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Chapter

An Overview of Leishmaniasis: Historic to Future Perspectives

Mümtaz Güran

Abstract

Human leishmaniasis is a major public health problem with a wide clinical spectrum. Despite there is an epidemiological diversity of the disease, cases mostly occur in the developing countries around the subtropical region, and the incidence is significantly rising. The disease is usually classified into three groups: cutaneous leishmaniasis, mucosal leishmaniasis, and visceral leishmaniasis. But to ensure their survival in different conditions, *Leishmania* spp. have developed many adaptation mechanisms and can be seen in different clinical forms as well. Herein, an overview of the characteristics of the disease and the parasite, interactions with the host, clinical aspects, and latest developments in the diagnosis and treatment is presented.

Keywords: leishmaniasis, kala-azar, vector borne diseases

1. Introduction

Human leishmaniasis is a sandfly-mediated parasitic disease that can lead to severe conditions in individuals especially with underdeveloped immune system. It usually affects people living in developing tropical countries and has high mortality rates [1]. Transmission of the parasite starts with an infected sandfly bite. After getting bit by a female sandfly vector carrying the promastigote form of the *Leishmania* protozoan, the promastigotes transform into amastigote form in mammalian hosts [2]. Once amastigotes enter the cells, immune system starts reacting to it. Phagocytes absorb the parasite, and destructive mechanism is initiated in order to kill the parasite. However, parasite has different ways of preventing or lowering the activity of immune system, and three distinct forms of leishmaniasis can be observed as a result which are cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), and mucocutaneous leishmaniasis (ML). CL usually occurs around the uncovered sites such as face, neck, and extremities which are susceptible to sandfly bite and often can result in the formation of ulcers or nodules around exposed areas. In certain conditions, macrophages infected by the parasites at the initial bite site spread among the reticuloendothelial system causing VL. Abnormal growth of internal organs such as the spleen and liver is common in VL, and it can cause death if necessary treatment methods are not applied. Another form of leishmaniasis is the ML in which parasites enter the mucocutaneous tissue, and its effects are usually seen around the oral and upper respiratory tract [3].

Leishmaniasis is considered to be an endemic disease effecting more than 98 countries with a global prevalence of 12 million people. Among different types of disease, CL makes up great percentage of the total amount of cases compared to other two. East Africa, Brazil, and Indian subcontinent are hot spots for VL cases, whereas

CL cases are high in the Middle East, Mediterranean region, Central Asia, and Latin American countries [4]. In European countries where leishmaniasis is not endemic, people traveling to endemic regions for various reasons such as military duty, tourism work, and vacation are the major cause of leishmaniasis occurrence [5].

There are more than 20 *Leishmania* species responsible from leishmaniasis [3]. In general, *Leishmania* major causes CL, *Leishmania donovani* causes VL, and *Leishmania infantum* results in both CL and VL [3]. These species can be further classified into subgenera depending on anatomical varieties of infection sites. Old World sandfly species are common in desert and semidry areas, whereas New World sandfly species transmit the disease to human near forest habitation [6]. *Leishmania* parasite has promastigote form in sandfly and amastigote form in mammalians. It can be transmitted by the vectors from an animal carrying this parasite or humans affected by VL. Amastigotes develop within the phagocytes and spread to other macrophages as a result of cell lysis. Once a sandfly bites an infected host, amastigotes then transform into promastigote form inside the sandfly restarting the transmission process for the next host that will be infected.

Leishmaniasis is ranked second in mortality right after malaria and ranked fourth in terms of morbidity among other communicable diseases [2]. HIV outbreak in the 1990s resulting in HIV/VL coinfection and general global warming of the world increasing the possible habitat for the sandfly led to doubling the amount of cases from 1987 to 2014 despite developing medical technologies [6]. It is estimated that each year around 400,000 people are having VL with a mortality rate of 10% going up to 20% in some areas [2, 3]. The Mediterranean region, Western Asia, and the Americas make up the 90% of 1 million CL cases, whereas ML is represented by 35,000 cases in these regions [3]. Among the other common forms of the disease, CL has the highest amount of cases reported each year. On the other hand, VL is the most fatal one where death usually occurs 2 years after the first transmission.

