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Current Review of the Use of Linezolid in the Treatment of Multidrug-Resistant Tuberculosis: Effectiveness and Management of Side Effects

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ABSTRACT

In recent years, multi-drug resistant tuberculosis (MDR-TB) sufferers have increased by 10% from 186,883 sufferers in 2018 to 206,030 in 2019. MDR TB treatment poses its own challenges because it is a long-term treatment, there are interactions between TB treatment, toxicity problems and patient compliance. Linezolid has demonstrated high in vitro antibacterial activity against Mycobacterium tuberculosis and has been used in several programs to treat complications of MDR-TB. The objective of this study is to assess the effectiveness and management of side effects from using the drug Linezolid in multidrug-resistant tuberculosis patients. The data sources used were PubMed, PubMed Central (PMC), and ScienceDirect databases with a literature search without restrictions on the type of research or year of publication with the keywords "linezolid, "tuberculosis" and "multi-drug resistance". Linezolid was found to be effective in treating MDR-TB patients. The side effect experienced by patients from using lizenolide (LZD) in all articles was peripheral neuropathy in the first three months of LZD use but this could be overcome by administering B6 at a dose of 200 mg, mecobalamin, reducing the dose of LZD and there was 1 article that stopped giving LZD. Optic neuropathy was also experienced by patients in 4 articles and could be resolved by stopping LZD use. One article stated that the side effect of using LZD was diabetic neuropathy with urine protein (+) and the patient's condition returned to normal after receiving symptomatic treatment. Hematological side effects in the form of neutropenia, thrombocytopenia, myelosuppression, and mild to severe anemia were also experienced by patients and could be treated with blood transfusions for severe anemia in 1 article, administration of erythropoietin in 2 articles to treat anemia. reducing the LZD dose from 1200 mg per day to 600 mg per day and some even stopping LZD. The results of the literature review indicate that linezolid is effective in treating MDR-TB. However, close monitoring is required regarding the side effects experienced by patients, especially neurotoxicity effects (peripheral or optic neuropathy).

Keywords: Linezolid; Tuberculosis; Multi-drug resistant.

1.0 Introduction

According to the World Health Organization (WHO), in 2019, an estimated 10 million (range, 8.9

– 11 million) people suffered from Tuberculosis (TB). Geographically, the highest TB sufferers are in Southeast Asia (44%), Africa (25%) and the West Pacific (18%), with smaller percentages in the Eastern Mediterranean (8.2 %), America (2.9%) and Europe (2.5%). Indonesia ranks second after India out of eight countries which contribute two-thirds of the total global TB (World Health Organization, 2020b).
The development of drug-resistant tuberculosis is causing concern worldwide. Globally in 2019, almost half a million TB sufferers developed TB that was resistant to the drug rifampicin (TB-RR), of which 78% suffered from TB that was multidrug-resistant or Multidrug-Resistant Tuberculosis (TB-MDR). In the last few years, RR/MDR TB sufferers have increased by 10% from 186,883 sufferers in 2018 to 206,030 in 2019. (World Health Organization, 2020b)

Multi Drug Resistant Tuberculosis (MDR-TB) is a strain that is resistant to Isoniazid (INH) and Rifampicin with or without resistance to other first-line drugs. Monoresistant is resistant to one OAT. Polyresistance is resistance to more than one OAT, other than the combination of isoniazid (H) and rifampicin (R). (Guarango, 2022)

The emergence of *Mycobacterium tuberculosis* (MTB) strains that are resistant to the most effective drugs is one of the main problems contributing to the slow decline in TB cases, posing a major threat to global TB control. (Espinosa-Pereiro et al., 2022) . Drug resistance by Mycobacterium tuberculosis primarily arises due to mutations in chromosomes, genes encoding drug targets or drug-activating enzymes, in response to antibiotic selection pressure. (Culyba et al., 2015) (Von Wintersdorff et al., 2016) . Sequential mutations in additional genes can lead to resistance to other drug targets and the development of multidrug - resistant strains (Palomino & Martin, 2014) .

