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Intermittent tuberculosis treatment for patients with isoniazid intolerance or drug resistance

R. Reves,* C. M. Heilig,† J. M. Tapy,* L. Bozeman,† R. P. Kyle,† C. D. Hamilton,‡ N. Bock,† M. Narita,§ D. Wing,¶ E. Hershfield,# S. V. Goldberg,† Tuberculosis Trials Consortium

*Denver Public Health Department, Denver, Colorado, †Centers for Disease Control and Prevention, Atlanta, Georgia, ‡Family Health International 360, Durham, North Carolina, ‡Duke University, Durham, North Carolina, §University of Washington, Seattle, Washington, ¶South Texas-Audie Murphy VA Hospital Research Collaboration, Harlingen, Texas, USA; #University of Manitoba, Winnipeg, Manitoba, Canada

SUMMARY

SETTING: Twenty tuberculosis (TB) clinics in the United States and Canada.

OBJECTIVE: To evaluate the efficacy and safety of a 6-month intermittent regimen of rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB) in human immunodeficiency virus (HIV) negative patients with culture-confirmed pulmonary or extra-pulmonary tuberculosis and either isoniazid (INH) resistance or INH intolerance.

DESIGN: Patients were enrolled in a single-arm clinical trial to receive intermittent dosing after at least 14 initial daily doses of RMP+PZA+EMB. Treatment was continued twice (BIW) or thrice weekly (TIW) per physician/patient preference for a total of 6 months, with 2 years of follow-up for relapse after treatment.

RESULTS: From 1999 to 2004, 98 patients were enrolled, 78 with reported INH resistance and 20 with INH intolerance. BIW dosing was used in 77 and TIW in 21. Study treatment was completed in 73 (74%). Reasons for discontinuation were hepatic adverse events ($n = 12$), other adverse effects ($n = 3$) and other reasons ($n = 10$). Failure ($n = 1$) and relapse ($n = 2$) occurred in 3 (3.5%, 95%CI 1.2–9.8) of 86 patients eligible for efficacy analysis, all occurring in patients with cavitary, acid-fast bacilli smear-positive pulmonary TB.

CONCLUSIONS: Intermittent RMP+PZA+EMB appears to be effective in HIV-negative patients, but the regimen is poorly tolerated, possibly due to the prolonged use of PZA. Alternative regimens of lower toxicity are needed.

KEY WORDS: tuberculosis; anti-tuberculosis agents; mycobacterial infections

ISONIAZID (INH), a key component of anti-tuberculosis treatment,[1] may not be used due to INH drug resistance, INH intolerance or toxicity, or when INH is unavailable.[2,3] For drug-susceptible TB, a 6-month regimen of INH, rifampin (RMP) and pyrazinamide (PZA) during an intensive 2-month period, followed by INH and RMP for the 4-month continuation phase, has been shown to be highly effective whether administered daily or on an intermittent twice- or thrice-weekly schedule. Intermittent regimens including ethambutol (EMB) or streptomycin (SM) for the first 8 weeks facilitate the use of directly observed therapy,[4–6] which in turn markedly improves adherence to and outcomes of anti-tuberculosis treatment.[7]

The 1993 US Public Health Service recommendations for anti-tuberculosis treatment in the United States that were operative at the time of this study included two options for the treatment of patients with TB due to INH-resistant strains (detected in >4% of previously untreated TB cases in the United States[8]) and those with INH-induced hepatitis, occurring in 4% of individuals on anti-tuberculosis treatment.[9] These options were a 12-month regimen of RMP+EMB and a 6-month regimen of RMP+EMB+PZA;[10] the latter was supported by data from 12 randomized studies of 6-month regimens, many administered thrice-weekly, demonstrating efficacy despite baseline INH resistance as long as RMP resistance was absent.[11]

We report the findings of a study evaluating the hypothesis that a 6-month directly observed regimen of RMP+PZA+EMB would be effective, safe and tolerable when given twice or thrice weekly.

METHODS

The Tuberculosis Trials Consortium conducted a

Footnote: A list of participating clinical sites can be found at the end of the article.

Correspondence to: Randall Reves, Denver Public Health Department, 605 Bannock Street, Denver, CO 80204, USA. Tel: (+1) 303 602 7257. Fax: (+1) 303 602 7270. e-mail: rreves@dhha.org

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prospective, open-label, single-arm study from 5 August 1999 to 27 October 2004. The primary outcome measure was the combined rate of failure during treatment and relapse after treatment completion. The secondary outcome measures were tolerability and safety. Institutional review boards at both the US Centers for Disease Control and Prevention (CDC) and participating sites approved the protocol.

Human immunodeficiency virus (HIV) negative adults aged ⩾18 years with culture-confirmed tuberculosis (TB) and a clinical decision not to use INH within the first 70 days of treatment were enrolled. Documentation of an adequate initial regimen was required, based on the then-current 1993 US guidelines,[10] with the specific requirement that RMP, PZA and EMB (or SM) be used along with INH until resistance or intolerance to INH was detected. Exclusion criteria included resistance or intolerance to RMP, PZA or EMB, >21 days of antituberculosis treatment with other drugs with known tuberculosis activity, pregnancy, diagnosis of silicotuberculosis or TB of the central nervous system, amino aspartate transaminase (AST) >3 times the upper limit of normal (ULN), and total bilirubin level >2.5 × ULN.

