A REVIEW ON PHARMACOTHERAPY FOR MULTIDRUG RESISTANCE TUBERCULOSIS

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Abstract- **Multidrug-resistant tuberculosis (MDR-TB) is a critical global health challenge characterized by bacterial strains of Mycobacterium tuberculosis that have developed resistance to at least two key first-line anti-TB drugs, isoniazid, and rifampicin. The emergence of MDR-TB is primarily attributed to factors such as inadequate treatment regimens, poor patient adherence, and suboptimal healthcare systems. This form of drug resistance not only complicates treatment efforts but also raises concerns about prolonged therapy, increased healthcare costs, and the potential for treatment failure. In more severe cases, extensively drug-resistant tuberculosis (XDR-TB) arises, indicating resistance to additional classes of second-line drugs. Effective management of MDR-TB requires a comprehensive approach, encompassing timely diagnosis through advanced molecular techniques, development of tailored treatment regimens involving second-line drugs, rigorous infection control measures, and innovative research to uncover new therapeutic options. Collaborative efforts between healthcare institutions, governments, and international organizations are imperative to curb the spread of MDR-TB, prevent its further escalation into XDR-TB, and ensure better patient outcomes. These abstract underscores the urgent need for a multifaceted approach to address the challenges posed by multidrug-resistant tuberculosis on a global scale.**

Key Words: **Multidrug-resistant tuberculosis, first-line anti-TB drugs and second-line drugs.**

1. INTRODUCTION

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis*. Although it mostly affects the lungs, it can also spread to other areas, leading to extrapulmonary TB. Five to fifteen percent of the estimated 1.7 billion M tuberculosis patients will develop TB at some point in their lives; this percentage is higher in immunosuppressed patients[1].Mycobacterium tuberculosis infects one third of the world's population, according to the WHO (World Health Organization). MDR-TB epidemics have occurred frequently in the US and other countries over the past two decades [2]. With the emergence of Extremely Drug Resistant Tuberculosis (XDR-TB), a type of Multi Drug Resistant Tuberculosis in which M. tuberculosis is resistant to both the first line and second line anti TB agents [3], the management of TB is becoming even more difficult. According to the Global TB Report 2016, there were 3.9% newly diagnosed cases and 21% of cases that had already been treated for TB. Only 132,120 (23%) of the predicted 580,000 MDR-TB/RR-TB cases were found, 124,990 (20%) of them began therapy, and only 52% of them were effectively treated. Every year, TB kills 10 million individuals around the world. MDR TB (multidrug-resistant TB) has been identified in 484,000 of them. When the two most potent drugs typically used to treat the disease's TB germs develop resistance to them, multidrug-resistant tuberculosis, or MDR-TB, develops. This indicates that these medications will not function as intended because they are unable to destroy the TB bacterium. Treatment for MDR-TB is more challenging than for typical TB. The medications used to treat it have more adverse effects and must be given for a longer period; as a result, patient contagious for a longer period, may feel ill, and are more likely to require hospitalization.

However, there is a very good possibility of a successful cure if you take all the medication for the entire time [4]. In many countries, MDR-TB is associated with increased mortality, lower cure rates, lengthier yet ineffective treatments, hazardous side effects, high costs, and challenging logistics. The reported rates of treatment success for MDR-TB and XDR-TB are 48–64% and 20–40%, respectively [5].The WHO DR-TB treatment update for 2022 is divided into seven main sections, including treatment regimens for MDR/RR-TB and isoniazid-resistant TB (Hr-TB), monitoring patient response to treatment, when to begin antiretroviral therapy in MDR/RR-TB patients who are HIV-positive, and the use of surgery for MDR/RR-TB patients[6]. Based on an assessment of new data, the 2022 update includes two new recommendations for MDR/RR-TB treatment regimens (i) the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB Patients.

(ii) the use of the 9-month all-oral regimen rather than longer (18-months) regimens in patients with MDR/RR-TB and they are resistance to fluoroquinolones (FQ) has been excluded. In some situations, longer regimens are still a viable alternative.

