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RESEARCH ARTICLE

Identification of Mitochondrial DNA Polymorphism on Linezolid-induced Toxic Optic Neuropathy Patients

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Abstract

Drug-resistant tuberculosis (DR-TB) is difficult to eradicate due to several factors, including insufficient treatment and medication side effects. Linezolid is among the medications with serious adverse effects. Linezolid toxicity is suspected to be related to the drug's binding to mitochondrial 16s rRNA. Some studies indicate that polymorphisms in patients' mtDNA may increase vulnerability to the development of toxic optic neuropathy. This study aims to identify a genetic influence on the vulnerability to the occurrence of toxic optic neuropathy side effects in drug-resistant tuberculosis patients receiving linezolid treatment. This research was conducted at the Faculty of Medicine, Universitas Sriwijaya, Palembang, from September to October 2023. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was undertaken to detect mutations in the G3010A mtDNA of the patients. Two patients experiencing toxic optic neuropathy side effects during drug-resistant tuberculosis treatment underwent blood sample collection. Blood samples were examined for mutations in the G3010A and A2706G genes using the PCR-RFLP method. The PCR-RFLP examination results indicated the presence of mutations in G3010A. In conclusion, polymorphism of G3010A mtDNA may contribute to the vulnerability to toxic optic neuropathy side effects in drug-resistant tuberculosis patients receiving linezolid. Further research with a larger population is needed to prove the involvement of mtDNA polymorphisms in the vulnerability to toxic optic neuropathy.

Keywords: DR-TB, linezolid, MtDNA, toxic optic neuropathy

Introduction

Tuberculosis (TB) is a disease that has been evolving over the last few decades. Disease conditions that continue to develop provide challenges in eradicating this disease. Cases of drug-resistant tuberculosis that continue to emerge in the world also raise their problems with comprehensive management. Data from the Global Tuberculosis Report 2023 indicate that the incidence of TB worldwide in 2022 is estimated to have reached 10.6 million people. This figure continues to increase from the previous year. Apart from that, TB is the second-biggest cause of death by infectious agents after COVID-19. The latest data also show that Indonesia remains in second place, after India, and is followed by China in third place with 1,060,000 cases. Globally, in 2022, it is estimated that 410,000 people will suffer from drug-resistant tuberculosis (DR-TB), multidrug-resistant (MDR), and rifampin-resistant (RR).[1] Meanwhile, in Indonesia, there are 12,531 patients confirmed as drug-resistant TB (MDR/RR), and only 8,089 have started treatment.[2]

The increasing number of cases of DR-TB that are currently being discovered presents challenges in eradicating TB. It is not only about patient compliance in undergoing ongoing treatment, but the presence of side effects in the treatment itself can reduce patient compliance in completing treatment.[1,2]

In addition to inadequate treatment, the presence of side effects to the drugs administered

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is also a significant constraint in eradicating DR-TB. One of the drugs with severe side effects is linezolid.[3] Conditions such as myelosuppression, peripheral neuropathy, and toxic optic neuropathy are frequently observed side effects of linezolid usage.[4] Linezolid toxicity is suspected to be related to the drug's binding to mitochondrial 16s rRNA. Some studies indicate that polymorphisms in patients' mtDNA may contribute to the vulnerability to toxic optic neuropathy. It has been suggested that the G3010A and A2706G polymorphisms in mitochondrial DNA play a role in toxic optic neuropathy.[5–7]

Toxic optic neuropathy (TON) is a condition where damage to the optic nerve occurs due to exposure to harmful substances, such as certain drugs.[8] One example of a drug known to cause TON is linezolid, which is used in the treatment of DR-TB. Several cases reported the occurrence of severe TON during long-term use of linezolid. Symptoms of TON can include decreased visual acuity, changes in the visual field, and impaired color perception. This condition has been associated with abnormalities in mitochondrial transport and mitochondrial defects along neurons.[5–7]

The mechanism by which linezolid causes TON is still not fully understood, but recent data support several hypotheses. Several reports suggest that susceptibility to linezolid-induced toxic optic neuropathy is related to mitochondrial DNA polymorphisms.[5–7] This study aims to determine the effect of mitochondrial DNA polymorphisms on susceptibility to linezolid-induced toxic optic neuropathy among drug-resistant tuberculosis.

