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A REVIEW ON ANTI LEPROTIC AGENTS

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ABSTRACT:

In this review, Leprosy is a chronic infectious disease which is caused due to the Mycobacterium leprae bacillus. Brazil has the second supreme number of leprosy cases around the world with about 30,000 new cases diagnosed in 2005. Anti leprotic agents inhibits mycobacterial growth and binds preferentially to mycobacterial DNA.The various drugs like Dapsone, Clofazimine, Rifampin, Ethionamide, Ofloxacin, Moxifloxacin, Minocycline, Clarithromycin are known for their antileprotic activity.

KEY WORDS: Leprosy, Mycobacterium leprae, Hansen's disease

INTRODUCTION:

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by Mycobacterium leprae, a microorganism that has a predilection for the skin and nerves. Though nonfatal, leprosy is one of the most common causes of nontraumatic peripheral neuropathy worldwide. DNA taken from the shrouded remains of a man discovered in a tomb next to the old city of Jerusalem shows him to be the earliest human proven to have suffered from leprosy. The remains were dated by radiocarbon methods to 1–50 A.D. The disease probably originated in Egypt and other Middle Eastern countries as early as 2400 BCE. An apparent lack of knowledge about its treatment facilitated its spread throughout the world. Mycobacterium leprae, the causative agent of leprosy, was discovered by G. H. Armauer Hansen in Norway in 1873, making it the first bacterium to be identified as causing disease in humans. Over the past 20 years, the WHO implementation of MDT has rendered leprosy a less prevalent infection in 90% of its endemic countries with less than one case per 10,000 population.(1)

DEFINITION OF A LEPROSY CASE

A person is considered leprosy whenever they present following signs or symptoms: pale or reddish patches on the skin; loss, or decrease, of feeling in the skin patches; numbness or tingling of the hands or feet; weak ness of the hands, feet or eyelids; painful or tender nerves; swelling of or lumps in the face or earlobes.

A case of leprosy is defined in every patient that presents with at least one of the following manifestations:

- definite loss of sensation in a pale (hypopigmented) or reddish skin patch;
- a thickened or enlarged peripheral nerve, with loss of sen sation and/or weakness of the muscles supplied by that nerve;
- the presence of acid-fast bacilli in a slit-skin smear.(2)

MYCOBACTERIUM LEPRAE

Mycobacterium leprae an intracellular, pleomorphic, acid-fast and pathogenic bacterium. M. leprae is an aerobic bacillus (like rod-shaped) surrounded by the characteristic of waxy coating and unique to mycobacteria.

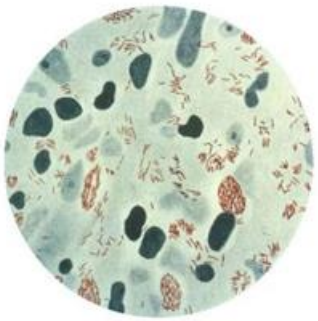

Fig 1: Mycobacterium leproae

Optical microscopy of M. leprae shows in clumps, rounded masses, or in groups of bacilli side by side and ranging from 1–8 μm in length and 0.2–0.5 μm in diameter.[3]

