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REVIEW ARTICLES

TREATMENT OF KALA-AZAR: PAST, PRESENT & FUTURE

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Abstract:

More than 90 percent of cases of kala-azar in the world occur in India, Bangladesh, Nepal, Sudan, and Brazil. Nearly 25 compounds are reported to have anti-leishmanial effects but not all are in use. The pentavalent antimony compounds have remained as mainstay of treatment for nearly 75 years. However, emergence of resistance led to the use of other compounds like amphotericin B, pentamidine, paromomycin, miltefosine etc. Miltefosine is the only oral agent available and recently has been recommended in the National guideline of Bangladesh. But it has a long half-life of 154 hour and this could encourage development of clinical resistance. Further, rapid therapeutic response along with unsupervised treatment can severely affect compliance, and bring a premature end to this very important arsenal against leishmania. Stimaquine is other oral agent coming in near future along with some promising immunotherapeutic agents and of course the possibility of a vaccine. We can assume that in future, combination of drug will be the desirable solution to combat Kala-azar.

Background:

Kala- azar is a disease caused by protozoan parasites that belong to the genus Leishmania and is transmitted by the bite of certain species of sand fly, including flies in the genus Lutzomyia in the New World and Phlebotomus in the Old World.[1] The disease was named in 1901 for the Scottish pathologist William Boog Leishman. This disease is also known as Leichmaniosis, Leishmaniasis and formerly, Orient Boils, Baghdad Boil, black fever, sandfly disease, Dum-Dum fever or espundia.

The Leishmania species that infect humans are mainly Leishmania donovani, which causes visceral leishmaniasis (VL/kala azar), and Leishmania tropica and Leishmania brasiliensis, which cause cutaneous leishmaniasis. In Indian subcontinent, Phlebotomus argentipes is the only proven vector for the disease. In the human host, Leishmania are intracellular parasites that infect the mononuclear phagocytes. The spectrum of human disease ranges from self-healing localized ulcers to widely disseminated progressive lesions of the skin, mucus membranes, and the entire reticuloendothelial system. The disease is prevalent throughout the world and in at least 88 countries (16 developed countries, 72 developing countries).[Fig: I]

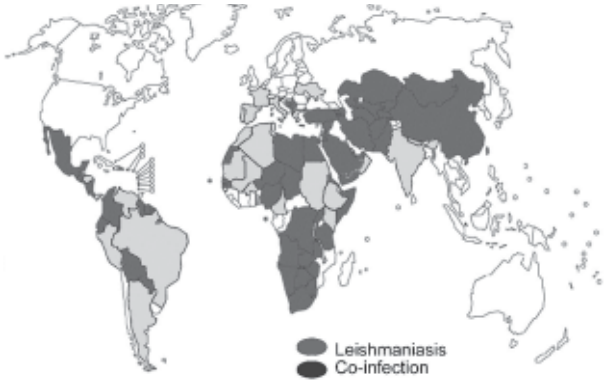

Fig.-1: *World wide distribution map of Visceral Leishmeniasis.*

More than 90 percent of the world's cases of VL occur in India, Bangladesh, Nepal, Sudan, and Brazil. A total of 350 million people are at risk. Nearly 25 compounds are reported to have anti-leishmanial effects but not all are in use. The pentavalent antimony compounds have remained mainstay for nearly 75 years. However, emergence of resistance led to the use of other compounds like amphotericin B, pentamidine, paromomycin, allopurinol etc. Other anti-fungals like ketoconazole, fluconazole and terbinafine are found less effective. Anticancer

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alkylphosphocholines have been found most effective oral compounds. Most promising of these are miltefosine, edelfosine and ilmofosine. However, the recent focus has been on identifying newer therapeutic targets in the parasite such as DNA topoisomerases.[2-4] This review enumerates the current approach of different drugs against Kala-azar, their past experience and future perspectives.

History of Kala-azar & Evolution of chemotherapy: Lesions similar to cutaneous leishmaniasis has been discovered from King Ashurbanipal from the 7th century BC, some of which may have been derived from even earlier texts from 1500 to 2500 BC. Arab physicians including Avicenna in the 10th century gave detailed descriptions of what was called Balkh sore.[5] In 1756, Alexander Russell, after examining a Turkish patient, gave one of the most detailed clinical descriptions of the disease. Physicians in the Indian subcontinent would describe it as Kala-azar. [6]

Surgeon Cunningham of the British Indian army saw it first in 1885 without being able to relate it to the disease.[7,8] In 1901, Leishman identified certain organisms in smears taken from the spleen of a patient who had died from "dum-dum fever" and in 1903 Captain Charles Donovan (1863-1951) described them as being new organisms.[6] Eventually Ronald Ross established the link with the disease and named the organism Leishmania donovani.

