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Two-stage activity-safety study of daily rifapentine during intensive phase treatment of pulmonary tuberculosis

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Abstract

Background: Rifapentine has potent activity against *Mycobacterium tuberculosis* but the optimal dose for tuberculosis treatment is unknown.

Objective: to determine antimicrobial activity, safety, and tolerability of rifapentine 450 mg or 600 mg administered daily during the first 8 weeks of pulmonary tuberculosis treatment.

Design: Two-stage, randomized, open-label study. Adults with sputum smear-positive tuberculosis were randomized to receive rifapentine 450 mg, rifapentine 600 mg, or rifampin 600 mg daily for 8 weeks with isoniazid, pyrazinamide, ethambutol. The primary endpoint was sputum culture status on Löwenstein-Jensen (LJ) medium at completion of 8 weeks of treatment.

Results: 153 participants were enrolled. Both rifapentine regimens met pre-specified criteria to advance into stage 2. At completion of 8 weeks, LJ culture conversion occurred in 85% (35/41), 96% (43/45), and 94% (34/36) of participants in the rifapentine 450 mg, rifapentine 600 mg, and rifampin groups. Proportions of participants discontinuing treatment were similar (2.0% [1/54], 2.0% [1/51], and 8.3% [4/48] in the rifapentine 450 mg, rifapentine 600 mg, and rifampin groups), as were grade 3 adverse events (0% [0/54], 2.0% [1/51], and 8.3% [4/48]).

Conclusions: There was a trend towards greater efficacy with rifapentine 600 mg compared with rifapentine 450 mg; daily rifapentine was safe and well-tolerated.

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CONFLICTS OF INTEREST AND FINANCIAL DISCLOSURES

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Keywords

tuberculosis; therapeutics; mycobacterium; rifamycin; rifapentine; rifampin

INTRODUCTION

The relatively long duration of therapy required for cure is a barrier to tuberculosis control. For drug-susceptible pulmonary tuberculosis, potent treatment regimens that shorten therapy might increase treatment completion and cure rates and possibly decrease transmission.¹

Rifamycins are key components of tuberculosis treatment because of their sterilizing ability, that is, their ability to kill the slowly metabolizing bacillary subpopulation hypothesized to be responsible for relapse.² Rifampin is the most commonly used rifamycin. The currently recommended dose of rifampin, approximately 10 mg/kg, is at the low end of the dose-response curve.^{3–10} Optimizing rifamycin dose is a strategy for enhancing regimen potency and consequently shortening treatment duration. Rifapentine is a cyclopentyl ring-substituted rifamycin that compared with rifampin has a longer half-life and lower minimum inhibitory concentration against *Mycobacterium tuberculosis*.^{11–15} Preclinical studies using mouse models have shown that regimens containing daily rifapentine can achieve cure after only three months of treatment.^{16–18} Whether daily rifapentine-containing regimens are sufficiently active to shorten treatment duration for human tuberculosis is not known.

When this trial was conceived, there were no published data on efficacy, safety, or tolerability of rifapentine administered daily in combination with other anti-tuberculosis drugs. This 2-stage design clinical trial was undertaken to determine whether intensive phase regimens containing daily rifapentine 450 mg or 600 mg had sufficient antimicrobial activity and were sufficiently safe and tolerable to warrant more extensive study.

METHODS

Study Population

Participants were enrolled at one center in Cape Town, South Africa. Inclusion criteria were age ≥ 18 years, suspected pulmonary tuberculosis with a sputum smear that was positive for acid fast bacilli, weight 45 to 80 kg, liver and renal chemistries within specified ranges around normal, and HIV testing. Exclusionary criteria were pregnancy, prior tuberculosis treatment, and for HIV-infected participants a CD4 lymphocyte count < 200 cells/mm³ and/or planned antiretroviral therapy during the first eight weeks of tuberculosis treatment. Enrolled participants were excluded and study treatment was stopped if baseline sputum cultures were negative for *M. tuberculosis* or grew *M. tuberculosis* resistant to isoniazid and/or rifampin (late exclusions). Participants provided written informed consent. This study was approved by ethics boards of the University of Cape Town and Johns Hopkins Medicine.

