A Prospective, Randomized, Double-Blind Study of the Tolerability of Rifapentine 600, 900, and 1,200 mg Plus Isoniazid in the Continuation Phase of Tuberculosis Treatment

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Once-weekly rifapentine 600 mg plus isoniazid (INH) during the continuation phase treatment of tuberculosis is associated with a relapse rate higher than that of twice-weekly rifampin plus INH. The safety and tolerability of higher rifapentine doses need to be determined. We conducted a prospective, randomized, double-blind trial of rifapentine at three doses (600, 900, and 1,200 mg) plus INH 15 mg/kg once weekly in the continuation phase treatment of culture-positive tuberculosis in 150 human immunodeficiency virus–seronegative adults. Outcome measures were discontinuation of therapy for any reason and adverse events on therapy. Treatment was discontinued in 3 of 52 (6%), 2 of 51 (4%), and 3 of 47 (6%) in the rifapentine 600-, 900-, and 1,200-mg treatment arms, respectively. Only one discontinuation, in the rifapentine 1,200-mg arm, was due to an adverse event possibly associated with study therapy. There was a trend toward more adverse events, possibly associated with study therapy, in the highest-dose arms ($p = 0.051$). Rifapentine 900-mg, once-weekly dosing appears to be safe and well tolerated and is being evaluated in Phase III efficacy trials of treatment of latent tuberculosis. Further evaluation of the safety and tolerability of rifapentine 1,200 mg is warranted.

Rifapentine is a rifamycin derivative that can be given once weekly with isoniazid (INH) in the continuation phase of treatment of active tuberculosis in human immunodeficiency virus (HIV)–seronegative adults, following 8 weeks of intensive phase therapy (1). Once-weekly directly observed therapy provides advantages for both patients and tuberculosis control programs over the current standard of twice-weekly directly observed therapy. However, studies of once-weekly rifapentine 600 mg plus INH have demonstrated higher tuberculosis relapse rates compared with twice- or thrice-weekly rifampin plus INH (1–3). One possible explanation for the decreased effectiveness of rifapentine 600 mg plus INH is the very high (97%) protein binding of rifapentine, possibly resulting in low concentrations of biologically active rifapentine at the site of disease (4). A dose-ranging study established the minimal effective dose of rifampin for the treatment of tuberculosis (5), but no such study of rifapentine has been conducted. If safe and tolerable, higher doses of rifapentine might improve treatment efficacy. In this study, we assessed the tolerability of higher doses of rifapentine when given once weekly with INH in the continuation phase of tuberculosis treatment in HIV-seronegative adults.

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METHODS

A multicenter, Phase II, prospective, randomized, double-blind study of the tolerability and safety of three doses of rifapentine (600, 900, and 1,200 mg) given with INH 15 mg/kg once weekly in the continuation phase of antituberculosis treatment was conducted by the Tuberculosis Trials Consortium (TBTC), which includes 20 sites in the United States and three in Canada.

Eligibility Criteria

Patients aged 18 years or older were eligible if they had culture-confirmed, drug-susceptible pulmonary or extrapulmonary tuberculosis and documentation of adequate induction phase therapy, as recommended by the American Thoracic Society and the Centers for Disease Control and Prevention (CDC) (6). Patients also needed documentation of a negative serologic test for HIV within 3 months of starting therapy and willingness to practice effective contraception if applicable, and signed informed consent. Patients were excluded if they had known intolerance or contraindications to INH or rifamycins, a history of more than 70 days of continuous antituberculosis therapy immediately before randomization, or any of the following abnormal laboratory values: aspartate aminotransferase (AST) greater than three times the upper limit of normal ($\times$ ULN), a bilirubin concentration of greater than 2.5 $\times$ ULN, a creatinine concentration greater than 2 $\times$ ULN, hemoglobin less than 7 gm/dl, or a platelet count less than 50,000/mm^3. They were also excluded if they were pregnant or breast-feeding or if they had silico- or skeletal tuberculosis.

