Levofloxacin pharmacokinetics, pharmacodynamics and outcome in multidrug-resistant tuberculosis patients

To the Editor:

Fluoroquinolones (levofloxacin (Lfx) and moxifloxacin) belong to the class A drugs for treating multidrug-resistant (MDR) tuberculosis (TB), which is characterised by resistance to both rifampicin and isoniazid [1]. The drugs have become a mainstay in both longer and shorter MDR-TB regimens, as well as isoniazid resistance [1, 2]. Despite this potential, currently used doses have become a major concern due to subtherapeutic concentrations achieved, leading to acquired drug resistance [3–5]. Therefore, moxifloxacin dose has been increased from the conventional 400 mg in the longer 24-month regimen to 600–800 mg in a new shorter 9-month MDR-TB regimen, based on body weight. Likewise, a randomised phase II dose-finding trial (OptiQ trial; www.clinicaltrials.gov identifier number NCT01918397) that compared four weight-based regimens of Lfx (11, 14, 17 and 20 mg·kg⁻¹·day⁻¹) found that higher doses from 17 to 20 mg·kg⁻¹·day⁻¹ (equivalent actual dose of 1250–1500 mg) showed more than a three-fold increase in peak serum concentration (C_{max}) and area under the concentration–time curve over 24 h (AUC_{0–24}) compared to the currently used 750–1000 mg once-daily dosing. If this dose increment correlates with favourable treatment outcomes, without an increased risk of toxicity, we do not have any reason to continue traditional dosing [6–8]. The efficacy of Lfx is best predicted by an AUC_{0–24}/minimum inhibitory concentration (MIC) ratio of 146, which has been recently identified as an optimal target exposure for maximum *Mycobacterium tuberculosis* kill and is likely to be associated with better clinical response in MDR-TB patients [9].

In this prospective pharmacokinetic study (May 2016 to October 2017; ethical review board approval number 115/2016), we aimed to evaluate the factors associated with time to sputum culture conversion in MDR-TB patients. These factors included age, body mass index (BMI), sex, baseline sputum smear grading, chest radiography with cavitory lesions, diabetes mellitus, alcohol abuse, prior anti-TB therapy, AUC_{0–24}/MIC ratio at month 1 and 2 of treatment, and creatinine, bilirubin, aspartate aminotransferase and alanine aminotransferase levels. MDR-TB patients receiving Lfx (750–1000 mg once-daily dosing) at the German Nepal Tuberculosis Project (GENETUP) (www.clinicaltrials.gov NCT03000517) were included after providing signed informed consent. Steady-state blood samples were collected 0, 1, 2, 4 and 8 h post-medication. Lfx concentrations were quantified using liquid chromatography–tandem mass spectrometry [10] and pharmacokinetic (PK) parameters were computed by noncompartmental kinetics (MwPharm version 3.82; MwPharm BV, Zuidhorn, the Netherlands). Phenotypic drug susceptibility testing was performed in Löwenstein–Jensen media by the indirect proportion method at the National Reference Laboratory, GENETUP. The concentrations tested ranged from 0.25 to 16 mg·L⁻¹. The H37Rv strain was used as a control strain with an MIC of 1 mg·L⁻¹. Genotypic drug susceptibility testing was performed by molecular line probe assay (GenoType MTBDRsl version 2.0; Hain Lifescience, Nehren, Germany).

A total of 23 MDR-TB patients were enrolled, of whom 21 (91.30%) had pulmonary TB. The majority, 19 (82.61%) patients, had received anti-TB therapy previously: eight (34.78%) had relapsed, eight (34.78%) had failed a 6-month treatment regimen with first-line drugs and three (13.04%) had failed an 8-month retreatment regimen with first-line drugs including streptomycin. Before initiation of MDR-TB treatment, 17 (73.91%) out of 23 patients were sputum culture positive and 16 (94.11%) converted within 30 days

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50% of MDR-TB patients with higher MICs do not have enough Lfx exposure with currently prescribed once-daily dosing of 750–1000 mg. Therefore, it is suggested that MDR-TB patients should receive higher 1250–1500 mg Lfx dosages. <http://ow.ly/ZQsN30nuNBx>

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(interquartile range (IQR) 30–105 days). The median time to culture conversion in our study was early compared to another study that reported a median time of 3.1 months [11]. At 90 days of treatment, 16 (84.21%) out of 19 patients showed sputum culture conversion. The percentage of patients converting in our study was similar to that of Koh *et al.* [12]. Treatment outcomes of 23 patients showed eight (34.78%) were cured, four (17.39%) were shifted to pre-extensively drug-resistant TB after the results of drug susceptibility testing, four (17.39%) were transferred out and seven (30.43%) are still on treatment.

