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STUDY OF ADVERSE DRUG REACTIONS OF LINEZOLID IN DRUG RESISTANT TUBERCULOSIS PATIENTS

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ABSTRACT
The estimated number of DR TB patients in Indonesia is increasing. High adverse drug reactions have the potential to affect the success of DR TB patient treatment. Linezolid is one of the drugs in combination with DR TB therapy that has the potential to cause adverse drug reactions in the form of hematological disorders and visual impairment. This study aims to determine the incidence of Linezolid ADRs, including the incidence, severity, and risk factors associated with the occurrence of ADRs. This type of study is observational with a cross-sectional design conducted retrospectively in DR TB patients at the lung clinic of Hospital 'X" and Hospital "Y" in Indonesia. The results of the study showed that the incidence of ADRs suspected of Linezolid that met the criteria was 70 patients out of a total of 215. The most common type of ADRs was hematological disorders at 89%, the rest were visual impairment. The type of regimen and type of ADRs correlate with the severity of ADRs. It is necessary to monitor drug levels in the blood in order to monitor and prevent the potential for more severe ADRs so that therapy can be individualized.

Keywords: Adverse Drug Reactions; Linezolid; DR TB

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease that is a major cause of ill health, one of the top 10 causes of death in the world, and the leading cause of death from a single infectious agent (ranking above HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome)). Indonesia is included in the 3 countries with a high burden for TB, TB-HIV and Drug-Resistant Tuberculosis (DR TB) (World Health Organization, 2020; World Health Organization, 2022). The estimated number of DR TB patients in Indonesia is 2.40% of all new TB patients and 13% of previously treated TB patients with a total incidence of DR TB cases of 24.000 people (Kemenkes RI, 2020; PDPI, 2021). Adverse drug reactions (ADRs) of DR TB drugs are a separate problem in treatment, considering that DR TB drugs contain new drugs and have regimens that have more types of drugs than Drug-sensitive TB. Over the past decade, several studies have shown that morbidity and mortality related to drug use are among the main health problems. Adverse drug reactions in the United States are estimated to be the fourth to sixth leading causes of death. Adverse drug reactions result in the death of several thousand patients each year. As an illustration, in several countries, the percentage of patients treated in

hospitals for ADRs is more than 10% (Norway 11.5%, France 13.0%, and England 16.0%) (BPOM RI, 2019). One study stated that antituberculosis drugs are a separate cause of ADRs, which results in patients requiring hospitalization (Sahilu et al., 2020). High adverse drug reactions affect the success of treatment for DR TB patients (Felly, I., 2019). Linezolid is a drug in combination with DR TB therapy that has the potential to cause adverse drug reactions in the form of hematological disorders and visual disturbances (Kemenkes RI, 2022). The adverse reactions of the drug caused by linezolid on the nervous system and eyes are anemia, retinopathy, peripheral neuropathy, and optic neuropathy (Comín et al., 2019; Hyun et al., 2015; Mikiashvili et al., 2021; Padmapriyadarsini et al., 2023). It has been studied by the author that drug adverse drug reactions cannot be ignored, because the more severe the adverse drug reactions of the drug, the lower the patient's quality of life (Susilo et al., 2022). Adverse drug reactions that occur in patients with tuberculosis also affect patient compliance, interfere with the completion of treatment, and can even stop treatment, which causes the outcome of therapy not to be achieved (Anna et al., 2023; Wang et al., 2019; Yudisia Ausi et al., 2021). This study aimed to determine the incidence of adverse reactions to linezolid and the factors that influence it.

Research on the adverse drug reactions of linezolid in patients with DR TB in Indonesia is rare. Based on the density visualization of bibliometric analysis, studies on linezolid worldwide have indeed been quite numerous, but studies on the adverse drug reactions of the drug are still lacking. Likewise, the analysis of the correlation between the occurrence of adverse drug reactions of and its effect on compliance and quality of life of DR TB patients. This is based on a literature review using the bibliometric analysis presented in **Figure 1**.

