

Substitution of Rifapentine for Rifampin During Intensive Phase Treatment of Pulmonary Tuberculosis: Study 29 of the Tuberculosis Trials Consortium

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Background. Rifapentine administered 5 days per week has potent activity in mouse models of antituberculosis chemotherapy, but efficacy and safety data are limited in humans. We compared the antimicrobial activity and safety of rifapentine vs rifampin during the first 8 weeks of pulmonary tuberculosis treatment.

Methods. In total, 531 adults with sputum smear-positive pulmonary tuberculosis were randomized to rifapentine 10 mg/kg/dose or rifampin 10 mg/kg/dose, administered 5 days per week for 8 weeks (intensive phase), with isoniazid, pyrazinamide, and ethambutol. Coprimary outcomes were negative sputum culture on liquid and on solid media at completion of intensive phase.

Results. Negative cultures on solid media occurred in 145 of 174 participants (83.3%) in the rifampin group and 171 of 198 participants (86.4%) in the rifapentine group (difference, 3.0%; 95% confidence interval [CI]: –4.3, 10.5); negative cultures in liquid media occurred in 110 of 169 (65.1%) in the rifampin group and 133 of 196 (67.9%) in the rifapentine group (difference, 2.8%; 95% CI: –6.9, 12.4). Among 529 participants who received study therapy, 40 of 254 participants (15.7%) in the rifampin group and 40 of 275 participants (14.5%) in the rifapentine group prematurely discontinued treatment ($P = .79$).

Conclusions. The rifapentine regimen was safe but not significantly more active than a standard rifampin regimen, by the surrogate endpoint of culture status at completion of intensive phase. Assessment of higher exposures to rifapentine for tuberculosis treatment is warranted.

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A major obstacle to tuberculosis control is the long duration of treatment required—at least 6 months—for drug-susceptible pulmonary tuberculosis. Highly potent tuberculosis regimens of shorter duration would facilitate treatment completion and improve individual and public health [1]. Rifamycins are key sterilizing components of modern tuberculosis treatment [2, 3]. Rifapentine, a cyclopentyl ring-substituted rifamycin with a longer half-life than rifampin, has potent activity against *Mycobacterium tuberculosis* in vitro and in mouse models [4–13]. In humans,

rifapentine is approved by the US Food and Drug Administration for treatment of active tuberculosis, at a dose of 600 mg (approximately 10 mg/kg) administered once or twice weekly in combination with other antituberculosis drugs.

Recent work using the mouse model of antituberculosis chemotherapy has shown that regimens containing rifapentine administered more frequently—5 days/week—can achieve durable cure without relapse after only 3 months [10, 11]. However, in humans there are no data on the safety and antimicrobial activity of rifapentine administered 5 days/week as a component of combination chemotherapy for treatment of active tuberculosis, and the potential for such a rifapentine regimen to shorten overall tuberculosis treatment duration is therefore unknown. We reasoned that, for a 5 days/week rifapentine-containing regimen, demonstration of robust efficacy using a surrogate marker of durable cure in a phase 2 study would provide a strong rationale for future treatment shortening studies. The Tuberculosis Trials Consortium (TBTC) therefore conducted a randomized, multicenter, phase 2 study to determine the safety, tolerability, and antimicrobial activity of a regimen in which rifampin 10 mg/kg was replaced by rifapentine 10 mg/kg administered 5 days/week during the first 8 weeks (intensive phase) of combination treatment for pulmonary tuberculosis (ClinicalTrials.gov identifier: NCT00694629). A dosing frequency of 5 days/week instead of 7 days/week was selected to replicate the frequency used in the mouse studies and to facilitate direct observation of all doses. Antimicrobial activity was assessed through determination of sputum culture status at completion of 8 weeks of treatment – a commonly used efficacy surrogate endpoint in phase 2 tuberculosis treatment studies [14–16]. Some of the results of this phase 2 study have been reported previously in abstract form [17, 18].

MATERIALS AND METHODS

Setting, Population, and Design

Participants were enrolled at 24 TBTC sites (16 in North America, 3 in South Africa, and 1 each in Uganda, Spain, Brazil, Peru, and Vietnam). Adults (age ≥ 18 years) with suspected pulmonary tuberculosis and acid-fast bacilli (AFB) in a sputum specimen were eligible. Additional inclusion criteria were Karnofsky score ≥ 60 ; serum alanine aminotransferase (ALT) ≤ 3 times upper limit of normal (ULN), total bilirubin ≤ 2.5 times ULN, and creatinine ≤ 2 times ULN; hemoglobin ≥ 7.0 g/dL; platelets $\geq 100\,000/\text{mm}^3$; negative pregnancy test for women; ≤ 5 days of multidrug antituberculosis treatment in the preceding 6 months; and ≤ 7 days of fluoroquinolone treatment in the preceding 30 days. Individuals meeting any of the following were excluded: pregnancy or breast-feeding; weight < 40 kg; central nervous system tuberculosis; pulmonary silicosis; allergy, intolerance, or contra-indicating condition to any of the study drugs; current therapy or therapy planned in the

