Linezolid: a Promising Agent for the Treatment of Multiple and Extensively Drug-Resistant Tuberculosis

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Abstract

Tuberculosis is a severe, infectious disease caused by Mycobacterium tuberculosis. The aim of this review was to present the efficacy of linezolid as an agent against multidrug and extensively drug-resistant tuberculosis as gathered from many recent research studies. Linezolid seems to have strongly the potential of being used as an anti-tuberculosis agent because it blocks bacterial ribosomal protein synthesis. Nevertheless caution is required because of the adverse effects it causes, especially when the linezolid daily dosage exceeds 600 mg. The most severe adverse effects include anemia, peripheral neuropathy, optic neuropathy and thrombocytopenia. Still, more trials and research need to be done in order to gather more information and value the cost-benefit dosage of the treatment.

Keywords

adverse effects, efficacy, extensively drug-resistant TB, linezolid, multi-drug resistant TB

INTRODUCTION

Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis, constitutes one of the most severe diseases around the globe. Although it was thought to be incurable until the middle of the 20th century, new drug regimens are added to our armamentarium with favourable results. It is still one of the most challenging public health problems worldwide with an estimated 9 million people infected worldwide. In recent years, TB has shown a significant boost in developed countries because of immigration from countries with high prevalence as well as a rising incidence of TB and HIV co-infection. As a result, an increase of TB burden is also anticipated over the next few years owing to population migration patterns. According to the World Health Organization (WHO) report in 2010, there were an estimated 9.4 million new cases of TB and 14.0 million prevalent cases causing death to 1.3 million people in 2009. In India there were an estimated 2.0 million cases (21% of the estimated worldwide burden).

Multiple and Extensively Drug-Resistant Tuberculosis

Drug-resistant TB has been reported since the early days of chemotherapy. The first line agents that have been and are
still used for the treatment of TB are isoniazid, rifampin, pyrazinamide, streptomycin, and ethambutol. Resistance emerged and then second-line agents were introduced such as fluoroquinolones, ethionamide, amikacin, capreomycin, p-aminosalicylic acid, cycloserine, and kanamycin. TB with bacillary resistance to at least isoniazid and rifampin is defined as Multi-Drug Resistant TB (MDR-TB) and has become a global epidemic issue. Surveillance data indicate that MDR-TB is an emerging problem, especially in countries of the former Soviet Union (FSU), Israel, and areas of the People's Republic of China. Since active TB will develop in only a proportion of persons infected with M. tuberculosis directly after primary infection, the prevalence of MDR-TB may still be underestimated. Furthermore, strains of M. tuberculosis that are resistant to second-line drugs are also emerging. Drug resistance of M. tuberculosis to any fluoroquinolone and to at least one of the injectable drugs (capreomycin, kanamycin, or amikacin), in addition to isoniazid and rifampin resistance, is defined as Extensively Drug-Resistant TB (XDR-TB). Anti-TB drugs have to cross various physical barriers before reaching their targets: (i) the granuloma as a host-derived containment for the pathogen, (ii) the infected host cell, and (iii) the pathogen’s envelope. The phenotypic drug resistance observed in M. tuberculosis is mediated by the physiological downshift to dormancy. Nutrient starvation causes the pathogen to arrest growth, minimize respiration, and become resistant to drugs while maintaining viability, thereby mimicking some of the features of M. tuberculosis persistence.