Study Design and Medication

Patients were enrolled into the study after they had completed a standard 8-week, four-drug induction course of therapy (6). The study was conducted in two stages. In Stage 1, 75 patients were randomized in a 2:1 ratio to receive once-weekly rifapentine 900 mg plus INH 15 mg/kg or once-weekly rifapentine 600 mg plus INH 15 mg/kg. Preliminary data on treatment discontinuation and adverse events from Stage 1 were reviewed by the Data Safety and Monitoring Board before patients were enrolled in the next stage. In Stage 2, 75 patients were randomized in a 2:1 ratio to receive once-weekly rifapentine 1,200 mg plus INH 15 mg/kg or once-weekly rifapentine 600 mg plus INH 15 mg/kg. Thus, 50 patients were expected in each of the three treatment arms. Rifapentine was provided as 150-mg tablets. All patients received eight tablets once weekly: four, six, or eight of them were rifapentine, depending on the assigned dose, and the remainder were dummy tablets. Study (continuation phase) therapy was given for 16 weeks, thus completing 6 months of total tuberculosis treatment. Patients with positive sputum cultures at randomization or after 4 weeks on study therapy (i.e., after 2 or 3 months of tuberculosis treatment) were treated for an additional 12 weeks, for 9 months of total treatment. The decision to prolong the treatment was based on the very high relapse rates (15–23%) seen in patients who were culture-positive at the

end of induction therapy in both the rifampin and the rifapentine treatment arms in TBTC Study 22 (2).

Randomization

The TBTC Data and Coordinating Center at the CDC randomized patients at enrollment. Randomization was blocked by study site.

Study Procedures

Patients were seen every 4 weeks for clinical and laboratory evaluation. Clinical evaluation included questioning about symptoms of tuberculosis (fever, night sweats, cough) and adverse events (gastrointestinal complaints, arthralgias, paresthesias, open-ended questions). Laboratory evaluation included complete blood cell count, serum liver enzymes and creatinine levels, and acid-fast bacilli sputum culture (for pulmonary tuberculosis patients). All study patients were followed for at least 2 weeks after the completion of study phase therapy or until any toxicity resolved.

Definition of Study Outcomes

Completion of study therapy. This occurred when all 16 or 28 doses of the prescribed study medications had been administered within a 22- or 34-week period, respectively. Patients were considered not to have completed study therapy when they discontinued treatment for any reason, including adverse events, intolerance to the medications, clinical or bacteriologic failure, refusal to undergo further study therapy, or withdrawal of consent.

Adverse events. This included all reportable, serious adverse events as defined by the U.S. Food and Drug Administration (7), as well as any Grade 3 or Grade 4 toxicity (based on defined clinical and laboratory parameters), pregnancy, any new medical diagnosis, or any event that resulted in permanent discontinuation of the study drug. The physician–investigator caring for the patient designated each adverse event as "probably," "possibly," or "not at all" due to study drugs.

Sample Size and Analysis

The primary outcome of the study was the proportion of subjects who failed to complete study therapy for any reason. A one-sided Z test (8) was used to test the study hypothesis that the observed outcome rate would be equal to the expected value. Phase II studies are not generally powered to detect statistically significant differences in outcomes among treatment groups, as they are usually too small. Among HIV-negative patients in TBTC Study 22 (2), the rate of failure to complete study therapy was 7.22%. Using a significance level of 5% and a one-sided test (because we were interested only in excess events in the higher-dose arms), combining patients on the lowest dose from the two stages, and performing pairwise comparisons, the power of the study to detect a 3-fold increase in failure to complete the study treatment was 70%. Because rifapentine absorption is increased when it is taken with meals, we compared the rate of adverse events "possibly" associated with study medications in those patients who reported taking more than two-thirds of their medication doses with meals with the rate in those who did not. We also performed a post hoc analysis of outcomes compared across four rifapentine dose-by-weight categories (5–10, > 10–15, > 15–20, and > 20 mg/kg). Data analysis used SAS version 6.12 (SAS Institute, Inc., Cary, NC) and Epi Info version 6.04d (CDC, Atlanta, GA).

Human Subjects Protection

The study was approved and overseen by Institutional Review Boards at CDC and at each study site. Each participant provided written informed consent. A Data and Safety Monitoring Board reviewed outcome data four times, using the Lan–DeMets spending function approach with an O'Brien–Fleming stopping rule (9, 10).

RESULTS

From July 26, 1999, through January 3, 2000, 75 patients were enrolled in Stage 1; from January 3, 2000, through October 6, 2000, 75 patients were enrolled in Stage 2. In Stage 1, 24 patients were randomized to receive rifapentine 600 mg and 51 to receive rifapentine 900 mg. In Stage 2, 28 patients were randomized to receive rifapentine 600 mg and 47 to receive rifapentine 1,200 mg. Demographic features of all 150 patients are shown in Table 1. There were no significant differences in demographic features, presence of comorbid conditions, baseline laboratory tests, or functional capacity among the patients compared within each stage. When the same variables were compared across the three dose groups (combining both stages), there were significantly more Hispanic persons in the rifapentine 1,200-mg group (14/47 [30%] versus 4/51 [8%] in the rifapentine 900-mg group and 10/52 [19%] in the rifapentine 600-mg group; $p = 0.02$, chi-square). There were no other significant differences among the three dose groups.