There are 98 countries and territories with *Leishmania* cases recorded each year [7]. It affects around 12 million people worldwide, and 1.5–2 million new cases are reported each year. Being an ignored tropical disease, leishmaniasis has the highest prevalence in poor countries such as India, Brazil, Ethiopia, and Afghanistan. Notably, there has been an increase in the CL case reports for Syria in the Middle East, Algeria in the Mediterranean, and India [6]. Poor housing, insufficient sanitary conditions, poor waste management, poverty, malnutrition, and change in climate conditions such as temperature, rainfall, and humidity are common features of these countries. Children living in these countries are considered the main reason of parasite transmission as they are the most vulnerable population group to sandfly bite.

Among species, *L. major* shows the biggest geographical distribution in the Middle East region compared to *Leishmania tropica* and *Leishmania infantum* [8]. *L. infantum* caused zoonotic and *L. tropica* caused anthroponotic transmissions to occur. Domestic dogs, rodents, and wild animals in endemic regions hold epidemiological importance as they take part in transmission of the parasite by serving as reservoirs.

Parasites can only reach infective stages in certain species of sandfly which as a result limits its transmission [9]. In addition, parasite-vector contact is rare for great majority of the sandfly species [10]. Epidemiological concerns about the leishmaniasis have increased greatly in the last 30 years. HIV/*Leishmania* coinfection, sandflies becoming more apparent in areas that they were less present such as the United States and Canada, and great risk of *Leishmania* gaining resistance to drugs over time make it a high-risk factor globally [11]. Another major concern for leishmaniasis is the increased resistance gain by parasite to current treatment methods which makes it even more dangerous considering there is an ongoing effort to develop a human vaccine against the disease [12].

Here, we aim to provide a general conceptualization of leishmaniasis by summarizing the historical development of the disease to provide a better understanding for possible future approaches.

2. History of the disease

In 1885, after observing *Leishmania* organism for the first time, Cunningham stated that the organism was not a bacteria. Thirteen years later, a Russian military surgeon Peter Borovsky further found out that the organism was a protozoan which was also confirmed by Wright in 1903. During that time, William Leishman and Charles Donovan described the agent responsible from VL. Leishman conducting his study in India observed enlargement of the spleen and fever in patients which he further observed the samples he took from the patients under the microscope using Romanowsky method for staining and stated that it was not like anything he had seen before [13]. Finally, in 1942, female phlebotomine sandflies had enough evidence to be accepted as the main vector for CL and VL due to the fact that clinical conditions observed following a sandfly bite described as histiocytoses [14]. In terms of changing face of diagnosis of leishmaniasis, starting from the microscopical identification of the agents, medical technologies have progressed in time further into PCR-based DNA sequencing methods for determination of specific species.

L. donovani was the first identified *Leishmania* species taking its name from William Leishman and Charles Donovan which was given by Ross in order to give credit to their studies [15].

Despite being a neglected tropical disease, our knowledge about the disease has been increasing continuously. Case reports involving uncommon laryngeal leishmaniasis- and HIV-infected individuals showing leishmaniasis effects such as skin lesions and nodules have shown that leishmaniasis can occur again even after treatment hinting to the incubation period of parasite (**Figure 1**) [16, 17].

