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CLINICAL THERAPEUTICS

Clinical Relevance of Rifampicin-Moxifloxacin Interaction in Isoniazid-Resistant/Intolerant Tuberculosis Patients

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ABSTRACT Moxifloxacin is an attractive drug for the treatment of isoniazid-resistant rifampicin-susceptible tuberculosis (TB) or drug-susceptible TB complicated by isoniazid intolerance. However, co-administration with rifampicin decreases moxifloxacin exposure. It remains unclear whether this drug–drug interaction has clinical implications. This retrospective study in a Dutch TB center investigated how rifampicin affected moxifloxacin exposure in patients with isoniazid-resistant or -intolerant TB. Moxifloxacin exposures were measured between 2015 and 2020 in 31 patients with isoniazid-resistant or -intolerant TB receiving rifampicin, and 20 TB patients receiving moxifloxacin without rifampicin. Moxifloxacin exposure, i.e., area under the concentration-time curve ($AUC_{0\text{-}24h}$), and attainment of $AUC_{0\text{-}24h}$/MIC $>$ 100 were investigated for 400 mg moxifloxacin and 600 mg rifampicin, and increased doses of moxifloxacin (600 mg) or rifampicin (900 mg). Moxifloxacin $AUC_{0\text{–}24h}$ and peak concentration with a 400 mg dose were decreased when rifampicin was co-administered compared to moxifloxacin alone (ratio of geometric means 0.61 (90% CI (0.53, 0.70) and 0.81 (90% CI (0.70, 0.94), respectively). Among patients receiving rifampicin, 65% attained an $AUC_{0\text{-}24h}$/MIC $>$ 100 for moxifloxacin compared to 78% of patients receiving moxifloxacin alone; this difference was not significant. Seven out of eight patients receiving an increased dose of 600 mg moxifloxacin reached the target $AUC_{0\text{-}24h}$/MIC $>$ 100. This study showed a clinically significant 39% decrease in moxifloxacin exposure when rifampicin was co-administered. Moxifloxacin dose adjustment may compensate for this drug–drug interaction. Further exploring the impact of higher doses of these drugs in patients with isoniazid resistance or intolerance is paramount.

KEYWORDS *Mycobacterium tuberculosis*, isoniazid, moxifloxacin, pharmacokinetics, rifampicin

Tuberculosis (TB) continues to take a devastating toll on global health with an estimated 10 million new cases and 1.4 million deaths from TB in 2019 (1). The ongoing COVID-19 pandemic is expected to have led to major setbacks in the global elimination of TB (1, 2). Considering these setbacks, mitigating unsuccessful TB treatment remains a priority. While the standard treatment for pan-susceptible disease exhibits favorable outcomes in at least 85% of patients, overall treatment success is complicated by factors such as HIV co-infection, poor adherence, high interindividual variability in drug exposure, and, perhaps most worrisome of all, increasing drug resistance (1).

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Multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are strongly linked to poorer treatment success rates (1, 3), but isoniazid-resistant rifampicin-susceptible tuberculosis (Hr-TB) should not be overlooked. Hr-TB remains the most common TB resistance pattern worldwide, registered in on average 7.4% of new patients and 11.4% of previously treated patients (4). Hr-TB has also been associated with poorer treatment outcomes than drug-susceptible tuberculosis (DS-TB) and an increased risk of progression to MDR-TB (5–8). A recent study linked treatment of Hr-TB with standard first-line TB drugs to increased rates of treatment relapse for 10%, failure for 11%, and acquired rifampicin resistance for 8% of patients (5). Another study of data from 24 European countries between 2002 and 2014 reported an absolute difference in treatment success (cure or treatment completion) between DS-TB and Hr-TB of 5.3% (6).

Based on available evidence, including an individual-patient meta-analysis, the World Health Organization (WHO) recently issued the recommendation that for Hr-TB, the later-generation fluoroquinolone levofloxacin should be administered with rifampicin, ethambutol, and pyrazinamide (8, 9). However, the WHO graded this as a conditional recommendation, with very low certainty in the estimates of effects. The decision to recommend levofloxacin instead of moxifloxacin, another later-generation fluoroquinolone, in the conditional treatment recommendation was based on its supposed better studied safety profile and fewer known drug interactions (9).

