Smythe, W; Merle, CS; Rustomjee, R; Gninafon, M; lo, MB; Bah-Sow, O; Olliaro, PL; Lienhardt, C; Horton, J; Smith, P; McIlerson, H; Simonsson, USH (2013) Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations. Antimicrobial agents and chemotherapy, 57 (9). pp. 4164-4171. ISSN 0066-4804 DOI: https://doi.org/10.1128/AAC.00479-13

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Antimicrobial Agents and Chemotherapy

Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations

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Published Ahead of Print 17 June 2013.

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Evaluation of Initial and Steady-State Gatifloxacin Pharmacokinetics and Dose in Pulmonary Tuberculosis Patients by Using Monte Carlo Simulations

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A 4-month regimen of gatifloxacin with rifampin, isoniazid, and pyrazinamide is being evaluated for the treatment of tuberculosis in a phase 3 randomized controlled trial (OFLOTUB). A prior single-dose study found that gatifloxacin exposure increased by 14% in the combination. The aims of the study are to evaluate the initial and steady-state pharmacokinetics of gatifloxacin when daily doses are given to patients with newly diagnosed drug-sensitive pulmonary tuberculosis as part of a combination regimen and to evaluate the gatifloxacin dose with respect to the probability of attaining a pharmacokinetic/pharmacodynamic target.

We describe the population pharmacokinetics of gatifloxacin from the first dose to a median of 28 days in 169 adults enrolled in the OFLOTUB trial in Benin, Guinea, Senegal, and South Africa. The probability of achieving a ratio of $\geq 125$ for the area under the concentration time curve to infinity ($\text{AUC}_{0-\infty}$) for the free fraction of gatifloxacin over the MIC ($\text{fAUC/MIC}$) was investigated using Monte Carlo simulations. The median $\text{AUC}_{0-\infty}$ of 41.2 mg·h/1L decreased on average by 14.3% (90% confidence interval [CI], $-90.5\%$ to $+61.5\%$) following multiple 400-mg daily doses. At steady state, 90% of patients achieved an $\text{AUC/MIC}$ of $\geq 125$ only when the MIC was $<0.125 \mu g/ml$. We conclude that systemic exposure to gatifloxacin declines with repeated daily 400-mg doses when used together with rifampin, isoniazid, and pyrazinamide, thus compensating for any initial increase in gatifloxacin levels due to a drug interaction. (The OFLOTUB study has been registered at ClinicalTrials.gov under registration no. NCT00216385.)

Fluoroquinolones represent a promising class of drug for the treatment of tuberculosis. Gatifloxacin distributes widely throughout the body (1), achieving MICs for Mycobacterium tuberculosis observed in vitro of 0.031 to 0.5 $\mu g/ml$ (2, 3, 4), and demonstrates strong bactericidal activity in the mouse model (2, 5). Furthermore, gatifloxacin displays excellent early bactericidal activity (EBA), only slightly lower than that of isoniazid (6); replacing ethambutol with gatifloxacin in the standard first-line regimen resulted in accelerated killing of $M. tuberculosis$ in the sputum of patients with pulmonary tuberculosis (7). A single-dose crossover study in healthy volunteers showed a reduction in the elimination rate of gatifloxacin resulting in a 14% increase in the area under the concentration time curve to infinity ($\text{AUC}_{0-\infty}$) when it was given together with rifampin, isoniazid, and pyrazinamide (8). Reports of dysglycemia related to the use of gatifloxacin in elderly patients with renal insufficiency (9, 10, 11, 12) have raised concerns that pharmacokinetic interactions may lead to an increased risk of toxicity related to higher gatifloxacin exposure. On the other hand, in vitro and in vivo studies suggest a target ratio of $\geq 125$ for the free drug area under the concentration versus time curve to MIC ($\text{fAUC/MIC}$) for maximal bactericidal effect and prevention of resistance to fluoroquinolones (13, 14).