subsequent 8 weeks with antiretroviral medications, cyclosporine, or tacrolimus; and initial sputum cultures negative for *Mycobacterium tuberculosis* or with growth of an *Mycobacterium tuberculosis* strain resistant to rifampin, isoniazid, or pyrazinamide. All participants underwent human immunodeficiency virus (HIV) testing. This study was approved by the Centers for Disease Control and Prevention (CDC) and site institutional ethics review boards. Human subject protection guidelines of the US Department of Health and Human Services and those of authors' institutions were followed during the conduct of this research. Participants gave written informed consent.

Participants were randomly assigned to receive either rifampin (approximately 10 mg/kg) administered once daily for 5 days/week or rifapentine (approximately 10 mg/kg) administered once daily for 5 days/week, in addition to isoniazid, pyrazinamide, ethambutol, and pyridoxine for the intensive phase of tuberculosis treatment. Rifapentine and rifampin were open-label. Randomization was stratified by the presence of cavitation on baseline chest radiograph and by region of enrollment (Spain, North America, South America, Uganda, and South Africa). All treatment was given by directly observed therapy. The study protocol recommended that treatment doses be administered on an empty stomach. Dosages of isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine were in accordance with published guidelines [19]. Completion of study treatment was defined as ingestion of 40 directly observed therapy doses within 54–70 calendar days. Rifapentine and rifampin were donated by Sanofi-Aventis; other study drugs were obtained from licensed suppliers. After completing intensive-phase tuberculosis treatment, participants completed tuberculosis treatment with a CDC/ATS/IDSA guidelines-recommended continuation-phase regimen, typically isoniazid plus rifampin [19].

Information on symptoms, blood for serum ALT, bilirubin, creatinine a complete blood count, and a sputum specimen were collected at baseline and at completion of weeks 2, 4, 6, and 8 of treatment. For the primary efficacy endpoint, 2 sputum samples were collected at completion of intensive-phase (1 sputum sample on the day of completion and 1 sputum sample prior to the second dose of continuation phase treatment). Sputum samples were collected monthly during continuation-phase tuberculosis treatment unless 2 or more prior consecutive cultures were already negative. Sputum samples were tested at local site laboratories according to procedures set forth in a study manual. Sputum samples were processed using conventional N-acetyl-L-cysteine-NaOH methods; dwell time of NaOH with sputum was 15–20 minutes, final [NaOH] was 1%–2%, and the digested, decontaminated pellet was resuspended to a volume of 2–2.5 mL in pH6.8 phosphate buffer. Cultures were performed using both Lowenstein-Jensen (LJ) solid media (inoculum volume, 0.2 mL) and BACTEC mycobacterial growth indicator tube (MGIT, Becton Dickinson

and Co, Franklin Lakes, New Jersey) liquid media (inoculum volume, 0.5 mL) with the MGIT 960 system. *Mycobacterium tuberculosis* isolates underwent initial drug susceptibility testing at site laboratories; confirmatory testing was performed at the CDC using the indirect agar proportion method for isoniazid, rifampin, and ethambutol, and MGIT medium for pyrazinamide. Hepatitis was defined as transaminases ≥ 5 times upper limit of normal or ≥ 3 times upper limit of normal with symptoms, or bilirubin ≥ 3 times upper limit of normal.

Data Analysis

The trial was designed to test the primary hypothesis that at the end of the intensive phase, 50% of participants in the rifampin standard therapy arm would have negative cultures in MGIT (on the basis of results of TBTC Study 28, a prior TBTC phase 2 clinical trial) against the alternative that 65% would have negative cultures in the rifapentine arm (experimental therapy) [20]. We reasoned that an increase of 15% over the standard regimen might allow overall tuberculosis treatment shortening on the basis of prior trials showing that the addition of pyrazinamide to regimens including isoniazid and rifampin increased 2-month culture conversion by an average of 13% and allowed reduction of total treatment duration by 3 months (from 9 months to 6 months)[15]. A sample size of 183 protocol-correct subjects per arm permitted detection of a difference of 15% with a type 1 error rate of 0.05 and a type 2 error rate of 0.20. This sample size also accommodates a coprimary analysis of results on solid media.

The coprimary efficacy endpoints were *Mycobacterium tuberculosis* culture status, as measured in MGIT media and separately on LJ media, at completion of intensive-phase treatment. Culture status was considered to be negative at completion of intensive phase if neither of the 2 specimens collected at that time point grew *Mycobacterium tuberculosis*. Time to stable culture conversion was defined as the number of days from initiation of study treatment to the first of 2 consecutive culture-negative (for *Mycobacterium tuberculosis*) sputum sample collected on nonconsecutive days that were not followed by a culture-positive specimen. For efficacy analyses, a modified intention-to-treat (MITT) group included participants with *Mycobacterium tuberculosis* growth in a baseline culture, and absence of resistance to isoniazid, rifampin, or pyrazinamide. A protocol-correct (PC) efficacy analysis group was a subset of the MITT group and also required at least one evaluable culture at the end of intensive phase and completion of the assigned treatment within 54–70 days. Safety analyses included all participants who received at least 1 dose of study therapy.

