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NEWER DRUGS FOR MULTI DRUG RESISTANT TUBERCULOSIS AND SPECIAL EMPHASIS ON LINEZOLID

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ABSTRACT

MDR tuberculosis and XDR tuberculosis are serious threats to TB control. ***Multidrug resistant TB (MDR- TB)*** *is TB strains which is resistant to Isoniazid and Rifampicin.* ***Extensive drug resistant tuberculosis (XDR-TB)*** *is defined as resistance to at least Rifampicin and Isoniazid in addition to any fluoroquinolone and to at least one of three following injectable drugs used in anti-TB treatment: Capreomycin, Kanamycin and Amikacin. Current treatment for drug-resistant tuberculosis is inadequate and outcomes are poorer than for drug-susceptible TB. Linezolid is an oxazolidinone, a relatively new class of antibiotic and has demonstrated high in vitro antibacterial activity against Mycobacterium tuberculosis, and has been used to treat complicated cases of resistant TB in several programmes.However, linezolid is a toxic drug with significant side effects including severe neuropathies and haematological adverse events. This literature review provides a brief discussion of existing drugs,emerging drug targets and also immune modulators in order to improve the existing treatment regimen in terms of better efficacy, reduced drug administration frequency, shortened period of treatment and reduced drug related toxicity.*

KEYWORDS

MDR-TB, XDR-TB, Linezolid, Immunomodulators.

INTRODUCTION

MDR tuberculosis and XDR tuberculosis are serious threats to TB control. **Multidrug resistant TB (MDR TB)** is TB strains which is resistant to Isoniazid and Rifampicin. **XDR-TB** is defined as resistance to at least Rifampicin and Isoniazid (which is the definition of MDR-TB) in addition to any fluoroquinolone and to at least one of three following injectable drugs used in anti-TB treatment: Capreomycin, Kanamycin and Amikacin. From 424,203 MDRTB cases estimated world-wide by the WHO more than half cases are estimated to be in China and India.[1] Identifying this problem 'Revised National Tuberculosis Control Programme' (RNTCP) in India has introduced DOTS-Plus services into management programme of MDR-TB patients.[1,2]

The patients with MDR and XDR have to be treated with second line drugs which are more toxic and expensive (50-200 times costlier than first line drugs).[3], with longer treatment schedules of up to 2 years. The cost Finally, after the initial intensive phase of the treatment, when the disease symptoms subside, many patients stop taking medication mainly because of high pill count and associated toxic effects. The discontinuation of therapy facilitates the emergence of MDR and XDR strains. The emergence of MDR and XDR-TB underscore the necessity of a new line of tuberculosis drugs. For the last 50 years, no new anti-TB drug has been discovered.

This literature review provides a brief discussion of existing drugs and emerging drug targets, and also of the advantages of incorporating modern drug delivery systems and immune modulators in order to improve the existing treatment regimen in terms of better efficacy, reduced drug administration frequency, shortened period of treatment and reduced drug related toxicity. The investigation for a new drug target is essential to

continue the battle against MDR and XDR-TB. However, owing to the enormous cost and time involved in new drug development, improvement of the existing treatment regimen or by modifying the existing ones can revolutionise the entire global scenario of the disease or seen to be a valid alternative.

FACTORS RESPONSIBLE FOR DRUG RESISTANCE

- Deficient or deteriorating TB control programme resulting in inadequate administration of effective treatment
- Poor case holding, administration of sub-standard drugs, inadequate or irregular drug supply and lack of supervision
- Ignorance of health care workers in epidemiology, treatment and control
- Improper prescription of regimens
- Interruption of chemotherapy due to side effects
- Non-adherence of patients to prescribed drug therapy
- Availability of anti-TB drugs at counter without prescription
- Massive bacillary load
- Illiteracy and low socio-economic status of the Patients
- The epidemic of HIV infection
- Laboratory delays in identification and susceptibility testing of M. tuberculosis isolates
- Use of non-standardized laboratory techniques, poor quality drug powders and lack of quality control measures
- Use of anti-TB drugs for indications other than tuberculosis

TREATMENT

Current treatment for drug-resistant tuberculosis (DR-TB) is inadequate and outcomes are significantly poorer than for drug-susceptible TB particularly for patients previously treated with second-line drugs, treatment failures or extensively drug-resistant (XDR-) TB patients (complicated DR-TB).

