(REVIEW ARTICLE)

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MDR TB current treatments: A literature review

Satrio Pinayungan [1, *] and Nurul Wiqoyah [2]

[1] Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2] Department of Microbiology, Faculty of Medicine. Universitas Airlangga, Surabaya, Indonesia.

Abstract

The number of MDR TB cases continues to increase. Various new drugs are being developed to provide effective therapy in handling TB. In-depth understanding is required by clinicians to monitor the progress of therapy for MDR TB. This article aims to explain the pathophysiology of resistance in TB and the pharmacological aspects of the latest antituberculosis drugs in MDR TB.

Keywords: MDR TB; Drugs; Tuberculosis

1. Introduction

Currently, the sustained spread of MDR-TB is one of the most urgent and challenging issues faced by global TB control. MDR-TB is an infection caused by *Mycobacterium tuberculosis* strains that are resistant to isoniazid and rifampicin, making it incurable with first-line [1]. In 2022, there was an addition of 21,900 treated MDR-TB cases in Indonesia out of a total of 67,200 treated MDR-TB cases. This figure indicates an increase compared to the number of MDR-TB cases treated in 2021, which was 20,500. With the rising number of MDR-TB cases, the success of MDR-TB therapy has declined from 74% in 2011 to 49% in 2018 [2] [3].

Until 2016, the therapy for MDR-TB was based on injectable drugs combined with fluoroquinolones such as moxifloxacin, levofloxacin, or gatifloxacin, lasting for 18-20 months or even longer. In 2016, for the first time, a 9-month MDR-TB therapy was recommended by the World Health Organization (WHO) [4].

WHO recommends a 6-month therapy regimen (BpaLM) for MDR/RR-TB. The therapy regimen consists of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin. This therapy regimen is preferred over the 9-month or longer therapies (18 months). Another new recommendation is the use of an all-oral regimen for 9 months, with specific criteria [5].

This literature review aims to provide a simple explanation of the pathophysiology of resistance in *Mycobacterium tuberculosis* and the pharmacological aspects of the drugs used in the therapy of MDR-TB. This explanation serves as a foundational understanding for doctors to comprehend the topic.

2. Discussion

Broadly, resistance of *Mycobacterium tuberculosis* to antibiotics can be divided into two types: intrinsic natural resistance and acquired resistance. Intrinsic resistance in TB, for example, occurs when *Mycobacterium tuberculosis* shows resistance to macrolide antibiotics due to the expression of erm37 protein, a regulatory protein on 32-Srrna

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* Corresponding author: Satrio Pinayungan.

through methylation. This results in decreased permeability of the cell wall of *Mycobacterium tuberculosis* to macrolide antibiotics. Another example is resistance of *Mycobacterium tuberculosis* against hydrophilic antimycobacterial agents, which happens through the activity of MspA, a gene factor associated with porin on the cell wall of *Mycobacterium tuberculosis* that can reduce the permeability of the cell wall. A transcriptional autoregulator activator, WhiB7, is also associated with intrinsic resistance of *Mycobacterium tuberculosis* through the modification of multiple drug transporters that perform efflux mechanisms against tetracycline [6]. Another mechanism of resistance is acquired resistance. The majority of acquired resistance mechanisms occur through horizontal transfer of genetic material such as plasmids and transposons. Acquired resistance in *Mycobacterium tuberculosis* can also occur through chromosomal mutations under selection pressure from antimycobacterial agents. Mutations in the S315T gene of catalase peroxidase 9 (katG) are the most common mutations in isoniazid resistance. Mutations in this gene make katG less able to convert isoniazid into iso-nicotinic acid, a precursor for the formation of INH-NAD that can disrupt mycolic acid formation. Mutations in the promoter region of enolacyl carrier protein reductase (inhA) are also often associated with the emergence of isoniazid resistance. Meanwhile, resistance to rifampicin is often caused by mutations in the S531L gene. The cell wall of *Mycobacterium tuberculosis* is composed of three main interconnected macromolecules: peptidoglycan, arabinogalactan, and mycolic acid. These three components are the main targets in the development of antimycobacterial drugs. Drugs such as isoniazid and ethambutol target mycolic acid as their working site. Resistance to ethambutol is developed through mutations in decaprenyl-phosphoryl-5-phosphoribose (DPPR) synthase) [6].

Mycobacterium tuberculosis is a bacterium that requires a long time to grow in culture media. Diagnostic methods for resistance using phenotyping analysis, such as Colorimetric assays, require a shorter time but still cannot be used specifically for resistance to new first-line anti-tuberculosis drugs. Methods currently under development include molecular analysis methods, including Xpert® MTB/RIF, Ultra, MTB-XDR, BDMax, Line probe assay (LPA), and Loop-mediated isothermal amplification (LAMP) [7]. These methods have their respective advantages and disadvantages, including aspects of time, cost, operator, sensitivity (depending on the sample type), and types of drug resistance mutations. The latest molecular test developed is GenoScreen's Deeplex® Myc-TB, which can evaluate bacterial resistance to 15 types of drugs, including bedaquiline, clofazimine, and linezolid in less than 48 hours [8].

