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Comparative Efficacy of Rifapentine Alone and in Combination with Isoniazid for Latent Tuberculosis Infection: a Translational Pharmacokinetic-Pharmacodynamic Modeling Study

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ABSTRACT Rifapentine has facilitated treatment shortening for latent tuberculosis infection (LTBI) in combination with isoniazid once weekly for 3 months (3HP) or daily for 1 month (1HP). Our objective was to determine the optimal rifapentine dose for a 6-week monotherapy regimen (6wP) and predict clinical efficacy. Rifapentine and isoniazid pharmacokinetics were simulated in mice and humans. Mouse lung CFU data were used to characterize exposure-response relationships of 1HP, 3HP, and 6wP and translated to predict clinical efficacy. A 600-mg daily dose for 6wP delivered greater cumulative rifapentine exposure than 1HP or 3HP. The maximum regimen effect (E_{max}) was 0.24 day^{-1}. The regimen potencies, measured as the concentration at 50% of E_{max} (EC_{50}), were estimated to be 2.12 mg/liter for 3HP, 3.72 mg/liter for 1HP, and 4.71 mg/liter for 6wP, suggesting that isoniazid contributes little to 1HP efficacy. Clinical translation predicted that 6wP reduces bacterial loads at a higher rate than 3HP and to a greater extent than 3HP and 1HP. 6wP (600 mg daily) is predicted to result in equal or better efficacy than 1HP and 3HP for LTBI treatment without the potential added toxicity of isoniazid. Results from ongoing and future clinical studies will be required to support these findings.

KEYWORDS latent TB, translational pharmacology, rifapentine, pharmacokinetics-pharmacodynamics, latent infection, population pharmacokinetics, tuberculosis

Treatment of latent tuberculosis (TB) infection (LTBI) has been facilitated by short-course regimens that range in duration from 1 to 4 months (1, 2). These short-course regimens have significantly shortened the length of treatment compared to the historical standard of 6 to 12 months of isoniazid monotherapy, which in turn has led to improved treatment completion rates (3). All current short-course regimens include a rifamycin (e.g., rifampin or rifapentine) either as monotherapy or in combination with isoniazid. Rifapentine is a newer rifamycin that has a longer elimination half-life than rifampin (15 h versus 4 h) (4), making it an ideal candidate for a shortened treatment duration and/or less frequent dosing. Rifampin given daily for 4 months and rifapentine in combination with isoniazid once weekly for 3 months (3HP) or daily for 1 month (1HP) have demonstrated noninferior effectiveness compared to 9 months of daily isoniazid (9H) in preventing active TB disease (2, 5, 6).

The use of isoniazid is associated with significant dose-limiting toxicities, namely, hepatotoxicity, which can be fatal (7, 8). Intermittent dosing of rifapentine and isoniazid, as in 3HP, has shown significantly less hepatotoxicity than 9H (9), but when rifapentine

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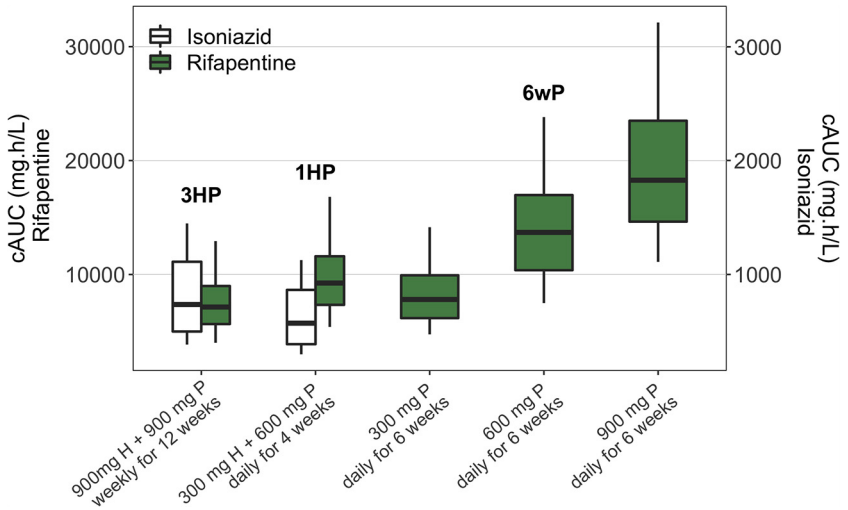