Study treatment

After pre-enrollment treatment of 14–70 days, study treatment consisting of intermittent, directly observed RMP+EMB+PZA was started, preferably twice weekly, although thrice weekly was permitted. Medications followed the then-current guidelines for twice-weekly weekly dosing:[10] RMP 600 mg, EMB 40–50 mg/kg and PZA 40–70 mg/kg. Participants changing from twice to thrice weekly to manage intolerance were assigned the following recommended dosing: RMP 600 mg, EMB 25–35 mg/kg, and PZA 30–40 mg/kg. Completion of treatment was defined initially as receiving 26 weeks of RMP+EMB+PZA within 32 calendar weeks, and was later extended to 38 weeks within 44 calendar weeks for participants who had both cavitary lung disease and positive sputum cultures after 2 months of treatment.[1]

Study procedures

The study divided participant involvement into treatment (combining pre-study and study treatment) and follow-up (Figures 1 and 2). During study treatment, participants were evaluated monthly for toxicity. Sputum specimens were collected monthly from participants with pulmonary TB until two negative cultures were obtained, at the first three post-treatment visits, at 24 months, and when relapse was suspected.

Baseline *Mycobacterium tuberculosis* isolates and isolates obtained on suspicion of treatment failure or relapse were sent to the CDC mycobacteriology laboratory for identification and drug susceptibility testing (DST), when available. An independent adjudication committee evaluated all participants with positive cultures occurring after early discontinuation or after 16 weeks of treatment, and reviewed clinical information and DNA profiling of relevant isolates to confirm endpoints. Treatment failure was suspected for a positive TB culture following 16 calendar weeks of treatment, and relapse was suspected for a positive TB culture within 2 years of treatment completion.

Adverse events were reported to the data center by the site investigators. They were defined as hepatic at the discretion of site investigators or were identified as hepatic if the AST or alanine aminotransferase (ALT) value was >5 x ULN or if the AST or ALT value was >3 x ULN in the presence of symptoms consistent with hepatitis.

Sample size and statistical considerations

A sample size of 215 participants would allow the study to distinguish a failure and relapse rate of ⩾10% from the historically acceptable rate of 5% (range 4–6), with a one-sided comparison of proportions, 95% confidence, 80% power and up to 30% loss to follow-up.

To assess risk factors for failure and relapse and for hepatic events, we used the Wilson score method[12] to construct confidence intervals (CIs) for proportions and exact logistic regression to quantify strength of association. All calculations were carried out in SAS 9.2 (SAS Institute, Cary, NC, USA) and *R* 2.14.0 (R Development Core Team, Vienna, Austria). Probabilities of developing hepatic events were calculated with time-to-event analysis using the Kaplan-Meier method.[13]

RESULTS

Enrollment and baseline characteristics

The trial enrolled 98 participants between August 1999 and October 2004, including 78 with reported resistance and 20 with INH intolerance; 89% had pulmonary TB, with or without additional extrapulmonary disease, and 48% had evidence of cavitary disease on chest radiograph (Table 1). Because of slow accrual, enrollment was stopped early after consultation with the data monitoring committee. Interim analysis indicated that data on participants enrolled by the time of stopping would be sufficient to support the primary hypothesis.[14] All participants were included in tolerability and safety analyses. The assessment of successful treatment, characterized by the lack of treatment failure and relapse, uses the data from 86 participants, with ⩾6 months of follow-up after treatment.

Enrollment was based on a site report of INH resistance in 78 (80%) participants; subsequent tests

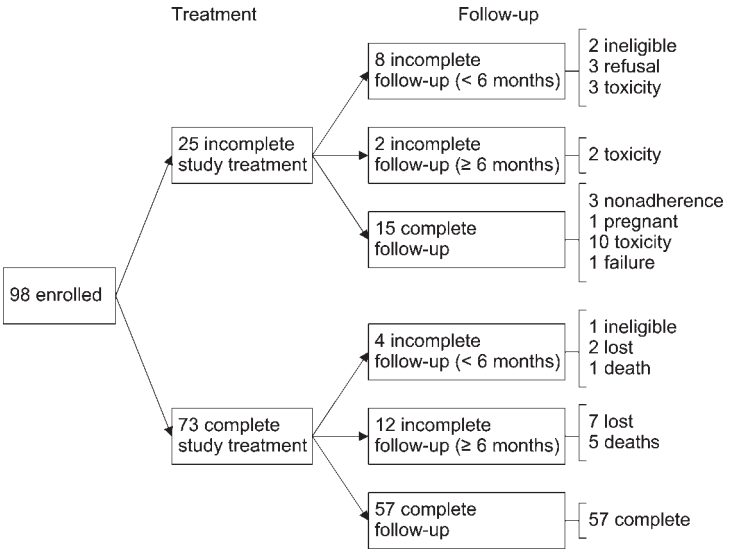

Figure 1 Treatment lasted up to 9 months, and follow-up lasted up to 2 years. All patients were evaluated for safety and tolerability, including patients found to be ineligible for efficacy analysis. Two participants experienced relapse after 11 and 26 months of follow-up, and were considered to have completed post-treatment follow-up. All six deaths occurred after completion of study treatment; four were attributed to cancer, one to cocaine toxicity and one to complications following surgery for multiple decubitus ulcers after an incapacitating cardiac event.

found 6 of these to be INH-susceptible, leaving confirmed resistance in 72 (73%). CDC mycobacteriol evaluation of enrollment isolates from 41 participants detected resistance to one or more other drugs besides INH (Table 1); none had resistance to RMP. One patient with INH susceptibility at the CDC discontinued study treatment and one with PZA resistance stopped study treatment due to hepatitis.