Methods

This research represents an initial study to identify whether there is a genetic influence on the vulnerability to toxic optic neuropathy side effects in DR-TB patients receiving linezolid treatment in Indonesia, especially in Palembang. This research was conducted at the Biotechnology Laboratory, Faculty of Medicine, Universitas Sriwijaya, Palembang, from September to October 2023. The study has been approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya, Palembang, for ethical approval with registration number 250-2023.

This study's subjects were DR-TB patients at the DR-TB Polyclinic, Dr. Muhammad Hoesin General Hospital, Palembang. A total of 145 patients who received linezolid therapy were used as subjects. Data from medical records were used to determine the variables of age, gender, history of diabetes mellitus, history of HIV, and TON complications. The chi-square or Fisher exact test was used to analyze the relationship between variables.

We also collected blood samples from two patients with DR-TB who experienced TON as a side effect after undergoing linezolid therapy. Mitochondrial DNA was isolated according to the protocol of the QIAamp® DNA Mini Kit (cat. no. 51304 and 51306). The G3010A and A2706G polymorphisms in mitochondrial DNA were identified by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP).

Results

The average age of the patients in this study was 43 years, ranging from 16 to 79 years. The prevalence of TON in this study was 22.8%. The results of statistical tests showed that there was no relationship between age and HIV with the incidence of TON. Still, a relationship was observed between age and diabetes mellitus in terms of the incidence of TON (Table).

Blood samples were taken from two patients who were undergoing treatment for DR-TB and had severe optic neuropathy side effects. Using the PCR-RFLP technique, blood samples were analyzed for mutations in the G3010A and A2706G genes. The findings of the PCR-RFLP analysis are shown in Figure 1 and Figure 2.

In PCR-RFLP, the G3010A gene shows a band of 1074 bp (UC) for the wild type, and the A2706G gene shows 237 bp (UC) for the wild type. In this study, neither patient (1 or 2) had the A2706G gene mutation in their mitochondrial DNA. PCR-RFLP results showed only one band at 237 bp for both patients (Figure 1). In contrast, we identified a mutation in the G3010A gene of the mitochondrial DNA in both patients. PCR-RFLP results showed the presence of two bands, namely 96 bp and 978 bp (Figure 2).

Table Relationship between Age, Sex, Comorbid Diabetes Mellitus, and HIV with the Incidence of TON

Variables	TON		Total (n=145)	p	PR (95% CI)
	Yes (n=33)	No (n=112)			
Age (years)					
≤40	8	55	93	0.026[a]	0.345 (0.143–0.834)
>40	25	57	52		
Sex					
Male	19	74	93	0.625[a]	0.751 (0.335–1.681)
Female	14	38	52		
Diabetes mellitus					
Yes	12	17	29	0.012[a]	3.353 (1.387–8.103)
No	21	95	116		
HIV					
Yes	0	2	2	1.000[b]	–
No	33	110	143		

Note: TON: toxic optic neuropathy, PR: prevalence ratio, [a]chi-square test, [b]Fisher exact test

Discussion

The incidence of tuberculosis is increasing every year. The latest data from the WHO Global Tuberculosis Report 2023 shows that in 2022, an estimated 10.6 million people in the world will suffer from tuberculosis. The estimated death toll in 2022 will reach 1.3 million people. Apart from that, TB is the second-deadliest infectious disease after COVID-19. Indonesia itself contributes 10% of tuberculosis cases in the world. This fact makes Indonesia ranked second after India, with the most cases of tuberculosis in the world.