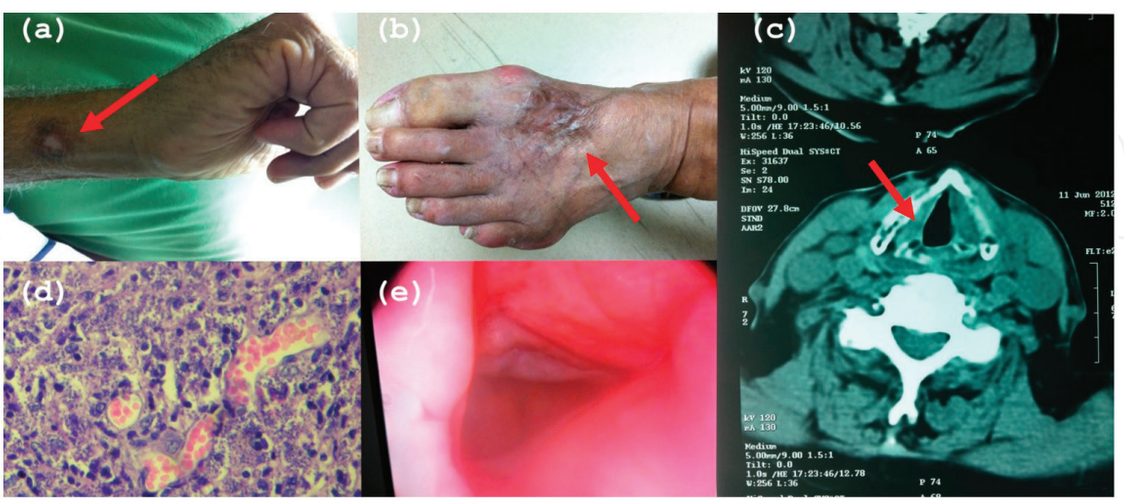

Figure 1.
A rare case of treated laryngeal ML which originated from a previous CL of hands and feet. Isolated agent is L. infantum in this 81-year-old male patient resident in Adana, Turkey, a subtropical area. (a) CL lesions on a patients hand on his first application to clinic. (b) CL lesions on patients foot on his first application to clinic. (c) BT of neck showing papillomatous push elongating into ventricles. (d) Histological examination of laryngeal biopsy specimen (May-Grunwald-Giemsa staining; original magnification, ×1000) showing intracellular amastigotes of Leishmania species and histiocytes with vacuolated cytoplasm and corpuscles inside. (e) Laryngoscopic examination showing lesions with edema and erythema due to ML. Reprinted from [16].

Treatment of leishmaniasis started with the use of pentavalent antimonials in the 1940s. Parasite gaining resistance and high level of toxicity for these drugs made it necessary to find an alternative. Amphotericin B is an alternative drug that has been in use since 1980. The main action mechanism of amphotericin B is to interfere with the membrane lipids and cause disruption. The length of the therapy changes between 15 and 45 days for different cases, whereas dosage can vary. Combinatorial use of this drug with some other drugs has shown great increase in the effectiveness of treatment.

3. Epidemiology

Leishmaniasis is a globally common disease that affects more than 98 countries and territories. Even though its effects are mainly observed in underdeveloped or developing countries, this parasite has spread to Europe and the United States due to the traveling to these areas and immigration from these areas. Old World leishmaniasis is endemic in Asia, Africa, the Mediterranean, and the Middle East. *L. tropica*, *L. major*, *Leishmania aethiopica*, and *L. donovani* are the four common species causing Old World leishmaniasis. New World leishmaniasis is caused by the *Leishmania mexicana*, *Leishmania braziliensis*, and *Leishmania guyanensis*. In total, six Old World countries (Afghanistan, Algeria, Arabian Peninsula, Syria, Sudan, and Iran) and two New World countries (Brazil and Peru) make up 90% of all leishmaniasis reports [18].

Poor process of record taking in underdeveloped and developing countries makes it difficult to determine its incidence and prevalence in certain areas. Syria is reported to have highest amount of incidence in the Middle East with 52,983 cases being reported in 2012 [19]. In Iraq, leishmaniasis had a prevalence of 45.5 cases per 100,000 of population in 1992 due to the war and population migration which can give an estimate of current situation [19].

In Asia, Afghanistan, Iran, and Syria are the three Middle Eastern countries where CL is endemic and reported most. Syria having the most amount of CL cases also named the disease as Aleppo boil [20]. Moving toward Eastern Asia, Pakistan holds great number of CL cases, whereas India and Bangladesh can be considered as the sole reservoir for VL [7]. In China, there are three defined VL types: anthroponotic VL, which is caused by *L. donovani*; zoonotic mountain-type zoonotic VL; and zoonotic desert-type VL in which both are caused by *L. Infantum* [21]. Depending on the habitat, there are four vectors when it comes to VL transmission in China [21]: *Phlebotomus chinensis* and *Phlebotomus longiductus* for anthroponotic VL in domiciliary habitats, *P. chinensis* for mountain-type zoonotic VL in wild and peridomestic habitats, and *Phlebotomus wui* and *Phlebotomus alexandri* for zoonotic desert-type VL in wild habitats [21].

