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Six Months of Bedaquiline-Pretomanid-Linezolid (BPaL) Regimen in Patients with Drug-Resistant Tuberculosis: A Narrative Review

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ABSTRACT.

Background: Drug-resistant tuberculosis (DR-TB) is more difficult to treat with multiple therapies and a longer duration than drug-sensitive tuberculosis. Pre-XDR and XDR-TB are highly DR-TB with a lower success treatment than MDR-TB. Therapy for high DR-TB with fewer drugs and shorter treatment is required to increase the success of treatment. We comprehensively reviewed the risk factors for unfavorable outcomes (death, treatment failure, and loss of follow-up) related to all oral regimens containing bedaquiline and or delamanid in patients with MDR-TB.

Method: This was a narrative review to summarize the role of the BPaL regimen to manage highly DR-TB patients.

Results: The six months of BPaL regimen was reported to provide treatment success in two previous trials, Nix and Zenix TB. BPaL offers treatment success, especially in highly DR-TB compared to standard regimens containing bedaquiline. However, several adverse effects, such as myelosuppression, peripheral neuropathy, and optic neuritis were more common in BPaL regimens than in standard regimens. In addition, the incidence of QTc interval prolongation was lower in BPaL regimens compared with standard regimens. It is mandatory to monitor adverse effects associated with linezolid in the BPaL regimen and how to manage them.

Conclusion: This review concludes that the BPaL regimen provides treatment success over six months of treatment. Health facilities should prepare for the implementation of BPaL to manage DR-TB patients.

Keywords: Drug-resistant TB, BPaL, Efficacy, Safety

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ABSTRAK.

Latar Belakang*: Drug-resistant tuberculosis (DR-TB) lebih sulit diobati dengan beberapa terapi dan durasi yang lebih lama daripada drug-sensitive tuberculosis. Pre-XDR dan XDR-TB sangat DR-TB dengan keberhasilan pengobatan yang lebih rendah daripada MDR-TB. Terapi untuk DR-TB tinggi dengan obat yang lebih sedikit dan pengobatan yang lebih singkat diperlukan untuk meningkatkan keberhasilan pengobatan. Dilakukan review secara komprehensif terhadap faktor risiko terhadap hasil yang tidak menguntungkan (kematian, kegagalan pengobatan, dan kehilangan tindak lanjut) terkait dengan semua rejimen oral yang mengandung bedaquiline dan atau delamanid pada pasien dengan MDR-TB.*

Metode: *Ini adalah tinjauan naratif untuk meringkas peran rejimen BPaL untuk mengelola pasien yang sangat DR-TB.*

Hasil*: Enam bulan rejimen BPaL dilaporkan memberikan keberhasilan dalam pengobatan dua percobaan sebelumnya, Nix dan Zenix TB. BPaL menawarkan keberhasilan pengobatan, terutama pada DR-TB yang tinggi dibandingkan dengan rejimen standar yang mengandung bedaquiline. Namun, beberapa efek samping, seperti myelosuppression, neuropati perifer, dan neuritis optik lebih sering terjadi pada rejimen BPaL daripada rejimen standar. Selain itu, insiden perpanjangan interval QTc lebih rendah pada rejimen BPaL dibandingkan dengan rejimen standar. Kewajiban untuk memantau efek samping yang terkait dengan linezolid dalam rejimen BPaL dan bagaimana mengelolanya.*

Kesimpulan*: Analisis menyimpulkan bahwa rejimen BPaL memberikan keberhasilan pengobatan selama enam bulan pengobatan. Fasilitas kesehatan harus mempersiapkan penerapan BPaL untuk mengelola pasien DR-TB.*