The probability of Lfx target attainment (PTA) was calculated for 21 patients (two with an MIC of $16 \text{ mg}\cdot\text{L}^{-1}$ were excluded). The results of phenotypic susceptibility testing ($n=14$) showed median MIC of $1 \text{ mg}\cdot\text{L}^{-1}$ (IQR $0.5\text{--}1 \text{ mg}\cdot\text{L}^{-1}$), whereas genotypic testing ($n=17$) revealed that 13 (76.47%) patients had isolates with a wildtype *gyrA* gene, three (17.64%) had wildtype *gyrA* and *gyrB* genes, and in one (5.88%) patient, *gyrA* mutation MUT-3C was detected (MIC $16 \text{ mg}\cdot\text{L}^{-1}$). PTA analysis showed that 67% ($n=12$) of the patients achieved $\text{AUC}_{0-24}/\text{MIC} > 146$ during the first month and 70% ($n=10$) in the second month. These values are on a par with the actual MDR-TB treatment success rate of 70% in 2016 in Nepal. The low PTA is not surprising as large interindividual variability in Lfx concentrations were observed with a coefficient of variation of 19.13–67.28% (figure 1a and b). When an MIC of $0.5 \text{ mg}\cdot\text{L}^{-1}$ was assumed, PTA increased to 87% ($n=23$) and 89% ($n=19$) for first and second month. However, with MIC $1 \text{ mg}\cdot\text{L}^{-1}$, PTA dropped substantially to 17% ($n=23$) in first month and 21% ($n=19$) in second month (figure 1c).

Multiple linear regression analysis was performed to assess independent predictors of time to sputum culture conversion. $p \leq 0.05$ was considered statistically significant. Although nonsignificant, median BMI of $16.23 \text{ kg}\cdot\text{m}^{-2}$ (IQR $17.96\text{--}18.83 \text{ kg}\cdot\text{m}^{-2}$, $p=0.141$), median aspartate aminotransferase level $19 \text{ IU}\cdot\text{L}^{-1}$ (IQR $26\text{--}33.50 \text{ IU}\cdot\text{L}^{-1}$, $p=0.150$), median alanine aminotransferase level $10.5 \text{ IU}\cdot\text{L}^{-1}$ (IQR $19\text{--}37.5 \text{ IU}\cdot\text{L}^{-1}$, $p=0.136$) and $\text{AUC}_{0-24}/\text{MIC}$ ratios at both first ($p=0.137$) and second ($p=0.166$) months of treatment showed a trend to influence time to sputum culture conversion. In our study, baseline sputum smear grading ($>3+$) was the best predictor ($r=0.75$ and $p=0.006$) of a prolonged time to sputum culture conversion as expected.

Our study has limitations. First, in this intensive PK study, the sample size was small. The independent predictors showed a nonsignificant trend to influence the time to sputum culture conversion. Second, baseline clinical isolates of some patients were not archived due to which, some of the MIC values were missing. These patients had rapidly converted, as shown by a negative sputum culture after the first month

FIGURE 1 Levofloxacin (Lfx) plasma concentration *versus* time curves at the a) first ($n=23$) and b) second month ($n=18$) of treatment. c) Probability of target attainment *versus* minimum inhibitory concentration (MIC) in patients with an assumed MIC of $0.5 \text{ mg}\cdot\text{L}^{-1}$ and $1 \text{ mg}\cdot\text{L}^{-1}$ during first ($n=23$) and second month of treatment ($n=19$). d) Area under the concentration-time curve over 24 h (AUC_{0-24})/MIC ratios of Lfx *versus* actual MIC of 0.5 and $1 \text{ mg}\cdot\text{L}^{-1}$ for first and second month of treatment. Dashed horizontal line: $\text{AUC}_{0-24}/\text{MIC}$ 146.

of treatment. A larger confirmatory study will be needed to evaluate the triangular relationship between drug exposure, efficacy and treatment outcomes. Pooling individual patient data from several PK studies, as has been done for the shorter regimen [13], would be likely to improve the statistical power of future studies to detect a difference in response between patients with adequate drug exposure and those without.

Importantly, Lfx plasma exposure remained unchanged during the first and second month of treatment. The stable drug concentrations over the course of treatment implies that patients who have adequate drug levels determined by first therapeutic drug monitoring might not need a second measurement. However, 50% of the patients with higher MICs did not have enough exposure to the drug and only 70% of the patients were reported to achieve the target exposure on currently prescribed Lfx dosages of 11–14 mg·kg⁻¹·day⁻¹ (figure 1d). These patients could benefit from weight band dose increment from 17 up to 20 mg·kg⁻¹. Regarding dosing frequency, Lfx bactericidal activity is concentration dependent and efficacy is predicted by AUC_{0–24}/MIC. C_{max} is the second important PK parameter after AUC_{0–24} for concentration-dependent antibiotics. The attainment of a certain peak threshold is necessary to prevent the amplification of resistant strains. Therefore, to optimise the efficacy, once-daily dosing should be preferred over administering the same dose in divided fashion, since AUC_{0–24} might be similar but C_{max} is lower when total daily dose is divided [9, 14]. However, caution should be applied before using the recommended high doses in the clinic as the use of Lfx has been associated with side-effects involving tendons, muscles, joints, nerves and the central nervous system. Furthermore, it is imperative to identify patients with diminished renal function and concomitant use of corticosteroids as the latter has potential to aggravate the serious side-effects [15]. Last, the evidence on safety data from the OptiQ trial will give the green light for the use of higher Lfx doses in MDR-TB patients if the efficacy benefits outweigh the risk of toxicity [7].

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