STM JOURNALS

Research & Reviews: A Journal of
Drug Design & Discovery

ISSN: 2349-9036
Volume 11, Issue 2, 2024
May–August
DOI (Journal): 10.37591/RRJoDDD

https://journals.stmjournals.com/rrjoddd

Review RRJoDDD

Evaluating Linezolid: A Comprehensive Analysis

Divyani R. Patil[1,*], Sunila A. Patil[2], Sunil P. Pawar[3]

Abstract

Treatments for infections caused by Gram-positive bacteria, such as methicillin-resistant staphylococci and VRE, including skin and soft tissue infections, community-acquired pneumonia, and other infections treated with linezolid, an oxazolidinone antimicrobial agent that functions by specifically inhibiting protein synthesis. Even while antibiotic resistance is becoming more frequent in many nations, linezolid resistance among these pathogens is still low, typically less than 1%. Thus, the emergence of resistance in clinical isolates should draw more attention from clinical labs to the need to regularly test for linezolid susceptibility for this crucial medication and should be taken into consideration when deciding whether to use it therapeutically. This study was conducted to maximise the therapeutic usage of linezolid because of its significance in treating infections brought on by Gram-positive bacteria. One may argue that the first antibiotic in the family of oxazolidinone antibiotics was linezolid. It is a synthetic antibiotic that attaches itself to rRNA to stop bacteria from making proteins. Additionally, it prevents the formation of the initiation complex during protein synthesis, which can shorten formed peptide chains and slow down the pace at which translation elongation occurs. Linezolid has been approved for the treatment of several conditions, including vancomycin-resistant Enterococcus faecium infections, hospital-acquired pneumonia (Staphylococcus aureus), complicated skin and skin structure infections (SSSIs), uncomplicated SSSIs (Streptococcus pyogenes or methicillin-susceptible S. aureus), and community-acquired pneumonia (Streptococcus pneumoniae). The investigation of high-resolution structures has demonstrated that linezolid binds to a deep gap surrounded by 23S rRNA nucleotides on the 50S ribosomal subunit. A mechanism of linezolid resistance was demonstrated to involve mutations in 23S rRNA. Furthermore, there is a growing correlation between linezolid resistance and mutations in certain areas of the ribosomal proteins uL3 and uL4. These proteins are situated further off from the drug that is bound, though. Methicillin-resistant S. aureus and vancomycin-resistant enterococci are expected to be the most common Gram-positive bacteria in intensive care units (ICUs). Linezolid is a popular antibacterial medication used to treat ICU patients who have infections. Due to its favourable in vitro and in vivo action against the pathogens, the medication is recommended for the treatment of infections in intensive care units. The prevalence of antibiotic-resistant microorganisms is rising globally. Given the importance of antibiotics to the public and the decline in the number of new antimicrobial registrations by regulatory bodies, adequate quality control is necessary to prevent the spread of bacterial resistance, guarantee a treatment's efficacy, and protect patient safety.

***Author for Correspondence**
Divyani R. Patil
E-mail: patildivyani7779@gmail.com

[1]Student, Department of Pharmaceutical Quality Assurance, Poojya Sane Guruji Vidya Prasarak Mandal's College of Pharmacy, Shahada, Maharashtra, India
[2]Professor, Department of Pharmaceutical Quality Assurance, Poojya Sane Guruji Vidya Prasarak Mandal's College of Pharmacy, Shahada, Maharashtra, India
[3]Principal, Poojya Sane Guruji Vidya Prasarak Mandal's College of Pharmacy, Shahada, Maharashtra, India

Received Date: April 05, 2024
Accepted Date: April 22, 2024
Published Date: June 21, 2024

Citation: Divyani R. Patil, Sunila A. Patil, Sunil P. Pawar. Evaluating Linezolid: A Comprehensive Analysis. Research & Reviews: A Journal of Drug Design & Discovery. 2024; 11(2): 11–16p.

Keywords: Linezolid, oxazolidinone, gram positive, MRSA, VRE

INTRODUCTION

Antimicrobial resistance, as defined by the World Health Organisation, is the term used to describe changes in microorganisms (bacteria, fungi, viruses, and parasites) that render the medications used to treat the diseases they have caused ineffective. Multidrug-resistant bacteria are

spreading alarmingly quickly, which is concerning for world health as they exhibit resistance to a wide range of pathogenic agents. Bacterial resistance to first-line medications has increased significantly in recent years, and regrettably, resistance to second- and third-line medications has also increased significantly. Multidrug-resistant and cross-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are a particular concern since they are the cause of treatment failure with conventional methods, a high death rate, and extended hospital admissions.

