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Comparing The Hematological Effects of BPaL/BPaLM Regimens to Those of Standard Regimens in the Treatment of Drug-Resistant Tuberculosis: A Narrative Review

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ABSTRACT

Drug-resistant tuberculosis (DR-TB) is a problem for health around the world, and standard treatments don't work very well. The new treatment plan that includes bedaquiline, pretomanid, and linezolid (BPaL) and its variant with moxifloxacin (BPaLM) has a shorter treatment time and higher success rates, but there is still a chance of hematological side effects. Based on recent studies, this article looks at the hematological effects of BPaL/BPaLM regimens compared to standard regimens in DR-TB therapy in great detail. The study found that BPaL/BPaLM has a different effect on blood cells than standard regimens. It increases the risk of anemia (31.9% vs. 25.4%) and thrombocytopenia (47.8% vs. 23.1%), but it lowers the risk of leukopenia (2.2% vs. 14.6%). The main way that BPaL/BPaLM causes hematological toxicity by linezolid is affecting mitochondrial dysfunction, activating inflammatory pathways, and throwing off iron homeostasis. BPaL/BPaLM is a better choice because it has a shorter treatment time (24–26 weeks vs. 78–96 weeks) and fewer pills (923–924 vs. 5,460–7,296). However, it does require close monitoring of blood levels. A thorough understanding of the hematological effects of the BPaL/BPaLM regimen makes it easier to handle side effects and makes DR-TB treatment more likely to work.

INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is one of the biggest problems in global health, especially in developing countries where TB is common. The success of treating DR-TB with standard long-term regimens is still low, with low cure rates and a high risk of side effects, including hematological problems like anemia, thrombocytopenia, and leukopenia. These blood-related effects often make it hard for patients to keep getting treatment and lower their quality of life (Bagcchi, 2023; Haley, et al., 2023).

The growth of clinical pharmaceutical sciences and antituberculosis therapy has led to the creation of new, shorter, and more effective treatment plans. One example is the combination of bedaquiline, pretomanid, and linezolid (BPaL) and its variant with the addition of moxifloxacin (BPaLM). Compared to traditional regimens, BPaL/BPaLM regimens have shorter treatment times, higher success rates, and better safety profiles (Khan, Ismail, Ghafoor, et al., 2024). However, using linezolid in these regimens still poses a risk of hematological side effects that need to be closely watched and handled properly (Burhan, et al., 2025).

Comparing the hematological effects of BPaL/BPaLM and traditional long-term regimens is an important issue in clinical pharmacy practice because clinical pharmacists are responsible for monitoring, detecting, and managing drug side effects (Minardi, et al., 2021). The purpose of this narrative review is to look at all the most recent evidence about the

hematological effects of BPaL/BPaLM regimens compared to long-term regimens for MDR-TB therapy and how they affect clinical pharmacy practice in Indonesia and around the world.

METHODS

The purpose of this narrative review was to provide an overview of the hematological effects of BPaL/BPaLM regimens compared to long-term regimens in the treatment of MDR-TB. There were several steps in the review process: finding relevant literature, choosing articles based on inclusion and exclusion criteria, extracting data, and analyzing and combining the relevant findings.

We searched for literature on electronic databases like PubMed, ScienceDirect, Google Scholar, and Web of Science using the following keywords: "multidrug-resistant tuberculosis," "BPaL," "BPaLM," "bedaquiline," "pretomanid," "linezolid," "moxifloxacin," "hematological effects," and "treatment outcomes."

To be included, studies had to meet the following criteria: (1) they had to be about the effects of BPaL/BPaLM on blood cells and/or long-term treatments for MDR-TB patients; (2) they had to be published in English and Indonesian; and (3) they had to be published in the last 10 years (2015–2025). Single case reports, editorials, and studies that only looked at kids were not included.

RESULT

Several large clinical studies show that BPaL/BPaLM regimens work just as well as standard regimens (Haley, Schechter, Ashkin, et al., 2023; Khan, Ismail, Ghafoor, et al., 2024). The Nix-TB study showed that the BPaL regimen worked 90% of the time in MDR and extensively drug-resistant (XDR) TB patients who had a bad prognosis before (Conradie, et al., 2017).

The ZeNix study helped find the right balance between safety and effectiveness and the best dose of linezolid. The results showed that a 600 mg dose for 26 weeks worked 91% of the time and was safer than a 1200 mg dose. BPaL was very successful in Indonesia, with a treatment success rate of 97.6% and 100% sputum conversion within 3 months (Wasserman, et al., 2022).

The administration of linezolid 600 mg for 26 weeks in the BPaL regimen can maintain clinical success > 90% and reduce the incidence of peripheral neuropathy side effects compared to the 1200 mg dose. This advantage is explained by the narrow therapeutic window of linezolid (2-7 µg/mL) and the threshold for toxicity occurring at concentrations > 2 µg/mL. Evidence based on the ZeNix study, TB-PRACTECAL recommends starting linezolid at a dose of 600 mg with adjustments based on therapeutic drug monitoring (TDM) if necessary (Sangsayunh, et al., 2024).