Kata kunci*: TB resistan obat, BPaL, Khasiat, Keamanan*

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1 Introduction

Tuberculosis (TB) is a highly infectious disease with low cures rate worldwide.[1] Drug-resistant tuberculosis (DR-TB) is more common in patients who were previously treated with antitubercular drugs. The estimated DR-TB cases in Indonesia are 2.4% of all new TB patients and 13% of those previously treated, with a total case of 24.000 or 8.8 per 100.000 population. [2] Those who were previously treated with antitubercular drugs are an independent risk factor for DR-TB. The administration of second-line injectable drugs (SLID), such as amikacin, kanamycin, and capreomycin for the treatment of DR-TB was associated with poor clinical outcomes, severe adverse effects, and a low cure rate.[3,4] WHO recommended a fully oral regimen containing bedaquiline to treat DR-TB patients. [5]

Bedaquiline, a novel antituberculosis drug, offers a high proportion of treatment success and cure rate in MDR-TB patients.[6] It has high activity antimycobacterial, especially in resistant strains

by inhibiting ATP synthase and thus depleting the energy of *M. tuberculosis* both in active replicate and dormancy.[7] Van Deun *et al*. proposed bedaquiline as a core drug since its highly bactericidal and sterilizing activity and no evidence of cross-resistance to other drugs [8] In Patients with MDR-TB who received regimens containing bedaquiline, the culture conversion was higher and the mortality rate was lower compared to those without bedaquiline.[9]

Adding bedaquiline in DR-TB treatment increases intracellular killing activity against M.Tb. [10] Bedaquiline has been included in a fully oral regimen either for shorter treatment or individual longer treatment.[5] Theoretically, an increase in bedaquiline use without drug-susceptibility testing (DST) will face a high frequency of acquired resistance to bedaquiline. However, resistance rates of bedaquiline appeared to be low in the bedaquiline treatment-naive MDR-TB patients, ranging from 0.4%-0.6%.[11] Although regimens containing bedaquiline have shown high success rates, the long duration of treatment can be a challenge. Shorter treatment regimens (STR) are administered for 9-12 months with seven all oral, while individual longer regimens (ITR) are given for 18-24 months with five drugs. Thus, medication adherence is a crucial factor related to treatment success. Furthermore, patients with XDR-TB are a challenge due to limited therapeutic options and a lower therapy success rate than those with MDR-TB.[12] Patients with XDR-TB have thicker walls and a larger size of lung cavities compared with MDR-TB patients and it is a significant risk factor to develop XDR-TB.[13]

Therefore, a safe and highly effective regimen with fewer drugs and a shorter duration is urgently needed to simplify administration and increase patient adherence. The all-oral, 6-month BPaL regimens comprise three drugs: the new drug pretomanid combined with bedaquiline and linezolid. The World Health Organization has informed that BPaL may be used programmatically for all people with rifampicin-resistant TB who are 14 years and have not had previous exposure to more than a month of bedaquiline, pretomanid, and linezolid. BPaL may be used in place of the previously recommended 9–11 months shorter treatment regimen (STR) and 18–24 months individual or longer treatment regimens (LTR). The evidence from the available studies suggests that these regimens may be used in eligible patients with MDR/RR-TB and pre-XDR-TB regardless of their HIV status. Further, The Global Fund has indicated a willingness to support countries transitioning to this regimen. In the Nix-TB trial, patients with high DR-TB, after administration of a regimen containing bedaquiline, pretomanid, and linezolid (BPaL) for twenty-six weeks, 90% of them had treatment success. However, adverse events were relatively highly associated with linezolid.[14]

Pretomanid should be administered only in combination with bedaquiline and linezolid. Pretomanid has a different mechanism from bedaquiline. Deaflazin-dependent nitroreductase (Ddn) activates pretomanid to intermediate products of nitric oxide and nitrous acid, inhibiting the synthesis of methoxy mycolic acid, a vital component that is responsible for the survival of M.Tb either actively replicating or dormant.[15] Inhibition of mycolic acid potently disrupts the

cell wall of M.Tb and reduces inflammatory cell infiltration as a result of interaction with the host. Furthermore, desnitro derivatives of pretomanid lead to respiratory poisoning of M.Tb.[16] A systematic review by Gils *et al*. reported 91% of RR-TB patients had favorable outcomes after administration of a regimen containing pretomanid. Meanwhile, in highly resistant TB, the favorable outcome was 90% at six months after treatment. [17]

