Early report

Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid

Andrew Vernon, William Burman, Debra Benator, Awal Khan, Lorna Bozeman, for the Tuberculosis Trials Consortium

Summary

Background Rifapentine is a cyclopentyl-substituted rifamycin whose serum half-life is five times that of rifampin. The US Public Health Service Study 22 compared a once-weekly regimen of isoniazid and rifapentine with twice weekly isoniazid and rifampin in the continuation phase (the last 4 months) of treatment for pulmonary tuberculosis in HIV-seropositive and HIV-seronegative patients. This report concerns only the HIV-seropositive part of the trial, which has ended. The HIV-seronegative part will stop follow-up in 2001.

Methods Adults with culture-positive, drug-susceptible pulmonary tuberculosis who completed 2 months of four-drug (isoniazid, rifampin, pyrazinamide, ethambutol) treatment (induction phase) were randomly assigned 900 mg isoniazid and 600 mg rifapentine once weekly, or 900 mg isoniazid and 600 mg rifampin twice weekly. All therapy was directly observed. Statistical analysis used univariate, Kaplan-Meier, and logistic and proportional hazards regression methods.

Findings 71 HIV-seropositive patients were enrolled: 61 completed therapy and were assessed for relapse. Five of 30 patients in the once-weekly isoniazid/rifapentine group relapsed, compared with three of 31 patients in the twice-weekly isoniazid/rifampin group (log rank χ^2=0·69, p=0·41). However, four of five relapses in the once-weekly isoniazid/rifapentine group had monoresistance to rifamycin, compared with none of three in the rifampin group (p=0·05). Patients who relapsed with rifamycin monoresistance were younger (median age 29 *vs* 41 years), had lower baseline CD4 cell counts (median 16 *vs* 144 μL), and were more likely to have extrapulmonary involvement (75% *vs* 18%, p=0·03) and concomitant therapy with antifungal agents (75% *vs* 9%, p=0·006). No rifamycin monoresistant relapse has occurred among 1004 HIV-seronegative patients enrolled to date.

Interpretation Relapse with rifamycin monoresistant tuberculosis occurred among HIV-seropositive tuberculosis patients treated with a once-weekly isoniazid/rifapentine continuation-phase regimen. Until more effective regimens have been identified and assessed in clinical trials, HIV-seropositive people with tuberculosis should not be treated with a once-weekly isoniazid/rifapentine regimen.

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Division of Tuberculosis Elimination, Centers for Disease Control & Prevention, Mailstop E-10, Atlanta, GA 30333, USA (A Vernon MD, A Khan PhD, L Bozeman MS)**, Department of Public Health, Denver Health and Hospitals, Denver CO** (W Burman MD)**, and Veterans Affairs Medical Center and Georgetown University, Washington, DC** (D Benator MD)**, USA**

Correspondence to: Dr Andrew Vernon

Introduction

Rifapentine is a cyclopentyl-substituted rifamycin with excellent activity against *Mycobacterium tuberculosis*[1] in animal studies and early clinical trials.[2–5] Rifapentine's long serum half-life (10–15 h, compared with 2–3 h for rifampin[6]), suggests the possibility of once-weekly treatment. The US Public Health Service organised Study 22 to assess the use of once weekly isoniazid and rifapentine in the last 4 months of standard 6-month short-course tuberculosis therapy (the continuation phase). Compared with a standard twice-weekly 6-month regimen, this regimen would reduce by 28% the number of contacts required between patient and provider of directly observed therapy (DOT).

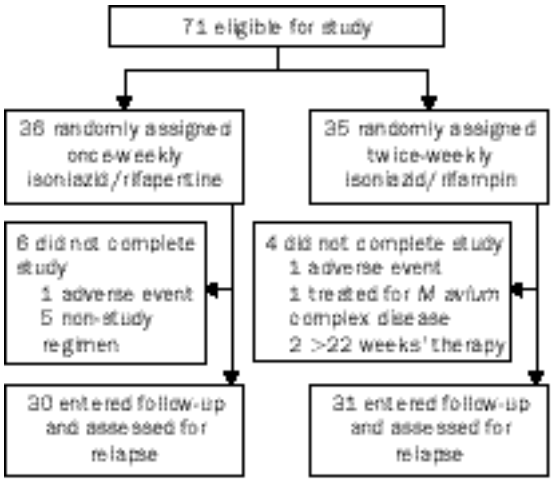
Enrollment of HIV-seropositive people stopped when acquired rifamycin monoresistance occurred in four of 36 people treated with once-weekly isoniazid and rifapentine (the subject of this report). The trial of HIV-seronegative people completed enrollment in October, 1998, and follow-up will continue until 2001. However, relying principally upon data from another trial among HIV-seronegative patients, the US Food and Drug Administration granted accelerated approval to rifapentine in mid-1998. Because rifapentine will probably soon be available in other countries we believe it important to share our experience with rifapentine in HIV-infected tuberculosis patients.

