Impact of Linezolid on Toxic Optic Neuropathy in Patients with Drug-Resistant Tuberculosis

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Abstract: **Background**: The global burden of drug-resistant tuberculosis (DR-TB) has emerged as a significant public health challenge, necessitating the development and use of effective treatment regimens. Linezolid, an oxazolidinone antibiotic, has shown promise in the management of DR-TB due to its ability to inhibit the growth of mycobacteria that are resistant to traditional anti-TB drugs. However, its use has been associated with several adverse effects, one of which is toxic optic neuropathy (TON). **Objective**: This study aims to investigate the development of toxic optic neuropathy induced by linezolid in patients with drug-resistant tuberculosis. **Method**: We report a case of a patient with drug-resistant tuberculosis who received linezolid therapy. The reported side effect was the onset of toxic optic neuropathy symptoms. **Result**: There are two MDR-TB patients who received linezolid therapy. Both patients have been undergoing treatment for one year. They reported complaints of blurred vision after nearly one year of receiving linezolid therapy. Visual acuity tests showed values of up to 2/60 in both eyes. Fundus photographs depict the condition of the patients' eyes, showing vision problems due to defects in the visual field and possible abnormalities in the macula and optic nerve head. **Conclusion**: There was a disturbance in visual function after undergoing treatment for resistant tuberculosis (TB-RO). Linezolid, which is part of this treatment regimen, is strongly suspected to be the cause of the side effect known as toxic optic neuropathy (TON). Visual acuity improved again after the linezolid therapy was discontinued. The mechanism by which linezolid causes TON is likely related to mitochondrial dysfunction, disruption of blood flow to the optic nerve, and nutritional factors.

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1 INTRODUCTION

Tuberculosis (TB) has emerged as a persistent and evolving global health challenge over the past few decades. The increasing prevalence of this disease presents significant obstacles to its eradication, particularly as drug-resistant tuberculosis (DR-TB) cases continue to surface worldwide, complicating comprehensive treatment strategies. According to the Global TB Report 2023, the estimated incidence of TB worldwide reached 10.6 million in 2022, reflecting a troubling upward trend compared to previous years. Alarmingly, TB remains the second leading cause of death from infectious agents, surpassed only by COVID-19. Indonesia ranks second globally in TB cases, following India, with an estimated 1,060,000 reported cases, and China in third place. In 2022, approximately 410,000 individuals globally were estimated to suffer from drug-resistant TB (MDR/RR-TB). (WHO, 2023). In Indonesia, 12,531 patients were confirmed to have multidrug-resistant TB (RR/MDR-TB), yet only 8,089 of these patients-initiated treatment. (Kemenkes RI, 2023).

The rising incidence of drug-resistant TB poses significant challenges for eradication efforts. This issue is not merely about patient adherence to treatment but also encompasses the adverse effects associated with these medications, which can hinder patients' ability or willingness to complete their treatment regimens (Kemenkes RI, 2023; WHO, 2023).

One serious side effect associated with certain treatments for drug-resistant TB is toxic optic neuropathy (TON), a condition characterized by damage to the optic nerve due to exposure to toxic substances, including specific medications. Linezolid, a drug utilized in the management of drug-resistant TB, has been linked to severe cases of TON, particularly with long-term use. Symptoms of TON may include significant vision loss, alterations in the visual field, and disturbances in color perception. Alongside insufficient treatment, the occurrence of side effects from administered medications poses a significant challenge in the eradication of drug-resistant tuberculosis. One notable drug known for its severe adverse effects is linezolid. Commonly reported side effects associated with linezolid include myelosuppression, peripheral neuropathy, and toxic optic neuropathy. Linezolid toxicity is thought to be linked to the drug's interaction with mitochondrial 16s rRNA. Some studies have identified polymorphisms in patients' mitochondrial DNA (mtDNA) that may increase susceptibility to toxic optic neuropathy. Specifically, it has been proposed that the G3010A and A2706G polymorphisms in mitochondrial DNA are implicated in the development of this condition (Lifan et al., 2019; Sharma et al., 2017; Spinazzi, 2016).

Toxic optic neuropathy (TON) is a condition characterized by damage to the optic nerve resulting from exposure to harmful substances, including specific medications. Linezolid, a drug utilized for the treatment of drug-resistant tuberculosis, is one such medication recognized for its potential to cause TON. Numerous cases have documented significant instances of TON following prolonged use of linezolid. Symptoms of this condition may manifest as a decline in visual acuity, alterations in the visual field, and difficulties with color perception. Additionally, TON has been linked to irregularities in mitochondrial transport and defects within mitochondria along the neurons (Lifan et al., 2019; Sharma et al., 2017; Spinazzi, 2016).