In Africa, three *Leishmania* species, *L. infantum*, *L. major*, and *L. tropica*, are responsible from the CL cases [8]. Egypt, Algeria, Morocco, Tunisia, and Libya are the Northern African countries with the highest amount of reported CL cases between 2003 and 2009 [7]. Among East Africa, countries such as Ethiopia, Sudan, and Somalia have highest number of reported VL cases between years 2004 and 2009, which contribute to a large portion of total amount of 8569 cases in the region [7]. In Cameroon, survey done in Mokolo region consisting of 32,466 people showed 146 active CL lesions and 261 people having scars probably as a result of prior CL infection [22]. Interestingly, it was also noted that 4.8% of the patients with CL observed to be positive for HIV infection [22].

Realizing the importance of leishmaniasis in most of the African countries is a challenge compared to other countries because of the low quality healthcare

services, poor data management, and absent reports. East Africa and sub-Saharan Africa are the geographical regions where leishmaniasis was the least common until 2012 [7]. Considering leishmaniasis is endemic in these regions, it is safe to say that observed value will be much different than the real outcome once enough data are gathered.

When it comes to Europe, countries in the Mediterranean region such as Italy, Greece, Turkey, and Albania have highest prevalence of VL cases [7]. In addition, few number of VL cases were observed in France, Spain, Portugal, and Croatia [7]. In terms of CL cases, Turkey holds great percentage of reports compared to others. In the Netherlands, 185 CL, 8 VL, and 2 MCL cases were observed between 2005 and 2012 [23]. In general, traveling to endemic regions such as Afghanistan or Morocco is shown as a significant risk factor of *Leishmania* cases in developed countries. Due to the nature of leishmaniasis infection, developed European countries have low amount of reported cases, and in most of the cases, insufficient immune system is the other most important risk factor in addition to trips to endemic regions [24].

American region has low VL and high amount of CL cases reported in general with a 1–20 difference. Brazil has the highest amount of reported cases both in VL and CL. Colombia, Peru, Nicaragua, and Venezuela are other areas where CL cases happen frequently [7].

Mexico, the United States, and Canada have relatively low amount of reported cases in terms of global occurrence. A total of 811 CL and 7 VL cases were reported in Mexico between 2004 and 2008. The US Army Forces going to endemic regions such as Afghanistan for military duty resulted in few reported *Leishmania* cases in the United States.

Australia and Antarctica are the two continents where leishmaniasis is not considered to be endemic [2]. Between the years 2008 and 2014, 52 CL and 3 VL cases were reported in Australia [25]. Traveling to *Leishmania* parasite endemic regions is thought to be the reason for most of these cases as similar with the cases seen in Europe [25]. *L. tropica* was identified in 30 patients and was the highest compared to 4 other identified species [25].

4. Transmission and prevention

Only vector responsible for transmitting leishmaniasis is the female sandfly, belonging to the genera *Phlebotomus* spp. in the Old World and *Lutzomyia* spp. in the New World [3]. Out of the many known sandfly species, 93 of them are known to spread leishmaniasis. Sandflies are usually active during night time, and they have limited ability to move. They are usually 2 mm large and are capable of tearing the skin in order to feed on blood. Mainly observed in the tropical regions, they have spread to the Northern European regions due to the increasing temperatures and climate changes.

Transmission can be zoonotic or anthroponotic depending on the reservoir. Domestic dogs are considered to be the major reservoir for zoonotic transmission. In the Americas and Central Asia, interaction between wild animals and humans also causes zoonotic transmission. Humans with VL or post kala-azar dermal leishmaniasis serve as the only reservoir in anthroponotic transmission.