Rifampin (rifampicin) is the key drug in modern tuberculosis regimens. Resistance has been well-described but generally occurs in the setting of resistance to isoniazid and other antituberculosis drugs. However, isolated resistance to rifampin is increasingly recognised, and patients with HIV-related tuberculosis seem to be at increased risk.[7] Because there appears to be substantial cross-resistance among rifampin, rifabutin, and rifapentine, this form of resistance is better termed "rifamycin monoresistance".[8] Mycobacterial resistance to rifamycins poses a serious challenge to the treatment of tuberculosis. Our study offers insights into the possible mechanisms of acquired rifamycin monoresistance.

Patients and methods

Patients

Study 22 is a randomised, open-label multicentre comparison of two regimens in the continuation phase of short-course



Trial profile

tuberculosis therapy. All patients received standard four-drug therapy during the first 8–10 weeks (induction phase), with daily, twice-weekly, or thrice-weekly isoniazid, rifampin, pyrazinamide, and ethambutol. If daily therapy was given throughout induction, the patient had to have received at least 40 DOT doses and at least 45 total doses of daily therapy to be eligible; if some induction doses were twice- or thrice-weekly patients had to have received the equivalent of 56 daily doses, all intermittent doses and five of every seven daily doses being given as DOT. Patients were then enrolled and randomised to 16 once-weekly doses of isoniazid 15 mg/kg (maximum 900 mg) and rifapentine 600 mg or to 32 twice-weekly doses of isoniazid 15 mg/kg (maximum 900 mg) and rifampin 10mg/kg (maximum 600 mg), all given as DOT. Randomisation was blocked by study site and HIV serostatus.

Inclusion criteria were: culture-positive pulmonary tuberculosis susceptible to isoniazid and rifampin; completion of an American Thoracic Society and US Centers for Disease Control and Prevention (CDC) recommended induction regimen[9] in the previous 70 days; age of 18 years or more; known HIV status; a Karnofsky performance status[10] of 60 or more; haemoglobin above 70 g/L; platelet count above 50×10^9/L; serum aspartate transaminase of less than three times the upper limit of normal; serum bilirubin less than 2·5 times the upper limit of normal; and serum creatinine less than twice the upper limit of normal. Exclusion criteria were: contraindications to study drugs; the need for treatment with other antituberculosis drugs; pulmonary silicosis; skeletal tuberculosis; and pregnancy or breast-feeding.

Study 22 had a planned sample size of 1000 HIV-seronegative patients plus about 100 HIV-seropositive participants. 10% seropositives is too small a proportion to permit a definitive comparison of the two regimens in this important group of tuberculosis patients but the results of this trial in HIV-seronegative patients would probably be applied to HIV-seropositive patients too, and we felt it important to gain clinical experience with the once-weekly regimen in HIV-seropositive people. Patients were followed for two years after completion of treatment. For HIV-seropositive participants, available CD4 cell counts (within 12 months of enrollment) were obtained retrospectively.

The study protocol was approved by an Institutional Review Board at CDC and at each of the clinical sites, and each participant provided written informed consent.

Microbiological methods

Cultures were done at field sites in liquid media. A baseline isolate obtained from each participant was sent to CDC for confirmatory drug-susceptibility testing. Baseline and relapse isolates were compared using *IS6110* restriction fragment length polymorphism (RFLP) testing.[11] Analysis of *rpo*β genes in the relapse isolates[12] was done at CDC.

Endpoints

Patients who could be assessed for relapse had to have completed 16 weeks of study phase therapy within 22 weeks of enrollment. Patients treated for more than 14 days with other antituberculosis drugs, were designated as having received a "non-study regimen", and were censored at that point. "Bacteriological failure" was a positive culture for *M tuberculosis* from any site after the patient had received 50% or more (≥8 weeks) study therapy. "Bacteriological relapse" was defined as a positive culture from any site after the patient had successfully completed study therapy.

