Research Article

Linezolid as a Treatment for Multidrug-resistant Tuberculosis: A Literature Review

Rhea Veda Nugraha[1]*, Tazkia Fauziyyah[2], and Nafisa Silmi Kaffah[2]

[1]Department of Pharmacology, Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi, Indonesia
[2]Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi, Indonesia

ORCID
Rhea Veda Nugraha: https://orcid.org/0000-0002-6266-4107

Abstract.
Multidrug-resistant tuberculosis (MDR-TB) emerges when Mycobacterium tuberculosis develops resistance to both rifampicin and isoniazid, representing a significant threat that undermines global efforts to combat tuberculosis. The unfavorable prognosis of MDR-TB can be attributed to prolonged treatment duration, the utilization of multiple medications, and the adverse effects associated with drug therapy. This drug moved from Group C (third line) in 2016 and Group 5 (unclear efficacy) in 2011. This is a synthetic oxazolidinone antimicrobial drug and a non-selective mono oxidase inhibitor. Antimicrobials that are both vulnerable to and resistant to gram-positive bacteria can be effectively combatted by linezolid. This study investigates and appraises the utilization of linezolid as a therapeutic intervention in individuals afflicted with MDR-TB, while also scrutinizing the pharmacological attributes of the drug. We also discuss Linezolid's safety, efficacy, and tolerability for treating MDR-TB. Linezolid medication should be utilized for most patients and is a part of more recent short-course regimens since it has been known to increase the success rate of treatment of DR-TB by increasing the conversion sputum rate. However, primarily hematologic and neurologic, linezolid toxicity is typically treatment-limiting yet should be monitored. Recent studies suggest that dose modification and intermittency can reduce linezolid toxicity. Also, using linezolid in the regimen potentially reduces the treatment duration, but it needs further research.

Keywords: efficacy, linezolid, safety, MDR-TB, tolerability

Corresponding Author: Rhea Veda Nugraha; email: dr.rheaveda@gmail.com

Published: 4 October 2024

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the 4th ICONISS Conference Committee.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB), marked by resistance to both isoniazid and rifampicin, presents a formidable challenge to the global community, complicating tuberculosis treatment regimens and necessitating the implementation of innovative therapeutic approaches [1]. To effectively treat MDR-TB, several medications must be used in combination, including linezolid, fluoroquinolones, bedaquiline, ethambutol, clofazimine, terizidone or cycloserine ,imipenem-cilastatin, pyrazinamide, delamanid or

ethionamide, meropenem, streptomycin, amikacin [2]. On the WHO linezolid include of The three medicines in Group A used for classification of second-line medicines with bedaquiline and fluoroquinolones [3]. In vitro and animal investigations have demonstrated the promising effectiveness of linezolid, the inaugural oxazolidinone sanctioned for human use, against drug-resistant variants of Mycobacterium tuberculosis [4-6]. We tought to evaluate the function of linezolid in MDR-TB, talk about this medication and its characteristics, and present fresh data on the clinical advantages of clofazimine in MDR- TB treatment.

2. Multidrug-Resistant Tuberculosis

2.1. Epidemiology

According to the WHO, between 2015 and 2020, the predicted number of people who annually developed MDR-TB or RR-TB (MDR/RR -TB) was largely steady; however, it increased in 2021. The range of estimated incident cases was 450 000 to 501 000 (95% UI: 399 000 to 501 000), representing a 3.1% increase from 437 000 (95% UI: 390 000-483 000) in 2020. The main cause of the increase is believed to be the general increase in tuberculosis incidence between 2020 and 2021, which was exacerbated by the COVID-19 pandemic's effects on tuberculosis detection. Twenty-six percent of cases worldwide in 2021 came from three countries: Pakistan (79.9%), the Russian Federation (8.5%), and India (26%). With more than 50% of previously treated MDR/RR-TB patients, the Russian Federation and a number of other countries in Eastern and Central Asia have the highest rates [2].

