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Review on Leishmaniasis: A Neglected Global Disease

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Abstract

As per World Health Organization, Leishmaniasis is a neglected, tropical disease. It is initiated by intracellular transmission of a parasite to humans, by sand fly bite. Factors like population variability, climate change etc. lead to the expansion of this disease. This article provides review of epidemiology and management of leishmaniasis i.e., cutaneous, mucosal, and visceral. Literature was studied by systematic exploration in PubMed including various articles from 2012-2022 without setting any exclusion criteria. There have been reports of development of strains, resistant to traditional therapy of leishmaniasi, along with simultaneous infections like HIV/Leishmania spp., and other targeted pharmaceutical resources i.e., amphotericin B and formulations, miltefosine, pentavalent antimonials. Since long, only few drugs are available for the management of the disease, having adverse effects and toxicity due to which the treatment control program is put in check globally. New strategies are required to manage this neglected disease adequately.

Keywords: Leishmaniasis; Tropical disease; Leishmania spp; Visceral leishmaniasis; Cutaneous leishmaniasis

Abbreviations: MCL: Mucocutaneous Leishmaniasis; VL: Visceral Leishmaniasis; PKDL: Post Kala-azar Dermal Leishmaniasis; HAT: Human African Trypanosomiasis; CR: Complete Remission; DCL: Diffuse Cutaneous Leishmaniasis; CL: Cutaneous: LCL: Localised Cutaneous Leishmaniasis; IDSA: Infectious Diseases Society of America; ASTMH: American Society of Tropical Medicine and Hygiene; SSG: Sodium Stibogluconate; MA: Meglumine Antimoniate; MPL-SE: Monophosphoryl Lipid A Plus Squalene: WHO: World Health Organization; qPCR: quantitative PCR; HRM: High Resolution Melt; kDNA: Kinetoplast DNA; SSG: Sodium Stibogluconate; MA: Meglumine Antimoniate; OWCL: Old World CL; NWCL: New World CL

Introduction

Leishmaniasis is initiated by intracellular transmission of a parasite to humans, by sand fly bite [1], mostly Lutzomyia and Phlebotomus and in North Africa, Asia, Middle Eastern countries, Europe and certain South American countries; exceptional spread can also be due to a mishandling of specimen in the laboratory [2]. Leishmaniasis is considered as a tropical and subtropical ailment [1]. The World Health Organization (WHO) considers leishmaniasis among one of the seven grave tropical ailments that portends a poor prognosis. This disease has a possible fatal consequence due to a broad range of clinical manifestations. Leishmaniasis is being observed worldwide except Oceania [3] and is endemic in confined geographical zones of Southern Europe, Southeastern Mexico, the Middle East, Central and South America and Northeastern Africa [4]. The cases are rising globally due to various reasons like urbanization, deforestation [5], resistance to therapy, enhanced diagnosis and also for the reason of inadequate coverage of health services [6,7]; vector control strategies are influenced by armed encounters and masses shift in regions [8,9].

It is reported that 98 species of the genera Lutzomyia and Phlebotomus are recognized or assumed vectors for human

leishmaniasis, spread via infected phlebotomine sand flies [10,11]. Mammals are attacked by female sand flies only for blood meals necessary to complete egg development cycle. Apart from mammals, certain sand flies have wide-ranging hosts that include rodents, marsupials canids and hyraxes. Consequently, human leishmaniasis may have zoonotic or anthroponotic spread forms [12,13]. Leishmania parasites reside and grow in phagocytic cells intracellularly (within phagolysosomes) in the mammals. More than 20 diverse pathogenic Leishmania species are defined for humans at present [9,14-16] among which the 3 chief types are visceral, cutaneous, and mucocutaneous leishmaniasis [9]. The clinical presentation of this ailment is related to the specie of the parasite, tropism, its infectivity and immune system of the host [17].

Different Leishmania species are much alike morphologically. Depending on the types of invaded phagocytic cells, these species cause 2 chief forms of clinical leishmaniasis i.e., cutaneous (CL) and visceral leishmaniasis (VL), [18]. In case of CL, macrophages in the skin are infected by the parasites. The host cell bursts when it is full of parasites, releasing amastigotes that then infect adjacent macrophages. On the contrary, the free amastigotes are transmitted via blood circulation in VL and contaminate the mononuclear phagocytic cells of reticulo-endothelial system of spleen, liver, lymph nodes, intestine, and bone marro [12].

