

Perspective

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BPaL/BpaLM regimen: A bright future for drug-resistant tuberculosis

Oki Nugraha Putra[1]✉, Telly Purnamasari[2]

[1]*Department of Clinical and Community Pharmacy, Faculty of Pharmacy, Hang Tuah University, Surabaya, Indonesia*

[2]*Pre-Clinical and Clinical Studies, National Research and Innovation Agency, Bogor, West Java, Indonesia*

Indonesia is one of the countries with the highest burden of tuberculosis and drug-resistant tuberculosis (DR-TB) across the world. Based on data from the World Health Organization (WHO) Global TB Report 2023, it is estimated that there are 10000 cases of DR-TB in Indonesia. Bedaquiline, a novel antitubercular drug, has been implemented to treat DR-TB globally. It was administered either a shorter (9 months) or individualized treatment regimen (18 months). However, long treatment duration with various adverse events affects patient compliance. Therefore, a short treatment with less medication is urgently required. In 2022, the WHO announced an alternative regimen-bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) to treat DR-TB patients for six months without resistance to fluoroquinolones[1]. This recommendation is based on previous clinical trials of TB, Zenix TB, and TB-PRACTECAL. The introduction of BPaL and BPaLM provided a bright future for treating DR-TB patients.

In the TB-PRACTECAL, the treatment success rate was 89% using a BPaLM regimen for multi drug-resistant tuberculosis (MDR-TB) patients[2]. Similarly, in the Nix-TB trial, the success rate was 89% and 92% for extended drug-resistant tuberculosis (XDR-TB) and MDR-TB[3]. It demonstrates that regimens containing pretomanid and BPaL or BPaLM were associated with favorable outcomes (cured). BPaLM consists of bedaquiline (400 mg once daily for the initial two weeks, followed by 200 mg thrice weekly for 22 weeks), pretomanid (200 mg once daily for 24 weeks), linezolid (600 mg daily for 16 weeks, followed by 300 mg for 8 weeks), and moxifloxacin 400 mg daily for 24 weeks[1].

In the TB-PRACTECAL, six patients (22.2%) experienced peripheral neuropathy and two patients (7.1%) experienced optic neuritis. The other adverse effects were nausea and dizziness but they improved over time. It indicates that either BPaL or BPaLM regimen demonstrates tolerable adverse effects[2]. It was supported by a recent meta-analysis from three clinical trials investigating BPaL-containing regimens, which reported that grade 3-4 adverse events were observed in 35% of patients receiving a daily dose of 1200 mg linezolid, compared with 22% of patients receiving 600 mg linezolid[4]. The WHO recommends a dose of linezolid of 600 mg daily, either for the BPaLM or BPaL regimen. The duration of the BPaLM regimens was standardized for 24 weeks (6 months); meanwhile for BPaL regimens, it can be extended for 39 weeks (9 months), if sputum cultures are still positive between the fourth and sixth month[1]. BPaL or BPaLM regimen can be applied for DR-TB patients who meet any of the following criteria: (1) Patients with rifampicin resistant or MDR-TB; (2) Adults or adolescents > 14 years regardless of HIV status; (3) Patients with pulmonary TB and all form of extrapulmonary TB, except for central nervous system, osteoarticular, and milary TB; (4) Patients had not received bedaquiline, pretomanid, linezolid, or delamanid for > 1 month. If patients had received more than one month, these patients may still receive these regimens if drug susceptibility testing results for each medicine has been identified; (5) BPaL or BPaLM regimen can not be used for pregnant and breastfeeding women since the safety of pretomanid is lacking in such conditions; (6) Drug susceptibility for fluoroquinolones was used to assess the eligibility for moxifloxacin. If drug susceptibility testing result demonstrates resistance to fluoroquinolones (pre-XDR-TB), regimens can be continued without moxifloxacin (BPaL); (7) If drug susceptibility testing results demonstrate resistance to bedaquiline, linezolid, or pretomanid,

✉To whom correspondence may be addressed. E-mail: okinugrahaputra@yahoo.com

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patients were declared "defaulter". Patients will be administered individualized treatment regimens; (8) Patients with rifampicin resistant or MDR-TB who were not eligible for these criteria will be administered shorter regimens for nine months; meanwhile pregnant and breastfeeding woman will be administered individualized regimens.

Drug susceptibility testing results for fluoroquinolones are strongly recommended; however, it should not delay treatment initiation. DR-TB treatment should be initiated within a maximum of seven days after diagnosis. If the line probe assay results are not available more than 7 days, treatment should be started immediately. Dose modification of bedaquiline, pretomanid, and moxifloxacin as well as replacing moxifloxacin with levofloxacin is not recommended in the BPaLM regimen. In case of any adverse events of linezolid, linezolid can be discontinued or its dosage can be reduced. Dosage reduction or temporary discontinuation can only be done after the first nine weeks of linezolid at a dose of 600 mg daily have been completed. The treatment pathway for treating DR-TB patients is shown in Figure 1[5].

Study in Asian population reported the effectiveness and safety of BPaL/BPaLM. A study in Thailand by Sangayuh *et al*. reported that the sputum culture conversion at eight weeks for BPaL and BPaLM regimen was 8/10 (80%) and 18/18 (100%), respectively. Time to sputum culture conversion was 4.48 weeks[6], shorter than our previous study in the individualized treatment regimens containing bedaquiline, 1.7 months or 6.8 weeks[7]. The shorter the time to culture negativity, the lower the possibility of spreading TB infection into the community. Since the WHO announced the implementation of BPaL/BPaLM globally, hopefully, it will expand to include all eligible patients.

