been used in several clinical trials for CL and VL[lix]. The most common side effect associated with the paromomycin is the ototoxicity, as well as problems in liver function[lx].

8. Other Drugs Clinically Used

8.1 Azoles: The azoles such as fluconazole, ketoconazole and itraconazole are well known oral anti-fungal drugs which also shows anti-leishmanial activity. The azoles have been tested in several trials for CL and VL with differing results[lxi-lxiv].

8.2 Allopurinol: The purine analogue allopurinol shows anti-leishmanial activity, the allopurinol has been investigated in clinical trials for CL and VL. However, the outcomes of

allopurinol has been unsatisfactory. In recent years, allopurinol has been used as part of maintenance therapy for canine leishmaniasis[lxv].

8.3 Sitamaquine: Sitamaquine (WR 6026) is an orally active 8-aminoquinoline analogue. Animal studies displayed very hopeful outcomes against VL although in clinical trials sitamaquine did not shows high efficacy after treatment during twenty eight days[lxvi].

9. Combination Therapy

For reducing the toxic adverse effects and prevent drug resistance of anti-leishmanial drugs combination therapy are used[lxvii]. For the treatment of visceral leishmaniasis, paromomycin have been used in combination with sodium stibogluconate in Sudan[lxviii-lxx].This clinical evidence demonstrated the superiority of the combination therapy and can be a hope to develop new formulations.

10. Prevention and Control of Leishmaniasis

Control of *Leishmania*infections relies primarily on [xxvii]:

- ❖ Early diagnosis and treatment of infected person.
- ❖ Avoid sandfly bites by using insect repellents, parathyroid impregnated bed nets and curtains, staying away of endemic areas and stopping outdoor activities especially at the insect active time[lxxi].
- ❖ Vector control by using light traps, sticky papers and insecticides[xxxiii]. Destruction of reservoirs such as infected dogs, stray dogs and rodents.Setting human residents away from animal reservoir habitats where sandfly usually breeds.

11. DNAas a Therapeutic Molecular Target for *LeishmaniaDonovani*

Current chemotherapies to treat parasitical diseases (leishmaniasis) are expensive and many have undesirable side effects. In addition, many drugs used for parasitic diseases require long treatment times. Because of the side effects and poor bioavailability the patients need to be under surveillance in an advanced health care system. It can easily be seen that this is impossible for patients who live in developing countries. Under these circumstances, there is an urgency to develop new therapeutic agents against parasitical diseases.In recent times, linear dicationic and a benzimidazole diamidines have exposed strongDNA minor groove binding and effective anti-parasitic activity[lxxi]. As a result, the DNA minor groove of the helix is a potential target for many drugs in modern medicine[lxxii].

12. Conclusion

Visceral leishmaniasis is the most severe form of leishmaniasis. Visceral leishmaniasis is the second largest parasitic killer in the world responsible for an estimated 500,000 cases each year worldwide. Currently, the chemotherapy is the main weapon to combat the infection. Some drugs are commercially available such as pentavalent antimonial, amphotericin B, pentamidine, miltefosine, aminosidine, azole derivatives, llopurinol, sitamaquine and immunomodulators. New formulations of lipid-associated of amphotericin B and ointments with aminosidine have been under evaluation in clinical trials that has given promising therapeutic options together with the combination of recommended drugs. In recent times, DNA minor groove of the helix is a potential target for many drugs in modern medicine.

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