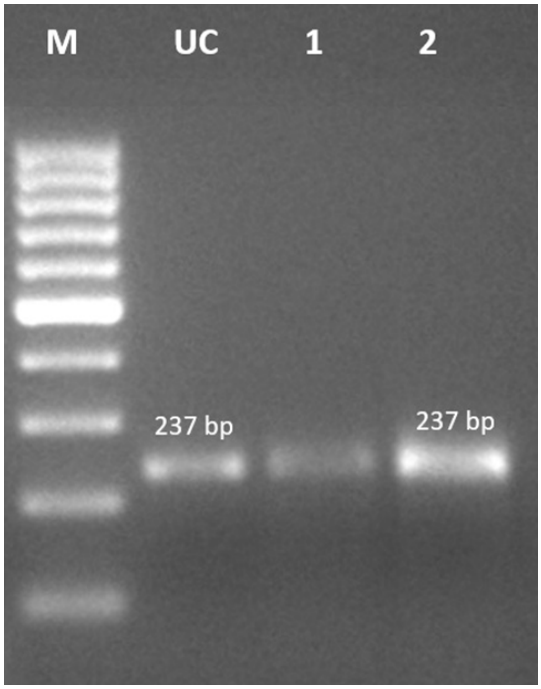

Figure 1 PCR-RFLP Bands of the A2706G Gene
Note: M: marker, UC: uncut gene, 1: patient 1, 2: patient 2

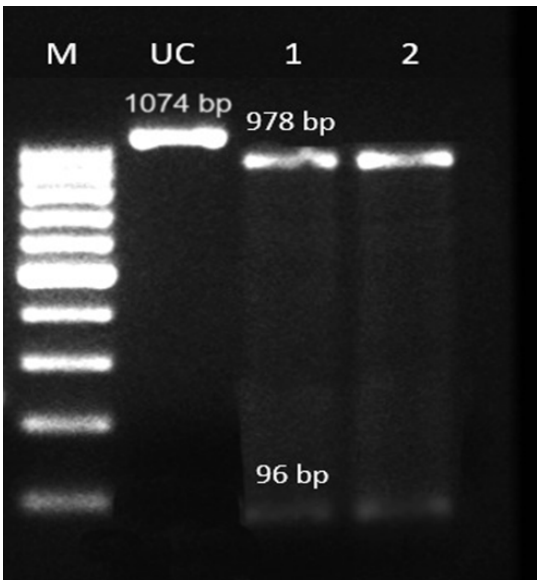

Figure 2 PCR-RFLP Bands of the G3010A Gene
Note: M: marker, UC: uncut gene, 1: patient 1, 2: patient 2

Meanwhile, for DR-TB cases globally in 2022, it is estimated that there will be 410,000 people with DR-TB or RR-TB with a treatment success rate of 63%.[1] In Indonesia alone, the incidence of TB MDR/RR will reach 31,000 cases in 2022. Based on tuberculosis information system (*sistem informasi tuberkulosis*, SITB) data for the province of South Sumatra, as of early December 2023, 326 cases of DR-TB were recorded, and 89 new cases were found in the city of Palembang. However, only 60 people (67.42%) had started DR-TB treatment. One of the obstacles in eradicating tuberculosis, especially DR-TB, is that the treatment period is quite long compared to DR-TB. According to the technical instructions for DR-TB treatment issued by the Ministry of Health of the Republic of Indonesia in 2020, the duration of short–term treatment ranges from 9 to 11 months, while long-term treatment lasts from 18 to 24 months.[9] Prolonged exposure to drugs carries the risk of drug side effects and drug toxicity to the body.

One DR-TB drug that causes side effects is linezolid. Linezolid is an antibiotic commonly used to treat various bacterial infections. As a synthetic antibiotic, linezolid has proven effective in treating severe diseases, including pneumonia and skin infections caused by resistant bacteria.[3] However, recent studies have raised concerns about possible neuro-optical side effects associated with linezolid use. These side effects can manifest as toxic optic neuropathy, leading to progressive vision loss and damage to the optic nerve.[10–12]

In this study, the average age of patients was 43 years, aged 16 to 79 years. This fairly varied age reflects the broad spectrum of DR-TB patients, given that this disease can affect populations of all ages. This finding is in line with previous studies showing that drug resistance in TB can occur in older age groups, who may be more susceptible to side effects of treatment, including TON. Another study also reported that older age groups experienced more side effects of second-line drugs, such as linezolid, which is consistent with the age distribution in this study.[10,13,14]