The proportion of patients on each of the three rifapentine doses who did not complete study treatment or who experienced an adverse event during study treatment is shown in Table 2. The proportion who did not complete study treatment or who experienced an adverse event during study treatment, according to four dose-by-weight categories, is shown in Table 3. Using Fisher's exact test, there were no statistically significant differences in any of the outcomes when compared within each stage (data not shown), across the three treatment doses, or across the four rifapentine dose-by-weight categories. Chi-square for trend toward adverse events "possibly" due to study treatment across the three treatment doses was of borderline statistical significance ($p = 0.051$) when a first trimester spontaneous abortion was considered as possibly related, nonsignificant ($p = 0.14$) when it was not; it was also of borderline statistical significance across the four rifapentine dose-by-weight categories ($p = 0.06$). Finally, there were no significant differences in reported symptoms or routine monthly laboratory test results among the three treatment dose groups, including thrombocytopenia, rashes, or flu-like symptoms, all of which have been seen with higher doses of rifampin (data not shown).

The number of doses of study medication received before discontinuation of treatment and the reason for the discontinuation in the eight patients who did not complete study treatment

TABLE 1. DEMOGRAPHICS OF TUBERCULOSIS PATIENTS RANDOMIZED TO THREE RIFAPENTINE TREATMENT DOSAGES IN TWO STUDY PHASES

	Rifapentine Dosage*		
Variables	600 mg (*n = 52, # %*)	900 mg (*n = 51, # %*)	1,200 mg (*n = 47, # %*)
Age, yrs			
Mean (SD)	46 (14)	43 (15)	42 (13)
Race			
White	23 (44)	15 (29)	18 (38)
Black	17 (31)	24 (47)	20 (43)
Asian/Pacific Islander	9 (17)	9 (18)	7 (15)
Other	1 (02)	3 (6)	2 (4)
Sex			
Male	41 (79)	39 (76)	31 (66)
Female	11 (21)	12 (24)	16 (34)
Ethnicity†			
Hispanic	10 (19)	4 (8)	14 (30)
Birthplace			
United States or Canada	29 (56)	30 (59)	23 (49)
Other	23 (44)	21 (41)	24 (51)
Site of tuberculosis			
Pulmonary only	41 (79)	43 (84)	42 (89)
Extrapulmonary only	5 (10)	5 (10)	2 (4)
Both	6 (11)	3 (6)	3 (6)

* Each patient also received once-weekly isoniazid 15 mg/kg.
† $p = 0.02$; other comparisons not statistically significant.

TABLE 2. ADVERSE EVENTS AND PERMANENT RIFAPENTINE TREATMENT DISCONTINUATION DURING STUDY TREATMENT BY RIFAPENTINE TREATMENT DOSE

	Treatment Arm		
Outcomes	RPT 600 mg/INH (*n = 52*)	RPT 900 mg/INH (*n = 51*)	RPT 1,200 mg/INH (*n = 47*)
Any event			
Treatment discontinuation	3 (6%)	2 (4%)	3 (6%)
Adverse event	5 (10%)	11 (21%)	7 (15%)
Event possibly related to study treatment			
Treatment discontinuation	0	0	1 (2%)
Adverse event*	0	1 (2%)	3 (6%)

Definition of abbreviations: INH = isoniazid; RPT = rifapentine.
* p = 0.051, chi-square for trend.

are described in Table 4. The one treatment discontinuation that was "possibly" associated with study treatment was in a patient with chronic hepatitis B antigenemia who received rifapentine 1,200 mg plus INH and developed nausea, weakness, and stomach pain at Week 11. AST and alanine aminotransferase (ALT) were normal at baseline; at Week 11, AST was 89 U/L and ALT was 217 U/L; after 2 weeks off of the study medication, AST was 157 U/L and ALT was 765 U/L. Bilirubin remained normal throughout. The supervising physician decided to discontinue rifapentine and INH, and the patient completed tuberculosis treatment with a regimen that did not contain a rifamycin.

