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Chapter

Limited-sampling strategies for therapeutic drug monitoring of moxifloxacin in patients with tuberculosis

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Abstract

Background

Moxifloxacin (MFX) is a potent drug for multidrug resistant tuberculosis (TB) treatment and is also useful if first-line agents are not tolerated. Therapeutic drug monitoring may help to prevent treatment failure. Obtaining a full concentration-time curve of MFX for therapeutic drug monitoring is not feasible in most settings. Developing a limited-sampling strategy based on population pharmacokinetics (PK) may help to overcome this problem.

Methods

Steady-state plasma concentrations after the administration of 400 mg of MFX once daily were determined in 21 patients with TB, using a validated liquid chromatography-tandem mass spectrometry method. A one-compartment population model was generated and crossvalidated. Monte Carlo data simulation (n=1000) was used to calculate limited-sampling strategies. The correlation between predicted MFX AUC_{0-24h} (area under the concentration-time curve 0 to 24 hours) and observed AUC_{0-24h} was investigated by Bland-Altman analysis. Finally, the predictive performance of the final model was tested prospectively using MFX profiles from patients with TB receiving 400, 600, or 800 mg once daily.

Results

Median minimum inhibitory concentration of *Mycobacterium tuberculosis* isolates was 0.25 mg/L (interquartile range: 0.25 – 0.5 mg/L). The geometric mean AUC_{0-24h} was 24.5 mg*h/L (range: 8.5 – 72.2 mg*h/L), which resulted in a geometric mean AUC_{0-24h}/minimum inhibitory concentration ratio of 72 (range: 21 – 321). PK analysis, based on PK profiles of 400 mg of MFX once daily, resulted in a crossvalidated population PK model with the following parameters: apparent clearance (Cl) 18.5 ± 8.6 L/h per 1.85 m², V_d 3.0 ± 0.7 L/kg corrected lean body mass, K_a 1.15 ± 1.16 h⁻¹, and F was fixed at 1. After the Monte Carlo simulation, the best predicting strategy for MFX AUC_{0-24h} for practical use was based on MFX concentrations 4 and 14 hours postdosing (r² = 0.90, prediction bias = -1.5 %, and root mean square error = 15 %).

Conclusions

MFX AUC_{0-24h} in patients with TB can be predicted with acceptable accuracy for clinical management, using limited sampling. AUC_{0-24h} prediction based on 2 samples, 4 and 14 hours postdose, can be used to individualize treatment.

Introduction

Recently, increased breakpoints for susceptibility of the first-line tuberculosis (TB) agents isoniazide (INH), rifampicin (RIF), and pyrazinamide have been suggested (1). These new breakpoints, together with the emerging epidemic of multidrug resistant TB, have fuelled the need for new active drugs against TB even more. Moxifloxacin (MFX), a powerful second-line agent with high *in vitro* and *in vivo* activities against *Mycobacterium tuberculosis* with a minimal inhibitory concentration (MIC) of 0.25-0.5 mg/L may fulfil this need (2-4). The drug is advised in cases of resistance or intolerance to first-line agents (3) but is recommended as a first-line drug because, in a murine animal model, it was able to reduce the time to culture conversion with 2 months compared with INH in the standard 6-month TB treatment (4;5), and there is increasing evidence from clinical studies for the treatment-shortening potential of MFX in drug-susceptible TB (6-9). Finally, MFX is promising in cases of resistance against early generation fluoroquinolones (10).

In vivo efficacy of MFX treatment is best predicted by the area under the concentration-time curve relative to the MIC (AUC_{0-24h}/MIC) (11;12). An AUC_{0-24h}/MIC ratio of 100 (based on total, i.e. protein-unbound plus bound MFX) is desirable for killing of the isolate (13). MFX in a daily dose of 400 mg is efficacious against *M. tuberculosis* although target AUC_{0-24h}/MIC values are not reached in a substantial percentage of patients, even though a higher dosage is feasible as the drug is generally very well tolerated (6;7;14;15). However, to suppress drug resistance, higher doses of 600-800 mg once daily are required (16). Furthermore, concomitant treatment of RIF decreases MFX exposure by approximately 30% and is therefore the clinically most relevant drug interaction with MFX in patients with TB (17;18). The large variability in AUC_{0-24h}/MIC , MIC, and concomitant drugs results in a high inter-individual variability in AUC_{0-24h}/MIC values. Therefore, therapeutic drug monitoring (TDM) should be considered to individualize the dose of MFX in patients with TB in case of MIC values >0.25 mg/L and in cases of drug-drug interactions.