Regimens containing rifampicin have repeatedly been shown to alter moxifloxacin pharmacokinetics (10–12). This can be explained by rifampicin-led induction of UDP glucuronosyltransferase (UGT) and sulfotransferase, both phase II metabolizing enzymes of moxifloxacin (10, 12, 13). Additionally, rifampicin induces P-glycoprotein (P-gp), a membrane protein expressed in intestinal mucosa, among other locations, that is responsible for the efflux of several xenobiotics, possibly including moxifloxacin (10, 14). Rifampicin has reduced the Cmax of other orally administered P-gp substrates such as talinolol, digoxin, or fexofenadine by 19–70% (15). The key pharmacokinetic parameter area under the concentration-time curve over the span of 24 h ($AUC_{0\text{-}24h}$) of moxifloxacin can decrease by approximately 30% with rifampicin co-administration (10–12). Lower moxifloxacin exposures are likely to result in worse treatment outcomes as its bacteriological activity is known to be concentration-dependent (16).

Moxifloxacin dosing is considered optimal when the pharmacokinetic/pharmacodynamic parameter $fAUC_{0\text{-}24h}$/MIC, representing the free (protein unbound) $AUC_{0\text{-}24h}$ divided by the MIC, is above 53 (17). Protein binding is often set at approximately 50%, although it can vary considerably per patient (18–20). Since unbound or free concentrations are seldom analyzed in clinical practice, a total (bound and unbound) $AUC_{0\text{-}24}$/MIC exceeding 100 can also be used instead (10, 11). As earlier studies did not include MIC measurements for moxifloxacin and drug exposure across different rifampicin and moxifloxacin doses, with the exception of Pranger et al., who included data on patients receiving 150 mg, 300 mg, or 600 mg, it is unclear what the net result of drug–drug interaction between rifampicin and moxifloxacin is and whether it is clinically relevant (18). Resolving this uncertainty remains vital considering moxifloxacin may still play a role in the treatment of Hr-TB or of patients with intolerance to isoniazid in settings where levofloxacin is too expensive or inaccessible.

In addition, high-dose rifampicin is steadily gaining a more important role in TB treatment regimens, with some patients receiving dosages up to approximately 40 mg/kg of rifampicin (21–23). There is already some evidence on the effect of high-dose rifampicin on drug–drug interactions involving non-TB drugs (24, 25). Yet it is essential to understand how an increase in rifampicin dose will influence the exposure of other TB drugs such as moxifloxacin.

Therefore, this study aimed to analyze the effect of rifampicin co-administration on moxifloxacin exposure in patients diagnosed with Hr-TB and patients diagnosed with DS-TB who demonstrated intolerance to isoniazid across varying rifampicin and moxifloxacin doses.

TABLE 1 Demographic and clinical characteristics of patients[a]

Variable name	Group MFX+RIF ($n = 31$)	Group MFX ($n = 20$)	Statistical test results[b]
Male sex, n (%)	24 (77)	14 (70)	$P = 0.599$
Age, median (IQR)	34 (24–52)	37 (25–43)	$P = 0.656$
Born in a foreign country, n (%)	28 (90)	16 (80)	$P = 0.416$
Body weight in kg[c], median (IQR)	61.6 (52.1–71.2)	63.9 (55.1–76.7)	$P = 0.569$
Body mass index (BMI)[c], median (IQR)	22.0 (18.1–24.3)	21.0 (19.0–23.2)	$P = 0.883$
PG-SGA (malnutrition) score $\geq$ 9 n (%)	12 (75)	4 (44)	$P = 0.200$
Localization of disease, n (%)			$P = 0.407$
Pulmonary TB	21 (67)	10 (50)	
Extrapulmonary TB	6 (19)	7 (35)	
Pulmonary + extrapulmonary TB	4 (13)	3 (15)	
Previously treated for TB, n (%)	4 (13)	3 (15)	$P = 1.00$
Co-infections, n (%)			
HIV	0 (0)	2 (10)	
Hepatitis B	1 (3)	1 (5)	
Hepatitis C	1 (3)	1 (5)	
Comorbidities, n (%)			
Diabetes	8 (26)	3 (15)	$P = 0.489$
Mental health condition/ symptoms[d]	6 (19)	3 (15)	$P = 0.724$
Intermittent hemodialysis	1 (3)	0 (0)	NA
Risk factors, n (%)			
Smoking history	14 (45)	10 (50)	$P = 0.817$
Alcohol abuse	3 (10)	0 (0)	NA
IV drug use	0 (0)	1 (5)	NA