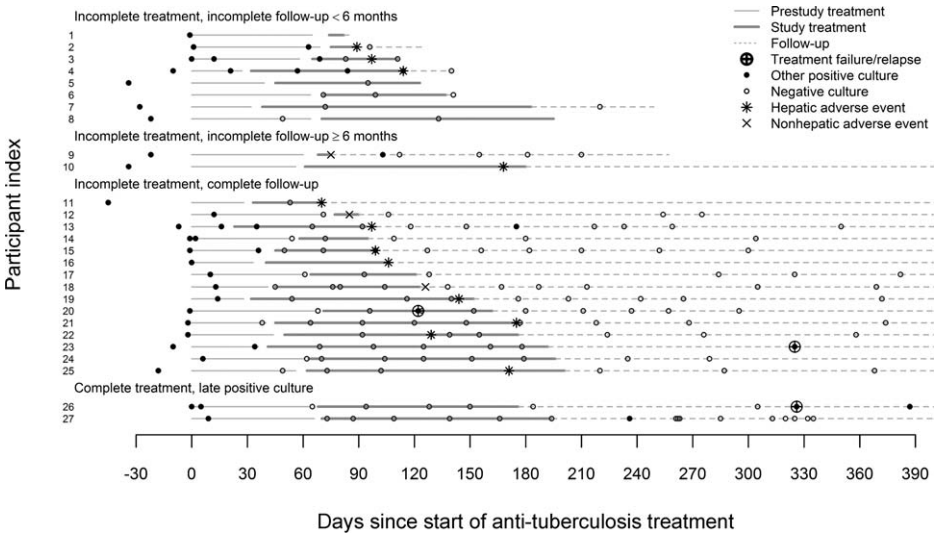

Figure 2 Each participant's time since start of treatment is represented as gray line segments: pre-enrollment treatment (thin, solid), on-study treatment (thick, solid) and post-treatment follow-up (thin, dotted). The top three sections (index 1–25) correspond to the three subgroups with incomplete treatment in Figure 1. Participants 11, 15 and 16 discontinued treatment after pyrazinamide rechallenge. Participants 26 and 27 had both complete treatment and complete follow-up. Participant 20 experienced treatment failure. Participants 23 and 26 experienced relapse. Participants 13 and 27 had false-positive culture results based on both clinical evaluation and results of DNA fingerprint analysis. Participant 9 had a true-positive culture after stopping study treatment for an adverse event only 14 days after enrollment. This participant completed 75 days of pre-enrollment and study treatment, had negative follow-up cultures through completion of non-study treatment with daily rifampin, ethambutol and pyrazinamide, and thus was determined not to have had treatment failure or relapse. See Table 2 for further details on treatment-limiting adverse events. The other 71 participants are not shown in this Figure.

Table 1 Baseline demographic and clinical characteristics, and their associations with incomplete study treatment

Characteristic	All *n*	Incomplete *n* (%)	Complete *n* (%)	OR	*P* value*
Total	98	25 (26)	73 (74)		
Completion of follow-up					
Incomplete, <6 months	12	8 (67)	4 (33)	7.4	
Incomplete, ⩾6 months	14	2 (14)	12 (86)	0.64	
Complete	72	15 (21)	57 (79)	Reference	<0.01
Sex					
Male	65	18 (28)	47 (72)	1.4	
Female	33	7 (21)	26 (79)	Reference	0.63
Age, years					
⩾45	44	10 (23)	34 (77)	0.77	
<45	54	15 (28)	39 (72)	Reference	0.65
Race/ethnicity					
American Indian	1	0 (0)	1 (100)	2.0†	
White	15	4 (27)	11 (73)	0.70	
Black	20	5 (25)	15 (75)	0.64	
Asian	27	4 (15)	23 (85)	0.34	
Hispanic (white or black)	35	12 (34)	23 (66)	Reference	0.54
Region of birth					
Europe	3	0 (0)	3 (100)	0.84†	
Africa	7	3 (43)	4 (57)	2.2	
Other Americas	12	5 (42)	7 (58)	2.1	
Mexico	18	5 (28)	13 (72)	1.2	
Asia	26	4 (15)	22 (85)	0.55	
US/Canada	32	8 (25)	24 (75)	Reference	0.40
Body mass index, kg/m^2					
<18.5	18	8 (44)	10 (56)	2.9	
⩾18.5	80	17 (21)	63 (79)	Reference	0.07
Diabetes					
Yes	20	6 (30)	14 (70)	1.3	
No	78	19 (24)	59 (76)	Reference	0.77
Alcohol use					
Yes	23	7 (30)	16 (70)	1.4	
No	75	18 (24)	57 (76)	Reference	0.59
Sputum smear status‡					
Positive	53	13 (25)	40 (75)	1.0	
Negative	38	9 (24)	29 (76)	Reference	1.00
Anatomic site of TB					
Both	4	2 (50)	2 (50)	3.1	
Extra-pulmonary	11	3 (27)	8 (73)	1.2	
Pulmonary	83	20 (24)	63 (76)	Reference	0.69
Chest cavities‡					
Present	47	13 (28)	34 (72)	1.3	
Absent	49	11 (22)	38 (78)	Reference	0.64
Previous TB episode					
Yes	13	4 (31)	9 (69)	1.4	
No	85	21 (25)	64 (75)	Reference	0.73
Enrollment group					
Reported INH intolerance§	20	7 (35)	13 (65)	1.8	
Reported INH resistance	78	18 (23)	60 (77)	Reference	0.39
Laboratory-confirmed resistance					
INH-resistant	72	16 (22)	56 (78)	0.54	
INH-susceptible	26	9 (35)	17 (65)	Reference	0.29
PZA- or EMB-resistant	5	1 (20)	4 (80)	0.72	
PZA- and EMB-susceptible	93	24 (26)	69 (74)	Reference	1.00
Any resistance other than INH¶	41	13 (32)	28 (68)	1.7	
No resistance besides INH	57	12 (21)	45 (79)	Reference	0.25
INH treatment duration, days					
⩽28	45	12 (27)	33 (73)	1.1	
>28	53	13 (25)	40 (75)	Reference	0.82
Days of pre-study treatment, days					
⩽55	49	13 (27)	36 (73)	1.1	
>55	49	12 (24)	37 (76)	Reference	1.00
Doses in first 70 days, doses					
⩽40	54	16 (30)	38 (70)	1.6	
>40	44	9 (20)	35 (80)	Reference	0.36

