

Adverse Effects of Linezolid in Tuberculosis Patients at Dr. Soetomo General Hospital Surabaya

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ABSTRACT

An infectious respiratory disease known as tuberculosis (TB) is commonly treated with Linezolid when it is considered as drug resistant. However, Linezolid has several severe adverse effects. This study aims to give a better depiction of TB patients treated with Linezolid. This retrospective cohort designed study was conducted at Dr. Soetomo General Hospital Surabaya using secondary data obtained from medical record. The data collected were patient's identity, tuberculosis type based on its drug resistance, the therapy duration, and the adverse effect experienced by subjects. Male patients dominated the study's population (52.6%) with most patients were aged 40-60 years old (55.3%). Most of the patients had MDR TB (n = 27) and treated for ≥6 months (n = 33). Myelosuppression became the most common adverse effects in this study (31.6%). TB patients who undergo prolonged Linezolid therapy tend to experience adverse effects.

Keywords: tuberculosis; linezolid; myelosuppression; peripheral neuropathy; toxic optic neuropathy

INTRODUCTION

Tuberculosis (TB), an infectious disease, is caused by *Mycobacterium tuberculosis*. It affects the lung and spread through air, although in recent years it has been categorized as curable disease as the medication to treat TB were discovered (1). However, some of the patients didn't get better even after consuming the anti TB combination regimen, these patients were then fell into the category of drug resistant TB. It has been estimated that the number of MDR-TB cases in 2021 reach up to 450.000 cases, which 3.6% of the total case are new cases and 18% was previously treated cases in 2021 (2).

Linezolid, a group A classified drug, is recommended by WHO and included in the longer regimen for MDR-TB treatment. Based on a study, the use of Linezolid successfully increases the culture conversion from positive to negative and improve the outcome and success rate of therapy in TB patients (3,4). However, several studies reported severe adverse effects from Linezolid usage such as hematological toxicity (thrombocytopenia, anemia, and leukopenia), peripheral neuropathy, optic neuropathy, and lactic acidosis although it is rarely occurs (5,6). A result of a study shows that out of 33 patients, 19 patients were confirmed to acquire toxic optic neuropathy (4). Another study also shows that TB patients who use Linezolid suffers from visual disturbance (7).

The effect of Linezolid usage on tuberculosis patients shows several concerning side effects beside its effective effect on treating MDR-TB patients. Hence, a deeper understanding of TB patients treated with Linezolid and its adverse effect is needed to improve the management of TB patients. This study will be focusing on the clinical profile of TB patients and its correlation to Linezolid as the anti-tuberculosis medication.

METHODS

This study was conducted on September 2021 – July 2022 at Dr. Soetomo General Hospital Surabaya with a retrospective cohort design. The subjects' data was collected from the medical records from the Tuberculosis polyclinic. The data collected were patient's identity including sex and age, tuberculosis type based on its drug resistance, the duration of therapy, and the adverse effect experienced by subjects. All subjects had eye baseline examination, the subjects who found to have prior optic nerve abnormalities such as diabetic retinopathy and retinopathy or optic neuropathy induced by other causes on the baseline examination were excluded from this study. A total of 65 DR-TB patients were registered to the Tuberculosis polyclinic during January 2020 – July 2021 period. Among those, 11 patients were excluded for not getting Linezolid in the therapy regimen.

3 other patients were excluded because one patient stopped the therapy before it was finished, one patient changed the healthcare during the treatment, and one patient died during the therapy period. 13 patients were also excluded due to the prior optic nerve or retinal abnormalities. There were 38 subjects who eventually included in this study. This study has been accepted by Dr. Soetomo General Hospital Ethic Committee with the ethical number 1007/109/4/X/2021.

RESULT

Most observed TB patients treated with Linezolid was male (52.6%), and the most common age group was 40-60 years old (n=21), followed by <40 (n = 16) and >60 (n = 1) years old with the average age of 40.7 ± 12.3 years old (Table 1). Based on the data obtained, the most common type of TB was the MDR TB group (71.1%).

TABLE 1: Subject characteristics.

Variables	Mean \pm SD	n	%
Sex			
Male		20	52.6
Female		18	47.4
Age (years)			
	40.7 \pm 12.3		
<40		16	42.1
40-60		21	55.3
>60		1	2.6
Type of TB			
Monoresistant TB		5	13.2
RR TB		2	5.3
MDR TB		27	71.1
Pre-XDR TB		4	10.5

The treatment duration in this study was dominated by patients who undergo the treatment ≥ 6 months (86.8%) with all of them enrolled in the treatment for approximately 9.7 ± 4.0 .

Most observed adverse effects seen in patients treated with Linezolid was myelosuppression (n = 12) followed by peripheral neuropathy (n = 10) and toxic optic neuropathy (n = 7).

TABLE 2: Therapy Duration and Adverse Effects.

Variables	Mean \pm SD	n	%
Duration of Therapy			
	9.7 \pm 4.0		
≥ 6 months		33	86.8
<6 months		5	13.2
Adverse Effects			
TON		7	18.4
Myelosuppression		12	31.6
Peripheral Neuropathy		10	26.3
Duration to Cause Adverse Effects			
TON	7.7 \pm 2.1		
Myelosuppression	3.6 \pm 1.5		
Peripheral Neuropathy	5.0 \pm 1.8		

DISCUSSION

Tuberculosis, an infectious respiratory disorder, affect 10 million individual every year. Multidrug-resistant tuberculosis (MDR-TB) has been identified in 484,000 of them with deaths estimated occurs in 191,000 in 2021 (2). Outcomes for patients who suffers from tuberculosis especially in endemic countries are relatively poor with cure rate about 20%. However, highly effective drugs such as Linezolid that is recommended by WHO shows a significant effect in curing drug resistant TB patients with its overall cure rate up to 80% (7). Even though Linezolid is proven highly effective in terms of curing drug resistant TB, it also presents a concerning severe adverse effect such as toxic optic neuropathy (TON), myelosuppression, and peripheral neuropathy (4).