The targeted isothermal amplification method was introduced by Gliddon et al. in 2021. This method utilizes recombinase polymerase amplification at a temperature of 37 °C for 90 minutes on three regions of the *Mycobacterium tuberculosis* genome (rpoB, the main region responsible for rifampicin resistance, and katG and inhA, two main regions responsible for isoniazid resistance). It is followed by nanopore sequencing using a specific device. This method takes less than 3 hours and costs less than 100 USD. It can be considered as an alternative option for low-cost and rapid antibiotic sensitivity testing (isoniazid and rifampicin) [9].

2.1. Six months therapy

The 6-month therapy regimen for MDR-TB includes bedaquiline, pretomanid, linezolid (600 mg once daily for up to 26 weeks), and moxifloxacin (BPaLM). The World Health Organization (WHO) recommends this therapy regimen with a conditional recommendation status and low-level evidence. This recommendation is applied to MDR/RR TB and MDR-TB with resistance to fluoroquinolones (PRE-XDR TB), pulmonary and extrapulmonary TB except for TB of the central nervous system (CNS), osteoarticular TB, and miliary TB, for patients aged above 14 years, and with no resistance to the four drugs used (sensitivity testing is conducted on patients who have been exposed to these drugs for more than 1 month). This regimen is not recommended for pregnant and breastfeeding women due to pretomanid; if fluoroquinolone resistance is found, moxifloxacin is eliminated [5].

Based on the TB PRACTECAL study, clinical trials were conducted on the BPaL, BPaLM, and BPaLC regimens, which include clofazimine. The study showed that the BPaLM therapy regimen had the highest success rate with the lowest side effects and a low rate of drug resistance. If resistance is found to the 6-month regimen, it can be replaced with a 9-month therapy or longer individualized therapy. There is insufficient evidence to support the use of this therapy regimen in cases of CNS TB, miliary TB, TB in individuals under 14 years of age, and in cases of TB in pregnant and breastfeeding women due to limited safety data for pretomanid. The use of clofazimine is not recommended due to increased pill burden and side effects such as skin discoloration [10].

2.2. Nine months all oral bedaquiline containing regiments therapy

The therapy regimen is administered when the 6-month regimen cannot be given. The intensive phase therapy consists of the following drugs: bedaquiline in combination with a fluoroquinolone (moxifloxacin or levofloxacin), ethionamide (linezolid at a dose of 600 mg per day or another type of ethionamide), ethambutol, pyrazinamide, high-dose isoniazid, and clofazimine. The continuation phase therapy includes fluoroquinolones, clofazimine, ethambutol, and pyrazinamide. The intensive phase is given for 4 months, except for bedaquiline, which is given for 6 months, and

linezolid, which is given for a maximum of 2 months, with the condition that if bacteriological conversion does not occur at the end of therapy, the intensive phase therapy can be extended up to 6 months. The continuation phase therapy is carried out for 5 months. The 9-month therapy regimen is still more recommended compared to long-term therapy in cases where the 6-month therapy cannot be conducted except in the case of line treatment (including BDQ), except in cases of extensive pulmonary disease, severe extrapulmonary, CNS, military, and osteoarticular TB [11].

This therapy regimen is recommended for the pediatric population under 14 years of age and pregnant or breastfeeding women compared to the BPaLM regimen due to limited safety data for the use of pretomanid in these populations. In the population of pregnant and breastfeeding women, the 9-month therapy regimen containing linezolid is contraindicated for the use of other types of ethionamide. In the selection of fluoroquinolones, levofloxacin is more recommended compared to moxifloxacin due to its lower potential for cardiotoxicity [10].

The regimen is recommended by the WHO with low-level evidence and a conditional recommendation. It is specified that patients should not have extensive pulmonary disease (defined as bilateral cavitary or extensive parenchymal damage visible on chest X-ray) and severe extrapulmonary disease (defined as TB miliary or TB CNS, and in the population under 15 years of age, defined as all cases of extrapulmonary TB except lymphadenopathy). The regimen is also recommended for patients without bacteriological confirmation showing MDR-TB but based on clinical manifestations and contact history indicating MDR-TB [5].

2.3. Longer regimens for MDR/RR TB

The choice of this regimen has not changed since the WHO recommendation in 2020. This regimen is recommended for cases of MDR/RR-TB that cannot be treated with the other two options. It should be specifically based on the results of antibiotic sensitivity tests and the patient's clinical history. The therapy is divided into two phases: the intensive phase and the continuation phase. The intensive phase uses at least 4 effective drugs (3 from group A and 1 from group B), while the continuation phase uses 3 drugs [5]. If drugs from group A or group B cannot be used, they can be replaced with drugs from group C. If group C drugs are included in the therapy regimen, a regimen with more than 4 types of drugs may be given [12]. To reduce the side effects of therapy, the therapy should be given with the lowest possible number of drugs and doses [12].