For the primary analysis, proportions were compared between arms using Pearson χ^2 test with Yates continuity correction, and the confidence interval for the difference in proportions used Wilson score method [21]. Proportions of

adverse events were compared using Fisher exact test. Logistic regression was used to assess association of predictors with the primary outcome.

For univariate and multivariate analyses, every model had 3 prespecified design variables, including treatment assignment (exposure of interest), evidence of pulmonary cavities at enrollment, and geographic region; the latter 2 variables were included because they were the basis for stratifying random allocation. No other potential regressors were specified in advance. Our regression models proceeded in 2 stages. First, we evaluated candidate predictors for association with culture status at the end of intensive phase therapy using the previous literature and TBTC experience. Each of these predictors was evaluated separately for outcomes on solid media and in liquid media. Pulmonary cavity presence and extent of disease on chest radiograph confounded the treatment effect. Following these partially adjusted models, we considered several multivariate models for outcomes on solid and liquid media, selecting final models with a common set of regressors to aid interpretation. The final models included the 3 design variables, one additional potential confounder (extent of pulmonary involvement), and other predictors that were significantly associated with the outcome on either solid or liquid media in multivariate analyses. Calculations were performed in SAS (v 9.2, SAS Institute, Cary, North Carolina) and R (v 2.12, R Development Core Team, Vienna, Austria).

RESULTS

In total, 531 participants were enrolled from 8 December 2008 to 5 November 2010 (Figure 1). Among 255 participants allocated to the rifampin arm, 183 (71.8%) were protocol correct, vs 206 of 276 (74.6%) allocated to the rifapentine arm. Safety analyses included 529 participants (254 assigned to rifampin and 275 assigned to rifapentine).

Table 1 shows baseline characteristics for 389 participants in the PC group. Overall, 204 of 389 participants (52.4%) were enrolled at African sites, and 266 of 389 participants (68.4%) had cavitation on the baseline chest radiograph. By chance, the rifampin arm contained a larger proportion of females (37% vs 30%) and more persons living with HIV (13% vs 9%) than the rifapentine arm. The median number of days of tuberculosis treatment immediately preceding the first study dose was 2 days.

Efficacy

Results for the coprimary efficacy endpoints are shown in Table 2. For the PC analysis group, negative cultures at the end of intensive-phase were achieved in liquid culture for 65.1% (110/169) of participants in the rifampin group vs 67.9% (133/196) of participants in the rifapentine group (difference, 2.8%; 95% confidence interval [CI]: -6.9, 12.4;