The COVID-19 pandemic continues to exacerbate the burden of tuberculosis and hinder access to its diagnosis and treatment [7-9].

Global TB objectives are not on pace, and progress made in the years leading up to 2019 has slowed, stopped, or even reversed. The most obvious and immediate result was a notable and immediate drop in the reported number of new TB diagnoses worldwide. At its highest point of 7.1 million in 2019, this fell to 5.8 million in 2020 (-18%), reaching a level last observed in 2012. At 6.4 million, there was a little uptick in 2021 (compared to the 2016–2017 level). The three countries that made up the majority of the drop in 2020 were Indonesia, India, and the Philippines, which together accounted for 67% of the entire world population [9].

2.2. Treatment of MDR-TB

There are currently two regimens available for treating MDR-TB. Based on the length of the treatment, the WHO classed these regimens as either short or lengthy. A long regimen lasts 18–20 months (15 months following culture conversion, at least), while a short regimen lasts 9–11 months [10]. WHO made a public appeal (44) for IPD for the treatment of DR-TB in June 2021. Following details were requested for each patient: bacteriologically proven MDR/RR-TB patients (including MDR/RR-TB, MDR/RR-TB with added resistance to second-line TB medicines, and patients with pre-XDR-TB or XDR-TB) application of the modified, shorter (12 months or less) all-oral regimens that include at least linezolid and bedaquiline. Application of the shorter, all-oral bedaquiline-containing regimen (9–11 months), as advised by the WHO, in the following combinations: Levofloxacin (or moxifloxacin), ethambutol, pyrazinamide, clofazimine, ethionamide, and high-dose isoniazid were administered for 4 or 6 months (used for at least 6 months), and then for 5 months clofazimine, pyrazinamide, ethambutol, and levofloxacin (or moxifloxacin). WHO also recommend use of the longer, all-oral treatment plan that the WHO recommends, which must include at least linezolid and bedaquiline [2].

3. Linezolid

3.1. Introduction to linezoid

Linezolid belongs to the oxazolidinone drug class that is effective against gram-positive rods, such as corynebacteria, L monocytogenes, and Nocardia sp., and gram-positive bacteriae, including enterococci, streptococci, staphylococci, and gram-positive anaerobic cocci. Its primary activity is bacteriostatic, even if it has antibacterial properties against streptococci. It also exhibits anti-Mycobacterium TB properties [11].

Linezolid is used for disease treatments resulting from gram-positive bacterial infections, not negative gram bacterium treatment. It was first introduced in 1978 because of the effectiveness of the linezolid drug on plant diseases. Then linezolid was introduced as antimicrobial medicine; after 6 years, linezolid had antibacterial properties that felt better than the previous antibacterial compounds [12]. Linezolid is an effective drug against drug-resistant TB treatment, and linezolid is effective for treating pneumonia bacteria, skin infections, Infections, and complications from bacterial infection [13].

3.2. Chemical properties of linezolid

The chemical known as linezolid is an organofluorine made composed of 1,3-oxazolidin-2-one containing an N-3-fluoro-4- (morpholine-4-yl) phenyl group and an acetamido methyl group at position 5 (see Fig. 1). A synthetic antibacterial drug that stops the development of a functional 70S initiation complex by binding to a specific location on the 50S subunit of the 23S ribosomal RNA and inhibiting the synthesis of proteins by bacteria. As a protein synthesis inhibitor and antimicrobial, it serves both purposes. It belongs to the class of acetamides, morpholines, oxazolidinones, and organofluorine compounds [14].