Although genetic resistance to an anti-TB medication happens naturally, in consequence of chromosomal mutations that accompany mycobacterial replication, MDR-TB is a man-made phenomenon that has emerged owing to improper TB treatment. MDR-TB and XDR-TB are more difficult to treat than drug-susceptible TB, with substantially worse outcome alongside mounting drug resistance. It is often necessary to include the WHO group 5 drugs in the treatment of XDR-TB and fluoroquinolone-resistant MDR-TB. The WHO group 5 drugs classification refers to anti-TB drugs with unclear efficacy or an unclear role in MDR-TB treatment. These include thioacetazone, linezolid, high-dose isoniazid, clofazime, amoxicillin with clavulanate, macrolides, carbapenems, and thioridazine. Both cohort analysis using robust Poisson regression models and meta-analysis using random-effects models showed that use of linezolid substantially and significantly increased the probability of a favourable outcome by 57%. Defining clinically significant improvement by risk ratios 1.2 or 0.9, neither cohort analysis nor meta-analysis demonstrated any add-on benefit from the use of the other group of 5 drugs (high-dose isoniazid, clofazime, amoxicillin with clavulanate, macrolides, carbapenem, and thioridazine) with respect to outcome for XDR-TB or fluoroquinolone-resistant MDR-TB patients treated with linezolid.

Epidemiology of tuberculosis

According to the global tuberculosis report that was presented by WHO in 2019, the number of people with tuberculosis was estimated to about 10 million, an equivalent of 132 cases per 100,000 population. The number of deaths caused by tuberculosis among HIV-negative people decreased from 1.7 million in 2010 to 1.2 million in 2018 (a 27% reduction), and this decrease was even more pronounced among HIV-positive people from 624,000 in 2000 down to 251,000 in 2018 (a 60% reduction). The estimated number of patients with multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) amounted to 484,000 incident cases in 2018 and 78% of these were MDR-TB. The number of people registered to undergo a second-line MDR-TB treatment was 156,071 in 2019 compared to 139,114 people in 2017 and 30,500 in 2009. The registered patients for XDR-TB treatment numbered 11,403 and this was elevated by 16% compared to those in 2017. Fifty-six percent of MDR/RR-TB patients completed the treatment successfully in 2016, whereas in 8% of the cases the treatment failed, 15% died, 15% were lost to follow-up, and 6% of the treatment outcome was not evaluated. Similarly, among 9,258 patients who started XDR-TB treatment in 2016, 39% completed the treatment successfully, 26% died, the treatment of 18% failed, and 18% were lost to follow-up or their treatment outcome was not evaluated. Current treatment for tuberculosis requires multiple drug combinations with varying treatment periods starting at 6 months for drugs susceptible to tuberculosis and up to 9-20 months in the case of rifampicin-resistant tuberculosis (RR-TB) or MDR-TB and sometimes the treatment period may be longer if there is additional drug resistance or if the clinical and laboratory outcomes after the completion of the treatment are unsatisfactory.

Linezolid Pharmacology

Oxazolidinones are a new class of antimicrobials that inhibit protein synthesis at a site not targeted by other antimicrobials. Linezolid, the first of these compounds to be approved by the U.S. Food and Drug Administration, is a synthetic antibiotic that is licensed for the treatment of serious skin and soft tissue infections, bacteremia and pneumonia due to resistant in beta-lactams and glycopeptides gram-positive bacteria, including methicillin-resistant staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE). It is also active in vitro against many gram-positive actinomycetes, including Nocardia, Actinomadura and Mycobacterium tuberculosis. Linezolid is a bacteriostatic drug that blocks the initiation step of bacterial ribosomal protein synthesis by a novel mechanism of action. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit thus inhibiting the formation of a functional 70S initiation complex that is essential for the bacterial translation process. This inhibition does not...
affect the formation of mammal proteins, but the prolonged treatment of linezolid can interfere with the mitochondrial protein synthesis in mammals, thus causing its dysfunction. Linezolid is also a weak, reversible, non-selective inhibitor of monoamine oxidase and therefore it may cause drug-drug interactions with adrenergic and serotonergic agents. Linezolid is rapidly and extensively absorbed in both the oral suspension and tablet formulation, with oral availability approaching 100%. In healthy volunteers the time to maximum concentration (T_{max}) is 0.5-2 h. Co-administration with a high-fat meal may delay the T_{max} and slightly reduce the maximum plasma concentration (C_{max}), but does not affect the area under curve (AUC). Protein binding is reported to be 31%. Linezolid has complex metabolism with two primary and multiple minor metabolites. Its main metabolic route is the non-enzymatic oxidation of the morpholine ring that produces two inactive ring-opened carboxylic acid derivatives, the aminoethoxycetic acid metabolite and the hydroxyethyl glycine metabolite. Linezolid does not pass through the hepatic P450 metabolism and therefore it does not inhibit the activities of CYP isofoms. Major route for linezolid excretion is urine. As linezolid is metabolized to its main metabolites, they are excreted via urine. Thirty percent of the dose given is excreted as linezolid, 40% is excreted as hydroxyethyl glycine and 10% as aminoethoxycetic acid. The rate-limiting step in linezolid clearance is the non-enzymatic formation of the primary metabolite, and both renal and non-renal routes are involved in elimination, with non-renal elimination accounting for roughly 65%. Linezolid has good tissue penetration, including lung and epithelial lining fluid. Penetration into cerebrospinal fluid (CSF) is good and as a result linezolid can be used in the treatment of tuberculous meningitides. Linezolid appears to have both time and concentration dependent killing, with both the AUC/MIC ratio and per cent time above MIC (%T > MIC) correlated with linezolid activity against Gram-positive bacteria.