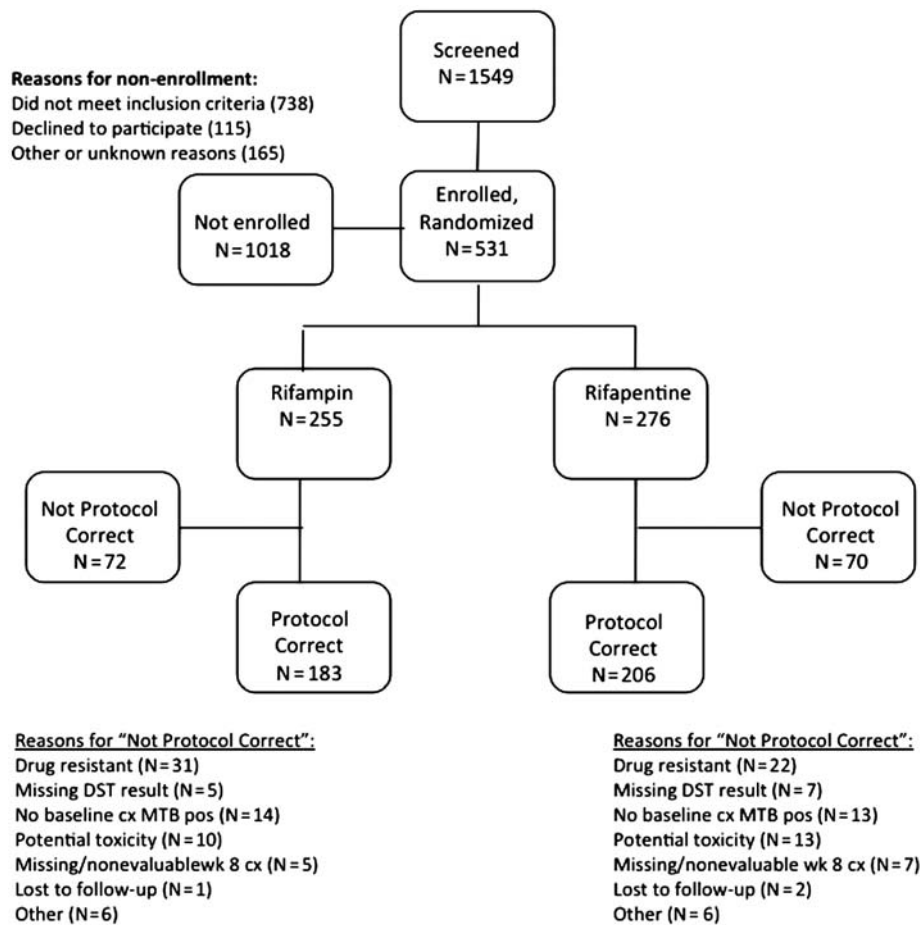


Figure 1. Enrollment and disposition of study participants.

$P = .65$); negative cultures at the end of intensive phase were achieved on solid culture for 83.3% (145/174) in the rifampin group vs 86.4% (171/198) in the rifapentine group (difference, 3.0%; 95% CI: $-4.3, 10.5$; $P = .50$). Findings were similar for the MITT analysis group.

A post hoc analysis showed that, among the subset of participants with noncavitary pulmonary tuberculosis, negative cultures in liquid media at completion of intensive phase were achieved in 39 of 56 rifampin recipients (69.6%) vs 48 of 64 rifapentine recipients (75.0%) (difference, 5.4%; 95% CI: $-10.4, 21.1$; $P = .65$), and on solid media were achieved in 48 of 56 rifampin recipients (85.7%) and 56 of 61 rifapentine recipients (91.8%) (difference, 6.1%; 95% CI: $-5.7, 18.4$; $P = .45$). Among participants with cavitary pulmonary tuberculosis, negative cultures in liquid media were achieved in 71 of 113 rifampin recipients (62.8%) vs 85 of 132 rifapentine recipients (64.4%) (difference, 1.6%; 95% CI: $-10.3, 13.5$; $P = .90$), and on solid media were achieved in 97 of 118 rifampin recipients (82.2%) vs 115 of 137 rifapentine recipients (83.9%) (difference, 1.7%; 95% CI: $-7.4, 11.2$; $P = .84$).

In models that included treatment assignment and assignment stratum, the following were independently significantly associated with failure to achieve sputum culture negative status in both media (unless otherwise specified) at completion of intensive phase in the PC group (Table 3): increasing age (liquid only), cigarette use, high bacillary burden (grade 3 or 4) on smear microscopy, fever, and productive cough (solid only). Female sex and increasing number of doses of prestudy tuberculosis medications (solid only) were associated with greater odds for achieving negative sputum culture status at completion of intensive phase. Significant associations were not present for HIV status or body mass index.

For the PC group, in a multivariate logistic regression model (Table 4), assignment to rifapentine was not significantly associated with sputum culture negativity at completion of intensive phase as assessed using liquid culture (odds ratio [OR], 1.34; 95% CI: $.82, 2.19$; $P = .25$) or solid culture (OR, 1.53; 95% CI: $.81, 2.89$; $P = .19$) when adjusted for Africa stratum, sex, number of prestudy tuberculosis medication

Table 1. Baseline Characteristics of Participants in the Protocol Correct Efficacy Analysis Group

Characteristic	Overall	Rifampin	Rifapentine
Total participants, no.	389	183	206
Cavitary stratum	267 (69)	126 (69)	141 (68)
Assignment stratum			
Spain, noncavitary	10 (3)	6 (3)	4 (2)
Spain, cavitary	16 (4)	5 (3)	11 (5)
North America, noncavitary	44 (11)	23 (13)	21 (10)
North American, cavitary	94 (24)	43 (23)	51 (25)
South America, noncavitary	1 (0)	1 (1)	0 (0)
South America, cavitary	20 (5)	12 (7)	8 (4)
Uganda, noncavitary	43 (11)	18 (10)	25 (12)
Uganda, cavitary	93 (24)	43 (23)	50 (24)
South Africa, noncavitary	24 (6)	9 (5)	15 (7)
South Africa, cavitary	44 (11)	23 (13)	21 (10)
Median age, years (IQR)	33 (26, 46)	34 (26, 47)	32 (26, 46)
Female	129 (33)	68 (37)	61 (30)
History of smoking cigarettes	158 (41)	72 (39)	86 (42)
Tuberculosis treatment before enrollment			
Any treatment within 14 d	233 (60)	109 (60)	124 (60)
Median no. of days of prestudy treatment (IQR)	2 (0, 4)	2 (0, 4)	2 (0, 4)
Clinical features at enrollment			
High bacillary load on smear	237 (61)	108 (59)	129 (63)
Median no. of days to detection in MGIT culture (IQR)	7 (5, 9)	7 (5, 9)	7 (5, 10)
Median body mass index, kg/m ² (IQR)	20 (18, 23)	20 (18, 22)	20 (18, 23)
HIV-positive	42 (11)	24 (13)	18 (9)
Median CD4 count, cells/uL (IQR)	312 (210, 399)	350 (228, 467)	279 (193, 343)
Median hemoglobin, g/dL (IQR)	12.2 (10.9, 13.4)	12.2 (10.9, 13.3)	12.2 (10.9, 13.6)
ALT > ULN	46 (12)	22 (12)	24 (12)

