Levofloxacin pharmacokinetics and pharmacodynamics and outcome in MDR-TB patients

Ghimire, Samiksha; Maharjan, Bhagwan; Jongedijk, Erwin M; Kosterink, Jos G W; Ghimire, Gokarna R; Touw, Daan J; van der Werf, Tjip S; Shrestha, Bhabana; Alffenaar, Jan-Willem C

Published in:
European Respiratory Journal

DOI:
10.1183/13993003.02107-2018

Publication date:
2019

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 $mg \cdot kg^{-1} \cdot day^{-1}$) found that higher doses from 17 to 20 $mg \cdot kg^{-1} \cdot day^{-1}$ (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 cavitary 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 $mg \cdot L^{-1}$. The H37Rv strain was used as a control strain with an MIC of 1 $mg \cdot L^{-1}$. Genotypic drug susceptibility testing was performed by molecular line probe assay (GenoType MTBDR*sl* 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

@ERSpublications
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

Cite this article as: Ghimire S, Maharjan B, Jongedijk EM, *et al*. Levofloxacin pharmacokinetics, pharmacodynamics and outcome in multidrug-resistant tuberculosis patients. *Eur Respir J* 2019; 53: 1802107 [https://doi.org/10.1183/13993003.02107-2018].

(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 mg·L^{-1} were excluded). The results of phenotypic susceptibility testing (n=14) showed median MIC of 1 mg·L^{-1} (IQR 0.5–1 mg·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 mg·L^{-1}). PTA analysis showed that 67% (n=12) of the patients achieved AUC_{0-24}/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 mg·L^{-1} was assumed, PTA increased to 87% (n=23) and 89% (n=19) for first and second month. However, with MIC 1 mg·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. $p \leqslant 0.05$ was considered statistically significant. Although nonsignificant, median BMI of 16.23 kg·m^{-2} (IQR 17.96–18.83 kg·m^{-2}, p=0.141), median aspartate aminotransferase level 19 IU·L^{-1} (IQR 26–33.50 IU·L^{-1}, p=0.150), median alanine aminotransferase level 10.5 IU·L^{-1} (IQR 19–37.5 IU·L^{-1}, p=0.136) and AUC_{0-24}/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

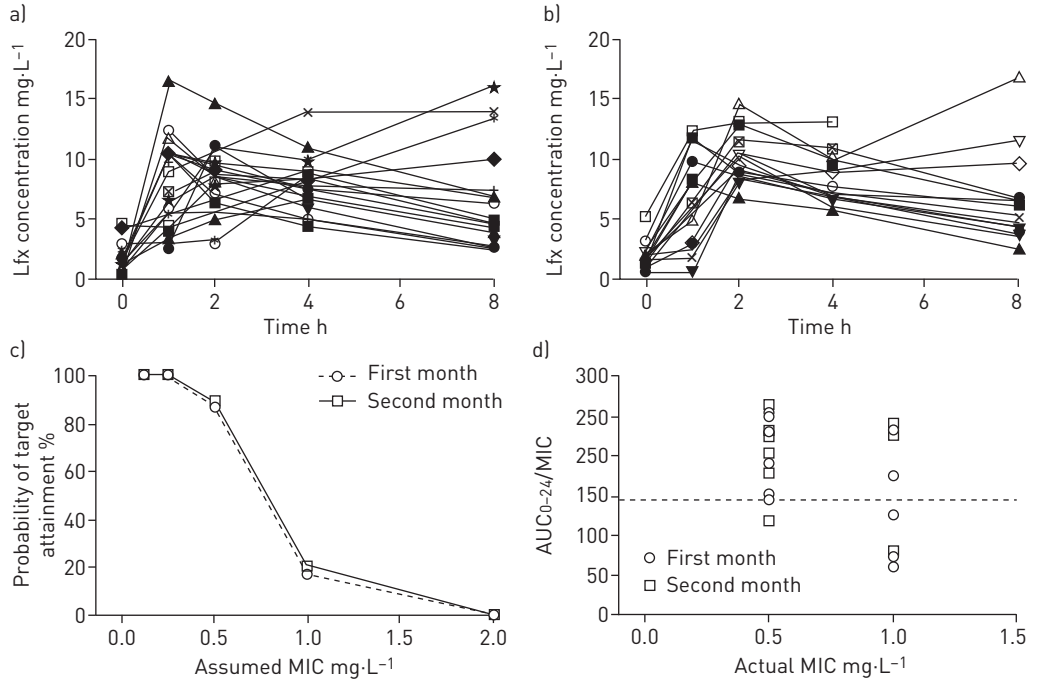

FIGURE 1 Levofloxacin (Lfx) plasma concentration *versus* time curves at the a) first (n=23) and b) second month (n=18) of treatment. c) Probability of target attainment *versus* minimum inhibitory concentration (MIC) in patients with an assumed MIC of 0.5 mg·L^{-1} and 1 mg·L^{-1} during first (n=23) 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 mg·L^{-1} for first and second month of treatment. Dashed horizontal line: AUC_{0-24}/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 $mg \cdot kg^{-1} \cdot day^{-1}$ (figure 1d). These patients could benefit from weight band dose increment from 17 up to 20 $mg \cdot kg^{-1}$. 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].

