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Anti-Tuberculosis Drugs and Mechanisms of Action: Review

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Abstract

Tuberculosis is the most important communicable disease in the world caused by the bacillus Mycobacterium tuberculosis. Mycobacterium is intrinsically resistant to most antibiotics and grows more slowly than other bacteria. Antibiotics are only active against rapidly growing bacterial cells. The cell wall of M. tuberculosis made up of lipid-rich polysaccharides, which are impermeable to many antibacterial agents as a result of poor penetration of drugs they develop resistance with increased level of antibiotic efflux and become Multiple Drug Resistance (MDRs). Prevention and quality diagnosis and treatment of MDR- and XDR-TB are part of the crucial interventions included in the new World Health Organization (WHO) End TB Strategy, which is focused on the goal of TB elimination program. Combinations of two or more drugs are used to overcome the obstacles to prevent emergence of resistance during the course of treatment. Based on drugs used for mycobacterial infections, treatment is administered for months to years. Anti-tuberculosis drugs are classified based on clinical response as first-line drugs and second-line drugs. First Line drugs with high anti-tubercular efficacy as well as low toxicity – routinely used Isoniazid (H), Rifampin (R), Pyrazinamide (Z), Isoniazid (H), Rifampin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S) – HRZES. Second Line drugs are with low anti-tubercular efficacy or high toxicity Paraminosalicylic Acid, Cycloserine, Kanamycin, Amikacin, Ciprofloxacin, Olfloxacin, Clarithromycin, and Azithromycin. Modes of action of majority of the anti-mycobacterial drugs either inhibit their cell wall synthesis or their protein synthesis. In spite of the limitations, the evidence accumulated in the last few years suggests that a new classification of the anti-TB drugs is necessary in the near future.

Keywords: Tuberculosis, Resistance, Antibiotics, Efficacy, Inhibition, Mycobacterium tuberculosis.

Introduction

Tuberculosis (TB) is a communicable disease that is a major cause of mortality worldwide until coronavirus (Covid-19). It is caused by slow growing bacillus *Mycobacterium tuberculosis* and occasionally by *M. bovis* or *M. africanum*. Other species include of M. caprae, M. canettii M. *microti* and M. *pinnipedii*. This bacterium usually affects the lungs (Pulmonary TB), but it can also affect other parts of the body if left untreated such as kidney, spine and brain. TB spreads when people who are sick with TB expel bacteria (germs) into the air by coughing sneezing, speaking. The germs grow in the lungs and move through the blood, lymphatic system, airways and to other parts of the body. Despite the availability of Bacille Calmette-Gue´rin (BCG) vaccine and the effective short-course chemotherapy DOTS (Directly Observed Therapy Shortcourse), the tubercle bacillus continues an increased incidence than any other infectious agent. It is estimated to cause 2 million deaths annually and it has spread over one-third of global population (Jeremiah et al., 2021) and it is declared a tuberculosis (TB) global emergency by WHO. The M. *tuberculosis* incidence is increasing day by day as emergence of drug-resistant Mtb strains [multidrug-resistant Mtb (MDR-Mtb), extensively drug-resistant Mtb (XDR-Mtb) and totally drug-resistant Mtb (TDR-Mtb)] as well as the lack of medical compliance (Zumla et al., 2013; Kim et al., 2008). The M. *tuberculosis*, a Gram-positive, slow growing bacterium with a complex cell envelope and G + C rich genome, that contains an additional outer layer beyond the peptidoglycan cell wall that is exceptionally rich in unusual lipids, glycolipids and polysaccharides that act in intracellular pathogenesis and genetic homogeneity (Cole et al., 1998). In the infected animals or in synthetic medium the generation time of M. tuberculosis, is typically 24 hrs. This attributes to the chronic nature of the disease by imposing lengthy treatment regimens. At present, the standard TB treatment regimen consists of a 6–9-month course of first-line anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) for drug-susceptible TB. However, long-

term therapies are not only notably toxic, but also frequently lead to poor compliance of patients, and in turn, facilitate the development of drug-resistant TB. These conventional anti-tuberculosis drugs are insufficient to completely eradicate tubercle bacillus that remains in a state of latent infection (Yan et al., 2022).