The basic 2-oxazolidone nucleus of a novel family of synthetic antibiotics called oxazolidinones confers activity against a range of multidrug-resistant Gram-positive bacteria (GPB), such as *Mycobacterium tuberculosis* (Mtb), MRSA, and vancomycin-resistant Enterococcus (VRE). By binding to the 50S ribosomal subunit, oxazolidinones prevent bacteria from synthesising proteins. Linezolid (LNZ), which was developed in 1996 and granted FDA (US Food and Drug Administration) approval for clinical usage in 2000, was the first oxazolidinone to be made accessible in a therapeutic setting. In addition to being often used to treat GPB infections, LNZ is also thought to be an effective medication for surgical infections, drug-resistant pulmonary infections, and MDR-TB infections.

One important characteristic of this class is that structural alterations to linezolid can essentially prevent resistance to the drug, which is uncommon in GPB and virtually non-existent in GNB. Data on the structure/activity relationship (SAR) associated with antibacterial activities can be taken into consideration when evaluating novel oxazolidinones preclinically for pharmacokinetic/pharmacodynamic (PK/PD) characteristics in order to predict their clinical effectiveness [1].

Linezolid can inhibit *in vitro* various drug-resistant aerobic Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and methicillin-resistant coagulase-negative staphylococci (MRCoNS). It specifically inhibits the production of bacterial proteins by binding to domain V of the 23S rRNA on the 50S ribosomal subunit. It also prevents the creation of a functioning 70S-initiation complex, an essential stage in the translation process, and has no chemical relationship to other antibacterial drugs. It is challenging for cross-resistance with other antibacterial agents to develop because of this unique mode of action. Instead of having a bactericidal effect, linezolid mostly has a bacteriostatic one [2].

Linezolid is authorised by the FDA to treat both complex and non-complex skin/soft tissue infections, including MRSA and MRCNS, nosocomial and community-acquired pneumonia caused by *S. aureus*, and penicillin-susceptible pneumonia. This study mostly addresses adult patients, however, there have been a number of recent evaluations assessing the safety and effectiveness of linezolid in treating paediatric patients with Gram-positive infections [3].

MECHANISM OF ACTION OF LINEZOLID

Researchers interested in the mechanism of action of these novel compounds have taken an interest in the oxazolidinones since they are genuinely the first new class of antibiotics to be licenced in 30 years. Due to the early discovery by DuPont researchers that these chemicals impeded protein synthesis in growing bacteria, the main emphasis of these compounds was on translation. The DuPont group's ongoing work led to the creation of many *in vitro* tests that assessed how oxazolidinones affected the beginning, lengthening, and ending of protein synthesis. These substances, however, were unable to suppress any of the reactions that were examined, which suggested that the target was a very early, possibly undetectable step in the commencement of protein synthesis. Later research revealed that the quantity of mRNA supplied to the *in vitro* system significantly influenced the mode of action, with too much mRNA decreasing the effectiveness of the oxazolidinones. The eperezolid (or linezolid) titration in the presence of different mRNA quantities produced an IC50 of 15 μM (6 μg/ml), which was quite near to the linezolid-sensitive *E. coli* strain's minimum inhibitory

concentration (MIC) that was utilised to create the cell extracts. Oxazolidinones were unable to suppress the elongation or termination of protein synthesis using the same *in vitro* translation system, which further suggests that an early event, such as initiation, was the target [4].

To prevent bacteria from synthesising proteins, a synthetic antibiotic known as linezolid binds to rRNA on the 30S and 50S ribosomal subunits. It prevents the initiation complex from forming, which can shorten formed peptide chains and slow down the translation activity [5]. All other protein synthesis inhibitors that stop the elongation process occur later than the initiation process at the point of inhibition [6]. Cross-resistance to other inhibitors of protein synthesis has not yet been shown due to the distinct location of inhibition. Additionally, linezolid may inhibit the production of virulence factors, which would reduce the amount of toxins that Gram-positive infections generate [7]. The compound's activity is increased by the morpholino group in the first ring (from the left) and the fluoride atom in the second ring [8].

STRUCTURE-ACTIVITY RELATIONSHIP OF LINEZOLID

Studies on the link between structure and activity in oxazolidinones have shown that the activity requires the N-aryl group and the 5-S configuration. For the activity, the 5-acylaminomethyl group is to blame. It has been demonstrated that the aryl ring's electron-withdrawing group increases activity. While additional substituents on the proximal aromatic ring can alter solubility and pharmacokinetics, they have no effect on antibacterial efficacy (Figure 1) [9].