[a]Patients who had blood sampled while on 400 mg/day moxifloxacin (Group MFX+RIF and Group MFX) and 600 mg/day rifampicin (Group MFX+RIF). Missing values: PG-SGA (Malnutrition Score), 15 (48.4%) of Group MFX+RIF and 11 (55.0%) of Group MFX. PG-SGA: Patient-Generated Subjective Global Assessment, a score of 9 or above indicates a critical need for a nutritional intervention.
[b]Results of Mann-Whitney U test for continuous variables and Chi-Square or Fisher's Exact test for categorical variables.
[c]Weight and BMI at time of blood sampling.
[d]Also includes patients without an explicit diagnosis of mental illness but who received medication or psychological support as a result of mental health symptoms.

RESULTS

Thirty-one patients were included in Group MFX+RIF (77% male, median age of 34 and a median BMI 22.0) and 20 patients were included in Group MFX (70% male, median age of 37 and a median BMI of 21.0) (see Table 1). Most patients in both groups were foreign-born, were diagnosed with pulmonary TB, and were treatment naive. The daily dose of moxifloxacin per kg body weight did not differ significantly between the groups (median of 6.47 for Group MFX+RIF versus 6.49 mg/kg for Group MFX, $P = 0.613$).

In Group MFX+RIF, 24/31 patients were intolerant to isoniazid; 15 had previously experienced hepatotoxicity, 7 had peripheral polyneuropathy, 1 had psychiatric complaints, and 1 had a combination of the already mentioned adverse effects. Hr-TB was diagnosed in 6/31 patients, and one patient did not start isoniazid because of failed isoniazid monotherapy for latent tuberculosis infection. In Group MFX, 17 patients had MDR-TB, 1 patient was intolerant to rifampicin, 1 had rifampicin-resistant TB without resistance to isoniazid, and 1 had DS-TB and had temporarily received moxifloxacin due to at first being erroneously diagnosed with rifampicin-resistant TB. One patient in Group MFX+RIF was removed from further analyses because of an extreme moxifloxacin $AUC_{0\text{-}24h}$ value of 80 mg*h/liter. Blood sampling was performed on this patient 5 days after beginning co-treatment with rifampicin and moxifloxacin. Therefore, maximal rifampicin-led enzymatic induction would likely not have been achieved yet, although dosing or lab errors cannot be excluded.

The main pharmacokinetic and pharmacodynamic variables for MFX for both groups are shown in Table 2. For a 400 mg moxifloxacin dose, the geometric mean for the moxifloxacin $AUC_{0\text{-}24h}$ was 16.8 (geometric standard deviation 1.34) in Group MFX+RIF and 27.6 (geometric standard deviation 1.29) in Group MFX. The geometric

TABLE 2 Main pharmacokinetic and pharmacodynamic variables for MFX[a]

Variable name (unit)	Group MFX+RIF (n = 30) Arithmetic Mean (SD)	Group MFX+RIF (n = 30) Geometric Mean (SD[b])	Group MFX (n = 20) Arithmetic Mean (SD)	Group MFX (n = 20) Geometric Mean (SD[b])	GMR (90% CI)
$AUC_{0\text{-}24h}$ (mg*h*L^{-1})	17.5 (5.45)	16.8 (1.34)	28.5 (7.30)	27.6 (1.29)	0.61 (0.53–0.70)
Cmax (mg/L)	2.16 (0.67)	2.06 (1.37)	2.62 (0.69)	2.54 (1.30)	0.81 (0.70–0.94)
T_{max}[c] (h)	2.00 (1.03–2.89)		2.02 (1.32–4.06)		
MIC[d], n%	17 (55)		18 (90)		
MIC[d] (mg/L), n%					
0.125	12 (39)		9 (45)		
0.25	3 (10)		9 (45)		
0.5	2 (6)		0 (0)		
$AUC_{0\text{-}24h}$/MIC[c] (h)	117 (74.1–145)		156 (100–214)		
$AUC_{0\text{-}24h}$/MIC > 100[d], n%	11 (65)		14 (78)		