The World Health Organization has developed an effective strategy to end global TB by 2030 by adopting high-quality diagnosis and patient-centered treatment to reduce socio-economic burden associated with TB and support vulnerable populations from TB, TB/HIV and multidrug-resistant TB. Moreover, the ideal anti-TB drug must possess high safety and efficacy profile against drug-resistant target strains (Quan et al., 2017). Generally, anti-TB drugs are classified into two groups based on efficacy and tolerance.

First line drugs - kill active bacteria, important in the early stages of infection (chemoprophylactic agents). This includes isoniazid, rifampin, ethambutol, streptomycin, and pyrazinamide.

Second line drugs - hinder bacterial growth and strengthen treatment in the case of resistant bacteria. This is less efficient and generally more toxic than first line drugs. Second line drugs include amikacin, aminosalicylic acid, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin and ofloxacin. Majority of patients with MDR-TB are treated with second-line drugs worldwide. The number of 4-7 drugs used with prolonged treatment of about 1–2 years may be administered orally. Interestingly, anti-TB drugs work through a variety of mechanisms, including inhibition of mycolic acid synthesis, altering cell membrane permeability, disrupting nucleic acid or protein synthesis by creating possible point mutations.

The mode of action and target genes summarized in Table 1. The crucial clinical problem in treating tuberculosis is that the number of validated drugs available is limited. This obstacle becomes even more severe in the treatment of MDR/XDR-TB. The overall, clinical trials and developments have not been sufficient and have not yet addressed the main shortcomings of long, toxic treatment regimes and the rise of drug resistance.

Drug name	Targets	Mechanisms of action	Genes involved in resistance	Reference
Rifampicin	RNA polymerase, β subunit	Inhibits RNA synthesis	rpoB	(Goldstein, 2014; Howard et al., 2018)
Isoniazid	Enoyl- [acyl-carrier protein] reductase (InhA)	Inhibits mycolic acid biosynthesis and affects the metabolism of DNA, lipid, carbohydrate, and NAD	katG, inhA, ahpC, ndh	
Pyrazinamide	S1 component of the 30S ribosomal subunit	Inhibits translation and trans-translation, acidifes cytoplasm	pncA, FAS-I	(Shi et al., 2011)
Ethambutol	Arabinosyl transferase	Arabinogalactan biosynthesis inhibition	embCAB	
Streptomycin	S12 and 16S rRNA components of 30S ribosomal subunit	Inhibition of protein synthesis	rpsL, rrs	
Amikacin	30S ribosomal subunit	Inhibition of protein synthesis	rrs	(Sirgel et al ., 2012)
Para-amino salicylic acid	Thymidylate synthase (ThyA) and dihydropteroate synthase	Inhibits folic acid and iron metabolism	thyA, folC	(Chakraborty et al., 2013)
Capreomycin	Interbridge B2a	Inhibition of protein synthesis	tlyA	(Sirgel et al ., 2012)
Clofazimine	Exact target not yet known	Release of reactive oxygen species (ROS) and cell member disruption	Rv0678, and mmpL5	(Lechartier et al., 2015)
Bedaquiline	ATP synthase	Inhibition of mitochondrial ATP synthase	Rv0678, atpE	(Koul et al.,2007)
Cycloserine	D-alanine racemase and ligase	Inhibits peptidoglycan biosynthesis	alrA, ddl	(Bruning et al., 2011)
Ethionamide	Enoyl- [acyl-carrier protein] reductase (InhA)	Inhibition of mycolic acid biosynthesis	inhA, etaA/ ethA	

Kanamycin	30S ribosomal subunit	Inhibition of protein synthesis	rrs	(Salian et al., 2012)
Fluoroquinolones	DNA gyrase and DNA topoisomerase	Inhibition of DNA supercoiling	gyrA, gyrB, IfrA	(Takif et al., 2011)
Linezolid	50S ribosomal subunit	Inhibits protein synthesis	rplC	(Jadhavar et al., 2015)
Thiacetazone	Flavin monooxygenase EtaA	Inhibition cyclopropanation of cell wall mycolic acids	etaA	
Delamanid	Exact target unknown	Inhibits mycolic acid synthesis and cell respiration	Rv3547	(Fujiwara et al., 2018)
β-lactam/β-lactamase inhibitors	β-lactamases	Cell wall disruption via peptidoglycan modulation	blaC, Rv0194	