Linezolid treatment in multiple and extensively drug-resistant tuberculosis

After having searched the PubMed database, we found several studies as well as some systematic reviews that present the efficacy, the tolerability and adverse events of linezolid use for the treatment of the MDR-TB and XDR-TB.

Sotgiu et al. presented a systematic review and meta-analysis where they collected 12 studies (11 countries from three continents) reporting complete information on treating MDR-TB cases which were based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Meta-analysis was performed using the individual data of 121 patients with a definite treatment outcome (cure, completion, death or failure). Most MDR-TB cases achieved sputum smear clearance 92.5% and 93.5% culture conversion respectively after treatment with individualized regimens containing linezolid [median (inter-quartile range) times for smear and culture conversions were 43.5 and 61 days, respectively] and 81.8% of patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage ≤600 mg versus >600 mg). Adverse events were observed in 58.9% of the patients, of which 68.4% were major adverse events that included anemia 38.1%, peripheral neuropathy 47.1%, gastro-intestinal disorders 16.7%, optic neuritis 13.2%, and thrombocytopenia 11.8%. The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg.

Cox and Ford also included a total of 11 studies in their review, representing 148 patients. The pooled proportion for treatment success was 67.99%. There were no significant differences in success comparing daily linezolid dose (≤600 vs. >600 mg) and mean linezolid duration (≤7 vs. >7 months). The pooled estimate for the frequency of any adverse events was 61.48%, with 36.23% discontinuing linezolid due to adverse events. Nine studies reported the proportion of patients who had converted sputum cultures from positive to negative during linezolid treatment: the pooled proportion was 97.86%.

Similarly to the above meta-analyses, many more studies have been published giving approximately the same results. Gratifying efficacy of linezolid and a variety in the percentages of the same adverse effects compose the profile of the drug according to all examined references. Additionally, one study examined the intermittent dosing of linezolid over the daily dosing and found that intermittent use of the drug may optimize the serum linezolid profile thereby enabling safe, efficacious and prolonged use of linezolid. The high frequency of adverse events is an important limitation of linezolid and as a consequence therapeutic drug monitoring should be considered. Close monitoring for toxicity in long term treatment with linezolid can be achieved with conventional serum sampling and as an alternative with dried blood spot analysis or oral fluid sampling. Full blood count every month is necessary as well as active monitoring for neuropathy. Severe adverse events—predominantly neuropa.thies and bone marrow suppression—lead to discontinuation of linezolid in over a third of patients and dose reduction in others. These results indicate that a reduced daily dose of ≤600 mg from treatment initiation may lower the frequency of occurrence of adverse events without impacting treatment success. In particular, reducing the daily dose may reduce the impact of bone marrow suppression, particularly severe anemia. In addition, an incident of rhabdomyolysis occurred in individuals receiving long-term linezolid therapy, although it is not a common adverse effect. Elevated AST or CPK levels should draw attention if observed, as linezolid is thought to decrease mitochondrial protein synthesis that was dose-related and coincided temporarily with rhabdomyolysis. In this case, linezolid-induced inhibition of mitochondrial protein synthesis may be the mechanistic cause of this event and maybe a means of predicting toxicity and the dose-related degree of this toxicity.
Moreover, linezolid administration to children for the treatment of the MDR-TB raises serious concerns. Several types of research have been published about this topic. The results were quite similar to the adult research, especially the ones referring to the efficacy of the drug, which reaches 81.7%.[43,45] Regarding the side effects of linezolid, these are not quite the same as those in adults. Children present with nausea and vomiting as the most common adverse effects.[45] and treatment is rarely discontinued. Hematologic adverse events such as anemia and thrombocytopenia occur if treatment is highly dosed and prolonged. Peripheral neuropathy (“stocking and glove distribution”) or optic neuropathies are mentioned at prolonged use of linezolid.[65]