Data are no. (%) of participants unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; HIV, human immunodeficiency virus; IQR, interquartile range; MGIT, mycobacterial growth indicator tube; ULN, upper limit of normal for the testing laboratory.

doses, bacillary load on baseline sputum smear, fever, productive cough, sweats, cavitation at enrollment, and extent of disease.

There were no significant differences between treatment groups in time to stable culture conversion as assessed on solid ($P = .41$) or liquid ($P = .62$) media (Figure 2).

Safety and tolerability

In the rifampin arm 40 of 254 participants (15.7%) discontinued their assigned treatment vs 40 of 275 (14.5%) in the rifapentine arm ($P = .79$, Table 5). Discontinuation of assigned treatment due to toxicity occurred in 3 of 254 participants (1.2%) in the rifampin arm vs 4 of 275 participants (1.5%) in

Table 2. Percentages of Participants with Negative Sputum Cultures at Completion of Intensive Phase Treatment, by Treatment Group

Treatment group	Rifampin	Rifapentine	Difference (95%CI)	<i>P</i>
Protocol correct analysis group				
Liquid media	110/169 (65.1%)	133/196 (67.9%)	2.8 (−6.9, 12.4)	.65
Solid media	145/174 (83.3%)	171/198 (86.4%)	3.0 (−4.3, 10.5)	.50
Modified intention-to-treat group				
Liquid media	122/195 (62.6%)	152/228 (66.7%)	4.1 (−5.0, 13.2)	.44
Solid media	167/211 (79.2%)	193/233 (82.8%)	3.7 (−3.6, 11.0)	.38

Abbreviation: CI, confidence interval, computed using the Wilson-Newcombe method (18).

P value computed using Pearson χ^2 with Yates continuity correction.

Table 3. Individual Factors Associated with Negative Sputum Culture at Completion of Intensive Phase Treatment in the Protocol Correct Analysis Group

Characteristic at enrollment	Solid culture (n = 371)			Liquid culture (n = 365)		
	OR	95%CI	P	OR	95%CI	P
Rifapentine vs rifampin	1.22	.69, 2.17	.49	1.13	.73, 1.75	.58
Assignment stratum ^a			.04			<.01
North America, noncavitary	(ref)	(ref)
North America, cavitary	0.51	.16, 1.63	.25	0.40	.14, 1.14	.09
South America, cavitary	0.31	.07, 1.30	.11
Uganda, noncavitary	0.95	.22, 4.07	.94	0.18	.06, .56	<.01
Uganda, cavitary	0.45	.14, 1.42	.17	0.13	.05, .35	<.01
South Africa, noncavitary	<0.01	.00, .	1.00	0.32	.09, 1.15	.08
South Africa, cavitary	0.95	.22, 4.07	.94	0.23	.08, .70	<.01
Spain, noncavitary	0.15	.03, .79	.02	0.31	.06, 1.59	.16
Spain, cavitary	0.62	.10, 3.78	.60	0.57	.12, 2.72	.48
Models that included treatment assignment and assignment strata						
Female	4.44	1.89, 10.40	<.01	3.13	1.82, 5.39	<.01
Age, years	0.98	.96, 1.01	.14	0.98	.96, 1.00	.02
Cigarette use	0.47	.25, .88	.02	0.49	.30, .79	<.01
Number of pre-study doses of any anti-tuberculosis medicines ^a			.03			.08
0 doses	(ref)	(ref)
1–2 doses	0.50	.19, 1.29	.15	0.75	.37, 1.55	.44
3–4 doses	0.61	.27, 1.34	.22	1.38	.72, 2.63	.33
5 doses	2.31	.69, 7.76	.18	2.13	.96, 4.72	.06
Fever	0.47	.24, .93	.03	0.59	.36, .96	.03
Productive cough	0.13	.02, .98	.05	0.78	.33, 1.86	.58
Sweats	1.38	.76, 2.51	.29	0.72	.44, 1.15	.17
HIV positive status	0.80	.28, 2.32	.68	0.68	.32, 1.43	.30
High bacillary load (grade 3 or 4) on smear	0.35	.15, .82	.02	0.28	.16, .50	<.01
Cavitation on chest radiograph	0.53	.06, 4.99	.58	0.24	.06, 1.04	.06
Extent of disease on chest radiograph ^a			.02			.06
<25% of lungs	(ref)	(ref)
25%–50% of lungs	0.27	.09, .80	.02	0.43	.20, .94	.03
>50% of lungs	0.24	.08, .75	.01	0.40	.17, .90	.03