Currently, MDR-TB treatment takes at least 20 months to complete, during which time adverse drug reactions are carefully monitored. Despite the fact that five high-burden nations (Ethiopia, Kazakhstan, Myanmar, Pakistan, and Vietnam) reported 70% favourable outcome rates, only 48% of MDR-TB patients globally succeeded in receiving treatment in 2011. Out of 1269 XDR-TB patients, only 22% completed their treatments effectively, and 35% passed away. A cohort of 107 patients with XDR-TB who were treated in South Africa had a death rate at 70 months of 78%[7].

The second-line medications (SLDs) needed to treat MDR-TB and XDR-TB are costly and challenging to find. 17 of the 27 nations with a "high burden" of MDR-TB are categorized as "low" or "lower-middle" income nations, where these difficulties are the greatest. MDR-TB patients frequently cluster among difficult-to-reach demographics, even in "high-middle" or "high" income countries. In several regions, the difference between the number of patients diagnosed with MDR-TB and those who started treatment grew from 2012 to 2013. Approximately 60% of identified cases in ten high-burden nations received treatment in 2013; the lowest rates were reported in Tajikistan (30%), Myanmar (34%) and South Africa (41%).

1.1 CLASSIFICATION OF ANTI -TUBERCULOSIS DRUGS

Antitubercular drugs are classified into different types and shown in Table 1.

TABLE: 1 ANTITUBERCULAR DRUGS CLASSIFICATION

First Line Oral Drugs	Injectable Drugs	Fluoroquinolones	Second Line Oral Drugs	Unclear efficacy drugs
Isoniazid **Rifampin** **Pyrazinamide** **Ethambutol**	**Streptomycin** **Kanamycin** **Amikacin** **Capreomycin**	**Ofloxacin** **Levofloxacin** **Moxifloxacin** **Ciprofloxacin**	**Ethionamide** **Prothionamide** **Cycloserine** **Terizidone** **Rifabutin**	**Bedaquiline** **Clarithromycin** **Clofazimine** **Linezolid** **Imipenem**

2. MULTIDRUG RESISTANCE-TB

Multidrug-resistant TB (MDR TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs.

2.1TYPES OF DRUG-RESISTANT TUBERCULOSIS

The type of drug-resistant TB depends on whether the drug is resistant to medications of first-line treatment.

The types of drug resistant are

MONO-RESISTANT: Patients are resistant to only one first-line TB treatment.

POLY-RESISTANT: Resistant to more than one first-line treatment except for rifampin and isoniazid.

MULTIDRUG- RESISTANT: Resistant to more than one type of drugs, especially isoniazid and rifampicin.

2.1.1 MECHANISM OF DRUG RESISTANCE

- **CELLWALL:**

The cell wall of M. tuberculosis [TB] contains complex lipid molecules which act as a barrier to stop drugs from entering the cell.

- **DRUG MODIFYING AND INACTIVATING ENZYMES:**

The TB genome codes for enzymes [proteins] that inactivate drug molecules. These enzymes are usually phosphorylate, acetylate or adenylate drug compounds.

- **DRUG EFFLUX SYSTEMS:**

The TB cell contains molecular systems that actively pump drug molecules out of the cell

- **MUTATIONS:**

Spontaneous mutations in the TB genome can alter proteins which are the target of drugs, making the bacteria drug resistant.

It alsoarises mainly due to:

•**Inadequate treatment:** When TB patients do not complete their full course treatment.

•**Incorrect medication**: Incorrect usage of the medication can lead to the development of mdr-tb. •**Close contact with MDR-TB patients:** close and prolonged contact with the infected persons can increase the risk of transmission

•**Poor treatment**: failure to take medications as prescribed.