Despite anecdotal reports of TON associated with linezolid use across various countries, the precise mechanism by which linezolid induces this condition remains poorly understood. Several hypotheses have been proposed, including mitochondrial toxicity, neurotoxicity, and the effects of prolonged treatment duration (Lifan et al., 2019; Sharma et al., 2017; Spinazzi, 2016). This study aims to investigate the development of toxic optic neuropathy induced by linezolid in patients with drug-resistant tuberculosis.

2 METHODS

This study presents a case report of two drug-resistant tuberculosis patients who developed toxic optic neuropathy following long-term linezolid therapy. These cases illustrate the challenges of managing treatment-related side effects and underscore the necessity for vigilant monitoring and innovative strategies in the comprehensive care of patients with drug-resistant tuberculosis.

The subjects in this study were DR-TB patients at the DR-TB Polyclinic, Muhammad Hoesin General Hospital, Palembang. We investigated patients with drug-resistant tuberculosis (DR-TB) who experienced toxic optic neuropathy (TON) as a side effect after undergoing linezolid therapy.

We conducted a thorough history-taking, physical examination, and supplementary tests on both patients to establish the diagnosis. A consultation with a subspecialist in retinal ophthalmology was performed to confirm the presence of toxic optic neuropathy.

3. RESULT

Two patients diagnosed with multidrug-resistant tuberculosis (MDR-TB) underwent treatment with linezolid. One patient was a 40-year-old male, while the other was a 61-year-old female. Both reported a sudden decline in vision after 11 and 12 months of linezolid therapy, respectively. This sharp decrease in visual acuity progressively worsened with the duration of treatment, rendering them unable to read text on paper or screens.

Figure 1: Fundus photograph of the first patient.
Papilla: Round with indistinct borders, hyperemic red color, cup-to-disc ratio (c/d) of 0.3 mm, and a vessel ratio of 2:3. Macula: RF positive, normal appearance. Retina: Blood vessel contours are normal. Color Vision: Positive for dischromatopsia. Contrast Sensitivity: 0.15 in both eyes.

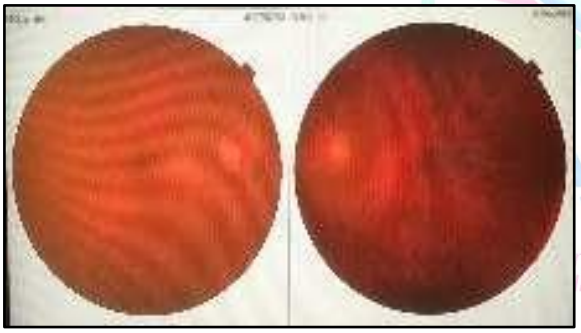

Figure 2: Fundus photograph of the second patient.
Papilla: Round with well-defined borders, hyperemic red color, cup-to-disc ratio difficult to assess, and a vessel ratio of 2:3. Macula: RF positive with decreased function. Retina: Blood vessel contours are normal.

To assess their ocular complaints, both patients underwent a comprehensive ophthalmological examination. Visual acuity tests revealed a significant reduction in vision, measured at 2/60 for both eyes of each patient. Fundus photography indicated potential optic nerve issues characterized by hyperemia of the optic disc and notable visual impairment, along with signs suggestive of possible color vision deficiencies (Figure 1 and Figure 2). The ophthalmologist recommended discontinuing linezolid immediately.

Following the cessation of the medication, the patients' visual acuity was evaluated again after two months. Remarkably, their vision improved to 6/7.5 in both eyes. Additionally, there was no indication of dischromatopsia, and contrast sensitivity showed significant enhancement. Intraocular pressure measurements remained normal, and the overall improvement in visual function, combined with the absence of color perception issues post-linezolid, clearly indicated that the toxic optic neuropathy experienced by both patients was induced by linezolid.

4 DISCUSSIONS

The rate of tuberculosis (TB) is rising annually. The WHO Global TB Report 2023 estimates that in 2022, around 10.6 million people worldwide were affected by tuberculosis, leading to approximately 1.3 million deaths. TB ranks as the second deadliest infectious disease following COVID-19, with Indonesia contributing 10% of global cases, making it second only to India in terms of the highest number of cases. That same year, roughly 410,000 individuals globally were estimated to have drug-resistant tuberculosis (DR-TB), achieving a treatment success rate of 63%. (WHO, 2023). In Indonesia, 31,000 cases of multidrug-resistant (MDR) or rifampicin-resistant tuberculosis (RR-TB) were documented. In South Sumatra, as per SITB records, there were 326 reported cases of DR-TB by early December 2023, with 89 new cases identified in Palembang, although only 60 patients (67.42%) began treatment. A significant obstacle to eradicating TB, particularly DR-TB, is the lengthy treatment duration compared to drug-susceptible TB (TB SO). As stated in the 2020 technical guidelines from Indonesia's Ministry of Health, short-term treatment requires 9 to 11 months, while long-term treatment spans 18 to 24 months (Rukmana et al., 2020). The prolonged exposure to medications increases the likelihood of side effects and toxicity.