For routine TDM, obtaining a full concentration-time curve of MFX is not feasible as it is a burden to the patient, is expensive, and is time consuming. A limited-sampling procedure based on a population pharmacokinetic model may help to overcome these problems. This relatively simplified TDM procedure should predict MFX exposure and optimize therapy. The objective of this study was to develop a model to predict individual AUC_{0-24h} values for MFX in patients with TB using limited-sampling strategies (LSSs).

Patients and methods

Study population

Patients with TB receiving MFX (Avelox; Bayer, Leverkusen, Germany) for at least 5 days (steady-state) (19) as part of their TB treatment at the Tuberculosis Centre Beatrixoord, University Medical Center Groningen, The Netherlands between January 1, 2006, and March 31, 2010, were considered to be eligible for inclusion in this study. Patients were included if a pharmacokinetic curve of MFX in plasma was obtained for routine TDM after at least 5 days of treatment, that is, at steady-state. Data for routine pharmacokinetic curves of patients starting with 400 mg of MFX after March 1, 2010, and patients receiving 600 or 800 mg of MFX based on earlier evaluations using a similar sampling scheme were used to evaluate the predictive performance of this model. In our hospital, routine TDM of MFX is performed in all patients at risk for insufficient treatment, including patients simultaneously treated with RIF or in patients with isolates for which the MIC of MFX is ≥ 0.25 mg/L. Demographic and medical data were collected from the hospital chart including age, sex, weight, height, ethnicity, comorbidity, diagnosis, localization of TB, MIC for MFX, and overall resistance pattern of isolated *M. tuberculosis* strains, medical history, dose, and duration of MFX treatment and dose and duration of (TB) comedication. The drug susceptibility tests of the available *M. tuberculosis* isolates were performed with the Middlebrook 7H10 agar dilution method at the Dutch National Tuberculosis Reference Laboratory (National Institute for Public Health and Environment) (20). This was a post hoc analysis of anonymized data collected earlier with no interventions, and, therefore, no approval by the local ethical committee was required, in accordance with the Medical Research Involving Human Subjects Act (Wet Medisch Wetenschappelijk Onderzoek met mensen).

Pharmacokinetics

MFX plasma concentrations were determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (21). C_{\max} was defined as the highest observed plasma concentration with t_{\max} as corresponding time. The AUC_{0-24h} for plasma was calculated using the log-linear trapezoidal rule, using a one-compartmental pharmacokinetic model (MW\Pharm 3.60, Mediware, The Netherlands).

One-compartment population model and limited-sampling strategies

A one-compartment model with first-order absorption and without lag time based on the body surface area, serum creatinine concentration, and the observed MFX concentrations of the patients was calculated using an iterative 2-stage Bayesian procedure (MW\Pharm 3.60). This iterative process yielded the population mean and SD of each parameter calculated

from the individual patient parameters, starting with literature-based estimates of each population parameter [i.e. $Cl: 7 \text{ (mean)} \pm 5 \text{ (SD)} \text{ L/h}$; $V: 1.5 \pm 0.5 \text{ L/kg}$; $K_a: 6 \pm 4 \text{ h}^{-1}$] (22). The pharmacokinetic parameters were assumed to be log normally distributed. The residual error was assumed to be normally distributed with an SD calculated using the formula $SD = 0.1 + 0.10C$ (C = concentration of MFX), based on the maximum observed analytical error of the validated LC-MS/MS assay (i.e. analytical error range: 2.7%–7.1%) (21) and model misspecification, including biological intersubject variation in pharmacokinetic parameters. Bioavailability was fixed at 1, derived from a previous study on population pharmacokinetics (PK) of MFX (23). MFX population pharmacokinetic models were developed using RIF as a variable. Differences between the pharmacokinetic parameters of patients with and without RIF after combined analysis (i.e. with and without RIF) were calculated using the Mann-Whitney U test. The final population pharmacokinetic model was validated by means of crossvalidation based on population pharmacokinetic models ($n-1$). This 'leave-one out' ($n-1$) model estimates how well the final model might perform to predict individual AUC_{0-24h} for future patients with TB (24). Therefore, a population pharmacokinetic model was developed based on $n-1$ subjects. The AUC_{0-24h} of the subject left out from the model development was subsequently predicted by the model based on $n-1$ (24).