3. PRE-TREATMENT EVALUATION

For pre-treatment evaluation and the start of treatment, the patient should be admitted to the hospital (at the DR-TB Centre). The pre-treatment evaluation should include a thorough clinical evaluation. A chest radiograph, a doctor's evaluation, and the relevant haematological and biochemical tests listed below. A thorough pre-treatment assessment is necessary to identify patients who are at an increased risk for side effects because MDR-TB medicines are known to cause them the possibility of such severe consequences. When making an assessment prior to starting treatment, a thorough clinical examination should be done.

Prior to treatment the below information is to be collected.

1. Detailed history (including screening for mental illness, drug/alcohol abuse etc.
2.Weight
3.Height
4.Complete Blood Count
5.Blood sugar to screen for Diabetes Mellitus
6.Liver Function Tests.
7.Blood Urea and S. Creatinine to assess the Kidney function
8.TSH levels to assess the thyroid function
9.Urine examination(Routine & Microscopic)
10. Pregnancy test (for all women in the childbearing age group)
11. Chest X Ray.

If the HIV status is unknown or the HIV test is negative, but the results are older than six months, all MDR-TB cases will be given the option of being sent to the closest centre for HIV counselling and testing. Usually, TSH readings are enough to determine the patient's thyroid function. An ECG, serum electrolytes, and a surgical examination should be added to the pre-treatment evaluation in cases of XDR TB. Patients should receive counselling on

1) the nature and duration of treatment,
2) need for regular treatment,
3) possible side effects of these drugs and
4) the consequences of irregular treatment or pre-mature cessation of treatment.

Since family support is a crucial element in the management, it is advisable to include close family members during the counselling.

Patients should be encouraged to report any negative side effects they may have. Protocol for MDR-TB 6 medications make up this regimen: Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol, and Cycloserine during the 6 to 9 months of the Intensive Phase, and Levofloxacin, Ethionamide, Ethambutol, and Cycloserine for the 18 months of the Continuation Phase.

Special adjustments to the standard Regimen for MDR TB are as follows:

• In case of intolerance to Kanamycin, then Capreomycin (or PAS if injectable agent not feasible) is the available substitute drug.
• In case of intolerance leading to discontinuation of other oral second-line drug, p-amino salicylic acid (PAS) is the available substitute drug.
• Baseline Kanamycin mono - resistance should lead to substitution of Kanamycin with Capreomycin.
• Baseline Ofloxacin mono - resistance should lead to substitution of Levofloxacin with the combination of Moxifloxacin and PAS.
• Baseline Ofloxacin and Kanamycin resistance (i.e., XDR TB) should lead to declaration of outcome, referral to DR-TB Centre for pre-treatment evaluation for Regimen for XDR TB.

A DOT Provider is required to provide all medications under directly observed therapy (DOT) in a single daily dosage. All patients will take medication while being closely monitored on six days of the week. On Sunday, oral drugs will be administered without supervision, while injectable the drug kanamycin will not exist. Ethionamide, cyclosporine, and other drugs may cause intolerance in drug users. Two doses of the morning PAS dosage can be administered under DOT. The evening dose will be consumed independently. The empty blister packs of the self-administered medication the following morning during DOT, a dose check will be performed. Every patient taking the MDR TB medication needs to take pyridoxine.

4. THERAPY FOR MDR-TB

•Drug Susceptibility Testing (DST):A precise DST is essential for determining which medications the TB bacteria are resistant to. •Drug Regimen: Based on DST results, patient history, and available medications, MDR-TB regimens are individually created. Fluoroquinolones, injectable medications (such amikacin), and other second-line medications are often utilized medications.

4.1 LEVOFLOXACIN

A fluoroquinolone antibiotic called levofloxacin is used to treat infections of the upper respiratory tract, skin and skin structures, urinary tract, and prostate as well as to treat inhaled anthrax and plague after exposure.