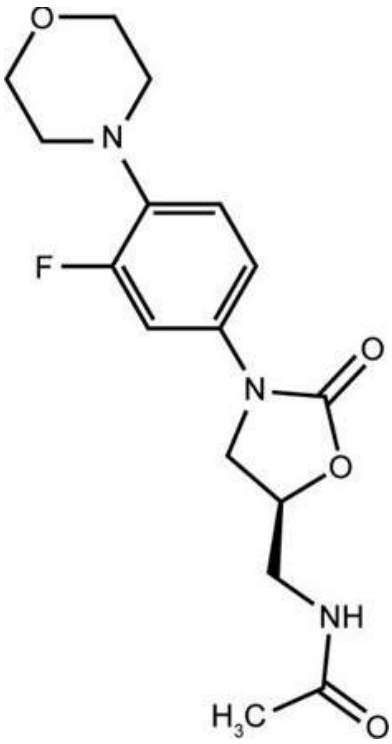

Figure 1: Chemical properties of linezolid.

3.3. Mechanism of action of linezolid

Linezolid, a synthetic antibiotic, functions by binding to the rRNA within the 30S and 50S ribosomal subunits, thereby impeding bacterial protein synthesis. This interference hampers the formation of the initiation complex, resulting in the truncation of the peptide chain and a decrease in the translation rate. While certain inhibitors of protein synthesis target elongation, they do not necessarily operate at this specific level of inhibition. Moreover, there is no indication that inhibition at this precise site leads to

cross-resistance to other protein synthesis inhibitors. Additionally, linezolid possesses the capability to suppress the synthesis of virulence factors, thereby diminishing the production of toxins associated with gram-positive bacterial infections [15]. Linezolid is bactericidal against most streptococcal strains and bacteriostatic against staphylococci and enterococci [13].

Linezolid is nonselective monoamine oxidase (MAO) inhibitor. Monoamine oxidase inhibition in the central and sympathetic nervous system can contain higher concentrations of the neurotransmitters dopamine, serotonin, norepinephrine, and epinephrine. Beta- and alpha-adrenergic and serotonin receptors may become desensitized because of inhibition. Inhibiting MAO can enable significant levels of tyramine from food to be absorbed throughout the body, which could lead to life-threatening hypertension. This can happen in the liver and digestive tract [13].

3.4. Synergism activity of linezolid

Synergism activity of linezolid with other drugs shown in some research, one showed between linezolid and clarithromycin. In MDR-TB patients, clarithromycin raises linezolid exposure by 44%. The research findings suggest that clarithromycin holds potential as a synergistic agent to enhance the therapeutic levels of linezolid, alongside low-dose ritonavir and protease inhibitors. Incorporating clarithromycin into multidrug-resistant tuberculosis (MDR-TB) treatment protocols is recommended based on the observed in vitro synergy. Consequently, with the heightened exposure to linezolid and enhanced drug susceptibility observed in both clarithromycin and linezolid, the dosage of linezolid can be further minimized, leading to cost reductions and mitigated adverse effects [16].

According to the in vitro findings from the current investigation, the majority of the combinations showed no difference or an additive impact, except LZD + CPM, which showed partial synergism (FIC = 0.75) for three of four isolates. Discussing the standards that characterize medication interaction patterns is essential because different definitions determine them. A common definition of interaction in antimicrobial drug combinations is as follows: FIC 0.5 indicates cooperative relationships; FIC > 0.5 but 4 indicates no cooperation; and FIC > 4.0 indicates aggressive behavior. All varieties examined would have 'no interaction' if this criterion evaluated the interaction patterns between LZD and second-line medications. LZD and CPM are potentially effective combinations that could be used in MDR-TB regimens. In vivo, LZD + CPM had the highest level of efficacy against H37Rv and only demonstrated limited synergism.

Compared to LZD and CPM alone, LZD + CPM had more excellent bactericidal action (p 0.05). After two months of treatment, LZD + CPM showed the highest activity against H37Rv of all the treatment groups, lowering CFU by 3.55 log10 [17].