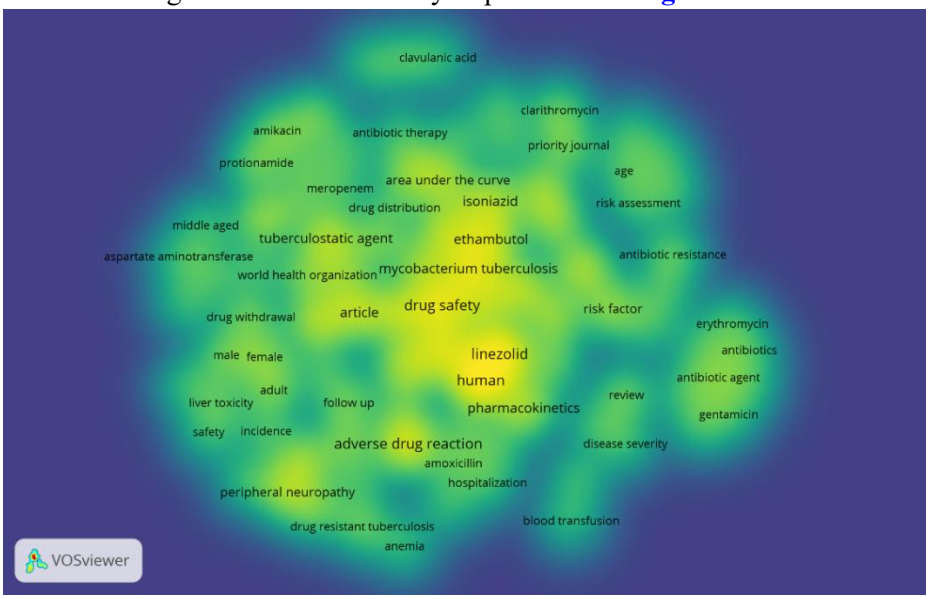

Figure 1. Density Visualization

Based on the literature review and bibliometric analysis, it is evident that the implementation of pharmacovigilance in hospitals is important for increasing the achievement of therapeutic targets and reducing ADRs. The novelty of this research plan in Indonesia is still very rare and needs to be addressed so that it is useful for policymakers in the tuberculosis control program in Indonesia.

2. METHODS

2.1. Research Design

This research design was cross-sectional with retrospective data collection.

2.2. Place and Time of Research

This study was conducted at Hospital “X” and “Y” Indonesia. Sampling was conducted from July to September, 2024.

2.3. Research Subjects

The subjects of the study were all medical records of DR TB patients who received linezolid therapy, experienced Linezolid-specific ADRs, and met the research criteria. The inclusion criteria for this study were as follows: medical Records of Patients > 18 years old who were diagnosed with DR TB and using Linezolid medication, medical records of patients experiencing adverse drug reactions of Linezolid based on the assessment of the DR TB team. The exclusion criteria: incomplete Patient Medical Records.

2.4. Operational Definition of Research

All patients were diagnosed with DR TB with linezolid and met the research criteria. Linezolid is a drug used in the management regimen of patients diagnosed with DR TB. The occurrence of adverse drug reactions to the drug is the occurrence of adverse drug reactions to linezolid experienced by patients based on the patient or the patient's family, as well as clinical and laboratory examinations, such as hematological disorders and visual disturbances. The severity of ADR was measured using the Hartwig et al. questionnaire, which is already in Indonesia and is used to measure the severity of ADR administered by health workers (Susilo, 2022).

2.5. Data Collection and Data Analysis Techniques

Data collection was conducted at the Lung Polyclinic of Hospital “X” and “Y” in the form of patient sociodemographic data from medical records. Quantitative data analysis was conducted as follows: identification of characteristics of DR TB patients treated with linezolid and their treatment profiles, identification of Adverse drug reactions in linezolid. The data were then analyzed, and the percentage results obtained based on patient characteristics were presented descriptively, pearson’s correlation was used to analyze the factors influencing the severity of adverse drug reactions to linezolid. The ethical approval letter was obtained from the Research Ethics Committee of Gunung Jati Hospital, Cirebon with the Number: 045/LAIKETIK/KEPPKRSGJ/VII/2024.