TYPES OF LEPROSY

There are different types of laprosy

A. Lepromatous leprosy (LL)

B. Tuberculoid leprosy (TL)

C. Borderline lepromatous leprosy (BL)

D. Borderline tuberculoid leprosy (BT)

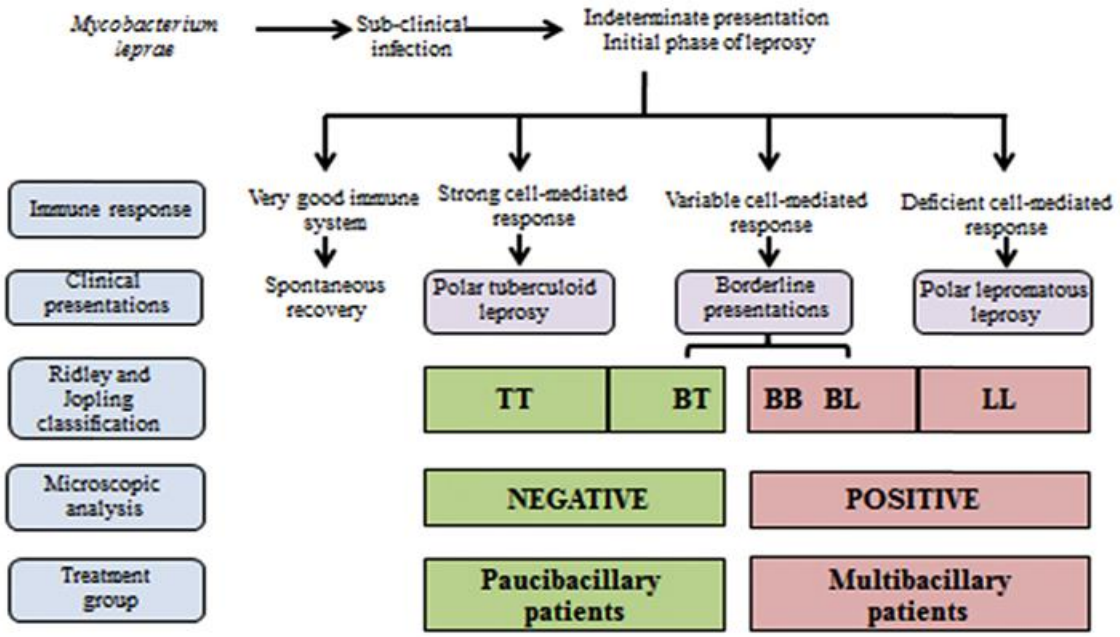

Fig 2: Clinical, biological, and therapeutic classification of leprosy

1.Tuberculoid leprosy

Tuberculoid leprosy is defined by skin lesions and nerve damage. Skin manifestations either include large hypochromic macules with well-defined edges that can sometimes be infiltrated, or large thickened and infiltrated plaques. Tuberculoid leprosy presents with very few lesions (hyposensitivity or anesthetic lesions). Nerve damage is usually observed around skin lesions and is associated with sensory and/or motor impairment when the hands and feet are affected.[4]

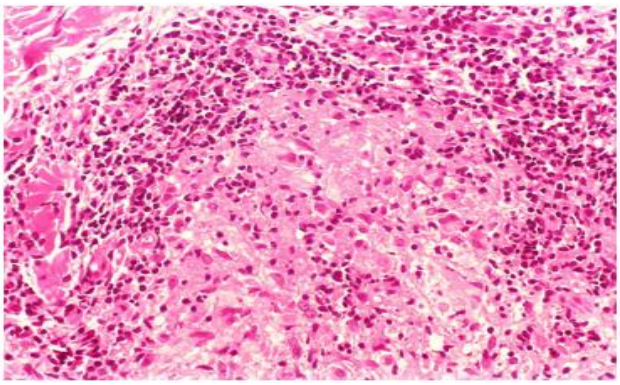

Fig 3: Tuberculoid leprosy

2. Lepromatous leprosy

The initial skin lesions are small-sized hypochromic macules with indistinct edges. If left untreated, they form copper colored papules or nodules known as leproma. Lepromatous leprosy patients present with a high number of bilateral and symmetrical leproma (20 to 100) that can develop everywhere on the skin but most frequently on the face, earlobes, fingers, and toes. Those lesions are not anesthetic.