The World Health Organization (WHO) reports that among 7063 patients from 13 countries who initiated second-line treatment for MDR-TB in 2007, only 37% were successfully treated and 20% either died or failed treatment[5]. Similarly poor outcomes are reported for XDR-TB patients many of whom were MDR-TB treatment failures. Treatment options for patients in whom second-line treatment for MDR-TB has failed or those who have XDR-TB are extremely limited. Treatment often relies on a set of drugs with poorly established efficacy and severe adverse event profiles. Poor efficacy and tolerability leads to treatment discontinuation in many settings which carries the risk of increased mortality and transmission of highly resistant strains[3, 4, 5, 6, 7]

Linezolid

It is an oxazolidinone, a relatively new class of antibiotic primarily used for the treatment of resistant gram-positive bacterial infections. It was first approved for use in January 2000 for non-tubercular infections.

Spectrum of activity

Includes MRSA, some VRSA, VRE, penicillin-resistant strep.pyogenes, streptococci viridance & strep.pneumoniae, M.tuberculosis, clostridia, cornibacterium & Listeria. It is primarily bacteriostatic but exert cidal action against certain organisms like streptococci, pneumococci & B.fragilis. No cross-resistance with other agents and broad spectrum of activity including gram-positive cocci and gram-negative anaerobes.

Mechanism of action

It inhibits the bacterial protein synthesis. It act at early step & different site than other AMA. It interferes in the formation of ternary N-formylmethionine- tRNA(tRNAfmet). It binds at 23S fraction of 50S ribosome. Biding of Linezolid distort the tRNA binding site & stops protein synthesis before it starts.

Pharmacokinetics

It has good oral bioavailability, plasma $t_{1/2}$ is 5hrs &dose alteration is not necessary in renal insufficiency. It metabolized partly non-enzymatic & excreted in urine. Potential for structural manipulation.

Adverse Effects

This includes mild abdominal pain & bowel upset, occasionaly rash, pruritus, headache, oral/vaginal candidiasis. Haematological like neutropenia, thrombocytopenia requiring frequent blood transfusion & neuropathies (peripheral and optic).

Drug interactions

It is MAO inhibitor hence shows interactions with Adrenergic, Serotonergic & excess of tyramine intake like cheese reaction.

Dosage & route of administration

It is given by oral as well as intravenous route. In case of MDR – TB, Linezolid dose varied considerably across studies, both at treatment initiation and after adjustment in the case of adverse events attributable to linezolid.

The starting dose ranged between 300 and 1200 mg daily. The higher daily dose of 1200 mg was always delivered twice daily, whereas lower doses were given either singly or twice daily.

Uses: Complicated & uncomplicated soft tissue infections. Community and hospital acquired pneumonias, bacteraemias & other drug resistant gram positive bacterial infection.

Drug resistant Tuberculosis

Linezolid has demonstrated high in vitro antibacterial activity against Mycobacterium tuberculosis, and has been used to treat complicated cases of resistant TB in several programmes. Considering that patients with refractory and/or XDR-TB have few treatment options, linezolid may well be a useful addition to the armamentarium. However, linezolid is a toxic drug with significant side effects including severe neuropathies and haematological adverse events. While use of linezolid is restricted to 28 days with dosage at 600 mg twice daily DR-TB requires much longer treatment duration often for ≥ 2 years and therefore carries an increased likelihood of severe adverse events. The balance between potential efficacy and drug toxicity has led some to explore a dose reduction for linezolid in the treatment of DR-TB but experience to date is limited and fragmented.[8]

Clinical trial data on Linezolid in tuberculosis

The poor safety profile associated with long-term use of linezolid and lack of evidence of clinical efficacy has led linezolid to be used primarily for patients considered to have 'intractable' or 'complicated' DRTB including those with whom a treatment using recommended second-line drugs has failed or those with XDR-TB with susceptibility to few available drugs. However, the high frequency of serious adverse events suggests that linezolid should be used with some caution in settings where adverse events can be monitored and patients hospitalized; if needed. Some adverse events such as optic or peripheral neuropathy may be irreversible and debilitating.

This risk needs to be balanced against paucity of effective treatment options for patients with DR-TB and possibility of cure afforded by the use of linezolid as has been done for other MDRTB drugs with important side effects such as kanamycin and Amikacin which are associated with significant and often irreversible hearing loss in more than a third of patients. Adverse events are not only barriers to linezolid use for DR-TB treatment. In South Africa where linezolid is patent protected and costly. In contrast in India, where linezolid is not patented, generic production has reduced the cost. In addition to lower cost, the quality of linezolid preparations and particularly non-validated generic forms needs to be assured before its use.