3. RESULTS AND DISCUSSION

The results of observations at both hospitals related to the number of active DR TB patients undergoing treatment when retrospective data collection was carried out were 215 patients using linezolid with the ITR (Individual Therapy Regiment) regimen of 130 patients and BPALM (Bedaquiline, Pretomanid, Linezolid, and Moxifloxacin) of 85 patients. Data tracing of 70 patients experiencing potential adverse drug reactions to linezolid was performed.

3.1. Patient Characteristics

The characteristics of DR TB patients from which retrospective data were obtained were as follows: age (**Table 1**), gender (**Table 2**), body weight (**Table 3**), type of regimen (**Table 4**), type of ADR (**Table 5**), severity of ADR (**Table 6**), and duration of anti TB treatment (**Table 7**).

3.1.1. Age

Table 1. Characteristics of DR TB Patients who are potentially exposed to ADR Linezolid Based on Age

Age (years)	Amount	Percentage
20-30	12	17
31-40	26	37
41-50	8	11
51-60	6	9
>60 years	8	11
Total	70	100

Based on age, DR TB patients who experience ADR Linezolid are predominantly aged 31-40 years, which is indeed the case because most DR TB patients are of productive age, as a study showed that DR TB patients aged ≤ 65 years dominate DR TB patients (Cheng J et al., 2024).

3.1.2. Gender

Table 2. Characteristics of DR TB Patients who are Potentially at Risk of ADR Linezolid Based on Gender

Gender	Amount	Percentage
Man	46	66
Woman	24	34
Total	70	100

The gender of DR TB patients who experienced ADR Linezolid was dominated by men, which is in line with other studies that showed that men dominate the number of DR TB patients (Anna et al., 2023; Cheng J et al , 2024).

3.1.3. Weight

Table 3. Characteristics of DR TB Patients who are potentially experiencing ADR Linezolid Based on Body Weight

Body Weight (Kg)	Amount	Percentage
35-40	12	17
41-45	28	40
46-50	12	17
51-55	13	19
56-60	5	7
Total	70	100

The weight of DR TB patients who experience ADR Linezolid is generally ≤ 45 kilograms. A study also stated that a body weight of less than 44 kg has the potential to cause greater adverse drug reactions to linezolid compared to a body weight above 44 kg, which is also correlated with linezolid levels in the blood; in a review, patients weighing less than 60 kg had a higher chance of linezolid levels in the blood (Cheng J., et al , 2024).

3.1.4. Type of Regimen

Table 4. Characteristics of DR TB Patients who are potentially experiencing ADR Linezolid Based on Regimen Type

Regimen	Amount	Percentage
ITR	42	60
BPALM	28	40
Total	70	100

The most common DR TB therapy regimen is ITR, while the BPALM regimen is less common because the BPALM regimen is a new regimen.

3.1.5. ADRs Types

Table 5. Characteristics of DR TB Patients who are potentially experiencing ADR Linezolid Based on ADRs Type

ADR Types	Amount	Percentage
Hematology Disorder	62	89
Visual Impairment	8	11
Total	70	100

The most common type of ADRs is hematological disorders, such as anemia and thrombocytopenia, but the most common is anemia, which is in line with a study showing that anemia ADR dominate Linezolid ADRs (Cheng J et al., 2024). Linezolid interacts with mitochondrial ribosomes, interferes with mitochondrial protein synthesis, and reduces ATP in bone marrow precursor cells in subjects at risk of drug accumulation and in those who are inherently more susceptible to mitochondrial toxicity. Mitochondrial dysfunction causes bone marrow suppression, which leads to anemia, leukopenia, and thrombocytopenia (Oehadian et al., 2022). Visual disturbances also appeared in 8 patients receiving linezolid, as previous studies have reported that linezolid can cause visual disturbances (Comin et al., 2019; Hyun et al., 2015).

3.1.6. ADR Severity Levels

Table 6. Characteristics of DR TB Patients who are potentially experiencing ADR Linezolid Based on the Severity of ADRs

ADR Severity Levels	Amount	Percentage
2	14	20
3	40	57
4	16	23
Total	70	100

The highest severity of ADR was level 4, in which 16 patients required inpatient care and were likely to require blood transfusion. Meanwhile, the severity of ADR with the largest number of 40 patients was level 3, the drug was stopped but did not require treatment, and only antagonist drugs such as folic acid were administered for anemia. In a journal review article, grade 1 and 2 anemia recommendations include close monitoring, dose reduction, and addition of erythropoietin by looking at the patient's condition, while grade 3 and 4 anemia recommendations stop linezolid (Oehadian et al., 2022).