Methodology for Review

Only English language articles are included in this review article. Literature was studied in PubMed using regular keywords (Table 1). The articles are included from 2012-2022 without setting any exclusion criteria (Figure 1).

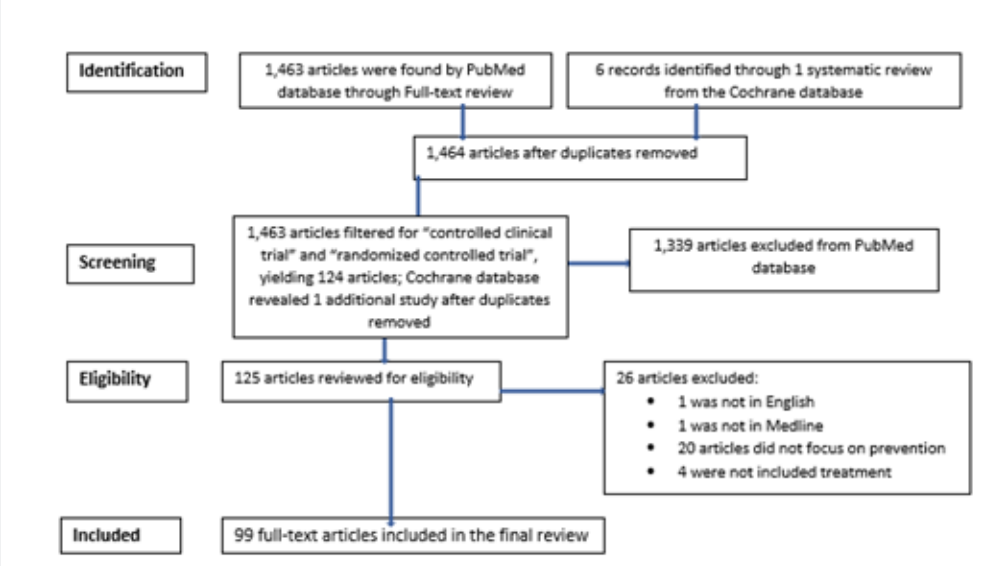

Figure 1: Article selection flow diagram.

Table 1: The articles are included from 2012 – 2022 without setting any exclusion criteria.

Keywords	Results	Results after applying inclusion criteria	MeSH Keywords used	Results after applying inclusion criteria
Leishmaniasis	29,528	12,883	Leishmaniasis/classification	416
Leishmaniasis current review	825	520	Leishmaniasis/Epidemiology	2059
Leishmaniasis epidemiology	6,951	2,998	Leishmaniasis/ Diagnosis	1,828
Leishmaniasis diagnosis	7,394	4,753	Leishmaniasis /therapy	3,307
Leishmaniasis management	1,472	898	Leishmaniasis/prevention and control	720

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Results

By systematic exploration in PubMed, 31,389 articles were found with the keyword Leishmaniasis of the skin. From 2012 to 2022, 12,884 articles were found out of which 99 are included in this review article.

Discussion

Leishmaniasis is the chief endemic health burden in many regions globally. In the 14 high-burden VL states, total of annually reported cases of VL has fallen from 60,000 (2006) to 30,000 (2014) which is chiefly owing to a drop of five-fold in Indian cases of visceral leishmaniasis [19]. In 12 CL high-burden countries, total of annually reported cases of CL is unchanged which is about 150,000 over the same retro [20]. Several factors have contributed to the rise in leishmaniasis cases during the former 25 years worldwide. In non-endemic areas, globalization and changes in climate are important factors for the transmission of leishmaniasis [21]. There has been a rise in the cases of Leishmaniasis over the last several years in international travellers [22]. Furthermore, Leishmania infections have ensued in patients who never went to leishmaniasis endemic areas due to the international movement of blood products [21]. It is observed that there is no blood bank screening to check the existence of anti-leishmanial antibodies in the preserved blood products. Also, there is an increased dispersal of sand flies towards north due to global warming which could consequently transmit leishmaniasis in hitherto non-endemic area [21,23].

