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Moxifloxacin Population Pharmacokinetics and Model-Based Comparison of Efficacy between Moxifloxacin and Ofloxacin in African Patients

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Pharmacokinetic exposure and the MIC of fluoroquinolones are important determinants of their efficacy against *Mycobacterium tuberculosis*. Population modeling was used to describe the steady-state plasma pharmacokinetics of moxifloxacin in 241 tuberculosis (TB) patients in southern Africa. Monte Carlo simulations were applied to obtain the area under the unbound concentration-time curve from 0 to 24 h ($fAUC_{0-24}$) after daily doses of 400 mg or 800 mg moxifloxacin and 800 mg ofloxacin. The MIC distributions of ofloxacin and moxifloxacin were determined for 197 drug-resistant clinical isolates of *Mycobacterium tuberculosis*. For a specific MIC, the probability of target attainment (PTA) was determined for target $fAUC_{0-24}$/MIC ratios of ≥53 and ≥100. The PTAs were combined with the MIC distributions to calculate the cumulative fraction of response (CFR) for multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains. Even with the less stringent target ratio of ≥53, moxifloxacin at 400 mg and ofloxacin at 800 mg achieved CFRs of only 84% and 58% for multidrug-resistant isolates with resistance to an injectable drug, while the 800-mg moxifloxacin dose achieved a CFR of 98%. Using a target ratio of ≥100 for multidrug-resistant strains (without resistance to injectable agents or fluoroquinolones), the CFR was 88% for moxifloxacin and only 43% for ofloxacin, and the higher dose of 800 mg moxifloxacin was needed to achieve a CFR target of >90%. Our results indicate that moxifloxacin is more efficacious than ofloxacin in the treatment of MDR-TB. Further studies should determine the optimal pharmacodynamic target for moxifloxacin in a multidrug regimen and clarify safety issues when it is administered at higher doses.

Fluoroquinolones play an important role in the treatment of multidrug-resistant tuberculosis (MDR-TB) (1), which is defined as resistance to both rifampin and isoniazid (2). Fluoroquinolones differ from each other in their efficacy against *Mycobacterium tuberculosis* as measured by the ratio of the area under the unbound concentration-time curve from 0 to 24 h ($fAUC_{0-24}$/MIC) and also display differences in their clinical pharmacokinetics. The *in vitro* bactericidal activity of moxifloxacin against *M. tuberculosis* is superior to that of ofloxacin (3); its improved potency has also been confirmed in mice (4). The substitution of ethambutol by moxifloxacin, but not ofloxacin, in combination with isoniazid, rifampin, and pyrazinamide in the treatment of susceptible TB resulted in faster culture conversion (5, 6). New fluoroquinolones are usually preferred to the earlier-generation ones (7), but ofloxacin is still widely used to treat MDR-TB because of its affordability and availability.

Moxifloxacin is rapidly absorbed, and the major fraction of the dose reaches the systemic circulation within 2 h (8, 9). It has a long half-life in humans (8, 9), with moderate renal excretion of 6% to 20% of total elimination after intravenous administration (9). Moxifloxacin is a substrate of inducible p-glycoprotein (10), sulfotransferases (11), and glucuronosyltransferases (12). Coadministration of moxifloxacin with rifapentine (enzyme and transporter inducer) gave 17.2% (8) and 8% (13) decreases in moxifloxacin exposure in healthy volunteers (dosed three times a week) and tuberculosis patients (dosed once or twice weekly), respectively. Ofloxacin is rapidly absorbed, with peak concentrations reached within 2 h and with a half-life of 6 h, and those characteristics are comparable between healthy volunteers (14) and infected patients (15). Ofloxacin is primarily renally eliminated (16); its concentrations were reported to increase linearly with dose, but elimination of ofloxacin decreases with declining renal function and increasing age (17).