Linezolid, an oxazolidinone antibiotic, is indicated for Gram-positive infections and is approved for treating bacterial pneumonia, skin infections, and infections caused by vancomycin-resistant enterococci (VRE), including those with associated bacteremia. It is important to note that it is not approved for Gram-negative infections, catheter-related bloodstream infections, or catheter site infections. Linezolid shows strong efficacy against

Mycobacterium tuberculosis and has demonstrated positive results in sputum conversion and high cure rates when combined with DR-TB treatment. As a result, the WHO includes linezolid in the treatment regimen for DR-TB, categorizing it as group A among second-line TB medications alongside bedaquiline and levofloxacin/moxifloxacin (Conradie et al., 2020; Wasserman et al., 2016; WHO, 2022).

Linezolid functions by inhibiting the initiation of bacterial protein synthesis via a unique mechanism that binds to the peptidyl transferase centre (PTC) in the 23S rRNA of the 50S ribosomal subunit of prokaryotes. It also attaches to the peptidyl complex at the mature 70S initiation complex, ultimately halting mRNA formation and exerting a bacteriostatic effect (Wasserman et al., 2016).

Toxic optic neuropathy (TON) refers to visual disorders due to damage to the optic nerve caused by toxins. This condition is characterized by bilateral, usually symmetrical, visual loss, destruction of the papillomacular bundle, central or cecocentral scotoma, and decreased colour vision. This disease is often not diagnosed or diagnosed at a stage where recovery is difficult (Stacey et al., 2023).

Optic neuropathy arises from damage to the optic nerve, which may be due to obstructed blood flow, inflammation, various pathological conditions, or trauma. Causes include ischemic optic neuropathy, optic neuritis, genetic factors, neoplasms (compressive or infiltrative), compression, toxicity/metabolic conditions, and trauma. Toxic optic neuropathy (TON) specifically refers to visual impairments resulting from optic nerve damage caused by toxic substances and is characterized by bilateral, usually symmetrical, vision loss, damage to the papillomacular bundle, central or paracentral scotomas, and decreased color vision. This condition is frequently either undiagnosed or recognized at an advanced stage, impeding recovery. Linezolid is highly suspected of causing TON as a side effect in patients with drug-resistant tuberculosis treated with this medication (Stacey et al., 2023; Wasserman et al., 2016).

The way linezolid leads to optic neuropathy is related to its inhibition of mitochondrial protein synthesis. Linezolid binds to the bacterial 50S ribosomal RNA, which shares structural similarities with mitochondrial ribosomes. This binding results in mitochondrial toxicity, leading to side effects such as optic neuropathy due to impaired synthesis of vital proteins required for normal mitochondrial function, which is essential for the health of nerve cells, including those in the optic nerve (Wasserman et al., 2016).

Various case reports from multiple countries have highlighted instances of TON in patients with drug-resistant tuberculosis. A review of available studies indicates a troubling trend regarding the incidence of TON linked to linezolid treatment across diverse populations and methodologies. A retrospective study conducted in the Netherlands and Italy found that 1 in 58 patients developed TON after an average treatment duration of 89 days, demonstrating a clear relationship with cumulative dosage and treatment duration. Data from India, based on a retrospective study, indicated a 5.8% incidence (5 out of 86 patients) after 7 to 11 months of treatment. In China, a prospective observational study noted TON in 9 out of 73 patients within 2 to 6 months, highlighting the frequent association of long-term linezolid use with this adverse effect. A systematic review encompassing 39 case reports urged the need for early screening for TON, noting that vision impairment could be reversible upon discontinuation of the drug. A retrospective study from Korea demonstrated that a daily dose of 300 mg of linezolid was effective against MDR/XDR-TB while posing a lower risk of neuropathic effects compared to higher doses. A meta-analysis comprising 12 studies from 11 countries reported that 13.2% of patients experienced TON following treatment durations of 300 to 690 days, underscoring the importance of careful monitoring for serious side effects while continuing to support linezolid's efficacy at a 600 mg daily dose (Bano et al., 2022; De Vriese et al., 2016; Hirano et al., 2015; Kardani et al., 2021; Lee et al., 2018; Sharma et al., 2017; Srivastava et al., 2017; Toolan et al., 2023; Vallabhaneni et al., 2023).

In Indonesia, the management of side effects associated with resistant tuberculosis treatment adheres to guidelines set forth in the Technical Manual for Active Monitoring and Management of Drug Side Effects (MESO Aktif). This manual outlines the severity levels and management strategies concerning visual disturbances related to linezolid therapy. Visual impairments are observed across all severity levels, from mild (Grade 1) to critical (Grade 4), potentially progressing to blindness (20/200 vision or worse). Whenever there is a suspicion of optic neuritis, linezolid treatment must be discontinued immediately, and the therapy should not be resumed (Lukitosari et al., 2022).