[a]Based on a dose of 400 mg moxifloxacin (both groups) and 600 mg rifampicin (Group MFX+RIF). MFX: moxifloxacin; RIF: rifampicin; $AUC_{0\text{-}24h}$: 24-h area under the concentration-time curve; Cmax: peak observed concentration; T_{max}: time when Cmax occurs; GMR: geometric mean ratio (Group MFX+RIF/MFX).
[b]Geometric standard deviations.
[c]Expressed in median and interquartile range instead of means and standard deviation.
[d]Expressed in n (%) instead of means and includes all patients, n = 51.

mean for the moxifloxacin $AUC_{0\text{-}24h}$ in Group MFX+RIF was significantly lower than that of Group MFX. Similarly, Cmax was significantly lower in Group MFX+RIF.

In Group MFX+RIF, 11/17 (65%) patients attained the target of $AUC_{0\text{-}24h}$/MIC > 100 for moxifloxacin compared to 14/18 (78%) patients in Group MFX. These proportions were not significantly different (P = 0.471). In patients with an unknown MIC in Group MFX+RIF (14/31), 2/14 patients had a moxifloxacin $AUC_{0\text{-}24h}$ that would be too low for a MIC of 0.125 mg/liter, 11/14 patients had a moxifloxacin $AUC_{0\text{-}24h}$ lower than needed for a MIC of 0.25 mg/liter, and 13/14 had an $AUC_{0\text{-}24h}$ lower than needed for a MIC of 0.5 mg/liter.

The stepwise regression analysis with $AUC_{0\text{-}24h}$ as the outcome variable resulted in a model with the best overall fit (R^2 = 0.629) composed of group (B = 1.55, $P < 0.001$), sex (B = 1.31, P = 0.001) with female coded as 1, and diabetes mellitus (B = 0.79, P = 0.006).

The geometric mean of moxifloxacin $AUC_{0\text{-}24h}$ in six patients receiving 600 mg moxifloxacin and 600 mg rifampicin did not differ significantly from that of six patients receiving 600 mg moxifloxacin and 900 mg rifampicin (Table 3).

After a dose increase from 400 mg to 600 mg moxifloxacin in 10 patients, the $AUC_{0\text{-}24h}$ of moxifloxacin increased significantly resulting in a geometric mean ratio of 1.48 (90% confidence interval (CI) 1.29–1.71), which also indicates a linear dose–exposure relationship (Table 4). When linked to MICs available for 8/10 patients, 7 of these 8 patients (88%) reached an $AUC_{0\text{-}24h}$/MIC > 100 at 600 mg moxifloxacin. For the two patients without MIC data, the $AUC_{0\text{-}24h}$ of moxifloxacin was high enough to reach the target $AUC_{0\text{-}24h}$/MIC > 100 if, in the case of the first patient, the MIC was ≤ 0.125 mg/liter and, in the case of the second patient, the MIC was ≤ 0.25 mg/liter.

DISCUSSION

Patients receiving moxifloxacin with rifampicin showed considerably lower moxifloxacin exposure than patients receiving moxifloxacin alone. This effect does not

TABLE 3 Differences in MFX $AUC_{0\text{-}24h}$ between patients on 600 mg RIF 600 mg MFX versus patients on 900 mg RIF 600 mg MFX[a]

Dose combination	Group size	Arithmetic mean (SD)	Geometric mean (SD[b])	GMR (90% CI)
900 mg RIF 600 mg MFX	6	24.2 (8.11)	23.1 (1.40)	1.04 (0.72–1.48)
600 mg RIF 600 mg MFX	6	22.7 (4.49)	22.3 (1.23)	

[a]$AUC_{0\text{-}24h}$: 24-h area under the concentration-time curve; MFX: moxifloxacin; RIF: rifampicin; GMR: geometric mean ratio.
[b]Geometric standard deviation.

