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Review Article

A REVIEW ON NEW APPROACHES AND CURRENT THERAPIES INVOLVED IN THE TREATMENT AND PROPHYLAXIS OF TUBERCULOSIS

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ABSTRACT

Tuberculosis (TB) is a major contributor to the global burden of disease and has received considerable attention in recent years, particularly in developing countries where it is closely associated with HIV/AIDS. Poor compliance adherence to treatment is common despite various interventions aimed at improving treatment and prophylaxis of TB. During the past decades significant advances have been made in the development of novel anti tubercular drugs for treatment of tuberculosis. This brief review presents an update of the available information on anti tubercular drugs as well as recent developments in the therapy of TB. The review also involves information about drugs which are in pipeline for the treatment and prophylaxis of TB.

Key word: Tuberculosis, antitubercular drugs.

INTRODUCTION

Tuberculosis is an infectious disease, caused by many species of mycobacteria specially M.tuberculosis and M.bovis. Tuberculosis has been described as 'King of Diseases' in the Vedas by Charaka and Sushruta, about 600B.C. Physicians in ancient Greece called this illness "phthisis" to reflect its wasting character. During the 17th and 18th centuries, TB caused up to 25% of all deaths in Europe. In more recent times, tuberculosis has been called "consumption."[2]

With the discovery of tubercle bacillus by Robert Koch in 1882 the diseases become known as tuberculosis[3]. It typically attacks the lungs but can also affect other parts of the body. The disease is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air[4].

It is the world's second commonest cause of death from infectious diseases after AIDS. According to WHO reports the total number of new cases of tuberculosis had risen to 9 million. In 2010 there were an estimated 8.8 million new cases and 1.5 million associated deaths, mostly occurring in developing countries.[5] The absolute number of tuberculosis cases has been decreasing since 2006, and new cases have decreased since 2002[6].

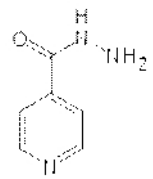
Signs and Symptoms

General signs and symptoms include chronic cough with blood-tinged sputum, fever, chills, night sweats, loss of appetite, weight loss, and fatigue,[7] and finger clubbing also occur.[8] Infection of other organs causes a wide range of symptoms. Tuberculosis may infect any part of the body, but most commonly occurs in the lungs known as pulmonary tuberculosis.[7] Symptoms of pulmonary tuberculosis may include chest pain and a prolonged cough producing sputum. Extrapulmonary tuberculosis occurs when tuberculosis develops outside of the lungs. Extrapulmonary tuberculosis may co-exist with pulmonary tuberculosis as well.[8] Extrapulmonary tuberculosis occurs more commonly in immunosuppressed persons and young children. In those with HIV this occurs in more than 50% of cases.[9] In 15–20% of active cases, the infection spreads outside the respiratory organs, causing Extrapulmonary tuberculosis.[10]

Anti Tubercular Drugs

First line Antitubercular Drugs

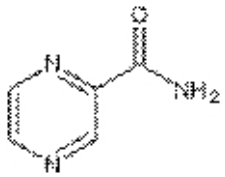
Isoniazid[12, 13, 14]



Isoniazid

- Isoniazid, the hydrazide of isonicotinic acid is highly bactericidal against replicating tubercle bacilli.
- A component of all tuberculosis chemotherapeutic regimens currently recommended by WHO.
- Isoniazid alone is occasionally used to prevent to transmission to close contacts at high risk of disease.
- Isoniazid is also used to stop the high progression of infection to primary complex in recently infected, asymptomatic individuals and to prevent the development of active tuberculosis in immunodeficient individuals.[12]

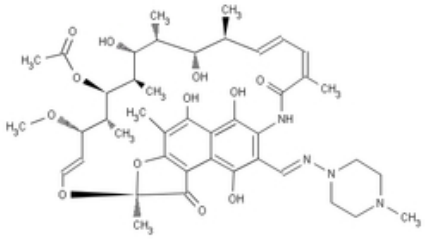
Pyrazinamide[15, 16,]



Pyrazinamide

- A synthetic analogue of nicotinamide that is only weakly bactericidal against M. tuberculosis, but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation.
- It is highly effective during the first two months of treatment while acute inflammatory changes persist and its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced.
- A component of all six and eight month TB chemotherapeutic regimens currently recommended by WHO.