Geographical distribution of leishmaniasis is restricted to tropical and temperate regions (natural habitat of the sand fly). Leishmaniasis has been considered a tropical affliction that constitutes one of the six entities on the World Health Organization tropical disease research (WHO TDR) list of most important diseases.[9] Coexistence of leishmaniasis with human immunodeficiency virus infection is a serious concern. Leishmaniasis is spreading in several areas of the world because of the rapidly spreading epidemic of acquired immunodeficiency syndrome (AIDS).[3]

In 1912, the first case of cutaneous leishmaniasis to be successfully treated with tartar emetic (potassium antimony tartrate) was reported by a young Brazilian physician, G. Vienna. A few years later, the same compound was used to treat visceral leishmaniasis in Italy and Asia. Pentavalent antimonials (Sb) became available in the 1920s, and sodium stibogluconate was introduced in 1945.[10]Pentamidine has been tried for the treatment of VL and was the first drug to be used for patients refractory to Sb. Pentamidine, since the early 1940s has been used to some extent in the treatment of visceral leishmaniasis. Nowadays, pentamidine is mainly used for prophylaxis and treatment of Pneumocystis jirovecii pneumonia (PCP). Amphotericin B is a polyene antifungal drug was originally extracted from Streptomyces nodosus in 1955 at the Squibb Institute for Medical Research. But its application on VL started in 1990s in different formulations. Paromyomycin is an aminoglycoside (identical to aminosidine) was tested alone and in combination with Sb in kala-azar patients in Kenya, India, and Sudan in the early 1990s. The first phase I/II study of Miltefosine was carried out in India in 1997, and its results opened the door to achieve the long-sought after objective of effective oral therapy. Immunochemotherapy especially in combination with other anti-leishmanial drugs is still required more studies and trials. A final drug in the early stages of clinical evaluation for treatment of visceral leishmaniasis is the oral 8-aminoquinolone/ stimaquine (GlaxoSmithKline). It is an oral 4-aminoquinoline initially designated as WR6026. [11-16] This also needs much more evaluation in future.

Different Option of Drugs:

(A)Parenteral Agents:

Pentavalent antimony (Sb): It has been used for more than about 60 years. There are two common therapies containing antimony (known as pentavalent antimonials), meglumine antimoniate (Glucantime) and sodium stibogluconate (Pentostam). It is not completely understood how these drugs act against the parasite; they may disrupt its energy production or trypanothione metabolism. Though there is some question about its efficacy now a day, it may not reflect the entire situation. Actually, resistance is encountered in some limited areas of the world, especially in Bihar State, which contains approximately 90% of the estimated 200,000–250,000 annual new cases in India. Failure rates, defined as initial unresponsiveness or prompt post-treatment relapse[17, 18] while Sb is still effective in other parts of India and surrounding countries. But sufficient document is unavailable to declare this drug resistance in our country.

Till late 1970s a small daily dose of Sb (10mg per kg, 600 mg maximum) for short duration (6-10 days) was considered adequate. Few years later, in 1982, Thakur et al randomized patients to receive Sb 20 mg per kg (maximum 600 mg) either for 20 days or longer and

found only 86 per cent cure rate. In the same year, WHO expert committee recommended that Sb be used in doses of 20 mg per kg per day up to maximum of 850 mg for 20-30 days in fresh case and for double duration (40-60 days) in relapse case. Subsequently in 1990 WHO recommend SSG in the dose of 20 MKD for 28 days. However, following the above recommendations Thakur et al reported a decline in cure rate to 71 per cent after 20 days of treatment at the same dose. One year later Jha et al found only 64 per cent cure rate in hyper endemic regions of Bihar. Incidentally, only 2 per cent patients from neighboring State of eastern UP failed treatment. Thus high level Sb unresponsiveness existed in Bihar State though the drug continued to be effective in other areas.[4]

Pentamidine isethionate (PIT): To combat the resistance to antimony, pentamidine has been tried for the treatment of VL and was the first drug to be used for patients refractory to Sb.[14] It is used at a dose of 4 mg/kg thrice weekly. Initially high cure rate were reported but its efficacy gradually declined over the years.[19] It now cures only 69-78 per cent of patients [20-22]. PIT induced diabetes mellitus was observed in 10 per cent cases. It is no longer recommended as first choice for use in VL.