APPLICATION OF LINEZOLID

The following circumstances have been approved by the Food and Drug Administration for the use of linezolid: Hospital-acquired pneumonia (a) is caused by *Streptococcus pneumoniae*, including multidrug-resistant strains; (b) is caused by vancomycin-resistant *Enterococcus faecium* (VREF) infections, including cases with concurrent bacteremia; (c) is caused by complicated skin and skin structure infections (SSSIs), including diabetic foot infections (DFIs) without concurrent osteomyelitis, caused by *Streptococcus aureus* (MSSA and MRSA); (d) are uncomplicated SSSIs caused by MSSA or *S. pyogenes*; (e) is caused by community-acquired pneumoniae, including cases with simultaneous bacteremia, or MSSA; and (f) is pneumococcal meningitis [11, 12].

LITERATURE SEARCH

Two authors (Kalil AC, and Murthy MH) separately conducted a comprehensive literature search in MEDLINE/PubMed, EMBASE, and the Cochrane Library from the database's launch until February 2010. Every dispute was settled by consensus. We also perused abstracts from conferences that took place during that time, such as Chest, the Infectious Diseases Society of America, the American Thoracic Society, and the Interscience Conference on Antimicrobial Agents and Chemotherapy. We also examined relevant websites, including reports from the Food and Drug Administration and trial results archives (www.clinicalstudyresults.org and www.clinicaltrialresults.org). Linezolid, oxazolidinone, glycopeptides, vancomycin, teicoplanin, Gram-positive, infections, randomised, prospective, lungs, respiratory, and pneumonia were the keywords that were employed. There were no language limitations applied. The Institutional Review Board waived its review requirements for this study [13].

ANTIBACTERIAL SPECTRUM ACTIVITY

The majority of clinically relevant Gram-positive cocci, including VRE, MRSA, and high-level penicillin-resistant *Streptococcus pneumoniae*, which may be able to acquire resistance genes from

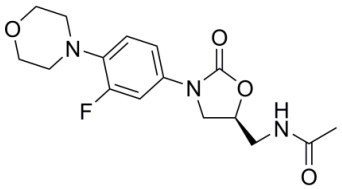

Figure 1. Structure of linezolid [10].

enterococci, have been demonstrated to be very resistant to linezolid *in vitro*. Using the common anti-TB drugs, Linezolid demonstrated *in vitro* efficacy against isolates of *Mycobacterium tuberculosis* (MTB) that were both drug-susceptible and -resistant without displaying cross-resistance. However, because to its severe side effects and expense, its long-term use in the treatment of MDR-TB may be limited. Additionally, Linezolid has shown efficacy against *Listeria monocytogenes*, *Bacteroides fragilis*, *Nocardia* spp., *Corynebacterium* spp., and *Moraxella catarrhalis*.

However, because Gram-negative infections are inherently resistant to oxazolidinones, they are not a good choice for treating them. Conversely, these antibiotics do not have any effect on whole cells, but they are very effective against permeabilized *E. coli* and profoundly active against protein synthesis in *Escherichia coli* cell-free extracts. This seeming paradox was clarified when it was discovered that null mutations in either the outer membrane protein Tol C or the acrAB efflux pump made WT *E. coli* extremely vulnerable to linezolid. Consequently, the lack of linezolid activity against whole Gram-negative cells can be explained by the cell's pumping of linezolid to the external environment via the transmembrane pump and consequent prevention of essential intracellular accumulation [14].

PHARMACOKINETICS

Since linezolid has a nearly 100% bioavailability when taken orally, dosage adjustments are not necessary when alternating between oral and intravenous (IV) delivery methods due to the drug's quick oral absorption. After an oral dosage, peak levels (Cmax) are attained 1–2 h later. When taking linezolid with high-fat diet, Cmax will drop by around 20% and the time it takes to achieve Cmax will increase by about 1–2 h. The serum concentration-time curve's (AUC) area under the curve will not change, though.

Co-administration of antacids had no effect on the oral absorption of linezolid. In a recent study, bioavailability was shown to be decreased to about 85% in eight adult patients with cystic fibrosis (CF), maybe because of pancreatic enzyme insufficiency. Over the therapeutic dosage range, the pharmacokinetics of linezolid are mostly linear, with the Cmax and AUC being proportionate to the dose. At high dose ranges, there is a small degree of nonlinearity, where a drop in clearance is seen. The most predictive pharmacokinetic/pharmacodynamic measures for linezolid effectiveness are the ratio of the AUC to the MIC (AUC/MIC) and the time above MIC (T. MIC). When administered 12-hourly, serum values are above the MIC90 for susceptible pathogens for the majority of the dosage period [15].

