Early View

Research letter

Levofloxacin pharmacokinetics and pharmacodynamics and outcome in MDR-TB patients

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Levofloxacin pharmacokinetics and pharmacodynamics and outcome in MDR-TB patients.

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To the Editor:

Fluoroquinolones (levofloxacin and moxifloxacin) belong to the class A drugs for treating multi-drug resistant tuberculosis (MDR-TB), characterized 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 sub-therapeutic concentrations achieved, leading to acquired drug resistance (3-5). Therefore, moxifloxacin dose has been increased from 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 randomized phase II dose-finding trial (OptiQ trial; NCT01918397), that compared four weight based regimen of levofloxacin (Lfx): 11, 14, 17 and 20 mg/kg/day found that higher doses from 17 to 20 mg/kg/day (equivalent actual dose of 1250 and 1500 mg) showed more than three-fold increase in peak serum concentration ($C_{\text{max}}$) and area under the concentration time curve ($\text{AUC}_{0-24}$) compared to currently used 750-1000 mg once daily dosing. If this dose increment correlates with the favorable treatment outcomes, without an increased risk of toxicity, we don’t have any reason to continue traditional dosing (6-8). The efficacy of Lfx is best predicted by $\text{AUC}_{0-24}$ and minimum inhibitory concentration (MIC) ratio of 146, which has been recently identified as an optimal target exposure for maximum $M.\,tuberculosis$ kill, and is likely associated with better clinical response in MDR-TB patients (9).

In this prospective pharmacokinetic study (May 2016 to October 2017; ERB approval no. 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), gender, baseline sputum smear grading, chest-X-ray with cavitory lesions, diabetes mellitus, alcohol
abuse, prior anti-TB therapy, $AUC_{0-24}/MIC$ ratio at month one and two of treatment; and
creatinine, bilirubin, aspartate amino transferase and alanine amino transferase levels.
MDR-TB patients, receiving Lfx (750-1000 mg once daily dosing) at German Nepal Tuberculosis Project (GENETUP), Nepal were included after signed informed consent (clinicaltrials.gov; NCT 03000517). Steady state blood samples were collected at 0 and 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 non-compartmental kinetics (MW/Pharm v3.82). Phenotypic drug susceptibility testing was performed in Löwenstein-Jensen media by indirect proportion method at National Reference Laboratory, GENETUP. The concentrations tested ranged from 0.25-16 mg/L.
H37Rv strain was used as a control strain with an MIC of 1 mg/L. Genotypic drug susceptibility testing was performed by molecular line probe assay (GenoType MTBDRsl v2.0, 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; among which 8 (34.78%) had relapsed, 8 (34.78%) had failed six-month treatment regimen with first-line drugs and 3 (13.04%) had failed eight-month retreatment regimen with first-line drugs including streptomycin. Before initiation of MDR-TB treatment, 17/23 (73.91%) patients were sputum culture positive and 16 (94.11%) converted within 30 days ($IQR$ 30-105). The median time to culture conversion in our study was early, compared to the another study that reported a median time of 3.1 months (11). At 90 days of treatment, 16/19 (84.21%) 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: 8
(34.78%) were cured, 4 (17.39%) were shifted to pre-XDR after the results of DST, 4 (17.39%) were transferred out, and 7 (30.43%) are still on treatment.

The probability of Lfx target attainment (PTA) was calculated for 21 patients (2 with MIC of 16 mg/L were excluded). The results from phenotypic susceptibility testing (n=14) showed median MIC of 1 mg/L (0.5-1 IQR) whereas, genotypic testing (n=17) revealed that 13 (76.47%) patients had isolates with wild type gyrA gene, 3 (17.64%) had wild type gyrA and B genes and in 1 (5.88%) patient gyrA mutation MUT-3C was detected (MIC was 16 mg/L). PTA analysis showed that 67% (n=12) of the patients achieved AUC\textsubscript{0-24}/MIC>146 during the first month and 70% (n=10) in the second month. These values are at par with the actual MDR-TB treatment success rate of 70% in 2016 in Nepal. The low PTA is not surprising as large inter-individual variability in Lfx concentrations were observed with a CV% (min, max) of 19.13% and 67.28% (Figure 1A). When an MIC of 0.5 mg/L was assumed, PTA increased to 87% (n=23) and 89% (n=19) for first- and second-month. However, with MIC of 1 mg/L, PTA dropped substantially to 17% (n=23) in first month and 21% (n=19) in second month (Figure 1B).

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 non-significant, median BMI of 16.23 kg/m\(^2\) (17.96-18.83 IQR; \( p=0.141 \)), median aspartate amino transferase level 19 IU/L (26-33.50 IQR; \( p=0.150 \)), median alanine amino transferase level 10.5 IU/L (19-37.5 IQR; \( p=0.136 \)), and AUC/MIC ratios at both first (\( p=0.137 \)) and second (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 pharmacokinetic study, the sample size was small. The independent predictors showed a non-significant 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 shown by a negative sputum culture after the first month 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 pharmacokinetic studies, as has been done for the shorter regimen (13), would likely improve 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 TDM, 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/day (Figure 1C). These patients could benefit from weight band dose increment from 17 up to 20 mg/kg. Regarding dosing frequency, Lfx bactericidal activity is concentration dependent and efficacy is predicted by $\frac{AUC_{0-24}}{MIC}$. The peak serum level ($C_{\text{max}}$) is 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 optimize the efficacy, once daily dosing should be preferred over administering the same dose in divided fashion since $AUC_{0-24}$ might be similar but $C_{\text{max}}$ 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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**CONFLICT OF INTEREST:** None to declare
REFERENCES


**Figure legend**

Figure 1: (A) Lfx plasma concentration vs time curves at first \((n=23)\) and second month \((n=18)\) of treatment; (B) Probability of target attainment vs MIC in patients at assumed MIC of 0.5 mg/L and 1 mg/L during first \((n=23)\) and second month of treatment \((n=19)\). First month is shown by dashed line (open circles) whereas, continuous line (open squares) represents second month; (C) AUC/MIC ratios of Lfx vs actual MIC of 0.5 mg/L and 1 mg/L for first and second month of treatment. Dotted horizontal line shows \(\text{AUC}_{0-24}/\text{MIC}\) ratio of 146, open circles represent \(\text{AUC}_{0-24}/\text{MIC}\) ratio for month one and open squares for month two of treatment.