Table 1 (continued)

Characteristic	All *n*	Incomplete *n* (%)	Complete *n* (%)	OR	*P* value*
Initial study dose frequency, /week					
2 times	82	23 (28)	59 (72)	2.7	
3 times	16	2 (12)	14 (88)	Reference	0.23
Hepatic event					
Yes	12	12 (100)	0 (0)	85.6†	
No	86	13 (15)	73 (85)	Reference	<0.01
Treatment failure/relapse					
Yes	3	2 (67)	1 (33)	6.1	
No	95	23 (24)	72 (76)	Reference	0.16

* The *P* value is for the score test in each bivariate exact logistic regression model.
† OR is median unbiased estimate.
‡ These categories do not add up to 98 because of missing data.
§ Reported reasons for prior INH intolerance include one or more of the following: liver abnormalities ($n=10$), skin rash ($n=9$), fever ($n=2$), intractable nausea ($n=4$) and neuropathy ($n=1$).
¶ Includes resistance to EMB, PZA, streptomycin ($n=33$), thioacetazone ($n=9$) or fluoroquinolone ($n=2$); no rifamycin or aminoglycoside resistance was seen.
OR = odds ratio; TB = tuberculosis; INH = isoniazid; PZA = pyrazinamide; EMB = ethambutol.

Treatment patterns and adverse events

Pre-study treatment lasted a median of 55 days (range 13–73) before the start of study treatment using INH until resistance or intolerance was detected, along with the required regimen of RMP+EMB+PZA in all but four, who received SM instead of EMB during pre-study treatment. Pre-study treatment for one participant was administered thrice weekly, but the remainder received at least 14 daily directly observed therapy (DOT) doses, followed by twice-weekly or thrice-weekly dosing. The focus on early implementation of intermittent dosing resulted in a median number of 39 observed doses (range 23–70, interquartile range 33–54) during the first 70 days of combined pre-study and study anti-tuberculosis treatment.

Among all participants, 74% completed the RMP+EMB+PZA study treatment regimen, while the remaining 26% did not complete the prescribed regimen, none due to death (Figure 1 and Table 1). The most common reasons for incomplete treatment were adverse drug events ($n=15$) and non-adherence ($n=5$). Among the 15 participants who permanently discontinued study treatment because of adverse events (Figure 2, Table 2), reasons included hepatic events ($n=12$), nausea ($n=1$), rash ($n=1$) and flu-like symptoms ($n=1$). None experienced renal impairment.

Physicians started thrice-weekly regimens for 16 participants (median PZA dose 33 mg/kg, range 29–43) and twice-weekly for 82 (median PZA dose 51 mg/kg, range 33–60), of whom 7 were changed to thrice-weekly to manage drug intolerance. Treatment was completed by 14/16 compared to 59/82 participants started on thrice-weekly and twice-weekly dosing, respectively. Of the five who changed to thrice-weekly dosing due to gastro-intestinal complaints, two completed study treatment, while three discontinued due to hepatic adverse events.

Twelve participants (12.2%, 95%CI 7.1–20.2) (Table 2) discontinued treatment due to hepatotoxicity. None of these had bilirubin elevations or other consequences of severe liver injury such as hospitalization or death. PZA was permanently discontinued for all 12: seven were presumed to have PZA intolerance as they tolerated the resumption of off-study regimens that included RMP and EMB (three had recurrent hepatic transaminase enzyme elevations with PZA rechallenge), two completed treatment with EMB and levofloxacin (one of whom failed an RMP re-challenge); two who had events occurring after completing 144 and 168 days of anti-tuberculosis treatment did not resume any treatment, and one was lost to follow-up. There were no significant associations of plausible risk factors with hepatic adverse events (Table 3).

The median enrollment twice-weekly PZA dose among patients discontinuing due to hepatic events was 51 mg/kg (range 42–54), very similar to enrollment doses administered to participants who did not experience treatment-limiting hepatic events (median 51, range 33–60). Probabilities for developing hepatic events from start of anti-tuberculosis treatment were as follows: days 0–84, 1%; 85–112, 5%, 113–140, 2%; 141–168, 2%; and 169–196, 2%.

Treatment failures and relapses

Overall, 87% of participants completed $\geqslant 6$ months of follow-up after treatment (Figure 1, Table 1). Persons who completed study treatment were more likely than those not completing treatment to complete $\geqslant 6$ months of follow-up (OR 7.4, $P < 0.01$), but only seven (7.1%) patients were lost to follow-up during the treatment phase (Figure 2).