3.5. Pharmacokinetics of linezolid

In healthy people, linezolid has a bioavailability of about 100% and is well absorbed.5 This feature is a significant advantage because it enables the agent to be used intravenously before moving to oral therapy or even starting infection treatment with oral therapy. After 600 mg oral dosages, steady- state peak serum concentrations (Cmax) are reached 0.5-2 hours later and range from 15 to 27 mg/L.3–8 Additionally, oral absorption was unaffected by co-administration with antacids such as magnesium hydroxide and aluminium hydroxide [12].

The volume of distribution is close to the 40–50 L total body water content, and the percentage of plasma protein binding is 31%. Half-life of plasma elimination is 3.4–7.4 hours. Two inactive metabolites, hydroxyethyl glycine (metabolite B) and aminoethoxy acetic acid (metabolite A), are produced during the metabolism of linezolid. The clearance rate (±SD) is 80 ± 29 mL/min and by non-renal (65%) and renal processes. Renal tubular reabsorption is possible. A percentage of the dosage is eliminated in the urine unaltered [12,18].

A portion of the dosage is eliminated in urine in its original state. In-depth research has been done on linezolid's pharmacokinetics in various patient groups receiving doses. After a dose was multiplied by five, there was discovered to be just a minimal amount of nonlinearity, with a 30% fall in clearance. The therapeutic dosage window has nothing to do with the nonlinearity. Plasma levels of linezolid exhibited comparability across various demographics, including young, healthy volunteers, elderly patients, and individuals with mild or chronic renal dysfunction. It has been suggested that there is no need to change the dosage when the concentration of females is higher than that of males. According to reports, persons with normal renal function are exposed to drug metabolites seven to eight times less frequently than patients with severe renal impairment who need hemodialysis. Patients who have significant renal impairment are advised to take Linezolid with caution. Pediatric patients necessitate a greater daily dosage per kilogram of body weight compared to adults due to the demonstrated higher clearance of linezolid in children relative to adults [12].

3.6. Effectivity of linezolid for treating MDR-TB

Irrespective of dosage regimen, linezolid is strongly advocated as the primary therapeutic agent for managing MDR-TB, contingent upon the absence of contraindications. However, this linezolid drug has side effects from this drug which is still a problem [3,19]. Several research, including the most recent ZEPHYR experiment, revealed higher linezolid effectiveness than vancomycin. However, the efficacy of linezolid, better than vancomycin, is still being debated for indications such as SSSI or nosocomial pneumonia. Linezolid's clinical usage in complex MRSA-SSSI, such as DFI without osteomyelitis, has been validated by multiple recent trials [20]. According to data from real-world studies, linezolid has been shown to be safe and effective in treating Gram-positive bacterial infections in critically ill patients. When treating SSTIs (pulmonary infections) brought on by Staphylococcus aureus, linezolid demonstrated superior clinical efficacy [21].

Linezolid use has been proven to boost effectiveness for at least 6 months, although its use may be restricted by harmful effects. According to the analysis, linezolid should be used for the entire course of therapy to have the most impact (According to the data received, almost 70% of patients used linezolid for six months or longer, and 30% for a full year). There are no patient factors for an early linezolid withdrawal shown by the IPD sub-analysis [3]. Some of the following studies demonstrate the effectiveness of linezolid (Table 1). The average result from 5 studies showed that linezolid became an effective drug for MDR TB treatment.

3.7. Linezolid's effectiveness in treating XDR-TB

Linezolid has been shown to be effective in the treatment of MDR-TB and XDR-TB in five case-control studies. Toxicity and side effects, including optic neuropathy, peripheral and bone marrow suppression, limit the use of linezolid. Contrarily with MDR-TB, reported their study for seven XDR-TB patients, all patients showed initial culture conversion and a low incidence of myelosuppressive and hematologic side effects although the use of the US Food and Drug Administration (FDA)-approved dosage of 600 mg orally twice a day and the result of this study showed that two patients had peripheral neuropathy, and none of them experienced severe myelosuppressive side effects [8].

Table 1: Description of safety and tolerability of linezolid.

