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Evaluation of Moxifloxacin for the treatment of Tuberculosis: 3 years of experience

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ABSTRACT

Background

Moxifloxacin (MFX) is a powerful second line anti-tuberculosis (TB) agent, but the optimal dose has not yet been established and long term safety data are scarce.

Patients and methods

We retrospectively reviewed the medical charts of TB patients treated at our Centre receiving MFX 400 mg once daily as part of their TB treatment between January 1st 2006 and January 1st 2009. Safety data and drug-drug interactions were evaluated. Efficacy was predicted based on the $AUC_{0\text{-}24h}$/MIC ratio.

Results

89 patients were treated with a median dose of 6.9 mg/kg MFX once daily for a median period of 74 days. Discontinuation of therapy occurred in only 3 patients due to gastro-intestinal side effects and hypersensitivity. Pharmacokinetic analysis showed an $AUC_{0\text{-}24h}$/MIC ratio below 100 in 9/16 patients. A large variation in protein binding affected the unbound $AUC_{0\text{-}24h}$ considerably.

Conclusions

These data show that MFX treatment was well tolerated in 89 patients, receiving a dose of 400 mg once daily for a prolonged period. Considering the variability in (un)bound $AUC_{0\text{-}24h}$/MIC ratio, therapeutic drug monitoring is recommended in selected patients (i.e. RIF co-medication; MIC ≥ 0.25 mg/L) to assess optimal therapy.

INTRODUCTION

Moxifloxacin (MFX), a fluoroquinolone with an *in vitro* and *in vivo* bactericidal activity against *Mycobacterium tuberculosis*, is used for the treatment of multidrug resistant tuberculosis (MDR-TB) or in case of intolerance to first line TB agents and is presently under evaluation for its potential to shorten TB treatment (1). In addition, MFX seems useful in case of resistance against early-generation fluoroquinolones (2). Although MFX has widely been prescribed for the treatment of TB, one should keep in mind that the drug is not labelled for this indication (3) and there is paucity of data on the optimal dose and safety/tolerability of treatment durations longer then 2 weeks of the current regimen of 400 mg MFX once daily.

Like for other fluoroquinolones, the area under the plasma concentration time curve (AUC) relative to the minimal inhibitory concentration (MIC) has been suggested as the best parameter to predict *in vivo* efficacy against gram-negative bacteria and *M. tuberculosis* (4-6). Modelling studies suggest that a daily dose of 600-800 mg MFX should be considered for optimal killing of the bacteria and to obtain a probability of 86 – 93% to reach the target associated with suppression of drug resistant mutants (i.e. unbound $AUC_{0\text{-}24h}$/MIC ratio 53) (7), which is higher than the currently used dose of 400 mg once daily. As the efficacy of the treatment is determined by the protein-unbound (free) concentration, the MFX protein binding should also be taken into account (5).

The clinically most relevant drug interaction in TB patients is that of MFX and rifampicin (RIF), resulting in a predicted decrease of MFX exposure of 31% (8;9). Mineral supplements like iron and zinc, or antacids might decrease the bioavailability of MFX as well (10), but after a daily dose of 400 mg MFX in combination with food or calcium supplements the MFX AUC is not significantly affected (10).

The major concern for prolonged treatment is that adverse effects may result in decreased compliance potentially resulting in drug resistance. The adverse effects of MFX, like vomiting and diarrhoea (10), could influence the tolerability of MFX during prolonged treatment. A potential serious but infrequent adverse effect of MFX is QT prolongation (11).

MFX 400 mg once a day is safe and well tolerated during prolonged treatment in studies with a small number of patients (12;13). Despite increasing experience with MFX in TB patients (14-16) larger studies are needed to confirm efficacy and long term safety of an adequate dosage. Safety data to support switching to the suggested higher dose is scarce (11;17;18).

The objective of this study was to evaluate pharmacokinetic and pharmacodynamic parameters, drug-drug interactions and safety/tolerability of MFX in TB treatment retrospectively in order to assess if optimal therapy has been given and as a result these findings will contribute to dose finding and enhance knowledge of pharmacokinetics of MFX in future TB patients.

