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REVIEW: ADVERSE DRUG REACTIONS AND PHARMACOKINETIC CHARACTERISTICS OF LINEZOLID AS A THERAPY FOR DRUG RESISTANT TUBERCULOSIS

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ABSTRACT

Introduction: Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that remains a global health challenge. One of the main problems in TB treatment is the emergence of drug resistance, such as in multidrug-resistant tuberculosis (MDR-TB). Linezolid is a class of oxazolidinones used as second-line therapy in the treatment of drug-resistant TB. However, its use is not free from serious adverse drug reactions such as peripheral neuropathy, myelosuppression, and lactic acidosis. Therefore, understanding the pharmacokinetic profile and adverse drug reactions of linezolid is important to increase the effectiveness of therapy and minimize the risk of toxicity. Objective: This study aimed to evaluate the adverse drug reactions caused by linezolid and analyze its pharmacokinetic characteristics in the treatment of drug-resistant tuberculosis (TB). Methods: This article is a literature review that collects data from national and international scientific sources over the past 10 years (2015-2025), including the addition of comparative studies or meta-analyses, as well as inclusion criteria, such as articles that discuss the pharmacokinetics, adverse drug reactions, and use of linezolid in drug-resistant tuberculosis therapy, either in clinical trials, observational studies, or relevant therapeutic guidelines. Results: Based on the results of various studies, linezolid has an oral bioavailability approaching 100%, which allows oral and intravenous administration with almost equivalent doses. Its pharmacokinetic profile shows an elimination half-life of approximately 5-7 hours, with primary metabolism via nonenzymatic oxidation in the liver and excretion in the urine as inactive metabolites. These characteristics make linezolid a flexible option for drug-resistant tuberculosis therapy. Conclusion: Linezolid is effective in the treatment of drug-resistant TB, either alone or in combination. However, side effects, such as thrombocytopenia, neuropathy, and lactic acidosis, require close monitoring to ensure safe and effective therapy.

Keywords: Linezolid, Drug-Resistant Tuberculosis, Adverse drug reactions, Pharmacokinetics

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* that remains a major global health problem. This disease not only affects the lungs but can also spread to various other organs, such as bones, kidneys, and the central nervous system. In many developing countries, the high incidence of TB is exacerbated by socioeconomic conditions, poverty, and limited access to adequate healthcare facilities (Natarajan et al., 2020).

Along with the increasing burden, the problem of drug resistance has also emerged, resulting in the development of *Multidrug-Resistant Tuberculosis* (MDR-TB) and *Extensively Drug-Resistant Tuberculosis* (XDR-TB). Cases of drug-resistant TB require

more complex therapeutic regimens, with longer treatment durations, and the use of more aggressive drug combinations. Drug resistance not only hinders the effectiveness of therapy, but also increases morbidity and mortality among patients with TB (Seung et al., 2015).

Linezolid has emerged as a promising second-line drug for overcoming drug resistance. The drug is an antibiotic from the oxazolidinone group that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. This mechanism prevents the formation of the 70S initiation complex, which is important in the protein translation process, thereby inhibiting the growth and reproduction of *Mycobacterium tuberculosis*. The uniqueness of this mechanism of action makes linezolid effective against TB strains resistant to first-line drugs (Singh et al., 2017).

Although the effectiveness of this drug in treating resistant strains has been proven through various clinical studies, its use is not free from challenges in the form of significant adverse drug reactions. The most frequently reported adverse drug reactions include myelosuppression, which can cause anemia, thrombocytopenia, and peripheral neuropathy, all of which have the potential to cause irreversible nerve damage. In addition, lactic acidosis, which results from mitochondrial metabolic disorders, is a serious concern, especially for long-term use. This condition requires close monitoring to prevent complications that can interfere with therapy continuity (Tornheim et al., 2020).