Linezolid has shown potent activity against MDR and XDR-TB cases. Linezolid is one of the essential drugs in the MDR-TB regimen and it is classified into group A according to WHO recommendation.[5] Linezolid demonstrates weak early bactericidal activity (EBA) and only slightly extended EBA activity (2-7 days). It indicates that linezolid has a small role in the sterilization effect. The efficacy of linezolid depends on the AUC/MIC ratio. A linezolid AUC/MIC ratio of more than 100 is required to prevent resistance together with companion drugs. Linezolid is licensed for individual longer treatment. A meta-analysis reported in regimens containing linezolid, 83% of DR-TB patients had favorable outcomes including cure and treatment completion and 89% had culture conversion at the end of treatment.[18] In addition to efficacy, drug safety is an important factor in managing TB DR patients. In the NixTB trial, patients were found to have myelosuppression and peripheral neuropathy associated with linezolid. Therefore, it is important to consider safety before implementing a BPaL regimen into programmatic use for highly DR-TB. Based on this description review the efficacy and safety of the BPaL regimen compared to existing regimens to treat patients with highly DR-TB.

2 Method

This was a narrative review to summarize the efficacy and safety of the BPaL regimen to manage patients with high DR-TB. We included all published articles in English including original articles and case reports or series from 2019 to December 2022. The results of this review were presented descriptively.

3 Results

Efficacy of BPaL regimen

WHO recommends the 6-month BPaL regimen for MDR and pre-XDR-TB with levofloxacin or moxifloxacin resistance. Furthermore, the recommendation includes patients with pulmonary TB and extrapulmonary TB, excluding meningeal, bone, and disseminated TB disease. The recommendation also includes patients with HIV infection with CD4 counts > 100 copies/ml. MDR-TB is an *M.tuberculosis* isolate resistant to both isoniazid and rifampicin, pre-XDR TB is MDR plus resistance to fluoroquinolones, and XDR-TB is MDR plus resistance to fluoroquinolones and resistance to either bedaquiline or linezolid.

BPaL regimen should be administered orally including 400 mg of bedaquiline for the initial two weeks then 200 mg thrice weekly for twenty-four weeks, with a total of 26 weeks, with a

combination of 200 mg of pretomanid once daily, and 1200 mg of linezolid once daily for 26 weeks as reported in Nix TB trial. The administration of BPaL should be accompanied by individual informed consent with adequate counseling of potential risks and benefits and active monitoring and management of adverse effects. Whether pretomanid can act as a core drug with high bactericidal and sterilizing activity or protect other drugs against acquired resistance remains unclear. Pretomanid contributed significantly to the sterilizing activity of bedaquiline-moxifloxacin-pirazinamid and pretomanid-bedaquiline-linezolid in mice. Pretomanid assisted in reducing treatment duration and contributed to avoiding the selection of bedaquiline-resistant mutants.

Thirty-eight and 71 patients with MDR-TB and XDR-TB, respectively, were enrolled in the Nix TB trial. Overall, 98/109 patients (90%) had culture conversion at 26 weeks. In addition, 63/71 (89%) patients with XDR and 35/38 (92%) MDR-TB had culture conversion at 26 weeks, respectively. 8/71 (11%) and 3/38 (8%) patients with pre-XDR and XDR-TB had unfavorable outcomes, respectively.14 XDR-TB is a case of DR-TB with additional resistance to fluoroquinolones and at least one drug from class A (bedaquiline and linezolid).[5] Patients with XDR-TB were 4.7 times more likely to have unfavorable outcomes than those with MDR-TB. Linezolid was used more frequently in the XDR-TB group compared with the MDR-TB group.[19] Of patients with pre-XDR and XDR-TB who received a regimen containing bedaquiline and delamanid, 22/32 (69%) had negative culture before 24 weeks.[20] A study by Huerga *et al* demonstrated that 358/458 patients (78.0%) had a favorable outcome in a regimen containing bedaquiline-delamanid.[21]