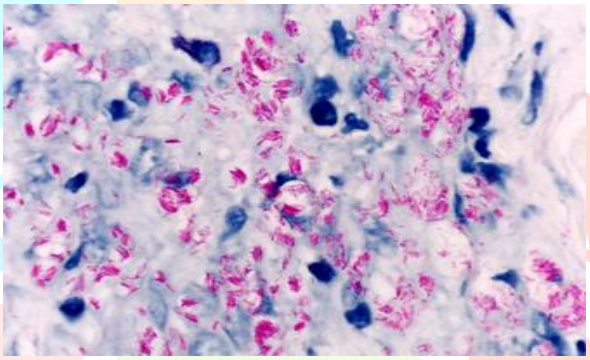

Fig 4: Lepromatous leprosy

3. Borderline leprosy

Borderline leprosy is defined by various clinical signs and corresponds to a transition status. Its classification depends on the number of clinical signs consistent with tuberculoid or lepromatous lesions. The borderline tuberculoid (BT) presentation of leprosy is defined by the presence of several large asymmetrical and hypoesthetic lesions with peripheral macules or infiltration of the skin. Smaller lesions can usually be observed near the larger ones. The borderline–borderline (BB) presentation is defined by the presence of several non-anesthetic annular lesions with indistinct edges. The borderline lepromatous (BL) presentation is defined by the presence of more than 10 bilateral and non-anesthetic lepromas and annular lesions.[5]

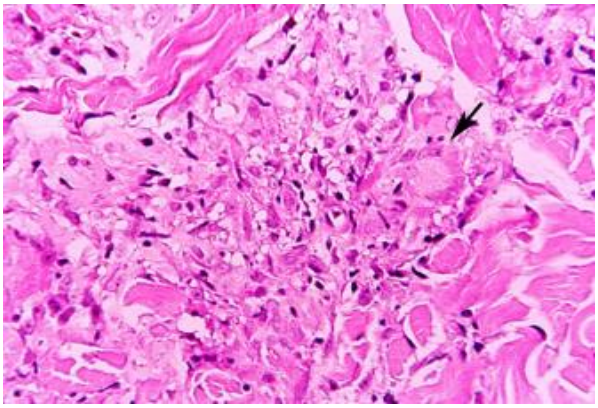

Fig 5: Borderline leprosy

DIAGNOSIS:

The diagnosis of leprosy is, in most cases, clinical-epide miological, and based mainly on dermatological and neurological examination. Testing for temperature, pain and touch sensation is essential for the clinical diagnosis; however, many lesions of the in determinate and multibacillary clinical forms can present with normal sensitivity

Whenever possible, the bacilloscopy must be made, and the following tests should be available: histamine test, pilocarpine test, histopathology, anti-PGL-1 (phenolic glycolipid antigen) serology and the polymerase chain reaction (PCR). Electroneuromyography, ultrasound or mag netic resonance of nerve trunks can be useful in the diagnosis of neural forms. Recent studies have shown that the rapid diagnostic tests, based on the detection of anti-peptide antibodies derived from bacillary PGL, are also important for the diagnosis.[6]

Table 1:Differential diagnosis of leprosy subtypes

Leprosy subtype	**Differential diagnostic considerations**
Tuberculoid; Indeterminate	Pityriasis alba; post-inflammatory hypopigmentation; vitiligo; segmental vitiligo; tinea versicolor; nummular eczema
Borderline tuberculoid	Granuloma annulare; interstitial granulomatous dermatitis; disseminated granuloma annulare; sarcoidosis; erythema annulare centrifugum; tinea corporis
Mid-borderline and borderline lepromatous	Necrobiosis lipoidica; granuloma annulare; necrobiotic xanthogranuloma; gummatous syphilis; Sweet's syndrome; lichen planus; ichthyosis vulgaris; parapsoriasis; mycosis fungoides; mastocytosis; morphea
Lepromatous	Alternative cutaneous mycobacterial infections (tuberculosis; M. marinum; M. avium-intracullare…etc); deep fungal infection (sporotrichosis; blastomycosis; chromoblastomycosis; lobomycosis); leishmaniasis; erythema elevatum diutinum; xanthogranulomas; trichoepitheliomas; verrucous lesions.
Isolated neural	Peripheral nerve sheath tumor

TREATMENT:

M. leprae, just like any other mycobacteria, is naturally resistant to most of the frequently prescribed antibiotics because of the high number of lipids in its cell wall, thus preventing antibi otic penetration and especially hydrophilic ones (-lactams, glycopeptides, fusidic acid, and chloramphenicol). Chaulmoogra oil, extracted from the fruit of the Taraktogenos kurzii tree, was the first leprosy treatment. One of its compounds, hydnocarpic acid (C16H28O2), has an in vitro activity against some mycobacteria species. It is however inactive against M. leprae.[7]

CLASSIFICATION OF ANTI-LEPROTIC DRUGS

Sulfones: Dapsone(DDS).