The pharmacokinetic characteristics of a drug are also important aspects that support its effectiveness. With almost 100% oral bioavailability, linezolid can be administered in tablet or infusion forms with equivalent results, providing flexibility in adjusting treatment according to patient conditions. After administration, the drug reaches peak plasma concentrations within 1–2 hours, and is well distributed in the lung tissue, alveolar fluid, and central nervous system. Drug metabolism occurs through non-enzymatic oxidation in the liver and elimination through urine in the form of inactive metabolites, which together support a twice-daily dosing strategy (Y. Liu et al., 2024).

This article discusses adverse drug reactions and pharmacokinetic characteristics of the drug in the treatment of resistant strains. This review aims to provide an in-depth understanding of the mechanism of action of the drug, as well as management strategies to optimize its use to increase the effectiveness of MDR-TB and XDR-TB treatment while reducing the risk of toxicity. With proper monitoring and careful dose adjustment, the use of linezolid is expected to make a significant contribution to global efforts to combat drug-resistant TB.

RESEARCH METHOD

The search strategy was developed based on the need to comprehensively understand the pharmacokinetic characteristics and adverse drug reactions of linezolid in the treatment of drug-resistant tuberculosis. This review uses a systematic literature approach by considering scientific publications relevant to the topic from 2015 to 2025. Reference sources were obtained from three main databases, namely Elsevier (6 articles), PubMed (4 articles), and Google Scholar (28 articles), with a total of 38 articles used. The search was conducted using a combination of keywords such as *"pharmacokinetics of Linezolid in drug-resistant TB," "adverse drug reactions of Linezolid in MDR-TB and XDR-TB," "Linezolid toxicity mitigation strategies," "Linezolid dose adjustment," and "Linezolid drug interactions with other TB therapies."* This combination of keywords was chosen to cover the aspects of pharmacokinetics, safety, and optimization strategies for linezolid therapy.

The inclusion criteria for this study were articles published between 2015 and 2025, written in Indonesian or English, and explicitly discussing the use of linezolid in the treatment of MDR/XDR-TB, including clinical studies, pharmacokinetic studies, retrospective studies, and systematic reviews. Meanwhile, articles that were not available in full-text form, did not specifically discuss linezolid, were not relevant to the context of drug-resistant TB, or were only editorial opinions were excluded from the analysis. These criteria were set to ensure data quality and relevance. After selection based on inclusion and exclusion criteria, data from the selected articles were extracted manually and systematically.

The collected information included linezolid pharmacokinetic parameters (such as bioavailability, half-life, metabolism, and excretion), side effect profiles, and reported toxicity mitigation strategies. The data obtained were then analyzed narratively to draw valid conclusions regarding the effectiveness and safety of linezolid as a line of therapy for drug-resistant TB.

RESULTS AND DISCUSSION

Definition of Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, which affects the lungs and other organs (Natarajan et al., 2020). Drug-resistant TB is a form of TB that does not respond to standard therapy with first-line anti-TB drugs such as isoniazid and rifampin. Drug-resistant TB is divided into Multidrug-Resistant Tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB), which require prolonged treatment with complex drug regimens (Seung et al., 2015; Singh et al., 2017).

Etiology of Tuberculosis

The etiology of tuberculosis involves several important causal factors, including internal and external factors. Drug-resistant TB is caused by several factors that can be categorized into internal and external factors (Liu et al., 2021; Xi et al., 2022). External factors include the use of anti-TB drugs that are not in accordance with the dosage or are irregular, lack of treatment supervision in health facilities, and exposure to drug-resistant TB patients, which increase the risk of transmission of resistant strains (Q. Liu et al., 2021) .