FIG 1 Predicted rifapentine exposure in experimental 6-week rifapentine monotherapy regimens at various dose levels compared to 3 months of weekly isoniazid plus rifapentine (3HP) and 1 month of daily isoniazid plus rifapentine (1HP). Data are based on 500 simulations. HIV-seronegative status was assumed for all regimens. cAUC, cumulative area under the curve for the complete regimen; H, isoniazid; P, rifapentine; 6wP, selected 6-week monotherapy regimen.

and isoniazid were given daily, the adverse effects were similar (2). Isoniazid may also contribute to hypersensitivity reactions reported with 3HP use (10, 11). Eliminating isoniazid from LTBI treatment altogether could prove beneficial from a safety perspective and would reduce pill burdens.

A novel regimen of daily rifapentine for 6 weeks is under investigation (ClinicalTrials.gov identifier NCT03474029). The optimal dose of rifapentine in the absence of isoniazid to prevent active TB disease is not well understood. In a murine model of LTBI, rifapentine monotherapy at 10 mg/kg of body weight daily (equivalent to 600 mg per day in humans) was similar to or better than rifapentine plus isoniazid in reducing lung CFU and relapse rates when given for the same duration (12, 13).

However, differences in rifapentine pharmacokinetics (PK) between mice and humans must be considered. In humans, rifapentine exhibits concentration-dependent autoinduction of clearance, resulting in lower concentrations over time with daily dosing (14). Rifapentine autoinduction may also occur in mice, as it does for rifampin, but the relationships to drug concentration and dosing frequency have not been well characterized (15, 16). Additionally, rifapentine bioavailability is affected by HIV infection, dose, and fasting/meal conditions, and interpatient variability is high in humans (17, 18). To determine the optimal dose for rifapentine monotherapy to treat LTBI, both the pharmacokinetic and pharmacodynamic (PD) relationships need to be characterized.

The aims of this study were to characterize the PK and PD of rifapentine and to build a translational model that accounts for species-specific PK parameters, plasma protein binding, and host adaptive immunity in the context of LTBI to predict the efficacy of a 6-week rifapentine monotherapy regimen in humans. To that end, we implemented a mechanistic model of murine immune responses to *Mycobacterium tuberculosis* infection and used drug efficacy data and population PK models in mice and humans to compare drug exposures and clinical effectivenesses of different rifapentine-containing regimens for the treatment of LTBI.

RESULTS

Clinical PK of rifapentine-based regimens. To determine the effective rifapentine dose for a 6-week daily monotherapy regimen (6wP), rifapentine exposures at various dose levels were compared to those of clinically tested regimens (i.e., 1HP and 3HP). After 300 mg daily for 6 weeks, the predicted total rifapentine cumulative area under the plasma concentration-time curve (cAUC) was similar to that following 900 mg once weekly for 3 months (i.e., 3HP) and 600 mg daily for 1 month (i.e., 1HP) (Fig. 1). With 600 mg rifapentine daily for

TABLE 1 PK/PD indices for rifapentine-containing LTBI regimens[a]

