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Chapter

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 the Tuberculosis Centre Beatrixoord, University Medical Centre Groningen (Haren, the Netherlands) 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 area under the concentration-time curve up to 24h post-dosage (AUC_{0-24h})/minimal inhibitory concentration (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 gastrointestinal side effects and hypersensitivity. Pharmacokinetic analysis showed an AUC_{0-24h}/MIC ratio < 100 in eight out of 16 patients. A large variation in protein binding affected the unbound AUC_{0-24h} considerably.

Conclusion

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_{0-24h}/MIC ratio, therapeutic drug monitoring is recommended in selected patients (i.e. RIF co-medication; $MIC \geq 0.25$ mg/L) to assess optimal therapy.

Background

Moxifloxacin (MFX), a fluoroquinolone with an *in vitro* and *in vivo* bactericidal activity against *Mycobacterium tuberculosis*, is used for the treatment of multidrug-resistant (MDR) tuberculosis (TB) or in the 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 the 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 than 2 weeks of the current regimen of 400 mg MFX once daily.

As 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% of reaching the target associated with suppression of drug resistant mutants (i.e. unbound area under the concentration-time curve up to 24h post dosage (AUC_{0-24h})/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 such as 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, such as 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. As a result, these findings will contribute to dose finding and enhance the 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 (Haren, 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, comorbidity, 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 ultrafiltrate (20 min at room temperature, 1,640xg in a fixed angle rotor, Hettich EBA 21; Andreas Hettich GmbH and Co.KG, Beverly, MA, USA) was determined by a validated liquid chromatography-tandem mass spectrometry analysing method (20). Samples were eligible for evaluation when obtained at steady state, which was at least 5 days after treatment (19). Different pharmacokinetic parameters, including AUC_{0-24h} for plasma were determined with a standard one-compartmental pharmacokinetic method using the KINFIT module of MW\Pharm 3.60 (Mediware, Zuidhorn, the Netherlands). The AUC_{0-24h} was calculated according to the log-linear trapezoidal rule. As the MFX protein binding may be concentration dependent (range 0.077-0.6) (5), we chose to determine the unbound concentration in plasma ultrafiltrate 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), Bilthoven, the Netherlands).

Both protein-bound and -unbound AUC_{0-24h}/MIC ratio could be calculated and the number of patients having an AUC_{0-24h}/MIC ratio > 100 was determined. Because efficacy of treatment is determined by the protein-unbound (free) concentration, a total (i.e. bound and unbound) AUC_{0-24h}/MIC ratio > 100 (5;22) is translated into an unbound AUC_{0-24h}/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: RIF, antacids, mucosal protectants, minerals (e.g. zinc and 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, the serum creatinine concentration 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, instead 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 contraindicated in patients with transaminase values more than 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 during MFX treatment along with no hepatic dysfunction (i.e. five times upper level of normal) observed at baseline (grade 3 common toxicity criteria (CTC)): aspartate aminotransferase (ASAT; >200 U/L), alanine transaminase (ALAT; >225 U/L), gamma-glutamyl transpeptidase (GGT; $>200-275$ U/L) (25). Renal injury was defined as serum creatinine level increased 25% compared with baseline (grade 1 CTC) (25). The upper level of normal was defined at a serum creatinine value of 112.5 $\mu\text{mol/L}$ (females) or 137.5 $\mu\text{mol/L}$ (males). A QT period of >500 ms is associated with increased risk of cardiac events (26). After ~ 2 weeks of treatment and in case of any dose escalation of

MFX, a routine three-lead ECG was obtained by a physician from each patient. 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 that (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 sex, hepatic dysfunction, pro-arrhythmic conditions (i.e. abnormal cardiac repolarisation on baseline ECG), hypokalaemia (<3.5 mmol/L serum), hypomagnesaemia (<0.7 mmol/L blood) and simultaneous treatment with anti-dysrhythmics class IA en class 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 (0-9 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, nonparametric tests were used, i.e. Mann-Whitney U test and Wilcoxon rank sum test for ordinal data, and Chi-squared tests were used for nominal data.

Results

Patient characteristics

A retrospective chart review was performed for 89 patients with a median (interquartile range (IQR)) age of 35 (27-47) yrs; 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 (75%) patients). In 32 (36%) patients MFX was started because of expected resistance (MDR-TB) on the basis of treatment history. Patients received MFX 400 mg once daily, which equals a median (IQR) dose of 6.9 (6.0 - 8.1) mg/kg. Patients were treated with MFX for a median (IQR) period of 74 (29 - 186) 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_{0-24h}/MIC ratio <100 (i.e. AUC_{0-24h}/MIC 56 – 83) in combination with an AUC_{0-24h} value <50 $mg \cdot h \cdot L^{-1}$ ($n = 3$) or a low AUC_{0-24h} (i.e. AUC_{0-24h} 24.1 $mg \cdot h \cdot L^{-1}$) in combination with an unknown resistance pattern at the start of therapy ($n=1$). Thereafter, the dose was reduced to 600 mg once daily based on an AUC_{0-24h}/MIC ratio >100 ($n=2$) or based on resistance pattern, which was unknown at the 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 tables 1 and 2.