Mechanism of action

Levofloxacin, like other fluoroquinolone antibiotics, blocks the function of DNA gyrase and topoisomerase IV [8], two essential bacterial enzymes, to exert its antimicrobial effect. Although both targets are type II topoisomerases, they each serve a different purpose inside the bacterial cell. To relieve the torsional strain caused by the introduction of positive supercoils during replication, DNA gyrase, an enzyme that is only found in bacteria, introduces negative supercoils into DNA. These negative supercoils are crucial for chromosome condensation and the promotion of transcription initiation. Two A subunits and two B subunits make up its four subunits, of which fluoroquinolone antibiotics seem to target the A subunits. In addition to aiding in the relaxing of positive supercoils, bacterial topoisomerase IV is crucial at the final steps of DNA replication, which serves to "unlink" freshly copied chromosomes to finish cell division.

Levofloxacin inhibits these enzymes by complexing with the topoisomerase enzymes [9].In the end, DNA replication is blocked, which prevents cell division and causes cell death.

4.2 MOXIFLOXACIN:

An antibiotic called a fluoroquinolone called moxifloxacin is used to treat different bacterial infections.

Mechanism of action: The enzymes topoisomerase II (DNA gyrase) and topoisomerase IV are inhibited by moxifloxacin, which has a bactericidal effect. The replication, transcription, and repair of bacterial DNA all depend on the important enzyme DNA gyrase. An enzyme known as topoisomerase IV is known to be essential for the division of chromosomal DNA during bacterialcell division [10].Fluoroquinolones likelevofloxacin and moxifloxacin mechanism of action wasshown in Fig 1.

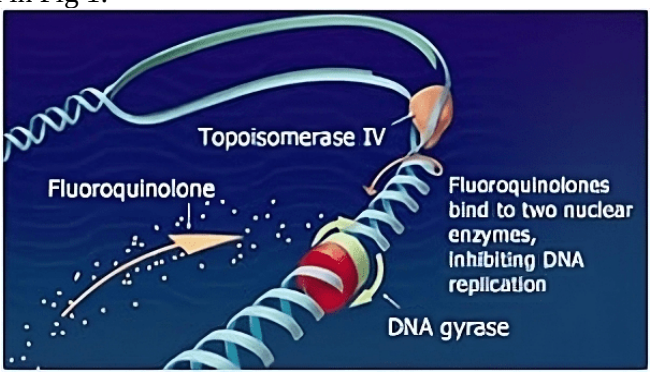

FIGURE: 1 MOXIFLOXACIN MECHANISM OF ACTION

4.3 BEDAQUILINE

A novel class of medications termed diarylquinolines, including bedaquiline (Bdq, formerly known as TMC207), is authorized for use in combination therapy in adult patients (>18 years) with pulmonary multidrug-resistant tuberculosis (MDR-TB). The first new medicine created expressly to treat TB in more than 40 years is bedaquiline.

MECHANISM OF ACTION

Bedaquiline is an oral medication that inhibits mycobacterial adenosine triphosphate synthase using a novel method shown in Fig 2.The most convincing evidence came from a multicenter phase II trial (TMC207-C208), in which a WHO-approved optimised background regimen (OBR) for pulmonary MDR-TB was supplemented with either bedaquiline or placebo for the first 24 weeks [11]. Bedaquiline causes QTc prolongation, is widely distributed in peripheral tissues, and has a terminal half-life of 5.5 months.

SIDE EFFECTS

1. Hepatotoxicity can also be brought on by bedaquiline. Additional hepatotoxic dangers could be posed by hepatotoxic conditions and drugs.

2.Bedaquiline has no known interactions with other anti-TB medications.

3. Bedaquiline is only administered for the first 24 weeks of treatment when it is introduced to a regimen. The Food and Drug Administration (FDA) gave SIRTURO expedited approval. On December 28, 2012, (Bedaquiline) tablets were added to the adult MDR-TB sufferers' second line antitubercular therapy. Since the BDQ works through a new mechanism, it is less likely to develop cross resistance to existing antitubercular medications used to treat MDR-TB. Additionally, the drug's combined long plasma and tissue half-life results in a terminal elimination half-life of around 5.5 months and high tissue penetration