PATIENTS AND METHODS

A retrospective chart review was performed for all patients receiving MFX (Avelox®; Bayer, Leverkusen, Germany) for at least five days (steady state) as part of their TB treatment (19) at the Tuberculosis Centre Beatrixoord, University Medical Center Groningen, The Netherlands between January 1st 2006 and January 1st 2009. Demographic and medical data were collected from the medical chart including age, sex, weight, height, ethnicity, co-morbidity, diagnosis, localization of TB, MIC, resistance pattern, medical history, dose and duration of MFX treatment, dose and duration of (TB) co-medication and MFX-induced adverse effects. According to the retrospective nature of this study, approval by our local ethical committee was not required.

Pharmacokinetics and pharmacodynamics

When available, MFX concentration in plasma and plasma ultra filtrate (20 min at RT, 1,640x*g* in a fixed angle rotor; Hettich EBA 21) was determined by a validated LC/MS/MS method (20). Samples were eligible for evaluation when obtained at steady state, which was at least five days after treatment (19). Different pharmacokinetic parameters, including the area under the concentration-time curve up to 24 hrs post dosage ($AUC_{0\text{-}24h}$) for plasma were determined with a standard one-compartmental pharmacokinetic method using the KINFIT module of MW\Pharm 3.60 (Mediware, The Netherlands). The $AUC_{0\text{-}24h}$ was calculated according the log-linear trapezoidal rule. As the MFX protein binding may be concentration dependent (range 0.077-0.6) (5), we have chosen to determine the unbound concentration in plasma ultra filtrate for a low (<1.0 mg/L) and a high MFX total plasma (protein bound + unbound) concentration (>1.0 mg/L) for each individual concentration-time-curve. The mean protein-unbound concentration was used to assess the unbound concentration-time curve.

The drug susceptibility test of the available *M. tuberculosis* isolates was performed with the Middlebrook 7H10 agar dilution method (21) at the Dutch National Tuberculosis Reference Laboratory (National Institute for Public Health and the Environment, RIVM).

Both protein-bound and unbound $AUC_{0\text{-}24h}$/MIC ratio could be calculated and the amount of patients having an $AUC_{0\text{-}24h}$/MIC ratio > 100 was determined. Because efficacy of treatment is determined by the protein-unbound (free) concentration, the total (i.e. bound and unbound) $AUC_{0\text{-}24h}$/MIC ratio > 100 (5;22) is translated in an unbound $AUC_{0\text{-}24h}$/MIC ratio exceeding at least 60. This ratio stems from the most frequently reported value of protein binding of approximately 40% for MFX (23), which results in an unbound fraction of 0.6.

Drug-drug interactions

Drug-drug interactions may influence MFX efficacy by interfering MFX absorption, metabolism or excretion. We evaluated co-medication for the following drugs: rifampicin, antacids, mucosal protectants, minerals (e.g. zinc, iron) and didanosine (8;10).

Based on the pharmacokinetic curves of both patients with and without concomitant use of MFX and RIF, two separate one compartmental pharmacokinetic population models with first order absorption without lag time were generated using the MFX dose, the body surface area of the TB patients, and the observed MFX plasma concentrations using an iterative two-stage Bayesian procedure (MW\Pharm 3.60) (24). All pharmacokinetic curves are obtained after reaching steady state concentrations of MFX and, in stead of concomitant use of MFX and RIF, after reaching steady state concentrations of RIF.

Safety/tolerability

To evaluate the safety of MFX treatment, all recorded adverse effects were retrieved from the medical chart, including diarrhoea, vomiting and QT prolongation. MFX is contra indicated in patients with transaminase values > five times the upper level of normal (3). Hepatic injury was characterized if the value of at least one of the following enzymes exceeds five times the upper level of normal: aspartate aminotransferase (ASAT; > 200 U/L), alanine transaminase (ALAT; >225 U/L), gamma glutamyl transpeptidase (GGT; >200-275 U/L), compared to baseline (grade 3 Common Toxicity Criteria (CTC)) (25). Renal injury was defined if the serum creatinine level is increased 25% compared to baseline (grade 1 CTC) (25). The upper level of normal was defined at a serum creatinine value of 112.5 µmol/L (females) or 137.5 µmol/L (males). A QT period of more than 500 msec is associated with increased risk of cardiac events (26). Of each patient, after approximately two weeks of treatment and in case of any dose escalation of MFX, a routine 3-lead ECG was obtained by a physician. Any abnormal observation on the ECG was recorded in the medication chart. To estimate the risk of QT prolongation by long term MFX treatment, we identified risk factors, which (apart from administration of MFX) can result in, or aggravate QT prolongation in TB patients treated with MFX. The following risk factors were evaluated in patients: female

gender, hepatic dysfunction, pro arrhythmic conditions (i.e. abnormal cardiac repolarisation on baseline ECG), hypokalemia (<3.5 mmol/L serum), hypomagnesaemia (< 0.7 mmol/L blood) and simultaneous treatment with anti-dysrhythmics class IA en III, antipsychotics, tricyclic antidepressants or the antihistaminic drug terfenadine (3;27;28).