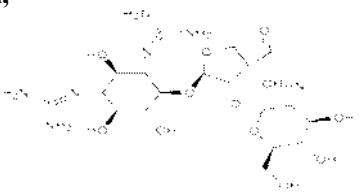
Rifampicin[17, 18, 19]



Rifampicin

- A semi synthetic derivative of rifamycin, a complex macrocyclic antibiotic, inhibits ribonucleic acid synthesis in a broad range of microbial pathogens.[58]
- It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extra cellular locations.
- A component of all six and eight month tuberculosis chemotherapeutic regimens currently recommended by WHO.

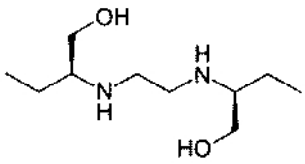
Streptomycin, [20, 21]



Streptomycin

- An aminoglycoside antibiotic derived from Streptomyces griseus that is used in the treatment of tuberculosis and sensitive Gram-negative infections.
- A component of several tuberculosis chemotherapeutic regimens currently recommended by WHO.

Ethambutol[22, 23]



Ethambutol

- A synthetic congener of 1, 2-ethanediamine that is active against M. tuberculosis, M. bovis and some non-specific mycobacteria. It is used in combination with other tuberculosis drugs to prevent or delay the emergence of resistant strains.
- An optional component of several chemotherapeutic regimens tuberculosis currently recommended by WHO.

Second Line Anti Tubercular Drugs[24]

- There are six classes of second-line drugs (SLDs) used for the treatment of tuberculosis.
- A drug may be classed as second-line instead of first-line for one of three possible reasons:

I. It may be less effective than the first-line drugs (e.g., *p*-aminosalicylic acid)
II. It may have toxic side-effects (e.g., cycloserine)
III. It may be unavailable in many developing countries. (e.g., fluoroquinolones):

Newer drugs

Some drugs that are useful, but are not in the WHO list of SLDs:

rifabutin, clarithromycin (CLR); linezolid (LZD); thioacetazone (T); thioridazine;

arginine; vitamin D; R207910.

Rifamycin derivatives

- Rifamycins are a group of antibiotics, which are synthesized either naturally by the bacterium Amycolatopsis mediterranei, or artificially.
- Rifamycin acts by binding specifically to the ß-subunit of bacterial DNA-dependent RNA-Polymerase, RpoB.
- Rifamycins are particularly effective against mycobacteria, and are therefore used to treat tuberculosis, leprosy and mycobacterium avium complex (MAC) infections.
- The rifamycin group mainly includes the following drugs:

1. Rifabutin
2. Rifapentine

Rifabutin[25, 26, 27]

Rifabutin is a semisynthetic spiropiperidyl derivative. Rifabutin inhibit mycobacterial RNA polymerase like rifampicin. Its activity is better against mycobacterium avium complex (MAC). This lipophilic drug after absorption from the gut is eliminated in the urine and bile. In patients with renal impairment dose adjustment is not needed. Rifampicin sensitive M. tuberculosis strains were also sensitive against rifabutin and about one third rifampicin resistant strains still sensitive to rifabutin. Rifabutin is effective for the prevention of mycobacterium avium complex (MAC) infection in HIV-infected individuals. At 300 mg/day, it decreases the frequency of mycobacterium avium complex (MAC) bacteremia by 50%. Rifabutin is commonly substituted for rifampicin in the treatment of tuberculosis in HIV-infected patients due to its less profound interaction with indinavir and nelfinavir. In combination with clarithromycin and ethambutol, it is also used in the treatment of mycobacterium avium complex (MAC) disease. Rifabutin is generally well tolerated. Main side effects occur when used in HIV patients are rash (4%), GI upset (3%), and neutropenia (2%).