Compared to the study by Phuong *et al*, reported in patients with RR-TB who received five drugs of STR (bedaquiline, levofloxacin, linezolid, clofazimine, and/or pyrazinamide), the successful treatment was 95/106 (90%). Meanwhile, unfavorable outcomes including treatment failure, death, and loss of follow-up were 4%, 1%, and 6%, respectively.[22] Furthermore, a study by Avaliani *et al*. demonstrated that in MDR-TB patients in Georgia receiving five drugs of STR (bedaquiline, linezolid, levofloxacin, clofazimine, and cycloserine), the treatment success was 22/25 (88%).[23] Treatment success of more than 90% in Bedaquiline, Pretomanid, and Linezolid (BPaL) regimen was higher compared to the study by Soeroto *et al*., who reported that 64.5% of successful treatment in Indonesian MDR/RR-TB patients treated with the second line injectable-containing 7-drug STR [3].

4 Discussion

Sputum culture conversion is the most common method to evaluate the effectiveness after administering antituberculosis drugs. Sputum culture conversion was significantly associated with treatment outcomes. The study by Javaid *et al*. reported that to estimate cure, sputum culture conversion at six months had sensitivity and specificity of 97.6% and 44.4, respectively.[24]

Furthermore, the cure rate was significantly associated with culture conversion at the sixth month (OR=32.10) than at four months (OR 14.13). Another study by Meyvisch *et al*. demonstrated that sputum cultures conversion at twenty-four weeks provided better predictive for the clinical outcome than culture conversion at eight weeks when assessing the effect of adding a new drug for the DR-TB regimen.[25]

However, the limitation of the Nix TB trial should be considered before implementing it into programmatic use. Since the non-randomized study with no controlled group, we could not compare the efficacy between BPaL and a conventional regimen containing bedaquiline and linezolid. In addition, the study was only conducted in one country. Therefore, the results are not fully applicable to the general population in different countries. Furthermore, the relapse incidence after treatment completion was not reported in that study. A study to explore the efficacy of linezolid with a dose lower than 1200 mg with a shorter duration was confirmed in the Zenix TB trial. The study enrolled 75 patients (41%) with XDR TB, 85 with pre-XDR TB (47%), and 21 with RR TB (12%). Patients receiving a BPaL regimen with linezolid with a dose of 1200 mg or 600 mg for twenty-four or nine weeks, 93%, 89%, 91%, and 84%, respectively, had treatment success. 3/44 (7%), 5/45 (11%), 4/45 (9%), and 7/44 (16%), respectively, had unfavorable outcomes for those in linezolid with a daily dose of 1200 mg or 600 mg for twenty-four or nine weeks.[26]

Pretomanid increased bactericidal activity when added to bedaquiline and linezolid. In TB-infected mice, concomitant administration of pretomanid with bedaquiline and linezolid was significantly associated with a reduction of bacterial burden after 1 and 2 months. Combination of BPaL in a mouse tuberculosis model, demonstrating good efficacy. In addition, the BPaL regimen had a significantly lower relapse rate than those without pretomanid. Furthermore, pretomanid also prevents the occurrence of M.Tb which is resistant to bedaquiline. [27] However, we can not conclude on pretomanid capacity as a core drug due to its limited follow-up time and the presence of bedaquiline. Sterilizing activity in BPaL could depend entirely on pretomanid.

In addition to pretomanid, delamanid can prevent relapse. In the mouse tuberculosis model, Pieterman *et al*. reported that negative cultures were obtained after eight and 20 weeks of BDL and HRZE administration. After 14 weeks of treatment, only one mouse from the BDL group was found to have a relapse, whereas, in the HRZE group, it was still observed until the 24th week. [28] It can be used to indicate that delamanid and pretomanid may replace each other. Nonetheless, further studies are urgently needed in DR-TB patients to compare BPaL regimens with bedaquiline-delamanid-linezolid. The safe and effective daily dose of linezolid for DR-TB patients is not fully understood. For a longer individual regimen, a daily of up to 600 mg of linezolid was administered either in the intensive or continuation phase with a total duration of 18-24 months.