Statistical analysis

Data analysis used Statistical Analysis Systems SAS for Windows (version 6.11) and CDC Epi Info software (version 6.04b). Categorical and continuous variables were compared by two-tailed Fisher's exact test and by the Wilcoxon two-sample test, respectively. Kaplan-Meier survival analysis was done using the log-rank test on a dataset available on Nov 11, 1998, about 43 months after enrolment in Study 22 began. Variables with $p\leq0{\cdot}05$ in univariate analysis were analysed using multivariate logistic and proportional hazards regression.

Results

Enrolment began in April, 1995. By early 1997, four rifamycin monoresistant relapses had occurred among HIV-seropositive patients randomly assigned weekly rifapentine/isoniazid, and the Data and Safety Monitoring Board, CDC, and the investigators decided not to enrol any more HIV-seropositive patients. Those still taking once-weekly isoniazid/rifapentine were switched to isoniazid, rifampin, and ethambutol, and treatment was extended to 9 months.

The trial enrolled 71 HIV-seropositive patients. Ten were censored during study phase therapy because of use of other antituberculosis drugs (one patient), drug discontinuation due to presumed drug-related hepatitis (two), defaulting from therapy (two), and the switch to standard therapy when the HIV-seropositive group was closed (five). The remaining 61 patients were assessed for relapse (figure) and at the time of this analysis, the median time at risk for relapse was 86 weeks.

Characteristic	Treatment group	
	Once-weekly isoniazid/rifapentine (n=30)	Twice-weekly isoniazid/rifampin (n=31)
Demographic		
Median age (years)	39	44
White/black/Hispanic (%)	13/73/13	10/74/16
Sex (M/F)	23/7	28/3
Clinical		
History illicit drugs (%)	50	52
History alcohol abuse (%)	47	51
Mean Karnofsky status	89	94
Previous tuberculosis (%)	13	16
Extrapulmonary disease (%)	23	19
Given streptomycin (%)	3	3
Cavitation on chest radiography (%)	33	32
Bilateral infiltrates (%)	43	61
Positive sputum smear at enrolment (%)	0	12
Positive sputum culture at enrolment (%)*	0	19
Mean induction DOT doses	53	51
Mean days for induction	64	65
Median haemoglobin (g/L)†	11·4	12·3
Median white-blood-cell count (/μL)†	3400	4500
Median (IQR) CD4 cell count (/μL)	118 (52–315)	137 (65–301)

*p=0·05. †p=0·03.

Table 1: **Baseline characteristics of HIV-seropositive participants for whom relapse data are available, by treatment group**

	Rifamycin monoresistant relapse (n=4)	All others (n=57)	p
Once-weekly isoniazid/rifapentine	4	26	0·05*
Median age (years)	29	41	0·04†
Median (IQR) CD4 count (/μL)	16 (8–106)	144 (67–349)	0·02†
Extrapulmonary and pulmonary disease	3 (75%)	10 (18%)	0·03*
Use of antifungal azoles	3 (75%)	5 (9%)	0·006*

*Fisher's exact test, 2-tailed. †Wilcoxon two-sample test.

Table 2: **Univariate analysis of rifampin monoresistant relapse among HIV-seropositive participants assessed for relapse**

The two groups were similar at enrolment (table 1). None of 22 people in the isoniazid/rifapentine group, and five (19%) of 26 people in the isoniazid/rifampin group had a positive sputum culture within 2 weeks of enrollment (table 1).

There were no treatment failures during study phase therapy. Five of 30 participants in the once-weekly group and three of 31 in the standard group relapsed after treatment (p=0·47). Five relapses occurred from 9 to 34 weeks (median 19) after end of therapy in the once-weekly group, and three relapses occurred from 11 to 24 weeks (median 14) after end of therapy in the twice-weekly group. The relapse rates for the 2-year endpoint, calculated by Kaplan-Meier analysis were 17·8% (95% CI 3·6–31·9%) in the isoniazid/rifapentine group and 10% (0–20·7%) in the isoniazid/rifampin group (p=0·41). Four of the relapses in the once-weekly group involved *M tuberculosis* strains with rifamycin monoresistance; no relapse strain in the standard group had acquired drug resistance (p=0·05). The eight relapses occurred at seven different clinic sites.