The adjudication committee reviewed data for six participants who had a positive culture result either after the last study dose or 16 weeks (112 days) after starting anti-tuberculosis treatment, and concluded that 1 participant experienced treatment failure

Table 2 Clinical features of participants who discontinued study treatment due to adverse events

Index*	Age (years), sex	Country of origin/ race or ethnicity	Risk factors†	Treatment days to enrollment	Enrollment AST ratio‡	Enrollment PZA dose, mg/kg	Enrollment DOT frequency	Onset days from enrollment	AST/ALT ratios‡	Symptoms	Final regimen and comments§
Participants with hepatic adverse events											
2	29, male	Guatemala/ Hispanic	—	70	1.0	51	2	19	8.9/19.3	Nausea, vomiting, fatigue	RMP+EMB, incomplete. Lost to follow-up. Presumed PZA toxicity
3	41, male	Guatemala/ Hispanic	Alcoholic hepatitis	63	0.7	52	2	34	16.4/10.4	Abdominal pain	Moved to Guatemala and lost to follow-up. Pancreatitis also diagnosed
4§	85, male	China/Asian	Alcohol, underweight	28	2.3	51	2	12	8.2/5.9	—	RMP+EMB+CFX completed. Attributed to PZA or alcohol
10	43, male	Mexico/Hispanic	—	57	0.7	52	2	111	2.5/3.4	Nausea	EMB-LFX completed
11¶	26, female	Canada/White	—	32	0.9	53	2	38	5.8/13.9	Headache, dizziness, fatigue	RMP-EMB completed. R/C: PZA toxicity
13	81, male	Mexico/Hispanic	Underweight	17	2.0	51	2	80	6.9/5.7	—	RMP+EMB+LFX completed. Presumed PZA toxicity
15	44, female	Mexico/Hispanic	Diabetes	41	0.5	51	2	58	5.0/8.4	Only during rechallenge, lethargy, anorexia	RMP-EMB completed. R/C: PZA toxicity
16	19, female	Philippines/Asian	—	40	1.7	54	2	66	13.5/7.2	Nausea, vomiting, loss of appetite	RMP-EMB completed R/C: PZA toxicity. Hepatitis A also diagnosed.
19	40, male	Dominican Republic/Hispanic	—	28	0.5	51	2	116	3.9/4.8	Nausea, decreased appetite	EMB+LFX completed. Event had continued on RMP+EMB rechallenge
21	29, female	US/White	—	44	0.8	51	2	131	29.7/36.3	Nausea, decreased appetite, headache, weakness, tea-colored urine	Permanently discontinued TB treatment. Viral hepatitis panel negative
22¶	38, female	Sudan/Black	—	44	0.5	39	3	85	4.8/11.2	—	RMP+EMB+LFX completed
25	54, male	Somalia/Black	—	60	1.4	42	2	111	7.3/8.2	Nausea, decreased appetite	Permanently discontinued TB treatment, considered sufficient by Site PI. Hepatitis B and C also diagnosed
Participants with non-hepatic adverse events											
9¶	59, male	US/White	Alcohol, non-injection drugs	61	1.3	54	2	14	Refused	Nausea	Daily RMP+EMB+PZA completed without nausea. Study regimen discontinued because of nausea and 'too many pills'
12¶	45, male	US/White	Alcohol, non-injection drugs, under-weight	72	0.9	50	2	13	0.9/0.5	Rash, pruritus	INH+EMB completed. Rifamycin allergy diagnosed. Peripheral neuropathy from enrollment did not recur.
18	37, female	Dominican Republic/ Hispanic	Diabetes	41	0.5	51	2	85	1.2/2.0	Weakness and 'heavy eyes' 1 h after twice-weekly doses	Daily RMP+EMB+PZA completed after syndrome persisted on thrice-weekly treatment. Rifamycin flu-like syndrome diagnosed.

* Index numbers in column 1 correspond to index numbers in Figure 2.
† Risk factors reported on enrollment history form: — = none identified; alcohol = 'using excess alcohol within the past year'; underweight = '>10% below ideal body weight'.
‡ Maximum AST and ALT value divided by the upper limit of normal for the laboratory performing the test. No abnormal bilirubin values were reported for these patients. Note that the maximum ratios for subjects 11, 15 and 16 reflect the values after PZA rechallenge.
§ R/C: PZA toxicity = resolution then recurrence of toxicity with PZA rechallenge; presumed PZA = presumptive PZA toxicity with no recurrent toxicity during treatment with RMP+EMB or RMP+EMB+FQ.
¶ Enrolled with suspected INH intolerance (#4, hepatitis; #9, nausea and vomiting; #11, rash; #2, peripheral neuropathy; #22, rash), the remainder were enrolled with reported INH-resistant *M. tuberculosis* isolate.
AST = aspartate aminotransferase; DOT = directly observed therapy; ALT = alanine aminotransferase; RMP = rifampin; EMB = ethambutol; CFX = ciprofloxacin; LFX = levofloxacin; PZA = pyrazinamide; FQ = fluoroquinolones; PI = principal investigator.

Table 3 Risk factors for hepatic adverse events

Characteristic	All *n*	Participants with hepatic events *n* (%)	Participants without hepatic events *n* (%)	OR	*P* value*
Total	98	12 (12)	86 (88)		
Sex					
Male	65	7 (11)	58 (89)	0.68	
Female	33	5 (15)	28 (85)	Reference	0.75
Age, years					
⩾45	44	3 (7)	41 (93)	0.37	
<45	54	9 (17)	45 (83)	Reference	0.22
Body mass index, kg/m^2					
<18.5	18	4 (22)	14 (78)	2.5	
⩾18.5	80	8 (10)	72 (90)	Reference	0.22
Alcohol use					
Yes	23	2 (9)	21 (91)	0.62	
No	75	10 (13)	65 (87)	Reference	0.73
Enrollment group					
Reported INH intolerance	20	3 (15)	17 (85)	1.3	
Reported INH resistance	78	9 (12)	69 (88)	Reference	0.71
Laboratory-confirmed resistance					
INH-resistant	72	9 (12)	63 (88)	1.1	
INH-susceptible	26	3 (12)	23 (88)	Reference	1.00
EMB- or PZA-resistant	5	1 (20)	4 (80)	1.8	
EMB- and PZA-susceptible	93	11 (12)	82 (88)	Reference	1.00
Any resistance other than INH†	41	8 (20)	33 (80)	3.2	
No resistance besides INH	57	4 (7)	53 (93)	Reference	0.12
INH treatment duration, days					
⩽28	45	7 (16)	38 (84)	1.8	
>28	53	5 (9)	48 (91)	Reference	0.54
Days of pre-study treatment, days					
⩽55	49	8 (16)	41 (84)	2.2	
>55	49	4 (8)	45 (92)	Reference	0.36
Doses in first 70 days, doses					
⩽40	54	8 (15)	46 (85)	1.7	
>40	44	4 (9)	40 (91)	Reference	0.54
Initial study dose frequency, /week					
2 times	82	11 (13)	71 (87)	2.3	
3 times	16	1 (6)	15 (94)	Reference	0.68