Pathophysiology of Tuberculosis

Drug-resistant tuberculosis occurs because of mutations in *Mycobacterium tuberculosis*, which makes it resistant to the bactericidal effects of first-line drugs. These mutations change the target enzyme or protein that the antibiotic targets, thereby inhibiting the mechanism of action of the drug (Liebenberg et al., 2022). For example, resistance to rifampicin is caused by mutations in the rpoB gene, which alter the structure of bacterial RNA polymerase (Kumar et al., 2024). Drug-resistant TB also causes a more aggressive inflammatory reaction in the lungs, increasing tissue damage and worsening the patient's condition. This results in higher morbidity and the possibility of more serious complications than in drug-sensitive TB (Seung et al., 2015).

Use of Other Active Ingredients in Drug-Resistant Tuberculosis Therapy

In addition to linezolid, other drugs used to treat drug-resistant tuberculosis include Bedaquiline, Delamanid, Pretomanid, Levofloxacin, Moxifloxacin, Clofazimine and Amikacin. These drugs are usually used in combination to increase the effectiveness of therapy and reduce the risk of further resistance (Johnson et al., 2024).

Table I. Active Ingredients And Dosage Forms Available On The Market (Johnson et al., 2024; Martínez-Campreciós et al., 2024)

Active Ingredients	Preparation
Linezolid	Tablets, Injections
Bedaquiline	Tablets
Delamanid	Tablets
Pretomanid	Tablets
Levofloxacin	Tablets, Injections
Moxifloxacin	Tablets, Injections
Clofazimine	Capsule
Amikacin	Injections

1. Linezolid

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, thus making it effective against *Mycobacterium tuberculosis*. One of the main advantages of linezolid is its almost 100% oral bioavailability, which allows its administration in tablet or injection form, without the need for dose adjustment. Linezolid also has excellent lung tissue penetration, allowing it to reach the site of infection optimally (Foti et al., 2021).

2. Bedaquiline

Bedaquiline is a new antibiotic that inhibits bacterial ATP synthase, thereby disrupting energy production in *Mycobacterium tuberculosis* and causing bacterial death. Bedaquiline's main advantage is its effectiveness against MDR-TB and XDR-TB, especially in cases that do not respond to other second-line drugs. Bedaquiline also has a long half-life, allowing less frequent dosing, thereby improving patient compliance (Zhu et al., 2023).

However, Bedaquiline has significant drawbacks related to cardiovascular adverse drug reactions, especially prolongation of the QTc interval on electrocardiogram (ECG), which can increase the risk of fatal arrhythmias. In addition, bedaquiline needs to be combined with other drugs because if used as monotherapy, the risk of resistance increases. Other adverse drug reactions include liver disorders (hepatotoxicity) and nausea; therefore, their use requires careful monitoring (Primadana et al., 2022).

3. Delamanid

Delamanid works by inhibiting the synthesis of mycolic acid, an important component of the cell wall of *Mycobacterium tuberculosis*. The main advantages of delamanid are its effectiveness in killing resistant bacteria and its ability to increase negative sputum conversion in patients with MDR-TB. Delamanid also has lower toxicity than many other second-line drugs (Lewis & Sloan, 2015).

However, Delamanid also has disadvantages, particularly the risk of QTc prolongation similar to that of bedaquiline; therefore, close ECG monitoring is required. In addition, delamanid does not have much long-term data on its safety compared to other drugs, such as linezolid or fluoroquinolones; therefore, its use still requires more research (Hewison et al., 2022).

4. Pretomanid

Pretomanid is a new drug in MDR-TB and XDR-TB therapy that works by inhibiting bacterial cell wall synthesis and producing oxidative stress in bacterial cells. Pretomanid is very effective when used in combination with Bedaquiline and Linezolid (BPaL regimen), and has shown a high success rate in the treatment of drug-resistant TB (Conradie et al., 2020).

However, Pretomanid causes adverse drug reactions, such as liver disorders, peripheral neuropathy, and nausea, which can be exacerbated when combined with linezolid. In addition, this drug does not have sufficient long-term data on its effectiveness and safety compared with other TB regimens (Conradie et al., 2020).