Descriptions of the 23 reported adverse events are provided in Table 5. The four adverse events considered by the local study investigators as "possibly" related to study drugs are highlighted. Elevated liver function tests were reported in three patients; of these, one discontinued study treatment (*see* previous text), and the other two completed treatment within the time allotted by the study protocol. The fourth event considered "possibly" related to study drugs was a spontaneous abortion. This occurred in a woman who was not using contraception despite her agreeing at the time of enrollment into the study, as all women of childbearing potential were required to, to avoid pregnancy during study treatment. She took her final three doses of study medication during the 3 weeks after her last menstrual period. Pregnancy was confirmed by plasma human chorionic gonadotropin beta subunit 2 weeks after her last dose of study medication. She reported a spontaneous abortion 3.5 weeks later.

Although no specific instructions were given regarding receiving rifapentine and INH with a meal (to increase rifapentine absorption), 78% of study patients took more than two-thirds of their study medication doses around the time of a meal. All four patients with adverse events "possibly" associated with study medications took more than two-thirds of their doses with meals. However, the difference in adverse events among those who received more than two-thirds of their doses near mealtime (4/125) and those who did not (0/23) was not statistically significant (p = 1.0, Fisher's exact test).

DISCUSSION

Rifapentine offers a major public health advantage over other current tuberculosis medications because its pharmacokinetic profile allows for once-weekly dosing (4, 11). Recent Phase III efficacy trials used a 600-mg, once-weekly dose, based on animal and Phase 1 human data. Unfortunately, these studies found that once-weekly rifapentine 600 mg with INH 900 mg is associated with an unacceptably high relapse rate (1–3). Several lines of reasoning indicate that higher doses of rifapentine are likely to improve its efficacy.

First, one hypothesized basis for the decreased effectiveness of once-weekly rifapentine-containing regimens is the higher protein binding of rifapentine compared with that of rifampin (97 compared with 85%), resulting in lower concentrations of unbound, biologically active drug at the site of action (4). If important, this effect could be counteracted by a higher rifapentine dose. Second, highly predictive animal model data show a strong correlation between increased doses of rifapentine (mg/kg) and increased efficacy (12). Finally, a clinically relevant dose–response curve, within the standard range of doses, has been demonstrated with another rifamycin, rifampin (5).

The safety of higher doses needs to be established before Phase III studies can be undertaken. The only previous safety data on rifapentine doses higher than 600 mg come from a pharmacokinetic study of eight healthy volunteers who received one dose each of 600, 900, and 1,200 mg, with a 21-day washout period between doses; no adverse events were observed (3).

This double-blind, dose-escalating study showed no statistically significant differences in the 900- and 1,200-mg doses of rifapentine compared with the 600-mg dose (the Food and Drug Administration–approved dose) with regard to the primary outcome measure of completion of tuberculosis therapy with the assigned dose. In fact, only one patient had treatment discontinued due to possible study therapy reaction; that pa-

TABLE 3. ADVERSE EVENTS AND PERMANENT TREATMENT DISCONTINUATIONS BY RIFAPENTINE DOSE BY WEIGHT CATEGORIES

	RPT mg/kg (+ INH)			
Outcomes	5–10 mg/kg (*n = 40*)	> 10–15 mg/kg (*n = 46*)	> 15–20 mg/kg (*n = 45*)	> 20 mg/kg (*n = 19*)
Any event				
Treatment discontinuation	2 (5%)	2 (4.3%)	3 (6.6%)	1 (5.2%)
Adverse event	6 (15.0%)	8 (17.4%)	6 (13.3%)	3 (15.8%)
Event possibly related to study treatment				
Treatment discontinuation	0	0	1 (2.2%)	0
Adverse event*	0	1 (2.2%)	1 (2.2%)	2 (10.5%)

For definition of abbreviations, *see* Table 2.
* p = 0.06, chi-square for trend.

TABLE 4. DESCRIPTION OF EIGHT PATIENTS WHO DID NOT COMPLETE RIFAPENTINE STUDY TREATMENT

Treatment Dose	No. of Doses Received	Reason Treatment Discontinued
Rifapentine 600 mg		
Patient 1	1	Refused further study treatment
Patient 2	4	Died (not tuberculosis related, *see* Table 5)
Patient 3	0	Withdrew consent
Rifapentine 900 mg		
Patient 1	5	Moved
Patient 2	3	Withdrew consent
Rifapentine 1,200 mg		
Patient 1	1	Lost to follow-up
Patient 2	9	Treatment failure
Patient 3	11	Physician discontinued treatment due to hepatotoxicity (*see text*)

tient was in the 1,200-mg dosing arm. There were also no significant differences in overall adverse events or in adverse events "possibly" associated with study therapy. The three events in the rifapentine 1,200-mg arm associated with study therapy indicate a borderline significant trend toward increased adverse events. Events were judged to be "probably" related, "possibly" related, or "not at all" related to study treatment by each site's principal investigator. Because both the investigator and the patient were blinded to the dosage, bias against higher doses is unlikely to explain this modest difference.