Epidemiology of Leishmaniasis

There is a global distribution of Leishmaniasis disease with its existence in approximately 89 countries in the world [24,25]. The endemic regions include the Mediterranean, Africa, the Americas, and Asia. It is mostly a jungle zoonosis in the America transmitted by mainly genera Phlebotomus and Lutzomyia of sand flies; yet leishmaniasis can be acquired in hot semi-desert like geographical regions or cold regions too. From southern parts of United States to northern part of Argentina shires, there is 0.17% seroprevalence of CL [26] except Uruguay, El Salvador, and Chile [25,27]. Worldwide 12 to 15 million individuals are infected while there is risk of disease acquisition in 350 million people. There is incidence of about 1.5 - 2 million cases of leishmaniasis annually due to which 70,000 mortalities per year occur [25,28]. WHO made reports in 2012 regarding the burden and distribution of VL and CL in over 100 parts of and the data acquired until 2010 showed that globally about 90% VL cases happened in India, South Sudan, Brazil, Ethiopia, Bangladesh, and Sudan. Approximately 70% CL cases were found in Syrian Arab Republic, Brazil, Algeria, Colombia, Afghanistan, Iran, Ethiopia, Sudan, and Costa Rica [29].

Due to the Syrian civil war, about 3 million expats were received by Turkey who were placed at the camps or houses in the southern parts of Turkey. Epidemiological research was done from 2009 to 2015 in Turkey employing semi-nested polymerase chain reactions in real-time which discovered the presence of 263 patients positive for leishmaniasis; among them there were, 33.46% Syrian, 66.15% Turkish, and 0.38% Afghani people. Species of Leishmania identified in Turkish and Syrian patients were Leishmania infantum and Leishmania tropica [30]. A 13 years report from Algeria confirmed 4,813 CL cases showing the influence of disease in all municipalities and entire age groups. Males were more affected (65%) and the age group among the most affected were 10 to 19 years (31.41%) and children less than 9 years (25.70%) [31]. Geographic and seasonal distribution of CL was found in Iran with 589,913 CL cases. The yearly incidence was around 30.9 per 100,000 with majority occurrence in the central parts of Iran [32] and in autumn the greatest prevalence rate (35.14%) of lesions was reported [33].

VL clinical type is endemic in Bangladesh, India, and Nepal. All VL cases (> 60%) globally relate to South Asia, predominantly in rural zones. Related to this, around 5.7 million individuals are at risk in Nepal confined chiefly to Terai state, bordering the VL-endemic areas of the Indian Bihar state. Between 1980 and 2007, 23,368 cases were reported together with 311 demises. The Department of Health Services of Nepal in 2006–2007 presented the annual health report showing 2.67 per 10,000 people at risk for VL incidence [34]. It is estimated in Latin America that about 60,000 incidences of all types of leishmanisis happen yearly. Leishmanisis is characteristic of environments having temperatures higher than 20°C, an altitude of 0 to 1,500 m beyond sea level and rainfall of 1,500 to 3,000 mm yearly. Still, some "Uta" cases have been identified in the cold and humid highlands of Peru where this ailment is spread by a tiny bug [35,36].

Reports show that Leishmaniasis affects men commonly; the high risks individuals include farmers, hunters, timber exploiters, military workers, biologists, and those practicing ecological tourism, etc. in Mexico while in Peru and Brazil, it influences the gatherers of rubber, tea, banana, coffee, and coca [2,37]. There is risk of contact in endemic sectors to women, children, and elderly. Leishmanisis has been recognized since the pre-Hispanic period in Mexico [37], reporting all the clinical forms of the ailment [38]. The very common are pure cutaneous and the cutaneous-chondral types which cause the typical chiclero's ulcer (gum tree harvester's ulcer) when affecting ears. The foremost endemic region in Mexico is in the Neotropical zone from the southeast [2,37,39,40]; new cases of 5.08 per 100,000 people has been detected in the Yucatán Peninsula annually [41,42]. Antibodies in 17% of the overall populace of southern state of Yucatán, Becanchén, have been acknowledged after serlogical investigations. Tabasco is regarded as high-endemic zone due to incidence and prevalence rate of 2.35 and 9.41 per 100,000 populace, correspondingly [37]. Positive serology of 20.42% military persons operational in this zone was observed. Lutzomyia olmeca and Lutzomyia cruciate are the two major vectors of the ailment in the Yucatán Peninsula [43].