Parameter	Value for regimen		
	3HP	1HP	6wP
Rifapentine			
Dose			
Human	900 mg wkly	600 mg daily	600 mg daily
Mouse	15 mg/kg wkly	10 mg/kg daily	10 mg/kg daily
Median cAUC (mg · h/liter) (2.5th–97.5th quantile range)			
Human	7,143 (3,610–14,281)	9,248 (4,838–19,697)	13,462 (7,113–27,736)
Mouse	10,130 (8,783–11,955)	7,100 (5,640–8,927)	10,677 (8,485–13,470)
Median AUC/MIC ratio (2.5th–97.5th quantile range)			
Human	1,405 (713–2,796)	4,972 (2,640–10,686)	5,010 (2,685–10,365)
Mouse	2,011 (1,743–2,374)	4,292 (3,384–5,449)	4,280 (3,385–5,434)
Median C_{max}/MIC ratio (2.5th–97.5th quantile range)			
Human	318 (156–646)	390 (206–730)	388 (208–718)
Mouse	333 (327–341)	311 (268–365)	313 (269–364)
Median % of treatment duration above MIC (2.5th–97.5th quantile range)			
Human	99 (57–100)	100 (100–100)	100 (100–100)
Mouse	93 (86–98)	100 (100–100)	100 (100–100)
Isoniazid			
Dose			
Human	900 mg wkly	300 mg daily	NA
Mouse	50 mg/kg wkly	10 mg/kg daily	NA
Median cAUC (mg · h/liter) (2.5th–97.5th quantile range)			
Human	745 (343–1,608)	579 (267–1,250)	NA
Mouse	667 (489–879)	156 (118–207)	NA

[a]Values represent total drug (free and bound) and are based on 500 simulations. Data are expressed as medians (2.5th to 97.5th quantile ranges). The MIC was 0.06 mg/liter. cAUC, cumulative AUC; AUC/MIC ratio, ratio of the average daily AUC to the MIC at steady state; C_{max}/MIC ratio, ratio of the maximum concentration to the MIC at steady state; NA, not applicable; 3HP, 3 months weekly of rifapentine and isoniazid; 1HP, 1 month daily of rifapentine and isoniazid; 6wP, 6 weeks daily of rifapentine.

6 weeks, the rifapentine cAUC was predicted to be nearly double that of 3HP and approximately 1.5 times that of 1HP. A 900-mg daily dose delivered even higher rifapentine exposures.

Given the favorable PK, the 600-mg dose for the daily 6-week regimen (i.e., 6wP) was chosen. The average daily total AUC/MIC and maximum concentration of drug (C_{max})/MIC ratios were comparable for 6wP and 1HP, which were higher than those for 3HP (Table 1). The percentage of the treatment duration with concentrations above the MIC was 100% for 1HP and 6wP (Table 1).

Isoniazid exposure over the full treatment course was slightly higher with 3HP than with 1HP (Fig. 1 and Table 1). The 6-week rifapentine monotherapy regimens tested did not include isoniazid.

Comparison of mouse and human PK. Rifapentine PK simulations in mice and humans are shown in Fig. 2. A rifapentine dose in mice of 10 mg/kg 5 days a week delivers concentration profiles similar to those of 600 mg once daily in humans, and 15 mg/kg rifapentine once weekly (1/7) in mice has PK similar to those of 900 mg once weekly in humans (Fig. 2). Clinical and murine PK/PD indices were similar (Table 1).

PK/PD model. The bacterial growth rates for the baseline model describing the primary immune response in the latent infection mouse model were estimated to be −0.048 and 0.0151 day^{-1} for the high-dose and low-dose studies, respectively. In the PK/PD model, the net maximal rifapentine drug effect (E_{max}) was estimated to be 0.24 day^{-1} for monotherapy (Table 2). The rifapentine concentration required to achieve half of the maximal effect (EC_{50}) was estimated to be 4.71 mg/liter for monotherapy (Table 2). For combination LTBI regimens (1HP and 3HP), the E_{max} and EC_{50} of rifapentine were assumed to be the same. Isoniazid increased the potency of these regimens by decreasing the apparent EC_{50} by 21% in the 1HP regimen (apparent EC_{50} of 3.72 mg/liter) and 55% in the 3HP regimen (apparent EC_{50} of 2.12 mg/liter) (Fig. 3 and Table 2).

Visual predictive checks (VPCs) of 500 simulations indicated that the observed data were within the 95% prediction intervals of the simulated CFU counts in the final PK/PD models (see Fig. S2 in the supplemental material).