Both patients described experienced visual function issues after undergoing treatment for drug-resistant tuberculosis. Linezolid, part of their therapeutic regimen, is strongly suspected of being

responsible for the toxic optic neuropathy side effect in these cases. Additionally, both patients reported sensations of tingling and numbness, which might be attributable to peripheral neuritis stemming from prolonged exposure to linezolid.

The exact mechanism through which linezolid causes optic nerve damage is not fully understood, though several hypotheses exist regarding the process involved. Some research points to potential mechanisms that include mitochondrial dysfunction, restricted blood flow to the optic nerve, nutritional deficiencies, and other unidentified factors. Mitochondrial dysfunction is thought to be significantly involved. Linezolid inhibits bacterial protein synthesis, and unfortunately, the mechanisms of protein synthesis in human mitochondrial cells closely resemble those in bacteria, suggesting that linezolid may also impact mitochondrial function. This interference could compromise normal mitochondrial operations, resulting in cellular damage, including injury to optic nerve cells (Stacey et al., 2023; Wasserman et al., 2016).

The binding sites of linezolid on *M. tuberculosis* and human mitochondria, along with its downstream effects on protein synthesis inhibition, underscore its importance in therapy. Linezolid inhibits the formation of the 70S initiation protein complex in M. tuberculosis by attaching to the peptidyl transferase centre (PTC) in the 23S rRNA of the 50S ribosomal subunit, contributing to its antimicrobial efficacy. The drug's toxicity is associated with its binding to analogous structures on human mitochondrial 16S rRNA, resulting in a reduction in the synthesis of crucial components of respiration chain complexes I, III, IV, and ATP synthase, as well as disruption of oxidative phosphorylation. These domains within the mitochondrial PTC are partially coded by mitochondrial DNA, and mutations in the 16S rRNA gene (A2706G and G3010A) have been linked to linezolid-induced mitochondrial toxicity. The complex II protein, however, is encoded in the cell nucleus and synthesized by cytoplasmic ribosomes, rendering it unaffected by exposure to linezolid (Stacey et al., 2023; Wasserman et al., 2016).

The G3010A polymorphism is a specific genetic variation located within the mitochondrial 16S rRNA gene, indicating a nucleotide alteration where guanine (G) is substituted by adenine (A) at position 3010. This polymorphism has been identified in several studies that have explored the relationship between lactic acidosis and linezolid use (Stacey et al., 2023; Wasserman et al., 2016).

Some studies suggest that the vulnerability and severity of side effects among TB patients treated with linezolid may be influenced by genetic predispositions, leading to significant variability in the clinical manifestations of these side effects. Single nucleotide polymorphisms (SNPs) within the 16S rRNA gene (A2706G and G3010A) have been reported in patients experiencing linezolid-induced lactic acidosis. However, these SNPs are commonly found in the general population and were not linked to adverse effects in a cohort of 38 Korean patients receiving linezolid for XDR tuberculosis. Nevertheless, these variations are situated close to the PTC, and the A2706G mutation is positioned on the open region of the 16S rRNA, which may enhance its interaction with linezolid. These considerations imply a possible relationship between these SNPs and the inhibition of mitochondrial protein synthesis by linezolid (Stacey et al., 2023; Wasserman et al., 2016).

The cessation of linezolid treatment in both patients led to improvements in their visual function, indicating that the side effect of toxic optic neuropathy may be reversible in their cases.

4 CONCLUSIONS

The increasing incidence of drug-resistant tuberculosis (DR-TB), particularly in Indonesia, presents significant public health challenges. As the detection of DR-TB cases rises, the need for effective treatment intensifies. Linezolid, a critical drug in DR-TB therapy, has shown efficacy in sputum conversion and high cure rates; however, its long-term use carries a risk of severe side effects, particularly toxic optic neuropathy (TON), which can lead to permanent vision impairment. Enhanced awareness and early recognition of these side effects are crucial to mitigate the risk of eye disabilities among patients.

The occurrence of TON in patients treated with linezolid underscores the importance of diligent monitoring and early screening. Research suggests a concerning trend of optic neuropathy linked to linezolid, potentially influenced by genetic factors such as polymorphisms in mitochondrial DNA (mtDNA), specifically A2706G and G3010A. While linezolid may provide significant therapeutic benefits for managing drug-resistant tuberculosis, healthcare providers must carefully weigh its advantages against the risk of severe side effects like TON. The discontinuation of linezolid can restore visual function, although recovery may be prolonged. Continued investigation into the association between mtDNA polymorphisms and susceptibility to TON is essential for improving patient outcomes and tailoring treatment protocols.

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