We aimed to evaluate the population pharmacokinetics of gatifloxacin after an initial dose and at steady state (28 days) when given in combination with rifampin, isoniazid, and pyrazinamide in African adult patients with newly diagnosed pulmonary tuberculosis. In addition, the probability of target ($\text{fAUC/MIC} \geq 125$) attainment (PTA) and the cumulative fraction of response (CFR) (15) across the MIC distribution of $M. tuberculosis$ for 400, 600, and 800 mg once daily of gatifloxacin at steady state in combination with rifampin, isoniazid, and pyrazinamide were investigated with Monte Carlo simulations using the final model.

MATERIALS AND METHODS

Patients. Newly diagnosed pulmonary tuberculosis patients participating in the multicenter phase 3 randomized controlled trial (OFLOTUB trial [ClinicalTrials.gov registration no. NCT00216385]) (16) at clinics in South Africa, Senegal, Guinea, and Benin were enrolled in the pharmacokinetic study, and those randomized to the 4-month regimen of gatifloxacin, rifampin, isoniazid, and pyrazinamide ($n = 169$) were included in this analysis. Written informed consent was obtained prior to enrollment. Adult males ($n = 116$) and nonpregnant females ($n = 53$), aged 18 to 58 years and weighing 35 to 80 kg were included in this analysis. HIV-infected patients ($n = 54$) were antiretroviral naive. During the first 2
months of treatment, all patients received 400 mg gatifloxacin (Lupin Pharmaceuticals Pvt Ltd., Mumbai, India) daily irrespective of weight together with a fixed combination of rifampin, isoniazid, and pyrazinamide (Lupin Pharmaceuticals Pvt Ltd., Mumbai, India) as follows: rifampin, 600 mg daily, and isoniazid, 300 mg daily, for 2 months of treatment, all patients received 400 mg gatifloxacin (Lupin Pharmaceuticals Pvt Ltd., Mumbai, India) daily irrespective of weight.

Blood sampling. Three venous blood samples per patient were taken after the first dose (initial dose) and repeated after approximately 28 days (steady state) for the determination of gatifloxacin pharmacokinetics. Samples were drawn 1 to 2 and 2.5 to 3.5 h postdose from each patient on both occasions. Patients were block randomized to a time for the third sample. After the first dose, the third sample was taken 4 to 6 h postdose from one half of the patients, and the remaining patients had a sample taken 8 to 10 h postdose. At steady state, the third sample was taken either predose, 4 to 6 h postdose, or 8 to 10 h postdose.

Drug quantification. Each 4-mL blood sample, collected in a heparinized vacuum plastic tube, was centrifuged at 750 × g for 10 min to separate the plasma using a benchtop centrifuge. Samples were kept on crushed ice during preparation, and the plasma aliquots were stored at −80°C until drug quantification within 30 min of sampling. Concentrations of gatifloxacin in plasma were quantified using high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS). Inter- and intraday coefficients of variation were below 10%. The lower limit of quantification was set at 0.2 μg/mL for pyrazinamide and 0.1 μg/mL for rifampicin, gatifloxacin, and isoniazid (8).

Population pharmacokinetic analysis. Data analysis was performed with a nonlinear mixed-effects approach, as implemented in NONMEM software, version 7.1.2 (Icon Development Solutions) (17), using Advan l3 and the first-order conditional estimation method with interaction (FOCE Inte r). R (version 2.12.1) was used for graphical analysis and data management (18). Xpose (version 4.0) was used for data exploration and visualization as well as model diagnostics and model comparison (19). PsN, version 3.3.2 (20, 21), was used for stepwise covariate model building (SCM) (22), visual predictive checks (VPCs) (23, 24), and prediction-corrected VPCs (pVPCs) (25) of the models. Model selection was performed using the objective function value (OFV) (which is minus twice the log likelihood of the data), standard error of parameter estimates, scientific plausibility, and goodness-of-fit plots together with VPC and, when indicated, pVPC.