Rifapentine[28, 29]

Rifapentine is a semi synthetic ansamycin antibiotic having similar structure to rifampin. Rifapentine is bactericidal against actively growing bacilli, with a rate of killing similar to that documented for rifampicin. Rifapentine halflife is 4 times greater in humans than rifampicin. The prolonged elimination half-life of rifapentine is likely due to its higher lipophilicity, which facilitates tissue penetration of the drug and lack of biotransformation to antimicrobially inactive metabolites. If rifapentine is administered after meal absorption is enhanced. Rifapentine inhibits DNA-dependent RNA polymerase activity in susceptible microorganisms. Specifically, these antibiotics interact with bacterial RNA polymerase interfering with initiation of biosynthesis but not elongation. The mammalian enzyme is unaffected by the rifamycins. Rifapentine is recommended for the treatment of pulmonary tuberculosis in combination with other effective antituberculosis drugs. Higher relapse rates may occur with rifapentine than the rifampin. The adverse reaction profile of rifapentine is similar to that of other rifamycin antibiotics. Rifapentine is an inducer of cytochromes P450 3A4 and P450 2C8/9 isoforms and may increase the metabolism of other drugs that are metabolized by these enzymes.

Fluoroquinolones[30, 31]

Fluoroquinolones(FRQs) have bactericidal activity against M. tuberculosis. Fluoroquinolones (FRQs) inhibit the gyrase, an enzyme involved in DNA replication. There is no cross resistance between these agents and other antituberculosis drugs. Ofloxacin, ciprofloxacin, lomifloxacin, levofloxacin,

sparfloxacin and moxifloxacin have shown activity against M. tuberculosis.

Ofloxacin[32, 33]

Ofloxacin is a bactericidal drug. It is active in vitro against M.tuberculosis as well as against M. kansasii, M. xenopi, M. fortuitutum, and M. marinum. Mycobacterium avium and most strains of M. chelonei are resistant to ofloxacin. Natural resistance to ofloxacin appeared to occur in about 1 in 105 organisms, a proportion similar to that for other drugs. The MIC for ofloxacin is less than 4 mg/l and after normal oral dose of ofloxacin peak serum level attained is 10.7 mg/l, which is quite high. Ofloxacin has an excellent activity against M. tuberculosis in clinical investigations.

Levofloxacin[34, 35]

It is less neurotoxic than ofloxacin. It is effective against M. tuberculosis. One of the studies concluded that levofloxacin-containing regimen resulted in a similar rate of adverse events compared with conventional first-line regimens when used for treatment of active tuberculosis.

Ciprofloxacin[36, 37, 38, 39]

Ciprofloxacin is active against all strains of M. tuberculosis sensitive to streptomycin, INH, rifampicin, and ethambutol and inhibit almost all strains showing intermediate sensitivity or resistance to one or more of the above agents. Nearly all isolates, including atypical one were inhibited at a concentration of 3.2 mg/1. Efficacy of ciprofloxacin is proven in clinical trials. Other fluoroquinolones like lomifloxacin and sparfloxacin have also shown efficacy in appropriate clinical settings.

Moxifloxacin[40, 41]

ATS guidelines state that among the new fluoroquinolones, moxifloxacin appears to be the most promising in the treatment of resistant tuberculosis. In experimental study, it is proved that addition of moxifloxacin as a companion drug provides better protection against development of drug resistance. The most potent of the currently available FQNs in descending order of in vitro activity against M. tuberculosis are moxifloxacin, gatifloxacin, levofloxacin, and ofloxacin.

Co-amoxyclav[42, 43,]

Amoxicillin is a semi synthetic beta-lactam antibiotic, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. The addition of a beta-lactamase inhibitor to amoxicillin greatly improves its in vitro activity against M. tuberculosis. The beta-lactam inhibitors (i.e., clavulanic acid) possess no intrinsic antimycobacterial activity, but they are able to inhibit the enzyme responsible for the resistance of M. tuberculosis to beta-lactam antibiotics. Beta-lactam antibiotics penetrate poorly into mammalian cells, and this characteristic may limit the effectiveness of these agents in therapy for tuberculosis.