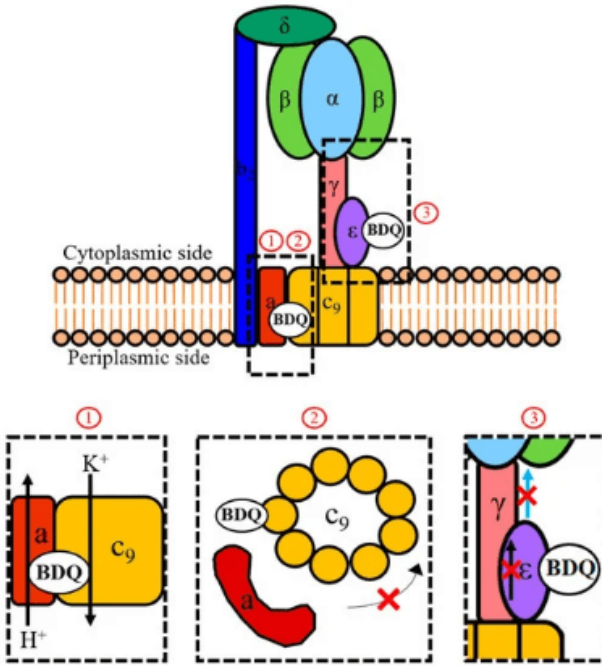

FIGURE: 2 BEDAQUILINE MECHANISM OF ACTION

4.4 LINEZOLID

Linezolid is an oxazolidinone antibiotic used to treat infections by susceptible strains of aerobic Gram-positive bacteria.

When treating multidrug-resistant tuberculosis (MDR-TB), linezolid is a viable alternative. Linezolid is recommended for use in a 6-month BPaLM regimen that includes bedaquiline, pretomanid, linezolid, and moxifloxacin in patients with MDR/RR-TB and those who have additional resistance to fluoroquinolones (pre-XDR-TB), according to the WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment 2022 update. Patients should be closely monitored nevertheless, for the occurrence of serious side effects such neuropathy and myelosuppression.

MECHANISM OF ACTION

Linezolid exerts its antibacterial effects by interfering with bacterial protein translation[12]. It binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is essential for bacterial reproduction, thereby preventing bacteria from dividing [13] as shown in Fig 3.

TABLE : 2 TREATMENT REGIMEN

Condition or disease	Intervention/treatment	Phase
Tuberculosis, Multidrug-ResistantTuberculosis Tuberculosis Pulmonary	Drug: Linezolid 600 mg Drug: Linezolid1200mg[QD] Drug: Linezolid1200mg[TIW] Drug: Bedaquiline 200mg Drug: Bedaquiline 100 mg Drug: Delamanid 300 mg Drug: Clofazimine 300 mg Drug: Clofazimine 100 mg	2

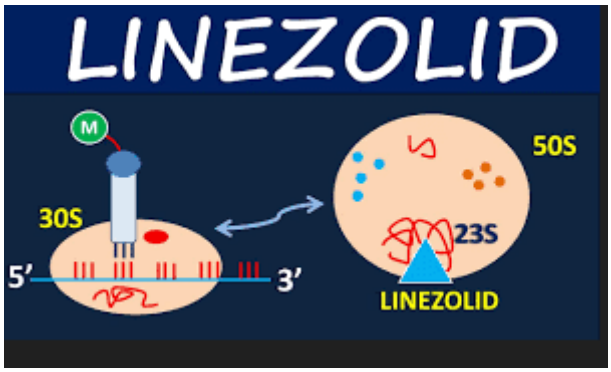

FIGURE: 3 LINEZOLID MECHANISM OF ACTION

4.5ETHAMBUTOL

Mycobacterium tuberculosis drug-resistant (DR) and multidrug-resistant (MDR) strains have emerged as one of the biggest obstacles in the fight against tuberculosis (TB). The bacteriostatic, antimycobacterial medication ethambutol (EMB), an arabinose derivative, has been used to treat tuberculosis (TB). The medication is frequently suggested as part of a four-drug combination that also includes isoniazid (INH), rifampicin (RMP), and pyrazinamide (PZA) during the intensive phase of TB therapy.