Several studies reported that a daily dose of 600-1200 mg of linezolid can be used for DR-TB patients.[29] Nonetheless, 600 mg of linezolid twice daily achieves a cumulative fraction ratio (CFR) > 90% for optimal eradication of M.Tb and prevents the emergence of resistance. Linezolid doses lower than 1200 mg provide an excellent treatment outcome. Drugs that potentially shorten TB therapy are associated with sterilizing activity. AUC0-24 with MIC of 119 is the ideal ratio to provide a sterilizing effect. This ratio can be achieved at a dose of linezolid 600 mg daily.[30] A case study by Haley *et al*. reported that in XDR-TB patients with no resistance to bedaquiline and linezolid, administration of a BPaL regimen with a daily dose of 600 mg of linezolid for six months provided a favorable outcome without recurrence at nine months after therapy completion. [31]

Pulmonary lesions in TB patients are a hypoxic condition characterized by induction of hypoxia-inducible factor-1α (HIF-1α) and synergistically increases collagenase activity leading to destruction and lung cavities. DR-TB patients with relapse cases have more lung lesions or cavities compared to those with new cases. Although delamanid demonstrated higher potency than pretomanid in vitro against MDR and XDR-TB isolates, the two drugs had the same resistance frequency and comparable plasma concentrations.[32] Like delamanid, pretomanid is active against both replicating and dormant TB bacteria. [15] They become dormant through decreased metabolism in hypoxic conditions, one of the factors for resistance. A daily dose of pretomanid attained 73% of early bactericidal activity.[33] Recently, it was discovered that *c*ompetence-*in*ducing gen A (*cinA*) is responsible for the emergence of drug-resistant TB bacteria through pyrophosphatase activity and disrupts the bactericidal effect of antituberculosis drugs. In-vivo, the deletion of *cinA* enhances the killing activity of BPaL by blocking the cleavage of NAD-drug adducts. [34]

A study comparing the efficacy of a BPaL regimen with an individualized regimen containing bedaquiline-linezolid in XDR-TB patients was reported by Oelofse *et al*.[35] The study demonstrated that the BPaL regimen had a significantly higher favorable outcome than the individual regimen for 18–24 months containing bedaquiline-linezolid, 98/109 (89.9%) vs. 56/86 (65.1), respectively. In addition, the BPaL regimen produced a lower unfavorable outcome, 11/109 (10.1%) than the individual regimen, 36/102 (35.3%). However, the study was conducted at a different time from the Nix TB trial and the results from the Nix TB trial were taken retrospectively. Furthermore, the number of patients by Oelofse *et al*. who received linezolid was 84%, whereas, in the Nix TB trial, all patients received linezolid. The dose of linezolid in the Nix TB trial was 1200 mg or 600 mg twice daily, whereas in Oelofse *et al*. the dose of linezolid was 600 mg daily. Therefore, further controlled studies are needed to clarify these findings. Besides effectiveness and safety, the cost is also an aspect that needs attention in patient care. Affordable medical prices will provide easy access for patients to get their medicine. The study by Mulder *et al*. reported that the six-month BPaL regimen was more cost-effective than the standard

regimen.[36] Therefore, this regimen may save the government's budget for treating DR-TB patients.