The Ministry of Health of the Indonesia Republic announced the BPaL and BPaLM regimen can be implemented in public hospitals in several provinces in Indonesia since August 2023. Thus, active monitoring for adverse effects should be carried out immediately. Health workers should monitor for any adverse effects and provide appropriate treatment accordingly. Early detection of adverse

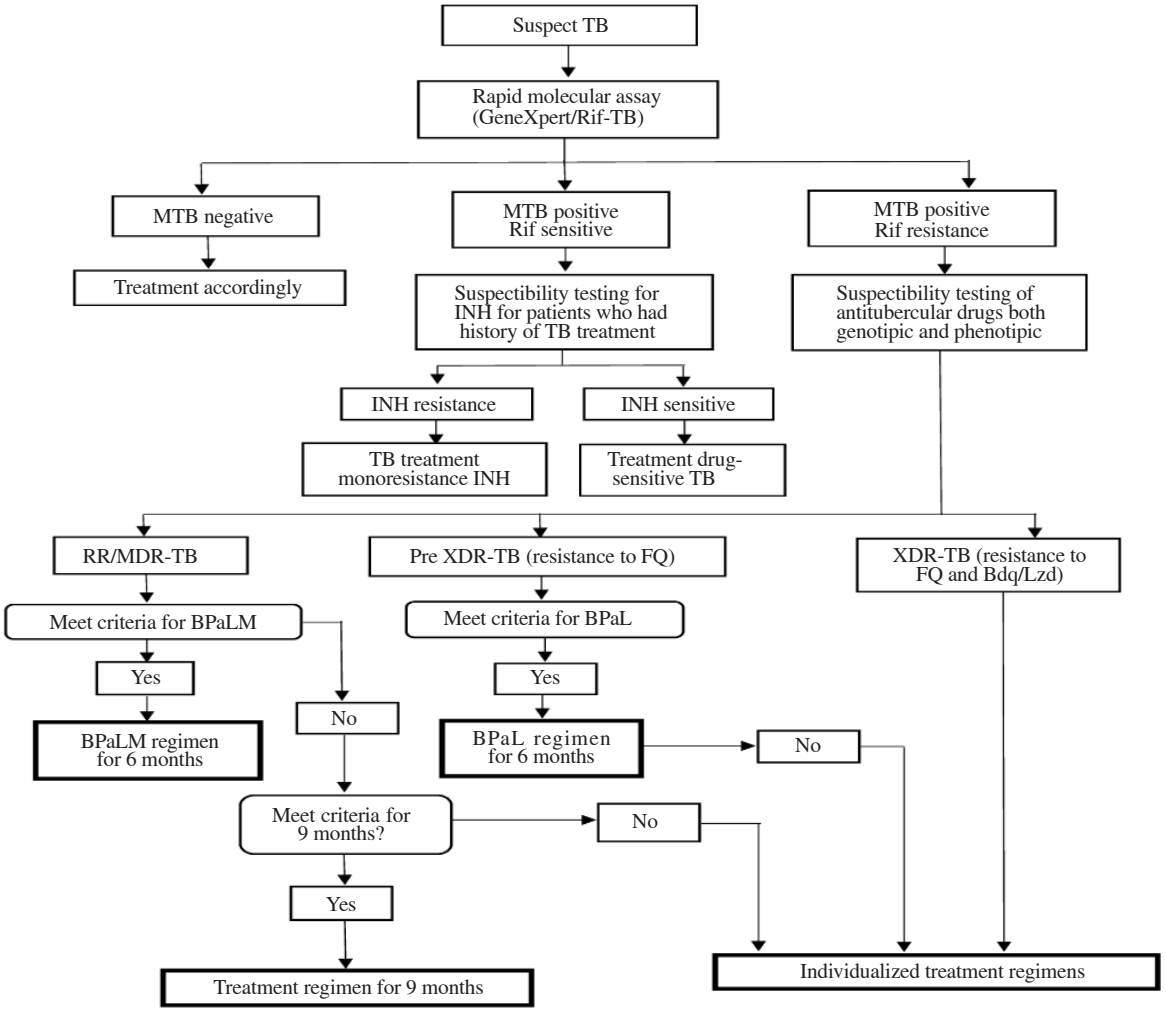

Figure 1. Treatment pathway for treating DR-TB patients. TB: tuberculosis; RR: rifampicin resistant; MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extended drug-resistant tuberculosis; Rif: rifampicin; FQ: fluoroquinolone; Bdq: bedaquiline; Lzd: linezolid; INH: isoniazid; BPaLM: bedaquiline, pretomanid, linezolid, and moxifloxacin; BPaL: bedaquiline, pretomanid, linezolid; MTB: *Mycobacterium tuberculosis*.

effects during treatment is the key to the treatment success of DR-TB. Therefore, monitoring of adverse effects should be carried out daily[5].

The global health community needs to prepare to introduce BPaL and BPaLM regimens as soon as possible and expand them to include all eligible patients. This will involve alignment of related stakeholders, updating national guidelines, enhancing drug susceptibility testing, and patient engagement to strengthen the safety and efficacy of the regimen, as well as drug procurement and distribution. Shorter regimens for DR-TB will improve compliance because they reduce the duration of treatment and side effects, which ultimately increases the treatment's success.

Conflict of interest statement

Authors declare there is no conflict of interest.

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Authors' contributions

OP and TP: Searched the literature. OP: Drafted the manuscript. TP: Edited the manuscript. All authors have approved the final of the manuscript.

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