One baseline isolate was not available. The remaining seven pairs of baseline and relapse isolates had identical DNA fingerprints by *IS6110*. Analysis of the *rpo*β gene for the four rifamycin monoresistant relapse isolates identified four distinct mutations (His526Tyr, Ser531Leu, Ser522Leu, 6-base deletion 516-517).

Time to relapse was similar for resistant and sensitive relapses (median 16 *vs* 19 weeks after end of therapy). Among baseline variables assessed for association with rifamycin monoresistant relapse, univariate associations were seen for age, CD4 cell count, combined extrapulmonary and pulmonary disease at baseline, and reported use of azole antifungal drugs (fluconazole, ketoconazole, itraconazole; table 2). Neither Mantel-Haenszel testing nor regression modelling improved on this statistical assessment. CD4 cell counts in the four patients with rifamycin monoresistant relapse were 8, 8, 23, and 188 per μL.

The same four variables distinguished relapses from non-relapses overall and in the once-weekly isoniazid/rifapentine group, but not when comparing relapses to non-relapses in the twice-weekly isoniazid/rifampin group only (table 3). Among patients in the isoniazid/rifampin group, one of five with positive sputum culture at enrolment and one of 21 without positive culture at enrolment relapsed.

No serious unexpected toxic effects were associated with rifapentine, and no significant differences in adverse events were observed between treatment arms. 16 (23%) patients have died (nine in the isoniazid/rifapentine group, seven in the isoniazid/rifampin group). Of those assessed for relapse, seven from each treatment group have died. No deaths were attributable to tuberculosis.

Drug-sensitive tuberculosis relapse occurred in three patients who did not complete study phase (one in the isoniazid/rifapentine group, two in the isoniazid/rifampin group). Two (one in each group) had been removed during the study phase due to presumed drug-related hepatitis (serum aspartate transaminase >10× upper limit of normal). The third (in the isoniazid/rifampin group) was removed during the study phase because she received additional antituberculosis drugs for suspected *M avium* complex disease, which was later ruled out. Two (one in each group) of the three received additional non-study antituberculosis therapy. Inclusion of these events in an intention-to-treat analysis with all 71 randomly assigned patients did not substantively change any conclusion.

Discussion

The four cases of acquired rifamycin monoresistance among HIV-infected tuberculosis patients randomly assigned once-weekly isoniazid/rifapentine led to the closure of the HIV-seropositive arm of Study 22. Drug resistance rarely develops in patients with initially drug-susceptible strains who are treated with modern DOT regimens[13,14] even among patients who are non-compliant.[15] Rifamycin monoresistance is very uncommon.[7] Given the critical role of rifamycins in short-course chemotherapy, the development of resistance to this class of drugs is worrying.

In the past decade, reports of acquired rifamycin monoresistance have increased, with growing evidence of an association with HIV co-infection.[16–18] In retrospective studies, non-compliance was associated with acquired rifamycin monoresistance,[17] but acquired rifamycin resistance has also been reported among a few patients who received DOT.[19] Rarely, rifabutin prophylaxis for *M avium* complex has been associated with the development of tuberculosis with rifamycin monoresistance.[16,20] Two recent large trials of once-weekly isoniazid/rifapentine in HIV-seronegative people did not report acquired rifamycin monoresistance.[21,22] In Study 22 no case of acquired rifamycin monoresistance has been observed among the 1004 HIV-seronegative participants enrolled.

Acquisition of drug resistance by *M tuberculosis* is thought to require active bacillary replication and exposure to a single drug. Animal studies support this hypothesis.[23] The best demonstration that active replication is necessary is the fact that single-drug treatment in latent tuberculosis is not associated with an increased rate of isoniazid resistance among patients

	Once-weekly isoniazid/rifapentine		p	Twice-weekly isoniazid/rifampin		p
	Relapse (n=5)	Non-relapse (n=25)		Relapse (n=3)	Non-relapse (n=28)	
Median age (years)	33	39	0·08	41	45	0·64
Median (IQR) CD4 count (/μL)	23 (8–67)	163 (80–361)	0·02	97 (73–248)	161 (57–349)	0·74
Extrapulmonary and pulmonary disease	3 (60%)	4 (16%)	0·07	1 (33%)	5 (18%)	0·49
Use of antifungal azoles	3 (60%)	3 (12%)	0·04	0	2 (7%)	1·0

