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Literatur Review

Safety and Efficacy of Bedaquiline-Pretomanid-Linezolid (BPaL) in Patients with Drug-Resistant Tuberculosis: Review from Clinical Evidence

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Abstract. Regimens containing bedaquiline were administered for up to 11 months and 24 months in shorter and longer regimen to treat patients with drug-resistant tuberculosis (DR-TB), respectively. Pre extensively drug resistant (Pre XDR) and extensively drug TB (XDR-TB) are highly DR-TB with a lower success treatment than multi drug resistant TB (MDR-TB). Therapy for highly DR-TB with fewer drugs and shorter treatment is required to increase success treatment. Bedaquiline-pretomanid-linezolid (BPaL) is considered to be used for highly DR-TB. This was a narrative review summarize the efficacy and safety of the BPaL regimen to manage patients with highly DR-TB. The 26-week of BPaL regimen was reported to provide favorable outcomes in two previous trials, Nix and Zenix TB. BPaL offers treatment success, especially in highly drug-resistant tuberculosis compared to standard regimens containing bedaquiline. Nonetheless, adverse effects, such as hematologic toxicity or myelosuppression, peripheral neuropathy, and optic neuritis were more common in BPaL regimens than in standard regimens. The incidence QT prolongation was lower with BPaL regimens compared with standard regimens. Adding pretomanid to the bedaquiline-linezolid regimen prevents TB bacteria that are resistant to bedaquiline. It is necessary to periodically monitor adverse effects associated with linezolid in BPaL regimen and how to manage them accordingly. This review concludes that the BPaL regimen provides favorable outcomes, reduces pill burdens, and shortenes treatment. Health facilities should prepare for the implementation of BPaL to manage DR-TB patients.

Keywords: *Drug-resistant tuberculosis, Bedaquiline-pretomanid-linezolid, Efficacy, and Safety*

INTRODUCTION

The rise in *Mycobacterium tuberculosis* (M.Tb), which resistant to the two main TB drugs, rifampicin and isoniazid, is a serious threat worldwide. Tuberculosis (TB) is a highly infectious disease with low cures rate worldwide (Panford et al., 2022). DR-TB is more common in patients who previously treated with antitubercular drugs (Farghaly et al., 2021). The success rate in DR-TB using second-line injection drugs was less than 50% (Indarti et al., 2022; Soeroto et al., 2022). WHO recommended a full oral regimen containing bedaquiline to treat DR-TB patients (WHO, 2020). Bedaquiline, a novel antituberculosis drug, resulted promising results in DR-TB patients with shortened treatment time, improved adherence, increased cure, and reduced mortality rates (Saravu & Pai, 2019). It has high activity antimycobacterial, especially in resistant strain by

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inhibiting of ATP synthase and thus depleting energy of *M. tuberculosis* both in in active and dormant phase (Lyons, 2022). It was considered as a core drug due to high bactericidal and sterilizing activity (van Deun et al., 2018). 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 (Wang et al., 2021).

Adding bedaquiline in DR-TB treatment increases intracellular killing activity against M.Tb (Giraud-Gatineau et al., 2020). Bedaquiline has been included in a fully oral regimen either for shorter treatment or individual longer treatment (WHO, 2020). Theoretically, an increase of bedaquiline use without drug-susceptibility testing (DST) will face of 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% (Jain, 2022). Although regimens containing bedaquiline have shown high success rates, the long duration of treatment can be a challenge. Shorter treatment regimens are administered for 9-12 months with seven all oral, while individual longer regimens 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 (Atif et al., 2022). 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 (Cheng et al., 2021).

Therefore, a safe and effective regimen with fewer drugs and a shorter treatment is needed to simplify administration and increase patient adherence. In the Nix-TB trial, patients with highly DR-TB, after administration of regimen containing bedaquiline, pretomanid, and linezolid (BPaL) for twenty-six weeks, 90% of them had a treatment success. However, adverse events were relatively high associated with linezolid, such as neuropathy and myelosuprresion (Conradie et al., 2020). In August 2019, the U.S Food and Drug Administration (FDA) approved BPaL regimen for patients with XDR-TB or patients who are intolerant or unresponsive to standard MDR-TB regimens and who have not previously been treated with bedaquiline and/or linezolid, or those who receive bedaquiline or linezolid not more than 4 weeks prior to first dose of BPaL.