A total of 954 gatifloxacin concentration observations from 169 patients were included in the analysis. Twelve observations, from 12 individuals, falling below the lower limit of quantification (LLOQ = 0.1 μg/mL) were replaced with LLOQ/2. There was not more than one LOQ observation in each individual absorption or elimination phase. One- and two-compartment distribution models with first-order elimination were fitted to the data. Potential differences in gatifloxacin pharmacokinetic parameters were evaluated after initial and multiple doses. A transit absorption compartment model described by Savic et al. (26) and applied by Wilkins et al. (27) for multiple dosing was used to capture the delay in the absorption characteristics. The absorption model used hypothetical transit compartments to mimic a delay in the onset of absorption, producing a gradual increase in absorption rate in a physiologically plausible manner. Drug transfer between transit compartments occurred via the rate constant $k_{as}$ (equation 1):

$$k_{as} = \frac{N + 1}{\text{MTT}}$$

where MTT is the mean transit time and $N$ is the number of transit compartments. Drug transfer from the final transit compartment to the central compartment occurred via the first-order rate constant $k_{ao}$.

Creatinine clearance ($CL_{cre}$) was estimated from serum creatinine using the Cockcroft-Gault formula (28) (equation 2):
in a univariate fashion within NONMEM. The covariate model that resulted in the best fit was carried forward to a multivariate search in which the remaining parameter-covariate relations were included based on a 5% significance level, and it was referred to as the “full forward model.” After identification of the full forward model, a backward deletion was performed to determine the final model. In the backward-deletion step, each parameter covariate relationship was left out one at a time and tested using a statistical significance criterion of 0.01%. This step was repeated until no further covariate could be excluded, and the resulting model was referred to as the “final model.” Continuous covariates were first introduced in a linear fashion (fractional change) and centered on the median covariate value. If a continuous covariate was included in a linear fashion, inclusion according to a nonlinear fashion (i.e., piece-wise linear, exponential, and power equation) was also tested. For categorical covariates, models were expressed as fractional change from the typical value.

Based on the final model, the AUC from zero hour to infinity (\(AUC_{0-\infty}\)) was derived to describe exposure after the first dose and at steady state (day 28), respectively. Total oral clearance was simulated for 10,000 virtual patients and \(AUC_{0-\infty}\) derived through the following equation:

\[
AUC_{0-\infty} = \frac{F \cdot dose}{CL}
\]  

(10)

The individual percentage change in \(AUC_{0-\infty}\) between first dose and steady state was calculated and reported as median (5th and 95th percentiles). The 10,000 virtual patients were derived by resampling subjects from the data used to develop the model.

As a pharmacokinetic/pharmacodynamic (PK/PD) index, we used the probability of target attainment \((PTA)\) as a surrogate for maximal bactericidal effect and reduced MIC as a function of the MIC with the 80% and 90% confidence intervals (CI) was derived. The lower boundary in an 80% CI of the total probability of target attainment \((i.e., PTA)\) was derived. The cumulative fraction of response \((CFR)\) was calculated, representing the proportion of the population achieving \(\frac{AUC}{MIC}\) of \(\geq 125\), given Monte Carlo simulation and the MIC distribution of \(M.\) tuberculosis for 400, 600, and 800 mg once daily of gatifloxacin at steady state in combination with rifampin, isoniazid, and pyrazinamide. The CFR was calculated using equation 11:

\[
\sum_{i=1}^{n} PTA_i \times F_i
\]

(11)

where \(i\) indicates the MIC category ranked from lowest to highest MIC value, \(PTA_i\) is the PTA of each MIC category, and \(F\) is the fraction of the \(M.\) tuberculosis population at each MIC category. \(F\) was calculated at each MIC as the number of isolates divided by the total number of isolates (234) yielding the frequency for each MIC.