Design, Intervention, and Evaluations

Participants were randomly assigned to receive rifapentine 450 mg, rifapentine 600 mg, or rifampin 600 mg administered once daily 7 days/week, along with isoniazid, pyrazinamide, ethambutol, and pyridoxine, for 8 weeks. Doses of isoniazid, pyrazinamide, ethambutol, and pyridoxine were in accordance with published guidelines.¹⁹ Study medicines were administered by directly observed therapy; individual drugs rather than fixed dose combinations were used for all treatment arms during intensive phase. Participants receiving rifapentine regimens were counseled to take rifapentine with food, but no specific meal was prescribed or provided by the study, and information about food intake was not recorded. Randomization was stratified by the presence of cavitation on baseline chest radiograph. The study was open-label; microbiologists did not have access to information about treatment assignment. After completing the 8-week study treatment, participants continued tuberculosis treatment with a conventional continuation phase regimen, typically isoniazid plus rifampin 600 mg for four additional months.

Sputum was collected at baseline, weekly for 8 weeks, and during continuation phase treatment at weeks 10 and 16. Sputa were processed using conventional N-acetyl-L-cysteine-NaOH methods and cultured using Löwenstein-Jensen (LJ) solid medium and BACTEC Mycobacterial Growth Indicator Tube (MGIT, Becton Dickinson and Co., Franklin Lakes, NJ) liquid medium with the MGIT 960 system. The baseline isolate was tested for susceptibility to isoniazid and rifampin using the MGIT 960 system. Information on symptoms, and blood for alanine aminotransferase, bilirubin, creatinine, and complete blood count were collected at baseline and at weeks 2, 4, 6, 8, 10, and 16.

Data Analysis and Statistical Considerations

The primary efficacy endpoint was sputum culture status assessed using LJ culture at completion of 8 weeks of treatment. Secondary efficacy endpoints were sputum culture status assessed using MGIT culture at completion of 8 weeks of treatment, and time to stable culture conversion. Stable culture conversion was defined as having two consecutive sputum specimens culture negative for *M. tuberculosis*, with no subsequent culture that was positive. Results from LJ and MGIT media were analyzed separately. The primary tolerability endpoint was discontinuation of assigned treatment during the first eight weeks. Safety parameters included the frequency and severity of adverse events.

For efficacy analyses, the primary analysis population was the per-protocol population comprised of participants meeting all of the following: a) growth in a baseline culture of *M. tuberculosis* that was susceptible to isoniazid and rifampin; b) completed assigned study intensive phase therapy within 56–70 calendar days; and c) had an end-of-intensive phase culture that was evaluable (i.e. not missing or contaminated). A microbiologically-eligible analysis population included participants with growth in a baseline culture of *M. tuberculosis* that was susceptible to isoniazid and rifampin. For efficacy analyses of culture status for the microbiologically-eligible population, participants with cultures that were missing or contaminated were considered to be positive for *M. tuberculosis* (i.e. missing = failure). The intention-to-treat (ITT) analysis population was comprised of all randomized participants and was used for tolerability and safety analyses. Differences in percentages of

participants culture-negative at completion of intensive phase were compared using the Fisher exact test. Survival curves were compared using the log-rank test. Pair-wise comparisons of median times to stable culture conversion were performed using the Wilcoxon two sample rank sum test for survival data.