Compared to standard regimens, studies show that BPaL/BPaLM regimens speed up sputum culture conversion by a lot (Khan, Ismail, Ghafoor, et al., 2024). The average time for sputum culture conversion from positive to negative was 6.4 weeks for BPaL and 7.6 weeks for BPaLM (Khan, Ismail, Ghafoor, et al., 2024). At the end of week 4 of treatment, 72.7% of people in the BPaLM group and 63.6% of people in the BPaL group had their cultures change (Burhan, et al., 2025).

The BPaL/BPaLM regimen has shown higher success rates compared to conventional regimens for drug-resistant TB. The ZeNix, Nix-TB, TB-PRACTECAL studies, and implementation studies in Indonesia demonstrate the advantages of the BPaL/BPaLM regimen in terms of shorter duration, lower pill burden, faster sputum conversion, and more controlled side effects (Puta and Faizah, 2023).

Comparing the Frequency of Hematological Side Effects

One of the biggest problems with treating MDR-TB with both conventional and BPaL/BPaLM regimens is hematological side effects. In a number of countries where BPaL/BPaLM was used, about 34% of patients had mild to moderate blood-related side effects. There are big differences in the side effects of the two types of regimens (Khan, et al., 2024; Pratama, et al., 2023).

The hematological side effects of BPaL/BPaLM regimens are mostly due to linezolid use. Anemia is the most common side effect (31.9%), followed by myelosuppression (34.0%) and thrombocytopenia (47.8%) (Khan, et al., 2024; Pratama, et al., 2023). In 25.4% of cases, conventional regimens cause anemia, in 23.1% of cases, thrombocytopenia, and in 14.6% of cases, leukopenia. These problems are often linked to the use of aminoglycosides,

clofazimine, and para-aminosalicylic acid (Adewole, et al., 2024).

The increase in the incidence of hematological side effects in BPaL/BPaLM compared to conventional regimens is primarily due to the mechanism of action of linezolid, which suppresses bone marrow. Pretomanid also contributes to bone marrow suppression but with milder effects. Bedaquiline and moxifloxacin are less likely to cause hematological side effects. The safety profile of BPaL/BPaLM remains overall better because hematological effects can be managed, and the BPaL/BPaLM regimen does not cause severe toxicity compared to conventional regimens such as aminoglycosides and para-aminosalicylic acid (Minardi, et al., 2021; Adewole, et al., 2024).

Specific Hematological Effects of BPaL/BPaLM Regimens

Anemia is the most common blood-related side effect of BPaL/BPaLM therapy, affecting 31.9% of patients compared to 25.4% of patients receiving conventional therapy (Khan, et al., 2024; Putra and Faizah, 2023). Linezolid, which is an important part of BPaL/BPaLM regimens, is mostly to blame for this side effect. Linezolid-related anemia works by temporarily suppressing the bone marrow and processes that are controlled by the immune system (Putra and Faizah, 2023; Mo, et al., 2024).

Four out of 68 patients (5.8%) who were getting BPaL needed a blood transfusion while they were being treated with linezolid. In those cases, the dose of linezolid was changed from 600 mg once a day to three times a week (Mo, et al., 2024). Three patients had linezolid levels higher than 2 μg/mL, which led to the development of anemia (Mo, et al., 2024).

Thrombocytopenia was found in 47.8% of patients on BPaL/BPaLM regimens, which is a lot more than the 23.1% who were on regular regimens (Mo, et al., 2024). This effect is mostly linked to the use of linezolid, which works by stopping the production of platelets and making them die faster (Mo, et al., 2024). Researchers looked at data from a number of studies and found that plasma linezolid levels above 7 μg/mL were a major risk factor for thrombocytopenia, with a critical value of 6.94 μg/mL (sensitivity 91.5%; specificity 92.2%) (Mo, et al., 2024).

Conventional regimens can cause thrombocytopenia associated with the use of rifampicin and streptomycin with moderate-severe severity, while thrombocytopenia in the BPaL/BPaLM regimen is generally mild-moderate and can be managed with linezolid dose adjustment without the need to permanently discontinue treatment (Massud, et al., 2022).

Leukopenia and neutropenia are relatively rare in the BPaL/BPaLM regimen compared to conventional regimens (2.2% vs 14.6% for leukopenia and 6.3% vs 12.8% for neutropenia) (Minardi, et al., 2021). Leukopenia in conventional regimens is often associated with the use of para-aminosalicylic acid and ethionamide, while in BPaL/BPaLM, moxifloxacin is more often associated with mild neutropenia (Minardi, et al., 2021).

The Pathophysiology of Hematological Effects in BPaL/BPaLM Regimens

The way that hematological effects happen in BPaL/BPaLM regimens is more complicated than in regular regimens, and linezolid is the main ingredient that causes most of the hematological problems (Oehadian, et al., 2022). The main ways that BPaL/BPaLM regimens cause hematological toxicity are by causing problems with mitochondria, activating inflammatory pathways, and messing up iron homeostasis, which leads to bone marrow suppression (Balepur and Schlossberg, 2017).