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 responsible for the survival of M.Tb either actively replicating or dormant (Stancil et al., 2021). Inhibition of mycolic acid potently disrupts the cell wall of M.Tb and reduces inflammatory cell infiltration as a result of interaction to the host. Furthermore, desnitro derivatives of pretomanid lead to respiratory poisoning of M.Tb (Pardeshi et al., 2022). A systematic review by Gils *et al*. reported 91% of rifampicin resistant TB (RR-TB) patients had favorable outcome after administration a regimen containing pretomanid. Meanwhile, in highly resistant TB, favorable outcome was 90% at six months after treatment (Gils

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et al., 2022).

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 (WHO, 2020). 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 outcome including cure and treatment completion and 89% had culture conversion at the end of treatment (X. Zhang et al., 2015). In addition to efficacy, drug safety is an important factor in managing DR-TB 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, we tried to review the efficacy and safety of the BPaL regimen compared to existing regimens to treat patients with highly DR-TB.

METHOD

This was a narrative review to summarize the efficacy and safety of the BPaL regimen to manage patients with highly DR-TB. We used secondary data from articles published from 2019 to December 2022 in Pubmed and Science Direct databases reporting on the safety and efficacy or effectiveness of bedaquiline/pretomanid/linezolid (BPaL) regimens containing bedaquiline and delamanid in patients with drug resistant tuberculosis. The search terms were: “drug-resistant tuberculosis” (DR-TB), “pre-XDR-TB”, “XDR-TB”, “MDR-TB”, “bedaquiline”, “pretomanid”, “linezolid”, “BPaL”, “efficacy”, “effectiveness”, and “safety”. Boolean operators with “OR”, “AND”, and “NOT” were used to combine these terms to search articles more specific. The inclusion criteria to conduct this review were (a) articles written in English; (b) articles as original articles with randomized controlled trial (RCT), cohort, cross-sectional, or case-control study designs; patients diagnosed with drug resistant tuberculosis including MDR-TB, pre XDR-TB, and XDR-TB; (c) reporting success rate with smear sputum and or culture conversion and safety during 24 week of treatment, and (d) DR-TB patients aged ≥ 18 years old. The exclusion as following: article was written as a review, letter to the editor, animal studies, and abstract proceeding or conferences. Articles in full text that meet the inclusion criteria will be summarized as descriptive.

RESULTS AND DISCUSSION

Efficacy of BPaL regimen

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

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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.

Thirty-eight and seventy-one 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 with the detail 63/71 (89%) patients with XDR and 35/38 (92%) patients with MDR-TB. Meanwhile, 8/71 (11%) and 3/38 (8%) patients with pre-XDR and XDR-TB had unfavorable outcome, respectively (Conradie et al., 2020). XDR-TB is case of DR-TB with additional resistance to fluoroquinolones and at least one drug from class A (bedaquiline and linezolid) (WHO, 2020). Patients with XDR-TB were 4.7 times more likely to have unfavorable outcome than those with MDR-TB. Linezolid was used more frequently in XDR-TB group compared with the MDR-TB group. (Bhering et al., 2019) Patients with pre-XDR and XDR-TB who received regimen containing bedaquiline and delamanid, 22/32 (69%) had negative culture before 24 weeks.(Das et al., 2020) A study by Huerga *et al*, demonstrated that 358/458 patients (78.0%) had favorable outcome in regimen containing bedaquiline-delamanid (Huerga et al., 2022).

In individual regimen, for pre-XDR or XDR-TB patients, one or more drugs from class C, such as ethambutol, delamanid, and pyrazinamide can be added to the regimen to retain five effective drugs. Several studies have reported the excellent efficacy of the regimen containing bedaquiline and/or delamanid either for MDR or XDR-TB patients. However, the use of this regimen is limited due to potential risk of QTc prolongation. QTc prolongation of bedaquiline and delamanid is related to their primary metabolites, M2 and DM-6705, respectively (Tanneau et al., 2022).

Favorable outcome was defined as sputum conversion at least for 24 weeks (six months) after initial and/or treatment completion. GeneXpert has a higher diagnostic value compared with Ziehl Neelsen smear to diagnose DR-TB and it provides a faster diagnosis than culture and detects rifampicin resistance (Abd et al., 2021). Sputum culture conversion is the most commonly method to evaluate the effectiveness after administering of 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 (Javaid et al., 2018). Furthermore, cure rate was significantly associated with culture conversion at 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 (Meyvisch et al., 2018).