**RESULTS**

The characteristics of the 169 patients contributing to this analysis are described in Table 1. More than one-half (59%) of the study participants were recruited at the South African study site, which had the highest frequency of HIV-infected patients (52% versus 12% in Benin and none in Guinea or Senegal).

The final gatifloxacin pharmacokinetic model described one-compartment with first-order elimination. Including an absorption transit model to account for the delay in absorption resulted in a drop in OFV of 125 points. The relationship between \(CL_{CR}\) and \(CL/F\) was described using equations 3 and 4 based on the prior knowledge that gatifloxacin is largely eliminated by the kidneys (1), and this resulted in OFV reductions of 19 and 24 points, respectively, compared to models not accounting for \(CL_{CR}\) or a combination of GFR-mediated and non-GFR clearance. In a 70-kg patient, gatifloxacin total \(CL/F\) was estimated to be 11.28 liters/h. Approximately 55% (6.17 liters/h) of \(CL/F\) was accounted for by renal filtration (a route scaled with \(CL_{CR}\)). Allometric scaling was applied to the remaining 45% (5.11 liters/h) of \(CL/F\) and to \(V/F\) (141 liters/h) using FFM as the optimal size descriptor, and the estimates were reported for a 70-kg patient (Table 2). \(F\) was 11.7% lower at steady state (day 28) than at the first dose. Age, sex, and HIV status had significant effects on the absorption rate constant, reducing interindividual variability of the parameter by 6.5, 3.4, and 17.7%, respectively (Table 2). The final model adequately described the concentration in plasma-time data at initial dose and at steady state as judged by the VPC (Fig. 1). Shrinkage for random effects between individuals and occasions ranged from 17 to 25% and from 38 to 99%, respectively. Shrinkage rates in IIV and IOV for \(CL/F\) were 25% and 42%, respectively. The epsilon (residual error) shrinkage was 39%.

Based on 10,000 Monte Carlo patient simulations, the median \(AUC_{0-\infty}\) \((41.2 \mu g \cdot h/ml after the first dose) decreased to 35.4 \mu g·

### Table 1: Demographics and covariates of patients included in the gatifloxacin population pharmacokinetic model

<table>
<thead>
<tr>
<th>Characteristic (unit)</th>
<th>All sites</th>
<th>South Africa</th>
<th>Senegal</th>
<th>Benin</th>
<th>Guinea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>169</td>
<td>99</td>
<td>26</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>No. of males/no. of females</td>
<td>116/53</td>
<td>62/37</td>
<td>23/3</td>
<td>20/5</td>
<td>11/8</td>
</tr>
<tr>
<td>No. of HIV+ patients</td>
<td>54</td>
<td>51</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>45 (39–49)</td>
<td>45 (38–48)</td>
<td>49 (46–52)</td>
<td>46 (41–48)</td>
<td>45 (35–46)</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>55 (51–60)</td>
<td>56 (51–61)</td>
<td>55 (52–59)</td>
<td>53 (46–57)</td>
<td>52 (50–55)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>29 (24–35)</td>
<td>30 (24–35)</td>
<td>28 (25–31)</td>
<td>30 (26–37)</td>
<td>25 (20–34)</td>
</tr>
<tr>
<td>(CL_{CR}) (ml · min(^{-1}))</td>
<td>94 (81–110)</td>
<td>100 (85–111)</td>
<td>87 (82–102)</td>
<td>75 (63–87)</td>
<td>89 (78–99)</td>
</tr>
</tbody>
</table>

\(^{a}\)Continuous variables are given as medians, with interquartile ranges in parentheses. FFM, fat-free mass; \(CL_{CR}\), creatinine clearance.
The median decrease in AUC_{0–\infty}/H_{11009} was 14.3% (5th and 95th percentiles, 90.4% and 61.5%) to 35.4 g · h/ml (5th and 95th percentiles, 15.2 and 80.4) at steady state (day 28).