Randomization was stratified by the presence of cavitation on baseline chest radiograph and by region of enrollment.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

^aFor assignment stratum, number of pre-study doses, and extent of disease on chest radiograph, a deviance P-value is included for each multicategory variable taken as a whole. A significant P-value implies that at least one category-specific odds ratio is different from the others.

the rifapentine arm. In the rifampin group there was 1 serious adverse event (SAE) related to study treatment (inadvertent administration of 2 doses of study treatment on 1 day). In the rifapentine group there were 3 SAEs attributed to study treatment (grade 4 hepatitis in 2 participants and hospitalization for grade 3 hepatitis in 1 participant). Similar proportions of participants in each treatment group experienced hepatitis: 7 of 254 (2.8%) in the rifampin group and 11 of 275 (4.0%, $P = .48$) in the rifapentine group. Three participants, all in the rifapentine group, died during intensive-phase treatment. Two died from complications of advanced pulmonary tuberculosis, and 1 died with an acute abdominal illness in the setting of advanced AIDS and suspected immune reconstitution

syndrome after initiation of combination antiretroviral therapy (antiretroviral therapy initiation, a protocol deviation, was determined by the site investigator to be in the participant's best interest); each death was judged not related to study drugs. Frequencies of other side effects including anemia, neutropenia, nausea or vomiting, rash, and itching were low and did not differ between treatment arms.

DISCUSSION

Our study is, to our knowledge, the first to explore the antimicrobial activity of a rifapentine-containing regimen administered 5 days/week for treatment of pulmonary tuberculosis. The

Table 4. Multivariate Logistic Regression Model for Sputum Culture Negativity at the End of Intensive Phase in the Protocol Correct Analysis Group

Characteristic at enrollment	Solid culture			Liquid culture		
	OR	95%CI	<i>P</i>	OR	95%CI	<i>P</i>
Rifapentine vs rifampin	1.53	.81, 2.89	.19	1.34	.82, 2.19	.25
Africa stratum	2.90	1.33, 6.32	<.01	0.53	.28, .99	.04
Female	3.75	1.56, 9.01	<.01	2.91	1.64, 5.16	<.01
Number of prestudy doses of any anti-tuberculosis medicines ^a			.03			.19
0 doses	(ref)	(ref)
1–2 doses	1.01	.40, 2.58	.98	1.01	.49, 2.09	.98
3–4 doses	0.69	.31, 1.55	.36	1.31	.66, 2.58	.44
≥5 doses	3.56	1.02, 12.50	.05	2.31	1.00, 5.36	.05
High bacillary load on smear	0.55	.26, 1.16	.11	0.35	.20, .62	<.01
Fever	0.36	.16, .81	.01	0.65	.36, 1.17	.15
Productive cough	0.12	.02, .96	<.01	0.89	.35, 2.22	.79
Sweats	2.18	1.06, 4.51	.04	0.92	.52, 1.63	.77
Cavitation on chest radiograph	0.70	.32, 1.49	.34	0.72	.41, 1.26	.24
Extent of disease on chest radiograph ^a			.34			.38
<25% of lungs	(ref)	(ref)
25%–50% of lungs	0.49	.17, 1.37	.17	0.58	.26, 1.28	.18
>50% of lungs	0.50	.17, 1.45	.20	0.68	.30, 1.58	.37

Cigarette use was not significantly associated with sputum culture negativity in the multivariate model and was not involved in confounding, and therefore was not included in Table 4.

Abbreviations: CI, confidence interval; OR, odds ratio.

^a For number of prestudy doses and extent of disease on chest radiograph, a deviance *P* value is included for each multicategory variable taken as a whole. A significant *P* value implies that at least 1 category-specific odds ratio is different from the others.

rationale for undertaking the study was the robust sterilizing activity of a similar regimen that, in the mouse model, reduces the duration of treatment required for stable cure [11]. We have shown that rifapentine in a dose of 10 mg/kg/day is well tolerated. Yet, the efficacy—as determined by the endpoint of culture status at the completion of intensive phase treatment—of the investigational rifapentine regimen was not significantly different than that of the conventional rifampin regimen.