Therapy for long-term treatment of MDR-TB, it is recommended to group antituberculosis drugs (OAT) into Group A, Group B and Group C according to their potency and ensure that treatment is started with at least four TB agents that are likely to be effective. Linezolid and Bedaquilin are recommended in combination therapy in the treatment of MDR-TB patients on longer regimens (strong recommendation, moderate certainty in effect estimates). A total treatment duration of 18-20 months is recommended for most patients, the duration may be changed according to the patient's response to therapy. (World Health Organization, 2020)

Linezolid belongs to the oxazolidinone class, a relatively new class of antibiotics used primarily to treat gram -positive bacterial infections, and is the best-known agent of the oxazolidinone group. Linezolid has demonstrated high in vitro antibacterial activity against Mycobacterium tuberculosis and has been used in the treatment of several complications of MDR-TB. (Anger et al., 2010) . In vitro and pharmacological data suggest that linezolid may be effective in the treatment of mycobacterial infections, including MDR-TB, although there are no clinical data on safety, tolerability and efficacy and limited data on the use of linezolid in the treatment of MDR-TB. (Migliori et al., 2009) .

In Indonesia, linezolid is registered with the Food and Drug Supervisory Agency (BPOM) since 2015. Considering that clinical and potential data regarding the use of linezolid to treat MDR-TB are limited regarding its safety, tolerability and efficacy, it is necessary to systematically evaluate

all available evidence regarding its effectiveness and effectiveness. the safety of Linezolid as preparation for a country, especially Indonesia, for the use of linezolid therapy, especially since Indonesia is ranked second in two-thirds of the total global TB.

This literature review aims to assess the effectiveness and treatment of side effects of using the drug Linezolid in Multidrug Resistant Tuberculosis (MDR-TB) patients.

2.0 Methodology

Searches for published literature were carried out independently by researchers using the online databases PubMed, PuMed Central (PMC), Google Scholar and Science Direct without limiting the type of research and year of publication. The keywords used in the research were "linezolid", "tuberculosis" and "multi drug resistant". In this systematic search, all articles published from 2010 to 2022 were included in this systematic review. All articles that met the inclusion criteria, even though they were published more than 10 years after this systematic review, were still used in the analysis to obtain a comprehensive picture. Data extracted from each research article includes: 1) article identity (name of researcher, and year of research), 2) country setting of research implementation, 3) sample size, 4) type of intervention provided, 5) methodology, 6) side effects 7) Handling of Side Effects and 8) research outcomes.

The Inclusion criteria were articles that contain: 1) MDR-TB patients, 2) MDR-TB cases with treatment regimen therapy, 3) linezolid as a replacement/additional drug in MDR-TB combination therapy, 4) side effects of using linezolid, 5) handling side effects from linezolid therapy. The exclusion criteria were studies in which MDR-TB was not confirmed by *M. tuberculosis* culture. The first step of a systematic review was to apply title/abstract screening. The aim of this step was to remove all publications that did not discuss linezolid in MDR-TB regimens. A total of 380 articles were found by database searches.

3.0 Results and Discussion

The number of articles identified during the literature search process was 380 articles, and only 5 of them used in the final study came from different countries (Figure 1). Articles included in the final study are included in Table 1 to make it easier to present the results of the test