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Leishmania braziliensis and mexicana are prevailant in Belize and Guatemala, while only Leishmania mexicana has been reported in Campeche and Yucatán in Mexico [4]. According to data of 2016, WHO reported 200,918 CL incidences and 22,233 VL incidences. Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan represented 90% VL cases globally, whereas Afghanistan, Algeria, Brazil, Colombia, Pakistan, and the Syrian Arab Republic, Morocco, Nicaragua, Peru, Sudan, Tunisia, and Yemen, are accounted for 90% CL cases. Information to WHO is still awaited from Iran and Iraq, having >10,000 of CL cases as per 2015 report [44].

Clinical Presentation of Leishmaniasis

CL is the commonest type of leishmaniasis with incidence of 0.7–1.3 million every year globally. There are 3 different forms of CL: localised cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL) and mucocutaneous leishmaniasis (MCL). Skin wounds and ulcers on bare body parts are characteristic of LCL that leave lasting scars on body. DCL is notable due to the growth of numerous, gradually developing nodules encompassing the full body without ulceration and is less common. MCL is constrained to Latin America. Next to healing of primary skin lesion, the disease extends to the mucous membranes of the nose, mouth and throat. Afterwards, the mucosal ulcers destroy the nasal septum, lips and palate causing facial mutilating extensively. VL is considered as the utmost severe type of leishmaniasis with each year likely 0.2–0.4 million incidences worldwide [45]. VL is lethal in more than 95% of patients if left untreated. The indications of VL are asymmetrical fever, loss of weight, splenomegaly, hepatomegaly, hepatosplenomegaly at times and anemia [12]. Other signs of VL can be alienated into disease-specific wounds at infected parts (i.e., papules, nodules, ulcers) and nonspecific wounds (i.e. purpura, kwashiorkor like hair discoloration, xerosis) [46].

An immunologically mediated outcome of VL is Post–kala-azar dermal leishmaniasis (PKDL) mostly noticed in Sudan and India. The onset of disease is typically 6 months - 1 or more years post therapy but it can happen later up to 20 years [46]. The hallmark injuries of PKDL can be generally described as erythematous or hypopigmented macules, papules, skin-colored nodules, and malar erythema, though variances are present in cutaneous findings as per geographic situation and existence or level of immune suppression [46,47]. The lesions appear typically in the perioral region at first and then become widespread. Maintenance of feeling in the lesioned skin supports to differentiate PKDL from leprosy [9].

Diagnosis of Leishmaniasis

The diagnosis depends on clinical signs, epidemiological and laboratory data. The clinical evidence for CL diagnosis include: travel history to or accommodation in endemic areas, a small number of lesions (1-3), lesions without pain, localization on bare body parts, patients having history of a number of months or slow variation over weeks, unresponsive persons to former systemic or topical antibiotics, rubber like feeling on palpation [9]. There is no gold-standard available for human patients or animals for the laboratory methods [48], which impairs precise epidemiological data assembly. Besides, false-negative results can cause deferment of therapy resulting in reservoirs maintenance. Due to non-availability of gold-standard parasitologic diagnostic test, it is suggested to associate histopathology, culture, and DNA amplification methods to escalate sensitivity to identify the disease on a species basis. It is suggested to connect with a reference laboratory in advance to attain specimen as nearly all specimen collection methods and laboratory diagnostic techniques require greatly specific information for Leishmaniasis; concurrent diagnostic methodology for other possible etiologies (like sporotrichosis, blastomycosis, mycobacterial infections, etc.) should be considered too [9,49].