Amphotericin B: Amphotericin B is the most effective antileishmanial drug, which induces high cure rates. At present it is extremely used in Bihar for all SSG unresponsive cases and even as a first line drug.[22] Use of formulation of amphotericin B, a pollen antibiotic, for treatment of leishmaniasis is biochemically rational because the target of amphotericin B is ergosterol like sterols, which are the major membrane sterols of Leishmania species. [23] Due to high affinity of amphotericin B for sterols, aqueous pores are formed in the membrane leading to increased membrane permeability and killing of Leishmania.[23,24] At dose of 0.75-1.0 mg per kg for 15 infusions on alternate days, it cures more than 97 per cent of patients.[25, 26] Primary unresponsiveness and relapse are uncommon.[22]

Lipid formulation of amphotericin B: The need to develop less toxic, more effective formulation of amphotericin B has led to three new clinical formulation of amphotericin B in which deoxycholate has been replaced by other lipids. These formulations are liposomal ampho B (LAMB: Ambiosome), amphotericin B colloidal dispersion (ABCD: Amphocil) and amphotericin B lipid complex (ABLC: Abelcit). These substitutes are well taken by reticuloendothelial system and poorly taken by kidney, the major target of organ toxicity.[27] The dose requirement varies from region to region. In Indian subcontinent a small dose (3.75 mg/kg) of ambiosome for five consecutive days induces high cure rates.[28] In another study, a single dose (15 mg/ kg) was compared with amphotericin B over 15 days (1 mg/kg) and all patients in both the groups had a final cure.[29] In another trial, a single total dose (5 mg of ambiosome/kg) was compared with a similar dose administered over 5 days and final cure was achieved in 91 and 93 per cent patients respectively.[30] Safety of liposomal amphotericin B permits administration of total dose requirement in a single infusion.[29,31] No problem of treatment failure or relapse has been encountered with this drug except when VL is associated with HIV/AIDS. However, prohibitively high cost makes these compounds unaffordable in VL endemic countries like Bangladesh, even in southern Europe.

Aminosidine: This aminoglycoside, identical to paramomycin sulfate and given once daily usually by i.m. injection, has been combined with Sb to successfully reduce duration of therapy. Aminosidine also appears to be active in India when used alone (16 to 21 mg/kg/day for 21 days) in a region of high-level Sb resistance. Its efficacy has been demonstrated in India and a dose of 16 mg per kg and 20 MKD intramuscularly for 21 days has cured 93 and 96.7 percent patients' respectively.[32-35] In a recent phase III multicentric double blind paromomycin study on Indian visceral leishmaniasis patients with a dose of 15 MKDx21 injections, a cure rate of 94 per cent has been achieved (unpublished Observation). This is a potential new drug, which may replace SSG as a first line of drug in visceral leishmaniasis. Problem of treatment failure and relapse case be anticipated in future when used as a monotherapy.

(B) Oral Agents:

Miltefosine: Miltefosine, an alkyl phospholipids developed as an anti-tumor agent, has excellent antileishmanial activity. It has been found uniformly effective in naïve as well as Sb refractory patients. In many clinical studies, a cure rate >94 per cent has been found consistently with this drug. The exact mechanism of its action is not known but it probably interacts with the cell membrane of Leishmania.[36] Recently,Miltefosine has been recommended as the

first choice of drug in Bangladesh for treatment of VL at a dose of 50-100 mg capsule (~2.5 mg/kg body weight) in two divided dose by mouth in the morning and evening after meal for 28 days and in children about 12 yr weighing 25 kg 50 mg daily for 28 days, and in pediatric group between 2-11 yr a dose of 2.5 mg/kg for 28 days is recommended.[22,37] Miltefosine may become the most important drug in endemic zone. A multicentric phase IV study sponsored by Indian Council of Medical Research (ICMR)/WHO(TDR) / Zentaris at 13 sites in 4 laboratories, a total of 1167 VL patients were enrolled. At 6 months follow up, 84 per cent cure rate was achieved (personal communication). However, there were 52 dropouts, 9 withdrawn, 11 had Serious Adverse Events (SAE) and 57 relapsed.[22] However; it is not beyond certain limitations. Miltefosine has a median long terminal half-life of 154 h, which could encourage development of clinical resistance and that's why some author recommend the best way to use this drug would be to use as a combination multi drug therapy. It is teratogenic and abortifacient, which means the drug, cannot be used in pregnancy, and females with child bearing potential must observe contraception for the duration of treatment and an additional two months. Further, rapid therapeutic response coupled with unsupervised treatment can severely affect compliance, and bring a premature end to this very important arsenal against leishmania.[4]