When used orally, linezolid is readily absorbed and has a bioavailability of about 100%. Compared to comparable treatment, which can only be administered parenterally, this enables the patient to switch from intravenous to oral therapy as soon as they reach clinical stability (i.e., vancomycin or quinupristin/dalfopristin {Synercid}). Hepatic oxidation is the mode of metabolism for linezolid; no cytochrome P-450 pathways are involved. Renal, faecal, and nonrenal processes account for 30, 5, and 60% of the mechanisms of elimination, respectively. 5-hours is roughly the half-life. An antibiotic is usually taken three times its half-life; the dosage interval for linezolid is every 12 h. For individuals with renal impairment, there is currently no suggested dose change; nevertheless, linezolid is eliminated by haemodialysis and should be given after dialysis [16].

ADVERSE EFFECT

A 4-year-old kid was brought in complaining of a 5-day period of high fever, coughing, and dyspnea. Upon inspection, the child's left side air entrance was decreased, and they were tachypneic. Ceftriaxone and cloxacillin were begun for her. CT chest revealed a little effusion and a lung abscess in the left lower lobe. Vancomycin was substituted for antibiotics because to the ongoing fever increases. When the youngster began to improve gradually, the antibiotic prescribed for 4 weeks, vancomycin, was switched to linezolid and given for 14 days. Following a 2-week period, the parents reported a blackish pigmentation on their tongue. Examining the tongue revealed a blackish discoloration on the dorsum. Linezolid was discontinued.

The youngster is doing well after the blackish discolouration disappeared. When treating methicillin-resistant *Staphylococcus aureus* infections, linezolid is frequently utilised. Typical adverse effects include nausea, vomiting, and headaches. Extended use may result in bone marrow suppression and neuropathy. One of the uncommon adverse effects of long-term linezolid medication is tongue discolouration. It could be brought on by chromogenic bacteria's actions and debris buildup on the tongue, which then stains the area. The tongue discolouration side effect of linezolid has a Naranjo probability rating of 6, meaning it was most likely the cause. Good dental hygiene and stopping the triggering substance are the major forms of therapy.

Patents of Linezolid

Many patents have been filed for innovations that aim to improve oral dosage formulations of linezolid. Here, a few instances are spoken about. Taste-masked microcapsules of linezolid were made possible by an innovation (publication number: US6451345B1), which are oral dosage forms in which a combination of microencapsulation hides the bitter taste of the medication [18]. The oral use of these dosage forms is appropriate. A different invention (publication number: US9492459B2) seeks to offer a unique pharmaceutical composition that includes linezolid form III in addition to excipients that are satisfactory to pharmaceuticals and a method for creating such a composition [18]. Publication number: US20170066728A1) describes an innovation that deals with the method of preparing enantiomeric pure linezolid form I. The process was converting an enantiomerically pure linezolid hydroxide compound of formula II into a linezolid form I compound of formula I.

Safety

Adverse events (AEs) are defined as unfavourable health outcomes that happen to patients or participants in clinical trials after they take linezolid, but which are not always linked to the medication. One or more of the following criteria had to be met in order for an adverse event to be classified as serious (SAE): (1) death; (2) life-threatening complications; (3) hospitalisation or extended hospitalisation; and (4) permanent or severe impairment. After receiving the drug, the researchers kept an eye on AEs and SAEs for a duration of 30 days. Regardless of whether they were connected to linezolid, local investigators assessed the severity of all reported adverse events. Five categories were used to group the AEs and SAEs: strongly associated, highly likely to be related, potentially related, probably related, and improbable or unrelated. Clinicians tailored the standard methods for AE diagnosis and treatment based on the individual patient's clinical situation.

CONCLUSION

There are currently few alternatives for treating infections brought on by common bacteria in the intensive care unit. Linezolid can be a useful addition to the antibiotic arsenal against MRSA and VRE, as evidenced by its inclusion in several clinical practice guidelines. The outcomes of the ongoing clinical trials on linezolid for VRE infections and MRSA pneumonia are important because they provide physicians confidence in the drug's efficacy. While linezolid is effective in stopping the spread of multidrug-resistant bacteria, researchers still need to improve infection control strategies.