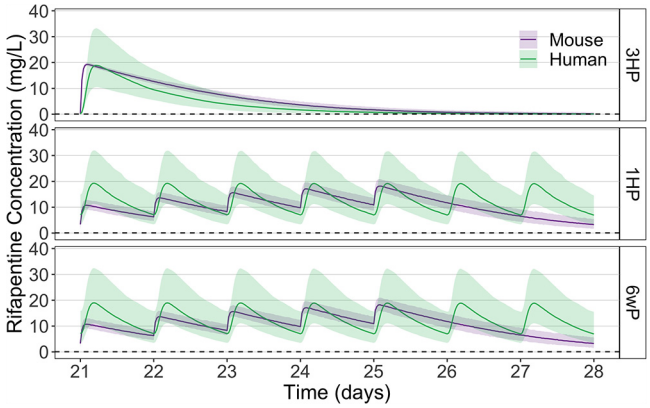

FIG 2 Steady-state rifapentine pharmacokinetics in mice and humans. Medians (solid lines) and 95% prediction intervals (shaded areas) are based on 500 simulations. 3HP, 3 months of once-weekly rifapentine and isoniazid; 1HP, 1 month of daily rifapentine and isoniazid; 6wP, 6 weeks of daily rifapentine (600 mg for human and 10 mg/kg for mouse) monotherapy.

Clinical efficacy predictions. Simulated CFU profiles in humans showed median CFU reductions of up to 1.5 $\log_{10}$ CFU with 1HP and 2 $\log_{10}$ CFU with 6wP and 3HP regimens at the end of treatment (Fig. 4). 1HP had the highest rate of decline in CFU but the highest remaining bacterial burden at the end of therapy. 6wP achieved greater or equal reductions in the bacterial load from baseline compared to 3HP but at a much higher rate and shorter treatment duration. The predicted absolute CFU after treatment depended on the baseline bacterial load, the assumption of the balance between immune killing and bacterial growth, and the interspecies ratio of the fraction unbound (Fig. S3 and S4). A lower baseline CFU, an immune kill rate higher than the bacterial growth rate, and an equal interspecies ratio of the fraction unbound each resulted in a lower bacterial burden at the end of treatment. The comparative efficacy remained consistent between regimens regardless of the assumption. The *in silico* clinical trial predicted that 12.8% of patients would develop active TB (>4 $\log_{10}$ CFU) with placebo compared to 1.2% or lower with a rifapentine-based treatment regimen after 2 years (Fig. 5). Notably, the predicted clinical efficacies were similar between rifapentine-based regimens in the *in silico* clinical trial.

DISCUSSION

In this study, we predicted that a 600-mg daily dose of rifapentine monotherapy for 6 weeks delivered sufficient drug exposure for effective treatment of LTBI based on PK simulations of experimental and clinically approved regimens. The cumulative rifapentine drug exposure was greater with 600 mg 6wP than with the clinically tested regimens of 1HP and 3HP. The translational PK/PD predictions showed that 6wP had an efficacy similar to those of 1HP and 3HP, suggesting that clinical efficacy will be similar to that of either combination regimen.

Currently, there is no established PK/PD relationship or target for rifapentine in the treatment of LTBI. Rifamycins are believed to exhibit concentration-dependent killing, and the AUC/MIC ratio has been linked to efficacy against TB disease (19, 20). Our PK

TABLE 2 Pharmacological parameters of rifapentine-containing regimens in the latent TB mouse study[a]

Parameter	Description	Value (RSE [%])
K_{netHD} (day^{-1})	Net rate of bacterial growth without drug for high-dose study	−0.048 (0)
K_{netLD} (day^{-1})	Net rate of bacterial growth without drug for low-dose study	0.0151 (0)
E_{max} (day^{-1})	Max efficacy of rifapentine monotherapy regimen	0.24 (20)
γ	Steepness of sigmoidal concn-response relationship	1.62 (16)
EC_{50_6wP} (mg/liter)	Rifapentine concn at 50% of E_{max} in daily rifapentine monotherapy regimen	4.71 (36)
EC_{50_1HP} (mg/liter)	Rifapentine concn at 50% of E_{max} in daily rifapentine and isoniazid regimen	3.72 (59)
EC_{50_3HP} (mg/liter)	Rifapentine concn at 50% of E_{max} in weekly rifapentine and isoniazid regimen	2.12 (54)

[a]RSE, relative standard error.