Attenuated parasite vaccines that will provide long-term immunity and prevent transmission are in development. Zoonotic transmission occurs with dogs, and treatment methods targeting infected dogs are not preferred due to the fact that it may result with increased resistance for parasite or there is a high chance of infection in the nature even after the treatment [6]. Deltamethrin-treated collars were tested for the control of the disease and a significant reduction in infection levels in dogs was observed [6]. Avoiding outdoor areas in endemic areas, using protective

clothing, using insect repellents, covering around the bed with a net, sleeping above the ground level, and avoiding night time activities are some of the useful methods in order to prevent transmission in humans.

5. Host-parasite interactions

Once *Leishmania* enters the human host, macrophages try to attack *Leishmania* with reactive oxygen and nitrogen molecules. *Leishmania* parasite produces protease with increased activity which considerably lowers macrophage activity. Inside the cell, phagosomes consume the parasite, but they are ineffective against the parasite as a result of parasite changing the destructive properties of phagosome.

Protective immune response to leishmaniasis mainly depends on the T-cell subset response accompanied with the specific cytokines, transcription factors, presenting of antigen, and production of various interleukins having direct or indirect effect on the main immune system. However, it is important to note that susceptibility or resistance to leishmaniasis is possible in individuals with altered genetics or depending on the environmental conditions as well as parasite strain starting the infection [26].

Immune response starts with the cells of innate immune system. Neutrophils are the first immune system cells responding to the sandfly bite starting the leishmaniasis infection [27]. Neutrophils are capable of producing microbicidal factors effective against *Leishmania* such as nitric oxide (NO) and neutrophil extracellular traps [27, 28]. Neutrophils are effective protective agent in most forms of the leishmaniasis, but this is usually affected by the host genetics and *Leishmania* strain effecting the host [27]. Neutral killers are also recruited to the site of infection after neutrophils, and their cytotoxic activity is effective against parasite by mediating lysis [29, 30]. Organ-specific protection during the early stages of infection is the case for natural killer T cells [31]. Increased natural killer T-cell concentration during the disease progress and decreased concentration following treatment indicates importance in early response [32]. T cells also play an important role in immune response. Nitric oxide production in order to fight with the parasite is induced by IFN-γ-producing Th1 cells [27]. However, Th2 is responsible from the susceptibility because of its ability to produce cytokines such as IL-4 and IL-13 [27]. The regulatory T cells maintain a critical role in IL-10 expression and continuity of parasite immunity [27, 33].

Leishmania parasites have developed their own way in order to reduce the effectiveness of immune system. Modifying toll-like receptors' pathogen recognition ability, delaying phagosomes ability to terminate parasite once consumed, altering macrophage antigen presentation, and modifying host signaling in order to effect production or inhibition of certain cytokines or chemokines such as IL-10 and IL-12 are some of the examples of immune evasion mechanisms used by parasites [27]. Being a progressive disease, increased concentrations of IFN-γ and TNF-α cytokines indicate immunosuppressive mechanism for leishmaniasis especially in VL [34–37]. IL-10, which is produced by many immune system cells such as B cells, T-cell subsets, and innate cells, is a regulatory cytokine responsible from immune suppression and reducing the effectiveness of antigen-presenting cells like macrophages and dendritic cells where initial response mainly depends on this process [34]. For VL, IL-10 was found to be majorly produced by CD4 + CD25-Foxp3- cells in the spleen suggesting that suppression of antileishmanial immunity in effected individuals depends on the expression of IL-10 by T cells. In addition, experiments done with mouse models have shown that IL-12 signaling and presence of high antigen dose can lead to the activation of Th1 cells which coexpresses IL-10 [38]. IL-27 is another immune system regulator which promotes T cells to produce IL-10 following an

infection [39]. Furthermore, upregulation of IL-21 by T cells in order to reach elevated levels of IL-10 is thought to be the role of IL-27 [40]. In order to determine immune system cells responsible from the production of IL-10 and IL-27, splenic aspirate cells obtained from the VL spleen was tested for expression levels of mRNA for various cells. CD14+ cells were found to be main source of IL-27-related mRNA expression, whereas CD3+ T cells were the main source of both IL-10 and IL-21 [40]. For CL, mouse models showed that IL-22 plays a critical role in the progression of pathology such that increased levels of IL-22 help maintain skin integrity and prevent further inflammation [41].