TABLE 4 Differences in MFX $AUC_{0\text{-}24h}$ between patients that first received 600 mg RIF 400 mg MFX followed by 600 mg RIF 600 mg MFX[a]

Dose combination	Arithmetic mean (SD)	Geometric mean (SD[b])	GMR (90% CI)
600 mg RIF 600 mg MFX	24.1 (4.61)	23.6 (1.22)	1.48 (1.29–1.71)
600 mg RIF 400 mg MFX	16.2 (2.68)	16.0 (1.19)	

[a]Ten patients in total. $AUC_{0\text{-}24h}$: 24-h area under the concentration-time curve; MFX: moxifloxacin; RIF: rifampicin; GMR: geometric mean ratio.
[b]Geometric standard deviation.

seem to be dependent on rifampicin dosing as the six patients receiving a higher dose of rifampicin (900 mg) did not have a significantly lower moxifloxacin exposure when compared to the six patients receiving a standard dose of rifampicin (600 mg). In addition, an increase in moxifloxacin dose from 400 to 600 mg resulted in target attainment of $AUC_{0\text{-}24h}$/MIC $>$100 in 7/8 patients.

These results are in agreement with previous studies. In crossover or sequential design studies, an absolute decrease of 27–31% has been reported in moxifloxacin $AUC_{0\text{-}24h}$ among patients with TB or volunteers receiving rifampicin compared to those receiving moxifloxacin alone (10–12). In 19 TB patients, decreases of 31% and 32% were registered for moxifloxacin $AUC_{0\text{-}24h}$ and Cmax, respectively (11). The difference in moxifloxacin $AUC_{0\text{-}24h}$ measured in this study between the two patient groups of 39% was comparable to earlier studies (11, 12). The same can be said about Cmax with a difference of 19% registered in this study that is slightly lower than previously reported by Nijland et al. (11). However, another study with 101 TB patients reported no difference in Cmax (26).

Variability in drug exposure across studies can be clarified by different dosing patterns, study designs, and study populations (patients with TB versus healthy volunteers) (10). In other clinical studies among TB patients with smaller sample sizes, no significant differences in $AUC_{0\text{-}24h}$ and Cmax of moxifloxacin between patient groups receiving both moxifloxacin and rifampicin and patients receiving moxifloxacin alone were detected (18, 26, 27). Close to a third of our patients receiving moxifloxacin and rifampicin for whom MICs for moxifloxacin were available did not reach the target $AUC_{0\text{-}24h}$/MIC $>$ 100. Our finding that a 400 mg moxifloxacin dose is often inadequate to attain the established PK/PD targets is mirrored in other published studies of drug-resistant TB (10, 17, 28).

Diabetes mellitus significantly contributed to a decrease in moxifloxacin $AUC_{0\text{-}24h}$ in the multivariate model, as was also the case in another retrospective study conducted at the same TB center that included most of the patients with diabetes that were included in this study. This effect might be attributed to an increased moxifloxacin clearance in patients with diabetes (29). Interestingly, female sex contributed to an increased moxifloxacin $AUC_{0\text{-}24h}$. However, confounding by other variables cannot be excluded as male patients differed considerably from their female counterparts. Male patients comprised all previously treated cases, most cases with a tobacco smoking history, all cases of alcohol abuse, and received a lower moxifloxacin dose in mg/kg compared to female patients.

Interestingly, patients receiving 600 mg or 900 mg of rifampicin showed no significant difference in moxifloxacin $AUC_{0\text{-}24h}$. Nevertheless, the extent of the effect of a 900 mg dose of rifampicin, usually corresponding to 15 mg/kg, on induction of P-gp or phase II metabolism enzymes and on moxifloxacin exposure could be better ascertained by adopting a 2-period sequential study design. In the majority of studies, only rifampicin doses up to 600 mg, typically equivalent to 10 mg/kg, were assessed (10, 15, 30). Meanwhile, daily doses of rifampicin of up to 35 mg/kg have already been studied or administered in patients with TB (21–23).