To determine potential causality between adverse effects and MFX treatment, the Naranjo algorithm was used (0 to 9 points, of which 9 represents the highest likelihood) (29). The correlation between total drug exposure (AUC) and adverse effects was explored.

Special attention was paid to discontinuation of MFX. Reasons were categorized into four categories; (1) MFX was started based on expected drug resistance (country of origin, medical history) and discontinued after the drug susceptibility pattern became available and showed an isolate susceptible to first line agents. (2) MFX was started because of intolerance to first line TB agents and discontinued after the adverse effects had been resolved and first line drugs were successfully re-introduced (3) completion of MFX treatment and (4) MFX-induced adverse events.

Statistics

When not normally distributed, non-parametric tests were used, i.e. Mann-Whitney *U* test and Wilcoxon rank sum test for ordinal data and Chi square tests were used for nominal data.

RESULTS

Patient characteristics

A retrospective chart review was performed for eighty nine patients with a median age of 35 (interquartile range (IQR): 27-47) years; 32 (36%) patients were female and 57 (64%) were male. One patient (transgender) was excluded, because of the unknown influence of administered hormones on several important clinical parameters. Pulmonary TB was the most common diagnosis (67 patients - 75.3%). In 32 (36%) patients MFX was started because of expected resistance (MDR-TB) on basis of treatment history. Patients received MFX 400 mg once daily, which equals a median dose of 6.9 (6.0 - 8.1) mg/kg. Patients were treated with MFX for a median period of 74 (IQR 29 - 184) days. During treatment there was a dose escalation to 800 mg once daily in four patients. The dose was in all cases escalated to 800 mg because of an $AUC_{0\text{-}24h}$/MIC ratio < 100 (i.e. $AUC_{0\text{-}24h}$/MIC = 56 – 83) in combination with an $AUC_{0\text{-}24h}$ value < 50 h*mg/L (n = 3) or a low $AUC_{0\text{-}24h}$ (i.e. $AUC_{0\text{-}24h}$ = 24.1 h*mg/L) in combination with an unknown resistance pattern at start of therapy (n=1).

Thereafter, the dose was reduced to 600 mg once daily based on an $AUC_{0\text{-}24h}$/MIC ratio > 100 (n=2) or based on resistance pattern, which was unknown at start of therapy (n=1). Two patients died from AIDS and TB, not related to MFX. An overview of the baseline patient characteristics and anti-TB drugs is shown in Table 1 and Table 2.

Pharmacokinetics and pharmacodynamics

From 16 patients a full pharmacokinetic curve in plasma was available. The mean plasma concentration time curve is shown in figure 1. Of nine of these patients plasma ultra filtrate was available. We observed an inter-individual variable plasma protein binding ranging from 11.0 to 41.7%. The median protein binding in plasma was 25.1 (18.1-34) % at a median concentration of 2.6 (IQR 2.3 – 2.8) mg/L (high) and 29.7 (24-35.6) % at a median concentration of 0.3 (IQR 0.24 -0.33) mg/L (low), which was not significantly different (P = 0.500). Steady state pharmacokinetic parameters of MFX are shown in Table 3. On MFX 400 mg once daily, geometric mean $AUC_{0\text{-}24h}$ in plasma was highly variable. A significant linear correlation was observed between the C_{max} or C_4 and the $AUC_{0\text{-}24h}$ (r = 0.8 and 0.9; P < 0.001, Spearman correlation coefficient). The median MIC of MFX was 0.25 (IQR 0.125 - 0.5) mg/L.