However, the limitation of Nix TB trial should be considered before implementing into programmatic use. Since the non-randomized study with no controlled group, we could not

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compare the efficacy between BPaL and 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. Study to explore the efficacy of linezolid with a dose lower than 1200 mg with shorter duration was confirmed in 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 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 a treatment success. 3/44 (7%), 5/45 (11%), 4/45 (9%), and 7/44 (16%), respectively, had unfavorable outcome for those in linezolid with a daily dose of 1200 mg or 600 mg for twenty-four or nine weeks (Conradie et al., 2022).

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 (Xu et al., 2019).

In addition to pretomanid, delamanid has capability to prevent relapse. In mouse tuberculosis model, Pieterman et al. (2021) reported that negative cultures were obtained after eight and 20 weeks of bedaquiline/delamanid/linezolid (BDL) and isoniazid/rifampicin/pirazinamid/ethambutol (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. 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 longer individual regimen, a daily for up to 600 mg of linezolid was administered either in intensive or continuation phase with a total duration of 18-24 months.

Several studies reported that daily dose of 600-1200 mg of linezolid can be used for DR-TB patients (Singh et al., 2019). 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. Area under curve (AUC)0-24 with minimum inhibitory concentration (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 (Yew et al., 2019). A case study by Haley *et al*. reported that in XDR-TB patient with no resistance to bedaquiline and linezolid, administration of a BPaL regimen with a daily dose 600 mg of linezolid for six months provided a favorable outcome without recurrence at nine months after therapy completion (Haley et al., 2021).

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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 case. Although delamanid demonstatred higher potency than pretomanid in vitro against MDR and XDR-TB isolates, the two drugs had the same resistance frequency and comparable plasma concentrations (Prosser et al., 2017). Like delamanid, pretomanid is active against both replicating and dormant TB bacteria (Stancil et al., 2021). 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 (Bigelow et al., 2020). 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, deletion of *cinA* enhances the killing activity of BPaL by blocking cleavage of NAD-drug aducts (Kreutzfeldt et al., 2022).

A study comparing the efficacy of a BPaL regimen with an individualized regimen containing bedaquiline-linezolid in XDR-TB patients was reported 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 (Oelofse et al., 2021). 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 (Mulder et al., 2022). Therefore, this regimen may save the government's budget for treating DR-TB patients.

Safety of BPaL regimen

In Nix-TB trial, 88 patients (81%) had peripheral neuropathy, although the symptom were mild to moderate and occurred after administration for three months. Twelve (11.0%) and eleven (10.1%) patients from 109 patients had elevation of alanine aminotransferase (ALT) and amino aspartate aminotransferase (AST) more than three times from 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.

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However, these adverse events were manageable by interrupting and or reducing the linezolid dose (Conradie et al., 2020).

In 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, patients who received 600 mg of linezolid, no patients had hemoglobin < 25% below baseline level. Neuropathy optic occurred in 4/45 patients (9%) receiving 1200 mg of linezolid for twenty-six weeks. Meanwhile, 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 3 of 181 patients (2%) had liver-related serious adverse event (Conradie et al., 2022). Interruption of linezolid including dose reduction or discontinuation was higher in linezolid at dose of 1200 mg compared at 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% (Gao et al., 2021; Li et al., 2021). 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 Torsade de Pointes (TdP) or death related cardiac arrythmia 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 (Ngwalero et al., 2021).

Myelosuppression and neuropathy are considered of the important causes of temporally or permanently discontinuation of linezolid in a regimen. Hematologic toxicity due to linezolid was associated with mitochondrial disruption. M.Tb damages 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 (Oehadian et al., 2022). Therefore, WHO recommends hematologic monitoring during linezolid treatment including complete blood count (platelet, hemoglobin, neutrophil) in two weeks initial treatment and then monthly until treatment was complete. Linezolid induces neuropathy by inhibiting the survival and autophagy flux of Schwann cell, indirectly leading to neuron cell damage. In addition, linezolid upregulated P-AKT and P62, and downregulated LC3B, thus inhibiting the proliferation of Schwann cell (Yuan et al., 2022). The incidence of neuropathy was associated with serum concentration of linezolid. A cut-off > 2 mg/L serum concentration of linezolid was associated with neuropathy. MDR-TB patients with serum concentration > 2 mg/L,

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peripheral and optic neuropathy was more frequent than that of < 2 mg/L (P. Zhang et al., 2022).