Additionally, in a couple of trials, resistance to linezolid has been observed in long term treatment. One of these trials has found genetic disposition, as mutations either in 23S rRNA or in ribosomal protein L3 have been detected.[58] Simultaneously, linezolid resistance was observed in 4 out of 210 MDR-TB patients with no mutations found in potential target genes and with an unclear mechanism. Possible effects of efflux pump inhibitors (reserpine) and the reduced input rate of the drug could account for the first hints of resistant mechanisms.[66]

Tang et al.[67] in a multicenter, prospective, randomized controlled study for treating extensively drug-resistant TB (XDR-TB) concluded that the patients exposed to linezolid (1200 mg per day for 4-6 weeks followed by 300-600 mg per day thereafter) had better treatment outcomes compared to those in the control group (78.8% versus 37.6%, p<0.001) by 24 months. Thus, the treatment success rate was significantly higher in linezolid therapy group (69.7%) compared to control group (34.4%, p=0.004). However, the main concern remained the safety and the tolerability of linezolid, as 82% of the patients experienced adverse events including gastrointestinal and hematological reactions, optic neuropathy and peripheral neuropathy.

The study of Liu et al.[68] used 600 mg of linezolid for the treatment of XDR-TB patients indicating a well-tolerated and efficient treatment with low rate of side-effects. Similarly, the systematic review and meta-analysis of Sotgiu et al.[48] suggested an excellent efficacy of linezolid at a dosage of ≤600 mg in the treatment of MDR-TB and XDR-TB as it minimizes the occurrence of adverse events. However, the administration of higher doses of linezolid (1200 mg daily), as reported by Xu et al.[69] resulted in severe adverse events to 82% of the patients and thus the linezolid therapy must be closely monitored for adverse side effects.

The systemic review and meta-analysis performed by Zhang et al.[70] suggested that the use of linezolid is a valid option for treating drug-resistant-TB patients and the benefits and the drawbacks like the adverse events of such treatment should be taken into account by the specific needs of individual patients.

A recent systematic review and meta-analysis by Millard et al.[71] reports that despite the increased use of linezolid treatment in patient with MDR-TB, its safe dosing still remains unclear. Thus, additional prospective clinical studies are required to better assess its daily dosage with minimal adverse effects.

The latest update of the WHO treatment guidelines for drug-resistant tuberculosis regrouped medicines used in the design of longer MDR-TB treatment regimens, based upon current evidence on their effectiveness and safety. Clofazidine and linezolid are now recommended as core second-line medicines in the MDR-TB regimen while p-aminosalicylic acid is an add-on agent.[72]

Nowadays, a new agent, PNU-100480, is being tested. Its structure differs from that of linezolid by a sulfur atom instead of the oxygen atom in the ring structure. Structure modification of oxazolidinones influences both activity and toxicity; PNU-100480 is more active against TB than linezolid and that the efficacy was similar to that of isoniazid (INH) and/or rifampin. Unfortunately, data on PNU-100480 in vitro activity have been obtained exclusively from testing drug-susceptible isolates. The clinical importance remains to be seen when phase III studies are performed.[73]