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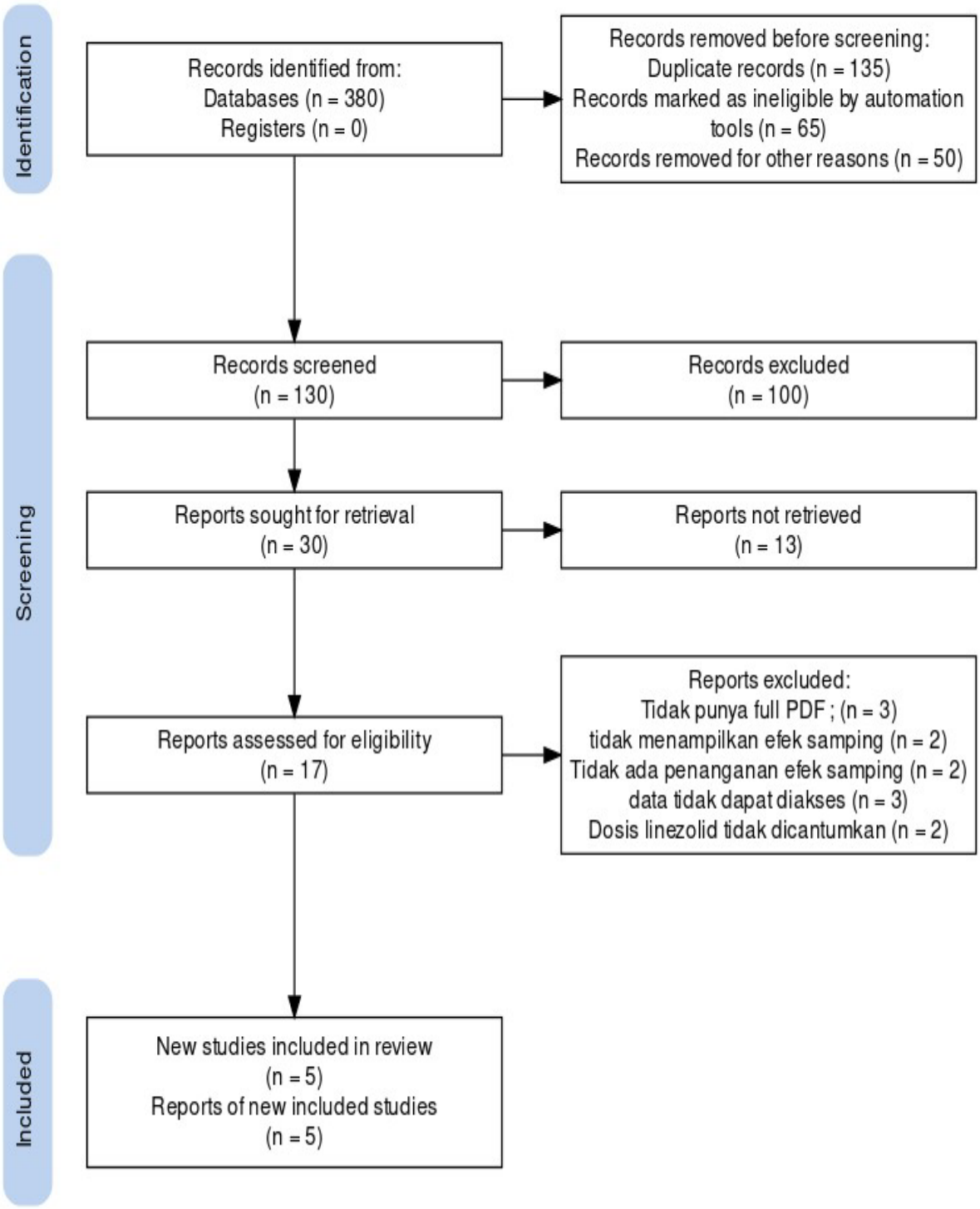
Gambar 1 Alur Penelusuran dan Pemilihan Pusataka



The research studies from the articles taken are generally retrospective studies. In some studies, linezolid was included in the treatment regimen after failure of previous treatment regimens. Linezolid is generally given at a minimum daily dose of 300 mg to a maximum dose of 1200 mg. The duration of treatment ranges from 1 to 24 months. All studies indicated linezolid dosage and individualized treatment regimens based on resistance test results. Of these 5 studies, four studies gave linezolid at a dose of 600 mg to 1200 mg per day, only the study by Koh et al. (2012) gave a linezolid dose of 300 mg every day. Conradie et al. (2022) study provided linezolid therapy of 1200 mg every day for 26 weeks, changing from 600 mg twice a day. Ramírez-Lapausa et al. (2016) research used a linezolid dose of 1200 mg or 600 mg every day.

Shen-Jie Tang et al. (2011) stated that patients received 600 mg linezolid twice daily for the first 1-2 months, followed by once daily thereafter. Eleven patients (78.6z) showed significant improvement in clinical symptoms. Chest tomography showed that 10 patients (71.4z) showed cavity closure. Smear conversion and culture conversion were achieved in all 14 patients (100z) at a mean of 64 and 63 days respectively. These data suggest that linezolid-containing chemotherapy for the treatment of TB- MDR can significantly improve clinical symptoms, increase lesion absorption and cavity closure, and accelerate sputum conversion. (Tang et al., 2011). The adverse reactions in linezolid therapy were: 1 (one) patient experienced side effects after undergoing linezolid treatment consisting of diabetic neuropathy with urine protein (+) and the patient's condition returned to normal after being given symptomatic treatment, 4 (28.6%) patients experienced gastrointestinal disorders with reactions nausea and after about 2-4 weeks of treatment with 600 mg LZD twice a day, but this resolved spontaneously after the LZD dose was administered with 600 mg once a day, 6 patients (42.9%) were hematological with 1 case of neutropenia, 4 cases of anemia moderate and 1 case of severe anemia in the second week of treatment with 600 mg LZD twice daily. Bone marrow function in patients with severe anemia normalized 2 weeks after blood transfusion and discontinuation of LZD. The anemia did not recur when treatment continued with 600 mg LZD once daily. Three patients (21.4%) experienced peripheral neuropathy between the 2nd and 3rd months which could be treated with B6 and mecobalamin. Two patients experienced optic neuropathy at 6 months and recovered completely after stopping linezolid one month (Tang et al., 2011) .