Compared to the study by Huerga *et al*. DR-TB patients who received linezolid for individual regimen, the incidence of myelosuppression, peripheral neuropathy, and optic neuritis was 6.0%, 26.4%, and 3.1%, respectively (Huerga et al., 2022). 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%). (Gao et al., 2021) Anemia and peripheral neuropathy were found to be significantly more common in patients who interrupted linezolid than in those who continued linezolid (Dayyab et al., 2021). Level of hemoglobin when decrease 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 until 600 mg daily can prevent up to 60% of severe anemia (Imperial et al., 2022).

The most common side effects after administration of pretomanid were GI disturbance (28,4%), liver disorders (25,5%), connective tissue disorders (16.6%), and headaches (11.0%). QTc prolongation was not observed during the pretomanid administration (Nedelman et al., 2020). Although pretomanid and delamanid are 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 (Stancil et al., 2021). 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 (Occhineri et al., 2022).

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 BPaL regimen was acceptable and feasible among stakeholders in the three countries with the highest TB burden, Indonesia, Kyrgyzstan, and Nigeria(van de Berg et al., 2021).

The limitation of this review is the data regarding the efficacy and safety of the BPaL regimen were 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 many patients are urgently needed to obtain more valid findings.

CONCLUSION

This review concludes that the BPaL regimen provides favorable outcomes in 26 weeks by

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reducing pill burdens and shortening treatment. BPaL regimens generally are relatively safe with a tolerable linezolid-related side effect profile. Early detection of adverse events including optic neuropathy and myelosuppression (moderate to severe anemia) can be used to modify therapy by adjusting the dose or temporarily discontinuing linezolid.

CONFLICT OF INTEREST

All authors declare there was no conflict of interest.

REFERENCES

Abd, H. E. S., Aaty, E., El-Hefnawy, M. Y., & Khalaf, F. S. (2021). *Study of diagnostic role of GeneXpert test in patients with pulmonary tuberculosis at El-Mahalla Chest Hospital*. https://doi.org/10.4103/ejcdt.ejcdt_135_19

Atif, M., Mukhtar, S., Sarwar, S., Naseem, M., Malik, I., & Mushtaq, A. (2022). Drug resistance patterns, treatment outcomes and factors affecting unfavourable treatment outcomes among extensively drug resistant tuberculosis patients in Pakistan; a multicentre record review. *Saudi Pharmaceutical Journal*, *30*(4), 462–469. https://doi.org/10.1016/j.jsps.2022.01.015

Bhering, M., Duarte, R., & Kritski, A. (2019). Predictive factors for unfavourable treatment in MDR-TB and XDR-TB patients in Rio de Janeiro State, Brazil, 2000-2016. *PLoS ONE*, *14*(11). https://doi.org/10.1371/journal.pone.0218299

Bigelow, K. M., Tasneen, R., Chang, Y. S., Dooley, K. E., & Nuermberger, E. L. (2020). *Preserved Efficacy and Reduced Toxicity with Intermittent Linezolid Dosing in Combination with Bedaquiline and Pretomanid in a Murine Tuberculosis Model*. https://journals.asm.org/journal/aac

Cheng, N., Wu, S., Luo, X., Xu, C., Lou, Q., Zhu, J., You, L., & Li, B. (2021). A comparative study of chest computed tomography findings: 1030 cases of drug-sensitive tuberculosis versus 516 cases of drug-resistant tuberculosis. *Infection and Drug Resistance*, *14*, 1115–1128. https://doi.org/10.2147/IDR.S300754

Conradie, F., Bagdasaryan, T. R., Borisov, S., Howell, P., Mikiashvili, L., Ngubane, N., Samoilova, A., Skornykova, S., Tudor, E., Variava, E., Yablonskiy, P., Everitt, D., Wills, G. H., Sun, E., Olugbosi, M., Egizi, E., Li, M., Holsta, A., Timm, J., … Spigelman, M. (2022). Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. *New England Journal of Medicine*, *387*(9), 810–823. https://doi.org/10.1056/nejmoa2119430