**Linezolid-induced adverse events**

Although linezolid is generally a well-tolerated drug, it can cause several adverse effects, especially in long-term use. The most common linezolid-related adverse reaction observed are nausea, headache, diarrhea, elevated liver enzymes levels, and myelosuppression including thrombocytopenia, sideroblastic anemia, and leukopenia. Other rare but severe adverse reactions are observed mostly in the case of long-term linezolid therapy (> 28 days) including lactic acidosis, peripheral and ocular neuropathy, and serotonin syndrome.

Thrombocytopenia is the most common linezolid-related adverse event among patients caused by myelosuppression with a reported incidence of about 15-50%.[74,75] Although thrombocytopenia is associated with long-term linezolid therapy, it is reversible after the discontinuation of linezolid and eventually recovery occurs within 4-13 days.[77,78] The mechanism by which linezolid induces thrombocytopenia was initially thought to be due to bone marrow suppression.[79] However, an alternative mechanism has been postulated[80] where the drug or its metabolites bind to platelet membrane glycoproteins forming a complex which is recognized by circulating IgG antibodies. Subsequently, the IgG-drug-platelet complex is removed by the reticuloendothelial system, producing thrombocytopenia. Thus, platelet count should be monitored every week during the course of treatment and discontinuation of linezolid should be considered in patients who have developed thrombocytopenia and the platelet counts eventually return to normal values.

Prolonged linezolid therapy, ranging from 4 weeks to 6 months, can cause anemia as an adverse effect which is caused by a decline in the hemoglobin levels, and an increase.
in serum iron levels and iron saturation. The mechanism by which linezolid can induce anemia is through a direct effect on bone marrow which is responsible for the production of erythrocytes with concurrent reticulocytopenia. Serum iron levels and iron saturation are increased which may be predictive of this adverse event. Bone marrow examination may indicate erythroid hypoplasia with vacuolated erythroblasts and megaloblastosis. In addition, special staining on bone marrow smears can reveal elevated levels of ringed sideroblasts (> 15%) which are characteristic of sideroblastic anemia. Sideroblasts consist of mitochondria loaded with iron due to the reduced heme synthesis. Severe cases of anemia are treated with blood transfusion, whereas linezolid withdrawal results in the disappearance of ringed sideroblasts and restoration of hemoglobin levels back to normal values.

Linezolid could induce abnormal liver function tests, such as elevated alanine transaminase (ALT) and γ-glutamyltransferase enzyme levels. However, it does not seem severe enough to warrant drug discontinuation.

Linezolid-associated lactic acidosis is an uncommon adverse drug reaction that can occur in adult patients with multidrug-resistant tuberculosis especially after prolonged use (> 28 days). Lactic acidosis occurs due to low pH in body tissues and blood and it is accompanied by increased levels of L-lactate. Lactic acidosis is characterized by repeated episodes of nausea, vomiting, and muscle weakness. It is a serious adverse effect that can result in multi-organ failure, such as liver and renal dysfunction, and death. The mechanism by which linezolid may induce lactic acidosis is due to mitochondrial toxicity where cytochrome c oxidase activity is decreased. Cytochrome c oxidases are partially synthesized by mitochondrial ribosomes but linezolid impairs mitochondrial protein synthesis, thus causing lactic acidosis. When lactic acidosis occurs, an immediate medical evaluation is required. Discontinuation of linezolid usually resolves lactic acidosis within two weeks.