*The *P* value is for the score test in each bivariate exact logistic regression model.
†Includes resistance to EMB, PZA, streptomycin ($n = 33$), thioacetazone ($n = 9$) or fluoroquinolone ($n = 2$); no rifamycin or aminoglycoside resistance was seen.
OR = odds ratio; INH = isoniazid; EMB = ethambutol; PZA = pyrazinamide.

(Figure 2, participant 20), 2 relapsed (participants 23 and 26) and 3 were determined not to have failure or relapse (Figure 2).

Among the 86 participants with ⩾6 months of follow-up, the combined failure/relapse rate was thus 3.5% (95%CI 1.2–9.8), excluding with 95% confidence the possibility that the true combined rate was ⩾10%. None of the three patients with treatment failure or relapse had follow-up isolates showing acquired drug resistance, and all three were successfully treated with alternative regimens. None of the participants with poor outcomes had treatment interruptions before their event, but all three participants started the study regimen on twice-weekly treatment, were aged ⩾45 years, had acid-fast bacilli smear-positive sputum and cavitary pulmonary TB (OR 5.1, $P = 0.08$). Of the 15 (20%) patients with all of these features, three experienced treatment failure or relapse, compared to 0/71 (0%) patients lacking all of these features (Table 4). The absence or level of INH resistance did not influence the incidence of treatment-limiting adverse events, hepatic events or treatment failure and relapse (data not shown).

DISCUSSION

The study results suggest that the intermittent, directly observed regimen of RMP+EMB+PZA had acceptable efficacy in HIV-negative patients with TB who are unable to receive INH due to resistance or intolerance. Similar outcomes were reported among 2682 patients treated in the 1970s and 1980s using 4- or 5-drug 6-month DOT regimens (largely thrice-weekly) for pulmonary TB, when INH resistance was identified in isolates from 230 patients.[11] Failures occurred in under 1%, and relapses occurred in 15 (6.5%) and 94 (4.0%) of those with and without resistance to INH, respectively.[11] More recent US retrospective studies found relapse rates of 5% and 2%.[15,16] Comparable results were observed in the

Table 4 Risk factors for treatment failure or relapse

Characteristic	All *n*	Participants with treatment failure or relapse *n* (%)	Participants without treatment failure or relapse *n* (%)	OR	*P* value
Total	86	3 (3)	83 (97)		
Sex					
Male	53	3 (6)	50 (94)	2.5†	
Female	33	0 (0)	33 (100)	Reference	0.28
Age, years					
⩾45	38	3 (8)	35 (92)	5.1†	
<45	48	0 (0)	48 (100)	Reference	0.08
Body mass index, kg/m^2					
<18.5	16	1 (6)	15 (94)	2.2	
⩾18.5	70	2 (3)	68 (97)	Reference	1.00
Diabetes					
Yes	16	1 (6)	15 (94)	2.2	
No	70	2 (3)	68 (97)	Reference	1.00
Alcohol use					
Yes	19	3 (16)	16 (84)	14.9†	
No	67	0 (0)	67 (100)	Reference	0.01
Sputum smear status‡					
Positive	48	3 (6)	45 (94)	2.8†	
Negative	34	0 (0)	34 (100)	Reference	0.26
Pulmonary TB					
No	8	0 (0)	8 (100)	2.5†	
Yes	78	3 (4)	75 (96)	Reference	1.00
Disseminated TB					
Yes	4	1 (25)	3 (75)	12.3	
No	82	2 (2)	80 (98)	Reference	0.13
Chest cavities‡					
Yes	44	3 (7)	41 (93)	3.6†	
No	40	0 (0)	40 (100)	Reference	0.24
Previous TB episode					
Yes	11	1 (9)	10 (91)	3.6	
No	75	2 (3)	73 (97)	Reference	0.34
Enrollment group					
Reported INH intolerance	18	0 (0)	18 (100)	0.97†	
Reported INH resistance	68	3 (4)	65 (96)	Reference	0.60
Laboratory-confirmed resistance					
INH-resistant	64	2 (3)	62 (97)	0.68	
INH-susceptible	22	1 (5)	21 (95)	Reference	1.00
EMB- or PZA-resistant	5	0 (0)	5 (100)	4.3†	
EMB- and PZA-susceptible	81	3 (4)	78 (96)	Reference	1.00
Any resistance other than INH§	38	1 (3)	37 (97)	0.62	
No resistance besides INH	48	2 (4)	46 (96)	Reference	1.00
INH treatment duration, days					
⩽28	39	0 (0)	39 (100)	0.30†	
>28	47	3 (6)	44 (94)	Reference	0.25
Days of pre-study treatment, days					
⩽55	43	1 (2)	42 (98)	0.49	
>55	43	2 (5)	41 (95)	Reference	1.00
Doses in first 70 days, doses					
⩽40	44	2 (5)	42 (95)	1.9	
>40	42	1 (2)	41 (98)	Reference	1.00
Initial study dose frequency, /week					
2 times	71	3 (4)	68 (96)	0.82†	
3 times	15	0 (0)	15 (100)	Reference	0.64

* The *P* value is for the score test in each bivariate exact logistic regression model.
† Odds ratio is median unbiased estimate.
‡ These categories do not sum to 86 because of missing data.
§ Includes resistance to EMB, PZA, streptomycin ($n=33$), thioacetazone ($n=9$) or fluoroquinolone ($n=2$); no rifamycin or aminoglycoside resistance was observed.
OR = odds ratio; TB = tuberculosis; INH = isoniazid; EMB = ethambutol; PZA = pyrazinamide.