Table 1: Validated potential anti-tuberculosis drugs and their characteristics

First line of drugs

Rifampicin: (rifampicin, rifabutin and rifapentine) is a derivative from the rifamycin family, it was first isolated from *Amycolatopsis rifamycinica* (Sensi & Timbal, 1957). Rifampicin resistance is caused by the point mutations in the rpoB gene, which encodes a minor part of the β-subunit of RNA polymerase enzyme near to the catalytic site. The so-called rifampicin resistance-determining region (RRDR) consists of 81 base pairs encoding amino acids 507–533 in the β-subunit. It have been known in the *rpoA, rpoB*, and *rpoC* genes, coding for different subunits of DNA-dependent RNA polymerase α, β- and β′ subunits, respectively (Wehrli & Staehelin, 1971). Rifampicin act by preventing RNA transcription and subsequent translation to proteins. Thus, rifampin is directly targeting messenger RNA (mRNA) synthesis. Rifampin is FDA approved for the treatment of tuberculosis and is a high lipid-soluble drug. Results showed that when given orally, it is rapidly absorbed and distributed throughout the body.

Isoniazid (INH): also known as isonicotinic acid hydrazide (INH), is a first-line tubercle prodrug that has been recommended since the 1950s and has been validated to target InhA gene. The molecular mechanism of isoniazid resistance involves multiple genes in several biosynthetic networks and pathways. Mutation in the katG (tuberculosis catalase-peroxidase enzyme) gene is the major cause for INH resistance, followed by inhA, ahpC, kasA, ndh, iniABC, fadE, furA, Rv1592c and Rv177 (Ameeruddin Nusrath Unissa et al., 2016). It requires the Mtb catalase-peroxidase KatG activation to generate its acyl radical or acyl anion form, which subsequently reacts with the cellular NAD+, resulting in an INH-NAD adduct, this complex ternary structure of InhA-NAD-INH has a covalent bond between the carbonyl carbon of the acyl group of INH and the C4 position of the nicotinamide ring of NAD, which consequently interferes with the synthesis of mycolic acid. Interestingly, same inhibition mechanism is also found in other anti-tuberculosis drugs such as ethionamide and propionamide (Yoanna Teneva et al., 2023).

Pyrazinamide: Pyrazinamide (PZA) is a distinctive anti-tuberculosis drug that plays a key role in reducing TB therapy. PZA acts by inhibiting multiple targets such as energy production, trans-translation, and probably pantothenate or coenzyme A required for bacterial survival. Mutations in the pncA gene encoding pyrazinamidase enzyme are a major cause of resistance to PZA, which is involved in conversion of the prodrug PZA to the active form pyrazinoic acid. In addition, mutations in the drug target ribosomal protein S1 (RpsA) are also found in some studies. PZA in combination with isoniazid (INH) is practiced for TB patients. Subsequent studies showed that the effects of RIF and PZA were synergistic. It was found to be almost as effective as rifampin (RIF) as a sterilizing drug and to shorten the 6–24 month-long treatment regimens (Pooja Gopal et al., 2019).

Streptomycin (STR): an antibiotic derived from *Streptomyces griseus* used in the TB monotherapy and it was the first *M. tuberculosis* DR described in earlier days. Now it is used as a send-line TB drug (Glasauer et al., 2019). It was the first aminoglycoside to be discovered from *Streptomyces* group in 1940. It has both immediate bactericidal effects and delayed bactericidal effects by disrupting of cell membrane and inhibiting protein synthesis. The aminoglycosides bind to the 16S rRNA in helix 44 (h44), near the Amino site of the 30S ribosomal subunit, altering interactions between h44 and h45. This also displaces two other residues, A1492 and A1493, from h44, these conformational changes that occur with successful codon-anticodon pairing in the Aminoacyl site misreading genetic code. Futher more, aminoglycoside interaction has several effects including inhibition of translation and ribosome recycling. Indeed recent studies show that the latter effect is due to a cryptic interaction at the site situated in h69 of the 23S rRNA of the 50S ribosomal subunit resulting in protein synthesis inhibition (Sheikh et al., 2021).