Conradie, F., Diacon, A. H., Ngubane, N., Howell, P., Everitt, D., Crook, A. M., Mendel, C. M., Egizi, E., Moreira, J., Timm, J., McHugh, T. D., Wills, G. H., Bateson, A., Hunt, R., van Niekerk, C., Li, M., Olugbosi, M., & Spigelman, M. (2020). Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *New England Journal of Medicine*, *382*(10), 893–902. https://doi.org/10.1056/nejmoa1901814

Das, M., Dalal, A., Laxmeshwar, C., Ravi, S., Mamnoon, F., Meneguim, A. C., Paryani, R.,

P-ISSN 2654-8364
E-ISSN: 2684-7361

Mathur, T., Singh, P., Mansoor, H., Kalon, S., Hossain, F. N., Lachenal, N., Coutisson, S., Ferlazzo, G., & Isaakidis, P. (2020). One Step Forward: Successful End-of-Treatment Outcomes of Patients With Drug-Resistant Tuberculosis Who Received Concomitant Bedaquiline and Delamanid in Mumbai, India. *Clinical Infectious Diseases*, *Xx Xxxx*, 1–9. https://doi.org/10.1093/cid/ciaa1577

Dayyab, F., Iliyasu, G., Ahmad, B., & Habib, A. (2021). Early safety and efficacy of linezolid-based combination therapy among patients with drug-resistant tuberculosis in North-western Nigeria. *International Journal of Mycobacteriology*, *10*(2), 129–135. https://doi.org/10.4103/ijmy.ijmy_57_21

Farghaly, S., Zin El-Abdeen, A., Shaaban, L. H., & Mahmoud, A. (2021). Epidemiology and outcome of rifampicin resistant tuberculosis in Upper Egypt. *The Egyptian Journal of Chest Diseases and Tuberculosis*, *70*, 183–187. https://doi.org/10.4103/ejcdt.ejcdt_125_20

Gao, M., Gao, J., Xie, L., Wu, G., Chen, W., Chen, Y., Pei, Y., Li, G., Liu, Y., Shu, W., Fan, L., Wu, Q., Du, J., Chen, X., Tang, P., Xiong, Y., Li, M., Cai, Q., Jin, L., … Li, L. (2021). Early outcome and safety of bedaquiline-containing regimens for treatment of MDR- and XDR-TB in China: a multicentre study. *Clinical Microbiology and Infection*, *27*(4), 597–602. https://doi.org/10.1016/j.cmi.2020.06.004

Gils, T., Lynen, L., de Jong, B. C., van Deun, A., & Decroo, T. (2022). Pretomanid for tuberculosis: a systematic review. In *Clinical Microbiology and Infection* (Vol. 28, Issue 1, pp. 31–42). Elsevier B.V. https://doi.org/10.1016/j.cmi.2021.08.007

Giraud-Gatineau, A., Coya, J. M., Maure, A., Biton, A., Thomson, M., Bernard, E. M., Marrec, J., Gutierrez, M. G., Larrouy-Maumus, G., Brosch, R., Gicquel, B., & Tailleux, L. (2020). The antibiotic bedaquiline activates host macrophage innate immune resistance to bacterial infection. *ELife*, *9*, 1–29. https://doi.org/10.7554/eLife.55692

Haley, C. A., Macias, P., Jasuja, S., Jones, B. A., Rowlinson, M. C., Jaimon, R., Onderko, P., Darnall, E., Gomez, M. E., Peloquin, C., Ashkin, D., & Goswami, N. D. (2021). Novel 6-month treatment for drug-resistant tuberculosis, United States. *Emerging Infectious Diseases*, *27*(1), 332–334. https://doi.org/10.3201/eid2701.203766

Huerga, H., Khan, U., Bastard, M., Mitnick, C. D., Lachenal, N., Khan, P. Y., Seung, K. J., Melikyan, N., Ahmed, S., Rich, M. L., Varaine, F., Osso, E., Rashitov, M., Salahuddin, N., Salia, G., Sánchez, E., Serobyan, A., Rafi Siddiqui, M., Grium Tefera, D., … Hewison, C. (2022). Safety and Effectiveness Outcomes From a 14-Country Cohort of Patients With Multi-Drug Resistant Tuberculosis Treated Concomitantly With Bedaquiline, Delamanid, and Other Second-Line Drugs. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciac176

Imperial, M. Z., Nedelman, J. R., Conradie, F., & Savic, R. M. (2022). Proposed Linezolid Dosing Strategies to Minimize Adverse Events for Treatment of Extensively Drug-Resistant Tuberculosis. *Clinical Infectious Diseases*, *74*(10), 1736–1747.

