NEW DRUG REGIMENS FOR OLD DISEASE TUBERCULOSIS: A REVIEW
Gupta Sandeep, Sharma Mona*, Gupta Mahesh Kumar, Nagla Kapil, Gupta Raman
Kota College of Pharmacy, Sp-1, Riico Industrial Area, Ranpur, Kota, Rajasthan, India

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ABSTRACT
Today ‘Tuberculosis (TB)’ is acknowledged as a global health threat. As resistant strains of Mycobacterium tuberculosis have emerged slowly and due to lack and treatment failure many countries have to adapt long term and costly treatment for the patients. Due to TB 1.8 million people die every year and 5000 every day. By this data we can analyze that there is an urgent need to improve its treatment by enhancing the activity of existing agents and introducing new agents. The new regimens should have better drug tolerability profile and longer duration of action and great patient acceptability. The new agents should be more effective against MDR/XDR TB and in HIV co infected patients and active against latent TB. This review presents the drug currently used and also the advanced drug undergoing clinical trials for the treatment of tuberculosis. A short description on their mechanism of action and inhibitors acting on related biochemical targets is also provided. The focus of this review is to consider the challenges in the development of new anti TB drugs and provide an up-to-date evaluation of current therapy status and progress of the developing new agents in the phase of clinical testing as one of the strategies for the improvement of TB treatment.

KEY WORDS: Tuberculosis, new regimens, current drug.

*Corresponding Author
Mona Sharma, Student, M.Pharm. I year, Department of Pharmaceutical Chemistry, Kota College of Pharmacy, Kota, Rajasthan, India E-mail: sharmon321@gmail.com

INTRODUCTION
Given the global scale of tuberculosis as a major public health problem, research activity has been maintained in the area of TB drug development, despite inadequate funding and some preclinical successes have been reported. Tuberculosis is a common and often deadly infection caused mainly by strains of Mycobacterium tuberculosis, a slow growing pathogen with unusual propensity to shut down its metabolism in the face of adverse condition, such as starvation or immune stress, and to enter a persistent, or latent, phase in which it displays phenotypic resistance to some antibiotics¹. The present review offers a critical overview of the current anti-TB drugs arsenal and of the contemporary trends in the development of new tuberculostatics capable to overcome the bacterial resistance, especially of new agents being in progress in the phase of clinical testing.

Need of new drug regimen
There are several major problems associated with currently available treatment of TB they are:

- The duration and complexity often resulting in nonadherence and leading to emergence of resistance and continuous spread of the disease.
- Adverse events in response to anti tubercular drugs.
- Some drugs for drug-resistant TB are not available everywhere and are less effective, more toxic, and have longer use.
- Co-infection of TB and HIV, where their combined treatment involves a high pill count with associated adherence problems, overlapping toxicity profiles, drug interactions and risk of immune reconstitution syndrome. Prophylactic therapy of latent TB is also associated with problems.

Due to above problems WHO developed a Directly Observed Therapy Short (DOTS) course, but due to its expensiveness and labor intensity it became a burden on public health programs running in developing countries².

Drug regimens used currently
The currently applied drugs for treatment of TB include broad spectrum, narrow spectrum and different drug
combinations, which target different types of TB. They are categorized under two heads:\(^1\):

1. First line drugs
2. Second line drug

**FIRST LINE DRUGS**

Streptomycin was the first antibiotic used to treat TB. It is an aminoglycoside antibiotic, the other agents of this category are: kanamycins, gentamycins tobramycin, dibecacin, sisomycin, netilmicyn, pentisomycin. Other effective drugs were searched and are: erythromycin, clarithromycin, and rifampicin which were used in combination with isoniazid and ethambutol

**Isoniazid:** It is a sulphonamide and act as a prodrug for TB. It acts by inhibition of mycolic acid biosynthesis by affecting enzyme mycolate synthetase in the bacilli.

**Ethambutol:** it is a synthetic amino alcohol and act by inhibiting mycolate and glucose synthesis.

**Pyrazinamide:** it is an analog of nicotinamide and active against semi dormant bacillus. And thought to act by sterilizing effect.

**SECOND LINE DRUGS**

The second line drugs used in the treatment of TB are: p-amino salicylic acid, ethionamide, protionamide, and cycloserine.

**p- Amino salicylic acid:** its antibacterial activity was reported in 1946. But rarely used now in the treatment of TB. The hydrazide of PAS exhibit good activity.