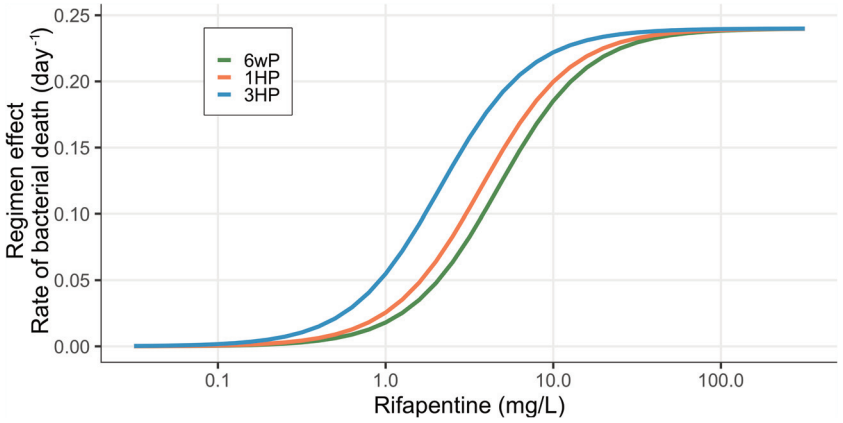

FIG 3 Concentration-response relationship of rifapentine-containing regimens. 3HP, rifapentine plus isoniazid given once weekly for 3 months; 1HP, rifapentine plus isoniazid given daily for 1 month; P, rifapentine monotherapy given daily.

simulations demonstrated that 6wP had an AUC/MIC ratio equivalent to that of 1HP and a higher AUC/MIC ratio than that of 3HP. This trend was consistent across other PK/PD indices (e.g., C_{max}/MIC ratio and time above the MIC).

The role of isoniazid in the efficacy of rifamycin-containing LTBI treatment regimens is not well understood. Given the toxicity concerns with isoniazid, rifapentine monotherapy would be appealing if it were sufficiently effective. The PK/PD relationships in this study showed that adding isoniazid only slightly increased the potency of a daily rifapentine regimen (i.e., 21% lower EC_{50} with 1HP than with 6wP) and comes with the cost of a cumulative isoniazid exposure of 156 mg · h/liter over 4 weeks. Our predictions of bacterial burdens showed similar bacterial burdens at 4 weeks with 1HP and 6wP and similar bacterial burdens at the end of treatment with 3HP and 6wP, which were lower than those with 1HP. Furthermore, the *in silico* clinical trial showed no difference in the probability of active TB between regimens. This suggests that the clinical efficacy of 6wP would likely be similar to those of 1HP and 3HP and promotes the elimination of isoniazid from ultrashort-course LTBI regimens.

The PK/PD relationship in the paucibacillary mouse model of LTBI was established with a few assumptions. The mouse PD data from which the PK/PD model was built are based on investigated regimens that mimicked rifapentine monotherapy and in combination with isoniazid, but dose ranging was available for rifapentine monotherapy only. As such, a continuous concentration-response relationship could be estimated for rifapentine monotherapy only. The maximum effect (E_{max}) of combination regimens was assumed to be equal to that