A Simon 2-stage design was adopted for each rifapentine dosing level, using the primary efficacy endpoint and per-protocol analysis population.²⁰ The clinically uninteresting response probability (p_0) was 60% based on the estimated response probability for standard rifampin-based intensive phase treatment as determined using LJ medium. The desirable response probability (p_1) was 80%, with $p_1 - p_0 = 20\%$ ($\alpha = 10\%$, $\beta = 10\%$). Using these parameters, in the first stage of the study if 7 of 11 evaluable participants in a rifapentine arm achieved negative culture status on LJ at completion of intensive phase then the recruitment into that arm would be expanded to a second stage for a total of 38 evaluable participants/arm. Enrollment was increased by 25% to account for enrolled individuals who did not meet requirements of the per-protocol analysis population. Therefore 15 participants/arm (45 total) were enrolled into stage 1, and an additional 36 participants/arm were enrolled into each advancing stage 2 arm. Maximum sample size was therefore 153 (51/arm for each of three arms). After enrollment of subjects into stage 1 there was a planned enrollment pause to allow for stage 1 participants to complete intensive phase treatment, week 8 cultures to mature, data analysis, and review of stage 1 results by an independent Data and Safety Monitoring Board (DSMB). In this uncontrolled Simon 2-stage design trial of rifapentine, a simultaneously enrolled rifampin conventional treatment arm was incorporated to provide a point-of-reference with respect to efficacy, safety, and tolerability outcomes.

RESULTS

Between April 2010 and March 2011, 45 participants were enrolled into stage 1. An enrollment pause occurred between April 2011 and December 2011. Both rifapentine regimens were advanced to stage 2 (see below), and between January 2012 and January 2013 an additional 108 participants were enrolled, for a total enrollment of 153 (Figure 1).

Table 1 shows participant characteristics at enrollment. Approximately three-quarters of participants had cavitary lesions on chest X-ray, median age was 29 years and the majority of participants (76%) were males. All participants were tested for HIV, and 23/153 (15%) were positive. There was a lower percentage of HIV-positive participants in the rifampin group (3/48 [6%]) compared to the rifapentine groups (10/54 [19%] in the rifapentine 450 mg group and 10/51 [20%] in the rifapentine 600 mg group).

For stage 1, in the per-protocol analysis population, negative LJ cultures at completion of intensive phase study treatment occurred in 6/9 (68%) of participants in the rifapentine 450 mg arm and 9/11 (82%) participants in the rifapentine 600 mg group. In the rifapentine 450 mg group, among 16 enrolled, only 9 participants were evaluable in the per-protocol analysis; 2 participants were late exclusions due to drug-resistance, one participant relocated residence during intensive phase and was lost to follow-up, 3 participants had contaminated cultures at completion of intensive phase, and sputum was not obtained at the end of

intensive phase for one participant. As per DSMB recommendations, both of the rifapentine regimens were advanced into stage 2.

For stages 1 plus 2, the results of cultures obtained at completion of study treatment are in Table 2. In the per-protocol analysis population, negative LJ cultures occurred in 35/41 (85%) of participants in the rifapentine 450 mg arm and in 43/45 (96%) in the rifapentine 600 mg arm ($p=0.14$). In accordance with the 2-stage design, when only the first 38 participants/arm meeting requirements for the per-protocol analysis were considered, negative LJ cultures occurred in 32/38 (84%) in the rifapentine 450 mg arm and in 36/38 (95%) in the rifapentine 600 mg arm, in both instances exceeding the target response proportion of 26/38. In the per-protocol analysis population, negative MGIT cultures occurred in 30/45 (67%) of participants in the rifapentine 450 mg arm and in 33/44 (75%) of participants in the rifapentine 600 mg arm ($p=0.49$). For reference, in the rifampin group 34/36 (94%) of participants were negative on LJ medium and 23/38 (61%) were negative in MGIT medium.

For the per-protocol analysis population, there were no differences in time to stable culture conversion between the rifapentine 450 mg, rifapentine 600 mg, and rifampin regimens as assessed using LJ medium (Figure 2A, $p=0.51$) or MGIT liquid medium (Figure 2B, $p=0.28$). On LJ medium, median time (IQR) to stable conversion was 37 (29–57) days for rifapentine 450 mg and 36 days (29–50) for rifapentine 600 mg. In MGIT medium, median times were 50 (38–61) days for rifapentine 450 mg and 57 (43–62) days for rifapentine 600 mg. Median time to stable conversion for the rifampin regimen was 43 (29–52) days on LJ medium and 59 (36–63) days in MGIT medium.