**TABLE 2** Parameter estimates based on the final gatifloxacin pharmacokinetic model

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Estimate</th>
<th>% RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CL/F\text{GFR})_{\text{STD}} (liters/h)</td>
<td>6.17</td>
<td>9.7</td>
</tr>
<tr>
<td>(CL/F\text{Other})_{\text{STD}} (liters/h)</td>
<td>5.11</td>
<td>15.4</td>
</tr>
<tr>
<td>(V/F)_{\text{STD}} (liters)</td>
<td>141</td>
<td>2.7</td>
</tr>
<tr>
<td>F_{\text{first dose}}</td>
<td>1 FIX</td>
<td></td>
</tr>
<tr>
<td>F_{\text{steady-state}} (% change from F_{\text{first dose}})</td>
<td>−11.7</td>
<td>17.4</td>
</tr>
<tr>
<td>k_{\text{e}} (h^{−1})</td>
<td>4.13</td>
<td>13.5</td>
</tr>
<tr>
<td>MTT (h)</td>
<td>0.65</td>
<td>8.1</td>
</tr>
<tr>
<td>N</td>
<td>12.6</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Covariate relationships

Age-\%k_{\text{e}} (%) | 3.2 | 15.2 |
Sex-\%k_{\text{e}} (%) | −54.8 | 10.7 |
HIV-\%k_{\text{e}} (%) | 61.9 | 38.4 |

IIV

IIV\text{CL/F} (%) | 33.0 | 7.7 |
IIV\text{V/F} (%) | 22.1 | 10.9 |

IOV

IOV\text{CL/F} (%) | 33.0 | 5.7 |
IOV\text{V/F} (%) | 13.2 | 13.9 |
IOV\text{MTT} (%) | 44.9 | 12.3 |

Residual variability

Additive error (\mu g/ml) | 0.341 | 5.1 |
Proportional error (%) | 7.35 | 12.5 |
Predose additive error (\mu g/ml) | 0.0418 | 40.7 |

**FIG 1** Visual predictive check (VPC) of the final gatifloxacin pharmacokinetic model stratified by occasion, i.e., first dose (a) and steady state (day 28) (b). The solid line and the two dashed lines are the median and 5th and 95th percentiles, respectively, of the observed gatifloxacin concentrations in plasma. Shaded areas are the 90% prediction intervals for the median and 5th and 95th percentiles of simulated data. The open circles are observed concentrations.

**FIG 2** Box plot of gatifloxacin area under the concentration-time curve from 0 h to infinity (AUC_{0–\infty}) at first dose and at steady state (day 28) based on 10,000 virtual patients and Monte Carlo simulations of 400 mg gatifloxacin daily together with rifampin, isoniazid, and pyrazinamide. In this population, the median gatifloxacin AUC_{0–\infty} of 41.2 \mu g · h/ml (5th and 95th percentiles, 17.9 and 93.8) after the first dose was reduced on an individual level by 14.3% (5th and 95th percentiles, −90.4 and 61.5) to 35.4 \mu g · h/ml (5th and 95th percentiles, 15.2 and 80.4) at steady state (day 28).

The CFR, i.e., the proportion of the population achieving an fAUC/MIC of 125 for daily 400-mg doses of gatifloxacin in combination with rifampin, isoniazid, and pyrazinamide, was calculated to be 61.4%. The respective CFRs for 600- and 800-mg doses of gatifloxacin were 79.3% and 88%.

The PK/PD breakpoint, defined as the MIC at which the calculated PTA was 90%, was 0.125 g/ml for daily gatifloxacin doses.