Even though the majority of patients handle linezolid well, it is crucial to conduct continuous monitoring to identify any potentially dangerous side effects, such as anaemia and thrombocytopenia,

as well as long-term side effects including peripheral neuropathy and optic neuritis. To understand the function of linezolid in treating specific illnesses and in a variety of patient demographics, more clinical research is needed. The cost-effectiveness of linezolid has to be further investigated since cost-control concerns have an impact on antimicrobial stewardship strategies. The metrics that emerge from this analysis are crucial for assisting in the reduction of healthcare costs in environments with limited resources.

REFERENCES

1. Claudia Foti, Anna Piperno, Angela Scala, Ottavia Giuffrè. Oxazolidinone Antibiotics: Chemical, Biological and Analytical Aspects. Molecules. 2021; 26(14): 4280.
2. John Dotis, Elias Iosifidis, Maria Ioannidou, Emmanuel Roilides. Use of linezolid in pediatrics: a critical review. Int J Infect Dis. 2010; 14(8): e638–e648.
3. Stevens Dennis L, Brian Dotter, Karl Madaras-Kelly. A review of linezolid: the first oxazolidinone antibiotic. Expert Rev Anti-Infect Ther. 2004 Feb 1; 2(1): 51–9.
4. Shinabarger D, Eliopoulos GM. Resistance to linezolid. In Antimicrobial Drug Resistance: Mechanisms of Drug Resistance. Totowa, NJ: Humana Press; 2009 Jul 6; 247–257.
5. Batts DH. Linezolid-a new option for treating Gram-positive infections. Oncology (Williston Park, NY). 2000 Aug 1; 14(8 Suppl 6): 23–9.
6. Ament PW, Jamshed N, Horne JP. Linezolid: its role in the treatment of Gram-positive, drug-resistant bacterial infections. Am Fam Phys. 2002; 65(4): 663–670.
7. Zurenko GE, Gibson JK, Shinabarger DL, Aristoff PA, Ford CW, Tarpley WG. Oxazolidinones: a new class of antibacterials. Curr Opin Pharmacol. 2001; 1(5): 470–476.
8. Watkins RR, Lemonovich TL, File TM Jr. An evidence-based review of linezolid for the treatment of methicillin-resistant Staphylococcus aureus (MRSA): place in therapy. Core Evid. 2012; 7: 131–143.
9. Poce G, Cocozza M, Consalvi S, Biava M. SAR analysis of new anti-TB drugs currently in pre-clinical and clinical development. Eur J Med Chem. 2014; 86: 335–351.
10. Kumar Mayur, Anthony Curtis, Clare Hoskins. Application of Nanoparticle Technologies in the Combat against Anti-Microbial Resistance. *Pharmaceutics*. 2018; 10(1): 11. https://doi.org/10.3390/pharmaceutics10010011
11. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ. Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. Clin Infect Dis. 2003; 36(2): 159–168. doi: 10.1086/345744.
12. Faella F, Pagliano P, Fusco U, Attanasio V, Conte M. Combined treatment with ceftriaxone and linezolid of pneumococcal meningitis: a case series including penicillin-resistant strains. Clin Microbiol Infect. 2006; 12(4): 391–394.
13. Kalil AC, Murthy MH, Hermsen ED, Neto FK, Sun J, Rupp ME. Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: a systematic review and meta-analysis. Crit Care Med. 2010 Sep 1; 38(9): 1802–8.
14. Abed Zahedi Bialvaei, Mohammad Rahbar, Mehdi Yousefi, Mohammad Asgharzadeh, Hossein Samadi Kafil. Linezolid: a promising option in the treatment of Gram-positives. J Antimicrob Chemother. 2016; 72(2): 354–364. doi:10.1093/jac/dkw450 Advance Access publication 5 December 2016.
15. Sally Ager, Kate Gould. Clinical update on linezolid in the treatment of Gram-positive bacterial infections. Infect Drug Resist. 2012; 5: 87–102.
16. Zyvox (linezolid). Package insert. Peapack, NJ: Pharmacia & Upjohn. Retrieved May 2001, from: http://www.zyvox.com/pdfs/zyvox_full_ prescribe_012001.pdf.
17. Muthu Meera, Naresh Kanna, Muthu Chidambaram. A Rare Adverse Effect Following Prolonged Linezolid Therapy. Indian J Pediatr. 2023Jun; 90(6): 618. https://doi.org/10.1007/s12098-023-04535-7.
18. Percel PJ, Vishnupad KS, Venkatesh GM, inventors; Aptalis Pharma Ltd, assignee. Functional coating of linezolid microcapsules for tastemasking and associated formulation for oral administration. United States patent US 6451345B1. 2000 Jan 20.