Recently, numerous immunological and molecular diagnostic tools to diagnose leishmaniasis have been established [50]. Due to their greater sensitivity, specificity, and potential use to different types of clinical samples, the usage of molecular procedures particularly has turned out to be ever more applicable. The real-time PCR or quantitative PCR (qPCR) has recently become very common as it is fast with extensive dynamic range and cross-contamination is significantly diminished as the reaction tubes for post-PCR investigation are not required to be open. High resolution melt (HRM) study can be employed to distinguish amplicons built on sequence variations for genotyping [51]. The use of probes permits multiplexing) and gives additional specificity to the assay but is more expensive typically, moderately decreasing the cost per assay. This methodology offers less false positives than the intercalating dye procedure [52]. Bretagne et al. [53] and Nicolas et al. [54] defined 2 qPCR-based procedures to spot and quantify Leishmanial parasites by use of DNA polymerase gene and minicircles kinetoplast DNA (kDNA) as a target, correspondingly. Subsequently, various qPCR-based assays have been instituted on diverse molecular targets for recognition, quantification, and genotyping of Leishmania species [55,56]. No uniformity is noted in published qPCR assays for sensitivity and specificity reports. For example, qPCR assays made for VL diagnosis in individuals indicated a specificity difference between 29.6–100% and sensitivity between 91.3–100%, demonstrating qPCR practicality for pivotal sensitive tool [50,57].

Dermatoscopy

Different dermatoscopic characteristics have been described like white starburst like form, tear drop like patterns, yellow tears, and salmon-colored ovoid forms. The specificity of these outcomes may necessitate additional analysis [58,59].

Leishmania Smear

A smear is regarded an economical, simple, and swift means to diagnose CL. It is commended to attain a smear sample in the initial assessment, pursued by direct inspection with Giemsa stain. There are 4 methods to take samples: slit-skin, scraping, touch (imprint) smear, and fine-needle aspiration

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[17]. The recognition of Leishmania amastigotes via microscope is adequate for diagnosis yet it involves ample proficiency [49]. Recently, a diagnostic algorithm has been recommended in which a positive direct microscopic investigation by means of smear is followed by anti-Leishmania therapy, while a negative preliminary investigation should be operated with a skin biopsy [17].

Culture

The isolation of the parasite in culture media should be done as it permits verification of the diagnosis and the isolates can be employed for additional analysis. The specimen gotten for culture can be assessed for further probable causative agents also. requires A sterile method is needed in sampling for parasitologic culture, with evasion of residual iodine and alcohol which may influence the growth of parasite on culture media [49].

Other Diagnostic Techniques

For VL diagnosis, serologic testing can be supportive though the current serologic assays are not adequately sensitive or specific to be employed [49]. The Leishmanin skin test (Montenegro test or Leishman reaction) is a delayed hypersensitivity assessment, which is positive in about 90% of CL or ML patients with a period of more than 3 months [46].

Existing and Evolving Antileishmanial Agents

Pentavalent antimonials (SbV)

SbV is present as sodium stibogluconate (SSG) and meglumine antimoniate (MA). For many decades, the standard treatment of VL was Antimonials with the dosage of 20 mg/kg body weight for 28–30 days till it became unsuccessful in India due to development of resistance [60,61]. While it is efficacious in other regions globally particularly Africa, its use is limited due to greater toxicity specifically cardiotoxicity in terms of cardiac arrhythmias, extended QTc interval, ventricular premature beats, ventricular tachycardia, ventricular fibrillation, and torsades de pointes [19]. The patients coinfected with HIV get marked side effects during SSG therapy with reduced efficacy and more deaths [62,63].

Amphotericin b (AmB)

Amphotericin B deoxycholate is a polyene drug which was widely used in India for VL noncompliant to antimonials. The cure rates were ~ 100% at a dosage of 0.75–1.0 mg/kg for 15–20 i.v infusions [64,65]. With dose of 1 mg/kg/ day, up to 60–80 doses for more than 4 months, it is also suggested to treat PKDL in the India [66]. The adverse effects of this therapy include infusion reactions, nephrotoxicity, hypokalemia, and myocarditis due to which the patient should be monitored and hospitalized hence increasing therapy cost. To reduce such adverse effects, lipid preparations of the drug were developed replacing deoxycholate with further lipids. These preparations are quickly taken up into organs like liver and spleen and concentrate in the site of VL disease i.e. reticuloendothelial tissue. The drug stays there for an extended time permitting provision of big doses of the agent in short time [19]. Three lipid preparations have been widely tried for leishmaniasis principally VL: liposomal amphotericin B (AmBisome; Gilead Sciences; L-AmB), amphotericin B lipid complex (ABLC; Abelcet, Enzon pharmaceuticals), and amphotericin B cholesterol dispersion (Amphotericin B colloidal dispersion (ABCD); Amphotec_, InterMune Corp.). among these, only L-AmB is US FDA permitted. For treatment of VL, the total dose requirements of lipid preparations differ by regions. In India, one dose of 10 - 30 mg/kg is the treatment of choice [65,67].