A Monte Carlo simulation of 1000 patients randomly drawn from the population model was used to calculate LSSs. LSSs with different combinations of 1-4 time points ranging from 0 to 24 hours were evaluated with a maximum time span between samples of 6 hours. The performance of an LSS was considered acceptable if the predictive bias defined as mean prediction error was $<5\%$ and the precision defined as root mean square error (RMSE) was $<15\%$. The best LSS was evaluated by a Bland and Altman analysis that showed the correlation between the AUC_{0-24h} values based on LSS models and the observed MFX AUC_{0-24h} values. Finally, prospective validation of the strategy was performed by predicting the AUC_{0-24h} of patients with TB starting with 400 mg of MFX ($n = 4$) and patients receiving 600 mg ($n = 1$) or 800 mg ($n = 5$) of MFX during earlier evaluation.

Results

Twenty-one patients with TB with a median age of 31 years (interquartile range (IQR): 25–44 years) were included in the population pharmacokinetic model. The *M. tuberculosis* isolates had a median MIC of 0.25 mg/L (IQR: 0.25–0.5 mg/L). Patients received a dose of 400 mg of MFX once daily, which equals to a median dose of 7.0 mg/kg (IQR: 6.4–8.1 mg/kg). Patients were treated with MFX for a median duration of 140 days (IQR: 54–311 days).

From all patients, concentration-time curves were obtained (Fig. 1). Steady-state pharmacokinetic parameters are shown in Table 1. The geometric mean AUC_{0-24h} was 24.5 mg*h/L (range: 8.5–72.2 mg*h/L), which resulted in a geometric mean AUC_{0-24h}/MIC ratio of 72 (range: 21–321). A significant linear correlation was observed between the C_{max} and the AUC_{0-24h} ($r = 0.7$; $P < 0.01$, Spearman correlation coefficient), and an even more significant correlation was observed between C_{trough} and the AUC_{0-24h} ($r = 1.0$; $P < 0.01$, Spearman correlation coefficient).

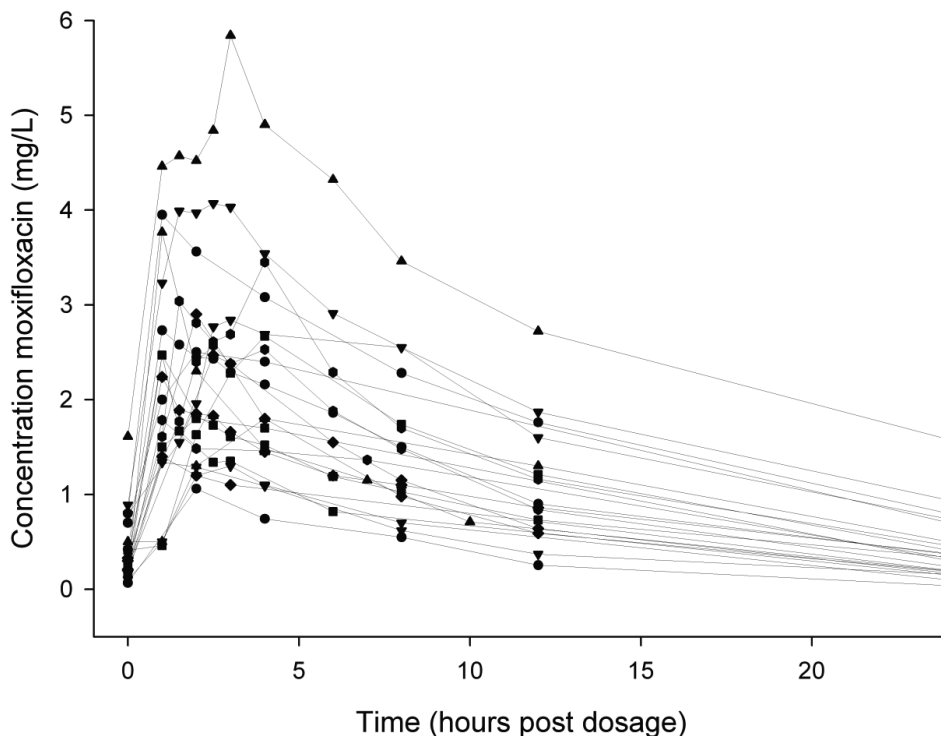


Figure 1. Spaghetti plot of MFX concentration-time curves in plasma.