The critical concentration for drug susceptibility is defined as the lowest concentration of a drug that inhibits ≥95% of wild-type strains lacking mechanisms of acquired or mutational resistance to the specific drug (18). Accordingly, the World Health Organization (WHO) recommends susceptibility testing breakpoint concentrations for moxifloxacin and ofloxacin of 0.25 and 2.0 mg/liter, respectively (19). The efficacy of fluoroquinolones has been related to the $fAUC_{0-24}$/MIC ratio (20). Based on *in vitro*, murine, and clinical studies, a $fAUC_{0-24}$/MIC ratio of at least 100 to 125 has been proposed as a reliable predictor of bactericidal activity against Gram-positive and Gram-negative bacteria (21, 22). The hollow-fi-

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TABLE 1 Characteristics of patients who received moxifloxacin in the RIFAQUIN trial or ofloxacin in a previous study[a]

Parameter	Value(s)		
	Patients on moxifloxacin (13, 24, 25)	Patients on moxifloxacin (24, 25)	Patients on ofloxacin (26)
Total no. of patients	28	213	65
No. (%) of males	19 (68)	134 (63)	52 (80)
No. (%) HIV^+ (%)	3 (11)	43 (20)	35 (54)
Median age, range (yrs)	39.7 (19.8–53.4)	31.6 (22.8–56.6)	34 (19–70)
Median wt, range (kg)	52.0 (41.0–71.0)	56.0 (37.7–74.0)	55 (35–91.8)
Median ht, range (cm)	163 (151–176)	167 (151–184)	167 (127–189)
BMI, range (kg/m^2)	19.6 (13.2–31.1)	20.1 (11.1–32.5)	19.3 (12.4–39.3)
No. (%) of patients on twice-weekly doses	15 (54)	101 (47)	N/A

[a] BMI, body mass index; N/A, not applicable.

TABLE 2 Parameter estimates of the final moxifloxacin pharmacokinetic model[a]

Parameter	Value(s) (RSE[%])	
	Typical	IIV[b]
CL (liters/h)	10.6 (2.68)	18.7 (4.05)
V_c (liters)	114 (1.36)	
k_a (h^{-1})	1.50 (2.15)	69.9 (3.62)
MTT (h)	0.723 (7.02)	73.4 (2.58)
No. of transit compartments	11.6 (2.39)	
Q (liters/h)	2.14 (2.92)	32.9 (3.17)
$V_{p\ (liters)}$	89.8 (3.66)	
F	1 FIX	17.7 (3.28)
Proportional error (%)	7.85 (1.44)	

[a] RSE, relative standard error reported on the approximate standard-deviation scale obtained from a bootstrap sample size of 200; CL, oral clearance; V_c, volume of distribution in the central compartment; k_a, first-order absorption rate constant; MTT, absorption mean transit time; Q, intercompartmental clearance; V_p, volume of distribution in the peripheral compartment; F, oral bioavailability fixed to 1 (since we did not have intravenous injection data). In this table, we report the values of parameters directly estimated by the model. To obtain CL/F, the values of CL must be combined with those of F. Since the typical value of F was fixed to 1, the typical value of CL/F has the same value as CL, while the between-subject variability (BSV) of CL/F needs to take into account both the BSV in CL and that in F. A similar consideration is valid for V_c/F, Q/F, and V_p/F.

[b] IIV, interindividual variability expressed as percent coefficient of variation (% CV).

ber bioreactor system (HFS) has suggested a minimum target $fAUC_{0-24}$/MIC ratio of 53 for *M. tuberculosis* as the identified target for suppressing the outgrowth of moxifloxacin-resistant mutants but not necessarily optimal bactericidal activity (23).

In this study, we aimed to describe the population pharmacokinetics of moxifloxacin using data from 241 South African and Zimbabwean patients with pulmonary tuberculosis who participated in the RIFAQUIN study ISRCTN 44153044 (24, 25). Monte Carlo simulations were then employed to assess the probability of reaching the $fAUC_{0-24}$/MIC ratio target using moxifloxacin and ofloxacin at the recommended doses for MDR-TB (2). For ofloxacin pharamcokinetics assays, we used a population model that we reported previously (26), while the MIC distributions of moxifloxacin and ofloxacin for drug-resistant *M. tuberculosis* isolates were previously determined (27).