The geometric mean $AUC_{0\text{-}24h}$/MIC ratio (n=16) for MFX in plasma was equal to 82 (range 21 - 320). In plasma eight of sixteen patients had an $AUC_{0\text{-}24h}$/MIC ratio above 100 and eight had a ratio below 100 (range 21 - 83). The geometric mean unbound plasma $AUC_{0\text{-}24h}$ and unbound $AUC_{0\text{-}24h}$/MIC were equal to 22 (range 12 – 64) mg*h/L and 59 (range 16 - 257) mg*h/L, respectively. In plasma ultra filtrate five of the nine patients had an unbound $AUC_{0\text{-}24h}$/MIC ratio above 60 and four had a ratio below 60 (range 16 – 49). Three patients had a high MIC of 1 mg/L and therefore a low unbound and total $AUC_{0\text{-}24h}$/MIC ratio.

Safety/tolerability

MFX was well tolerated; it was discontinued in only three (3.4 %) patients because of gastro intestinal adverse effects (n=2) and hypersensitivity (n=1). An overview of adverse effects is shown in Table 4. Renal function tests did not deteriorate during treatment. We observed a significant decrease (ASAT: P = 0.004; ALAT: P = 0.020) in liver enzymes during MFX treatment. However, in one patient normal GGT values increased to > 5x ULN (Naranjo score = 3). In four patients serum creatinine values increased during treatment, along with an increase in body weight, but remained within normal limits, and this increase in serum creatinine might reflect increased muscle mass with stable renal function. Vomiting was observed in two (2%; Naranjo score = 3) and diarrhoea in eight (9%; Naranjo score = 3 or 4) patients. Thirty five patients had at least one additional risk factor for QT prolongation, 17

patients had two additional risk factors and one patient had four risk factors, but no QT prolongation was observed. In our study population, female gender was the most common potential risk factor for QT prolongation. $AUC_{0\text{-}24h}$ values could not be related to adverse events as adverse events were scarce and $AUC_{0\text{-}24h}$ values were only determined in a subset of patients.

Drug-drug interactions

RIF was frequently co-administered with MFX. In 68.5, 10.1 and 1.1 percent of the patients MFX was combined with rifampicin (RIF) in a dose of 600, 450 and 150 mg, respectively.

Full pharmacokinetic concentration-time curves were available in six patients who received MFX alone and in ten patients who received RIF and MFX. Co-medication with RIF did not significantly reduce the plasma $AUC_{0\text{-}24h}$ value with a geometric mean of 36.8 (range: 12.7 – 50.4) vs. 21.3 (range: 8.5 – 72.2) mg*h/L (P = 0.104). No significant difference between MFX dose in mg/kg was observed between patients with or without RIF concomitant treatment of MFX (P = 0.871). Population pharmacokinetic analysis (Table 5) showed that the apparent clearance of MFX was (not significantly) induced in patients with concomitant use of MFX and RIF (P = 0.083), but this induction was due to inter patient variability in both groups. MFX was not simultaneously administered with antacids, mucosal protectants, minerals or didanosine.

DISCUSSION

We observed a large variation in protein binding. This is an important finding as only unbound drug contributes to antimicrobial effect. Malnutrition and deterioration in clinical condition upon admission is the most plausible explanation for these large variations. However, because of the retrospective nature of this study and the relative small sample size (n=9) with a known unbound MFX concentration, we cannot confirm this hypothesis. Therefore, it seems logical to determine the unbound MFX concentration in each individual where facilities are available. As the fraction of unbound MFX appeared not concentration dependent, contrary to earlier reports (5), a single blood sample can be used to assess plasma protein binding at a specific time in treatment as plasma protein levels may vary during treatment.

The $AUC_{0\text{-}24h}$/MIC ratio is the parameter to predict efficacy of MFX best and a ratio exceeding 100 is desirable (5;6;22). In eight of the sixteen patients $AUC_{0\text{-}24h}$/MIC ratio was below 100. By increasing the dose to 600 mg once daily, the $AUC_{0\text{-}24h}$ would expectedly increase by about 1.5 (11) resulting in an $AUC_{0\text{-}24h}$/MIC ratio ≥ 100. Measuring unbound plasma

concentration could obviate the need for dosage adjustment if the unbound $AUC_{0\text{-}24h}$/MIC ratio is over 60, while the total $AUC_{0\text{-}24h}$/MIC ratio is < 100.