3.1.7. Duration of Treatment

Table 7. Characteristics of DR TB Patients who are potentially experiencing ADR Linezolid Based on the Duration of Treatment

Duration of Treatment	Amount	Percentage
1-5 Months	13	19
6-10 Months	57	81
Total	70	100

Based on the duration of treatment, most subjects had a duration of 6-10 months of treatment, amounting to 81%. This has the potential to increase drug accumulation and the risk of ADR.

3.1.8. Analysis of Factors Affecting the Severity of Linezolid ADR

Adverse drug reactions that occur in DR TB patients must be managed properly, which affects patient compliance and quality of life (Yudisia Ausi et al., 2021). The results of the correlation analysis between the patient characteristics and ADR severity of ADR presented in **Table 8**.

Table 8. Correlation Analysis Between Patient Characteristics and Severity of ADR

Variables		ADR Severity Levels			Amount	P value	Pearson Correlation
		2	3	4			
Type of Regimen	ITR	14	21	7	42	**0.002***	**0.366**
	BPALM	0	19	9	28		
	Total	14	40	16	70		
Gender	Man	10	25	11	46	0.905	
	Woman	4	15	5	24		

	Total	14	40	16	70		
Age (years)	20-30	0	8	4	12	0.986	
	31-40	8	13	5	26		
	41-50	4	11	3	18		
	51-60	2	1	3	6		
	>60 years	0	7	1	8		
	Total	14	40	16	70		
Body Weight (Kg)	35-40	1	10	1	12	0.940	
	41-45	7	14	7	28		
	46-50	1	6	5	12		
	51-55	4	7	2	13		
	56-60	1	3	1	5		
	Total	14	40	16	70		
ADR Types	Hematology Disorder	14	31	16	61	**0.048***	**0.238**
	Visual Impairment	0	8	0	8		
	Hematology + Visual Disturbances	0	1	0	1		
	Total	14	39	16	70		
Duration of Treatment	1-5 Months	2	8	3	13	0.63	
	6-10 Months	12	32	13	57		
	Total	14	40	16	70		

Based on the correlation analysis between patient characteristics and the severity of linezolid ADR, the variables of regimen type and ADR type were correlated with the severity of ADR (sig. <0.05), while the variables of age, gender, weight, and duration of treatment did not have a significant correlation. Similar to the findings of other studies, 92% of DR TB patients experienced at least one ADR during treatment; factors such as therapy regimen and patient condition can affect the incidence of ADR and ADR, and often require adjustments in the therapy regimen (Lan et al., 2021; Shanshan Wu et al., 2016; Solomon et al., 2025). The type of BPALM regimen is slightly higher at level 4, while the ITR regimen is more common at levels 2 and 3, which has a weak correlation strength with a Pearson correlation value of 0.366. Likewise, the type of ADR of hematological disorders and visual disorders as a whole, hematological disorders have a higher level of ADR severity and have a significant correlation with the severity of ADR even though the correlation strength is weak (0.238) (Sugiyono, 2010). However, the results of the correlation analysis have clearly shown that linezolid has other effects besides the success of therapy, namely, the problem of drug side effects, especially those that are often hematological disorders. A consensus recommends that linezolid therapy should be individualized, as well as Therapeutic Drug Monitoring (TDM) in accordance with one of the clinical pharmacy services in the hospital pharmacy service standards (Kemenkes RI, 2016; Lin et al., 2022).

4. CONCLUSION

The type of regimen and adverse drug reactions correlated with the severity of ADRs. The occurrence of adverse drug reactions can potentially reduce patient compliance and quality of life, and have the potential to reduce the success of therapy. It is necessary to monitor drug levels in the blood to monitor and prevent the potential for more severe adverse drug reactions, so that therapy can be individualized.

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6. CONFLICT OF INTEREST

The author declares that there are no conflicts of interest in this research and publication, which is solely for the purposes of developing science and technology.

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