MECHANISM OF ACTION

Ethambutol appears to interfere with arabinosyl transferases, which are essential for the biosynthesis of arabinogalactan and lipoarabinomannan, two important structural elements of the mycobacterial cell wall. These enzymes are encoded by the embCAB operon, which is made up of three homologous genes with the names embC, embA, and embB. According to the hypothesized mechanism by which EMB affects M. tuberculosis, after interacting with the EmbCAB proteins, EMB suppresses the production of arabinans, which prevents the development of mycolic acid arabinan receptors and causes cell death[14].

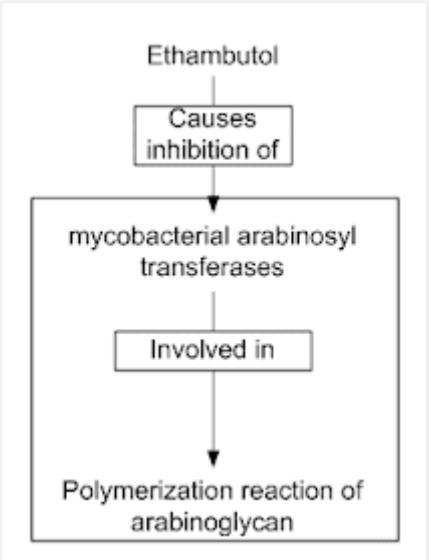

FIGURE: 4 ETHAMBUTOL MECHANISM OF ACTION

4.6 DELAMANID

Antibiotic delamanid is used to treat tuberculosis that is resistant to multipledrugs.Delamanid is a prodrug that must undergo biotransformation to exert its antimycobacterial effects on both mycobacteria that are developing and those that are not [15, 16].This biotransformation involves the mycobacterial F420 coenzyme system, which includes the deazaflavin dependent nitro reductase (Rv3547). Five coenzyme F420 genes—fgd, Rv3547, fbiA, fbiB, and fbiC—have had mutations suggested as the mechanism of delamanid resistance.

MECHANISM OF ACTION

The radical intermediate created when delamanid and desnitro-imidazooxazole derivative[17] react upon activation is thought to mediate antimycobacterial actions by inhibiting methoxy-mycolic and keto-mycolic acid synthesis, resulting in a reduction in the components of mycobacterial cell walls and the mycobacteria's ability to survive [18]. It is believed that nitroimidazooxazole derivatives produce reactive nitrogen species, such as nitrogen oxide (NO). Alpha-mycolic acid is not affected by delamanid, in contrast to isoniazid. Mechanism of action of delamanid resistance was shown in Fig 5.