We observed a large variability in $AUC_{0\text{-}24h}$, which is unique to this study. The observed variability (9 fold) could have clinical implications. Based on a median $AUC_{0\text{-}24h}$ of 24.8 mg*h/L (Table 3), a standard dose of MFX of 400 mg once daily can be used in the treatment of isolates with a maximum MIC of 0.25 mg/L. As both higher MIC values as well as lower $AUC_{0\text{-}24h}$ are measured the standard dose is not sufficient for all patients. Before increasing the standard dose the $AUC_{0\text{-}24h}$/MIC ratio should preferably be assessed by measuring both $AUC_{0\text{-}24h}$ and MIC. Finally, Therapeutic Drug Monitoring (TDM) of MFX was performed in selected patients (i.e. RIF co medication; MIC > 0.25 mg/L), and consequently this selection bias could explain the observed variability in MFX $AUC_{0\text{-}24h}$. Nonetheless, the standard dose of 400 mg MFX once daily results in variability in $AUC_{0\text{-}24h}$ values and consequently is probably not sufficient for all patients.

In 66 (74.2%) patients RIF was combined with MFX. However, in accordance with earlier reports (8;9), concomitant treatment of RIF and MFX did cause a decrease of MFX exposure. However, this decrease was not significant. In addition, we observed a non-significant increase in apparent clearance in patients with concomitant use of MFX and RIF. This is probably due to a lack of statistical power as full pharmacokinetic curves were not obtained in all patients; besides, intra group variability in $AUC_{0\text{-}24h}$ in both treatment groups was large. Therefore our results do not rule out a significant drug-drug interaction between RIF and MFX, especially as there was a trend of interaction.

In earlier published work, MFX (400 mg) was well tolerated in 19 TB patients for a period of 180 days (12), in 38 for a period of 174 days (13), in 74 for a period of 56 days (14) and in 48 for a period of 60 days (15). Less intensive schedules of MFX 3 to 5 times a week were also well tolerated (16). Our study with 89 patients with a median treatment 74 days adds important safety information as our patient population was unselected and therefore represented real life conditions. MFX was well tolerated in our study population; the Naranjo score showed a low probability for the observed adverse effects and MFX was discontinued in only three patients. While first-line anti-TB drugs induced elevated liver enzymes we did not observe any serious adverse events during MFX treatment – in fact, a decrease of liver enzymes was observed. This phenomenon could be due to switching of first line anti-TB drugs, which induced elevated liver enzymes, to MFX. A potential serious but infrequent adverse effect of MFX is the potency to aggravate QT prolongation (11). Despite several additional risk factors for QT prolongation, no QT prolongation was observed in our

population. To prevent treatment failure and suppress resistance against MFX a higher dosage of 600-800 mg will theoretically be needed in most TB patients (7). In healthy volunteers QT prolongation was observed after administration of 800 mg MFX (11). However, in these volunteers the observed geometric mean $AUC_{0\text{-}24h}$ value on 800 mg MFX was 87 mg*h/L, which is 1.8 times the expected $AUC_{0\text{-}24h}$ value of 24.8 * 2 = 49.6 mg*h/L (2 * $AUC_{0\text{-}24h}$ 400 mg MFX (Table 3)) on 800 mg MFX in our TB patients. Taking these results in account, a necessary dose escalation will be safe in most TB patients. However, ECG monitoring is recommended in patients having a high $AUC_{0\text{-}24h}$ and patients with additional risk factors for QT prolongation (3;11;18).

Large variability in plasma protein binding, $AUC_{0\text{-}24h}$, MIC and drug-drug interactions have a large impact on the $AUC_{0\text{-}24h}$/MIC ratio, and this problem has been incompletely addressed. We assume that C_{max} or C_4 may serve as a surrogate predictor for the $AUC_{0\text{-}24h}$ and consequently TDM should be possible with limited samples. In patients receiving rifampicin or in patients infected with isolates for which the MIC of MFX is $\geq$ 0.25 mg/L we recommend to measure at least a peak MFX level and determine plasma protein binding, as these cases are at risk for $AUC_{0\text{-}24h}$/MIC ratio < 100. Besides, in patients suspected of poor absorption due to diarrhoea or vomiting MFX plasma concentration should be evaluated as well. Patients with MDR-TB may potentially benefit most as the MIC for MFX is usually higher in these patients, but safety of MFX in a dose of 600 to 800 mg should be carefully monitored.