P-ISSN 2654-8364
E-ISSN: 2684-7361

https://doi.org/10.1093/cid/ciab699

Indarti, H. T., Kristin, E., Soedarsono, S., & Endarti, D. (2022). Treatment Outcomes of Multidrug-Resistant Tuberculosis Patients in East Java, Indonesia: A Retrospective Cohort Analysis. *International Journal of Mycobacteriology*, *11*(3), 261–267. https://doi.org/10.4103/ijmy.ijmy_86_22

Jain, N. (2022). Reply: Roll out of bedaquiline without drug susceptibility testing leads to emergence of bedaquiline-resistance in high burden countries with tuberculosis - Danger of losing a novel drug. *Lung India*, *39*(4), 389. https://doi.org/10.4103/lungindia.lungindia_31_22

Javaid, A., Ahmad, N., Afridi, A. K., Basit, A., Khan, A. H., Ahmad, I., & Atif, M. (2018). Validity of time to sputum culture conversion to predict cure in patients with multidrug-Resistant tuberculosis: A retrospective single-Center study. *American Journal of Tropical Medicine and Hygiene*, *98*(6), 1629–1636. https://doi.org/10.4269/ajtmh.17-0936

Kreutzfeldt, K. M., Jansen, R. S., Hartman, T. E., Gouzy, A., Wang, R., Krieger, I. v., Zimmerman, M. D., Gengenbacher, M., Sarathy, J. P., Xie, M., Dartois, V., Sacchettini, J. C., Rhee, K. Y., Schnappinger, D., & Ehrt, S. (2022). CinA mediates multidrug tolerance in Mycobacterium tuberculosis. *Nature Communications*, *13*(1). https://doi.org/10.1038/s41467-022-29832-1

Li, J., Yang, G., Cai, Q., Wang, Y., Xu, Y., Zhang, R., Lang, Y., & Cai, X. (2021). Safety, efficacy, and serum concentration monitoring of bedaquiline in Chinese patients with multidrug-resistant tuberculosis. In *International Journal of Infectious Diseases* (Vol. 110, pp. 179–186). Elsevier B.V. https://doi.org/10.1016/j.ijid.2021.07.038

Lyons, M. A. (2022). *Pharmacodynamics and Bactericidal Activity of Bedaquiline in Pulmonary Tuberculosis*. https://journals.asm.org/journal/aac

Meyvisch, P., Kambili, C., Andries, K., Lounis, N., Theeuwes, M., Dannemann, B., Vandebosch, A., van der Elst, W., Molenberghs, G., & Alonso, A. (2018). Evaluation of six months sputum culture conversion as a surrogate endpoint in a multidrug resistant-tuberculosis trial. *PLoS ONE*, *13*(7). https://doi.org/10.1371/journal.pone.0200539

Mulder, C., Rupert, S., Setiawan, E., Mambetova, E., Edo, P., Sugiharto, J., Useni, S., Malhotra, S., Cook-Scalise, S., Pambudi, I., Kadyrov, A., Lawanson, A., van den Hof, S., Gebhard, A., Juneja, S., & Sohn, H. (2022). Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis. *BMJ Global Health*, *7*(1). https://doi.org/10.1136/bmjgh-2021-007182

Nedelman, J. R., Salinger, D. H., Subramoney, V., Woolson, R., Wade, K., Li, M., Everitt, D., Mendel, C. M., & Spigelman, M. (2020). *An Exposure-Response Perspective on the Clinical Dose of Pretomanid*. https://doi.org/10

Ngwalero, P., Brust, J. C. M., van Beek, S. W., Wasserman, S., Maartens, G., Meintjes, G., Joubert, A., Norman, J., Castel, S., Gandhi, N. R., Denti, P., McIlleron, H., Svensson, E. M., &