Peripheral and ocular neuropathy are serious adverse events reported in patients treated with prolonged linezolid therapy for more than 28 days. These two neuropathies may be developed either independently or simultaneously in the same patient. Linezolid-related peripheral neuropathy is characterized by paresthesia, numbness and mild weakness of the distal limbs. However, symptoms do not improve after linezolid withdrawal revealing that peripheral neuropathy is an irreversible process. Linezolid-induced ocular neuropathy has a sudden onset with blurred vision, pain in the eye, tearing, bilateral visual loss and color discrimination throughout the duration of therapy with linezolid. The mechanism responsible for this type of neuropathy may be due to the mitochondrial toxicity where impaired mitochondrial protein synthesis occurs that leads to the death of neuronal axons. Alternatively, it inhibits monoamine oxidase activity. No other specific treatments exist for either of these conditions, apart from discontinuing linezolid treatment. Patients who are to receive linezolid treatment for more than 28 days should be considered for a baseline ophthalmological examination to assess visual acuity, color discrimination and visual fields, and a baseline neurological examination to assess sensory function. Additionally, patients that undergoing linezolid treatment for extended periods must be frequently monitored for peripheral neuropathy and/or ocular neuropathy.

Linezolid-related therapy may cause the life-threatening serotonin syndrome when it is co-administered with selective serotonin reuptake inhibitors such as monoamine oxidase (MAO) inhibitors. Serotonin syndrome is characterized by spasmodic jerky contractions of muscles, tremor, hyperpyrexia, hyper-reflexia, cognitive dysfunction and lack of coordination. Linezolid is a weak, competitive, reversible, non-selective inhibitor of MAO. MAO is a mitochondrial enzyme that deaminates aromatic amines and thus inactivates neurotransmitters such as serotonin and dopamine. MAO has two isoforms, MAO-A which deaminates serotonin and norepinephrine, and MAO-B which deaminates dopamine and phenylethylamine. Linezolid inhibits MAO-A because it is structurally similar to toloxatone, an inhibitor of MAO-A that is used for the treatment of depression. As a result, the concentration of serotonin increases intracellularly causing serotonin syndrome. The onset of serotonin syndrome caused by linezolid occurs within the first week after the initiation of the linezolid therapy while the patients receive concomitant serotonin reuptake inhibitors. However, the onset symptoms in older patients can be delayed for up to 3 weeks after the initiation of linezolid treatment. This may be caused by the decreased synthesis of serotonin and the reduced serotonin receptor expression found in the elderly. Immediate withdrawal of the offending agent and replacement of the antibiotic whenever possible should be considered. In practice, however, this may not be possible especially when pathogens are multidrug resistant and thus a dose reduction of the serotonin reuptake inhibitor should also be considered.

CONCLUSION

Despite the favourable efficacy, the necessity of caution in the prescription of linezolid for the treatment of MDR-TB and XDR-TB is strongly suggested. The high proportion of cases experiencing adverse events and requiring drug interruption or dosage reduction suggests that the use of linezolid should be limited to severe cases in specialized drug resistant-TB reference centres, where both inpatients and outpatients can be carefully monitored for any occurrence of serious adverse events and where facilities are well equipped to manage any serious problem. Balancing the long term risk-benefit ratio of linezolid requires identifying a dose with sufficient potency but less toxicity.
Linezolid Treatment for Tuberculosis

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Резюме

Туберкулёз – это тяжёлое инфекционное заболевание, вызываемое Mycobacterium tuberculosis. Целью настоящего обзора является представление эффективности линезолида в качестве лекарственного средства против мультирезистентного и экстенсивно резистентного туберкулёза, согласно многим современным научным исследованиям. Линезолид обладает большим потенциалом в качестве противотуберкулёзного препарата, поскольку он блокирует синтез рибосомального белка в бактериях. Тем не менее, следует соблюдать осторожность при использовании его из-за побочных эффектов, которые он вызывает, особенно если суточная доза линезолида превышает 600 мг. Наиболее серьёзные побочные эффекты включают анемию, периферическую невропатию, оптическую невропатию и тромбоцитопению. Тем не менее, необходимы дальнейшие исследования и испытания для сбора большего количества информации и анализа рентабельности дозировки лечения.

Ключевые слова

побочные эффекты, эффективность, экстенсивно резистентный туберкулёз, линезолид, мультирезистентный туберкулёз