Second-line drugs

Amikacin: It is an aminoglycoside semisynthetic antibiotic, derived from kanamycin A with similar pharmacokinetic properties. It also exerts excellent activity against *Mycobacterium* (*M. avium-intracellulare, M. chelonae,* and *M. fortuitum*). Amikacin is bactericidal Kills Gram positive and Gram-negative bacteria by causing misreading of t-RNA, prevent bacteria from synthesizing vital proteins to their growth. It also binds to bacterial 30S ribosomal subunits and interferes with mRNA binding and tRNA acceptor sites, proofreading capabilities of the ribosome are reduced, increasing mistranslation this leads to disruption of normal protein synthesis and production of non-functional or

toxic peptides interfering with bacterial growth (Ahmad & Mokaddas, 2014). Amikacin is also involved in inhibition of ribonuclease P which processes pre-t-RNAs (Ramirez et al., 2017).

Para-Aminosalicylic acid (PAS): is one of the anti-mycobacterial prodrug currently used for multidrug-resistant tuberculosis. Although it has been in clinical use for over 60 years in 2018, the World Health Organization recommended it on MDR-TB. The aminosalicylic acid's bacteriostatic action against *Mycobacterium tuberculosis* is explained in two mechanisms. Primarily, aminosalicylic acid inhibits the synthesis of folic acid by binding to pteridine synthetase enzyme responsible in folic acid synthesis. Aminosalicylic acid binds pteridine synthetase enzyme with high affinity and inhibits the synthesis of folic acid. As the tubercle bacteria unable to use external sources of folic acid, cell growth and multiplication slows. Moreover, aminosalicylic acid may inhibit the synthesis of the cell wall component, mycobactin, thus reducing iron uptake by M. tuberculosis (Zheng et al., 2013).

Capreomycin: is an antimicrobial cyclic polypeptide obtained from Streptomyces capreolus, is active against M. tuberculosis, including most MDR-TB. It is not administered as monotherapy but it is used in combination of capreomycin IA and capreomycin IB. Interestingly, capreomycin is listed by the WHO as a reserve drug for the drug-resistant TB patients as it inhibits bacterial protein synthesis by binding to 30S and 50S ribosomal subunits. Capreomycin also involved in the production of abnormal proteins. Therefore, the production of these abnormal proteins is ultimately affects bacterial survival (Igarashi et al., 2018).

Ethambutol: is tuberculostatic, recommended orally. Its resistance develops, although slowly, if it is used alone. Is one of the first-line agents for the management of *Mycobacterium tuberculosis* (Mtb) infections and of other pathogenic mycobacterial species. Its antimicrobial effect is known to be related to point mutations with three membrane-embedded arabinosyltransferases - EmbA, EmbB, and EmbC which is coded for by the embB gene and known to involve in the synthesis of the mycobacterial cell wall which results in increased cell permeability. (DeBarber et al., 2000).

β-lactam/β-lactamase inhibitors: *Mycobacterium tuberculosis* is known to produces β-lactamase (Blac), which splits the β-lactam ring and contributing resistance to β-lactam group of antibiotic. Hence β-lactams are not used in TB treatment. Recent studies suggest that the, using Blac inhibitors with B lactams can help to manage the drug resistance (Yan et al., 2022). Beta lactams interferes with the formation of peptidoglycans, transpeptidases are involved in the cross linking of peptides during cell wall formation, these beta lactam acylates the transpeptidases and thereby inhibits the cell wall formation. Through penicillin binding protein receptors, Beta lactams get their accesses into the cell. Upon binding, the last step of transpeptidation is hampered resulting in the viability loss of bacterial cell and cell lysis (Pandey et al., 2023).

Clofazimine: It belong to other core second line agents, it is riminophenazine dye and is highly lipophilic antimicrobial prescribed with other drugs. The exact mechanism of clofazimine is poorly understood. However, two theories have been proposed to elucidate the mechanism of clofazimine as it is involved in the production of intercellular reactive oxygen species (ROS) because of its lipophilicity through redox cycling especially hydrogen peroxide and superoxide, resulting in antimicrobial effect. In addition, clofazimine is involved to synthesize lysophopholipids by interacting with phospholipids of bacterial cell membrane (Arbiser & Moschella, 1995). The combined effect of clofazimine and lysophopholipids exerts bactericidal activity by destabilizing the bacterial membrane which in turn hinder the K+ uptake and there by ATP production. Clofazimine also meddle with T-lymphocyte activation and proliferation to develop anti-inflammatory activity (Holdiness, 1989).