Meanwhile research by Conradie et al. (2022) states that the toxic effects of linezolid after the first three months of treatment consist of peripheral neuropathy (occurring in 81% of patients) and myelosuppression (48%), although common, can be managed requiring dose reduction and/or discontinuation of use. linezolid. Two patients had optic neuropathy that resolved after discontinuation of linezolid. Some patients require dose reduction or discontinuation of linezolid during treatment. 37 (34%) patients completed 26 weeks of linezolid without any interruptions with dose reductions and 16 (15%) completed 26 weeks with a total daily dose of linezolid 1200 mg without interruptions or dose reductions. The results of research by *Conradie F et.al* 2022, a total of 181 participants were registered, 88% of whom suffered from XDR or pre-XDR tuberculosis . Among participants who received linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91%, and 84%, respectively, had a favorable outcome (Conradie et al., 2022)

Research by Schecter et al. (2010) showed that linezolid was well tolerated, had a low discontinuation rate, and was effective in the treatment of MDR-TB. Of the 30 cases, 29 (97%) were lung disease, of these 29 people, 21 people (72%) had positive acid fast bacilli smear results, and 16 people (55%) had cavitation test results. Culture conversion occurred in all pulmonary cases at a mean of 7 weeks. Based on censored data (31 December 2008), 22 (73%) of 30 patients had successfully completed treatment. Five people continue to receive treatment. No deaths. Three patients had poor outcomes, including 2 patients in default and 1 patient in treatment failure.

The side effects of linezolid therapy were 9 patients, 5 patients experienced peripheral neuropathy, 1 of whom had to stop linezolid therapy after 5 months because there was comorbid uncontrolled diabetes and 4 patients were able to continue linezolid with caution and monitoring of symptoms. Handling side effects by increasing the dose of vitamin B6 from 150 mg to 200 mg to overcome neurological complaints but peripheral neuropathy was not resolved in 3 patients. One patient lost his vision due to optic neuropathy after 10 months of linezolid therapy. This patient also received rifabutin for 3 months. This patient's condition improved after 3 weeks of discontinuing linezolid therapy. 7 patients suffered from mild to moderate anemia. 2 patients experienced symptoms of anemia (HB levels 10.6 and 8.6 g/dl) with dyspnea on exertion and fatigue while receiving linezolid. The use of erythropoietin was permitted to continue receiving linezolid. One patient experienced mild thrombocytopenia Despite this toxicity, no patient discontinued linezolid treatment due to myelosuppression (Schecter et al., 2010)

The research by Koh et al. (2012) found that 14 (27%) patients experienced one major side effect and discontinued linezolid treatment, among 13 patients (25%) experienced lower extremity peripheral neuropathy, 1 patient experienced optic neuropathy after a median of 278 days (IQR 174– 412 days). Patients with optic neuropathy recovered completely after lizenolide treatment was discontinued whereas symptoms of peripheral neuropathy, partially resolved in 8 patients, became worse in one patient and did not improve in four patients after lizenoid was discontinued. 14 patients who experienced side effects had a longer duration of linezolid treatment and 11 patients had successful treatment (median 314 days; IQR 254-415 days), 3 patients had unsuccessful treatment (median 156 days; IQR 125-180 days).