**a** IIV, interindividual variability expressed as coefficient of variation; IOV, interoccasion variability expressed as coefficient of variation; RSE, relative standard error reported on the approximate standard deviation scale; (CL/F\text{GFR})_{\text{STD}}, the oral clearance in a typical patient with a median CLCR of 94 ml/min, representing drug cleared via glomerular filtration (GFR); (CL/F\text{Other})_{\text{STD}}, the oral clearance not due to GFR in a typical 70-kg male patient and with a fat-free mass (FFM) of 55 kg; (V/F)_{\text{STD}}, typical apparent volume of distribution scaled to FFM and reported for a 70-kg male patient; F, bioavailability; MTT, mean transit time; N, number of transit compartments; AGE-\%k_{\text{e}}, % increase in k_{\text{e}} for every year change from the median AGE of 29 years; SEX-\%k_{\text{e}}, % decrease in k_{\text{e}} for female patients relative to male patients; HIV-\%k_{\text{e}} (%), % increase in k_{\text{e}} for patients with HIV relative to patients without HIV; predose additive error (\mu g/ml), additive error estimated uniquely for the predose concentrations following an unobserved dose; 1 FIX, fixed to 1 (not estimated).
of 400 mg and 0.25 \( \mu \text{g/ml} \) for 800-mg doses of gatifloxacin (dashed line in Fig. 3). The \( f_{\text{AUC}}/\text{MIC} \) as a function of the MIC is shown for 400-, 600-, and 800-mg doses in Fig. 4.

**DISCUSSION**

In our study, gatifloxacin exposure (bioavailability) was reduced following multiple doses when given together with rifampin, isoniazid, and pyrazinamide. This is in contrast to a single-dose study in healthy volunteers in which increased gatifloxacin exposure (\( AUC_{0-\infty} \)) was observed (8). Hence, any initial increase in gatifloxacin concentrations attributable to concomitant use of rifampin, isoniazid, and pyrazinamide was counteracted by a reduction in gatifloxacin concentrations with repeated doses of the four drugs in combination. Exposure-related toxicity is thus unlikely to increase with repeated doses of gatifloxacin when it is given with rifampin, isoniazid, and pyrazinamide.

Two interesting observations emerge when comparing exposure after single-agent and combination treatment. First, the steady-state gatifloxacin AUC achieved in our study was slightly lower than the steady-state AUC reported in studies where patients were given the drug alone (6, 38). Second, gatifloxacin pharmacokinetic parameters (including bioavailability) were reported not to change following multiple doses when the drug was given on its own (1, 39). Gatifloxacin is a known substrate of the transmembrane efflux transporter protein P-glycoprotein (Pgp) (40), and rifampin induces the expression of Pgp (41). Hence, repeated doses of rifampin may result in reduced gatifloxacin systemic bioavailability due to increased efflux by Pgp expressed on enterocytes and hepatocytes. Gatifloxacin is principally (>80%) cleared unchanged via the kidneys (1). The overall reduction in gatifloxacin concentrations, following multiple doses in combination with

**FIG 3** The probability of target attainment (PTA) versus Mycobacterium tuberculosis (MTB) MIC following daily administration of 400 mg (dashed line), 600 mg (solid line), and 800 mg (long dash-dot-dot line) gatifloxacin together with rifampin, isoniazid, and pyrazinamide based on 10,000 virtual patients and Monte Carlo simulations. The PTA was defined as the probability of achieving the target PK/PD index ratio of the area under the unbound concentration versus time curve from 0 h to infinity at steady state (\( f_{\text{AUC}} \)) divided by MIC (\( f_{\text{AUC}}/\text{MIC} \)) of \( \geq 125 \) (a correlate of maximal bactericidal effect and reduced probability of resistance (10, 40). The dashed horizontal line indicates the reference line of 90% PTA. The solid drop lines with crosses (\( x \)) represent the frequency distribution for MIC of gatifloxacin (y axis on the right) obtained from 243 clinical isolates of M. tuberculosis (37).