Linezolid is toxic to blood cells because it binds to mitochondrial ribosomes in a specific way, which stops the production of mitochondrial proteins (Oehadian, et al., 2022). This mechanism lowers the activity of the respiratory chain complex, especially complex IV (cytochrome c oxidase), by as much as 52.86% and the mass of the mitochondria by 26.23% (Garrabou, et al., 2017).

Linezolid activates NLRP3 in ways that don't involve reactive oxygen species (ROS), which is different from other NLRP3 activators (Iyer, et al., 2013). When linezolid activates NLRP3, it causes an inflammatory response in the body and suppresses bone marrow erythroid precursors. This is in line with the blood disorders seen in patients (Iyer, et al., 2013).

Taking Care of Hematological Side Effects

Monitoring hematological parameters closely is an important part of caring for patients on BPaL/BPaLM regimens (Mo, et al., 2024). During the first two months of treatment, a complete blood count should be done every two weeks. After that, it should be done once a month until the treatment is over.

Linezolid dose adjustment is the main way to deal with hematological side effects in BPaL/BPaLM regimens. If you have anemia and your hemoglobin level is less than 8.0 g/dL, you can lower your linezolid dose from 600 mg every day to 300 mg every day or 600 mg three times a week. If you have thrombocytopenia and your platelet count is less than 50,000/µL, you should lower your linezolid dose or stop taking it for a short time (Mo, et al., 2024).

Clinical Implications and Recommendations

The BPaL/BPaLM regimen has significant advantages in terms of treatment duration and pill burden compared to conventional regimens (Mulder, Rupert, Setiawan, et al., 2022). The duration of BPaL treatment is 26 weeks and BPaLM 24 weeks, much shorter compared to 78-96 weeks for conventional regimens (Mulder, Rupert, Setiawan, et al., 2022). The total number of pills during therapy is also significantly lower, with approximately 923-924 pills for BPaL/BPaLM compared to 5,460-7,296 pills for conventional regimens (Mulder, et al., 2022).

Findings from various studies provide recommendations that can be implemented to optimize the use of the BPaL/BPaLM regimen and minimize hematological side effects (Khan, et al., 2024). The use of a lower dose of linezolid (600 mg per day compared to 1200 mg) has been proven to maintain efficacy while reducing the risk of hematological side effects. The administration of vitamin B6 (pyridoxine) supplements at 50-100 mg per day is also recommended to reduce hematological and neurological side effects of linezolid (Court, et al., 2021). Patients at high risk of hematological side effects, such as those with renal function impairment or weighing <54 kg, may require stricter hematological monitoring and proactive dose adjustments (Khan, et al., 2024). Therapeutic drug monitoring for linezolid can also assist in dose individualization to minimize side effects while maintaining efficacy (Khan, et al., 2024).

The implementation of the BPaL/BPaLM regimen in Indonesia has shown very promising results with a treatment success rate of 97.6% (Burhan, et al., 2025). Although the cost of medication for the BPaL/BPaLM regimen is higher compared to medications in the conventional regimen, cost analysis shows that the BPaL/BPaLM regimen can save overall costs by up to 57% compared to the conventional regimen, primarily due to the shorter treatment duration, reduced need for injections, and fewer visits to healthcare facilities (Pradipta, et al., 2023).

CONCLUSIONS

The success rates of BPaL/BPaLM regimens in treating MDR-TB are 90–97%, which is much higher than the 51–60% success rates of traditional regimens. There are still concerns about hematological side effects, especially anemia (31.9%) and thrombocytopenia (47.8%) that are linked to linezolid use. However, these side effects are usually mild to moderate and can be managed with careful monitoring and dose changes. The hematological side effects of BPaL/BPaLM regimens are different from those of standard regimens. They have a higher risk of anemia and thrombocytopenia but a lower risk of leukopenia and neutropenia. BPaL/BPaLM regimens are better options for patients because they have a shorter treatment time (24–26 weeks instead of 78–96 weeks) and a much lower pill burden (923–924 pills instead of 5,460–7,296).

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CONFLICT OF INTERESTS

The authors say that there are no conflicts of interest in writing and publishing this article..

ETHICAL CONSIDERATION

This narrative review was conducted using published, peer-reviewed literature and publicly accessible data sources. As the article does not involve any original research with human participants, animal subjects, or any

intervention, there was no requirement for ethical approval or informed consent. All reviewed studies referenced within this manuscript were previously conducted in accordance with the ethical standards of the institutional and/or national research committees, and in line with the Helsinki Declaration and its subsequent amendments.

The authors ensured the integrity of this review by upholding principles of academic honesty, transparency, and avoidance of plagiarism. Proper attribution has been given to all sources, and due diligence was observed to maintain the confidentiality and intellectual property of original study authors. No confidential patient data or unpublished primary data were included in this narrative review.

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