From the study, 45 of 51 patients (88%) completed MDR TB treatment. Among the 45 patients, 33 patients recovered and 1 patient completed therapy. One patient died and 10 experienced treatment failure. From these results it can be concluded that Lizenolid at a dose of 300 mg is effective against intractable MDR TB and may be associated with fewer neuropathic side effects than a daily dose of 600 mg or 1200 mg (Koh et al., 2012)

A retrospective study regarding the tolerability and efficacy of linezolid in MDR-TB patients was conducted in Madrid, Spain by Ramírez-Lapausa et al. (2016), linezolid at a dose of 1200 mg or 600 mg daily was included to complement treatment if no other sensitive drugs were available. The results of the study showed that 55 MDR-TB patients received treatment. In 21 of these patients, linezolid was added. Median linezolid administration was 23.9 months (IQT 13.1–24.7). Patients taking linezolid showed greater resistance to the drug, with a median of 6 (IQR 5–7) compared with those not using it, with a median of 4 drugs (IQR 3–5) ($p < 0.001$). The median time to sputum culture conversion in patients in the linezolid group (73.5 days) was not

significantly different compared to the non-linezolid group (61 days) (p = 0.29).

It was reported that 81% of patients did not experience side effects while undergoing linezolid therapy. Only four patients experienced linezolid-induced toxicity. The most serious side effect in these patients was anemia which was observed in two patients treated with 1200 mg per day. One of them also experienced moderate paresthesia. Management of side effects in both cases, the dose of linezolid was reduced to 600 mg per day, with improvement in anemia and paresthesia. The use of Vitamin B6 is used to reduce toxicity. No patients discontinued linezolid therapy (Ramírez-Lapausa et al., 2016)

Table 1. Data analysis in the articles used

NO	Author and Year of Publication	Sample Size	Intervention	Study Type	Duration LZD treatment	Side effects	Handling side effects	Results
1	Koh et al. (2012) Country: South Korea	51 MDR TB patients used LZD as part of their anti-TB drug regimen	300 mg LZD once daily	Retrospective study series	Median 413 days (IQR 237-622 days)	14 (27%) experienced major side effects including: 13 (25%) patients experienced peripheral neuropathy affecting the lower extremities and 1 patient experienced optic neuropathy	All 14 patients discontinued LZD after 278 days of LZD use. Results: Peripheral neuropathy resolved in 8 patients, worsened in 1 patient And it did not improve in 4 patients after stopping LZD. So that LZD treatment took longer for 11 patients with successful treatment (median 314 days IQR 254-414 days),	Treatment results profitable (success treatment or still in treatment after culture conversion) achieved at 40 patients (78%) with culture conversion on median 55 days (IQR 41-91 days) since initiation of LZD therapy Conclusion: Linezolid at a daily dose of 300 mg is effective against intractable

							compared to 3 patients with unsuccessful treatment (median 156 days IQR 125-180 days) Action to reduce the LZD dose from 600 mg/day to 300 mg/day to reduce toxicity 2.Optic neuropathy resolved after LZD was stopped	MDR TB with fewer side effects compared to daily doses of 600 mg or 1200 mg.
2	Conradie et al. (2022) Country: South Africa	181 MDR TB patients	LZD 1200 mg daily for 26 weeks or 600 mg twice daily for 26 weeks	NIX TB, Open Label Single Group Study	For 6 months	Peripheral neuropathy 81% and optic neuropathy and myelosuppression 48% after the first 3 months of LZD use	1. Peripheral neuropathy with reduced LZD dose and 1 patient recovered after stopping LZD 2. Optic neuropathy resolved after LZD was discontinued 3. Myelosuppression resolved after reducing the dose and stopping LZD	A total of 181 participants were enrolled, 88% of whom had XDR or pre-XDR tuberculosis. Among participants who received linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91%, and 84%, respectively, had a

								favorable outcome.
3	Shen-Jie Tang et al. (2011) Country : Shanghai China	a total of 14 MDR-TB patients were treated with LZD	The LZD dose is 600 mg twice a day for the first 1-2 months and followed once a day thereafter	Quantitative cross-sectional study	6 months	Peripheral neuropathy in 3 (21%) months 2 and 3. Two patients experienced optic neuropathy at 6 months patient One (1) patient experienced diabetic neuropathy with urine protein (+), 4 patients experienced gastrointestinal disorders with nausea reactions 28.6% around 2-4 weeks of LZD 600 mg twice daily treatment, 6 patients (42.9% hematology with 1 case of neutropenia, 4 cases of moderate anemia and 1 case of severe	1. Peripheral neuropathy resolved with administration of methicobalamin and Vitamin B6 2. Optic neuropathy resolved after discontinuation of LZD treatment 3. Diabetic Neuropathy urine protein (+) can be cured with symptomatic treatment 4. Gastro intestinal disorders can be treated by reducing the LZD dose to 600 mg	The patients received 600 mg linezolid twice a day for the first 1-2 months, followed by once a day thereafter. Eleven patients (78.6z) showed significant improvement in clinical symptoms. Chest tomography showed that 10 patients (71.4z) showed cavity closure. Smear conversion and culture conversion were achieved in all 14 patients (100z) with a mean averages 64 and 63 days respectively These data indicate that chemotherapy containing linezolid for the treatment