**FIG 4** Median (solid thick line) total probability function, irrespective of the target, as a function of the Mycobacterium tuberculosis (MTB) MIC, with the 80th (solid line) and 90th (dashed lines) percentiles following daily administration of 400 (a), 600 (b), and 800 (c) mg of gatifloxacin together with rifampin, isoniazid, and pyrazinamide. The lower boundary in the 80th percentile of the total probability function is equivalent to 90% PTA. The dashed horizontal line indicates the reference line (\( f_{\text{AUC}}/\text{MIC} = 125 \)).
rifampin, isoniazid, and pyrazinamide, is thus likely to be the net result of drug-drug interactions observed both following single doses and at steady state.

Reduced gatifloxacin clearance and recovery in urine were reported following concomitant dosing with probenecid, suggesting that tubular secretion may contribute to its elimination (1). In our study, gatifloxacin clearance increased with creatinine clearance (CL_{CR}) and patient weight (FFM). Scaling drug clearance to both FFM and CL_{CR} allowed us to estimate that approximately 53% of the dose was cleared via glomerular filtration. Using CL_{CR} as our proxy for renal filtration might, however, overestimate the contribution of this pathway to drug clearance, since creatinine is actively secreted by the peritubular capillaries of the kidney (42). The remaining 47% of gatifloxacin’s clearance was scaled to FFM and accounted for drug cleared via all pathways other than glomerular filtration.

Gatifloxacin bioavailability was predicted to be approximately 12% lower at steady state than after an initial dose. This, combined with increased patient weight (FFM) and CL_{CR} (ml · min⁻¹) at the second occasion, resulted in a 14.3% reduction of AUC₀–₂₄. The reduction in gatifloxacin exposure following multiple doses is unlikely to be clinically significant, as on an individual level gatifloxacin AUC₀–₂₄ could increase by as much as 90% or decrease by as much as 62% between the two occasions due to the high IOV in CL/F. Age, sex, and HIV infection status were also identified as having significant covariate effects on the absorption rate constant. However, these covariates are also unlikely to be clinically relevant, as changes of the absorption rate do not alter the average steady-state concentration.

Based on 10,000 Monte Carlo simulations using the final model, 62, 79, and 88% of our study population were predicted to achieve the target fAUC/MIC ratio of ≥125 following daily 400-, 600-, and 800-mg respective doses of gatifloxacin. Only when the MIC of gatifloxacin fell below 0.125 µg/ml could 90% of the study population, irrespective of dose, achieve the target ratio. The simulations showed that at 800-mg daily doses of gatifloxacin, approximately 90% of the population would achieve the target ratio when the MIC was ≤0.25 µg/ml. These results suggest that the current 400-mg daily dosing of gatifloxacin does not achieve optimal drug exposure with respect to the MIC distribution used. However, using the target plasma fAUC/MIC ratio of ≥125 to predict the optimal dose of gatifloxacin in this context is a simplification and has its limitations. Forrest et al. (13) demonstrated that bacteriological and clinical outcomes correlated best with the pharmacodynamic index of an AUC/MIC of ≥125 in 74 acutely ill patients treated with ciprofloxacin for lower respiratory tract infections. In that study, an AUC/MIC ratio of ≥125 was significantly correlated with a faster bacterial eradication rate, which may decrease the likelihood of antibacterial resistance. Setting the target to a lower value (i.e., targets of AUC/MIC ratios of <125) could potentially create needless selective pressure, increasing the chance of resistance especially with a long duration of therapy (e.g., 4 months). Notably, in a review by Schentag et al. (14), the pharmacodynamic index target AUC/MIC ratio of ≥125 is recommended for both Gram-positive and Gram-negative organisms. Although fAUC/MIC is widely accepted as a correlate of fluoroquinolone efficacy (43), more work is required to determine whether an AUC/MIC of ≥125 truly correlates with in vivo efficacy against M. tuberculosis. In this work, we also present the total probability function for different gatifloxacin doses, which is not dependent on the target (Fig. 4). The lower boundary in the 80th percentile of the total probability function is equivalent to 90% PTA. The 90% PTA for any new future target can be visualized from this plot. Interestingly, a plasma AUC/MIC ratio of 112 to 220 was associated with optimal survival among patients with tuberculosis meningitis who were treated with a regimen containing gatifloxacin, levofloxacin, or ciprofloxacin in addition to standard antituberculosis treatment (44). Although this ratio is in keeping with the target AUC/MIC of ≥125, the optimal values for the plasma AUC/MIC ratios for pulmonary tuberculosis and tuberculous meningitis are likely to differ due to differences in tissue penetration and immunity at the site of action. Drug action occurs within pulmonary compartments, including epithelial cells and macrophages, where drug concentrations exceed those found in plasma (45). Assuming higher fAUC in pulmonary compartments, more patients could achieve the target fAUC/MIC ratio of ≥125. On the other hand, there are concerns that administering higher doses of gatifloxacin would increase the risk of toxicity such as dysglycemia. Lastly, the optimal dose of gatifloxacin would need to take into account the efficacy and safety profiles of the drug in the context of the contributions from companion drugs in the multidrug regimen and patient immunity.