Bedaquiline: belongs to Group D add on agents specifically D2 category. It also a non-part of the core MDR TB regimen (WHO Report). It is a diarylquinoline bactericidal anti-mycobacterial drug mainly used in adults with other anti-bacterials to treat pulmonary TB. ATP synthase is the enzyme involved in the generation of energy through ATP. Bedaquiline inhibits the ATP synthase of proton pump of Mycobacterium, resulting in the death of bacteria (Mahajan 2013).

Cycloserine: is a part of Group C other core second line TB regimen, it is produced from *Streptomyces garyphalus*, a broad spectrum antibiotic used in the treatment of TB and UTI. It is an oral bacteriostatic agent, known to inhibit the cell wall synthesis. It is an analog of D-alanine amino acid. It interferes with two enzymes involved in the early synthesis of cell wall in the cytoplasm by competitive inhibition. L-alanine racemase and D-alanylalanine synthetase are two enyzymes, which are inhibited by the Cycloserine. L-alanine racemase in involved in the conversion of D-alanine from L-alanine, whereas D-alanylalanine synthetase introduces D-alanine into the pentapeptide required for the construction of bacterial cell wall (Chen et al., 2017).

Kanamycin: is an aminoglycoside antibiotic belongs to Group B second line injectable drugs. It is obtained from the bacterium *Streptomyces kanamyceticus* and is generally used in the sulfate form that is Kanamycin sulfate (Drugbank). Kanamycin firmly attaches to the conserved. A site of 16S rRNA in the 30S ribosomal subunit and resulting in inhibition of protein synthesis (Chan et al., 2003). Kanamycin perpetually clamp precisely to 16S rRNA and 30S – subunit proteins. On the 16S rRNA, Kanamycin distinctly adheres to four nucleotides and on S12 protein a single amino acid. In the 16S rRNA of 30S subunit, it intrudes the decoding site in the proximity of nucleotide 1400. The wiggling base in the anticodon of tRNA tries to hook up with the above region, resulting in the meddling of the initiation complex, misinterpretation of mRNA subsequently erroneous amino acids are introduced into the polypeptide making the peptide either toxic or nonfunctional and non-functional monosomes are formed of the disassemble

of polysomes (Drugbank). When Kanamycin was treated against *M. tuberculosis* infected macrophages, it reduced 12 logs in CFU, suggesting that it scales down the bacterial load but does not have bactericidal activity. The success rate of second line injectable like kanamycin is higher when prescribed in a longer treatment regimen of MDR-TB. In adults with RR-TB or MDR TB, WHO recommends to impose a second line of injectable as a part of their treatment administration plan except for those who are having cross reactivity (Rastogi et al., 1996; Tuberculosis, 2008).

Ethionamide: Ethionamideia a part of thioamides, fits in Group C core regimen, is synthetic isonicotinic acid derivative analogous to isoniazid and it was discovered in 1956. When all the other treatments are failed the choice of anti-tubercular agent is ethionamide (Banerjee et al., 1994). Ethionamide inhibits the synthesis of myolic acid there by acting as bacteriostatic or bactericidal but the bacteriostatic nature depends on the susceptibility of the organism and also on the concentration of drug at the site of infection. Like isoniazid, it impedes with the myolic acid synthesis by going through intracellular modification (enzymatic activation). Isoniazid precisely suppresses InhA, the enoyl reductase by forming adduct bond with the NAD cofactor of Mycobacterium tuberculosis. The INH-NAD adduct forms a slow, tight-binding competitive inhibitor of InhA. Though the efficacy and toxicity of the drug is not well understood, but still the drug is administered to adults and children, as it is rarely life threatening in children (Baulard et al., 2000).