Stimaquine: Stimaquine, a primaquine analogue (8-aminoquinolene), is another orally administrable compound. It has been in the process of development for over 10 years by SmithKline Becham (now Glaxo SmithKline) and Walter Reed Army Institute of Research, USA. It has been tested in VL patients in Kenya and Brazil with limited success.[38, 39] It has also been tried in phase II study on 120 Indian VL patients in Bihar. Thirty patients were enrolled in each arm of 1.5, 1.75, 2.0 and 2.5 MKD for 28 days. Final cure rates of 81, 89,100 and 80 per cent were achieved at 6 months follow-up with the four doses. Common adverse events observed were vomiting 8 per cent, dyspepsia 8 per cent, cyanosis 3 per cent, nephrotoxicity like nephrotic syndrome 3 per cent and glomerulonephritis 2 per cent. However, further clinical trials need to be done to assess its safety before used in combination therapy with other antileishmanial agent.[22]

(C)Other possibilities:

Azoles and other steroid biosynthesis inhibitors: The azoles, like ketoconazole, triazoles, itraconazole, fluconazole and others like Allopurinol, Chloroquin, Isoniazid etc. produce an anti-leishmanial effect by blocking ergosterol synthesis and other way.[40] Varying results have been reported from few clinical trials.

Immunochemotherapy: In experimental visceral infection, at least five cytokines, IL-12, IL-2, IFN-ϒ, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF) are expressed (or likely expressed) in human kala-azar.[41]Except for TNF, each activating cytokine is also in clinical use and therefore potentially available for testing in exogenous form in combination with antileishmanial drugs. Because T-cell suppression leads to reduced levels of interleukin-2 and IFN-ϒ in patients with visceral leishmaniasis, recombinant IFN-ϒ has been added to pentavalent antimony in small clinical trials in Brazil and Kenya.[11,12] Interferon- (IFN-ϒ) and GM-CSF, graduated nearly 15 years ago to limited clinical testing in combination with Sb. Interferonϒ is one of the principal activators of macrophages. Interferonϒ as adjutants to Sbv has been used successfully in VL with high cure rate in comparison to Sb alone.[42] Later, it was observed that interferon ϒ(daily dose 100 ìg/m2) though improved the response rate to antimony, but overall cure rate was less than 50 per cent.[43]

Combination therapy:

In view of emergence of parasite resistant to antileishmanial drugs and limited availability of alternative medications, current monotherapy may need to be altered. Combination therapy with multiple drugs similar to that employed in tuberculosis or Leprosy may be established in near future particularly in case of co-infection. A combination of potent drugs, one with short half life, which would rapidly bring down the parasite load below which new mutants are less likely to emerge and a second drug with long half life, which will kill the remainder parasites may be used to prevent this infection. This will also help to shorten the duration of treatment. Combination of liposomal amphotericin B with miltefosine, liposomal amphotericin B with paromomycin, miltefosine with paromomycine needs to be evaluated in this regard. Some forms have already been tried in different settings for example SSG with allopurinol/SSg + Ketokonazole/SSG + levamisole, or SSG + aminosidine(paromomycin), or SSG + interferon gamma etc.[22]

Vaccines:

No vaccine is available still now. However, the genomic sequence of Leishmania has provided a rich source of vaccine candidates. One study screened 100 randomly selected genes as DNA vaccines against L. major infection in mice. Fourteen reproducibly protective novel vaccine candidates were identified. A separate study used a two-step procedure to identify T cell antigens. Six unique clones were identified: glutamine synthetase, a transitional endoplasmic reticulum ATPase, elongation factor 1 gamma, kinesin K-39, repetitive protein A2, and a hypothetical conserved protein. The 20 antigens identified in these two studies are being further evaluated for vaccine development.[1]

Conclusion:

Kala-azar is a neglected disease of 3rd world. For the last 4-5 decades SSG, Amphotericin, Mitefosine, paromomycin, ketoconazole, triazoles, Itraconazole, fluconazole, Allopurinol, Chloroquin, Isoniazid etc. were used with different efficacy. Without adequate treatment, the disease is fatal. So early diagnosis and proper treatment should be ensured. Our current concern needs to be focused on prevention of drug resistance. Combination of drug will be a desirable option in future. More trails and research are required in this regard to solve this problem.

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