MATERIALS AND METHODS

Study population. Patients ($n = 241$) with pulmonary TB received an initial intensive phase of therapy that included daily rifampin and moxifloxacin for 2 months. For the continuation phase, they were treated with either 400 mg moxifloxacin once weekly together with 1,200 mg rifapentine or with 400 mg moxifloxacin twice weekly with 900 mg of rifapentine. Pharmacokinetic sampling was carried out during the fourth month of therapy. Previously published pharmacokinetic data obtained during rifapentine and moxifloxacin cotreatment of 28 patients (13) were combined with concentration-time data obtained from 213 additional patients who participated in the RIFAQUIN study (24, 25). The doses of rifapentine and moxifloxacin were taken with 240 ml of water 15 min after the patients received 2 hard-boiled eggs with bread. Four hours after dosing, a light meal, snacks, and fluids were provided. Pharmacokinetic samples were obtained immediately before dosing and at 1, 2, 3, 5, 7, 10, 12, 26, and 50 h after the dose in 28 patients. For the remaining 213 patients, samples were obtained at 2 (± 0.5) h, 5 (± 0.5) h, and 24 (± 3) h or 48 (± 3) h after dosing. HIV-positive patients who required antiretroviral treatment at randomization were excluded. Separate written informed consent for the pharmacokinetic study was obtained from the RIFAQUIN study participants in Harare (Zimbabwe) and in Johannesburg (Gauteng) and Worcester (Western Cape, South Africa). The study protocol was reviewed and approved by the London-Surrey Borders Research Ethics Committee (reference no. 07/Q0806/58), the Research Ethics Committee of the University of Cape Town, the Medicines Control Council of South Africa, the Medicines Research Council of Zimbabwe, and the Medicines Control Authority of Zimbabwe.

Drug determination. After blood collection, plasma was separated and immediately stored at −80°C. Moxifloxacin concentrations were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) as previously described (13). The lower limit of quantification was 0.063 mg/liter.

MICs of clinical isolates. MICs of moxifloxacin and ofloxacin were determined for 197 drug-resistant *M. tuberculosis* isolates from patients in the Western Cape, South Africa, by Bactec MIGIT 960 as previously described (27). The 0.25 mg/liter and 2.0 mg/liter concentrations of moxifloxacin and ofloxacin were used as susceptibility breakpoints to differentiate between susceptible and resistant strains as suggested by WHO (19).

Pharmacokinetic analysis. Moxifloxacin plasma concentration-time data were analyzed using a nonlinear mixed-effects model as implemented in NONMEM 7.2 (28). The execution of runs was through Perl-speaks-NONMEM (29), and graphical diagnostics were created using Xpose 4 (30). The use of allometric scaling testing total body weight (WT), fat-free mass (FFM) (31), and fat mass (FAT) as predictors was applied on clearance (CL), intercompartmental clearance (Q), and volume of distribution of the central (V_c) and peripheral (V_p) compartments, as previously described (13). Various structural models were tested, including one- or two-compartment distribution with first-order absorption and elimination rate constants, absorption lag time, and transit compartment absorption (32). Estimation of typical population pharmacokinetic parameters, along with their random interindividual variability (IIV), was performed using a first-order conditional estimation method with ε-η interaction (FOCE INTER). A lognormal distribution for IIV was assumed, and additive and/or proportional models for the residual unexplained variability (RUV) were evaluated. Data below the lower limit of quantification (LLOQ) were described using the M3 method (33). The covariate relationships were screened by using a stepwise approach and forward inclusion using a delta objective function (ΔOFV) of ≥3.84 ($P \leq 0.05$) as the cutoff for inclusion, followed by a backward elimination using a ΔOFV of ≥6.83 ($P \leq 0.01$) for covariate retention. The tested covariates included age, HIV status, sex, site, and regimen/arm (drug administration once weekly versus twice weekly). The detected covariate effects were included in the final model if clinically significant (a cutoff of 20% was used). Estimates of the precision of parameters were obtained from a nonparametric bootstrap ($n = 200$).