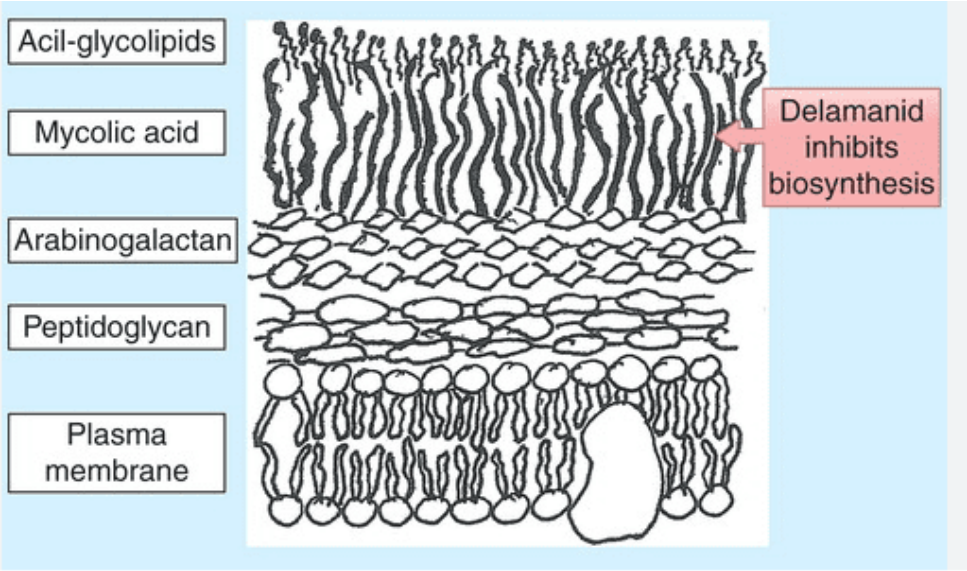

FIGURE: 5 DELAMANID MECHANISM OF ACTION OF RESISTANCE

4.7 PYRAZINAMIDE

A derivative of nicotinamide was initially chemically created in 1936, but its antituberculosis properties were discovered in 1952. Nicotinamides accidental discovery as a TB treatment was based on the observation that it demonstrated specific efficacy against mycobacteria in animal models. PZA, a special anti-tuberculosis medication, is essential to shortening the course of TB treatment. PZA is a crucial medicine for inclusion in any drug combinations for treating drug sensitive and drug-resistant TB because it kills non-replicating persisters that other TB drugs fail to kill MDR-TB.

MECHANISM OF ACTION:

Pyrazinamide diffuses into active *M. tuberculosis* that express pyrazinamidase enzyme that converts pyrazinamide to the active form pyrazinoic acid. Pyrazinoic acid can leak out under acidic conditions to be converted to the protonated conjugate acid, which is readily diffused back into the bacilli and accumulate intracellularly. The net effect is that more pyrazinoic acid accumulates inside the bacillus at acid pH than at neutral pH. Pyrazinoic acid was thought to inhibit the enzyme fatty acid synthase (FAS) I, which is required by the bacterium to synthesise fatty acids. However, this theory was thought to have been discounted[19].However, further studies reproduced the results of FAS I inhibition as the putative mechanism first in whole cell assay of replicating M. tuberculosis bacilli which have shown thatpyrazinoic acid and its ester inhibit the synthesis of fatty acids[20].

TARGETS OF PYRAZINAMIDE

Fatty acid synthase-I (Fas-I) was proposed as the target of PZA in a study utilizing M. smegmatis and 5-Cl-PZA14.Fas-I mutations have not, however, been discovered in M. tuberculosis strains that are resistant to PZA. Fas-I is the target of 5-Cl-PZA;however, it is not the target of a later investigation that revealed this. PZA15.Fas-I, a target of 5-Cl-PZA, and PzaA, a factor in inactivating 5-Cl-PZA, overexpression resulted in 5-Cl-PZA resistance in M. smegmatis. However, M. tuberculosis was hazardous when Fas-I was overexpressed. Because exceptionally high doses of PZA or POA above the physiological amounts were utilized, the findings on Fas-I as a potential target of PZA in cell-free assays or in whole cells are dubious[21].

MECHANISM OF PYRAZINAMIDE RESISTANCE

Although McDermott's group demonstrated in 1967 that PZA resistance in M. tuberculosis was associated with the loss of nicotinamidase and pyrazinamides, the mechanism of PZA resistance was unknown until 1996, when it was shown that mutation in the pncA gene encoding nicotinamidase and pyrazinamidase causes PZA resistance[22]. Mechanism of action was shown in Fig 6.