5. Levofloxacin

Levofloxacin is a fluoroquinolone antibiotic that inhibits DNA gyrase, which is important for bacterial replication. Levofloxacin shows good lung tissue penetration and is often used in MDR-TB regimens. Its main advantage is its effectiveness in killing *Mycobacterium tuberculosis* with relatively lower adverse drug reactions than other second-line drugs (Sarathy et al., 2019).

However, resistance to fluoroquinolones is increasing, particularly in patients who have previously received TB treatment. The main adverse drug reactions to levofloxacin are tendon disorders (tendinitis and tendon rupture), gastrointestinal disorders, and neurotoxic

effects such as dizziness and insomnia. Therefore, its use must be adjusted according to the patient's resistance profile and monitored properly (Rusu et al., 2023).

6. Moxifloxacin

Moxifloxacin has a mechanism of action similar to that of levofloxacin, which inhibits the enzymes DNA gyrase and topoisomerase IV, which are important in bacterial replication. Moxifloxacin has better tissue penetration than levofloxacin and is often used in MDR-TB regimens, especially if resistance to levofloxacin is observed (Geremia et al., 2024).

However, Moxifloxacin has a higher risk of prolonging the QTc interval; therefore, its use should be closely monitored, especially when combined with Bedaquiline or Delamanid, which have similar adverse drug reactions. In addition, like levofloxacin, moxifloxacin resistance is increasing, which may limit its effectiveness in the treatment of drug-resistant TB (Kusmiati et al., 2022).

7. Clofazimine

Clofazimine was originally developed for the treatment of leprosy, but it is also effective against drug-resistant TB. It disrupts the function of bacterial membranes and produces free radicals that kill the bacteria. The advantage of clofazimine is that its anti-inflammatory properties can reduce lung inflammation caused by TB (Stadler et al., 2023).

However, Clofazimine disturbs adverse drug reactions, especially darkening of the skin color (hyperpigmentation), digestive disorders, and hepatotoxicity. These adverse drug reactions often make patients reluctant to continue long-term treatment (Stadler et al., 2023).

8. Amikacin

Amikacin is an aminoglycoside antibiotic that inhibits protein synthesis by binding to its 30S ribosomal subunit. Amikacin is highly effective against MDR-TB, especially in cases that do not respond to other drugs (Ramirez & Tolmasky, 2017).

However, Amikacin has major drawbacks related to kidney toxicity (nephrotoxicity) and permanent hearing loss (ototoxicity), which are often reasons for discontinuing therapy. In addition, Amikacin is only available in an injectable form, making it less convenient for patients and increasing the risk of systemic adverse reactions (Rivetti et al., 2023).

Table II. Comparison of Mechanism of Action, Adverse Drug Reactions, and Drug Disadvantages in Drug-Resistant Tuberculosis Therapy

Drug	Working Mechanism	Adverse drug reactions	Lack	Reference
Linezolid	Inhibits protein synthesis by binding to the 50S ribosomal subunit.	Myelosuppression (thrombocytopenia, anemia), peripheral neuropathy, lactic acidosis	Risk of hematological and neurological adverse drug reactions with long-term use	(Foti et al., 2021)
Bedaquiline	Inhibits bacterial ATP synthase, disrupting cellular energy production.	QTc prolongation, hepatotoxicity, joint pain, nausea	Risk of fatal arrhythmias, requiring close ECG monitoring	(Zhu et al., 2023)
Delamanid	Inhibits the synthesis of mycolic acids in bacterial cell walls.	QTc prolongation, nausea, vomiting, insomnia	Long-term effectiveness has not been widely studied, risk of	(Lewis and Sloan, 2015)