Bedaquiline is given to all patient groups, including those under 6 years of age and pregnant women [5]. The GDG does not recommend the use of delamanid and bedaquilline due to insufficient evidence on the safety of therapy related to the prolongation of Qtc. However, based on recent data published by the DELIBERATE trial, it is shown that the prolongation of Qtc with the administration of these two drugs is only additive, so they may still be combined [13]. The above therapy regimens can be given with a treatment duration of 18-20 months and can be adjusted based on treatment response [10].

All three therapy regimens (6 months, 9 months, and longer treatments) can be given in cases of TB-HIV coinfection with careful evaluation of drug interactions and CD4+ count < 100 mm^3 [10].

Table 1 Summary of MDR/RR TB drugs

WHO classes	Name	Class of Compound	Effect	Mechanisms of action	Interactions	Adverse effects monitoring
A	Bedaquiline	Diarylquinolone	Bactericidal	Inhibit ATP synthetase and bacterial respiration	Interact with CYP3A4 Inhibitors	Basal ECG within 2 weeks and monthly ECG.
A	Linezolide	Oxazolanidione	Bacteriostatic possibly	Inhibit protein synthesis	Avoid coadministration with phetydine, tramadol, methadon and phentanyl

Interact with drugs that increase serotonin levels | Aware of peripheral neuropathy

CBC every 2-4 weeks to detect myelosuppresion effects |
| A | Levofloxacine | Flouroquinolone | Bactericidal | Promotes breakage of DNA strands | Interact with caffeine and drugs that prolonged QTc

May cause seizure | Long QTc
Check possible tendinitis effect
Aware in aortic aneurysms case |
| A | Moxifloxacine | Fluroquinolone | Bactericidal | Binding and blocking of DNA topoisomerases 2 and 4 play a role in the replication, translation, repair, and recombination of bacterial DNA. | Reduced efficacy if given with rifampicin

Absorption reduced with antacide | Same with levoflocaxine |
| B | Clofazemine | Riminophenazine | Bactericidal | Binding with NADH 2 dehydrogenase and disrupting the electron transport chain respiratory of bacteria. | - | Long QTc effect if given with potential cardiotoxicity drugs
Reversible skin discolouritation is frequent but do not imply treatment |
| B | Cycloserine/ Terezidone | Isoxazoline | Bacteriostatic | Inhibiting the enzyme that synthesizes peptidoglycan in the bacterial cell wall. | May induce seizures when administered with proepileptogenic drugs. | Close monitoring in neuropsychiatric drugs |

	(Terezidone is a structural analog of cyclocerine)					
C	Delamanide	Nitroimidazole	Bactericidal	Inhibits respiration and inhibit syntesis of cell wall	-	Long QTc
C	Amikacin	Aminoglycosides.	Baktericidal	Binds to the 30S ribosomal subunit, thereby capable of inhibiting protein synthesis.	May cause ototoxicity when administered with loop diuretics, and nephrotoxicity when given in conjunction with amphotericin and cidofovir.	Cek audiometry dan renal function
C	Ethionamide/ proteonamide	Thioamide	Bacteriostatic	The pharmacodynamic data for thioamide class of drugs are still limited	-	Monitoring thyroid function in at-risk patients. Monitoring electrolyte and kidney function in patients with severe GI symptoms
Others	Kanamicyn	Aminoglycosides.	Baktericidal	Inhibit protein synthesis	Similar to amikacin	Similar to amikacin
Others	Capreomycin	Aminoglycosides.	Baktericidal	Inhibit protein synthesis	Similar to amikacin. Additionally, interacts by enhancing the neuromuscular blockade effects of non-depolarizing muscle relaxants	Similar to amikacin
Others	Pretomanide	Nitroimidazole	Baktericidal	Inhibits the synthesis of the bacterial cell wall and respiration	Rifampicin and efavirenz reduce the levels of pretomanid	Long QTc
Others	Tedizolide	oxazolidinone	Bakteriostatic	Inhibits protein synthesis in bacteria by targeting the 23S ribosomal RNA on the 50S ribosomal subunit	The concurrent use of this drug with medications that increase serotonin levels may lead to serotonin syndrome	Similar to linezolid

3. Conclusion

The treatment of drug-resistant tuberculosis (TB) is a serious challenge in the global healthcare arena. A profound understanding of drug resistance and the development of effective therapies are crucial to addressing this issue. Ongoing research is being conducted to discover new drugs, both through testing natural and synthetic substances, to enhance the available therapeutic options. Furthermore, the development of rapid and accurate diagnostic methods is crucial in managing drug-resistant TB. Timely diagnosis allows for more effective therapy and can aid in controlling the spread of the disease.

Collaborative efforts from the scientific community, healthcare institutions, and governments are highly necessary to address this challenge comprehensively. Public awareness regarding the importance of prevention, early diagnosis, and adherence to treatment is also an integral part of global efforts to control drug-resistant TB.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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