Miltefosine (MIL)

It is the single oral medication accepted for leishmaniasis which is an alkyl phospholipid. It was registered for VL in 2002 for use in India, ensuing a Phase III clinical trial in which 50–100 mg/day dose for 28 days provided complete remission (CR) of 94% [65,68]. A Phase IV study in India similarly exhibited CR of 82%. The availability for oral use, comfort of consumption and effectiveness made MIL the medication of choice in India, Nepal, and Bangladesh for VL eradication [44].

Paromomycin (PM, aminosidine)

It is an aminoglycoside-aminocyclitol drug [19] which has been employed to treat VL in parenteral form and for CL in both topical and parenteral forms. It was used for treating dysentery in VL patients in southern Sudan in the 1989 VL epidemic. This drug reduced the dysentery incidence and showed synergism with SbV in VL management [44]. Then it was used in Africa in combination with SbV. The dose is 15mg/day for 21 days [65].

Pentamidine

It is an aromatic diamidine which was used for treating antimony resistant VL in India in the early 1980s [19]. But its effectiveness failed, and it was abandoned due to its severe toxicities i.e. pancreatitis causing insulin-dependent diabetes, hypoglycemia, hypotension, QT elongation and hyperkalemia. In recent times it has been employed as secondary prophylaxis with a dose of 4 mg/kg monthly for 12 months; to prevent VL relapse there can be 6-month extension if cluster of differentiation 4 (CD4) count was ≤ 200 cells/µl in Ethiopian HIV-VL coinfected individuals [44, 69].

Sitamaquine

It is an oral agent which is 8-aminoquinoline; it has undergone Phase II trials for VL in India and Kenya. At the dosage of 1.75 and 2 mg/kg/day for 28 days, the CRs were 89% and 100%, correspondingly while CR was 85% at 2 mg/kg/day for 21 days in India. The CRs were 80%, 82%, and 91% at doses of 2, 2.5, and 3 mg/kg/day respectively in Kenya. At doses > 2 mg/kg, nephrotoxicity was mainly observed, and it exhibits low efficacy in low doses [44].

Azoles

Ergosterol synthesis of Leishmania parasites are blocked by these drugs. For CL management, Ketoconazole, itraconazole, and fluconazole have been widely used. For L. major, fluconazole in

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dose of 200 mg per day orally for 6 weeks had CR of 44–59% in old world CL (OWCL). Gastrointestinal symptoms and hepatotoxicity were the main adverse effects observed. On escalating fluconazole dose to 400 mg, CR amplified to 81%. For L. braziliensis, fluconazole with dosage of 5–8 mg/kg/day for 4–12 weeks displayed 75-100% CR in new world CL (NWCL). A randomized controlled trial in Brazil for L. braziliensis infection exhibited 22% CR when associated to 53% for standard SbV with fluconazole 6.5–8 mg/kg/day for 28 days [44].

Nitroimidazole

Nitroimidazole is an anti-protozoal agent and Fexinidazole was revealed by Hoechst AG in the 1970s (now Sanofi-Aventis); it was reinvented as a favorable agent by the Drugs for Neglected Diseases initiative (DNDi) to treat Human African trypanosomiasis (HAT). Oral fexinidazole was administered once a day as 1800 mg for day 1–4, 1200 mg for day 5– 10 for the late stage of HAT and showed 91% CR with safety. Anti-leishmanial activity of fexinidazole and its principal metabolites namely fexinidazole sulfoxide and sulfone has been established in the in vitro studies [70] which was followed by DNDi in Sudan in a Phase II trial to evaluate safety and efficacy of fexinidazole to treat VL. 14 patients were enrolled in the trial and at the end of treatment majority showed parasite clearance however only 3 patients were healed at 6-month follow-up, hence terminating this study. Due to the safety and oral administration of the drug, DNDi is investigating to utilize fexinidazole and miltefosine combination in eastern Africa to treat VL [44].