			heart effects	
Pretomanid	Inhibits cell wall synthesis and causes oxidative stress	Peripheral neuropathy, hepatotoxicity, nausea, diarrhea	Still limited in use, needs combination with other drugs	(Conradie et al., 2020)
Levofloxacin	Inhibits the enzyme DNA gyrase, disrupting bacterial replication.	Tendon rupture, neuropathy, dizziness, GI disturbances	Resistance increases, interaction with metal ions	(Geremia et al., 2024)
Moxifloxacin	Inhibits DNA gyrase and topoisomerase IV	QTc prolongation, tendon disorders, neurotoxic effects	The risk of cardiotoxic effects is higher than Levofloxacin	(Kusmiati et al., 2022)
Clofazimine	Disrupts the function of bacterial cell membranes and produces free radicals.	Skin hyperpigmentation, GI disturbances, hepatotoxicity	Annoying cosmetic adverse drug reactions, requiring a long time for elimination	(Stadler et al., 2023)
Amikacin	Inhibits protein synthesis via the 30S ribosomal subunit	Nephrotoxicity, ototoxicity (hearing loss), balance disorders	Only available in injection form, high risk of toxicity	(Ramirez and Tolmasky, 2017)

Linezolid as a Therapy for Drug-Resistant Tuberculosis

Definition and Mechanism of Action of Linezolid

Linezolid, or $C_{16}H_{20}FN_3O_4$, is an antibiotic from the oxazolidinone group with the chemical name N-[[3-[3-fluoro-4-(morpholin-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl]amino]acetamide. Its chemical structure consists of an oxazolidinone ring, which is the core of its antibacterial activity, as well as functional groups such as a fluoro group on the phenyl ring, which increases lipophilicity and tissue penetration, and a morpholine group, which contributes to structural stability and interaction with bacterial protein targets (Shi et al., 2023).

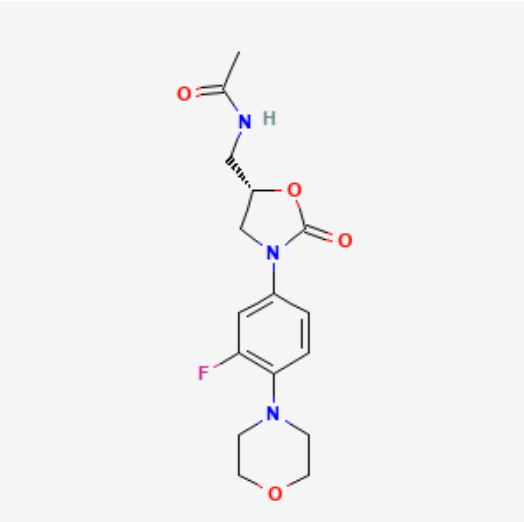

Figure 1. Chemical structure of Linezolid (PubChem)

This drug binds to the 50S ribosomal subunit, preventing the formation of the 70S initiation complex, which is essential for bacterial protein translation. The growth of *Mycobacterium tuberculosis* can be controlled by inhibiting protein synthesis, making linezolid effective in the treatment of Multidrug-Resistant Tuberculosis (MDR-TB/XDR-TB). Unlike other antibiotics that target the enzyme DNA gyrase or cell wall synthesis, the mechanism of action of linezolid is unique; therefore, the risk of cross-resistance is lower than that of fluoroquinolones or aminoglycosides (Foti et al., 2021).

In addition to its unique mechanism of action, linezolid is highly effective against gram-positive bacteria and several strains of *Mycobacterium tuberculosis* that have developed resistance to first-line drugs. In some cases, linezolid has a bacteriostatic effect, which inhibits bacterial growth without killing it directly; however, in certain strains, such as MDR-TB and XDR-TB, this drug shows bactericidal properties when administered in high doses and for a long time. Its high effectiveness, especially in combination regimens, makes linezolid one of the main choices for the treatment of drug-resistant tuberculosis (Gan et al., 2023).

Linezolid Adverse drug reactions

Long-term linezolid use is often associated with various serious adverse drug reactions, especially those related to hematology and the nervous system. One of the most frequently reported adverse drug reactions is myelosuppression, which includes thrombocytopenia (decreased platelet count), anemia, and leukopenia. This effect occurs because linezolid can suppress the production of blood cells in the bone marrow, especially after more than two weeks. Therefore, regular monitoring of platelet and red blood cell levels is essential to reduce the risk of complications, such as bleeding and severe anemia (Zou et al., 2024).