Table 3: **Univariate analysis of risk factors for relapse among HIV-seropositive participants assessed for relapse, by treatment group**

who develop active tuberculosis despite preventive therapy.[24] Rifamycin monoresistance was not anticipated in Study 22: previous studies had shown that a single drug (isoniazid) could be used alone in the continuation phase of treatment without engendering significant rates of isoniazid resistance.[25,26]

The fact that rifamycin monoresistance occurred only in one treatment group suggests that resistance was acquired after randomisation (ie, during the continuation phase). Thus induction phase therapy may not have eliminated mycobacterial replication. The association with lower CD4 cell counts, extrapulmonary disease, and use of antifungal drugs may indicate that replication is especially prolonged in advanced AIDS.[27] The association with younger age remains unexplained.

Periods of monotherapy are thought to be necessary for emergence of drug-resistance.[28] Our study used DOT throughout, before and after randomisation, so selective ingestion of one drug was not responsible for the rifamycin monoresistance. Mitchison[29] has hypothesised that functional monotherapy during sterilisation of special bacillary populations could explain the emergence of rifamycin monoresistance despite supervised therapy. He has also suggested that 600 mg rifapentine may be too little because this drug is 98% protein bound.[30] Selective malabsorption of isoniazid seems an unlikely explanation because isoniazid is more reliably absorbed than the rifamycins are,[31–33] particularly among HIV-infected tuberculosis patients; and selective malabsorption of rifamycins would be expected to lead to resistance to the better absorbed drug (isoniazid), but that is not what happened. On the other hand, the shorter half-life of isoniazid[34] (2 *vs* 12 h) could result in periods of functional monotherapy with rifapentine; and a rapid isoniazid acetylation phenotype might further increase the time of exposure to rifapentine alone.[35] Previous studies of once-weekly treatment regimens found that, compared with slow acetylators, rapid acetylators of isoniazid were more likely to fail during therapy and show emergence of drug-resistance.[36–38] The association between azole antifungal use and acquired rifamycin monoresistance suggests another mechanism. These antifungal drugs inhibit the p450 enzyme system and increase serum concentrations of rifabutin[39] but not isoniazid.[40] Whether rifapentine is similarly affected by azole antifungal drugs is unknown.

A final concern is the high rate of tuberculosis relapse after therapy (10%) even among HIV-infected people receiving standard twice-weekly therapy. Although the 95% CI for relapse rate does not exclude acceptable levels, the rate observed was three times higher than the currently acceptable rate of 3·5%.[41] The optimal treatment duration for pulmonary tuberculosis in HIV-infected people is not yet certain. Some clinicians and programmes still advise a 9-month regimen, with treatment for at least 6 months after culture conversion. Others adhere to more recent guidelines that recommend 6 months unless response is slow or suboptimal.[9,42]

On the basis of our findings the FDA cautioned that the appropriate use of rifapentine in HIV-seropositive patients with tuberculosis remains unclear. HIV-seropositive patients should not be treated with this once-weekly continuation-phase regimen of isoniazid and rifapentine. There is now a pressing need for a rifapentine-based regimen that can be used once weekly in HIV-infected people with active tuberculosis.

Contributors

This report was prepared by Andrew Vernon, William Burman, Debra Benator, Awal Khan, and Lorna Bozeman. Data analysis was done by Awal Khan, Yong Cheng Wang, and Andrew Vernon. The study protocol was prepared by M Elsa Villarino, Judy Rudnick, and Lawrence Geiter, with assistance from the study principal investigators, particularly Antonino Catanzaro, Fred Gordin, C Robert Horsburgh, and Randall Reeves. The original statistical design was by Philip Smith and continued statistical support was by Yong Cheng Wang. Comments on the paper were provided by Richard O'Brien, Fred Gordin, M Elsa Villarino, and Kenneth G Castro.

Participating centres that reported rifamycin monoresistance or that enrolled four patients or more*

New York University School of Medicine, New York, NY; *University of Medicine & Dentistry, Newark, NJ; Johns Hopkins University, Baltimore, MD; Emory University School of Medicine, Atlanta, GA; *University of California, San Diego, CA; Los Angeles County/USC Medical Center, Los Angeles, CA; Miami VAMC, Miami, FL; *Chicago-Westside VAMC, Chicago, IL; *San Francisco VAMC, San Francisco, CA, USA.

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