The occurrence of toxic optic neuropathy was said to happen because Linezolid binds to mitochondrial ribosomes, which are claimed to be comparable to Linezolid's target bacterial ribosomes, inhibits mitochondrial protein synthesis (8). Due to the high ATP needs of the axons in the retinal ganglion cells (RGC), which are a component of the optic nerve, mitochondrial dysfunction can lower the amount of ATP that RGCs take in, ultimately resulting in cell destruction and death and lead to declining visual acuity (9). As for the peripheral neuropathy, the pathomechanism hasn't been fully understood yet, but it is hypothesized that the same mechanism as toxic optic neuropathy also occurs in peripheral neuropathy which is mitochondrial dysfunction (10).

The myelosuppression which is also one of the adverse effects of Linezolid was postulated to be caused by the inhibition of mitochondrial respiration. The inhibition of mitochondrial respiration will eventually lead to anemia which is also commonly seen in drug resistant TB patients treated with Linezolid (11).

MDR-TB patients which undergo Linezolid treatment was dominated by male (52.6%). A study by Safaev et al. and Jaspard et al. supported this result (7,12). This phenomenon could be explained by the increase susceptibility to infection that is caused by men related factors such as smoking that could cause toxic lung injury and reduced immune cell function and alcohol consumption that have immunosuppressive effects. These behavioral factors that is more common in men is most likely the cause as why men dominated the population in this study (13).

Most prevalent age group in this study was the 40-60 age group (55.3%). Similar result is also seen in a study conducted in Myanmar and Korea (14,15). The phenomenon where 40-60 years old became the most prevalent group of age in TB is probably caused by the reduced immunity, more common comorbidities in this age group, and also higher mobility which cause easier transmission of the disease as this type of group is still considered as productive and more active compared to >60 years old age group (16,17).

Most observed type of TB drug resistance in this study population were the MDR-TB group. This result is similar to a study by Gardia et al. (18). According to WHO, the reason behind the emerging of MDR-TB are poor TB treatment management and person to person transmission. The poor management of MDR-TB is caused by the improper or inappropriate use of antimicrobial medications, the use of ineffective formulations of medications, such as the use of single medications, subpar medications, or poor storage conditions, and early treatment interruption can result in the development of drug resistance which then can be spread, particularly in crowded spaces like jails and hospitals (1).

Most of the patients observed in this study undergo the treatment for ≥6 months which means most of the patients have completed the early stage of the treatment recommended by WHO, as the early stage should be given for 4-6 months for the shorter regiment and 8-12 months for the longer regiment (19). The study population in the study by Cox et al. and Udwardia et al. also undergo the Linezolid treatment for ≥6 months. Both studies show that the Linezolid related adverse events occur in the first 6 months of the therapy. Similar result is also seen in this study as almost all of the Linezolid related adverse events manifest in the first 6 months of the therapy, 7.7 months for toxic optic neuropathy, 3.6 months for myelosuppression, and 5.0 months for the peripheral neuropathy (20,21).

Most observed Linezolid related adverse effect of TB patients in this study was myelosuppression and the most common manifestation is anemia. This result is similar to a study conducted by Tang et al. (22). This phenomena could be explained by the patient's duration of exposure to Linezolid which was said to affect the occurrence of Linezolid related adverse effect (23). Peripheral neuropathy placed second in terms of the occurrence of Linezolid adverse effect in this study. The patients presented symptoms such as numbness, paresthesia, impaired pain, temperature, and light touch sensations, as well as loss of proprioception in the distribution of the hands and feet.

The exact mechanism as to how the peripheral neuropathy occurs in long term Linezolid usage is not fully understood yet, but Lee et al. suggest that it is related to the prolonged mitochondrial toxicity due to protein synthesis inhibition. Further research is still needed to understand the pathomechanism on how peripheral neuropathy occurs in prolonged Linezolid usage [23].

Although toxic optic neuropathy doesn't have as much occurrence as myelosuppression and peripheral neuropathy in this study, it is also a common finding in patients who undergo Linezolid therapy. In this study, TON occurs at the average of 7.7 months after the Linezolid therapy started, although various studies show that the start of TON occurrence varied. It is said to be caused by the genetic variability in patients that makes them more susceptible to TON which is Leber Hereditary Optic Neuropathy (LHON). LHON occurs as a result of mitochondrial DNA point mutations ND4, ND6, and ND1 which cause electron transport chain dysfunction, decreased ATP production, and excessive formation of reactive oxygen species. This then causes the death of retinal ganglion cells and causes a decrease in visual acuity (9,24). As for the myelosuppression it is said to correlate with the oxidative stress. Although the exact mechanism of Linezolid induced pharmacological implications of hematological toxicity isn't fully understood yet (25).

CONCLUSION

Most TB patients who undergo Linezolid treatment in Dr. Soetomo General Hospital Surabaya was male and in the age range of 40-60 years old. Most patient fell into the MDR-TB category (71.1%) and undergo the treatment for ≥6 months. The most common adverse effect experienced were myelosuppression (31.6%). There's a possibility of correlation between adverse events and the duration of treatment in TB patients treated with Linezolid.

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