Table 2 also shows efficacy results for the microbiologically eligible analysis population. Negative LJ cultures occurred in 35/47 (74%) of participants in the rifapentine 450 mg arm and in 43/39 (88%) of participants in the rifapentine 600 mg arm ($p=0.12$). Negative MGIT cultures occurred in 30/47 (64%) of participants in the rifapentine 450 mg arm and in 33/49 (67%) of participants in the rifapentine 600 mg arm ($p=0.83$). For reference, in the rifampin group 34/44 (77%) of participants were negative on LJ medium and 22/44 (61%) were negative in MGIT medium for the microbiologically eligible analysis population.

In the rifapentine 600 mg arm 3/51 (5.9%) of participants discontinued assigned study treatment during the intensive phase, versus 7/54 (13.0%, $p=0.32$) in the rifapentine 450 mg group ($p=0.32$) (Table 3). However, most of the discontinuations were due to microbiological late exclusion. In each of the rifapentine arms there was only one participant/arm that discontinued for a reason other than microbiological late exclusion. In the rifampin arm 4/48 (8.3%) of participants discontinued for a reason other than microbiological late exclusion (p value not significant vs. either of the rifapentine regimens). The proportions of participants with a grade 3 or higher adverse event occurring within 70 days of treatment assignment was 0/54 (0%), 1/51 (2.0%) and 4/48 (8.3%) in the rifapentine 450 mg, rifapentine 600 mg, and rifampin 600 mg arms, respectively (p value not significant for any comparison). These included grade 4 hepatotoxicity in one participant receiving rifapentine 600 mg, grade 3 hepatotoxicity in two participants receiving rifampin, lower respiratory tract infection in one participant receiving rifampin, and hospitalization for

psychosis in one participant receiving rifampin. There were no deaths and no hematologic adverse events during study treatment.

DISCUSSION

In adults with pulmonary tuberculosis, rifapentine administered at 450 mg or 600 mg daily in combination with isoniazid, pyrazinamide, and ethambutol for eight weeks was well-tolerated and safe. For the efficacy endpoint of culture status at completion of intensive phase there was a trend towards greater efficacy of rifapentine 600 mg compared with rifapentine 450 mg, but this trend was not apparent when efficacy was assessed as time to stable culture conversion.

We used a 2-stage adaptive design, with the goal of identifying early a regimen whose activity was insufficient to warrant further study. To our knowledge, this was the first instance in which an adaptive design was applied to a tuberculosis therapeutic or global health trial.²¹ For both rifapentine regimens we tested the null hypothesis that the true response percentage was 60% versus the alternative hypothesis that the true response percentage was 80%, with α and β set at 10% each. In other words, for each regimen, we accepted a 10% probability of accepting for further study a regimen whose true response probability was 60%, and a 10% probability of rejecting for further study a regimen whose true response probability was 80%. In our study, both rifapentine regimens met the pre-specified efficacy threshold of >26/38 participants with negative LJ cultures at completion of intensive phase. Therefore, this study does not provide definitive information about which rifapentine dose should be selected for further study, although the absence of toxicity and the trend towards greater activity of the 600 mg dose would favor its selection over the 450 mg dose. A recent dose-ranging clinical trial conducted by the CDC Tuberculosis Trials Consortium and using rifapentine doses of 600 mg to 1500 mg daily showed that antimicrobial activity increased with increasing rifapentine exposures (as assessed using area under the plasma concentration time curve) and suggested that the optimal rifapentine dose may be in the vicinity of 1200 mg, which is higher than the dose used in the current study.^{22,23} Our study confirms that daily administration of rifapentine, at least at a dose of 600 mg given daily for eight weeks, is safe and well-tolerated.^{22,24}