1980s among 226 patients treated in Kenya with 2 months of RMP+EMB+PZA plus SM, followed by either 4 or 7 months of RMP+EMB given supervised on a daily basis rather than intermittently.[17]

This study has several limitations. We recruited only 45% of the planned sample size of patients before stopping due to slow enrollment. Patient accruals were on target early on when patients with

INH-resistant isolates or INH intolerance were being detected as exclusions during screening of patients for enrollment in a separate TB Trials Consortium Phase 3 study of drug-susceptible TB.[18,19] Unfortunately, enrollment dropped dramatically when this became a stand-alone consortium-wide study. CIs were therefore wider than expected, although the upper limit was still below 10%. This study was not large enough to detect a modest risk for acquired resistance to RMP,[19] or the association of baseline cavitation with treatment failure and relapse.[18]

The study included patients with INH intolerance as well as with INH-resistant isolates identified from local rather than reference laboratory results. A number of participants with discordant laboratory results continued in the study due to delays in obtaining the CDC reference laboratory results. Poor treatment outcomes were not associated with category of resistance vs. INH intolerance or with discordance in DST results between local and CDC laboratories. The latter finding is consistent with known intra-laboratory variability for EMB and PZA.[20]

This multicenter prospective study provides valuable information in addition to a number of single-site, retrospective studies published in the last decade,[15,16,21–23] some of which reported acquired RMP resistance, particularly when DOT was not used[21] or treatment was inadequate for the initial 2–5 months.[23] Reflecting the paucity of new information, the only significant change in the US 2003 treatment guidelines for patients with INH-resistant TB was to 'consider adding' a fluoroquinolone to RMP, EMB and PZA for patients with extensive TB disease.[1] A Kenyan study,[17] however, supported the 2006 UK National Institute for Health and Clinical Excellence guidelines to treat INH-resistant TB with 9–12 months of daily RMP+EMB, depending upon whether PZA+SM or PZA alone were co-administered during the first 2 months.[24]

While the present study supports confidence in the efficacy of the currently recommended 6-month regimen of 6 months of RMP, EMB and PZA when INH cannot be used, it also raises concerns about tolerability. Study treatment was discontinued in 26% of participants, including 12% for hepatic events that were often attributed to PZA. Although not comparatively evaluated in this study, twice-weekly RMP+EMB+PZA appeared to be poorly tolerated, possibly due to the prolonged administration of the higher doses that World Health Organization (WHO) guidelines recommend for intermittent use of PZA,[25] the drug most strongly associated with liver injury in standard four-drug anti-tuberculosis regimens.[15,21,22,26] The study did not provide data to explore why PZA toxicity might be more prevalent in the absence of concurrent INH treatment.[27] Despite issues of tolerability, PZA is receiving increasing attention due to its importance in anti-tuberculosis treatment.[28,29]

A recent systematic review reported treatment failure rates of 18–44% when patients with INH-resistant TB were treated with the standardized WHO 8-month re-treatment regimen that includes INH+RMP+EMB for the final 6 months. This showed some evidence of benefit from prolonged PZA use, and the authors recommended further studies of regimens for INH-resistant TB.[30] The potential risk of acquired resistance to other second- or third-line drugs such as fluoroquinolones[31] also supports the need for further studies to identify better regimens for patients unable to receive INH.

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Participating clinical sites (principal investigators, study coordinators and microbiologists, with numbers of patients enrolled in parentheses) were as follows: South Texas-Audie Murphy VA Hospital Research Collaboration, San Antonio, TX, USA (19): M H Weiner, R Wing, D Wing, M Engle, A Calderin. University of North Texas Health Science Center, Fort Worth, TX, USA (12): S Weis, B King, L Turk, G Stevenson, N Shafer, D Dunbar. The University of Manitoba, Winnipeg, MN, Canada (9): E Hershfield, W Kepron, M Roth, D Hoban. Denver Public Health Department, Denver, CO, USA (8): R Reves, W Burman, J Tapy, R Belknap, G Sanchez, G Hildred. Columbia University College of Physicians and Surgeons, New York, NY, USA (8): N W Schluger, J Burzynski, V Lozano, M Wolk, A Ebrahimzadeh. Montreal Chest Institute, Montreal, QC, Canada (6): D Menzies, K Schwartzman, C Greenaway, M Pelletier, C Valiquette, P Plaisir, L Thibert. Michael Debakey Veterans Affairs Medical Center, Washington DC, USA (6): R Hamill, E Guy, T Scott, R Nickson, K Goodrich. Boston University Medical Center, Boston, MA, USA (4): J Bernardo, J Saukkonen, C R Horsburgh, Jr, C Murphy, D Brett-Curran, J Westerling. Public Health – Seattle & King County, Seattle, WA, USA (4): C Nolan, S Goldberg, M Narita, C Friedly, M Stone, D Schwartz, J Pass. Hines VA Medical Center, Hines, IL, USA (4) C Pachucki, S Marantz, A Lee, M P Samuel, S Kubba. Duke University/VA Durham, Durham, NC, USA (3): C D Hamilton, J Stout, A Mosher, E Hecker, S Bargothi. Bellevue Hospital, New York University, New York, NY, USA: (2) R Condos, W Rom, T Harkin, L Sandman Johns Hopkins University, Baltimore, MD, USA (2): S Dorman, R E Chaisson, G Maltas, J Fisher, N Hooper. University of British Columbia, Vancouver, BC, Canada (2): M Fitzgerald, K Elwood, B Peyvandi, T Kuang. University of California, San Francisco, CA, USA (2): P Nahid, P Hopewell, C Merrifield, I Rudoy, J Israel, A Babst. Washington, DC VA Medical