The prevalence of TON of 22.8% in this study is a significant finding. Linezolid is known to be one of the effective drugs against DR-TB, but its use is often associated with severe side effects, including optic neuropathy. The high prevalence of TON in this study is worth emphasizing, given that the toxicity of linezolid to the optic nerve is one of the important reasons for the limited duration of use of this drug. This figure is slightly higher than other reports that mention a prevalence of between 5% and 15% in DR-TB patients receiving linezolid therapy.[7,13,15,16]

We found that there was no relationship between age and HIV with the incidence of TON, but there was a relationship between age and diabetes mellitus with the incidence of TON. Regarding the relationship between age and the incidence of toxic optic neuropathy, older patients may have a higher risk of developing optic neuropathy, given the decreased nerve regeneration and increased sensitivity to neurotoxic drugs with increasing age. In addition, comorbid medical conditions such as diabetes mellitus and HIV, which are more common in the elderly population, can increase the risk of optic neuropathy. Other studies showed that patients with older age and a history of metabolic disease were at higher risk of developing linezolid-related neuropathy. It emphasizes the importance of individual risk assessment before starting linezolid therapy, especially in patients with advanced age or comorbidities.[13,16,17]

The association between diabetes mellitus and TON incidence in this study reinforces the importance of evaluating comorbid factors before initiating linezolid therapy. Diabetes mellitus, which affects nerve vascularization and glucose metabolism, is important in worsening the risk of optic neuropathy. Therefore, in patients with diabetes who require linezolid therapy, close monitoring of visual function needs to be carried out periodically, and optimal control of blood glucose levels should be maintained to minimize the risk of nerve complications.[13,14,17]

Linezolid works by inhibiting the initiation of bacterial protein synthesis through a unique mechanism of action by binding to the 23S RNA peptidyl transferase center (PTC) of the 50S subunit of prokaryotic ribosomes. On the other hand, binding with peptidyl also occurs in the mature 70S initiation complex. The result prevents the formation of mtDNA, which causes a bacteriostatic effect.[10,18]

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 color vision. This disease is often not diagnosed or diagnosed at a stage where recovery is difficult.[14,16,19]

Linezolid can cause toxic optic neuropathy as a result of its mitochondrial toxicity.[20] The drug's mechanism of action involves inhibiting bacterial protein synthesis by binding to the bacterial ribosome. However, linezolid also has an affinity for the mitochondrial ribosomes in human cells, which are similar to bacterial ribosomes. It can lead to inhibition of mitochondrial protein synthesis, which is essential for the function of mitochondria and, by extension, the health of nerve cells.[10,17,19]

Mitochondria play a crucial role in energy production and are particularly important in cells with high energy demands, such as those in the optic nerve.[18] When mitochondrial protein synthesis is impaired, it can lead to a decrease in cellular ATP production, resulting in cellular dysfunction and, ultimately, cell death. This can manifest clinically as optic neuropathy, which may present with symptoms such as vision loss and changes in visual acuity.[10,17,19]

The risk of developing toxic optic neuropathy from linezolid is associated with both the dose and duration of therapy. Prolonged use of linezolid, especially beyond the recommended duration, increases the risk of this adverse effect. Peripheral or optic neuropathy typically develops after 2 months of treatment with linezolid, and the risk continues to increase with longer durations of therapy.[10,17,19]

Linezolid can disturb human mitochondrial DNA at the points where it encodes for the 16S ribosomal RNA (rRNA) subunit, which is a critical component of the mitochondrial ribosome.[18] The mitochondrial ribosome is responsible for protein synthesis within the mitochondria, and its proper function is essential for the synthesis of key components of the respiratory chain complexes that are involved in oxidative phosphorylation.[17,19]