Another potent compound of nitroimidazole group called pretomanid (PA-824) has been found potent against both replicating and non-replicating Mycobacterium tuberculosis. PA-824 was found to be tolerated well and safe showing higher bactericidal action in drug susceptible tuberculosis in a Phase IIb trial in combination with moxifloxacin and pyrazinamide, during 8 weeks of therapy [71]. Antileishmanial activity has been exhibited by both the S and R enantiomers of PA-824, yet the R enantiomer having insignificant activity against M. tuberculosis proved to be a 5 fold more potent inhibitor of L. donovani as compared to the S-enantiomer in vitro. The combined medication research in vitro pointed out that fexinidazole and (R)-PA-824 have additive effects [72].

Delaminid

This oral antitubercular agent is a very effective inhibitor of Leishmania donovani in vitro and in Expert Opinion on Pharmacotherapy 5 vivo research also. This drug was found to be more effective than miltefosine and fexinidazole drugs [73].

Local therapy

Thermotherapy

Thermotherapy is built on in vitro laboratory investigation that Leishmanial parasites do not increase in number at temperatures > 39°C. Thermotherapy with radio-frequency waves has been done for Old and NWCL both. Mostly investigations have employed a battery-operated, localized current field radio frequency (RF) generator (ThermoMed) or RF heat generator (Ellman International Inc., NY, USA). A single use of thermotherapy at 50°C for 30 seconds provided the CR between 69.4% - 82.5% in Afghanistan [74], 98% in India [75] for lesion by L. tropica, whereas for L. major infection, the CR was 48% in Iraq and Afghanistan [76]. For L. Mexicana infections, thermotherapy with a single therapy of 50°C for 30 seconds at 8 weeks exhibited 90% CR [77]. The CRs were found to be 58–59% as compared to 72% for MA and 59% for miltefosine in Columbia [78,79]. A 60% CR was achieved when a low-cost heat pack (HECT-CL) was used at preliminary temperature of 52°C ± 2°C for 3 minutes to every wound and repeated for 7 days daily in Peru [80]. The efficacy of thermotherapy was found to be 73% as compared to 70% with SbV in a meta-analysis [81]. The disadvantages observed were pain, local anesthesia requirement, probe sterilization and likelihood of producing burns. Overall, thermotherapy is effective with least scarring, fewer treatments, no laboratory observations, increases patient compliance and is economical comparatively. It is preferred for CL treatment when there is low prevalence of mucocutaneous type and in patients contraindicated for systemic therapy [65].

Cryotherapy

Owing to smaller risk of mucosal involvement, cryotherapy (liquid nitrogen at −195°C) has been generally used for OWCL. This therapy involves intracellular ice formation producing cell destruction and leading to localized ischemic necrosis. Cryotherapy is applied to the lesion once or twice weekly up to 6 weeks and it was found > 90% efficacious in many countries for L. aethiopica and L. donovani infections except Turkey having less than 80% efficacy [82,83]. For single lesion NWCL cryotherapy against L. braziliensis infection, a CR of only 20% was seen in Bolivia [84]. Recently a meta-analysis showed that cryotherapy had similar efficacy as SbV but it was linked with adverse effects like erythema, hypo- or hyperpigmentation edema onsite, secondary infections and burning at times [65].

Carbon dioxide (CO2) laser

This procedure performs by explicit thermolysis of infested tissue with slight adverse effects in normal tissue [85]. CO_2 laser therapy showed complete response in Iran between 93% - 93.7% and it was found to be more effective than MA showing 83.8% results. A single use of this therapy in Cuba healed all 10 patients without reverts in more than 2-year follow-up time. The adverse effects of this therapy most commonly were found to be hyperpigmentation, continuous erythema and hypertrophic scarring [44].