Tuberactinomycin[44, 45]

Tuberactinomycin resembles viomycin structurally as well as in its mode of action. It acts by inhibiting protein synthesis. Tuberactinomycin containing regimens have shown good clinical response. Negative sputum culture at six months ranged from 73% to 80% in the tuberactinomycin containing regimens compared to 63% in a similar viomycin containing regimen. In advanced cases, this ranged from 67% to 76% in the tuberactinomycin containing regimens compared to 59% in the viomycin containing regimen. Thus tuberactinomycin was better than viomycin.

Clarithromycin[46, 47]

The second generation macrolide, clarithromycin, is effective against Mycobacterium avium-complex, and other NTM (Non-tubercular mycobacteria) including M. paratuberculosis. It is also recommended in the treatment of infections caused by Mycobacterium marinum and mycobacterium fortuitum complex. It has been shown to cause a reduction in the bacillary load and clinical improvement of M. avium disease in AIDS patients.

Amikacin[48, 49]

Amikacin, an aminoglycoside, is highly bactericidal against M. tuberculosis. It is given five days a week in a dose of 15 mg/kg/day as a single dose, usually by intramuscular injection. The major side effect of amikacin is nephrotoxicity and vestibular damage. Hearing loss, hypocalcaemia, hypokalaemia and hypomagnesaemia are other side effects. In comparison to kanamycin, it is less ototoxic and less painful.

Capreomycin [50, 51]

Capreomycin is an aminoglycoside which is bactericidal against M. tuberculosis. It is given in a dose of 15 mg/kg/day intramuscularly with maximum of 1 G. It is toxic to the eighth cranial nerve, causing high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs. Renal toxicity is somewhat more common with capreomycin than with streptomycin, and it may be associated with electrolyte disturbances secondary to tubular damage. It is suggested that in elderly patients when there is similar susceptibility to capreomycin and amikacin, capreomycin should be used since older patients seem to experience more renal and ototoxic effects with amikacin than with capreomycin.

Clofazimine[52, 53, 54]

Clofazimine is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription. The MICs of clofazimine against M. tuberculosis have not been published. Adverse reactions include discolouration of the skin, gastrointestinal upset, severe and life-threatening abdominal pain and organ damage caused by clofazimine crystal deposition, and asymptomatic discolouration of the eye.

Nitroimidazopyran[55, 56]

A series of new compounds containing a nitroimidazopyran nucleus that possess antitubercular activity has been reported. This compound is related to metronidazole.It seems that it will be available in future for clinical evaluation. After activation by a mechanism dependent on M.tuberculosis F420 cofactor, nitroimidazopyran inhibited the synthesis of protein and cell wall lipid. In contrast to current antitubercular drugs, nitroimidazopyrans exhibited bactericidal activity against both replicating and static M. tuberculosis. Lead compound PA-824 showed potent bactericidal activity against multi-drug resistant M. tuberculosis and promising oral activity in animal infection models. The nitroimidazopyran compound PA-824 has bactericidal activity comparable to that of INH.

Oxazolidinones[57, 58, 59]

Oxazolidinones like eperezolid and linezolid are an appealing class of antimicrobials due to their unique bacteriostatic mechanism of action, lack of cross-resistance with other agents, good oral bioavailability, potential for structural manipulation, and broad spectrum of activity. The mechanism of action is the ability to inhibit protein synthesis by binding to the 50S subunit and preventing the 30S complex from forming the 70S complex, resulting in inhibition of translation. Eperezolid and linezolid were shown to have activity against a wide variety of organisms,

including gram-positive cocci, gram-negative anaerobes, and mycobacteria. Due to their predominantly gram-positive activity, these agents were compared to vancomycin, penicillins, macrolides, minocycline, and similar antibiotics. Linezolid have shown activity against M. tuberculosis in a murine model. Linezolid appear to be well tolerated when given both orally and parenterally. Drug related adverse events occurred in 32.7% of patients, which were mild to moderate in severity and which resolve on discontinuation of therapy. They were nausea, diarrhoea, tongue discolouration, oral thrush, taste perversion and headache. Thrombocytopenia is related to duration of therapy.