P-ISSN 2654-8364
E-ISSN: 2684-7361

Wiesner, L. (2021). Relationship between plasma and intracellular concentrations of bedaquiline and its m2 metabolite in South African patients with rifampin-resistant tuberculosis. *Antimicrobial Agents and Chemotherapy*, *65*(11). https://doi.org/10.1128/AAC.02399-20

Occhineri, S., Matucci, T., Rindi, L., Tiseo, G., Falcone, M., Riccardi, N., & Besozzi, G. (2022). Pretomanid for tuberculosis treatment: an update for clinical purposes. In *Current Research in Pharmacology and Drug Discovery* (Vol. 3). Elsevier B.V. https://doi.org/10.1016/j.crphar.2022.100128

Oehadian, A., Santoso, P., Menzies, D., & Ruslami, R. (2022). Concise Clinical Review of Hematologic Toxicity of Linezolid in Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: Role of Mitochondria. In *Tuberculosis and Respiratory Diseases* (Vol. 85, Issue 2, pp. 111–121). Korean National Tuberculosis Association. https://doi.org/10.4046/TRD.2021.0122

Oelofse, S., Esmail, A., Diacon, A. H., Conradie, F., Olayanju, O., Ngubane, N., Howell, P., Everitt, D., Crook, A. M., Mendel, C. M., Wills, G. H., Olugbosi, M., del Parigi, A., Sun, E., Calatroni, A., Spigelman, M., & Dheda, K. (2021). Pretomanid with bedaquiline and linezolid for drug-resistant TB: A comparison of prospective cohorts. *International Journal of Tuberculosis and Lung Disease*, *25*(6), 453–460. https://doi.org/10.5588/ijtld.21.0035

Panford, V., Kumah, E., Kokuro, C., Adoma, P. O., Baidoo, M. A., Fusheini, A., Ankomah, S. E., Agyei, S. K., & Agyei-Baffour, P. (2022). Treatment outcomes and associated factors among patients with multidrug-resistant tuberculosis in Ashanti Region, Ghana: a retrospective, cross-sectional study. *BMJ Open*, *12*(7). https://doi.org/10.1136/bmjopen-2022-062857

Pardeshi, V., Lokhande, T., Shelke, A., Tuse, T., Pawar, B., & Bonde, C. (2022). A breakthrough in the treatment of multidrug-resistant tuberculosis: A novel and effective approach. *The Egyptian Journal of Chest Diseases and Tuberculosis*, *71*(4), 413. https://doi.org/10.4103/ecdt.ecdt_24_22

Pieterman, E. D., Keutzer, L., van der Meijden, A., van den Berg, S., Wang, H., Zimmerman, M. D., Simonsson, U. S. H., Bax, H. I., & de Steenwinkel, J. E. M. (2021). Superior Efficacy of a Bedaquiline, Delamanid, and Linezolid Combination Regimen in a Mouse Tuberculosis Model. *Journal of Infectious Diseases*, *224*(6), 1039–1047. https://doi.org/10.1093/infdis/jiab043

Prosser, G., Brandenburg, J., Reiling, N., Barry, C. E., Wilkinson, R. J., & Wilkinson, K. A. (2017). The bacillary and macrophage response to hypoxia in tuberculosis and the consequences for T cell antigen recognition. *Microbes and Infection*, *19*(3), 177–192. https://doi.org/10.1016/j.micinf.2016.10.001

Saravu, K., & Pai, M. (2019). Drug-resistant tuberculosis: Progress towards shorter and safer regimens. In *Lung India* (Vol. 36, Issue 5, pp. 373–375). Wolters Kluwer Medknow Publications. https://doi.org/10.4103/lungindia.lungindia_350_19

P-ISSN 2654-8364
E-ISSN: 2684-7361

Singh, B., Cocker, D., Ryan, H., & Sloan, D. J. (2019). Linezolid for drug-resistant pulmonary tuberculosis. In *Cochrane Database of Systematic Reviews* (Vol. 2019, Issue 3). John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD012836.pub2

Soeroto, A. Y., Nurhayati, R. D., Purwiga, A., Lestari, B. W., Pratiwi, C., Santoso, P., Kulsum, I. D., Suryadinata, H., & Ferdian, F. (2022). Factors associated with treatment outcome of MDR/RR-TB patients treated with shorter injectable based regimen in West Java Indonesia. *PLoS ONE*, *17*(1 January). https://doi.org/10.1371/journal.pone.0263304