**Ethionamide and Protionamide:** these are two homologous compounds used as tuberculostatics due to their different mode of action. They are active against M. tuberculosis, M. bovis, M. smegmatis, and M. avium.

**Cycloserine:** D-cycloserine is a structural analogue of D-alanine, it inhibit M. tuberculosis. Its major side effect CNS toxicity and also causes psychotic states with suicidal tendencies\(^4\).

**NEW REGIMENS UNDER DEVELOPMENT**

A number of new anti-TB drugs are in the stage of development with new mechanism of action that overcome the resistance caused by first line drugs and exhibit excellent activity against *M. tuberculosis* and reduce duration and dosing of the treatment.

**Diarlyquinolines**

TMC207

It is a new anti TB agent with unique spectrum and specificity to mycobacteria. They are currently in phase2a clinical trials\(^5\).

**Nitroimidazofurans and Nitroimidazopyrans**

These posses in-vivo activity against TB. But due to mutagenic side effects it is not used clinically. The compounds are: PA-824, PA 1343, and OPC-67683. They act by inhibiting replicating and latent phase of bacillus\(^6,7\).

**Thioacarlide**

Thioacetazone and isoxyl. These are diacyl thioureas and act by inhibiting mycolic acid biosynthesis. Isoxyl is useful than toxic thioacetazone\(^8,9\).

**Tryptanthrin**

It is a novel potent indolo-quinazolinoline alkaloid active against MDR-TB. But in-vivo data and in-vitro toxicity are needed before this structural prototype is applied\(^10,11\).

**Oxazolidinones**

These are orally active synthetic antibacterial. Thiromorpholine analogue of U-100480 showing potent in-vitro activity against M. tuberculosis. Linezolid

It is an oxazolidinone and act by inhibiting ribosomal protein synthesis by interfering with initiation complex formation. It is used in the treatment of MDR-TB and does not have any cross resistance with existing anti-TB agents\(^12\).

**Fluoroquinolones**

Novel fluoroquinolones have been considered of special interest for treating TB as they are far effective\(^13\). They are also preferred as they have minimum side effects and no cross-resistance. So they provide a better choice in the treatment of serious infections and mainly MDR-TB\(^14\). The new fluoroquinolones are:

**Moxifloxacin**

The in-vitro study of moxifloxacin shows to kill sub population of tubercle bacteria which was not shown by previous fluoroquinolones and rifampicin. It is highly effective due to inhibition of effluxes out of bacteria and causing higher concentrations resulting in improved activity\(^15\).

**Gatifloxacin**

Gatifloxacin has showed greater activity than moxifloxacin but have a cross-resistance with it. Its clinical indications are found to be effective and have similar activity as moxifloxacin and isoniazid\(^16\).

**Gamifloxacin**

It is a drug which has shown activity in phase 3 trials but used for respiratory infections. Its in-vitro activity shows that at very high non-toxic dose also it not effective in treatment of TB\(^17\).

**Sitafloxacin**

It is in phase 3 trials and has outstanding activity and is highly effective than other fluoroquinolones. It inhibits both DNA gyrase and topoisomerase 4 and its IC\(_{50}\) against these enzymes were lowest among the fluoroquinolones\(^18\).
Phenothiazines
Phenothiazines are active against variety of bacteria, mycobacteria, viruses and protozoa. Chlorpromazine and thioridazine are the drugs having activity against mycobacteria of TB. These are methylene blue derivatives which render bacteria immobile. Its anti-TB activity is due to presence of calmodulin protein in bacteria. These act synergistically with other antimicrobial agents\textsuperscript{19}.

Pyrrole: LL-3858
It is a pyrrole derivative which showed antmycobacterial activity in preclinical studies. Its activity has showed good results in mice and dog and found to be well absorbed and showed better activity then isoniazid\textsuperscript{20}. Information related to molecular mechanism is currently in phase 1 trials.

Nitroimidazoles
M. tubercle is an obligate aerobe which is capable of long-term persistence under conditions of low oxygen tension. Metronidazole is a drug which showed activity against dormant tubercle. It undergoes reduction at low redox potential in susceptible micro-organism to form nitro group which damages DNA and causes cell death. Shows synergistic activity in combination with first line drugs\textsuperscript{21}.

ATP Synthase Inhibitor
FAS20013 (FASgene)
It is a novel compound of sulphonylecarboxamides class. The compound is effective against mycobacterium and act by inhibiting ATP synthase. It is mainly effective in MDR-TB and superior to sterilize TB lesions and kill latent TB compared to other drugs\textsuperscript{22}. It is 100% bioavailable on oral administration and no dose toxicity even on administration of 10 times the effective dose.