Population pharmacokinetic parameters of patients receiving RIF ($n = 9$) and patients not receiving RIF ($n = 12$) simultaneously with MFX were not significantly different (Cl; $P = 0.13$, K_a ; $P = 0.13$, V_d ; $P = 0.75$). Population pharmacokinetic parameters based on all concentration-time curves are shown in Table 2. During crossvalidation ($n-1$), the median values were Cl 18.5 L/h per 1.85 m² (IQR: 18.4–18.8 L/h per 1.85 m²), V_d 3.0 L/kg (IQR: 2.9–3.0 L/kg) corrected lean body mass (LBMc), K_a 1.15 h⁻¹ (IQR: 1.10–1.20 h⁻¹), which was not different from that of the population pharmacokinetic model. The predicted AUC_{0-24h} values of the patients who were omitted during crossvalidation were overestimated by 0.6% (IQR: -2.8% to 5.9%).

Table 1. Steady-state pharmacokinetic parameters of MFX ($n = 21$).

Parameter	Median (interquartile range)
AUC _{0-24h} (mg*h/L)	24.8 (20.5–32.6)
C_{max} (mg/L)	2.1 (1.8–2.8)
t_{max} (h)	1 (1–2)
$t_{1/2}$ (h)	8 (6–10)

C_{max} , highest observed plasma concentration; t_{max} , time corresponding with the C_{max} .

Table 2. Population pharmacokinetic model parameters combined analysis.

Parameter	Geometric mean (range)
Cl (L/h per 1.85 m ²)	18.5 (6.1–45.2)
V_d (L/kg LBMc)	3.0 (2.0–3.9)
K_a (h ⁻¹)	1.2 (0.2–3.6)
F	1 (fixed)

F , oral bioavailability; K_a , absorption rate constant; V_d , volume of distribution.

In Table 3, LSS values, suitable for clinical practice, are shown. Based on bias, precision, and correlation, 4 samples during 1, 7, 9, and 17 hours postdose seemed to be the best LSS ($r^2 = 0.95$; bias = -1.9%; RMSE = 11%). However, a blood sample 4 and 14 hours postdose also gives an acceptable bias, precision, and correlation. In Figure 2, the Bland-Altman analysis illustrates the correlation between predicted AUC_{0-24h} based on this LSS (4 and 14 hours postdose) and the observed AUC_{0-24h} value.

Table 3. Limited-sampling strategies.

Time point of sampling (h)				R^2	Bias (%)	RMSE (%)
10				0.85	2.0	19
13				0.83	2.2	20
14				0.82	3.5	21
4	14			0.90	-1.5	15
5	14			0.90	-1.4	15
3	14			0.90	-1.4	15
5	13			0.90	-2.1	15
3	9	14		0.93	-3.3	13
1	7	9	17	0.95	-1.9	11

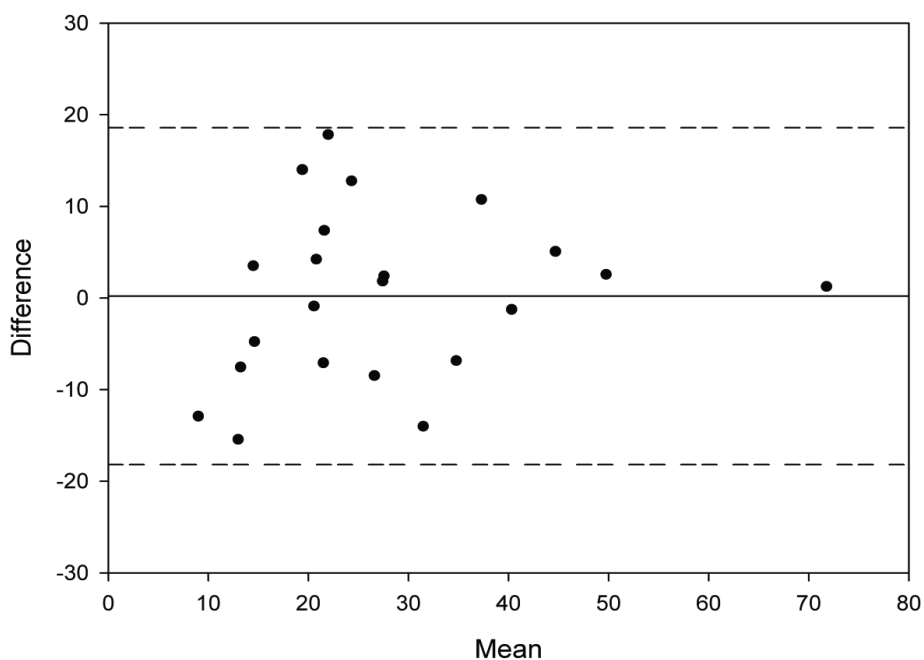


Figure 2. Bland-Altman plot of mean AUC_{0-24h} versus difference between calculated and predicted AUC_{0-24h} of MFX. The solid lines represent the mean difference; the dashed lines represent the limits of agreement (mean difference \pm 2SD difference).