Encouragingly at least two randomized controlled trials are underway to assess the use of linezolid in DR-TB treatment. Preliminary results are promising with high levels of culture conversion but as yet no published treatment outcomes. [9, 10, 11 & 12]

OTHER NEW ANTI-TUBERCULOSIS DRUGS

1. **Rifamycin derivatives**: This group of drugs have better pharmacokinetic behaviour, less toxicity and relatively new so that no resistant strain has evolved against it. This includes Rifabutin, Rifamide, Rifalazil, Rifapentine and many others. These compounds are a modified form of Rifampicin . They are usually more active than the parent compound Rifampicin.
   a. **Rifabutin:** It is an orally active, semi synthetic antibiotic which is derived from Rifamycin S. It is 4-8 times more active than Rifampicin against M. Tuberculosis and has a longer half-life and good tissue penetration properties. Another major advantage of Rifabutin over Rifampicin is its relatively low level of drug interaction. The Centre for Disease Control and Prevention (CDC) in the USA recommends Rifabutin instead of Rifampicin for simultaneous treatment of TB and HIV because of its better compatibility with other antiretroviral drug regimens than Rifampicin. It has been shown that

Rifampicin sensitive M. tuberculosis strains were also sensitive against Rifabutin and about one third Rifampicin resistant strains still sensitive to Rifabutin.[13,14,15,16]

b. **Rifalazil**: It is particularly more potent against M. Tuberculosis. In vitro activity of this drug is 100 times higher than Rifampicin and also shows better in vivo activity in the mouse model. Better efficacy in humans has been reported for once weekly administration of it along with daily INH, compared to daily administration of both Rifampicin and INH without any significant adverse toxicity. [17]

c. **Rifamide:** A derivative of Rifamycin B is used against gram-positive cocci causing respiratory tract infections and against gram-negative and gram-positive organisms in biliary tract infections.

d. **Rifapentine**: Has a longer half-life than Rifampin and is similar to it. The in vitro activity of Rifapentine is 2-4 times that of Rifampicin against a variety of clinical mycobacterial isolatesInitial results of a study of Rifapentine in tubercular patients, indicated comparable efficacy with Rifampin in producing negative sputum cultures for M. tuberculosis. (18) Higher relapse rates were reported in the Rifapentine-treated group (10%) than the Rifampin-treated group (5%) during follow-up.In a TRC study6, of 103 strains of M. tuberculosis tested, 52 strains were sensitive to both. The remaining 51 strains resistant to Rifampicin were also resistant to Rifapentine, indicating complete cross- resistance. It was interesting to note that among sensitive strains Rifapentine has a 2 to 16 fold higher activity than Rifampicin.The results of Rifapentine in pulmonary TB with HIV are disappointing. [19]

2. **Fluoroquinolone:** Most potent and currently used Fluroquinolones in the treatment of MDR tuberculosis are **Moxifloxacin**, Gatifloxacin, Levofloxacin, Ofloxacin. Though some of the drugs were discovered earlier but their anti TB activities have been reported recently. There is no cross resistance between these agents and other anti -tubercular drugs. This group of drugs has good pharmacokinetic properties which may help to reduce the frequency of drug administration.They also can penetrate the tissues very well,including macrophages.[20,21] the primary docking site for the TB bacteria.Their toxicity levels were also less adverse when administered alone. [22]However, Moxifloxacin, when administered along with Rifampicin & Pyrizinamide, showed considerable toxic effects, the combination regimen of these three showed better performance than INH, Rifampicin and Pyrizinamide in the mouse model.[23]. Many of the fluoroquinolones are used as second line drugs in TB patients but fluoroquinolone resistant bacteria are emerging at a faster rate. In the Philippines, 51% of the MDR-TB cases were found to be resistant to both ciprofloxacin and ofloxacin. [23]

a. **Ofloxacin:** 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. Use of Ofloxacin in MDR TB patients was associated with favorable outcome. Ofloxacin has an excellent activity against M.tuberculosis in clinical investigations. In a recently reported study from Hong Kong use of Ofloxacin in MDR TB patients was associated with favorable outcome.[24]

b. **Levofloxacin**: It is less neurotoxic than Ofloxacin. Its efficacy against M. tuberculosis is proven in clinical trials. Similar rate of adverse events compared with conventional first-line regimens when used for treatment of has seen in clinical trial. [25]

c. **Moxifloxacin**: Anti tuberculosis guidelines stress that among the new fluoroquinolones, Moxifloxacin appears to be the most promising in the treatment of resistant tuberculosis. [26]