IFN-γ is another important immune system molecule produced by parasite-dependent Th1 CD4+ lymphocytes and is related to intracellular control of parasites upon infection. On the other hand, Th2 CD4+ cells are responsible from the progression of the disease. This difference in Th1 and Th2 cell line responses was further confirmed by Holaday et al.'s study done on mouse models carrying specific mutations. The study showed that in the presence of antigen, Th1-like cell line response was to produce IL-2 and IFN-γ, whereas Th2-like cell line response was to produce IL-4 and IL-5 upon stimulation [42].

In another study, Th1, Th2, and Th17 CD4+ T-cell subsets were found to induce production of IL-10 despite having different signaling pathways and transcription route. ERK1 and ERK2 transcriptional activation was common in all these Th cell subsets. c-Maf is an important transcription factor in macrophages for the process of IL-10 expression and was also found to be common for the previously mentioned three different T-cell subsets. c-Maf expression was also found to be dependent on ERK activation in Th1 and Th17 cells [38].

6. Clinical characteristics of the disease in humans

Cutaneous leishmaniasis is the milder form of leishmaniasis and usually leads to formation of skin lesions or nodules around the exposed bite sites such as face, neck, or limbs [8, 24]. Lesions can heal spontaneously in few months, or in some extreme cases, it can take few years to resolve [8]. Although CL is self-curing and nonlife-threatening, accumulation of CL often leads to disfigured formations on skin. Lesion number can vary between 1 and 20, and upon healing, distinct scars are left on the skin. Various treatment methods are used in order to speed up the healing process for CL.

Depending on the disease forms observed clinically such as uncomplicated form, chronic recurrent form, and diffuse form, there are four causative pathogens in the Old World and five causative pathogens in the New World [18]. *L. major*, *L. tropica*, *L. infantum*, and *L. aethiopica* are the pathogens of Old World, whereas *L. L. mexicana*, *L. L. amazonensis*, *L. V. braziliensis*, *L. V. guyanensis*, and *L. V. panamensis* are the pathogens of New World in the case of CL [18].

VL also known as kala-azar is the fatal form of leishmaniasis with a mortality rate of 75–95%. Macrophages affected by the parasite spread the infection throughout the body, and patients develop pancytopenia and immunosuppression [6, 43, 44]. VL is often discussed together with HIV as they both affect immune system heavily making patients susceptible to other infections. Incubation period is between 2 weeks and 2 years. Liver- and spleen-related problems are common in patients with VL.

Parasite spreading around the initial bite site using the lymphatic way and infecting the nose or mouth mucosa leads to ML (**Figure 1**) [45]. Immune system reacting to parasite at the tip of the nose effects airway walls causing lumen obstruction which is related to necrosis of the cartilage in the nose. Unlike CL, ML is not a self-healing disease and can cause permanent skin problems. Destruction of the tip

of the nose is a severe condition that may affect patients in their social life. Breathing problems are common result of ML in patients due to the blocked airways [46].

Another form of the disease, post kala-azar dermal leishmaniasis is a complication of VL in which patients cured of VL develops nodular, macular, or maculopapular rash on skin as a result of immune suppression following VL. It is mainly observed in Sudan and India where majority of the VL cases progress into post kala-azar dermal leishmaniasis [47].

7. Treatment and resistance in humans

There are various treatment methods depending on the host immune system effectiveness and the type of *Leishmania* effecting the host as well as the way parasite is transmitted. Host factors such as genetics or immune response or factors related to treatment such as dosage, duration, and completion of the therapy and finally factors related to the parasite, such as intrinsic sensitivity of the species and lack of resistance to the medication are important determinants regarding to treatment of the disease. Long incubation period of *Leishmania* parasite makes it a challenge in detection and early treatment methods. If applicable early treatment should be applied in order to further prevent the spreading of the parasite. Having no effective human vaccines puts the disease at a critical point.