						anemia in the 2nd week of LZD 600 mg treatment twice a day	once daily 5. Bone marrow function in severe anemia became normal 2 weeks after blood transfusion and LZD cessation and anemia did not recur after treatment with a single dose of 600 mg.	of MDR-TB can significantly improve clinical symptoms, increase lesion absorption and cavity closure, and accelerate sputum conversion. Conclusion LZD is recommended for the treatment of MDR TB
4	Ramírez-Lapausa et al. (2016) Country: Spain	55 MDR-TB patients received treatment. 21 patients had LZD added.	LZD, at a dose of 1200 or 600 mg daily,	Retrospective study With the control group	Median LZD administration was 23.9 months	4 patients experienced toxicity, Anemia was observed in two patients treated with a dose of LZD 1200 mg per day and one of them experienced moderate paresthesia	Vitamin B6 to reduce symptoms of toxicity and in both cases (toxicity and anemia) the LZD dose was also reduced to 600 mg per day and no patient stopped linezolid therapy	Treatment outcomes and clinical status at last contact were compared between patients on LZD-containing regimens and those without Country: Spain LZD A daily dose of 600 mg LZD was well tolerated without stopping

								treatment in cases. Treatment efficacy and outcomes in all groups were similar in LZD and non-LZD Conclusion: Daily Dose of 600mg Linezolid was well tolerated without stopping treatment in any case.
5	Schecter et al. (2010) Country: California (US)	30 MDR TB patients	The linezolid dosage is 600 mg daily. Vitamin B6 at a dose of 50-100 mg every day	Retrospective study Note review	18-30 months	5 patients experienced peripheral neuropathy and one patient lost vision due to optic neuropathy, 7 patients suffered from mild to moderate anemia. 2 patients experienced symptoms of anemia (HB levels 10.6 and 8.6 g/dl) with dyspnea on activity and fatigue. 1 patient had mild	1. Increasing the dose of Vitamin B6 from 150 mg to 200 mg can overcome neurological complaints and in 1 case stopped LZD 2. Patients with optic neuropathy improved again after 3 (three) weeks of stopping LZD 3. Use of erythropoietin in anemia to continue using LZD	Results: During 2003-2007, 30 patients received linezolid for the treatment of MDR-TB. Patients had isolates that were resistant to a median of 5 drugs (range 2-13 drugs). Of the 30 cases, 29 (97%) were pulmonary; Of the 29 people, 21 people (72%) had positive acid-fast bacilli smear results, and 16 people (55%) suffered from

						thrombocytopenia		cavitation disease. Culture conversion occurred in all lung cases at a mean of 7 weeks. Based on censored data (31 December 2008), 22 (73%) of 30 patients had successfully completed treatment. Five people continue to receive treatment. No deaths. Three patients had poor outcomes, including 2 patients in default and 1 patient in treatment failure. Conclusion: Linezolid is well tolerated, has a low discontinuation rate, and has efficacy in the treatment of MDR-TB

Conclusion

The safety of using linezolid for the treatment of MDR-TB has side effects including peripheral neuropathy, optic neuropathy, and myelosuppression from mild to severe anemia. Handling side

effects given to patients can help minimize the condition of MDR -TB patients regarding side effects caused by the use of linezolid by administering vitamin B6 at 200 mg, reducing the dose of linezolid from a dose of 600 mg twice a day to 600 mg once a day, even lowering the dose to 600 mg once a day. who reduced the dose of linezolid to 300 mg/day and stopped using linezolid and this was proven by the patient's condition returning to normal. Five research articles show that linezolid therapy is effective in treating MDR-TB with a safe daily dose of 300 mg/day. Monitoring and supervision of symptoms is needed to overcome the side effects arising from linezolid therapy so that patients can carry out treatment safely and comfortably.

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