Table 1. Patient characteristics at baseline.[#]

Female	32 (36)
Age (yrs)	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	
<i>Localisation</i>	
Pulmonary	67 (75.3)
Extrapulmonary	29 (32.6)
Other	5 (5.6)
<i>Diagnosis</i>	
Sputum	60 (67.4)
Other ^{†,*}	29 (32.6)
<i>Resistance pattern</i>	
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)

Data are presented as n (%) or median (interquartile range). [#]: $n = 89$. BMI: body mass index; MDR: multidrug resistant; INH: isoniazid. [†]: diagnosis based on clinical conditions, chest radiograph, histology and/or response to therapy. ^{*}: in 29 cases, diagnosis is based on clinical conditions, chest radiograph, histology and/or response to therapy; in 17 out of 29 patients the resistance pattern was determined at a later stage.

Table 2. Anti-tuberculosis (TB) medication.[#]

First-line oral anti-TB drugs	
Isoniazide	69 (77.5)
Rifampicin	68 (76.4)
Pyrazinamide	69 (77.5)
Ethambutol	65 (73.0)
Rifabutin	2 (2.3)
Injectable anti-TB drugs	
Amikacin	24 (27.0)
Kanamycin	16 (18.0)
Fluoroquinolones	
Ofloxacin	1 (1.1)
Moxifloxacin	89 (100)
Oral bacteriostatic second-line anti-TB drugs	
Protionamide	17 (19.1)
Cycloserine	4 (4.5)
Anti-TB 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)

Data are presented as n (%). [#]: n = 89. MDR: multidrug resistant.

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 ultrafiltrate was available. We observed an interindividual variable plasma protein binding ranging from 11.0 to 41.7%. The median (IQR) protein binding in plasma was 25.1 (18.1-34)% at a median concentration of 2.6 (2.3 – 2.8) mg/L (high) and 29.7 (24-35.6)% at a median concentration of 0.3 (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, AUC_{0-24h} in plasma was highly variable. A significant linear correlation was observed between the highest observed plasma concentration (C_{max}) or the plasma concentration 4h post-MFX dosage (C_4) and the AUC_{0-24h} ($r=0.8$ and 0.9 , $p<0.001$; Spearman correlation coefficient). The median (IQR) MIC of MFX was 0.25 (0.125 - 0.5) mg/L.

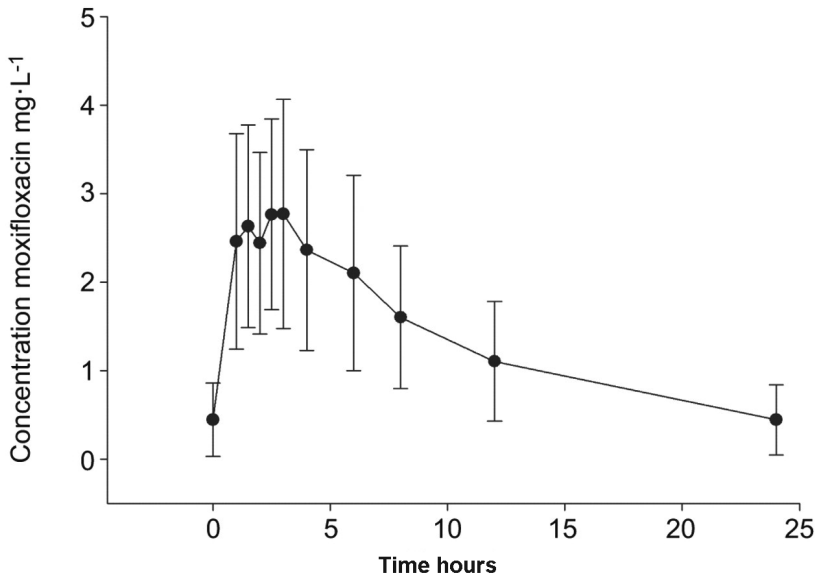


Figure 1. Mean moxifloxacin concentration-time curve in plasma (n=16). Mean moxifloxacin plasma concentrations are represented by solid circles. Standard deviations are presented as error bars.

Table 3. Steady-state pharmacokinetic parameters of moxifloxacin.

AUC _{0-24h} (mg·h·L ⁻¹)	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 _{0-24h unbound} (mg·h·L ⁻¹) [#]	17.3 (15.8-24.2)

Data are presented as median (interquartile range). AUC_{0-24h}: area under the concentration-time curve up to 24h post-dosage; C_{max}: highest observed plasma concentration; T_{max}: time corresponding with C_{max}; T_{1/2}: half-life. [#]: n = 9.