Study	Drug Resistance	Linezolid Daily Dose	Outcome
			Treatment Success Rate
Rodvold and McConeghy [22]	MDR-TB (resistant to isoniazid and rifampicin), XDR-TB (resistant to at least one injectable drug, amikacin, capreomycin, or kanamycin), and MDR-TB (resistant to any fluoroquinolone)	1200 mg daily Duration: 26 weeks	Ninety-eight individuals (90%; 95% CI 82.7-94.9%) showed positive results at six months after the completion of treatment. Of the 38 MDR patients, 35 (92%) had good results (78.6-98.3%). A total of seven deaths occurred due to withdrawal of consent during treatment (n=1), relapse in follow-up (n=2), and loss to follow-up (n=1), as opposed to one death from an unidentified cause that was not connected to TB or drugs during follow-up (n=1).
Conradie et al. [23]	MDR-TB is distinguished by its resistance to isoniazid and rifampicin, streptomycin/ amikacin/ capreomycin, XDR-TB	600 mg once day and 300 mg twice day. Time: 56 days	This study involved eight patients. A median cumulative dose of 51 000 mg (IQR 33 850-60 450 mg) was administered throughout the course of a median 56-day course of linezolid treatment (interquartile range [IQR] 44-82 days). The median linezolid AUC over 12 hours (AUC12) values were 57.6 mgh/L with the 300 mg dosage and 145.8 mgh/L with the 600 mg dose (IQR 101.2-160.9 mgh/L). The AUC24/MIC ratios for the 300 and 600mg doses were 452 (IQR 343-513) and 1151 (IQR 656-1500). It was easy to tolerate linezolid.
Esmail et al. [24]	MDR-TB, which is susceptible to rifampicin, isoniazid, fluoroquinolones, and aminoglycosides but resistant to both of these drugs.	Dose: NA Duration: 6 months or 24 months	A favorable outcome was recorded in 22.7% (10 of 44) of the patients in the SOC arm and 51.0% (25 of 49) of the participants in the intervention arm 24 months after the start of treatment, representing a relative risk of 2.2 (95% CI, 1.2-4.1) and risk difference of 28.3% (9.6-46.7)
Singla et al. [25]	Capreomycin, moxifloxacin, levofloxacin, and amoxicillin-clavulanic acid	600 mg (N/A). Duration: >12 months	The high cost of therapy at 10 and 14 months, respectively, and one was displaced at 16 months. These three had negative ongoing smear and culture results at default. Due to chronic sputum positive and no clinical response at 15 months, two patients (6.8%) were deemed unsuccessful, and the therapy had to be stopped. Nine patients have been cured and receive follow- up care for an average of 12.8 months (6-28 months). So yet, nobody has relapsed. Two individuals with XDR-TB had surgery. The outcomes for both patients were favorable.

Table 1: Description of safety and tolerability of linezolid.

Study	Drug Resistance	Linezolid Daily Dose	Outcome
			Treatment Success Rate
Anger et al. [26]	KAN, CIP, PZA, LVX, ETH, CAP, AMK, OFX, RFB, PAS, AMC, CLO	600 mg twice daily and 600 or 400 mg once daily dose. Duration: 16 months	MDR TB regimens included linezolid for a median of 16 months (range: 1-29). 11 patients (69%) finished their treatment; four (25%) passed away, and one (6%) stopped without relapsing. After beginning treatment with linezolid, myelosuppress ion happened over in a median of 5 weeks (range: 1–11) in 13 patients (81%), gastrointestina l side effects in 13 (81%) patients in a median of 8 weeks (range: 1-57), and neurotoxicity in seven (44%) patients in a median of 16 weeks (range: 10-111). Combinations of brief linezolid suspension, linezolid dose decrease, and symptom management were used to treat adverse effects. Five patients (31%) needed to stop using Linezolid eventually. Compared to neurotoxicity, myelosuppress well to clinical treatment techniques. Males were likelier to experience leucopenia and neuropathy, and greater age was linked to thrombocytopenia (P 0.05).