In addition to hematological effects, peripheral neuropathy is another worrying adverse drug reaction, especially with long-term use. Peripheral neuropathy is characterized by tingling, numbness, or pain in the hands and feet, which can be irreversible if linezolid use is not stopped immediately. This adverse drug reaction is caused by interference with the mitochondria, which play a role in the energy metabolism of nerve cells. In addition, linezolid can cause optic neuropathy, which is characterized by visual disturbances, including blurred vision and permanent vision loss in more severe cases. Therefore, nerve function should be monitored periodically in patients undergoing long-term linezolid therapy (Bano et al., 2022).

Therapeutic Drug Monitoring (TDM) Linezolid

Linezolid has the potential for hematological toxicity and peripheral neuropathy, which often occur when the concentration of the drug in the body is too high. Therefore, the application of TDM is important for periodically monitoring drug levels in plasma to minimize the risk of adverse drug reactions. By understanding the relationship between toxicity and drug concentration, medical teams can adjust doses to achieve a balance between therapeutic effectiveness and safety of use (Lau et al., 2023).

In TDM Linezolid, the main parameters observed were the peak concentration (approximately 2–7 mg/L) and the minimum concentration (<5 mg/L), which aims to reduce the risk of toxicity. This approach is especially beneficial in patients with renal insufficiency or genetic variations that affect drug metabolism. Through TDM-based dose adjustments, it is hoped that linezolid will remain effective in suppressing the growth of infection-causing bacteria, while avoiding serious adverse drug reactions that can interfere with the sustainability of therapy (Lau et al., 2023).

Linezolid Pharmacokinetics

The pharmacokinetic profile of linezolid shows favorable characteristics for the treatment of drug-resistant tuberculosis. Linezolid has an oral bioavailability of almost

100%; therefore, the orally administered dose is equivalent to the intravenous dose. After administration, the drug was rapidly absorbed, reaching peak plasma concentrations within 1–2 hours. Its distribution is very good, with a volume of distribution of approximately 40–50 liters in adults, allowing optimal penetration into target tissues, such as the lungs, alveolar fluid, and central nervous system. This good penetration is very important in the treatment of resistant TB, as it ensures that linezolid reaches effective therapeutic concentrations at the site of infection, including granulomas typical of TB (Resendiz-Galvan et al., 2023).

Linezolid metabolism occurs mainly through non-enzymatic oxidation in the liver; thus, it does not rely on the CYP450 enzyme system and reduces the potential for drug interactions. Approximately 30% of the dose is excreted in the urine as an active drug, 50% is excreted as inactive metabolites, and the remainder is excreted in the feces (Obach, 2022). The elimination half-life of linezolid ranges from 5 to 7 hours, allowing twice-daily dosing to maintain stable therapeutic concentrations. This pharmacokinetic profile supports the use of linezolid in the treatment of drug-resistant TB, although monitoring liver and kidney function is essential to anticipate metabolite accumulation in patients with organ disorders (Li et al., 2020).

Pharmacodynamics of Linezolid

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, thereby preventing the formation of the 70S initiation complex, which is essential for mRNA translation. This mechanism provides high efficacy against Gram-positive bacteria such as *Staphylococcus aureus* (including MRSA and VRSA), *Enterococcus spp.* (including VRE), and *Streptococcus pneumoniae,* although it is ineffective against Gram-negative bacteria due to intrinsic resistance. The main pharmacodynamic parameter is the AUC/MIC ratio, which indicates whether the drug concentration achieved is sufficient to produce the bactericidal effect seen in some species such as *Streptococcus spp.* or is merely bacteriostatic, as in *Staphylococcus spp.* and *Enterococcus spp.* However, linezolid also carries the risk of serious adverse drug reactions, including myelosuppression (which can lead to thrombocytopenia, anemia, and leukopenia), peripheral and optic neuropathy, and lactic acidosis due to mitochondrial dysfunction. The risk of serotonin syndrome should also be considered if linezolid is used together with serotonin reuptake inhibitors or other serotonergic drugs, given its weak Monoamine Oxidase (MAO) inhibitor nature (Hashemian et al., 2018).