Why in this study was the antimicrobial activity of rifapentine not greater than that of rifampin, as it was in murine experiments? First, in our study the treatment doses were administered without food most of the time in accordance with the study protocol and tuberculosis treatment guidelines [19]. Food has been shown to increase rifapentine bioavailability by 33%–86% over that observed when administered under fasting conditions [22, 23]. Conversely, for rifampin, higher maximal concentrations (*C*_{max}) are achieved in the fasting than in the fed state [24, 25]. Therefore, in our study the administration of tuberculosis treatment without food would have minimized rifapentine exposures and could have blunted antimicrobial activity as measured by 2-month culture status. In support of this, rifapentine exposure at 10 mg/kg dosages appeared somewhat lower in a preliminary analysis of 43 participants from our study (median AUC_{0–24} 218 µg^h/mL and

median *C*_{max} of 12.6 µg/mL at steady state) than in ad-libitum-fed mice at similar dosages (median AUC_{0–24} 373 µg^h/mL and *C*_{max} of 18.6 µg/mL) or healthy adults administered 10 mg/kg rifapentine with food (steady state median AUC_{0–24} 330 µg^h/mL, *C*_{max} 21.7 µg/mL) [10, 18, 26, 27]. It is worth mentioning that prior work showed rifapentine equipotency (based on AUC) in humans and mice at doses of 10 mg/kg and 15 mg/kg [28]. The robust antimicrobial and sterilizing activity of 10 mg/kg given daily in combination with other drugs in the mouse model of tuberculosis chemotherapy was part of the rationale for selection of the same rifapentine dose in our phase 2 clinical trial. In murine experiments, rifapentine bactericidal and sterilizing activities increased essentially without plateau up to doses of 160 mg/kg when the drug was administered ad-lib with food, underscoring the importance of maximizing rifapentine exposures during the treatment of human tuberculosis [29]. Dooley and colleagues recently conducted a rifapentine dose-escalation study in healthy adults and showed that daily rifapentine doses of up to 20 mg/kg administered with food were safe and produced rifapentine exposures exceeding those in mice receiving 10 mg/kg [26].

Second, the pharmacodynamics of rifapentine may be different in mice and humans. In tuberculosis patients, high

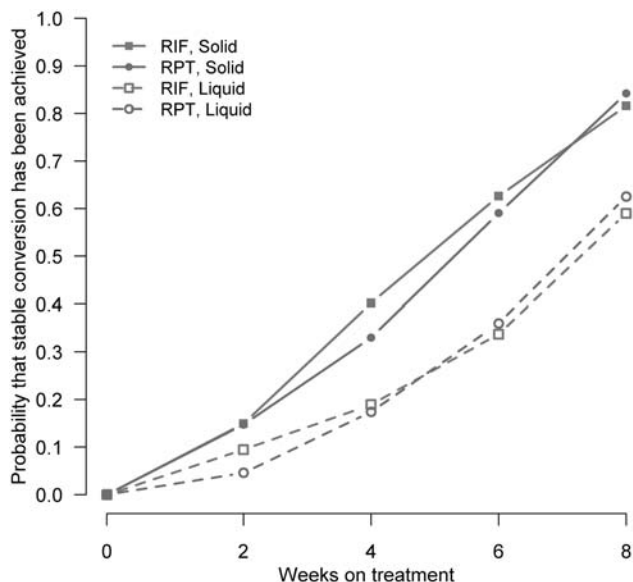


Figure 2. Time to stable culture conversion for the protocol correct analysis group on liquid (*dashed lines*) and solid (*solid lines*) media for rifampin (*squares*) and rifapentine (*circles*) treatment groups. Abbreviations: RIF, rifampin; RPT, rifapentine. ‘Solid’ (n = 371) refers to Lowenstein Jensen solid culture medium; ‘Liquid’ (n = 365) refers to Mycobacterial Growth Indicator Tube liquid culture medium. *P* values (log-rank): solid medium, .41; liquid medium, .62.

protein binding of rifapentine and its active 25-desacetyl-rifapentine metabolite (97.7% and 93.1%, respectively, in healthy volunteers) potentially could limit access of free, active drug to disease sites such as pulmonary cavities—a histopathological feature common in human tuberculosis yet absent from experimentally induced tuberculosis in mice [30]. Consistent with this is our finding of a slightly larger difference between treatment arms in proportion of 2-month culture-negative status among noncavitary participants (5.4% in liquid and 6.1% on solid media) than among cavitary participants (1.6% in liquid and 1.7% on solid media). Whether higher doses of rifapentine could overcome a possible limitation of penetration into pulmonary cavities is unclear.

Third, it is important to note that there are limitations to the efficacy endpoint—dichotomous status of sputum cultures at the end of intensive-phase treatment—that we used in this phase 2 study. These limitations might impair our ability to detect a treatment shortening potential of rifapentine, should it exist [16, 31]. Although this endpoint has been used in multiple recent phase 2 studies, it has imperfect specificity and sensitivity as a predictor of the “gold standard” clinical outcomes of treatment failure and relapse [14, 32–35]. As recently highlighted by Andries and colleagues in a murine model, bacterial killing in the early weeks of tuberculosis treatment is

Table 5. Participants with Adverse Events Reported Within 70 days After First Study Drug Dose, Among Participants Who Received at Least 1 Dose of Study Treatment