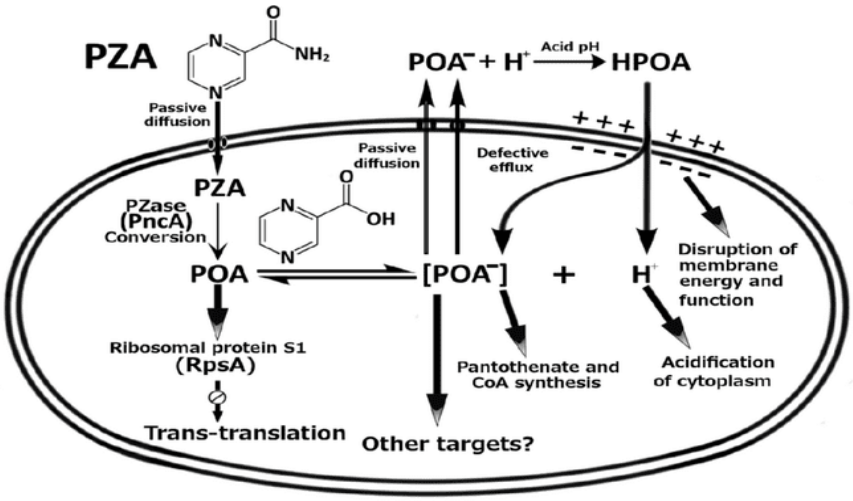

FIGURE: 6 PYRAZINAMIDE MECHANISM OF ACTION

5. REGIMEN FOR MDR TB DOSAGE:

Different drugs for MDR-TB are to be given in different dose for different age groups and it is given in Table 3 and 4.

TABLE: 3 REGIMEN FOR MDR TB DOSAGE AND WEIGHT BAND RECOMMENDATION

S.No	DRUGS	16-25Kg	26-45Kg	46-70Kg
1	Kanamycin	500 mg	500 mg	750 mg
2	Levofloxacin	250 mg	750 mg	1000 mg
3	Ethionamide	375 mg	500 mg	750 mg
4	Ethambutol	400 mg	800 mg	1200 mg
5	Pyrazinamide	500 mg	1250 mg	1500 mg
6	Cycloserine	250 mg	500 mg	750 mg
7	Pyridoxine	50 mg	100mg	100mg
8	Na-PAS (80% w/v)	5 gm	10 gm	12 gm
9	Moxifloxacin	200 mg	400 mg	400 mg
10	Capreomycin	500 mg	750 mg	1000 mg

TABLE: 4 DOSAGE OF REGIMEN FOR MDR TB FOR PADIATRIC AGE GROUP <16 Kg

Drugs	Daily Dose–mg/kg body weight
Kanamycin/ Capreomycin	15-20
Levofloxacin / Moxifloxacin	7.5-10
Ethionamide	15-20
Cycloserine	15-20

5.1 BENEFITS OF USING MULTIPLE DRUGS IN MDR TB

•**Enhancing Efficacy**: Some of the most potent first-line drugs are no longer effective against MDR-TB germs. Utilizing a variety of medications with various modes of action increases the likelihood of getting rid of the infection because each medication targets the germs in a little different way.

•**Relapse Prevention**: The process of treating MDR-TB is time-consuming and challenging. It is possible to ensure that all pathogens are eliminated and that no drug-resistant strains are left behind, which could result in a relapse after treatment is complete by using a combination of medications for a prolonged length of time.

•**Reducing Treatment Length**: Using various drugs can frequently shorten the course of treatment. The course of treatment can be optimized to reduce the chance of relapse and shorten the overall treatment period, which can be crucial for patient adherence and lowering side effects by using a combination of drugs that are efficient against MDR-TB.

•**Reducing adverse Effects**: Some TB drugs may cause severe adverse effects. The overall risk of adverse effects is reduced while the effectiveness of the treatment is maintained by using multiple drugs at lower doses of each medication.

•**Individualized Treatment**: Depending on the patient's TB strain's unique drug susceptibility profile, the drugs utilized and the length of treatment for MDR-TB may differ. Treatment can be personalized for each patient by utilizing a variety of drugs.

6. CONCLUSION

Multidrug-resistant tuberculosis treatment is time-consuming and challenging as well as it involves pre-treatment evaluation by thorough clinical evaluation. There is a need of adjustments to the standard Regimen in case of intolerance to other drugs like Kanamycin and dose variation also to be done depending on age group.These all ultimately give benefits like enhancing efficacy, reduces treatment length and adverse effects by the personalised treatment.

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