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LETTER TO THE EDITOR

Optimal Dose or Optimal Exposure? Consideration for Linezolid in Tuberculosis Treatment

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Exploring different ways of minimizing linezolid toxicity without compromising efficacy is a major quest in the treatment of drug-resistant tuberculosis (TB). The recently published study by Diacon et al. (1) indicates superior early bactericidal activity (EBA) from an intensive linezolid regimen (1,200 mg daily); however, this dosage has been associated with significant toxicity (2). Given the importance of optimal dose titration, the EBA of linezolid remains to be better characterized in relation to the area under the concentration-time curve (AUC_{0-24})/MIC ratio, which is the optimal pharmacokinetic/pharmacodynamic (PK/PD) marker of efficacy from hollow fiber system model (2, 3). The authors' current analysis of EBA refers only to dose category, which is a crude measure of drug exposure. Clinical validation of the current efficacy and resistance suppression target of an AUC_{0-24}/MIC of >100 (2, 3) is also needed from studies like that by Diacon et al. (1). Since in clinical practice, the MIC data are often unavailable during the early phase of the treatment, dose selection could be guided by AUC_{0-24}/MIC thresholds based on the "critical concentration" of linezolid (1 mg/liter) for *Mycobacterium tuberculosis* (4).

Defining the linezolid AUC_{0-24}/MIC toxicity threshold from clinical studies will enable proactive drug monitoring rather than dose de-escalation or discontinuation of the drug depending on patient tolerance (1). A proactive drug monitoring approach is crucial to help retain an important WHO group A drug like linezolid in patients' anti-TB regimens (5), instead of replacing it with less effective drugs. A high linezolid dose (e.g., 1,200 mg daily), as suggested by Diacon et al. (1), could unnecessarily increase the risk of toxicity without a gain in drug efficacy against *M. tuberculosis*. Therefore, PK/PD measures should be used to guide linezolid optimal dosing.

The rationale for using AUC_{0-24}/MIC for dose selection is that the expected pharmacological effect is determined by the drug exposure relative to the pathogen's drug susceptibility (3). A patient with low drug exposure but a highly susceptible pathogen (e.g., a MIC of <0.25 μg/ml) would attain the AUC_{0-24}/MIC target at a lower dose. Moreover, linezolid demonstrates nonlinear PK, an observation also made by Diacon et al. (1). Therefore, dose-based analysis does not accurately reflect the exposure-response relationship for linezolid.

Therapeutic drug monitoring (TDM), as recommended elsewhere (5, 6), can facilitate optimal drug dosing of linezolid (5, 6). Precision dosing strategy for linezolid should be guided by PK/PD target attainment using point-of-care TDM together with active TB drug safety monitoring and management (7). The use of simple, noninvasive point-of-

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care tests (e.g., testing of saliva samples) could facilitate TDM implementation in resource-limited, high-TB-burden settings, where this is most needed (8, 9).

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