As for the prospective validation of the model, the median AUC_{0-24h} value for the patients who started with 400 mg ($n = 4$) or who were previously treated with 600 mg ($n = 1$) or 800 mg ($n = 5$) of MFX was equal to 22.4 mg*h/L (IQR: 17.4–26.1 mg*h/L), 18.8 mg*h/L, and 36.1 mg*h/L (IQR: 31.1–44.6 mg*h/L), respectively. Based on the population model, the prospective predicted AUC_{0-24h} values of these new patients with TB showed a median difference of -6.3% (IQR: -11.3% to -3.0%) for 400 mg, -19% for 600 mg and -2.6% (IQR: -7.3% to -1.2%) for 800 mg in comparison with the calculated AUC_{0-24h} value.

Discussion

The main finding of our study is that blood samples 4 and 14 hours post-MFX dose provide easy-to-obtain low-burden, high-quality information that helps to target individual treatment at low cost.

We developed a limited-sampling procedure based on population PK to predict MFX AUC_{0-24h} values sufficient to kill isolates with particular MIC values. An iterative 2-stage Bayesian procedure was performed, because of the good performance under a wide variety of conditions, including a small number of subjects and covariance between parameters, in comparison to other population pharmacokinetic analysing methods (22). Based on bias, precision, and correlation, 4 samples collected 1, 7, 9, and 17 hours postdose seemed to be the best LSS ($r^2 = 0.95$; bias = -1.9%; RMSE = 11%). However, for sampling, these 4 divided plasma samples, patients would be required to spend a period of 16 hours at the clinic, which does not make this strategy suitable for outpatient clinics in high burden countries. The difference between choosing 2 samples (4 and 14 hours postdose) and 4 samples (1, 7, 9, and 17 hours postdose) decreased the correlation from 0.95 to 0.90, but this small disadvantage, resulting in only a slight loss in precision, makes it much more attractive for use in clinical practice. A blood sample 4 and 14 hours postdose still leaves an acceptable bias, precision, and correlation, as reflected in the Bland-Altman plot but is obviously less onerous for the patient. This strategy could be combined easily with outpatient consultations during routine follow-up visits. In clinical practice, for example, time of onset of MFX could be at 7 in the evening. The patient has to wait for 4 hours to obtain the first sample. In the morning, the last sample (i.e. at 9 in the morning) will be obtained. This method presents an important tool for high burden countries where, at present, TDM is not available. Finally, this strategy is justified by satisfactory crossvalidation and prospective validation of the population model. During development of an LSS for TDM of MFX, variability in lag time seemed to be a confounder of the pharmacokinetic model. In contrast to suggestions that a peak concentration (C_{max}) is a predictive parameter for the AUC_{0-24h} value

(25), no time points between expected (23) or observed t_{\max} (i.e. 0-2 hours postdose) were selected for LSS. In our opinion, using a peak concentration to assess the AUC_{0-24h} of MFX may lead to the wrong conclusion of inadequate exposure, if a patient shows delayed absorption (17).

Table 4. Separate population pharmacokinetic model parameters combined analysis.

Parameter	Mean (\pm SD)		P
	RIF	Non-RIF	
Cl (L/h per 1.85 m ²)	23.3 (\pm 10.6)	18.0 (\pm 7.6)	0.129
V _d (L/kg LBMc)	3.0 (\pm 0.6)	2.9 (\pm 0.4)	0.754
K _a (h ⁻¹)	1.7 (\pm 1.0)	1.2 (\pm 0.8)	0.129
F	1 (Fixed)	1 (Fixed)	

F, oral bioavailability; K_a, absorption rate constant; RIF, rifampicin; V_d, volume of distribution.