ROLE OF SURGERY: [60, 61]

Recently few studies on the role of surgery emerged as a light of hope in the management of difficult to treat pulmonary tuberculosis. A recent study concluded that the use of resection lung surgery was associated with overall improved outcome in patients with highly resistant MDR-TB, with a trend toward improvement for those taking fluoroquinolone antibiotics. It is hoped that in future we will have more data on the role of surgery but it is a disease, which can be managed medically, and surgery is the last hope as an adjuvant not as sole mode of treatment.

IMMUNOTHERAPY FOR TUBERCULOSIS[62, 63]

Mycobacterium vaccae

M. Vaccae is found in the soil, first described in a study from Uganda. It was found that prior sensitization of animals with M. vaccae could optimize the protective effect of subsequently administered BCG vaccine. A single intradermal injection of 0.1 ml suspension of dead M. vaccae containing 109 bacilli is administered a week or more after starting effective chemotherapy. Following effects have been noted: weight gain, rapid clearance of tubercular bacilli from sputum and decrease ESR. Further work is needed to evaluate the role of M. vaccae in the management of tuberculosis.

Interleukin-2[64, 65]

It is believed that immunity against M. tuberculosis is mediated by T-lymphocytes that produce the type 1 (Th1) helper T cell cytokines IFN and interleukin (IL)-2. In tuberculosis patients, Th1 cytokines predominate at the site of disease, but the systemic immune response in peripheral blood is characterized by enhanced production of the type 2 (Th2) helper T cell cytokine IL-4, and by reduced secretion of IFN and IL-2 by peripheral blood T cells. The systemic Th1 response in tuberculosis patient is low which inclined researchers to use IL-2 as an immunotherapeutic adjunct to treat tuberculosis. IL-2 strongly induces IFN and is a potent growth factor for CD4+ and CD8+ T cells, both of which contribute to immunity against tuberculosis. Furthermore, IL-2 stimulates expansion and enhanced functional capacity of natural killer cells, which can eliminate intracellular M. tuberculosis. Rapid sputum conversion was noted in a pilot study from Bangladesh and South Africa, in which intradermal IL-2 (225, 000 IU) twice daily was used during the first month of tuberculosis therapy as an adjuvant. A later randomized trial in South Africa comparing daily and pulsed IL-2 with placebo in MDR tuberculosis found improved sputum clearance with daily treatment. A recent study concluded that IL-2 did not enhance bacillary clearance or improvement in symptoms in human immunodeficiency virus-seronegative adults with drug-susceptible tuberculosis.

It seems that we have again gone into an era similar to that of early forties when no cure for tuberculosis was available and only hope was fresh air, rest, good diet and sunlight. The present era when anti-TB drugs are available, is more dangerous because of the development of MDR tuberculosis due to irregular use of anti tubercular treatment, problems in implementation of effective tuberculosis control programme in many countries, over the counter sale of anti tubercular treatment and others. It is hoped that effective implementation of tuberculosis control programme under DOTS strategy, awareness of the mass as well as the health care providers about tuberculosis, judicious use of presently available medication, and control over the counter sale of anti tubercular treatment would have an impact on the control of MDR menace of tuberculosis. Recently WHO published current drugs in pipeline for the resistant tuberculosis. Diarylquinoline TMC207 is bactericidal, and is currently in phase-IIa clinical trial. Pyrrole LL-3858 is active against drug sensitive mycobacteri and currently in phase-I clinical trial. Other promising drugs are Pleuromutilins, Didiperidine SQ-609, ATP Synthetase Inhibitor FAS20013 (FASgene), Translocase I Inhibitor, InhA Inhibitors and Isocitrate Lyase Inhibitors.

PROSPECTS

Tuberculosis is major problem now the days as new case of resistance out come to all ready existing drugs. So it increases the demand of newer drug for the tuberculosis. All ready existing drugs are better lead for the screening of new drugs. Rapid screening of molecules through HTS, innovative drug design by combinatorial chemistry and target based assays are the novel strategies for drug development.

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