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Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis: Concern to Bedaquiline: Authors' Reply

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We thank Oki Nugraha Putra and colleagues[1] for their comments on our article reporting the impact of public-private mix on the treatment outcomes of patients with multidrug-resistant tuberculosis (MDR-TB)[2]. Multivariate analysis showed that the use of bedaquiline or delamanid for ≥1 month increased the treatment success rate of patients with MDR-TB. Given the poor treatment outcomes and limited treatment options, the clinical introduction of new and repurposed anti-TB drugs (bedaquiline, delamanid, linezolid, and clofazimine) may offer new hope. Bedaquiline is the first anti-TB drug with a novel mechanism of action to be approved in more than 50 years. In a Phase 2b clinical trial, bedaquiline-containing regimens were associated with unexpected increases in mortality, despite culture conversion rates were higher than placebo[3]. However, further studies discovered that bedaquiline reduced the mortality of patients with MDR-TB[4,5]. A meta-analysis of individual patient data revealed that bedaquiline improved treatment success and reduced mortality; bedaquiline was thus reclassified as a core anti-TB drug (group A) for MDR-TB patients according to the revised World Health Organization (WHO) guidelines[5,6]. Consequently, all patients with MDR-TB should receive bedaquiline-containing regimens unless they exhibit resistance or intolerance to bedaquiline.

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As mentioned by Oki Nugraha Putra and colleagues, the major safety concern is QT interval prolongation on electrocardiography (ECG) and the potential risk of cardiac arrhythmia. However, contrary to such concerns, real-world data supported the safety of bedaquiline in terms of QT interval prolongation. The proportion of patients on bedaquiline who exhibited serious QT interval prolongation (e.g., absolute QTcF interval >500 msec) was around 2%–3%, even when they were also taking other anti-TB drugs that caused QT prolongation[7,8]. Furthermore, permanent discontinuation of bedaquiline because of QT interval prolongation is rare, with fetal cardiac arrhythmia being rarer. There were no significant QT prolongation events reported in a recent DELIBERATE study that examined the effects of bedaquiline and delamanid on the QT interval. QT effects of combined use of bedaquiline and delamanid were not more than additive[9].

The treatment outcomes of patients with MDR-TB are closely related to adverse drug reactions (ADRs) to anti-TB drugs. In a recent meta-analysis of individual patient data that focused on the ADRs of anti-TB drugs used to treat MDR-TB, bedaquiline was one of the safest, i.e., had a high rank in terms of its safety profile[10]. Most bedaquiline ADRs are anticipated, reversible, and manageable. Given such patient-friendly characteristics, and its excellent efficacy and safety profile, bedaquiline now serves as a core drug in many of the all-oral-shorter MDR-TB treatment regimens that either are already endorsed by WHO (e.g., the Nix-TB regimen) or are still under investigation[11]. The shorter treatment duration of bedaquiline-containing regimens may reduce loss to follow-up, and ultimately increase the treatment success rate of patients with MDR-TB.

Nevertheless, physicians must be aware of the ADRs of bedaquiline. Regular ECG follow-up, monitoring and adjustment of serum electrolyte levels, are required. Inappropriate/uncontrolled use of bedaquiline inevitably increases drug resistance. Several vital steps should be initiated, including the universal use of accurate and reproducible drug susceptibility tests for bedaquiline, active TB drug-safety monitoring and manage-

ment at the national level, and implementation of antibiotic stewardship.

Authors' Contributions

Conceptualization: Mok J. Writing - original draft preparation: Kang Y, Mok J. Writing - review and editing: Kang Y, Mok J. Approval of final manuscript: all authors.

Conflicts of Interest

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

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