The Advantages of Linezolid Compared to Other Drug-Resistant TB Drugs

Compared with other drugs used in MDR-TB and XDR-TB therapy, linezolid has several key advantages that make it a frequently used choice. One of its main advantages is its high oral bioavailability, which allows its administration in tablet or injection form with equal efficacy. This is particularly advantageous for patients undergoing long-term therapy, as it can reduce their dependence on hospital care. In addition, its excellent lung tissue penetration allows linezolid to achieve optimal therapeutic concentrations at the site of infection, making it more effective than other drugs that have more limited tissue distribution (Singh et al., 2017). Another advantage is its unique mechanism of action, which lowers the risk of cross-resistance compared with fluoroquinolones or aminoglycosides. Unlike Bedaquiline and Delamanid, which are at risk of cardiotoxicity due to prolongation of the QTc interval, linezolid does not cause this adverse drug reaction, making it safer for patients with a history of heart disease. In addition, although there are some serious adverse drug reactions, this risk can be reduced by strategies such as dose adjustment, intermittent therapy, or close monitoring of platelet levels and nerve function. Owing to these advantages, linezolid remains one of the main components of MDR-TB and XDR-TB treatment regimens (Kim et al., 2023).

Linezolid Disadvantages

Despite its many advantages, linezolid has some disadvantages that need to be considered, especially in relation to long-term adverse drug reactions. The use of linezolid for more than 28 days has been associated with a high risk of peripheral neuropathy and myelosuppression, which may be a reason for discontinuation of therapy in some patients. In addition, hematological adverse drug reactions require regular laboratory monitoring, which may increase the burden of treatment costs for patients (Zou et al., 2024).

Linezolid Combination with Other Drugs

Combination of Linezolid with Bedaquiline:

The combination of Linezolid with Bedaquiline has shown promising results in the treatment of drug-resistant TB. In this regimen, Linezolid at a dose of 600 mg/day is used with Bedaquiline, for example, 400 mg/day in the initial phase, then 200 mg three times a week. Studies have shown that the synergy between the two drugs maintains optimal Linezolid levels without interfering with its pharmacokinetics, so that drug distribution and elimination remain stable. This combination results in a significant reduction in bacterial load and increases cure rates in MDR-TB/XDR-TB patients, although close monitoring of cardiovascular adverse drug reactions, especially prolongation of the QTc interval from Bedaquiline, is still needed (Chang et al., 2018) .

Linezolid in Combination with Pretomanid

The BPaL regimen, which combines Linezolid, Pretomanid, and Bedaquiline, is an innovative approach to the treatment of drug-resistant TB. In this combination, Linezolid at a dose of 600 mg/day is combined with Pretomanid, for example 200 mg/day, to achieve optimal synergy. The pharmacokinetics of Linezolid are not compromised when used with Pretomanid, thus maintaining therapeutic concentrations. Treatment outcomes show significant improvements in bacterial load reduction and cure rates, although intensive monitoring is required to anticipate adverse drug reactions, such as peripheral neuropathy and potential hepatotoxicity (Pratt et al., 2024).

Linezolid Combination with Moxifloxacin:

The combination of Linezolid with Moxifloxacin is an effective alternative for patients with drug-resistant TB, especially when resistance to other fluoroquinolones occurs. In this regimen, linezolid at a dose of 600 mg/day was used with moxifloxacin at a dose of 400 mg/day, which inhibits DNA gyrase and topoisomerase IV. The synergy of these two drugs supports optimal penetration into the lung tissue and maintains effective therapeutic concentrations, resulting in a significant reduction in bacterial load. However, the higher risk of QTc prolongation with moxifloxacin requires careful monitoring during therapy (Johnson et al., 2024).