Adverse event or symptom	Rifampin	Rifapentine	<i>P</i>
No.	254	275	...
Study drugs permanently discontinued	40 (15.7) ^a	40 (14.5) ^b	.79
Study drugs permanently discontinued due to toxicity	3 (1.2)	4 (1.5)	1.00
Any SAE	10 (3.9)	19 (6.9)	.18
SAE attributed to study treatment	1 (0.4) ^c	3 (1.1) ^d	.62
Death during intensive phase treatment	0 (0)	3 (1.1)	.25
Hepatitis	7 (2.8)	11 (4.0)	.48
Neutropenia (<1000/mm ³)	6 (2.4)	4 (1.5)	.53
Anemia (<8.0 g/dL)	4 (1.6)	1 (0.4)	.20
Thrombocytopenia (<75 000/mm ³)	0 (0)	0 (0)	1.00
Hyperglycemia (nonfasting glucose >250 mg/dL)	1 (0.4) ^e	4 (1.5) ^e	.37
Nausea and/or vomiting	0 (0)	2 (0.7)	.50
Pruritis and/or rash	5 (2.0)	6 (2.2)	1.00

Data are no. (%) of participants unless otherwise indicated. *P* value for Fisher exact test.

Abbreviation: SAE, serious adverse event.

^a Reasons for discontinuation: drug toxicity, n = 3 (1.2%); baseline *M. tuberculosis* isolate drug resistant, n = 17 (6.7%); baseline culture negative for *M. tuberculosis*, n = 10 (3.9%); participant non-adherence, n = 4 (1.6%); withdrawal of consent, n = 3 (1.2%); other, n = 3 (1.2%).

^b Reasons for discontinuation: drug toxicity, n = 4 (1.5%); baseline *M. tuberculosis* isolate drug resistant, n = 12 (4.4%); baseline culture negative for *M. tuberculosis*, n = 9 (3.3%); participant non-adherence, n = 3 (1.1%); withdrawal of consent, n = 3 (1.1%); death, n = 3 (1.1%); other, n = 6 (2.2%).

^c Overdose of 1 extra dose of study treatment.

^d Hepatitis.

^e At enrollment a history of diabetes mellitus was reported by the one participant with hyperglycemia in the rifampin arm and by 3 of the 4 participants with hyperglycemia in the rifapentine arm.

not necessarily predictive of sterilizing activity [36]. Treatment shortening activity may be predicted better with a continuous endpoint or with a binary endpoint at a different time.

In our study, end of intensive-phase liquid culture negativity was lower among participants at African sites compared with non-African sites. A similar finding was observed in TBTC Study 28 and was not fully explained by baseline severity of disease, HIV status, age, smoking, diabetes, or race [37]. Interestingly, in the current study, end of intensive-phase negativity on solid media was significantly higher among participants at African sites compared with non-African sites. In TBTC Study 28 a trend in the same direction but of lesser magnitude was observed and prompted a thorough review of mycobacteriological laboratory procedures and quality monitoring, but no potentially causal issues were identified at the African study sites. An unexpectedly large difference in conversion rates between solid and liquid media was also observed in the OFLOTUB study conducted in South Africa [38]. The role of microbial factors and host factors as well as heterogeneity in laboratory procedures should be explored in order to understand differences in bacteriologic response rates of participants at African vs non-African sites.

The rifapentine regimen was safe and well tolerated as administered in our study. The relatively high proportion of participants (approximately 15% in each treatment arm) who discontinued study treatment was driven by microbiological ineligibility, specifically absence of *Mycobacterium tuberculosis* from baseline cultures of smear positive sputum samples and drug resistance of baseline *Mycobacterium tuberculosis* isolates, and not by medication side effects. In the future, microbiological eligibility for enrollment in tuberculosis drug trials may be assessed more efficiently through the use of molecular tests. The proportions of participants with hepatitis—2.8% in the rifampin group and 3.6% in the rifapentine group—were similar to that observed with the conventional rifampin intensive-phase tuberculosis treatment regimen (3.4%) in another recent phase 2 clinical trial conducted by the TBTC [20].

In conclusion, rifapentine 10 mg/kg/dose administered 5 days/week without food was well tolerated, safe, and as effective as rifampin. Our study points out some of the challenges of directly extrapolating results from preclinical studies to human trials. Rifapentine remains a promising drug with potential for tuberculosis treatment shortening, and recent work by Dooley and colleagues indicates that higher rifapentine daily doses appear to be safe and tolerable in healthy volunteers [26]. However, Dooley observed that although steady-state rifapentine concentrations increased with daily doses from 5 to 15 mg/kg, concentrations were similar in study participants receiving 15 and 20 mg/kg doses, suggesting a decrease in bioavailability (at 20 mg/kg) that could in turn have implications for antimicrobial activity [26]. To continue to evaluate the potential for rifapentine to support shorter-

course therapy for drug-susceptible tuberculosis, assessment of safety, activity, and pharmacokinetics of higher daily rifapentine doses in patients with active tuberculosis is warranted.

Notes

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