Currently, rifapentine dosing is not based on weight, in contrast to many other antituberculosis drugs. Therefore, study subjects were randomly assigned to the three possible treatment arms without consideration of their weight. However, because other antituberculosis agents have dose-related toxicities, we performed a post hoc analysis of toxicity according to rifapentine dose in milligrams per kilogram. This analysis also found a nonsignificant trend ($p = 0.06$) toward higher study drug–related toxicity at a dose higher than 20 mg/kg.

With only approximately 50 patients in each treatment arm, small differences in tolerability might have existed but may not have been detected. In addition, the study drug, rifapentine, was not given alone; every patient was also treated with 15 mg/kg of once-weekly INH, which may have influenced toxicity. Currently, this issue is not relevant because rifapentine would always be given with INH. However, for treatment of latent tuberculosis or with the advent and testing of new drugs for tuberculosis (such as the fluoroquinolones), it would be important to know the extent of toxicity attributable to rifapentine alone.

Acquired rifamycin monoresistance has been documented in HIV-seropositive adults who fail or relapse after treatment with intermittent regimens with INH and each of the three rifamycins, rifampin (13), rifapentine (14), and rifabutin (15). Although higher-dose rifapentine will likely improve sputum sterilization, further research on different companion drugs for use in intermittent regimens will also be necessary (16).

In conclusion, rifapentine 900-mg, once-weekly dosing appears to be safe and well tolerated. Phase III efficacy trials of treatment for latent tuberculosis with once-weekly rifapentine 900 mg and INH have been initiated by the TBTC and others. Studies on alternative companion drugs to be used with higher-dose rifapentine for treatment of active tuberculosis are in progress. In addition, this is the first reported study in humans of rifapentine at the 1,200-mg dose. We found a borderline significant trend ($p = 0.051$) toward increased study drug–associated adverse events in this treatment arm only when the first trimester spontaneous abortion, a common outcome in early pregnancy, was included as "possibly" associated with study treatment. When this event was excluded, because attribution is uncertain, and rifampin has an extensive history of safety in use during pregnancy, the trend disappeared ($p = 0.14$). Thus, further evaluation of the safety and tolerability of the 1,200-mg dose is warranted.

TABLE 5. DESCRIPTION OF 23 ADVERSE EVENTS BY RIFAPENTINE TREATMENT DOSE

RPT 600 mg + INH	RPT 900 mg + INH	RPT 1,200 mg + INH
New diagnosis type II diabetes	Elevated hepatic transaminases (AST 227 U/L)*	Elevated hepatic transaminases (ALT 745 U/L) in patient with chronic Hb_sAg antigenemia*†
Elevated random blood glucose in a patient known to have diabetes who was on oral hypoglycemic agents	Hospitalized for traumatic subdural hematoma and hyponatremia	Elevated hepatic transaminases (AST 358 U/L)*
Hospitalized for thoracentesis of pleural effusion present at enrollment 2 wk earlier	Hospitalization for chest pain, diagnosed with angina	First trimester spontaneous abortion in pregnant woman*
Death due to thromboembolic stroke following abdominal aortic aneurysm repair (normal platelet count)†	Hospitalized with acute myocardial infarction	Pancreatitis; reported nausea and vomiting for 2–3 mo, hospitalized 2 wk after enrollment with amylase 226
Diabetic foot ulcer requiring hospitalization for intravenous antibiotics	Hospitalized with perforated ulcer	Chest pain, outpatient evaluation, diagnosis possible ischemia
	Elevated blood glucose in a patient known to have diabetes who was on insulin	Elevated random blood glucose in a patient known to have diabetes who was on oral hypoglycemic agents
	Elevated blood pressure in patient with known hypertension	Ulcer and leioma of gastric fundus
	New diagnosis of hypertension	
	Depression	
	Hydrocele drained	
	Leg fracture after fall	

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hb_sAg = hepatitis B surface antigen; INH = isoniazid; RPT = rifapentine.
* Events that are possibly associated with study drugs.
† Did not complete study therapy.

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