Fluoroquinolones: Fluoroquinolones belongs to group of quinolones. Group a fluoroquinolones like moxifloxacin, gatifloxacin and levofloxacin are generally used as second line anti- TB drugs (Ginsburg et al., 2003). The above three are third generation quinolones and informally called as respiratory quinolones due to their increased activity against gram-positive respiratory pathogens. All three fluoroquinolones are synthetic antibiotics, Moxifloxacin was developed by Bayer AG for oral treatment, Gatifloxacin was introduced by Bristol-Myers Squibb in 1999 and FDA approved Levofloxacin in 1996. The bactericidal action of all three fluoroquinolones is by the inhibition of Topoisomerase II and IV. Topoisomerase II or DNA gyrase found only in bacteria that introduces negative supercoils into DNA during replication, positive super coils produces torsional stress on the chromosomes, which would be relieved by negative supercoils initiated by DNA gyrases, further it is required for the condensation of chromosomes and in the initiation of transcription promotion. DNA gyrases consists of four sub units, two a subunit and two b sub unit, the target for the fluoroquinolones are subunits. Similar kind of mechanism is also seen in topoisomerase IV, it is also involved in unlink the newly replicated chromosomes at the terminal stage of DNA replication and thus helps to complete the cell division. Thus, fluoroquinolones inhibits the topoisomerases through complication resulting in the hindrance of DNA replication thereby hampering the cell division and causing cell death (Miotto et al., 2015).

Linezolid: are an oxazolidinone synthetic antibiotic and a part Group C core regimen. It is also known as monoamine oxidase. Among the oxazolidinone, linezolid was the first to get approval in 2000. It is generally prescribed along with ethionamide. The bactericidal activity of Linezolid is by restricting the bacterial protein translation. 70S functional initiation complex formation is inhibited by adhering the linezolid to bacterial 23S rRNA of the 50S subunit, thus halting the bacterial cell division (Rendon et al., 2016).

Thiacetazone: belongs to Group D add on agents specifically D3 category. It also non-part of the core MDR TB regimen (3). Amithiozone is the generic name of thioacetozone. It was one of the first agents used for the treatment of TB and was extensively used after Second World War in Germany (Peter R Donald and Helen McIlleron 2009). It was synthesized by Behnisch and Schmidt and investigated clinically by Gerhard Domagk and co-workers in Germany in the year 1940 (16). Monooxygenase EthA coded bacteria is required for the activation of the prodrug Thiacetazone. Its mechanism of action is not well understood, but it is thought to inhibit the myolic acid cyclopropane synthesis (Seddon et al., 2012).

Delamanid: Delamanid belongs to Group D add on agents specifically D2 category. It also non-part of the core MDR TB regimen (3). Delamanid is derived from nitro-dihydro-imidazooxazole class of compounds that are known to interfere with mycolic acid synthesis and hence used in multidrug and extensively drug resistant TB, in regimen comprising of other antibiotics. It's developed and marketed by Otsuka Pharmaceutical Co., Ltd (Tokyo, Japan) (Drugbank). The prodrug Delamanid requires bio activation to impart its antibacterial activity against growing and non-growing mycobacteria, through the mycobacterial F420 coenzyme system along with the deazaflavin dependent nitroreductase (Rv3547). After activation, suppression of methoxy mycolic and ketomycolic acid synthesis occurs through the radical intermediate formed between delamanid and desnitro-imidazooxazole derivative, leading to the exhaustion of cell wall components of mycobacteria and finally cell disruption (Szumowski & Lynch 2015).

Conclusion

In conclusion, low concentrations of anti-TB drugs and the short-course treatment strategy may influence the pathogen's drug susceptibility for fighting TB, the WHO has recently provided an important and useful evidence-based new classification of anti-TB drugs. The anti-TB drugs known to cause severe adverse effects new drugs to treat multidrug-resistant tuberculosis are urgently needed with less toxicity. Inclusion of natural compounds may reduce toxicity as all the available validated anti-TB drugs reported to be hepatotoxic, and cause damage to kidney emphasis on biopharmaceuticles to be made in near future to shorten the treatment regimes and lower the risks of antibiotics. Intensive research studies are needed towards End TB strategy to control TB epidemic by developing novel drugs.

Conflict of Interest Statement

None to declare.

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No

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