The geometric mean AUC_{0-24h}/MIC ratio (n=16) for MFX in plasma was equal to 82 (range 21 - 320). In plasma, eight out of 16 patients had an AUC_{0-24h}/MIC ratio >100 and eight had a ratio <100 (range 21 - 83). The geometric mean unbound plasma AUC_{0-24h} and unbound AUC_{0-24h}/MIC were equal to 22 (range 12 - 64) mg·h·L⁻¹ and 59 (range 16 - 257), respectively. In plasma ultrafiltrate, five of the nine patients had an unbound AUC_{0-24h}/MIC ratio >60 and four had a ratio <60 (range 16 - 49). Three patients had a high MIC of 1 mg/L and therefore a low unbound and total AUC_{0-24h}/MIC ratio.

Safety/tolerability

MFx was well tolerated; it was discontinued in only three (3.4%) patients because of gastrointestinal 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 more than five-times the upper level of normal (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. 35 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 sex was the most common potential risk factor for QT prolongation. AUC_{0-24h} values could not be related to adverse events as adverse events were scarce and AUC_{0-24h} 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% of the patients, MFx was combined with 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 10 patients who received RIF and MFx. Co-medication with RIF did not significantly reduce the plasma AUC_{0-24h} value with a geometric mean of 36.8 (range 12.7 – 50.4) *versus* 21.3 (range 8.5 – 72.2) $mg \cdot h \cdot L^{-1}$ (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 interpatient variability in both groups. MFx was not simultaneously administered with antacids, mucosal protectants, minerals or didanosine.

Table 4. Adverse effects of moxifloxacin (MFX) treatment.#

Hepatic enzymes and function			
	Baseline	During treatment	p-value
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-value
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 for stopping 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)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. #: n=89. ASAT: aspartate aminotransferase; ALAT: alanine transaminase; GGT: gamma-glutamyl transpeptidase; TB: tuberculosis.

Table 5. Moxifloxacin population pharmacokinetic model parameter values.

Parameter	RIF	No RIF	p-value
CL (L/h/1.85 m ²)	22.6 ± 8.5	15.5 ± 7.5	0.083
V _d (L/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)	

Data are presented as mean ± SD, unless otherwise stated. n=16. RIF: rifampicin; CL: apparent clearance; V_d: volume of distribution; LBMc: lean body mass; K_a: absorption rate constant; T_{lag}: lag time; F: bioavailability.

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 relatively 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 whenever facilities are available. As the fraction of unbound MFX appeared not to be 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_{0-24h}/MIC ratio is the best parameter to predict efficacy of MFX and a ratio exceeding 100 is desirable (5;6;22). In eight of the 16 patients AUC_{0-24h}/MIC ratio was <100 . By increasing the dose to 600 mg once daily, the AUC_{0-24h} would expectedly increase by about 1.5-fold (11), resulting in an AUC_{0-24h}/MIC ratio ≥ 100 . Measuring unbound plasma concentration could obviate the need for dosage adjustment if the unbound AUC_{0-24h}/MIC ratio is >60 , while the total AUC_{0-24h}/MIC ratio is <100 .

We observed a large variability in AUC_{0-24h} , which is unique to this study. The observed variability (nine-fold) could have clinical implications. Based on a median AUC_{0-24h} of 24.8 $mg \cdot h \cdot L^{-1}$ (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_{0-24h} are measured, the standard dose is not sufficient for all patients. Before increasing the standard dose the AUC_{0-24h}/MIC ratio should preferably be assessed by measuring both AUC_{0-24h} 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_{0-24h} . Nonetheless, the standard dose of 400 mg MFX once daily results in variability in AUC_{0-24h} 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 nonsignificant 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_{0-24h} 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 53 for a period of 60 days (15). Less intensive schedules of MFX 3-5 times a week were also well tolerated (16). Our study with 89 patients with a median treatment of 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_{0-24h} value on 800 mg MFX was $87 \text{ mg}\cdot\text{h}\cdot\text{L}^{-1}$, which is 1.8 times the expected AUC_{0-24h} value of $24.8 \times 2 = 49.6 \text{ mg}\cdot\text{h}\cdot\text{L}^{-1}$ ($2 \times AUC_{0-24h}$ 400 mg MFX (table 3)) on 800 mg MFX in our TB patients. Taking these results in account, a necessary dose escalation would be safe in most TB patients. However, ECG monitoring is recommended in patients having a high AUC_{0-24h} and patients with additional risk factors for QT prolongation (3;11;18).

Large variability in plasma protein binding, AUC_{0-24h} , MIC and drug-drug interactions have a large impact on the AUC_{0-24h}/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_{0-24h} and, consequently, TDM should be possible with limited samples. In patients receiving RIF or in patients infected with isolates for which the MIC of MFX is $\geq 0.25 \text{ mg/L}$ we recommend measurement of at least a peak MFX level and determination of plasma protein binding, as these cases are at risk for AUC_{0-24h}/MIC ratio <100 . However, 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 600-800 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_{0-24h}/MIC ratio is needed to develop the optimal dosing schedule (fixed or TDM guided) to treat TB patients and prevent resistance.

Statement of interest

A statement of interest for the present study can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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