Samiksha Ghimire[1], Bhagwan Maharjan[2], Erwin M. Jongedijk[1], Jos G.W. Kosterink[1], Gokarna R. Ghimire[3], Daan J. Touw[1], Tjip S. van der Werf[4,5], Bhabana Shrestha[2] and Jan-Willem C. Alffenaar[1]

[1]University of Groningen, University Medical Center Groningen, Dept of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands. [2]German Nepal TB Project, Nepal Anti-Tuberculosis Association, Kathmandu, Nepal. [3]Government of Nepal, Ministry of Health and Population, Dept of Health Services, National Tuberculosis Center, Kathmandu, Nepal. [4]University of Groningen, Groningen Research Institute of Pharmacy, Dept of Pharmacokinetics, Toxicology and Targeting, Groningen, The Netherlands. [5]University of Groningen, University Medical Center Groningen, Infectious Diseases Service and Tuberculosis Unit, Groningen, The Netherlands.

Correspondence: Jan-Willem C. Alffenaar, University of Groningen, University Medical Center Groningen, Clinical Pharmacy and Pharmacology, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. E-mail: j.w.c.alffenaar@umcg.nl

Received: Nov 05 2018 | Accepted after revision: Dec 28 2018

Acknowledgements: We are grateful to the Nepalese patients for their participation and thank the clinical, and the laboratory staff of GENETUP for their kind cooperation and assistance.

Conflict of interest: None declared.

Support statement: This study was funded by the Dept of Clinical Pharmacy and Pharmacology of University Medical Center Groningen, University of Groningen, the Netherlands. In addition, the authors acknowledge Eric Bleumink Fund of University of Groningen for providing academic support to S. Ghimire. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 World Health Organization. Rapid Communication: Key changes to treatment of multi-drug and rifampicin-resistant tuberculosis (MDR/RR-TB). www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1. Date last accessed: September, 2018. Date last updated: 2018.
2 Falzon D, Schunemann HJ, Harausz E, *et al.* World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *Eur Respir J* 2017; 49: 1602308.
3 Pranger AD, van Altena R, Aarnoutse RE, *et al.* Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. *Eur Respir J* 2011; 38: 888–894.
4 Cegielski JP, Dalton T, Yagui M, *et al.* Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2014; 59: 1049–1063.
5 Forsman LD, Bruchfeld J, Alffenaar JC. Therapeutic drug monitoring to prevent acquired drug resistance of fluoroquinolones in the treatment of tuberculosis. *Eur Respir J* 2017; 49: 1700173.
6 Peloquin CA, Phillips PP, Mitnick CD, *et al.* Increased doses lead to higher drug exposures of levofloxacin for the treatment of tuberculosis. *Antimicrob Agents Chemother* 2018: AAC.00770-18.
7 Bouton TC, Phillips PPJ, Mitnick CD, *et al.* An optimized background regimen design to evaluate the contribution of levofloxacin to multidrug-resistant tuberculosis treatment regimens: study protocol for a randomized controlled trial. *Trials* 2017; 18: 563.
8 Horsburgh CR. Efficacy and Safety of Levofloxacin in the treatment of MDR-TB (Opti-Q). https://clinicaltrials.gov/ct2/show/NCT01918397. Date last accessed: December, 2018. Date last updated: 2018.

9 Deshpande D, Pasipanodya JG, Mpagama SG, *et al.* Levofloxacin pharmacokinetics/pharmacodynamics, dosing, susceptibility breakpoints, and artificial intelligence in the treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2018; 67: Suppl. 3, S293–S302.
10 Ghimire S, van Hateren K, Vrubleuskaya N, *et al.* Determination of levofloxacin in human serum using liquid chromatography tandem mass spectrometry. *J Appl Bioanal* 2018; 4: 16–25.
11 van't Boveneind-Vrubleuskaya N, Seuruk T, van Hateren K, *et al.* Pharmacokinetics of levofloxacin in multidrug-and extensively drug-resistant tuberculosis patients. *Antimicrob Agents Chemother* 2017; 61: 00343-27.
12 Koh W, Lee SH, Kang YA, *et al.* Comparison of levofloxacin *versus* moxifloxacin for multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2013; 188: 858–864.
13 Ahmad Khan F, Salim MAH, du Cros P, *et al.* Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017; 50: 1700061.
14 Ghimire S, Van't Boveneind-Vrubleuskaya N, Akkerman OW, *et al.* Pharmacokinetic/pharmacodynamic-based optimization of levofloxacin administration in the treatment of MDR-TB. *J Antimicrob Chemother* 2016; 71: 2691–2703.
15 US Food and Drug Administration. FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. 2018 https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm612995.htm. Date last accessed: December, 2018. Date last updated: 2018.