InhA Inhibitors
Isoniazid is first line drug in TB treatment it requires activation in which inherent protective enzyme of mycobacteria-Kat G plays major role. InhA, the enoyl reductase enzyme from Mycobacterium tuberculosis, catalysis the last step in fatty acid biosynthesis pathway\textsuperscript{23}. The main purpose is to bypass the activation step and directly inhibit InhA.

Novel rifamycin derivatives
Rifabutin
It is 4 to 8 times more active than rifampin and favourable feature is it has good tissue penetration. Prime reason for it is that it can be co-administered with antiretroviral treatment. It is used in multi drug treatment with other drugs.

Rifapentine
It is 2 to 4 times more active and has better pharmokinetic profile than RIF. It has longer duration of action and high serum peak levels which extend the dosing intervals in patients. Its adverse effects are very less and can be administered with indinavir\textsuperscript{24}.

Rifametane
It is a novel semi-synthetic rifamycin having same spectrum and potency but with better pharmokinetic profile\textsuperscript{25}.

Rifalazil
It is a new semi synthetic rifamycin, characterized by long half life and more active than rifampicin and rifabutin both in-vivo and in-vitro. Due to severe side effects its development have been terminated\textsuperscript{26}.

Capuramycin analogs
They posses antmycobacterial activity both in-vivo and in-vitro by inhibition of enzyme phospho-MurNAc-pentapeptide translocase and inturn inhibit the peptidoglycan assembly. Drugs are: RS-118641, RS-112997, and RS124922. They are used for MDR-TB treatment\textsuperscript{27}.

Pleuromutilins
They inhibit the growth of bacteria and act by interfering with protein synthesis by binding to 23S r RNA and result in inhibition of peptide bond formation. It represents novel class of antibiotic and effective in MDR-TB\textsuperscript{28}.

Dipiperidine
SQ-609
It is a novel compound and act by interfering with cell wall biosynthesis. The activity is shown in-vivo in mouse but is less effective than Isoniazid .

Diterpenoids
These are the compounds which are isolated from natural sources. They have been recently screened for antituberculosis activity as it has many other activities also. It was found that benzoaxazole is not necessary for the activity.

Purines
Substitutions at various positions of 9-benzyl purines like 2-,6- and 8- have shown high inhibitory activity against M. tuberculosis.

Thiazidine thiones
These compounds are derivatives of dithiocarbamic acid and have shown potent activity against M. tuberculosis. One of its compounds has activity in-vitro even in resistant strains of the bacteria.

Carbohydrate derivatives
These compounds were screened on the basis that sugars have property of inhibiting the enzyme activity
responsible for cell wall biosynthesis. On screening sugars simple monosaccharides showed potent activity against M. tuberculosis strains and used in MDR-TB.

**Natural Marine Products**

Cyclic depsipeptides were isolated from pseudomonans, a marine alga and a tune worm. These were tested against M. avium-intracellulare having MIC value 2.5-5 and 5-10 µg/ml respectively of massetolide A, viscosin B. other isolated from Sacoglossan mollusk Elysia rufescens named Kahalalides inhibited bacterial growth at 12 µg/ml. similarly litosterol and naphsterol is isolated from red sea nephtheasp. Heteronemin isoxazoles and cynopyridines are mainly two sources of new chemical entities, the first number of and second deals with conforming the necessary and sufficient conditions of flourishment. Finally, the registration of new synthetic transformations.

The current antitubercular drugs offer treatment which demands continuous administration of drugs for 6 months. Newer drugs are needed to shorten the total duration of treatment and significantly reduce the number of doses need to be taken under DOTS. There are mainly two sources of new chemical entities, the first one is provided from natural product extraction, evaluation, and characterization and second deals with the original compounds made more accessible by design of new synthetic transformations. The new regimens have exceptional safety profiles and avoid the drug-drug interactions presently conforming the TB and HIV therapy.

The “road ahead” i.e. the search of new regimens for TB treatment is full of challenges and success depends on the necessary resources and innovative ideas flourishment. Finally, the registration of novel drugs represents the necessary and sufficient conditions of success in improving the treatment of TB patients and impacting the epidemic globally.

**REFERENCES**


Fig. 7: Structure of dipiperidine

Fig. 8: Structure of diterpenoids

Fig. 9: Structure of purines

Fig. 10: Structure of thiazidine thiones

Fig. 11: Structure of carbohydrate derivatives

Fig. 12: Structure of natural marine products