LZD, linezolid; INH, isoniazid; INH (900), 900 mg high dose isoniazid; RIF, rifampicin; EMB, ethambutol; PZA, pyrazinamide; STR, streptomycin; CAP, capreomycin; KAN, kanamycin; AMK, amikacin; ETH, ethionamide; CYC, cycloserine; CIP, ciprofloxacin; LVX, levofloxacin; OFX, ofloxacin; RFB, rifabutin; PAS, para-aminosalicylic acid; AMC, amoxicillin/clavulanate; CLO, clofazimine; MXF, moxifloxacin; GAT, gatifloxacin; IPM, imipenem; IFN-G, recombinant human interferon-γ; COPD, chronic obstructive pulmonary disease; M, male; F, female.

3.8. Safety and tolerability of linezolid

According to recent study, dose modification and intermittent therapy may help reduce the toxicity associated with linezolid. Linezolid is secure and generally well tolerated in 600 mg twice daily doses for up to 28 days. Adverse drug reactions are often mild to moderate in severity and transitory. Common adverse reactions observed predominantly in adults include nausea, diarrhea, headaches, loose stools, while vomiting is prevalent in children [27].

It is safe to combine linezolid with aztreonam, yet not enough information is available to assess how linezolid and rifampicin interact. The co-administration of ceftazidime, ciprofloxacin, gentamicin, and meropenem with Gram-negative antibiotics did not result in any unfavorable side effects. Linezolid did not interfere with the efficacy of other antifungal medications, including aminoglycosides, antivirals, amphotericin B, fluoroquinolones, azoles, or -lactams. Therefore, linezolid can be combined with other antibiotics without causing any interactions [28,29]. When used with serotonin

reuptake medications, linezolid, a non-specific inhibitor of monoamine oxidase, can cause lethal serotonin poisoning [28,29]. Findings show that Linezolid does not present contraindications in this particular illness, even though doctors need to be aware of this potentially dangerous combination and keep careful monitoring on patients receiving linezolid in addition to serotonergic medications [30].

3.9. Mechanisms of resistance to linezolid

Linezolid binds to the 23S rRNA nucleotides around the 50S ribosomal subunit gap, according to an examination of high-resolution structures of the medication [31]. Accordingly, 23S rRNA mutation has been identified as one of the mechanisms behind linezolid resistance. Furthermore, mutations in a few of these proteins are increasingly associated with resistance to linezolid, despite the fact that the ribosomal proteins uL3 and uL4 are situated farther away from the bound drug. Additionally, new studies on the Cfr methyltransferase have shown that considerable linezolid resistance might result from the transferable alteration of 23S rRNA. The creation of a new class of oxazolidinones with improved characteristics against the identified resistance mechanisms has been made possible by the accurate localization of the linezolid-binding site [32].

Recently, optr A is resistance gene of a novel oxazolidinone has been discovered, and this gene has been expressed in E. faecium and E. faecalis [33]. OptrA is an adenosine triphosphate-binding cassette (ABC) transporter. A common mechanism showed that the antibiotic-resistant bacteria use the ABC transporters to forcefully pump the medications out of the cell. Proteins which confer resistance to a variety of therapeutically relevant ribosome-targeting antibiotics are found in the ABC-F family. It has been observed that these proteins interact with the ribosome and move the drug away from its binding site in order to use ribosome protective mechanisms [34].

4. Conclusions

The requirement for a more practical treatment is highlighted by the growing incidence of MDR-TB and the poor efficacy of existing therapies. When it comes to bacteria that are resistant to many drugs, linezolid works well. Further study is required to find the best effective treatment approach to lessen neurological adverse effects without compromising multidrug-resistant tuberculosis results and predisposing factors for linezolid toxicity.

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