Model evaluation. Model selection was based on graphical assessment of conditional weighted residuals (CWRES) versus time, basic goodness-of-fit plots (GOF), changes in the NONMEM objective function (OFV),

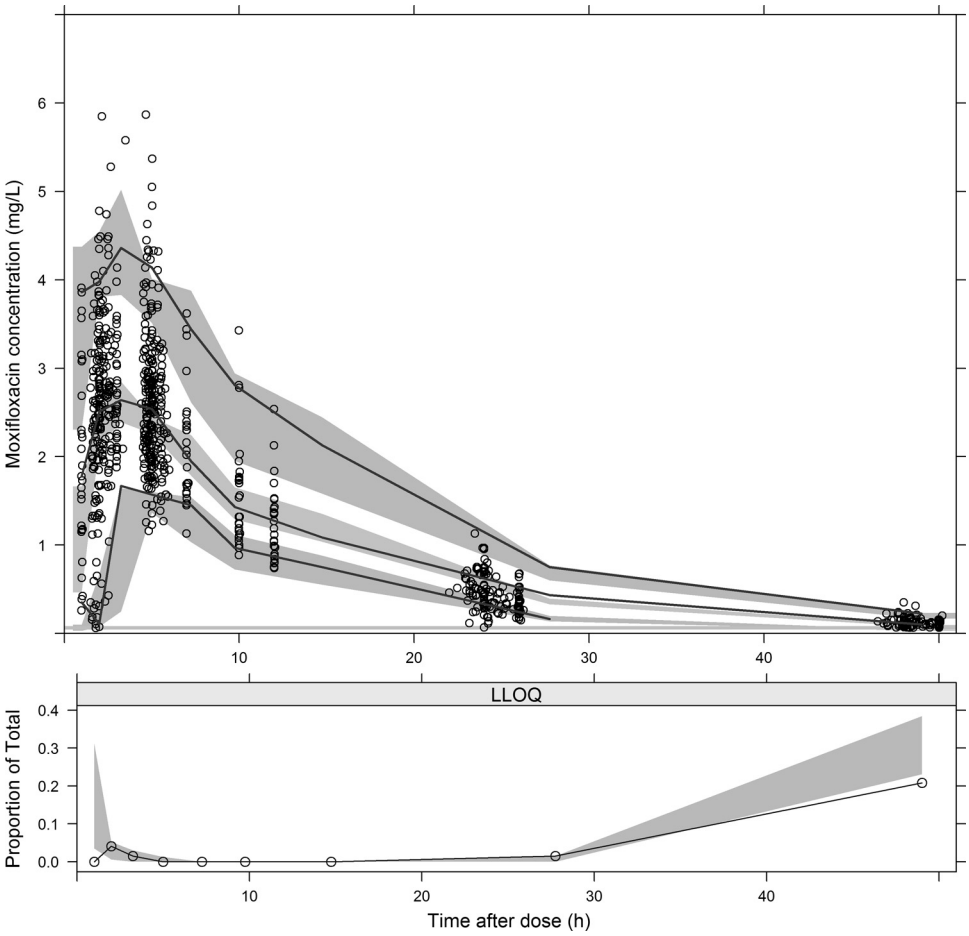

FIG 1 Visual predictive check (VPC) for the final moxifloxacin population pharmacokinetic model. In the upper panel, the lower, middle, and upper solid lines are the 5th, median, and 95th percentiles of the observed plasma concentration, respectively, while the shaded areas are the 95% confidence intervals for the same percentiles of the simulated data. The lower panel shows the fraction of observed data below the lower limit of quantification (LOQ), which is represented by the solid line. The shaded area shows the simulation-based 95% confidence interval around the median of the LOQ data.

estimates of the precision of parameters as provided by the NONMEM covariance step (if successfully completed), and, most importantly, visual predictive checks (VPC) (34).

Pharmacokinetic simulations and probability of target attainment. The final pharmacokinetic model was used to perform Monte Carlo simulations for 10,000 individuals after administration of multiple daily doses of 400 mg moxifloxacin to obtain steady-state $f\mathrm{AUC}_{0-24}$ values. Daily doses of 800 mg of moxifloxacin were also explored. The simulated $f\mathrm{AUC}_{0-24}$ values were obtained by using covariate distributions similar to those used for the population on which the model was developed and assuming 50% plasma protein binding for moxifloxacin (9, 35, 36). Similar simulations were performed to obtain the $f\mathrm{AUC}_{0-24}$ values for ofloxacin using a previously published model, developed from South African patients with MDR-TB (26), and an unbound fraction value of 0.75 in humans (16).The estimated $f\mathrm{AUC}_{0-24}$/MIC ratios were obtained by dividing $f\mathrm{AUC}_{0-24}$ values by MICs ranging from 0.125 to 8 mg/liter. The MIC distributions of moxifloxacin and ofloxacin of drug-resistant *M. tuberculosis* isolates were from a separate study in patients from the Western Cape, South Africa (27). For the comparison, we used targets of $f\mathrm{AUC}_{0-24}/\mathrm{MIC} \geq 100$ and $f\mathrm{AUC}_{0-24}/\mathrm{MIC} \geq 53$. The probability of target attainment (PTA) was calculated as the proportion of individuals achieving $f\mathrm{AUC}_{0-24}/\mathrm{MIC} \geq 100$ (or ≥ 53) for a specific MIC. The cumulative fraction of response (CFR) (37) was calculated as the weighted average of the PTA across the MIC strata, as shown below:

$$\mathrm{CFR} = \sum_{i=1}^{n} \mathrm{PTA}(\mathrm{MIC}_i) \cdot p(\mathrm{MIC}_i)$$

The PTA at each MIC_i level was multiplied by the relative frequency of that MIC in the study population, $p(\mathrm{MIC}_i)$. Our target was CFR $\geq$ 90%.

RESULTS

Although the RIFAQUIN study patients had drug-susceptible pulmonary tuberculosis, while the patients in the ofloxacin pharmacokinetic study had MDR-TB, their demographic and patient characteristics were similar and differed only by HIV status and sex (Table 1). The 241 patients on moxifloxacin provided 856 concentration-time points, and only 4% were below LLOQ. As in our previous analysis (13), the population pharmacokinetics of moxifloxacin was well described by a two-compartment model with first-order elimination and transit absorption compartments. FFM was used for allometric scaling of CL, Q and V_c, while V_p was better scaled with FAT. The final parameter estimates are shown in Table 2, and a VPC of the final model is shown in Fig. 1. No significant differences in the pharmacokinetic parameters were found between the once-weekly and twice-weekly dosing approaches, and no additional covariates were included except for body size, which was incorporated via allometric scaling. The Monte Carlo

TABLE 3 The MIC distributions of moxifloxacin and ofloxacin in 197 *Mycobacterium tuberculosis* isolates

Resistance profile[a]	No. of isolates with indicated drug MIC (mg/liter)									Total no. of isolates
	≤0.125	>0.125 ≤ 0.25	>0.25 ≤ 0.5	>0.5 ≤ 1.0	>1.0 ≤ 2.0	>2.0 ≤ 4.0	>4.0 ≤ 6.0	>6.0 ≤ 8.0	≥10.0	
Moxifloxacin										
INH	68									68
RIF	5									5
MDR	55	2	1							58
MDR+INJ	12	2	3							17
MDR+FLQ				3	2					5
XDR		2	1	17	22	2				44
Ofloxacin										
INH			59	9						68
RIF			5							5
MDR			47	9	1	1				58
MDR+INJ			9	2	6					17
MDR+FLQ						3		1	1	5
XDR					1	10	6	10	17	44

[a] Resistance to either isoniazid (INH) or rifampin (RIF) represented monoresistance. MDR, resistance to both INH and RIF; MDR+INJ, MDR plus resistant to an injectable; MDR+FLQ, MDR plus resistant to either fluoroquinolone; XDR, MDR plus resistance to both a FLQ and an injectable.

simulations predicted a median AUC_{0-24} value of 38.7 after 400-mg daily moxifloxacin administration, while the 2.5th and 97.5th percentiles were 21.9 and 69.6 mg·h/liter, respectively.

The MIC distributions of moxifloxacin and ofloxacin are listed in Table 3. The PTA with a target $fAUC_{0-24}$/MIC ratio of ≥53 across the range of MIC values for daily 400-mg and 800-mg moxifloxacin doses is shown in Fig. 2, while the PTA for daily 800-mg ofloxacin doses is shown in Fig. 3. Table 4 shows the CFR for daily 400 mg and 800 mg moxifloxacin and for daily 800 mg ofloxacin with a target $fAUC_{0-24}$/MIC value of either ≥53 or ≥100. Moxifloxacin at 400 mg had a higher CFR than ofloxacin at 800 mg in both scenarios (target ratios of 53 and 100).