In previous studies, a decline in MFX exposure was observed due to an increase in MFX clearance by concomitant treatment of RIF (17;18). We observed no significant difference in population pharmacokinetic parameters, when comparing the pharmacokinetic parameters of patients receiving RIF (n = 9) and patients not receiving RIF (n = 12) during combined analyses (Table 4). However, there was a trend to increased MFX plasma clearance in the patients co-medicated with RIF, and this difference may be significant in a larger patient population. In our study, pharmacokinetic data from patients who received MFX with and without RIF were combined, and this was justified by satisfactory validation of the resulting PK model with 3 approaches. More detailed evaluation of the leave-one-out (n-1) validation adequately predicted the AUC_{0-24h} values of both patients who received MFX without RIF [overestimation median = 0.0% (IQR: -2.5% to 8.1%)] and patients on MFX with RIF [overestimation median = 0.7% (IQR: -5.2% to 4.6%)]. Likewise, prospective validation adequately predicted the AUC_{0-24h} of patients on MFX with or without RIF. In addition, based on the LSS developed here, including one sample at the clearance part of the concentration-time curve, plasma clearance will be the most important factor for prediction of MFX AUC_{0-24h} . In addition, the optimal sampling time for plasma clearance, and consequently for prediction of AUC_{0-24h} , will be $1.44 \times t_{1/2}$ (26) = $1.44 \times 9.3 \approx 13$ hours post intravenous dosage. Most patients received and will receive MFX orally and, consequently, there will be a delay of approximately 1 hour for the optimal sampling time in these patients, corresponding to the observed mean t_{\max} . The final LSS corresponds to this optimal sampling time (i.e. sampling time 14 hours postdose) but needs to be evaluated with more patients to confirm its validity in a heterogeneous population of patients with TB who receive MFX.

TDM of MFX is only driven by the need to prevent sub-therapeutic plasma concentrations of MFX and not to prevent toxic drug concentrations, as the drug is well tolerated at higher concentrations (6;7;14;15;27). Thus, to achieve a desirable AUC_{0-24h}/MIC ratio of 100 (13), an AUC_{0-24h} value of 50 is needed to treat clinical isolates with an MIC value of 0.5 mg/L. However, our patients harboured isolates that had an MIC value <0.25 mg/L, and, therefore, an AUC_{0-24h} value of at least 25 is desirable to reach the same ratio. In our study population, the geometric mean AUC_{0-24h} was 24.5 (range: 8.5–72.2) and the *M. tuberculosis* isolates had a median MIC of 0.25 mg/L (IQR: 0.25–0.5 mg/L). Variability in AUC_{0-24h} values and distribution of MIC values will result in a wide range of AUC_{0-24h}/MIC ratios. Nonetheless, dose finding is still needed to reach an adequate AUC_{0-24h}/MIC ratio (16) to ensure adequate exposure and to prevent resistance against MFX in each individual patient. In most patients, a dose of 600–800 mg will be needed to suppress resistance against MFX (16). Although safety data on higher doses are limited, data on higher AUC_{0-24h} values are not. The mean MFX AUC values in healthy volunteers receiving a dose of 400 mg ($AUC_{0-\infty}$ 42 mg*h/L) tend to be twice those achieved in patients with TB (28). As QT_c prolongation is observed at $AUC_{0-\infty}$ values of about 87 mg*h/L a 2-fold dose increase in patients with TB is likely to be safe, if baseline QT_c is normal and no additional risk factors for arrhythmias are present (29;30). In addition, TDM guided dose escalation would only take place in a case of an AUC_{0-24h}/MIC ratio <100 in combination with an AUC_{0-24h} value <50 h*mg/L, associated with the breakpoint MIC of MFX (i.e. $R = 0.5$ mg/L) or a low AUC_{0-24h} in combination with an unknown resistance pattern.

Blood sampling twice (4 and 14 hours postdose), including the optimal sampling time for maximum variation of plasma clearance, is a rapid method to predict the MFX AUC_{0-24h} with an acceptable accuracy for individual clinical management and is also less onerous for the patient. MFX treatment could be individualized based on 2 samples and the MIC value for MFX of the isolated strain. Besides routine TDM, this LSS could also be used in a prospective clinical trial to assess AUC_{0-24h} values.

Conclusions

This study showed that MFX AUC_{0-24h} in patients with TB could be predicted with an acceptable accuracy for clinical management, using limited sampling; we developed and crossvalidated a population pharmacokinetic model. The predicted MFX AUC_{0-24h} , based on 2 samples, 4 and 14 hours postdose, can be used to individualize treatment so as to improve adequate exposure and to prevent resistance.

Statement of interest

The authors declare no conflicts of interest.

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