Therapeutic drug monitoring and fluoroquinolones for multidrug-resistant tuberculosis

To the Editor:

We read the paper by Davies Forsman *et al.* [1] and could not agree more with their findings. The authors report that in the studied geographical area and clinical population, the dose of levofloxacin and moxifloxacin should be increased to achieve the optimal exposure target in order to effectively treat multidrug-resistant tuberculosis, and suggested therapeutic drug monitoring (TDM) to avert any adverse event [1, 2]. The target drug exposure and dose in the study were selected based on the evidence collected using pharmacokinetic/pharmacodynamic studies in both pre-clinical models and in the clinic [3]. Indeed, pre-clinical studies using the *in vitro* hollow fibre system model of tuberculosis (HFS-TB) in tandem with Monte Carlo clinical trial simulations, as well as machine-learning-based analyses of clinical data, have identified that moxifloxacin 800 mg per day could achieve the 24 h area under the concentration–time curve ($AUC_{0–24}$) to minimum inhibitory concentration (MIC) ratio of 53, and levofloxacin 1500 mg per day for pulmonary tuberculosis and 25 $mg{\cdot}kg^{-1}$ per day for meningeal tuberculosis to achieve the target $AUC_{0–24}$/MIC of either 146 (HFS-TB) or 160 (clinical data-based) [4–8]. Therefore, the high dose could be effective against isolates with a broader MIC range of these drugs. While these fluoroquinolones are used to treat multidrug-resistant tuberculosis, there are clinical studies exploring the probability of tuberculosis treatment-shortening regimens [9] in patients with drug-susceptible tuberculosis.

The $AUC_{0–24}$ achieved at site of infection is based on the dose and drug penetration ratio to lung lesion or meninges [8, 10], while the MIC is based on the infecting isolate. Therefore, it is necessary to use the optimal clinical dose of each fluoroquinolone to improve the treatment outcome, irrespective of drug susceptibility or multidrug resistance. While the outcomes such as treatment shortening and resistance suppression by achieving the target AUC/MICs were discussed by Davies Forsman *et al.* [1], the study has a major limitation as no dose adjustment was reported in the studied population: a missed opportunity.

The use of high fluoroquinolone doses may make them less tolerable for some patients. Since it is difficult to guess the $AUC_{0–24}$ achieved in each patient due to pharmacokinetic variability, TDM becomes a necessity, as proposed by Davies Forsman *et al.* [1]. We would also like to emphasise the importance of the MIC. With TDM and MIC monitoring, in those select patients, drug dose can also be decreased based on Bayes theory if the $AUC_{0–24}$/MIC is achieved when driven by a low MIC of isolates below the thresholds they identified. This would reduce concentration-driven drug toxicity. We acknowledge that TDM has its own limitations, however, the technology to measure drug levels in saliva [11] and using dried blood spot [12] in resource-limited settings is evolving.

While the findings presented here are important in demonstrating utility of TDM of fluoroquinolones, it is interesting that, despite a lack of target attainment with a regimen that does not include bedaquiline and linezolid, successful treatment outcome was observed in 28/32 patients (87.5%), and some patients with fluoroquinolone-resistant isolates had successful treatment outcome. However, target attainment demonstrates exposures below which patients have a greater likelihood of failing therapy: it does not mean all who do not achieve target attainment will fail therapy. Furthermore, while the authors used MICs for isolates in sputum, we have found that intracavitary isolates often have different MICs from sputum: indeed, the lowest accuracy for sputum MICs predicting cavitary MICs was for moxifloxacin, which was

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Fluoroquinolones at currently prescribed standard dose are suboptimal for treatment of multidrug-resistant tuberculosis. The dose should be increased with therapeutic drug monitoring to determine the drug exposure and to prevent adverse events. https://bit.ly/3nMip2Z

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only 31% accurate [10]. Thus, while we firmly agree that MICs as part of *f*AUC/MIC targets are indispensable as discussed in detail earlier, the authors, like all of us clinicians, are limited by the poor accuracy of sputum isolate-based MICs and inaccessibility of lung isolates in routine care. Another possibility is that perhaps the target *f*AUC/MICs identified in the HFS-TB for the quinolones are not predictive of clinical outcomes. That is less likely because indeed the forecasting accuracy of the moxifloxacin targets have been demonstrated to be within 94% of those identified in combination therapy in the clinic [13]. In addition, the target AUC/MICs and breakpoint MICs for levofloxacin and gatifloxacin (not discussed here) were derived using both HFS-TB and clinical trial data from patients with multidrug-resistant tuberculosis on combination therapy and were identical by either method [8, 14]. Thus, despite the shortcomings of the paper [1] and the clinical difficulty of sampling cavities of TB patients, TDM and MICs are tools at our disposal to allow better personalising of fluoroquinolone doses for better treatment outcome.

Shashikant Srivastava[1,2] and Tawanda Gumbo[3]
[1]Dept of Pulmonary Immunology, University of Texas Health Science Center at Tyler, Tyler, TX, USA. [2]Dept of Immunology, UT Southwestern Medical Center, Dallas, TX, USA. [3]Quantitative Preclinical and Clinical Sciences Dept, Praedicare Inc., Dallas, TX, USA.

Correspondence: Shashikant Srivastava, Dept of Pulmonary Immunology, University of Texas Health Centre, 11937 US Highway 271, Tyler, TX, 75708, USA. E-mail: Shashi.kant@uthct.edu

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