In the Nix-TB trial, 88 patients (81%) had peripheral neuropathy, although the symptom was mild to moderate and occurred after administration for three months. Twelve and eleven patients had an elevation of ALT and AST more than three times from the upper normal limit. A maximum increase of QTc interval was 10 ms at week 16 and no patients had QTc more than 480 ms. Furthermore, 40 patients had myelosuppression including anemia, and occurred after two months of treatment, either those receiving linezolid at a dose of 1200 daily or 600 mg twice daily. However, these adverse events were manageable by interrupting and or reducing the linezolid dose.[14]

In the Zenix-TB trial, patients who received 1200 mg of linezolid for nine and twenty-six weeks, 4/46 patients (9%) and 9/45 (20%) had hemoglobin < 25% below baseline level, respectively. Meanwhile, of patients who received 600 mg of linezolid, no patients had hemoglobin < 25% below the baseline level. Neuropathy optic occurred in 4/45 patients (9%) receiving 1200 mg of linezolid for twenty-six weeks. Meanwhile, the incidence of peripheral neuropathy occurred in 17/45 (38%), 11/46 (24%), 11/45 (24%), and 6/45 (13%) for 1200 mg and 600 mg of linezolid, twenty-six or six weeks, respectively. QTc interval of 500 ms was observed in 4% and 2% for 1200 mg and 600 mg of linezolid, respectively. A total of 3 of 181 patients (2%) had liver-related serious adverse events.[26] Interruption of linezolid including dose reduction or discontinuation was higher in linezolid at a dose of 1200 mg compared to at a dose of 600 mg.

Compared with the standard regimen containing bedaquiline, QTc interval prolongation of more than 500 ms was found to be higher, between 6.2% and 25.6%.[37,38] A standard regimen includes fluoroquinolones (levofloxacin, moxifloxacin), clofazimine, and delamanid, potentially causing QT interval prolongation. Several studies have shown, although bedaquiline was associated with QTc prolongation, however, the grade of severity was low or middle, and no TdP or death-related cardiac arrhythmia was found. QT prolongation is associated with phospholipidosis. Although the M2 metabolite is found in lower concentrations than bedaquiline, this metabolite contributes significantly to prolonging the QT interval. M2 intracellular affinity for cardiac muscle is more potent than bedaquiline, and it is highly suspected to cause QT interval prolongation. Hypokalaemia is a risk factor for QTc prolongation. A study by Li *et al*, demonstrated when the QTc interval was prolonged in patients who received bedaquiline, serum potassium levels decreased by 10.71% and sodium levels increased by 1.07% from baseline. Low extracellular potassium paradoxically decreases IKr via enhanced inactivation or exaggerated sodium competitive block. As a consequence, hypokalemia causes prolonged QT intervals. However, low extracellular potassium increases drug-induced IKr blockade is crucial in clinical practice. Extracellular potassium correction to the normal range shortens the QT interval.[39]

Myelosuppression and neuropathy are considered the important causes of temporally or permanent discontinuation of linezolid in a regimen. Hematologic toxicity due to linezolid was associated with mitochondrial disruption. M.Tb damages the mitochondrial permeability transition pore complex (mPTPC) and leads to mitochondrial disruption. Initially, linezolid and M.Tb inhibited mitochondrial protein biosynthesis, reduced precursor cell ATP synthesis in the spinal cord, and resulted in myelosuppression, including anemia, neutropenia, and thrombocytopenia. Furthermore, linezolid interferes with the phosphorylation process of myosin light chain 2 in megakaryocyte cells. It binds to membrane glycoprotein IIb/IIIa, resulting in the inhibition of platelet formation.[40]

The safe and effective daily dose of linezolid for DR-TB patients is not fully understood. For ITR, a daily of up to 600 mg of linezolid was administered either in the intensive or continuation phase. Several studies reported that a daily dose of 600-1200 mg of linezolid can be used for DR-TB patients with favorable outcomes. However, the moderate to severe adverse effects associated with linezolid limit its use during DR-TB treatment, resulting in temporary or permanent discontinuation of the drug. Hematological toxicity is one of the side effects of linezolid that is most often found in DR-TB patients and requires intervention by reducing the dose or temporary to permanent discontinuation. The myelosuppressive effect associated with linezolid was significantly dose related. High exposure to linezolid was associated with hematologic toxicity.[41]