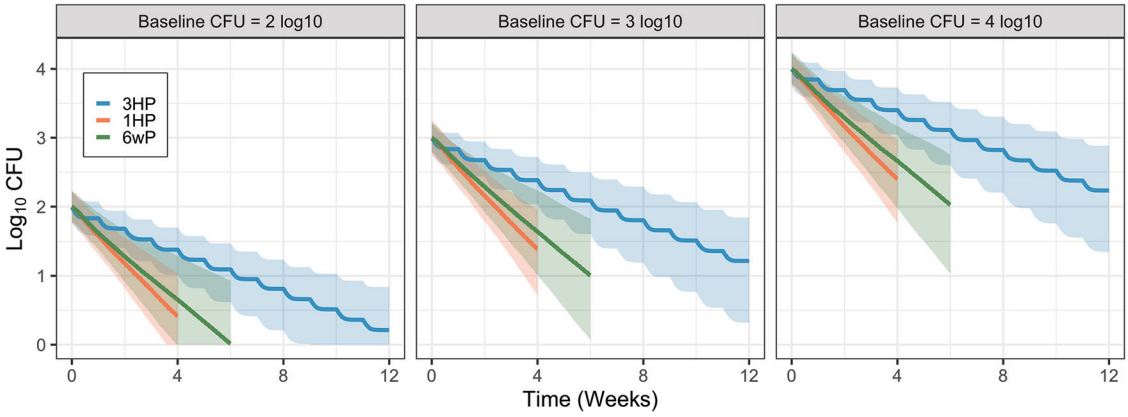

FIG 4 Predicted bacterial load over time in humans following LTBI treatment with rifapentine-containing regimens. Panels represent different baseline bacterial loads of 2, 3, and 4 $\log_{10}$ CFU (left to right). Data show medians (lines) and 90% prediction intervals (shaded areas) based on 500 simulations for each regimen.

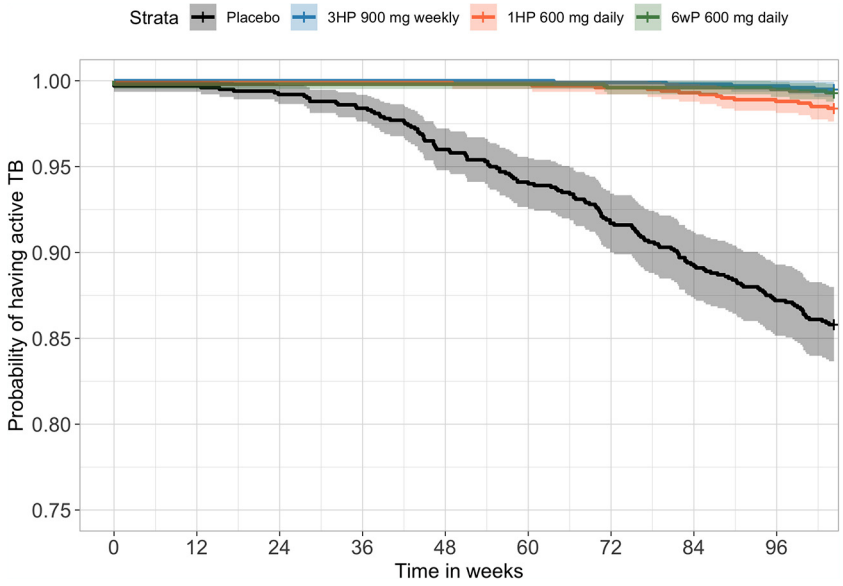

FIG 5 Kaplan-Meier plot of *in silico* patients treated with rifapentine-based regimens or placebo for LTBI. Clinical trial simulations included 1,000 patients per arm with baseline bacterial loads of 2.5 ± 0.5 log CFU. *In silico* patients were monitored for 2 years. Active TB was defined as >4 $\log_{10}$ CFU.

estimated for rifapentine monotherapy from the dose-ranging data, and only the EC_{50} (potency) differed by regimen. This assumption is reasonable as rifamycins are thought to drive bacterial killing. Another assumption was that the net bacterial growth rate (K_{net}) (in the absence of drug killing) was the same in untreated and treated mice. Despite these assumptions, the VPC demonstrated good predictability of our mouse PD model.