Table III. The Efficacy of Linezolid and Combination with Other Drugs in the Therapy of Drug-Resistant Tuberculosis

Dosage Form	Method	Pharmacokinetics	Treatment Results	Reference
Tablet	Oral administration; Linezolid dose 600 mg/day according to guidelines	Bioavailability almost 100%, peak concentration in 1–2 hours, wide distribution to lung tissue and CNS	Can achieve optimal therapeutic concentrations; however, use as monotherapy is limited to complex drug-resistant TB cases.	(Lin et al., 2022)
Intravenous	IV infusion;	Pharmacokinetic	Therapeutic	(Xu et al.,

	dose is adjusted based on the patient's critical condition.	profile similar to oral preparation; effective in hospitalized and critically ill patients	efficacy equivalent to oral preparations; an option for patients who cannot tolerate oral administration	2023)
Combination with Bedaquiline	Combination regimen: Linezolid 600 mg/day + Bedaquiline (example: 400 mg/day initially, then 200 mg three times a week)	There is no significant interaction; Linezolid levels remain optimal in combination so that distribution and elimination are not affected.	Significantly increases cure rates and reduces bacterial load, especially in MDR-TB/XDR-TB patients.	(Chang et al., 2018)
Combination with Pretomanid	BPaL regimen: Linezolid 600 mg/day + Pretomanid (example: 200 mg/day) + Bedaquiline; dose adjusted for optimal synergy	Linezolid pharmacokinetics are not altered; levels are maintained in the maximal combination.	The BPaL regimen has shown high cure rates in MDR-TB/XDR-TB with significant reduction in bacterial load.	(Pratt et al., 2024)
Combination with Moxifloxacin	Alternative combination: Linezolid 600 mg/day + Moxifloxacin 400 mg/day	Minimal interactions; Linezolid still achieves optimal therapeutic concentrations with good lung tissue penetration.	Effectiveness is increased in cases of resistant TB with the support of a fluoroquinolone profile, although the risk of QTc prolongation must be closely monitored.	(Johnson et al., 2024)

Linezolid is one of the most effective drugs for the treatment of MDR-TB and XDR-TB because of its high bioavailability, good lung tissue penetration, and unique mechanism of action, which reduces the risk of cross-resistance. However, serious adverse drug reactions such as myelosuppression, peripheral neuropathy, and lactic acidosis remain challenging (Hashemian et al., 2018). Therefore, strategies such as dose adjustment, intermittent therapy, and close monitoring are essential to ensure the effectiveness of therapy, while reducing the risk of toxicity. With the right combination and approach, linezolid remains one of the most important components in drug-resistant TB therapy.

CONCLUSION

Based on the literature review that has been conducted on the treatment of drug-resistant tuberculosis, the use of linezolid has shown significant success. The superior pharmacokinetic profile of linezolid, with almost 100% oral bioavailability and optimal lung tissue penetration, supports its effectiveness in suppressing the growth of *Mycobacterium*

tuberculosis. Although long-term use of linezolid can cause adverse drug reactions, such as myelosuppression, peripheral neuropathy, and lactic acidosis, strict monitoring strategies and dose adjustments have been shown to reduce the risk of these toxicities.

In addition, the combination of linezolid with other drugs in drug-resistant TB regimens, such as Bedaquiline or Pretomanid, has shown optimal synergy in reducing the bacterial load and increasing cure rates. This approach ensures that the drugs can reach the target infection more efficiently and provide optimal therapeutic effects. Thus, the use of linezolid in the treatment of MDR-TB and XDR-TB has proven effective in increasing the success of therapy and in improving the overall health of patients.

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