DISCUSSION

Our results revealed that the CFR for 400 mg moxifloxacin was 98% versus 84% for 800 mg ofloxacin by using a target $fAUC_{0-24}$/MIC ratio of ≥53. With the more stringent target ratio of ≥100, the differences in the performances of the drugs were even more marked, and both regimens fell short of the 90% CFR threshold (the CFR for moxifloxacin was 88% versus 43% for ofloxacin). On the other hand, with 800-mg doses of moxifloxacin in the same patients with MDR-TB and the target ratio of ≥100, a CFR of 98% would be achieved (Table 4 and Fig. 3). The higher moxifloxacin dose (800 mg) also achieved the pharmacodynamic target ratio of ≥53 in 98% of MDR-TB patients with resistance to an injectable agent (Table 4 and Fig. 3), whereas the standard 400-mg dose had a marginal CFR of 84% (Table 4).

Moxifloxacin has structural differences from ofloxacin at the C-7 position that reduce the ability of the bacterium to efflux moxifloxacin across the cell wall, thus lowering the MIC. Moxifloxacin also has intracellular killing kinetics superior to those of ofloxacin. Experimental data show that moxifloxacin MICs in macrophages increased by only 2-fold compared to the MIC in extracellular broth, while 4-fold increases were demonstrated for ofloxacin (20).

Using a target $fAUC_{0-24}$/MIC ratio of ≥53, the currently recommended 400-mg daily dose of moxifloxacin obtained a PTA greater than 90% when the isolates had MICs ≤ 0.25 mg/liter. On the other hand, ofloxacin failed to achieve a PTA of more than 90% when the MIC was >0.5 mg/liter, as found in about 20% of the isolates, classified by standard procedures as resistant to rifampin and isoniazid but not to injectable second-line drugs (such as capreomycin, kanamycin, and amikacin) or to fluoroquinolones. Hence, our findings suggest that a 4-fold reduction in the susceptibility breakpoint for ofloxacin, which is currently set at 2.0 mg/liter, may be warranted. However, clinical correlates for the $fAUC_{0-24}$/MIC targets are lacking for patients with tuberculosis, and using the target of 100 would suggest revision of the ofloxacin susceptibility breakpoint down to 0.25 mg/liter. It should be noted that the target ratio of 53 which we used for comparisons of fluoroquinolones was derived only for moxifloxacin and that this value is not necessarily applicable to ofloxacin. The current doses for moxifloxacin (400 mg) and ofloxacin (800 mg) may thus be suboptimal for the treatment of drug-resistant tuberculosis if a pharmacodynamic target of $fAUC_{0-24}$/MIC ≥ 100 correlates better with successful clinical outcomes. Our simulations suggest susceptibility breakpoints of 0.125 mg/liter for 400-mg doses of moxifloxacin and 0.25 mg/liter for 800 mg ofloxacin. Doubling the dose of ofloxacin is unlikely to achieve acceptable PTA in many patients as previously reported (26). On the other hand, our simulations show that doubling the moxifloxacin dose to 800 mg daily could lead to acceptable PTA (Fig. 2), and this is consistent with previous reports (23). Higher doses of moxifloxacin may increase moxifloxacin side effects, including prolongation of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (QT interval) (39), and this concern is particularly serious, given the long duration of MDR-TB treatment. However, limited studies seem to suggest the safety of higher doses. A recent study by Ruslami et al. (40) which evaluated daily 800-mg doses of moxifloxacin did not show increased toxicity, while a study by Alffenaar et al. showed tolerability at 600 mg and 800 mg moxifloxacin (41). An ongoing clinical trial by Alffenaar et al. is evaluating the safety of moxifloxacin at escalated doses of 600 and 800 mg (NCT01329250; http://clinicaltrials.gov/show/NCT01329250).