The absolute bacterial burden at the end of treatment was dependent on the baseline bacterial load and the human immune effect assumption. Postmortem examinations of apparently healed tuberculous lesions and adjacent areas have found viable bacteria in smear-negative lesions, suggesting that the bacterial burden in latent tuberculous lesions is <4 $\log_{10}$ CFU/ml (21, 22), the lower limit of sensitivity of acid-fast smears for the detection of *M. tuberculosis*. As such, the median baseline bacterial load for clinical efficacy predictions was assumed to be 2, 3, or 4 $\log_{10}$ CFU with active infection defined as >4 $\log_{10}$ CFU. While complete eradication of bacteria was achieved only with a baseline bacterial load of 2 $\log_{10}$ CFU, all regimens showed <1.2% active TB patients at the end of a 2-year trial period, consistent with data from LTBI clinical trials. The true range and distribution of baseline bacterial loads in individuals with LTBI are unknown. It is also unknown what end-of-treatment bacterial load is sufficient for clinical success of LTBI treatment, typically defined as the lack of confirmed active TB after a 2- to 5-year follow-up period. LTBI is diagnosed by the immune response to *M. tuberculosis* antigen, and *M. tuberculosis* bacteria are undetectable in clinical samples; otherwise, the individual is considered to have active disease (1). Furthermore, we assumed that immune killing of bacteria was in equilibrium with bacterial growth. While this is an accepted phenomenon, it is likely an oversimplification of reality. There is increasing recognition that tuberculosis is more heterogeneous than a two-state condition (i.e., active or latent) and likely exists on a spectrum from complete immune dominance (successful bacterium elimination but retained immune memory) to bacterial dominance (resulting in active disease) (23–26). Assuming modest immune dominance over bacterial growth ($K_{net} = -0.01$ day^{-1}) and a baseline bacterial load of <4 log CFU, all regimens were predicted to have 90% of individuals with <1 $\log_{10}$ CFU 1 year after the start of treatment. As such, given the unknowns with LTBI, our clinical efficacy simulations are not contradictory to the phase 3 clinical trial results for 1HP and 3HP. Importantly, our predictions showed that 6wP efficacy is within the efficacy ranges of 1HP and 3HP, implying that 6wP would perform equally well.

There were limitations of this study. First, there is a lack of good clinical PK or PK/PD targets for LTBI regimens linking rifapentine exposure to efficacy. We compared drug exposures and

translational efficacies of the 600-mg 6wP experimental regimen with regimens that have demonstrated clinical efficacy (i.e., 1HP and 3HP). Second, assumptions were made with the translational PK/PD model. In addition to those mentioned above is that rifapentine protein binding in mice was assumed to be equal to that in Wistar rats (another murine species). While this assumption would impact the extent of bacterial killing, the relative efficacy of the three regimens would remain consistent. The same is true for the other PK/PD assumptions and initial conditions. Both the nonclinical experiments and clinical simulation predictions support that 6wP will have noninferior efficacy to both 1HP and 3HP.

With the above-noted limitations, the following conclusions can be drawn. First, comparisons of rifapentine clinical PK profiles indicate that 6wP would achieve exposure comparable or superior to those of previously studied regimens of 1HP and 3HP. Second, by quantifying the relationship between the rifapentine concentration and bacterial kill in mice, we found that the relative efficacy of an experimental 6wP regimen at a 600-mg dose level is similar to those of 1HP and 3HP. Finally, we conclude that isoniazid's contribution to efficacy is minimal in ultrashort-course regimens where rifapentine is administered daily. The comparisons of PK profiles, data from nonclinical analyses, and subsequent clinical simulations performed in this study indicate that 6wP is a promising regimen for LTBI and could serve as a safer, simpler solution for TB prevention.

MATERIALS AND METHODS

Clinical PK simulations. Rifapentine clinical PK were simulated using a population PK model reported previously by Hibma et al. generated from an individual participant data meta-analysis of 9 clinical PK studies (27). The model captures dose, HIV status, and meal effects on rifapentine bioavailability and autoinduction of clearance as a function of the rifapentine concentration. Simulations were performed to compare the rifapentine PK of clinically tested rifapentine-based LTBI regimens with the PK of an experimental 6-week once-daily rifapentine monotherapy regimen (6wP) at various dose levels. For comparator regimens, we evaluated 1HP (300 mg isoniazid plus 600 mg rifapentine daily for 1 month) and 3HP (900 mg isoniazid plus 900 mg rifapentine once weekly for 3 months). For isoniazid-containing regimens (i.e., 1HP and 3HP), isoniazid clinical PK were also simulated with a population PK model (28). Simulations (n = 500) were performed for an HIV-seronegative population receiving a low-fat meal (relative rifapentine bioavailability = 1) and with a 50/50 slow/fast acetylator status for isoniazid. PK profiles were summarized as maximum concentration (C_{max}), area under the plasma concentration-time curve (AUC), and time above the MIC. The rifapentine MIC was set to 0.06 mg/liter (4).