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Combination Therapy

Multidrug therapy offers synergistic or additive action at diverse sites; it also reduces therapy duration and dosing requisite thus decreasing risks of toxicities, cost, and prevention of drug resistance [19]. In the 1980s, multidrug treatment with SSG and PM was accidentally revealed during VL epidemic in southern Sudan. Ever since, many African investigations and very few Indian studies have exhibited the advantage of 17 days therapy of PM with SbV. This combination was not adopted in India due to growing resistance to SbV. Yet, it was employed widely initially in relapse patients using conventional SbV and also as first-line VL treatment in Africa by Me´decins Sans Frontie'res (MSF) since 2002, which was permitted by WHO in 2010. A big pharmacovigilance study i.e. with (n = 3126) in Africa included individuals from Sudan, Kenya, Ethiopia, and Uganda and found an initial CR of 95%. It was observed to be safe and effective in the patients except those with co-infection HIV/VL having 56% CR or patients of more than 50 years of age showing 81.4% CR [86].

For Indian VL, a short course of amphotericin B with miltefosine due to the easy administration, efficacy and tolerance is preferred. In addition to protection of miltefosine from drug resistant parasites, the decrease in time and quantity of drug utilized contributes to decreased toxicity and cost [87]. Pentoxifylline is an inhibitor of tumour necrosis factor alpha; its use with pentavalent antimonial has proven to be effective against aggressive types of leishmaniasis like mucocutaneous leishmaniasis [88, 89]. This combination was also observed to be effective in Iranian CL patients [90]. For The use of topical or local therapy is not recommended in severe types of CL, nevertheless, combining a topical drug with a systemic agent may denote a stimulating choice and should be studied additionally [87].

Current Treatment Recommendations

The efficacy and essential dose of the antileishmanial therapies differ in various regions, therefore WHO issued the management recommendations in 2010 based on these variances [91]. In 2016 the guidelines were issued by the Infectious Diseases Society of America (IDSA) and the s. PAHO and WHO issued the treatment guidelines for leishmaniasis in 2018 in America [44].

Leishmaniasis Control: Future Directions

There is a strong need to invest in basic research focusing leishmaniasis control against its emergence and expansion. Effective vaccines against human leishmaniasis are required as they are not easily achievable due to long-life immunity convened by specific healed infections caused by Leishmania species [92]. The features of CL and VL are distinct as they are caused by diverse parasites. L. donovani infections require treatment if clinically obvious and relapse cases are common while a cured infection by L. major generally convenes immunity. This steered to investigation of cross-protection concept from a severe leishmaniasis type via immunity to a more benign type; in an animal infection model, safety from VL was accomplished by generation of a robust immunity to CL [93]. It logically supports for live vaccines and proposes that only one antigen vaccine against leishmaniasis may not be adequate to convene immunity. To date, the identified vector-derived virulence causes include promastigote secretory gel, exosomes, and saliva components. It is well-known that these vector-derived virulence factors are integral part of disease pathogenesis as they give rise to creation of parasites ensuing sand fly spread of Leishmania [94, 95].

Apart from vaccine exploration, new medications and insecticides are needed to avoid emergence of resistance in parasites and vectors both while enhancing the existing usage of diagnostic procedures and multidrug treatments [96]. Five vaccines have been approved and licensed to counter Leishmanial species so far. Among these 2 had been approved for human use; one is used in Brazil for immunotherapy of CL using killed L. amazonensis parasites and another in using live L. major parasites in Uzbekistan. In Brazil, recombinant proteins for prophylactic immunization of dogs are employed [97,98]. Licensed vaccines for human CL are unavailable currently and the ones forwarded to clinical trials are: (a) 2 killed L. amazonensis vaccines which have produced varying results between vaccine and placebo groups, and (b) defined polyprotein-containing subunit vaccine LEISH-F1+monophosphoryl lipid A plus squalene (MPL-SE) which was proven to be safe while producing an antigen-specific T helper 1(Th1) response [99].

Conclusion

Leishmaniasis is a neglected, vector-borne, complex disease that has been offering formidable challenges worldwide. Factors like population variability, climate change and globalization are lead to the expansion of this disease. Research advancements with combined commitments of governments and non-profit groups are continuously working for leishmaniasis control and the commitment of endemic states is essential for the success in long term. Development of effective vaccines is the ideal solution for leishmaniasis abolition from the world. It is possible to eliminate this disease in a few decades with new investigations discovering the realms of improved therapy of this ailment.

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