Mutations in the mitochondrial DNA that affect the 16S rRNA can confer susceptibility to linezolid toxicity. For example, single-nucleotide polymorphisms (SNPs) such as A2706G and G3010A in the 16S rRNA gene have been associated with linezolid-induced mitochondrial toxicity. These mutations are situated close to the PTC of the mitochondrial ribosome, which is the primary binding site for linezolid. The A2706G mutation, in particular, lies in an exposed position on the 16S rRNA that could enhance its interaction with linezolid, potentially leading to greater inhibition of mitochondrial protein synthesis.[10,19]

The inhibition of mitochondrial protein synthesis by linezolid can lead to a reduction in the synthesis of key subunits of mitochondrial respiratory complexes I, III, IV, and ATP synthase, which are translation products of mitochondrial ribosomal 16S RNA. This impairment of oxidative phosphorylation can result in tissue-specific dysfunction and clinical phenotypes such as myelosuppression, neuropathy, and hyperlactatemia.[10,19]

The results of our pilot study, which included two patients, are consistent with earlier investigations. These results provide a foundation for a more thorough investigation with a larger sample size, which would yield better scientific evidence, particularly regarding the adverse effects of linezolid, such as TON, for which there is currently insufficient information in Indonesia.

Several case reports from several countries show the incidence of TON in DR-TB patients.[7,15,16,21,22] Palenzuela et al.[23] show that linezolid may cause lactic acidosis by binding to mitochondrial 16S rRNA, with genetic polymorphisms potentially contributing to the toxicity in some patients. A case report showcasing the occurrence of TON following the extended use of linezolid in patients with extensively drug-resistant tuberculosis (XDR-TB). The incidence of TON was observed to be reversible.[24] Another study shows that long-term use of linezolid in XDR-TB patients can cause optic neuropathy, which resolves completely when the drug is withdrawn.[25] Lee et al.[26] reported that long-term use of linezolid to treat drug-resistant tuberculosis may reverse severe optic neuropathy, but not peripheral neuropathy.

Conclusions

Several factors may influence the manifestation of side effects associated with the use of linezolid. However, in this study, TON-induced linezolid was influenced by age and the presence of comorbid diabetes mellitus. The presence of polymorphisms in G3010A mtDNA found in these two patients may contribute to the vulnerability to toxic optic neuropathy side effects in drug-resistant tuberculosis patients

receiving linezolid. Further research with a larger population is needed to prove the involvement of mtDNA polymorphisms in the vulnerability to toxic optic neuropathy.

Conflict of Interest

All Authors declare no conflict of interest in this research.