CONCLUSION

MFX treatment was well tolerated in 89 patients, receiving a dose of 400 mg once daily (median dose of 6.7 mg/kg) for a median duration of 74 days. Evaluation of (un)bound $AUC_{0\text{-}24h}$/MIC ratio is needed to develop the optimal dosing schedule (fixed or TDM guided) to treat TB patients and prevent resistance.

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Table 1: Patient characteristics at baseline (total n = 89)

Common parameters		**n (%) or median (IQR)**
Female (%)		32 (36)
Age (yr)		35 (27-47)
Weight (kg)		58.3 (49.6-66.7)
Length (cm)		170 (162-175)
BMI (kg/m^2)		20.1 (17.9-23.0)
Ethnicity (%)		
	-Caucasian	29 (32.6)
	-Asian	17 (19.1)
	-African	41 (46.1)
	-other	2 (2.3)
Duration of hospital stay (days)		62.5 (35-112.3)
Tuberculosis		
Localisation		
Pulmonary (%)		67 (75.3)
Extra pulmonary (%)		29 (32.6)
Other (%)		5 (5.6)
Diagnosis		
Sputum (%)		60 (67.4)
Other (%)‡ *		29 (32.6)
Resistance pattern		
Fully susceptible (%)		54 (60.7)
MDR (%)		20 (22.5)
INH resistant (%)		2 (2.3)
INH and ethambutol resistant (%)		1 (1.1)
Unknown (%)		12 (13.5)
Comorbidity		
Chronic pre-existent liver disease (%)		5 (5.6)
Chronic renal dysfunction (%)		1 (1.1)
Epilepsy		1 (1.1)
Diabetes Mellitus (%)		10 (11.2)
HIV co-infection (%)		10 (11.2)
Alcohol abuse (%)		8 (9.0)

Results are presented as median with interquartile range between brackets or as number of patients (n) with the percentage between brackets (%). BMI = body mass index; MDR = Multi Drug Resistant; HIV = human immunodeficiency virus; INH = isoniazid

‡ Diagnosis based on clinical conditions, chest X ray, histology and/or response to therapy

* In 29 cases, diagnosis is based on clinical conditions, chest X ray, histology and/or response to therapy. In 17/29 patients' resistance pattern was determined in a later stage.

Table 2 Anti-tuberculosis medication (total n=89)

First line oral antituberculosis drugs	n (%)
Isoniazide	69 (77.5)
Rifampicin	68 (76.4)
Pyrazinamide	69 (77.5)
Ethambutol	65 (73.0)
Rifabutin	2 (2.3)
Injectable antituberculosis drugs	
Amikacin	24 (27.0)
Kanamycin	16 (18.0)
Fluoroquinolones	
Ofloxacin	1 (1.1)
Moxifloxacin	89 (100)
Oral bacteriostatic second-line antituberculosis drugs	
Protionamide	17 (19.1)
Cycloserine	4 (4.5)
Antituberculosis drugs with unclear efficacy or unclear role in MDR-TB treatment	
Linezolid	22 (24.7)
Clofazimine	17 (19.1)
Thioacetazon	3 (3.4)
Azithromycin	3 (3.4)
Clarithromycin	2 (2.3)

Results are presented as number of patients (n) with the percentage between brackets (%)

Table 3 Steady state pharmacokinetic parameters of MFX

Parameter	
$AUC_{0\text{-}24}$ (mg*h/L)	24.8 (20.7- 35.2)
C_{max} * (mg/L)	2.5 (2.0-2.9)
T_{max} * (h)	1 (1-2)
$T_{1/2}$ (h)	8 (6-10)
Fraction unbound #	0.76 (0.62-0.79)
$AUC_{0\text{-}24\ unbound}$ (mg*h/L) #	17.3 (15.8-24.2)

= n = 9. Data are presented as median with inter quartile range.