The continued use of fluoroquinolones in suboptimal doses

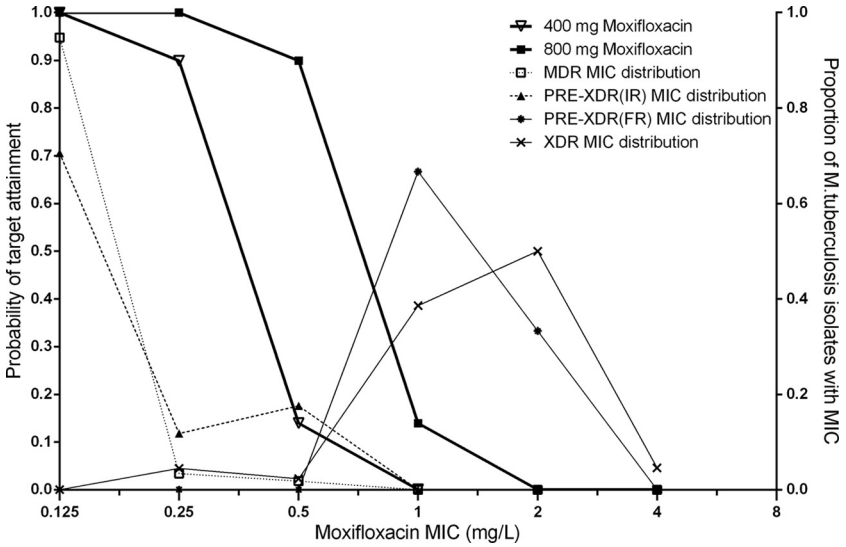

FIG 2 Probability of target attainment (target $fAUC_{0-24}$/MIC ratio ≥ 53) versus *Mycobacterium tuberculosis* isolate MICs for 400-mg and 800-mg moxifloxacin doses. MDR and XDR data represent MIC distributions from multidrug-resistant and extensively drug-resistant isolates, respectively. PRE-XDR(IR) and PRE-XDR(FR) data represent MIC distributions from isolates resistant to injectables and fluroroquinolones, respectively.

may hinder their use in the future due to the development of fluoroquinolone resistance (42). The target $fAUC_{0-24}$/MIC ratio of ≥53 is based on studies showing suppression of resistance emergence with moxifloxacin monotherapy in a HFS (23). In our study, 400 mg moxifloxacin was shown to attain a CFR ≥ 90% for *M. tuberculosis* strains resistant to isoniazid and rifampin but not injectable agents, while ofloxacin at 800 mg daily did not. However, for MDR-TB strains resistant to injectable agents, only the 800-mg daily doses of moxifloxacin achieved a CFR ≥ 90%. The target ratio of ≥100 is based on review of studies in Gram-positive and Gram-negative bacteria conducted in animals (22) and humans (21). In patients, values of 125 to 250 were associated with clinical cure and speed of bacterial eradication for Gram-negative infections of the respiratory tract (43), and the target value of >100 was linked to decreased emergence of bacterial resistance (44). For Gram-negative organisms, a target of 100 to 125 achieved acceptable activity, although more-rapid eradication was achieved with a target $fAUC_{0-24}$/MIC ratio of ≥250 when ciprofloxacin, grepafloxacin, levofloxacin, and gatifloxacin were evaluated (43). Considering sterilizing activity, including killing of *M. tuberculosis* within macrophages, the target of 100 may be more appropriate, as penetration to the site of action should be considered (20). Fluoroquinolones generally achieve higher concentrations in epithelial lining fluid (ELF) than in plasma (45), which means that our PTA and CFR would be higher at the site of action than when plasma concentrations are used. Compared with other