Pentavalent antimonials, sodium stibogluconate and N-methylglucamine, liposomal amphotericin B, miltefosine, and paramycin are some of the widely used drugs in routine treatment [6, 48]. Compared to liposomal amphotericin B which is a less toxic form, conventional amphotericin B has complicated application procedure and harmful side effects making liposomal amphotericin B a better choice in treatment of both CL and VL which is also an antifungal agent. Still in some underdeveloped or developing countries that cannot afford liposomal amphotericin B treatment, pentavalent antimonials are used. Despite their toxic effects on the liver and kidneys, pentavalent antimonials are still highly effective [49]. On the other hand, emerging resistance limits the therapy frequently. Miltefosine is another drug with known effect of inducing parasite resistance if not used properly.

Global antibiotic resistance problem has emerged in the treatment of leishmaniasis too, and a number of papers reporting treatment failures are increasing [50]. Anthroponotic transmission is the main cause of drug resistance in *Leishmania* species. Humans being the anthroponotic host, various effects can lead to drug resistance for parasite once treatment starts. Ignoring the recommended consuming amount and frequency of the drug, reduced concentration of the drug effecting the parasite, inhibition of drug activation, inactivation of active drug, and alterations in host gene amplifications are some important example mechanisms for parasites gaining drug resistance. Although, the mechanisms of drug resistance in *Leishmania* species are not well elucidated in detail, but the involvement of P-glycoprotein (Pgp)-like ABC transporters and ldmdr1 gene has been detected in hard-to-treat parasites [51–54]. In addition, high amount of thiol levels was found to play a role in developing resistance as they prevent reduction of pentavalent antimonials to trivalent antimonials [55].

8. Latest developments in the diagnosis, prevention, and treatment

Permanent solution for the leishmaniasis in terms of successful human vaccination is still a major challenge. However, there are different vaccinations currently

being tested in mouse model. One of them uses "killed but metabolically active" parasites to induce host immune system reaction. Mice infected by "killed but metabolically active" *L. infantum chagasi* showed no signs of organomegaly or parasite presence 6 months after infection compared to mice infected with live parasite. Finally "killed but metabolically active" *L. infantum chagasi* has also shown to induce parasite-specific protective host immune response that is similar to response induced by live *Leishmania* [56].

Using salivary peptides of the sandfly holds potential to be used as a vaccine component; however, complex immune response makes it a challenge. Novel drug combinations have been tested in some endemic regions in order to lower the treatment cost and toxicity and preventing resistance gain by the parasite. Nitroquinolines were found to show leishmanicidal activity. Antimicrobial peptides including dermaseptin, andropin, and cecropin have been found effective against CL. Edelfosine is an oral drug with greatly increased activity compared to miltefosine. There are also compounds isolated from plants which are tested and observed to have antileishmanial activity. For example, a polyphenolic flavanoid, quercetin, has shown antileishmanial activity in treatment of VL [57]. Four plant species named *Agave americana*, *Azadirachta indica*, *Eclipta alba*, and *Piper longum* showed important antileishmanial activity too [58–61].

Macrophage targeted drug delivery system is another novel approach to directly effect *Leishmania* parasites that live in the macrophages as their infection mechanism. As getting into macrophages is a challenge, liposomes, microspheres, nanoparticles, and carbon nanotubes are some of the various drug carriers that are studied to target macrophages [62]. In addition, use of specific receptors expressed by macrophages to actively deliver a drug is also used [63].

9. Conclusion and future perspectives

Leishmaniasis still remains as a big public health challenge in some parts of the world. Despite developments in scientific knowledge and medical technology, there is still a need for quick and cheap detection of *Leishmania* infections especially in endemic areas. Studies focusing on molecular microbiological methods can help to develop new diagnostic methods.

In terms of treatment of leishmaniasis, emerging resistance is a big threat for infectious disease specialists like in other microbial diseases. There are two arms of fight. One is the development of a successful vaccine, and the other is the progress of finding new compounds to cure the infection. If applicable early treatment should be applied in order to further prevent the spreading of the parasite. Having no effective human vaccines puts the disease at this critical point. That is why studies focusing on the development of vaccine will be pathfinder in the future decade. On the other hand, studies evaluating the antileishmanial activity of various natural products or chemically modified compounds are needed to find new opportunities in successful treatment of *Leishmania* infections for the future.

Acknowledgements

The author wants to express his special thanks to Namık Refik Kerküklü for his kind help during the preperation of this chapter.

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