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References

1. World Health Organization. Global tuberculosis report 2023. Geneva: World Health Organization; 2023.
2. Kementerian Kesehatan Republik Indonesia. Dashboard data kondisi TBC di Indonesia [Internet]. 2023 [cited 2023 Sep 19]. Available from: https://tbindonesia.or.id/pustaka-tbc/dashboard/.
3. Bolhuis MS, Tiberi S, Sotgiu G, De Lorenzo S, Kosterink JG, van der Werf TS, et al. Linezolid tolerability in multidrug-resistant tuberculosis: a retrospective study. Eur Respir J. 2015;46(4):1205–7.
4. Dempsey SP, Sickman A, Slagle WS. Case report: linezolid optic neuropathy and proposed evidenced-based screening recommendation. Optom Vis Sci. 2018;95(5):468–74.
5. Lifan Z, Sainan B, Feng S, Siyan Z, Xiaoqing L. Linezolid for the treatment of extensively drug-resistant tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2019;23(12):1293–307.
6. Spinazzi M. Optic neuropathies caused by micronutrient deficiencies and toxins. In: Preedy VR, editor. Handbook of nutrition, diet and the eye. Oxford: Elsevier; 2014. p. 383–92.
7. Sharma P, Sharma R. Toxic optic neuropathy. Indian J Ophthalmol. 2011;59(2):137–41.
8. Ishii N, Kinouchi R, Inoue M, Yoshida A. Linezolid-induced optic neuropathy with a rare pathological change in the inner retina. Int Ophthalmol. 2016;36(6):761–6.
9. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, Kementerian Kesehatan Republik Indonesia. Petunjuk teknis penatalaksanaan tuberkulosis resistan obat di Indonesia. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.
10. Wasserman S, Meintjes G, Maartens G. Linezolid in the treatment of drug-resistant tuberculosis: the challenge of its narrow therapeutic index. Expert Rev Anti Infect Ther. 2016;14(10):901–15.
11. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893–902.
12. Santini A, Ronchi D, Garbellini M, Piga D, Protti A. Linezolid-induced lactic acidosis: the thin line between bacterial and mitochondrial ribosomes. Expert Opin Drug Saf. 2017;16(7):833–43.
13. Mehta S, Das M, Laxmeshwar C, Jonckheere S, Thi SS, Isaakidis P. Linezolid-associated optic neuropathy in drug-resistant tuberculosis patients in Mumbai, India. PLoS One. 2016;11(9):e0162138.
14. Brandariz-Núñez D, Hernández-Corredoira V, Guarc-Prades E, García-Navarro B. Optic neuropathy associated with linezolid: systematic review of cases. Farm Hosp. 2019;43(2):61–5.
15. Bano S, Nawaz A, Numan A, Hassan MA, Shafique MBA. A case report and literature review of the outcome of linezolid-induced optic and peripheral neuropathy in patients with multidrug-resistant pulmonary TB. Front Neurol. 2022;13:908584.
16. Toolan KJ, Fondriest J, Keenan K, Mizen T, Stosic M. Linezolid toxic optic neuropathy: a case report and review of visual prognosis. Am J Ophthalmol Case Rep. 2023;32:101922.
17. Shree R, Mahesh KV, Takkar A, Modi M, Goyal MK, Lal V. The neuro-ophthalmology of tuberculosis. Neuroophthalmology. 2023;48(2):73–92.
18. Song T, Lee M, Jeon HS, Park Y, Dodd LE, Dartois V, et al. Linezolid trough concentrations correlate with mitochondrial toxicity-related adverse events in the treatment of chronic extensively drug-resistant tuberculosis. EBioMedicine. 2015;2(11):1627–33.
19. Lin SY, Stacey AW, Al-Zubidi N, Ponce

CP, Bhat N, Bhatti MT, et al. Toxic optic neuropathy [Internet]. San Fransisco: American Academy of Ophthalmology; 2023 [cited 2024 Aug 15]. Available from: https://eyewiki.org/Toxic_Optic_Neuropathy.
20. Zhang P, Li W, Liu M, Zhan S, Zhang H, Deng G, et al. Linezolid-associated neuropathy in patients with MDR/XDR tuberculosis in Shenzhen, China. Infect Drug Resist. 2022; 15:2617–24.
21. De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, Van Haute LL, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis. 2006;42(8):1111–7.
22. Vallabhaneni S, Mendonca TM, Nayak RR, Kamath G, Kamath A. Linezolid induced toxic optic neuropathy in drug resistant tuberculosis-a case series. Indian J Tuberc. 2024;71(Suppl 1):S5–9.
23. Palenzuela L, Hahn NM, Nelson RP Jr, Arno JN, Schobert C, Bethel R, et al. Does linezolid cause lactic acidosis by inhibiting mitochondrial protein synthesis? Clin Infect Dis. 2005;40(12):e113–6.
24. Kardani S, Hadia R, Shah A, Parmar G, Maheshwari R, Seth A, et al. A case report on reversible toxic optic neuropathy on long term treatment of linezolid in extensively drug-resistant tuberculosis patient. J Pharm Res Int. 2021;33(37A):7–11.
25. Srivastava A, Kshetrimayum S, Gupta SK, Kant S. Linezolid-induced optic neuropathy in XDR pulmonary TB: a case series. Indian J Tuberc. 2017;64(2):129–33.
26. Lee S, Kang BH, Ryu WY, Um SJ, Roh MS, Son C. Is severe and long-lasting linezolid-induced optic neuropathy reversible? Intern Med. 2018;57(24):3611–3.