Short-Course Rifampin and Pyrazinamide Compared with Isoniazid for Latent Tuberculosis Infection: A Multicenter Clinical Trial

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Background: **Rifampin and pyrazinamide are recommended for treatment of latent tuberculosis infection in adults without HIV infection, but reports of severe hepatotoxicity have raised concerns about its safety. Clinical trials have not compared this treatment with isoniazid in adults without HIV infection.**

Objective: **To compare the safety and tolerance of a 2-month regimen of rifampin and pyrazinamide with that of a 6-month regimen of isoniazid for treatment of latent tuberculosis infection.**

Design: **Multicenter, prospective, open-label trial.**

Setting: **Three urban public health tuberculosis clinics in the United States.**

Patients: **589 adults with latent tuberculosis infection who met U.S. criteria for treatment.**

Intervention: **Patients were assigned in alternate weeks to receive rifampin and pyrazinamide daily for 2 months ($n = 307$) or isoniazid daily for 6 months ($n = 282$).**

Measurements: **Primary end points were hepatotoxicity, other adverse events, and percentage of patients who completed treatment.**

Results: **Sixteen of 207 (7.7%) patients assigned to rifampin and pyrazinamide developed grade 3 or 4 hepatotoxicity compared with 2 of 204 (1%) patients assigned to isoniazid (odds ratio, 8.46 [95% CI, 1.9 to 76.5]; $P = 0.001$). The rifampin plus pyrazinamide regimen was more likely than the isoniazid regimen to be discontinued because of hepatotoxicity (odds ratio, 5.19; $P = 0.033$). The overall percentage of nonhepatotoxic adverse events was 20% in the rifampin–pyrazinamide group and 16% in the isoniazid group. The proportion of patients who completed the study treatment was 61% and 57%, respectively.**

Conclusions: **A 2-month regimen of rifampin and pyrazinamide was associated with an increased risk for grade 3 or 4 hepatotoxicity compared with a 6-month regimen of isoniazid. Liver enzymes should be measured routinely during treatment to screen for liver injury and prevent progression to severe toxicity.**

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*For a list of the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) Study Investigators, see the Appendix.

As rates of tuberculosis cases in the United States have decreased (1, 2), the focus of prevention and control efforts has shifted toward identification and treatment of persons with latent tuberculosis infection who are at increased risk for developing tuberculosis. This approach was endorsed in a recent report from the Institute of Medicine (3).

Isoniazid given for at least 6 months has been the standard therapy for latent tuberculosis infection for decades, but its use has been limited by toxicity, especially hepatitis (4–6), and by poor adherence to treatment (7). A 2-month course of rifampin and pyrazinamide has been shown to be effective and well tolerated as treatment of latent tuberculosis infection in HIV-infected persons (8–10). Guidelines from the American Thoracic Society and Centers for Disease Control and Prevention (11) offer three main regimens for treatment of latent tuberculosis infection: isoniazid for 6 to 9 months, rifampin for 4 months, or rifampin and pyrazinamide for 2 months. However, there is relatively little experience with use of rifampin plus pyrazinamide to treat latent tuberculosis infection in persons without HIV infection, and case reports of severe hepatitis causing five deaths have raised concerns about the safety of the regimen (12, 13).

We therefore conducted a multicenter, prospective, open-label trial comparing daily treatment with rifampin and pyrazinamide for 2 months with daily treatment with isoniazid for 6 months in non–HIV-infected adults with latent tuberculosis infection (the Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection [SCRIPT] study). Our primary goals were to compare risk for toxicity, particularly hepatotoxicity, and completion of therapy. We also investigated whether persons with latent tuberculosis infection who were older than 35 years of age, a group known to have increased rates of hepatitis while taking isoniazid (5), would have fewer adverse events while taking rifampin plus pyrazinamide than while taking isoniazid.

METHODS

Patients

All adults older than 17 years of age who had a positive tuberculin skin test (as defined by American Thoracic Society/Centers for Disease Control and Prevention criteria [11]) and in whom active tuberculosis was excluded and treatment of latent tuberculosis infection would ordinarily be recommended (for example, persons with close contact to an infectious case or those with a medical risk factor, such as diabetes) were eligible for the study. In addition, we enrolled foreign-born persons older than 35 years of age who had been in the United States for fewer than 6 years. These latter patients were not included in the American

Thoracic Society/Centers for Disease Control and Prevention guidelines when the study was begun.