Mouse PK simulations. Mouse PK models were built in NONMEM 7.4 for rifapentine and isoniazid. Modeling details and results are provided in the supplemental material. Rifapentine PK were simulated 500 times under different dosing conditions that matched clinical rifapentine regimens: 10 mg/kg once daily for 6 weeks (6wP regimen), 10 mg/kg once daily for 4 weeks (1HP regimen), and 15 mg/kg once weekly for 12 weeks (3HP regimen). Similarly, isoniazid PK were simulated 500 times with 10 mg/kg once daily for 4 weeks (1HP regimen) and 50 mg/kg once weekly for 12 weeks (3HP regimen). For daily regimens, mouse PK were simulated as dosing 5 days/week in accordance with the original studies.

PD model. Mouse CFU data were acquired from two studies: "high-dose" rifapentine (13) and "low-dose" rifapentine (see the supplemental material). All animal procedures were approved by the Institutional Animal Care and Use Committee of Johns Hopkins University unless otherwise specified from the original publication. Data were used to describe the *in vivo* exposure-response relationships of different rifapentine-based regimens. The baseline immune effect was determined by estimating the net bacterial growth/death without treatment (K_{net}). A PK/PD model was developed using CFU data from treated mice by adding drug effect (*EFF*) to the baseline model (equation 1), where "*B*" is the bacterial load. *EFF* was modeled as a function of the rifapentine concentration (C_p). PK/PD relationships for the drug effect were optimized by fitting the mouse efficacy data to linear, nonlinear, log-linear, E_{max}, and sigmoidal functions (equations 2 to 4). An additive error model was used to describe the residual error for the mouse PK/PD models.

$$\frac{dB}{dt} = K_{\text{net}} \times B - EFF \times B \tag{1}$$

$$EFF = \text{slope} \times C_p + \text{intercept} \tag{2}$$

$$EFF = \text{slope} \times \ln(C_p) + \text{intercept} \tag{3}$$

$$EFF = \frac{C_p^{\gamma} \times E_{\max}}{\text{EC}_{50}^{\gamma} + C_p^{\gamma}} \tag{4}$$

Translational PK/PD. The clinical population PK model of rifapentine was linked to the PK/PD relationships established for three rifapentine-based regimens in the latent infection study. The clinical PK/

PD relationship was assumed to be the same as the estimated murine PK/PD relationship after correcting for the difference in unbound drug fractions. No murine protein binding information was available, so the unbound fraction from Wistar rats was used instead; the estimated ratio of the free fraction (human/mouse) was 0.422 (29, 30). The net bacterial growth (K_{net}) in humans was assumed to be zero, representing the balance between immune-mediated killing and any bacterial growth. Other assumptions (e.g., K_{net} of <0 and K_{net} of >0) were also tested. *EFF* was incorporated as an additional effect inhibiting bacterial growth. Simulations of the change in the bacterial load following treatment were performed 500 times with each regimen (6wP, 3HP, and 1HP), with a baseline bacterial load of 2 to 4 $\log_{10}$ CFU and a variance of 0.1 (equation 1).

***In silico* clinical trial simulations.** An *in silico* clinical trial was simulated based on our final model with 1,000 individuals per arm: placebo, 3HP, 1HP, and 6wP. The baseline bacterial load was set to 2.5 ± 0.5 $\log_{10}$ CFU. Active TB was defined as ≥ 4 $\log_{10}$ CFU as the lower limit of quantification of acid-fast smears is 10^4 CFU/ml (21). The number of individuals developing active TB was determined over a 2-year period.

Software. All modeling and simulation analyses were conducted using NONMEM (version 7.4). Perl speaks NONMEM (PsN), the R (version 3.5) statistical program, and the xpose4 and ggplot2 R packages were utilized for model diagnostics and data visualization. Survival analysis of *in silico* data was done with the survival R package. The first-order conditional estimation with interaction method was used. Mouse PK and PK/PD models were developed and selected based on graphical (goodness-of-fit plots), statistical (significant change in the objective function value), and simulation-based (visual predictive checks) diagnostics.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.8 MB.

ACKNOWLEDGMENTS

We have no conflicts of interest to disclose.

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