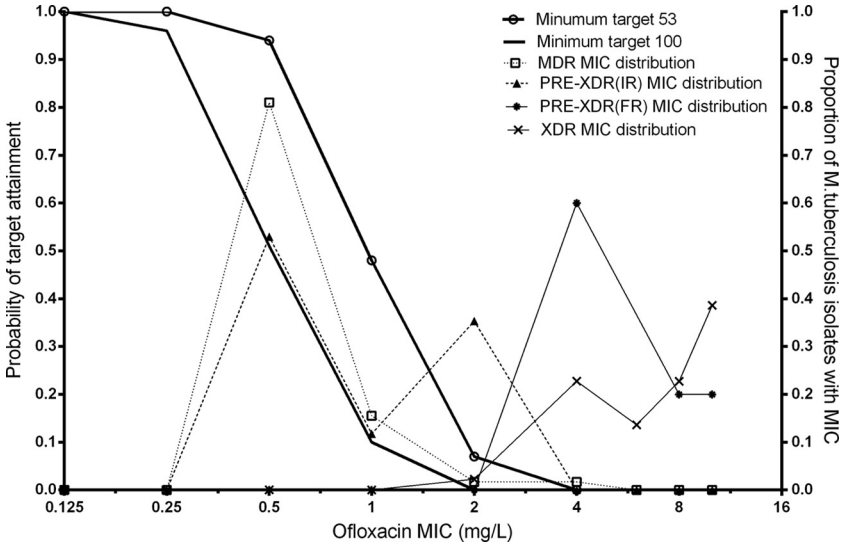

FIG 3 Probability of target attainment (target $fAUC_{0-24}$/MIC ratio ≥ 53 or 100) versus *Mycobacterium tuberculosis* isolate MICs for 800-mg ofloxacin dose. MDR and XDR data represent MIC distributions from multidrug-resistant and extensively drug-resistant isolates, respectively. PRE-XDR(IR) and PRE-XDR(FR) data represent MIC distributions from isolates resistant to injectables and fluroroquinolones, respectively.

TABLE 4 The cumulative fractions of response for daily doses of 400 mg and 800 mg of moxifloxacin and 800 mg of ofloxacin for target $fAUC_{0-24}$/MIC ratios of 53 (23) and 100 (21, 22, and 38)[a]

$fAUC_{0-24}$/MIC ratio and *M. tuberculosis* strain phenotype	CFR expectation		
	400 mg moxifloxacin	800 mg moxifloxacin	800 mg ofloxacin
≥53			
MDR	0.98	1.00	0.84
MDR+INJ	0.84	0.98	0.58
MDR+FLQ	0.00	0.09	0.00
XDR	0.04	0.12	0.00
≥100			
MDR	0.88	0.98	0.43
MDR+INJ	0.68	0.85	0.28
MDR+FLQ	0.00	0.00	0.00
XDR	0.01	0.04	0.00

[a] CFR, cumulative fraction of response; MDR, resistance to both isoniazid (INH) and rifampin (RIF); MDR+INJ, MDR plus resistant to an injectable; MDR+FLQ, MDR plus resistant to either fluoroquinolone; XDR, MDR plus resistance to both a FLQ and an injectable.

fluoroquinolones, moxifloxacin has been found to have greater efficacy than levofloxacin in mice despite a lower plasma AUC/MIC ratio (46), presumably due to higher intracellular concentrations of moxifloxacin. Levofloxacin, however, penetrates into cerebrospinal fluid of patients with tuberculosis meningitis better than ciprofloxacin and gatifloxacin (47). In comparison to another moxifloxacin population pharmacokinetic model (48), we found a reduced IIV for *V* but a significant IIV for CL and *F*. Our estimate of CL was 25% higher than that reported by Peloquin et al.; this may have been due to the differences in the study populations, but it may also have been a consequence of the differences in dosing schedules, sampling times, and structural models used to interpret the data.

Due to limited sample size, our MIC data may not represent the true distribution for some drug resistance categories. The *M. tuberculosis* isolates used to determine the MICs originated from patients in the same region as those contributing data to the pharmacokinetic model (Table 1). Given the limited geographical distributions of our study population and *M. tuberculosis* isolates contributing to our analysis, we cannot assume that the PTA and especially the CFR analyses will be applicable to other populations outside the region. In addition, our results compare the activities of moxifloxacin with those of ofloxacin using pharmacodynamic targets derived in experiments using the drugs administered alone (as monotherapy). Previous studies have shown that a combination of rifampin (a rifamycin) and moxifloxacin suppresses resistance emergence but at the price of slightly slowing bacterial killing (49, 50). Our comparisons did not take into account within-regimen synergy or antagonism (50), although these effects are unlikely to differ considerably within the fluoroquinolone class. Our pharmacodynamic targets are based on experimental models which differ from the organism-drug interface in patients. Importantly, the diversity of the *M. tuberculosis* growth states encountered in patients is not accounted for. Moreover, our analysis assumes unbound plasma concentrations as a marker of exposure, while tissue-free drug concentrations would be more appropriate.

Conclusions. Our analyses based on the pharmacokinetic and drug susceptibility distributions in African patients indicate that, in the currently used doses, moxifloxacin is more efficacious than ofloxacin for the treatment of MDR-TB. Doubling the dose of moxifloxacin to 800 mg daily improves the CFR. However, further clinical studies are required to evaluate the safety and tolerability of moxifloxacin at higher doses.

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