In this uncontrolled Simon 2-stage trial, the rifampin group was intended as reference group rather than a formal comparison group. In this regard, three observations are worth mentioning. First, the percentages of participants with negative sputum cultures at completion of intensive phase were generally comparable between the rifampin group and the rifapentine 600 mg group, in accordance with another recent study.²⁴ Second, our original estimate of 80% for the desirable response probability (p_1) for a rifapentine regimen was too low, since for the rifampin arm there was an observed response of 94% (95% CI 84%–99%) for the per-protocol analysis group as assessed using LJ cultures. Third, in the studied population, conventional tuberculosis treatment was not without side effects, helping to put into perspective the types, frequencies, and severities of adverse events observed in the rifapentine arms.

Implementation of the 2-stage design presented challenges, and our experience may help to guide the design and implementation of future adaptive design tuberculosis treatment trials. First, in our study, the enrollment pause between the first and second stages was approximately nine months. During this time the last enrolled participants completed eight weeks of intensive phase treatment, their week 8 cultures incubated for an additional eight weeks, data were cleaned and analyzed, and results were shared with the study DSMB for decision-making. Though better planning during our study could have reduced the enrollment pause, the shortest possible duration is nevertheless about four months. Second, unexpectedly, in the rifapentine 450 mg group only 9 of 16 participants enrolled in stage 1 met pre-specified definitions for inclusion in the per-protocol analysis population, whereas the 2-stage design required 11 evaluable per-protocol participants in each arm at completion of stage 1. In this situation, the DSMB recommended progression of the rifapentine 450 mg arm into stage 2 since the observed percentage of participants with negative cultures (6 of 9, or 68%) exceeded the minimum percentage (at least 7 of 11, or 64%) from the Simon's design and in addition it was not feasible to continue enrollment in stage 1 for only this arm while the other arms were paused. This predicament underscores the need to maximize the likelihood that enrolled individuals will be eligible for analysis. Strategies to accomplish this include use of rapid drug susceptibility tests at enrollment to minimize late exclusions due to drug resistance, and collection of at least two sputa at critical time points to reduce the likelihood that all sputa are 'contaminated' for a participant at that time point. Additional study limitations are that we did not systematically collect information about intake of food with study drugs, and that funding constraints did not allow investigation of more than two rifapentine doses.

Several design elements enhanced the internal validity of our study. These include a single study site with uniform mycobacteriology laboratory procedures, consistent safety monitoring, and consistent provision of directly observed therapy seven days per week. While acknowledging that these issues may restrict the generalizability of our findings, on balance we consider them to be strengths in the context of this explanatory phase 2 study. Overall, the trend towards greater efficacy with rifapentine 600 mg vs. 450 mg, and the absence of safety or tolerability signals, support future studies of daily rifapentine doses higher than 600 mg to identify the optimal dose.

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*received only 55 doses (instead of 56 doses) of study therapy due to error

Figure 1.
Enrollment and disposition of all study participants.

2A

2B

Figure 2.

Time to stable culture conversion for the per-protocol analysis group as assessed using (A) Löwenstein-Jensen (LJ) solid culture medium (p value=0.51 for comparing equality of the three survival curves), and (B) Mycobacterial Growth Indicator Tube (MGIT) liquid culture medium (p value = 0.28).

Table 1.

Baseline characteristics of participants in the intention-to-treat analysis population.