Before being invited to participate, all patients who met initial criteria for enrollment were asked about previous liver disease, current medications and illnesses, previous gout, and risk factors for HIV infection. Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase, and alkaline phosphatase), bilirubin, and creatinine were measured. Testing for and counseling about HIV infection were recommended for patients whose HIV status was not known, and a urine pregnancy test was performed for all women of childbearing age. During their baseline visit, patients underwent a review of symptoms that included history of nausea, vomiting, jaundice, abdominal pain, weight loss, arthralgia, headache, and neuropathy.

Exclusion criteria were pregnancy, HIV infection, serum creatinine concentration more than twice the upper limit of normal, serum aspartate aminotransferase or ALT level more than three times the upper limit of normal, and a history of gout. Institutional review boards at each site approved the study, and written informed consent was obtained from all patients.

Design

Persons who met study criteria and agreed to participate were allocated in alternate weeks to receive rifampin (600 mg/d) plus pyrazinamide (20 mg/kg of body weight daily) for 2 months or isoniazid (300 mg/d) for 6 months (the recommended minimum duration when the study started [14]). Tables were used to standardize weight-based dosing of pyrazinamide to the closest 250 mg. At each site, the allocation during the first week of patient enrollment was determined by a coin toss. For the remainder of the trial, allocation to treatment regimen was alternated weekly. This systematic allocation design was chosen for ease of implementation in busy public health tuberculosis clinics in San Francisco, Boston, and Atlanta.

Serum levels of liver enzymes and bilirubin were measured in all patients after 1 month of treatment. Patients receiving isoniazid had repeated liver enzyme testing at 3 months. Patients receiving rifampin and pyrazinamide also had a complete blood count and measurement of uric acid and creatinine after 1 month of treatment.

All treatment was self-administered, and specific incentives, financial or otherwise, were not provided. All patients received monthly supplies of medication and were instructed to take medication daily and return in 1 month (or sooner if any of the symptoms mentioned previously occurred). At each visit, patients were evaluated for signs and symptoms of adverse events by tuberculosis control nurses and evaluated for adherence to treatment.

Hepatotoxicity was based on the World Health Organization classification and was defined as grade 1 for any serum ALT level of 51 to 125 U/L, or 1.25 to 2.5 times normal; grade 2 for any serum ALT level of 126 to 250 U/L, or 2.6 to 5.0 times normal; grade 3 for any serum ALT level of 251 to 500 U/L, or 5.1 to 10.0 times normal; and grade 4 for any serum ALT level greater than 500 U/L, or >10 times normal, or greater than 250 U/L if accompanied by compatible symptoms (15).

At the 1-month evaluation in recipients of rifampin plus pyrazinamide or the 3-month evaluation in isoniazid recipients, patients who had grade 1 or 2 liver injury continued to take study medication and had repeated liver enzyme testing in 2 weeks. In patients with grade 3 hepatotoxicity, treatment with study drugs was stopped and not resumed unless another cause of hepatitis could be found (such as alcohol abuse). Treatment with study drugs was permanently discontinued in patients with grade 4 hepatotoxicity.

Outcomes

Primary end points were development of any adverse event, especially grade 3 or 4 hepatotoxicity, and completion of the prescribed amount of treatment. Adverse events were determined on the basis of interviews and by laboratory examination when indicated. Completion of the regimen was defined as taking at least 80% of prescribed medication.

Statistical Analysis

A sample of 540 patients was calculated to provide 80% power in two-sided tests, with an α value of 0.05, to detect an increase in the expected incidence of hepatotoxicity of any grade (the primary end point) from 15% in the isoniazid group to 25% in the rifampin plus pyrazinamide group. The first patient was enrolled on 15 February 1999. A scheduled interim analysis of the first 313 patients that was performed in July 2000 indicated no statistically significant differences between the two groups in terms of adverse events or completion of therapy. Enrollment continued until October 2000.

Context

Guidelines from the American Thoracic Society and Centers for Disease Control and Prevention for treating latent tuberculosis infection advocate 2 months of rifampin plus pyrazinamide as an effective alternative to 6 to 9 months of isoniazid or 4 months of rifampin. However, case reports have described severe liver injury in patients who were receiving the 2-month regimen.

