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Evolution in the treatment of *Mycobacterium tuberculosis.*

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ABSTRACT

Resistance to drugs in the treatment of Tuberculosis is a global problem that has emerged giving rise to XDR-TB, MDR-TB, and has made the control of this disease exceedingly difficult. An efficient way to treat it is by modifying the pre-existing anti-TB drugs and derive new drugs to contradict the effect of the resistant tubercle bacilli. In the 19th century, first-line drugs were mainly used but due to the evolution of *Mycobacterium tuberculosis* into resistant forms, the second and third-line drugs have been developed and are being employed in the current treatment regimen. Although the BCG vaccination has helped in protection from the disease for many generations, combinational drug therapies for intracellular, extracellular, and latent mycobacteria along with surgical intervention since the 19th century have proven to counter the infection. This review aims to highlight the progression in the treatment of this bacterial disease over the years since its discovery.

Keywords: *Mycobacterium tuberculosis*, drugs, Tuberculosis, treatment of TB, Drug-resistant TB strains

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INTRODUCTION

Tuberculosis is a disease caused due to *Mycobacterium tuberculosis.* Robert Koch discovered this bacterium in 1882. Tuberculosis is highly prevalent around the globe.[1]In 1993 TB was declared as a world health emergency by WHO and it remains the second most fatal infectious disease after AIDS.[2] It is a topic of interest for many scientists as a lot of research yet to be conducted as there is no definite line of treatment available for complete prevention or cure.[3] This bacterium has drastically evolved with the passing years and thus the treatment for this disease has parallelly evolved along with it as this caused the failure of the first line of treatment.[4] Strains resistant to the most sterilizing drugs from the first line i.e. Isoniazid and Rifampicin are termed multidrug-resistant tubercle bacilli or MDR.[5]The strains which are resistant to not only the aforementioned antibiotics but also any of the Fluoroquinolones and the second line injectables i.e. Amikacin, Kanamycin, Capreomycin are termed as XDR short for extremely drug-resistant tubercles.[6] High mortality rates have been observed because of *Mycobacterium tuberculosis* in the earlier years.[7] Due to *Mycobacterium tuberculosis,* one-third of the world population has been affected as reported by WHO.[8]But with a lot of research, revolving around the diagnosis, treatment, and drugs, the mortality rates have decreased around the early and mid-20th century.[9] The problem with the older line of drugs is not only resistance but the fact that none of the drugs yet discovered have sufficient efficacy along with low toxicity and also possess the characteristic of high absorptivity and retention in the body without causing harm or side effects.[8]

A century ago, Bacille Calmette Guerin (BCG) vaccine was developed. It is a widely used vaccine worldwide administered at the time of birth as a part of the Expanded Programme on Immunization of the WHO.[8] Many randomized control trials have concluded that BCG has 80 percent to no protection.[10] BCG mass vaccination has been cited as a reason for the emergence of this strain making TB prevention questionable.[11]*Mycobacterium tuberculosis* has been continuously under the radar of researchers to be able to study the drug resistance mechanisms and to devise drugs or treatment strategies with an unforeseen mode of action and one that is safe to administer to all kinds of patients.[12]

This review highlights the important drugs that have been used in treating TB since it was discovered and some new ones that are under trial.

Group I (First-line drugs):

Isoniazid:

In 1912, a well-known synthetic drug was discovered named Isoniazid. It is widely used for the treatment of tuberculosis.[13] This drug is fairly specific and selective for *Mycobacterium tuberculosis* and related strains and is a chemoprophylactic agent.[14]It is known to act on multiple targets.[15] It mainly targets and inhibits the carrier protein reductase (2-trans enoyl acyl) also known as Inh A.[16] Inh A inhibits mycolic acid of the cell wall through Tyr158 and restrain the effect of the disease[17]. More recent genetic studies observed the InhA resistant strains in tubercle bacilli which led to the observation of MDR varieties evolved by sensitive strains which are NADH-dependent enoyl causing mutation in the InhA structural gene. This led to the development and discovery of new drugs.[18]

Ethambutol:

Ethambutol is a significant first-line drug and is currently approved by the U.S FDA (Food and Drug Administration) for treating tuberculosis. The complete mechanism of ethambutol was not completely known. Ethambutol affects the cell wall and it uses its bacteriostatic activity by inhibition of ribosyl transferase. Ribosyl transferase is an enzyme that polymerizes arabinose into arabinan and finally to arabinogalactan. The mutation in gene embB at position embB306 is recognized as a mechanism of resistance to ethambutol.[19]

Rifampicin:

Food and Drug Administration (FDA) have approved Rifampicin for the treatment of tuberculosis in 1971. Rifampicin plays a critical role in combination therapy. It has been shown to act against the persistent, metabolically inactive residents of bacteria, which often occupies inside of host cell. Rifampicin, rifabutin,

rifapentine, and rifaximin are currently the approved rifamycins that are extracted from *Streptomyces* mediterranei (rifamycin SV) the natural product of *Amycolatopsis mediterranei*.[19] The rifamycin binds specifically to the β subunit of RNA polymerase and shows no activity against human RNA polymerases hence act as safe transcriptional inhibitors specific for bacteria. DNA replication error leads to the faulty encoding of RNA polymerase, which binds to rifamycins resulting in loose binding to the drug. This phenomenon is seen in clinical segregates of resistant strains of *M. tuberculosis* as they show mutations in the codons that encode the capacity to bind rifamycins. The above-mentioned rifamycin derivatives induce expression of human P450 cytochrome oxidases particularly CYP3A4 and P glycoprotein ABC transporter in humans which are the major complication since they can cause drug-drug interactions.[20]

Pyrazinamide:

Pyrazinamide is a first-line drug used for the treatment of tuberculosis. Since 1980, pyrazinamide is being used as an anti-tuberculosis drug. It plays an important role in the precision of anti-tuberculosis therapy from a period of 9–12 months to 6 months because it kills semi-dormant tubercle bacilli which stays in an acidic environment.[3] This drug acts on the bacterium at acidic pH of 5.6 and it kills 76% of the bacterial population.[21] The mode of action of pyrazinamide is very abnormal and puzzled researchers since its discovery. The primary reason being that pyrazinamide is different from other drugs active against growing bacteria and very little or no activity is seen for non-growing persisters. PncA gene converts pyrazinamide into the active form known as the pyrazinoic acid by *M.tuberculosis*. at acid pH.[22]

Group II (Second-line Drugs):

The first-line drugs used to cure tuberculosis have failed due to the growth of resistant bacteria. Resistance to isoniazid and rifampicin, the main drugs used when in combination with the other first-line drugs to treat the primary infections.[23] The *Mycobacterium* strains that are resistant to both these drugs are categorized under Multi-Drug Resistant. Treatment of such bacteria is mainly done through second-line drugs like fluoroquinolones and at times some aminoglycosides are also proven to be effective.[24] Various second-line drugs that are necessary for treating the drug-resistant strains of *Mycobacterium tuberculosis* are described below.

Fluoroquinolones:

Fluoroquinolones are being evaluated as a new mechanism under development for drug-sensitive TB. The ratio of MIC or MBC is generally between 2 to 4. Despite such progress, the success rate is reported to be 48% for MDR TB. Fluoroquinolones (FQ) are widely used antibiotics which shown to be useful in the treatment of TB in 1984 and became essential components of TB regimens, particularly for drug-resistant disease.[25] Fluoroquinolones were introduced for MDR-TB after demonstration of antimycobacterial activity in vitro and in vivo. They are recognized by the WHO for MDR-TB treatment. In certain conditions, patients cannot sustain the standard regimen at that time administration of fluoroquinolones is done.[26] The second-generation ofloxacin has a MIC range of 1- 2mg/ml. It has been used as a first and second-line agent. Usually, it is recommended in MDR-TB regimens but is currently not recommended as a first-line drug. Ciprofloxacin has a MIC value of 0.5 – 4 mg/ml. It shows an effect on in vitro activity as compared to in vivo efficacy. When the trial of this drug as first-line was done, it resulted in higher relapse rates that's why it is not recommended. Levofloxacin shows a MIC value of 1 mg/ml.[27]

Group III (Injectable drugs):

Amikacin:

The standardized regimens of MBR-TB are composed of amikacin, ethionamide, cycloserine, levofloxacin, and pyrazinamide. According to renal function analysis and WHO recommendations, the amikacin dosage was calculated and the dosage range was intramuscularly administered between 15 and 25mg/kg. The primary drug mechanism is the same as aminoglycosides. It interrupts the bacterial growth by binding with bacterial ribosomal 30s subunit and interferes with tRNA and mRNA binding acceptor.[28]

Kanamycin:

Kanamycin has the same mode of action as streptomycin. It is an aminoglycoside antibiotic. It inhibits the synthesis of protein by binding to the conserved A site of 16S rRNA in the 30s ribosomal subunit. The drug resistance mechanism spin around the changes that happen in the 16s rRNA2 ribosome subunit of *M. tuberculosis* which finally leads to cross-resistance.[29]

Capreomycin:

Capreomycin belongs to the second line for MDR tuberculosis. Ribosomal proteins L12 and L10 of *Mycobacterium tuberculosis* interrelate with each other. At 50S ribosomal unit constitute the stalk, which during translation recruit's initiation and elongation factors. Evidence shows that Capreomycin inhibits the function of L12-L10 interaction which is crucial for protein synthesis, by L12-L10 established interaction assay. The L12-L10 interaction is inhibited by this drug.[30]

Streptomycin:

Streptomycin is a drug that was discovered by Selman Waksman. It is an aminoglycoside and is employed as the first line of defense for the treatment of tuberculosis. It is often administered parenterally due to lower absorption from the gastrointestinal tract. This drug can also be administered intravenously. Streptomycin exerts a bactericidal action on the *Mycobacterium tuberculosis*. Even though it is considered to be one of the most efficient drugs for the treatment of this disease, many strains have emerged that are resistant to this drug. Due to this, Streptomycin is used in combination either with some beta-lactams or in addition to isoniazid, rifampicin, pyrazinamide also known as the intensive four-drug regimen.[31]Streptomycin binds to the 16s rRNA of the 30S subunit and inhibits protein synthesis. It mainly affects the initiation of the translation of proteins and can lead to the elongation of the partially elongated chains. It is known to affect both the A and P sites. Moreover, streptomycin causes misreading of the mRNA, that is, it affects the proof-reading activity of the mRNA for the selection of the correct aminoacyl t-RNA by the ribosomal subunits.[29]

Group IV (Less- effective second-line drugs):

Ethionamide:

ETH is a prodrug that was first used in the treatment of tuberculosis in the early 1950s. It is a part of the drug arsenal which is used in the treatment of multi-drug resistant tuberculosis that undergoes metabolic activation by exerting cytotoxic effects. Its main structural function is due to the presence of thionamide. ETH is involved in the Bioactivation of a hepatotoxic metabolite; the therapeutic effect of ETH is determined by oxygenation. Activation of ETH is done by mycobacterial enzyme EthA and the transcriptional repressor resulting in the exhibition of various intermediates and metabolite derivatives.[32] EthA acts as the mycobacterial enzyme used for ETH bio-activation. But, the physiological role of EthA remains unknown.[33]. Prothionamide (PTH) is the secondary drug used against *Mycobacterium tuberculosis* bacteria which is administrated through a conventional oral route. But, due to frequent administration and unpredictable absorption, its use is limited. An alternative method for administrating is through a pulmonary route using nanoparticles.[34]

D-Cycloserine (DCS):

As an alternative therapy, D-Cycloserine is used for the treatment. It is primarily used in inhibiting the sequential synthesis of peptidoglycan, an analog of D-alanine.[35] It is observed to inhibit cell wall synthesis in *M. tuberculosis* by competing with D-alanine for essential enzymes D-alanine racemase and D-alanine synthetase.[36]

Para amino-salicylic acid:

PAS was discovered as an antitubercular agent showed multiple hypotheses related to its antitubercular mode of action. Acceleration of PAS to increase oxygen consumption in *M.Tuberculosis* in 1940

and 1941was observed by Bernheim. But recent studies showed that the PAS principle mainly occurs by poisoning folate metabolism.[37]

Group V (Third-line Drugs):

The third-line drugs were categorized under Group V drugs by WHO. The major activity of these drugs was found to be comparatively less effective.[24] But certain drugs were known to show bactericidal activity in comparison to the 6 months of treatment with the standard regimen of drugs and combination with the previously mentioned drugs.[38]

Clarithromycin:

A macrolide antibiotic clarithromycin has been shown to have good bioavailability after oral dosage consumption. It gets metabolized to 14-hydroxyclarithromycin which is similar to the parent drug.[39] Clarithromycin is a wide spectrum antibacterial antibiotic particularly used for upper and lower respiratory tract pathogens which mainly cause pneumonia, bronchitis, sinusitis, and pharyngitis. Its activity is very less when used alone. It works against bacteria by inhibiting their protein synthesis. Its activity with other already used antituberculous drugs has been studied due to its low toxicity.[40]

Rifabutin:

Rifabutin is a rifamycin derivative with activity against *M. tuberculosis*. Rifabutin is commonly used in patients who already have HIV infection and along with it are infected with TB hence a co-infection[41]. Because of administered TB drugs, formulation, and food intake absorption of rifabutin is affected. Rifabutin is an important metabolite that induces CYP3A and glucuronosyltransferases notably less than rifampicin. Hence it shows lesser drug-drug interactions. Due to this characteristic, it was placed by the WHO in the List of Essential Medicines for the treatment of TB in patients with HIV receiving boosted protease inhibitors (bPIs). Some studies say, one in five patients with rifampicin-resistant TB shows benefit because of rifabutin in antituberculosis treatment.[42]

Bedaquiline:

Bedaquiline is also known as diarylquinoline. Bacterial adenosine triphosphate synthase is a novel antimycobacterial target; Bedaquiline inhibits adenosine synthase. It was the first antituberculosis drug from a novel class and it is approved by European Union and the US. It is bactericidal and this activity is concentration-dependent. In 2019, Bedaquiline was approved by WHO in regimens for MDR.[43] The reason for adding this drug despite the absence of results from phase 3 trials is that, in phase 2 randomized control trials, it has been shown to have improved time to sputum sample, cure rate, reduced mortality in a large cohort study. The application of bedaquiline for drug-resistant tuberculosis has begun ever since. Inclusion of a rare drug policy decision was taken based on the promising shorter regimen and low toxicity of the drug in murine models.[44]

Linezolid:

Oxazolidinones are a class of antibacterial protein synthesis inhibitors. Some studies showed linezolid and oxazolidinones despite their low early bactericidal activity; found to be effective against tuberculosis.[45] Linezolid is the first class of compounds to be approved by the U.S. Food and Drug Administration. Linezolid is mostly used against MDR tuberculosis and in adverse cases, it is used for XDR tuberculosis. The use of linezolid may lead to the reduction of WBC and platelet count.[44]

Thioacetazone:

Thioacetazone is one of the oldest, cheapest, and most widely used drugs to treat Tuberculosis. It only has bacteriostatic and thus weak action and it is highly toxic and also a cause of Steven-Johnson syndrome in patients with HIV.[44] Hence it is no longer used in the treatment regimen. It might be used but only in broad drug-resistant cases that too with a close follow-up of unfavorable events. It is not preferred for patients already having AIDS or to those at an increased risk of getting infected with HIV. It is only used in clinical

practice in absence of the most effective TB drugs like rifampin and ethambutol. But the patients must be warned before its use.[46]

Some other drugs:

Sometimes carbapenems like imipenem and meropenem and some beta-lactams like Amoxicillin clavulinic acid complex are used to treat TB in combination with already available anti tubercle drugs to counteract the beta-lactam resistant strains in MDR patients. The mechanism of how they work with the other drugs is not well known yet but the good tolerability, low cost, and low toxicity of co-aminoclavulante make it a considerable choice in group 5.

Recent advancement in TB :

Mycobacterium tuberculosis has natural intrinsic resistance to most of the antibiotics and also it has acquired resistance in response to antibiotics.[47] Newly acquired resistance helps most of the bacteria to evolve towards that Antibiotics. Strains stabilize further by regaining fitness through acquired mutation. So, even after the discovery of a new antituberculosis drug, always a new threat emerging from MDR and XDR strains.[48]

In recent years, because of advancements in genetics, the diversity of mechanisms of antimicrobial resistance has been increased greatly.[49] According to the future, the scope is a better understanding of the exact mechanism of antimicrobial resistance of mycobacterium tuberculosis to improve therapeutic outcomes in TB patients.[50]

Table 1: Classification of different groups of Anti-tuberculosis drugs[50]

Groups	Most important drugs covered in this Review
Group 1 First-line oral antituberculosis drugs which are all used mostly	Isoniazid Rifampicin Ethambutol Pyrazinamide
Group 2 Anyone of these fluoroquinolones is used at a time since they share genetic targets.	Ofloxacin Levofloxacin Moxifloxacin
Group 3 Injectables	Streptomycin Kanamycin Amikacin Capreomycin
Group 4 Less effective second-line drugs used when only very necessary	P-aminosalicylic acid Cycloserine Ethionamide
Group 5 Drugs that are under research or clinical trials	Linezolid Clarithromycin Thioacetazone Carbapenems

CONCLUSION

Developing drugs for treating the drug-resistant tubercle bacilli is much needed today due to higher mortality rates, longer durations of treatment, and poor tolerance to the already available drugs. In the past many decades, there is no new drug discovery for anti-tuberculosis drugs. Drug resistance mechanisms and the drug resistance pathways for the microbe are being studied extensively and have received recent increased interest. The main requirements from the new drugs that are needed are limited cytotoxicity, an improved half-life, 100% bioavailability, a more efficient mechanism of action, and being cost-effective so that they can be made available to the majority of the population. With the amount of research and advancing strategies for the development of drugs that have been conducted over the years new and more efficient drugs are

expected to be synthesized soon from the pre-existing drugs. Despite these advances, barriers like cross-resistance still pose a big problem. Thus, more effort needs to be taken and much more research is required for the development of drugs against MDR- TB, XDR-TB, and latent TB. This review summarizes the progress of anti-tuberculosis drugs (existing/newly discovered), their mode of action, and their resistance mechanism.

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