Linezolid has been reported to cause pancytopenia with a significant decrease in hematological parameters, including erythrocytes, leukocytes, Hb, and platelets, after 30 days of using linezolid. The hematological parameters gradually improved after the discontinuation of linezolid. It indicates the importance of periodic complete blood counts, especially in patients with a history of myelosuppression and taking other drugs that suppress the bone marrow. Therefore, WHO recommends hematologic monitoring during linezolid treatment including complete blood count (platelet, hemoglobin, neutrophil) within two weeks of initial treatment and then monthly until treatment was complete. Linezolid induces neuropathy by inhibiting the survival and autophagy flux of Schwann cells, indirectly leading to neuron cell damage. In addition, linezolid upregulated P-AKT and P62, and downregulated LC3B, thus inhibiting the proliferation of Schwann cells. [41] The incidence of neuropathy was associated with the serum concentration of linezolid. A cut-off > 2 mg/L serum concentration of linezolid was associated with neuropathy. In MDR-TB patients with serum concentration > 2 mg/L, peripheral and optic neuropathy were more frequent than that of < 2 mg/L. [42]

Compared to the study by Huerga *et al*. DR-TB patients who received linezolid for individual regimens, the incidence of myelosuppression, peripheral neuropathy, and optic neuritis was 6.0%, 26.4%, and 3.1%, respectively.[21] Furthermore, Gao *et al*. reported adverse events related to linezolid in MDR and XDR-TB were peripheral neuropathy (4.5%), thrombocytopenia (4.5%),

neutropenia (4.0%), and optic neuritis (1.1%). [38] Anemia and peripheral neuropathy were found to be significantly more common in patients who interrupted linezolid than in those who continued linezolid.43 Level of hemoglobin when decreasing more than 10% after administration of linezolid for four weeks confers sensitivity and specificity, 82% and 84%, respectively, to predict severe anemia. Reducing the dose of linezolid to 600 mg daily can prevent up to 60% of severe anemia.[44]

The most common side effects after administration of pretomanid were GI disturbance, liver disorders, connective tissue disorders, and headaches, 28.4%, 25.5%, 16.6%, and 11.0%, respectively. QTc prolongation was not observed during the pretomanid administration. 45 Although pretomanid and delamanid belong to the nitroimidazole groups, pretomanid does not cause QT prolongation like delamanid. DM-6705, the primary metabolite of delamanid, is responsible for prolonging the QT interval. Pretomanid is metabolized in the liver by CYP3A4 to the trifluoromethoxy-benzoic acid glycine conjugate. Furthermore, pretomanid was excreted in the urine and feces of about 53% and 38% of the total dose, respectively.[15] Liver toxicity is a potential side effect associated with pretomanid. Patients should avoid using other potentially hepatotoxic drugs or concurrent use with alcohol. Monitoring of liver function, including ALT and AST is recommended for the initial two weeks, then monthly until therapy is finished.[46]

Although two primary studies, Nix TB and ZeniX TB, have shown a good efficacy of the BPaL regimen for treating DR-TB patients, the readiness of healthcare providers is needed to implement BPaL into TB programs. Active surveillance of safety and side effect management is crucial for the safety of Linezolid. A study by van de Berg *et al*. demonstrated that the implementation of the BPaL regimen was acceptable and feasible among stakeholders in the three countries with the highest TB burden, Indonesia, Kyrgyzstan, and Nigeria.[47]

The limitation of this review is the data regarding the efficacy and safety of the BPaL regimen was only obtained from two trials without a control group. In addition, studies that directly compare BPaL regimens with standard regimens have yet to be made available. Therefore, prospective studies comparing head-to-head BPaL regimens with standard regimens with a large number of patients are urgently needed to obtain more valid findings.

5 Conclusion

This review concludes that the BPaL regimen provides successful treatment after six months of treatment. Compared to STR and ITR, the BPaL regimen reduces pill burdens and shortens treatment. BPaL regimens generally are relatively safe with a tolerable linezolid-related side effect profile. Early detection of adverse events can be used to modify therapy by adjusting the dose or temporarily discontinuing linezolid.

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