An important question deriving from previous studies was whether higher moxifloxacin doses could offset the reduction in drug exposure caused by rifampicin. In our study, a higher dose of 600 mg moxifloxacin per day was paired with an $AUC_{0\text{-}24h}$/MIC that

was satisfactory for seven of eight patients. Although not covered by this study, a dose of 800 mg moxifloxacin, which is already in use in the standardized shorter MDR-TB treatment, has been previously identified as maximizing the chances of resistance suppression, outperforming a 400 mg dose by far as well as performing slightly better than a 600 mg dose (17).

The strength of this study lies in describing the impact of the moxifloxacin–rifampicin interaction on moxifloxacin exposure and $AUC_{0\text{-}24h}$/MIC while using individual MIC values, contrary to other studies that used a preset MIC, usually set at 0.5 mg/liter (11, 31). The addition of levofloxacin in the WHO recommendations for treatment of Hr-TB marked an important step in improving treatment for patients with Hr-TB. Moxifloxacin may be of clinical interest in situations in which levofloxacin is not readily available or when there is a substantial difference in cost. We established that attainment of the $AUC_{0\text{-}24h}$/MIC target did not differ significantly between patients receiving both rifampicin and moxifloxacin and patients receiving moxifloxacin alone and explored the effect of increasing the dose of moxifloxacin or rifampicin on the exposure and $AUC_{0\text{-}24h}$/MIC of moxifloxacin. This could lead to further expanding the exploration of different moxifloxacin and rifampicin dose combinations.

The main limitation of this study is its retrospective design. The risk of selection bias is heightened in the control group because indications for therapeutic drug monitoring (TDM) included malnutrition, comorbidities, or MDR-TB, which may independently contribute to changes in drug exposure. Moreover, individual MIC were unattainable for a sizeable number of patients, especially in Group MFX+RIF, which is important for the interpretation of the resulting $AUC_{0\text{-}24h}/MIC > 100$ values. We were not able to evaluate the contribution of genetic variants in the UGT1A and ABCB1 genes coding for one of the main UGT involved in the formation of the moxifloxacin M2 metabolite and for P-gp, respectively, to the variability in moxifloxacin pharmacokinetics (12, 32) Lastly, the patients included were mostly HIV-negative. An interaction between moxifloxacin and efavirenz has been documented resulting in a 30% decrease in moxifloxacin AUC (33). However, potential interactions between moxifloxacin and antiretroviral drugs or supplements commonly used in the treatment of HIV, and how these may potentiate the moxifloxacin-rifampicin interaction, remain to be explored.

In conclusion, this retrospective study showed a 39% absolute decrease in moxifloxacin exposure when rifampicin was co-administered among patients with TB in whom an alternative drug for isoniazid was required. In a small subgroup of patients on moxifloxacin and rifampicin, an increased dose of 600 mg/day moxifloxacin resulted in promising attainment of the $AUC_{0\text{-}24h}/MIC > 100$ target. In situations where treatment of Hr-TB with levofloxacin is not possible, (high-dose) moxifloxacin may still be a viable alternative. TDM would then be performed to identify patients in need of a higher moxifloxacin dose. If TDM is not readily available, patients who possess risk factors for low moxifloxacin exposures could receive a higher moxifloxacin dose followed by monitoring for potential signs of toxicity with ECGs, for instance. Further pharmacokinetic/pharmacodynamic research comparing the effectiveness and safety of higher moxifloxacin doses when combined with (high-dose) rifampicin with the currently recommended levofloxacin for patients with TB that require an alternative for isoniazid is warranted.

MATERIALS AND METHODS

Study design. This study was a retrospective analysis of routinely collected data from patients with TB admitted to the Tuberculosis Center in the Beatrixoord location of the University Medical Center of Groningen (UMCG), situated in Haren, the Netherlands.

Ethics. Due to the retrospective nature of the study based on routine care collection of data, the need for the protocol to be reviewed and approved was waived by the Institutional Ethics Review Board of the UMCG (METc 2018/095).