Table 4 Adverse effects of MFX treatment (total n=89)

Hepatic enzymes & function			
	Baseline	*During treatment*	*P*
ASAT (U/L)	35.0 (22.5-42.5)	24.0 (19.0-36.0)	0.004
ALAT (U/L)	22.0 (14.5-45.0)	19.0 (11.0-34.5)	0.020
GGT (U/L)	73.5 (49.85-115.0)	54.5 (24.3-79.5)	0.158
Direct bilirubin (µmol/L)	2.0 (1.0-3.8)	2.5 (1.0-4.0)	1.000
Total bilirubin (µmol/L)	7.0 (5.0-9.0)	7.0 (5.0-9.0)	0.414
Missing data (%)	47 (52.8)	15 (16.9)	
Hepatic dysfunction (%)	5 (5.6)	6 (6.7)	
Renal function			
	Baseline	*During treatment*	*P*
Creatinine (µmol/L)	62.0 (53.5-70.8)	61.0 (49.0-74.5)	0.230
Urea (mmol/L)	4.1(3.0-5.4)	4.3 (3.4-5.4)	0.247
Missing data (%)	47 (52.8)	22 (24.7)	
Renal dysfunction (%)	1 (1.1)	1 (1.1)	
Adverse events			
Diarrhoea (%)	8 (9)		
Vomiting (%)	2 (2)		
QT prolongation (%)	0 (0)		
Hepatic injury (%)	1(1)		
Serum creatinine increase (%)	4 (4)		
Other (%)	2 (2)		
Reason to stop MFX treatment			
MFX until resistance pattern was available (%)	32 (36)		
Transient intolerance for standard TB medication; MFX prescribed temporarily (%)	16 (18)		
Completion of treatment (%)	32 (36)		
Adverse events of MFX (%)	3 (3)		
Other (%)	6 (7)		

Results are presented as median with interquartile range between brackets or as number of patients (n) with the percentage between brackets (%). MFX=moxifloxacin; ASAT= aspartate aminotransferase; ALAT= alanine transaminase; GGT= gamma glutamyl transpeptidase.

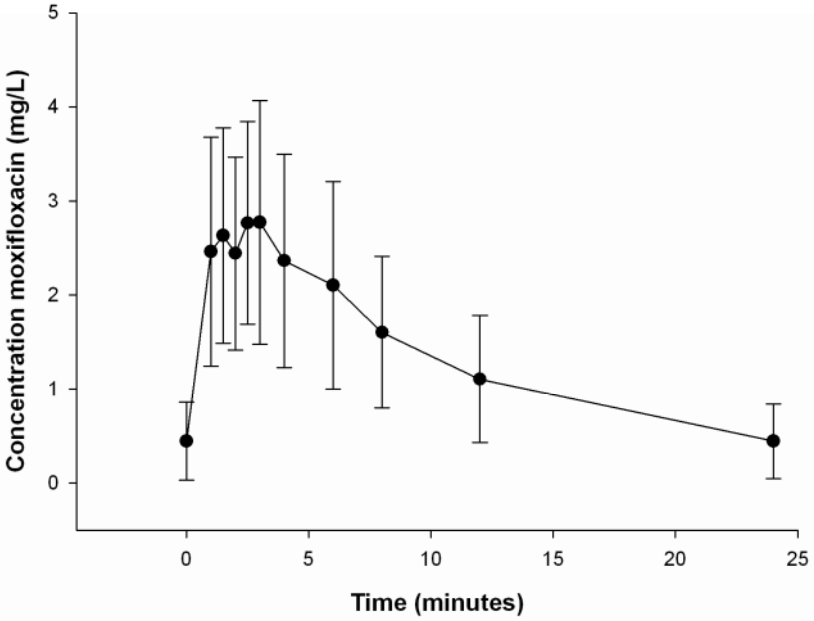
Table 5 Moxifloxacin population pharmacokinetic model parameter values (n=16)

Parameter	mean (± SD)		
	RIF	no RIF	*P* value
CL (liters/h/1.85 m^2)	22.6 ± 8.5	15.5 ± 7.5	0.083
V (liters/kg LBMc)	3.46 ± 0.32	2.90 ± 0.29	0.009
k_a (h^{-1})	3.638 ± 1.696	3.227 ± 1.423	0.515
T_{lag} (h)	0.55 ± 0.15	0.69 ± 0.12	0.009
F	1 (fixed)	1 (fixed)	

RIF, rifampicin; CL, apparent clearance; V_d, volume of distribution; K_a, absorption rate constant; T_{lag}, lag time; F, bioavailability

Figure 1: Mean MFX concentration-time curve in plasma (n=16)

Mean MFX plasma concentrations are represented by solid circles. Standard deviations are presented as error bars.


Concentration moxifloxacin (mg/L)
0
1
2
3
4
5
0
5
10
15
20
25
Time (minutes)