3. **Co-amoxyclav**

Amoxicillin is a semi synthetic beta-lactam antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. Addition of beta-lactamase inhibitor to amoxicillin greatly improves its in vitro activity against M. tuberculosis. There are no in-vivo studies using this drug combination against M. tuberculosis.[27]

4. **Tuberactinomycin**
   Tuberactinomycin resembles Viomycin structurally as well as in its mode of action. Tuberactinomycin containing regimens have shown good clinical response. (28) Tuberactinomycin was better than Viomycin.
5. **Clarithromycin**
   The second generation macrolide, Clarithromycin is effective against Mycobacterium avium-complex and other NTM (Non-tubercular mycobacteria) including M. paratuberculosis. It has been shown to cause a reduction in the bacillary load and clinical improvement of M. avium disease in AIDS patients. [29]
6. **Amikacin**
   Amikacin, an aminoglycoside is highly bactericidal against M. tuberculosis. The major side effect of Amikacin is nephrotoxicity and vestibular damage, hearing loss, hypocalcaemia, hypokalaemia and hypomagnesaemia. [30]
7. **Capreomycin**
   It is an aminoglycoside which is bactericidal against M. tuberculosis. Renal toxicity is somewhat more common with Capreomycin than with streptomycin and it may be associated with electrolyte disturbances secondary to tubular damage.[30]
8. **Clofazimine**
   It is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription.[30]
9. **Nitroimidazoles**
   A series of new compounds containing a nitroimidazopyran nucleus which possess anti-tubercular activity has been reported. The most effective drug in this group is nitroimidazopyran PA-824. 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 synthesis of protein and cell wall lipid exhibit bactericidal activity against both replicating and dormant populations of the bacteria. In contrast of current antitubercular. This drug has the potential to treat both active and latent TB. It is also mutagenic and carcinogenic but to a lesser extent than other parent compounds. This can be a major concern towards its development as a good anti-TB drug. [31]
10. **Azole Drugs**
    The drugs like miconazole and clotrimizole are active against M.Tuberculosis.They target the cytochrome P450 homologs in the bacteria. The subsequent crystallisation of M. Tuberculosis cytochrome P450 enzyme system initiated studies to evaluate new drug. [32]
11. **Diarylquinoline**
    TMC 207 is the lead compound of this series. It is effective against all the pathogenic strains of mycobacteria which cause TB. It is equally effective in drug susceptible as well as drug resistant strains of the bacteria. Human studies with this drug have showed good efficacy in MDR-TB, with acceptable toxic effect[33]. This drug targets a novel ATP synthase of the bacteria.[34, 35]
12. **Phenothiazines**
    Chlorpromazine and thioridazine are antipsychotic drugs with considerable anti-TB activity. In vitro, they show activity against susceptible as well as drug resistant bacteria (in vitro). Their anti-TB activity is partly due to their relative concentration in macrophages. [36, 37, 38]
13. **Some new emerging drug targets**
    Ever since the discovery of the complete genome sequence of a virulent strain of TB bacteria, lots of new drug targets have been identified, and some of them are showing promise in animal models. The evaluation of new drug targets is essential to carry on the constant battle against the drug resistant strains of TB. Some of the recent and promising drug targets are.

1. Peptide deformylase inhibitors: Metalloprotease enzyme essential for maturation of nascent polypeptides in bacteria but not essential for humans. This is a relatively new drug target having anti-TB activity and has the potential of a future drug target. [39,40]
2. 2C-methyl-D-erythritol 4-phosphate (MEP) pathway inhibitors: Fosmidomycin. [41]
3. Isocitrate lyase (ICL) enzyme inhibition.[42]
4. Amino acid biosynthesis is another important target for developing anti-TB drugs the inhibitor of this pathway acts as a promising herbicide and research is ongoing for developing an antimycobacterial drug by exploiting the enzymes involved in this pathway.[43]
5. The PhoPR is a two component signal transduction system found in mycobacteria the suitable inhibitor for this system can serve as an important drug for TB treatment. [44]
6. Another important set of emerging drug targets is the components of the siderophore biosynthesis of M. tuberculosis the carboxymycobactins and mycobactins are two types of siderophore present in M.tuberculosis. An antibiotic named 5'-O-[N- (salicyl)sulfamoyl] adenosine was reported to block the biosynthesis of both and hence the replication of M tuberculosis in vitro, under iron.[45]
7. Role of Nanoparticles in Anti-TB Drug Delivery: Poor compliance with therapy is important hurdle in the management. This leads to further complications. The poor compliance is caused by the prolonged treatment period and high daily pill count which also enhance the drug related toxicity. One of the major milestones to achieve good compliance rate is either to reduce the total period of drug treatment or to cut down the daily pill count. This can be achieved by incorporating sophisticated formulation techniques. Encapsulating the anti TB drugs within a micro or nanoparticle can greatly enhance the bioavailability of the drugs and thereby reduce the frequency of drug administration to, say, once weekly compared to the existing daily intake. [46, 47]