Study subjects. Group MFX+RIF were patients with Hr-TB or intolerance to isoniazid who received moxifloxacin in combination with rifampicin as part of their treatment regimen. Group MFX were patients that received moxifloxacin but no rifampicin. Patients were included regardless of age or disease localization, and if they had one serial blood sampling episode with more than four samples

between 1-1-2015 and 16-9-2020 for the estimation of plasma moxifloxacin exposure while receiving 600 mg/day rifampicin (only Group MFX+RIF) and 400 mg/day moxifloxacin as starting doses.

Resistance to isoniazid was confirmed by means of the BACTEC Mycobacterial Growth Indicator Tube (MGIT) test and molecular detection of mutations in the inhA and katG genes confidently associated with isoniazid resistance in the *M. tuberculosis* isolates. Low-level resistance to isoniazid, defined as an absence of growth at the breakpoint concentration of 0.4 mg/liter, was also considered. Intolerance was defined as isoniazid being interrupted due to adverse events likely to be caused by this drug, or isoniazid not being started altogether by the treating physician due to an underlying condition that would make the occurrence of adverse events highly probable.

Study procedures. Patients were included if a pharmacokinetic curve consisting of a predose sample and three to seven samples up to 8 h postdose was obtained as part of standard of care. All pharmacokinetic calculations were based on data collected in steady-state conditions. The analysis of moxifloxacin concentrations was performed using validated liquid chromatography-mass spectrometry methods (34). Clinical and demographic data were obtained from patient dossiers. Maximum concentration (Cmax) was defined as the highest observed concentration, with the time to maximum concentration (T_{max}) as the time to reach Cmax. The pharmacokinetic variables were calculated by means of one-compartmental population pharmacokinetic models in MWPharm ++ (version 1.87; Mediware, Prague, Czech Republic). The model parameters were apparent clearance 19.9 ± 8.8 liters/h and 14.7 ± 5.7 liters/h, apparent volume of distribution 2.82 ± 0.69 L/kg body weight and 2.75 ± 1.01 L/kg body weight, absorption constant 7.4 ± 6.8 h^{-1} and 6.3 ± 4.8 h^{-1} and lag time of 0.75 ± 0.11 h and 0.88 ± 0.24 h for the MFX+RIF model and MFX model respectively (26). Individual MICs of moxifloxacin for the included patients were requested from the National TB Reference Laboratory to calculate moxifloxacin $AUC_{0\text{-}24h}$/MIC.

Study endpoints and statistical analysis. The patient characteristics age, sex, country of birth, body weight and body mass index (BMI) at time of blood sampling, localization of disease, history of TB treatment, co-infections, comorbidities, risk factors for poor treatment outcome, and the PG-SGA score were obtained from the electronic health records. PG-SGA score stands for Patient-Generated Subjective Global Assessment score; this is a nutrition assessment tool where nine points or more indicate a critical need for nutritional interventions (35). Patient characteristics were compared between the groups MFX + RIF and MFX. Medians were compared using the Mann-Whitney U test. Proportions were compared using the Chi-Square or Fisher exact test. Characteristics associated ($P < 0.2$) with the main outcome in univariate analyses were included in stepwise regression analyses ($P < 0.05$ to enter, $P > 0.10$ to remove). The main outcome was moxifloxacin $AUC_{0\text{-}24h}$. Secondary outcomes included the pharmacokinetic variables Cmax and T_{max}.

The variables $AUC_{0\text{-}24h}$ and Cmax, were natural log (ln) transformed before analyses and later back-transformed. Arithmetic means with standard deviations, geometric means with geometric standard deviations, and geometric mean ratios with 90% confidence intervals (CI) were calculated for group comparisons. For T_{max}, medians and interquartile ranges were presented and the Mann-Whitney U test was applied for comparisons.

The moxifloxacin $AUC_{0\text{-}24h}$ of two patient subgroups, both receiving 600 mg moxifloxacin but receiving different rifampicin doses (600 mg or 900 mg), were compared. The moxifloxacin $AUC_{0\text{-}24h}$ in patients receiving first 400 mg moxifloxacin and later receiving 600 mg moxifloxacin was also studied.

A significance level of 0.05 was chosen for all analyses. All statistical analyses were performed using IBM SPSS Statistics version 23.

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