Phenazine derivatives: Clofazimine.

Anti tubercular drugs: Rifampin, Ethionamide.

Other Antimicrobials: Ofloxacin, Moxifloxacin, Minocycline, Clarithromycin.

First-line antibiotics: dapsone, clofazimine, and rifampicin

Dapsone:

Dapsone, sulfamide antibiotic, was a mile stone for millions of leprosy patients. It acts against bacteria and protozoa in the same way as sulphonamides, that is by inhibiting the synthesis of dihydrofolic acid through competition with para-amino-benzoate for the active site of dihydropteroatesynthetase. The researchers of the Parke-Davies company had synthetized the agent derived from dapsone, Promin®, which led to the discovery of the first effective treatment against leprosy more than 60 years after the identification of the disease-causing agent.

Clofazimine:

It inhibits mycobacterial growth and binds preferentially to mycobacterial DNA. Clofazimine, B663 or Lamprene®, is a red/orange phenazine which was synthetized in 1956. It was first proposed as a tuber culosis treatment, and later its usefulness in the treatment of leprosy was demonstrated.[8]

Rifampicin:

Rifampicin belongs to the rifamycin group and was first used as a tuberculosis treatment, just like all the other leprosy treatments. It inhibit bacterial DNA-dependent RNA polymerase.The better efficacy of the 600 mg daily dose of rifampicin as compared with the 600 mg monthly dose" had not be proven and because (ii) of the need to control the use of rifampicin as it was at the time more expensive than dapsone, but mainly because it was the most effective (bactericidal activity) agent to treat leprosy.

Second-line agents: fluoroquinolones, minocycline, and clarithromycin

Fluoroquinolones (ofloxacin, levofloxacin, and moxifloxacin), minocycline, and clarithromycin are intended as potential therapeutic alternatives. These antibiotics have the same broad-spectrum activity as rifampicin and target many Gram-positive and Gram-negative bacteria.[9]

NEW THERAPEUTIC APPROACHES

Multidrug therapy was recommended as the standard treatment of tuberculosis (i.e., the other mycobacterial infection) as early as the 1970s but its use for leprosy patients was only recommended by WHO in 1982. The use of the multidrug therapy was progressive; its geographical coverage was less than 1% between 1982 and 1985, 50% in 1992, and is now 100% since 1997.

Table 2: Standard multidrug therapy regimens for paucibacillary and multibacillary leprosy in adults and children (WHO recommendation, 2013)[10]

Clinical presentations	Population	Agents	Dosing regimen	Treatment duration
Paucibacillary leprosy	Adults	Rifampicin	600 mg/month	6 months
		Dapsone	100 mg/day	
	Children	Rifampicin	450 mg/month	6 months
		Dapsone	50 mg/day	
Multibacillary leprosy	Adults	Rifampicin	600 mg/month	12 months
		Clofazimine	300 mg/month and 50 mg/day	
		Dapsone	100 mg/day	
	Children	Rifampicin	450 mg/month	12 months
		Clofazimine	150 mg/month and 50 mg/day	
		Dapsone	50 mg/day	

CONCLUSION:

Chemotherapeutic agents make an enormous contribution to primary health care. This work aimed at searching for literature available data about plants and drugs that present anti leprotic activity. It could be observed that they played an important role as efficient therapeutic path against leprosy centuries ago. This fact is not so different from nowadays because it is necessary the use of natural origin drugs to which no similar synthetic compound has been found in the main polychemotherapeutic regimens proposed by modern medicine for the confirmed disease cases.

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