Stancil, S. L., Mirzayev, F., & Abdel-Rahman, S. M. (2021). Profiling pretomanid as a therapeutic option for tb infection: Evidence to date. In *Drug Design, Development and Therapy* (Vol. 15, pp. 2815–2830). Dove Medical Press Ltd. https://doi.org/10.2147/DDDT.S281639

Tanneau, L., Karlsson, M. O., Diacon, A. H., Shenje, J., de Los Rios, J., Wiesner, L., Upton, C. M., Dooley, K. E., Maartens, G., & Svensson, E. M. (2022). Population Pharmacokinetics of Delamanid and its Main Metabolite DM-6705 in Drug-Resistant Tuberculosis Patients Receiving Delamanid Alone or Coadministered with Bedaquiline. *Clinical Pharmacokinetics*, *61*(8), 1177–1185. https://doi.org/10.1007/s40262-022-01133-2

van de Berg, S. E. J., Pelzer, P. T., van der Land, A. J., Abdrakhmanova, E., Ozi, A. M., Arias, M., Cook-Scalise, S., Dravniece, G., Gebhard, A., Juneja, S., Handayani, R., Kappel, D., Kimerling, M., Koppelaar, I., Malhotra, S., Myrzaliev, B., Nsa, B., Sugiharto, J., Engel, N., … van den Hof, S. (2021). Acceptability, feasibility, and likelihood of stakeholders implementing the novel BPaL regimen to treat extensively drug-resistant tuberculosis patients. *BMC Public Health*, *21*(1). https://doi.org/10.1186/s12889-021-11427-y

van Deun, A., Decroo, T., Piubello, A., de Jong, B. C., Lynen, L., & Rieder, H. L. (2018). Principles for constructing a tuberculosis treatment regimen: The role and definition of core and companion drugs. In *International Journal of Tuberculosis and Lung Disease* (Vol. 22, Issue 3, pp. 239–245). International Union against Tubercul. and Lung Dis. https://doi.org/10.5588/ijtld.17.0660

Wang, M. G., Wu, S. Q., & He, J. Q. (2021). Efficacy of bedaquiline in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. *BMC Infectious Diseases*, *21*(1), 1–10. https://doi.org/10.1186/s12879-021-06666-8

WHO. (2020). Consolidated Guidelines on Tuberculosis Treatment. In *Who*.

Xu, J., Li, S.-Y., Almeida, D. v, Tasneen, R., Barnes-Boyle, K., Converse, P. J., Upton, A. M., Mdluli, K., Fotouhi, N., & Nuermberger, E. L. (2019). *Contribution of Pretomanid to Novel Regimens Containing Bedaquiline with either Linezolid or Moxifloxacin and Pyrazinamide in Murine Models of Tuberculosis*. https://journals.asm.org/journal/aac

Yew, W. W., Chan, D. P., & Chang, K. C. (2019). Does linezolid have a role in shortening treatment of tuberculosis? In *Clinical Microbiology and Infection* (Vol. 25, Issue 9, pp. 1060–1062). Elsevier B.V. https://doi.org/10.1016/j.cmi.2019.06.020

Yuan, Y., Li, J., Chen, Y., Cai, Q., Xu, Y., Lin, L., Lang, Y., Guo, S., Zhang, R., & Cai, X. (2022).

P-ISSN 2654-8364
E-ISSN: 2684-7361

Vol. 5 No. 2 Juni Tahun 2023

Mechanism underlying linezolid-induced peripheral neuropathy in multidrug-resistant tuberculosis. *Frontiers in Pharmacology*, *13*. https://doi.org/10.3389/fphar.2022.946058

Zhang, P., Li, W., Chen, X., Liu, M., Zhan, S., Zhang, H., & Deng, G. (2022). Linezolid-Associated Neuropathy in Patients with MDR/XDR Tuberculosis in Shenzhen, China. *Infection and Drug Resistance*, *15*, 2617–2624. https://doi.org/10.2147/IDR.S365371

Zhang, X., Falagas, M. E., Vardakas, K. Z., Wang, R., Qin, R., Wang, J., & Liu, Y. (2015). Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. *Journal of Thoracic Disease*, *7*(4), 603–615. https://doi.org/10.3978/j.issn.2072-1439.2015.03.10

P-ISSN 2654-8364
E-ISSN: 2684-7361