Letter to the Editor

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Treatment Outcomes of Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: An Implication for Delamanid

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We greatly appreciated a study by Choi et al.[1] reporting treatment outcomes in pre-extensively drug-resistant tuberculosis (pre-XDR-TB) patients (fluoroquinolone resistance) with propensity score matching. The data of pre-XDR-TB patients were collected retrospectively over 7 years[1]. Drug-resistant tuberculosis (DR-TB) is one of the most infectious diseases, with a low rate of treatment success and high mortality rates. It was proposed that the treatment success rate of pre-XDR TB was lower than that of rifampicin-resistant or multidrug-resistant tuberculosis (MDR-TB)[2]. Patients with pre-XDR have limited therapeutic options. The use of second-line injectable drugs (SLIDs), such as kanamycin and capreomycin, was significantly associated with treatment failure; therefore, the World Health Organization (WHO) announced the use of all oral regimens to treat DR-TB patients, either for shorter or longer regimens. Since SLIDs were no longer used to treat DR-TB patients, in 2021, the WHO revised the definition of pre-XDR TB to a case of MDR-TB with additional resistance to any fluoroquinolone (levofloxacin or moxifloxacin)[3]. Those who were previously treated with antitubercular drugs and with lung cavities were risk factors for pre-XDR TB and XDR-TB[4]. As reported by Choi et al.[1], more than 60% of DR-TB patients had a history of TB treatment.

According to the WHO, treatment for DR-TB is a fully oral regimen with a minimum of five effective drugs for longer regimens. Three drugs from class A (levofloxacin, bedaquiline, and linezolid) and two drugs from class B (clofazimine and cycloserine) were strongly recommended for DR-TB patients. However, suppose patients resisted one or more medications from class A as confirmed by drug-susceptibility testing (DST), one or more drugs from class C, such as ethambutol, delamanid, and pyrazinamide, can be used to complete the regimen[3]. Levofloxacin is one of the crucial drugs for managing DR-TB patients. It has shown excellent penetration into chronic lung lesions in DR-TB patients. Moreover, its concentration in the blood correlates with the concentration in the lung cavity[5].

Clinically, lung cavities in DR-TB patients delay sputum conversion, are associated with high recurrence rates, and increase acquired drug resistance. A study by Al-Shaer et al.[6] reported that the median time to culture conversion was significantly shorter in DR-TB patients who received levofloxacin and/or moxifloxacin than those who received ciprofloxacin and/or ofloxacin. Resistance to levofloxacin is one reason for switching from shorter to longer regimens[7]. Therefore, DST should be performed before and during treatment to detect possible resistance to second-line antitubercular drugs. However, even though DST is the most suitable method for determining treatment regimens, it takes a long time. Consequently, there is a high

possibility of delayed treatment while waiting for the DST results and patients often receive an initial regimen without DST results. A recent study in Indonesia by Lestari et al.[8], demonstrated that only 45.1% of DR-TB patients who initiated treatment regimens supported by DST results.

Interestingly, based on a study using propensity-score-matching, bedaquiline, linezolid, levofloxacin, and cycloserine showed favorable outcomes in susceptible strains. However, the use of delamanid was not associated with treatment success. Overall, the treatment success rate was 69.7% among the pre-XDR TB patients[1]. Our previous study reported that in DR-TB patients who received regimens containing bedaquiline and delamanid, favorable outcomes (treatment success and treatment completion) at the end of treatment ranged from 67.5% to 91.4%[9]. Furthermore, a study in South Korea by Kang et al.[10] and Hwang et al.[11], demonstrated that regimens containing bedaquiline and/or delamanid showed highly favorable outcomes without any significant differences in adverse events in MDR, pre-XDR, and XDR-TB patients. Median time to culture conversion was not different between bedaquiline and delamanid groups[11]. It indicated that regimens containing bedaquiline and delamanid promote favorable outcomes, even in highly DR-TB with tolerable adverse effects. If patients resist levofloxacin, it is strongly recommended to use delamanid to increase treatment success. Concomitant use of bedaquiline and delamanid was licensed for individual longer regimens. Interestingly, a recent study by Mok et al.[12] in patients with fluoroquinolone-sensitive MDR-TB, in South Korea, showed that the administration of delamanid, linezolid, levofloxacin, and pyrazinamide for 9 months demonstrated high treatment success compared with a 20 to 24 months regimen. It could represent a new treatment option to improve compliance in patients with fluoroquinolone-sensitive MDR-TB. However, concomitant use of bedaquiline and delamanid is rare in clinical settings due to their potential adverse events, such as corrected QT (QTc) prolongation[9]. Therefore, measurement of QTc interval should be closely supervised during these treatments. Until now, no study in Indonesia has reported treatment success using bedaquiline and delamanid-based regimens among MDR, pre-XDR, and XDR-TB patients. A prospective cohort study is urgently required to clarify the effectiveness and safety of bedaquiline and delamanid in DR-TB patients, especially in pre-XDR and XDR patients.

Authors' Contributions

Conceptualization: all authors. Writing - original draft preparation: all authors. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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