14. Immunotherapy for tuberculosis:

Although MDR TB has a poor prognosis, there are some effective antibiotics also for these drug-resistant strains. However, there are few chemotherapy options for XDR TB, so its mortality rate is high. Immunomodulation is now emerging as one promising therapeutic alternative. This approach is based on the belief that a particular microbe causes disease in an organism due to the host's susceptibility.[48] rather than due to the characteristics of the microbe alone. Bolstering the weakened immune system of the host may thus restore the equilibrium broken by the infection. Immunomodulators could be used for this purpose (immunostimulators), although they may be also useful in decreasing an exacerbated immune response (immunosuppresors).

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. Further work is needed to evaluate the role of M. vaccae in the management of tuberculosis [49, 50]

IL-2: 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 TB 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 TB 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.[51]

IFN-γ (Interferon-gamma): is another crucial immunomodulator that plays a vital role during TB infection, althoughthere are contradictory findings in literature regarding the role of IFN-γ in TB. Some older studies reported that IFN-γ pre-treated human macrophages were more susceptible to TB-bacterial growth.[52, 53] However, the researchers also found that IFN-γ administration in aerosol form resulted in rapid recovery in MDR-TB patients.

TNF-α: another crucial proinflammatory cytokine, activates macrophages to liberate nitric oxide synthase-2 which is responsible for killing the intracellular Mtb.[54,55] mice deficient of TNF-α secretion and corresponding receptor showed higher susceptibility towards TB.

IL-10: is an important munosuppressive cytokine that can polarise the immune response towards T-helper cells of type 2 (Th2). The mouse macrophages infected with Mtb showed increased production of IL-10 which suppresses the production of Th1 promoting cytokine, IL-12. The incorporation of anti-IL-10 receptor antibody in the multi drug regimen of anti MAC treatment showed enhanced efficacy in the mouse model Like all other bacterial infections, Th1 response, the intracellular cell mediated immunity,is vital for protection against TB infection. So the cytokines that promote the Th1 response should be able to provide better protection. [56, 57]

IL-12: plays an important role towards the enhancement of Th1 response. During TB infection, IL-12 promotes the secretion of interferon-gamma (IFN-γ), tumour necrosis factor α **(**TNF-α) and granulocytemacrophage colony-stimulating factor, all of them polarise the immune response towards Th1, *via* the activation of natural killer (NK) cells (71). The exogenous administration of IL-12 in mice showed enhanced resistance towards the intravenously infected Mtb bacteria. [58]

CONCLUSION:

There are some challenges towards the development of a new treatment regimen for TB. Firstly, the unavailability of a suitable animal model that can mimic the human disease profile.

The mouse model is used widely; it has some limitations like the reactivation of TB, the major mode of TB infection in human, cannot be mimicked in the mouse model. The mice also do not form caseous granuloma, the hallmark of human TB infection. Secondly, there is no suitable model that can mimic the latent stage of the Mycobacterium tuberculosis. Though various models have been tried, like the Wayne model and starvation model etc, but none can exactly reflect the scenario observed in the latent stage of the disease in humans. According to a recent study, it takes around $800 million to $1.7 billion to develop a drug from scratch and to bring it to the pharmacy shelf, with considerable involvement of time. It is difficult to assess the efficacy of a new drug when it is administered along with numerous other anti-TB drugs. If implementing the particle encapsulation with/without immunomodulators, can improve the existing treatment regimen then this option may be worthwhile to investigate. Moreover, better compliance with the treatment can reduce the chance of bacterial evolution towards the drug resistant strain by eradicating the bacteria at early stage. The discovery of a new chemotherapy regimen for TB, either by introducing novel drugs or by modifying the existing ones, can revolutionise the entire global scenario of the disease.One of such drug is Linezolid. Treatment success with linezolid was equal or better than that commonly achieved for uncomplicated DR-TB and better than previous reports for previously treated patients and those with XDR-TB. While data are limited linezolid appears be a useful drug, albeit associated with significant adverse events and should be considered in the treatment of complicated DR-TB.

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