Characteristic	Overall n=153	Rifapentine 450 mg n=54	Rifapentine 600 mg n=51	Rifampin 600 mg n=48
Median age, years (IQR)	29 (24, 38)	29 (23, 39)	29 (24, 38)	30 (25, 36)
Male, n (%)	116 (75.8%)	41 (75.9%)	40 (78.4%)	35 (72.9%)
Current or former cigarette smoker, n (%)	98 (64.1%)	38 (70.4%)	32 (62.7%)	28 (58.3%)
HIV-positive, n (%)	23 (15.0%)	10 (18.5%)	10 (19.6%)	3 (6.3%)
Median CD4 count in cells/ul, (IQR) for HIV-positive participants	395 (261, 674)	400 (261, 674)	483 (346, 797)	266 (253, 284)
Median body mass index, kg/m ² (IQR)	18.8 (18.0, 21.0)	18.8 (18.1, 21.2)	18.5 (17.4, 21.1)	19.3 (18.4, 20.8)
Baseline smear grade 2 or higher, n (%)	119 (82.0%)	44 (81.5%)	39 (76.5%)	36 (75.0%)
Cavitation on chest X-ray at enrollment, n (%)	116 (75.8%)	40 (74.1%)	40 (78.4%)	36 (75.0%)
Bilateral disease on chest X-ray at enrollment, n (%)	94 (61.4%)	32 (59.3%)	32 (62.7%)	30 (62.5%)

Abbreviations: IQR, inter-quartile range; ULN, upper limit of normal

Table 2.

Percentages of participants with negative cultures at completion of intensive phase treatment

	Rifapentine 450 mg n/n (%) 95% CI	Rifapentine 600 mg n/n (%) 95% CI	P value for Rifapentine 450 mg vs. Rifapentine 600 mg	Rifampin 600 mg n/n (%) 95% CI
<i>Per-protocol analysis population</i>				
Löwenstein-Jensen solid culture	35/41 (85%) 73% – 93%	43/45 (96%) 87% – 99%	0.14	34/36 (94%) 84% – 99%
MGIT liquid culture	30/45 (67%) 53% – 78%	33/44 (75%) 62% – 85%	0.49	23/38 (61%) 46% – 74%
<i>Microbiologically eligible analysis population</i>				
Löwenstein-Jensen solid culture	35/47 (74%) 62% – 85%	43/49 (88%) 77% – 95%	0.12	34/44 (77%) 64% – 87%
MGIT liquid culture	30/47 (64%) 51% – 75%	33/49 (67%) 55% – 78%	0.83	22/44 (61%) 37% – 63%

Abbreviation: CI, binomial exact confidence interval; MGIT, Mycobacterial Growth Indicator Tube

Table 3.

Discontinuation of assigned treatment during the intensive phase, and adverse events within the first 70 days after the initial dose of study drugs

	Rifapentine 450 mg n=54	Rifapentine 600 mg n=51	Rifampin 600 mg n=48
Regimen permanently discontinued, n (%)	7 (13.0%)	3 (5.9%)	7 (14.6%)
Regimen permanently discontinued for reasons other than microbiological late exclusion, n (%)	1 (1.9%)	1 (2.0%)	4 (8.3%)
Toxicity, n (%)	0	1 (2.0%) ^b	2 (4.2%) ^b
Participant lost or withdrew consent, n (%)	1 (1.9%)	0	2 (4.2%)
Regimen permanently discontinued based solely on microbiological late exclusion, n (%)	6 (11.1%)	2 (3.9%)	3 (6.3%)
Grade 3 or higher adverse event, n (%)^a	0	1 (2.0)^c	4 (8.3%)^d
Number of participants with Grade 1 or 2 adverse events	15	11	7
Total number of grade 1 or 2 adverse events, n^b	20	12	7
Elevation of hepatic enzymes, n	0	3	3
Pruritis and/or rash, n	3	3	2
Nausea and/or vomiting, n	4	1	1
Diarrhea	1	0	0
Musculoskeletal, n	7	4	1
Hemoptysis	3	0	0
Other	2 ^e	1 ^f	0

^a total number of events = total number of participants since no participant had more than one grade 3 or higher adverse event

^b total number of events; some individual participants had more than one adverse event of grade 1 or 2

^c hepatotoxicity

^d hepatotoxicity (n=2); lower respiratory tract infection (n=1); hospitalization for psychotic episode (n=1)

^e dyspnea (n=1); fracture of arm as a result of physical assault (n=1)

^f pleuritic chest pain