Center, Washington DC, USA (2): F M. Gordin, D Benator, D S Conwell, N Hooper. Northwestern University, Jesse Brown VA Medical Center, Chicago, IL , USA (2): M Bhattacharya, S Lippold, W Clapp, J Fabre, J Narwocki. New Jersey Medical School Global Tuberculosis Institute - University of Medicine and Dentistry of New Jersey, Newark, NJ, USA (1): B T Mangura, L B Reichman, M C Leus, M Owens, E Napolitano, M Burday, D Sickles. Emory University Department of Medicine, Atlanta, GA, USA (1): S M Ray, D P Holland, D Dixon, O Mohamed, K Folami, J Bush. Audie L Murphy VA Hospital, San Antonio, TX, USA (1): M H Weiner, M Engle, P Duran, L C Sadkowski.

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RESUME

CONTEXTE : Vingt dispensaires anti-tuberculeux aux Etats-Unis et au Canada.

OBJECTIF : Evaluer l'efficacité et la sécurité d'un protocole intermittent de traitement de 6 mois associant rifampicine (RMP), pyrazinamide (PZA) et éthambutol (EMB) chez des patients négatifs pour le virus de l'immunodéficience humaine (VIH) atteints de tuberculose (TB) pulmonaire ou extra-pulmonaire confirmée par culture et présentant soit une résistance soit une intolérance à l'isoniazide (INH).

SCHÉMA : Les patients ont été enrôlés dans un essai clinique à un seul volet et ont reçu d'abord 14 doses quotidiennes de RMP+PZA+EMB puis un traitement intermittent. Ce traitement était administré deux (BIW) ou trois (TIW) fois par semaine selon la préférence du médecin et du patient pendant 6 mois ; les patients ont ensuite été suivis pendant 2 ans afin de dépister une rechute.

RÉSULTATS : Entre 1999 et 2004, 98 patients ont été enrôlés, dont 78 avaient une résistance à l'INH et 20 une intolérance. Soixante-dix-sept patients ont bénéficié du traitement BIW et 21 du traitement TIW ; 73 patients (74%) ont terminé le traitement. Les motifs d'arrêt du traitement étaient des effets secondaires hépatiques (n = 12), d'autres effets secondaires (n = 3) et d'autres raisons (n = 10). Sur 86 patients chez qui l'analyse d'efficacité a pu être réalisée, deux ont rechuté et un traitement a échoué (3,5% ; IC95% 1,2–9,6). Ces trois patients présentaient tous une TB pulmonaire cavitaire à frottis bacilles acido-alcoolo-résistants positif.

CONCLUSION : Un traitement intermittent par RMP+PZA+EMB est efficace chez des patients VIH négatifs, mais ce protocole est mal toléré, sans doute à cause de l'utilisation prolongée de PZA. Il est nécessaire d'élaborer des protocoles de moindre toxicité.

RESUMEN

MARCO DE REFERENCIA: Veinte consultorios de tuberculosis (TB) en los Estados Unidos y el Canadá.

OBJETIVO: Evaluar la eficacia y la seguridad toxicológica de un régimen intermitente de 6 meses con rifampicina (RMP), pirazinamida (PZA) y etambutol (EMB) en pacientes sin infección por el virus de la inmunodeficiencia humana (VIH), con diagnóstico de TB pulmonar o extrapulmonar confirmado por cultivo, además de resistencia o intolerancia a isoniazida (INH).

MÉTODO: Los pacientes participaron en un estudio clínico en un solo grupo que recibía una pauta posológica intermitente después de recibir RMP, PZA y EMB durante los primeros 14 días. El tratamiento se continuó con dosis de dos (BIW) o tres veces (TIW) por semana, según la preferencia del médico o del paciente durante 6 meses y se practicó un seguimiento durante 2 años a fin de vigilar la recidiva después del tratamiento.

RESULTADOS: Participaron en el estudio 98 pacientes entre 1999 y el 2004 (en 78 se notificó resistencia a INH y en 20 pacientes intolerancia a la misma). Se usó un esquema BIW en 77 pacientes y 21 pacientes recibieron medicamentos TIW. Setenta y tres pacientes completaron el tratamiento del estudio (74%). Las razones aducidas de la interrupción fueron los efectos adversos hepáticos (n = 12), otras reacciones adversas (n = 3) y causas diferentes (n = 10). Se presentó un fracaso terapéutico y dos recaídas (n = 3) (3,5%; IC95% 1,2–9,8) en los 86 pacientes aptos para el análisis de eficacia y estos casos ocurrieron en pacientes con TB pulmonar, baciloscopia positiva y cavernas en el parénquima pulmonar.

CONCLUSIÓN: Un régimen intermitente con RMP, PZA y EMB parece ser eficaz en los pacientes sin infección por el VIH, pero se observa una baja tolerabilidad, tal vez debida al uso prolongado de PZA. Se precisan nuevas opciones terapéuticas que presenten una menor toxicidad.