Further limitations of our study include failure to measure free gatifloxacin concentrations and lack of study-specific information about the MICs. We assumed a 20% plasma protein binding for gatifloxacin that is independent of concentration (1), and we used the MIC distribution obtained from 234 clinical isolates of M. tuberculosis from Spain (3). The M. tuberculosis population reported in the Spanish study was slightly more sensitive to gatifloxacin than to moxifloxacin and levofloxacin, with reported MIC₉₀ of 0.25 and 0.5 µg/ml, respectively. In agreement with the Spanish study, a similar gatifloxacin MIC₉₀ of 0.25 µg/ml was reported against clinical isolates of M. tuberculosis obtained from numerous sources with broad geographical distribution (46). Additionally, the aforementioned study reported an MIC₉₀ and distribution range of MIC for M. tuberculosis similar to that reported in the Spanish study. Thus, our assumption that the frequency distribution of gatifloxacin MIC reported in the Spanish study correlates to the MIC distribution found within our study population appears to be valid. Nonetheless, as demonstrated by Peloquin et al. (38), a change in the MIC distribution (i.e., published versus actual MICs determined from clinical isolates obtained from study patients) can radically change the fAUC/MIC ratio. Since our study did not measure the MICs of M. tuberculosis in the study population, it is feasible that the true effective MIC could be lower. Moreover, the MICs reflect the activity of gatifloxacin alone; we did not account for synergism or antagonism within the regimen. The relevance of these findings needs to be evaluated alongside the eventual clinical outcomes of the study overall.

Conclusion. Although increased gatifloxacin exposure was observed in a previous single-dose study, gatifloxacin exposure, expressed as AUC₀–₂₄, declined following multiple doses of the 4 drugs in the multidrug regimen. Hence, exposure-related toxicity is unlikely to increase with repeated doses of gatifloxacin when given concomitantly with rifampin, isoniazid, and pyrazinamide. Based on predictions of fAUC/MIC and the derived proportion of the population achieving optimal bactericidal effect and reduced
probability of resistance (CFR), the CFR of the clinically used dose of 400 mg daily was 61%; simulations showed that doubling the dose would result in increasing the CFR to 88%. However, the pharmacokinetics of gatifloxacin needs to be studied in relation to efficacy and safety in pulmonary tuberculosis patients on the multi-drug regimen in order to evaluate the optimal gatifloxacin exposures in this context.

ACKNOWLEDGMENTS

The study was supported by grant ICA4-CT 2002-10057 from the World Health Organization (WHO)/Special Programme for Research and Training in Tropical Diseases (TDR) and the Research Institute for Development (IRD).

We acknowledge the contributions of the clinical sites and patients, without which this study would not have been possible.

P.I.O. and C.L. are staff members of the WHO.

We are responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy, or views of the WHO.

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