Contribution

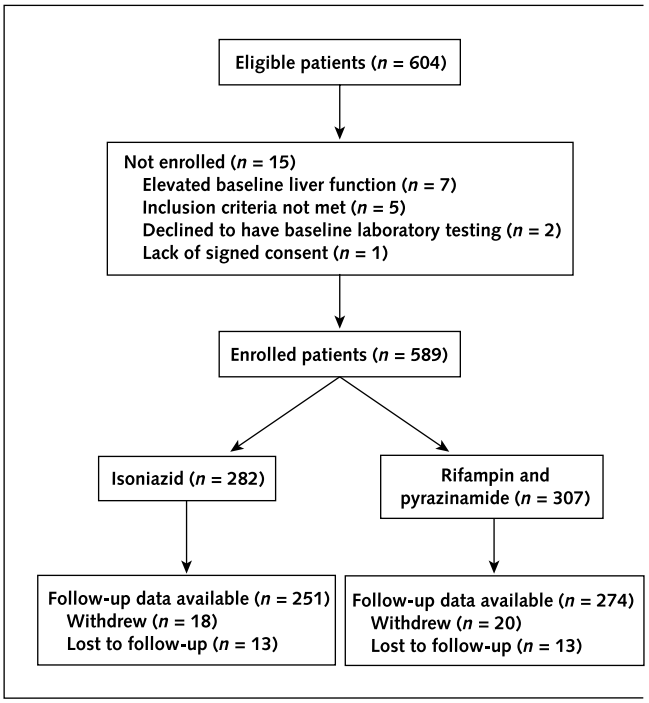
This nonrandomized, open-label trial found that the risk for grade 3 or 4 liver injury was higher in patients taking 2 months of rifampin plus pyrazinamide (7.7%) than in patients taking 6 months of isoniazid (1%).

Clinical Implications

If clinicians use the short-course regimen, they should vigilantly follow patients' liver enzyme levels.

–The Editors

Figure 1. **Flow of patients through the study.**



Fifteen of 604 patients were excluded. The proportion of patients for whom follow-up data were available was similar in the isoniazid group and the rifampin plus pyrazinamide group (89.0% vs. 89.2%, respectively).

Between-regimen comparisons of hepatotoxicity, other adverse events, and completion were based on the treatment initially assigned, without regard to the duration of treatment actually received. In an initial analysis of treatment effects on hepatotoxicity, the Fisher exact test was used to compare the proportion of patients with ALT values greater than 250 U/L among 411 participants who had liver enzyme testing at 1 or 3 months. Confirmatory analyses were then used to validate the initial result. Because the study was not randomized, treatment assignment was potentially confounded by imbalances in baseline covariates between the two treatment groups. In addition, grade 3 or 4 hepatotoxicity was uncommon. Therefore, to adjust for potential confounding, the initial exact analysis of hepatotoxicity was repeated with stratification by quintile of a propensity score that was estimated by using a multivariable logistic model for treatment assignment (16, 17). Furthermore, liver enzyme values were missing for 78 of 282 (27.7%) patients in the isoniazid group and 100 of 307 (32.6%) patients in the rifampin plus pyrazinamide group. To correct for this possible source of bias, we used multiple imputation. Specifically, the odds ratio for treatment was estimated in each of 10 data sets with imputed values for the missing liver enzyme tests by using logistic models to adjust for the propensity score as a continuous covariate. In the final step, a summary odds ratio estimate was calculated by using standard methods (18, 19).

In a further analysis, treatment-by-site interaction was examined in an exact analysis that was stratified by site. We also used logistic models to assess possible violations of independence due to clustering by site by comparing model-based standard errors with robust standard errors that accounted for within-site correlation. Finally, more common outcomes, including completion of treatment regimen and nonhepatotoxic adverse events, were analyzed by using the Fisher exact test. Analyses were done by using SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina), and StatXact software, version 4 (Cytel Software Corp., Cambridge, Massachusetts).

Role of the Funding Source

The funding source had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

RESULTS

Clinical and Demographic Characteristics at Baseline

Five hundred eighty-nine patients were enrolled from the three clinical sites (**Figure 1**). A high proportion of the patients were born outside the United States, the criterion that constituted the indication for treatment in 65.5% (**Table 1**). The two groups were similar in sex and body weight. A higher proportion of isoniazid recipients were older than 35 years of age and were born outside the United States.

Hepatotoxicity

Among patients who had follow-up liver enzyme tests, hepatotoxicity developed in 54 of 207 (26%) recipients of the rifampin–pyrazinamide regimen (of whom 16 had grade 3 or 4 hepatotoxicity) compared with 32 of 204 (16%) isoniazid recipients (2 of whom had grade 3 or 4 hepatotoxicity) (**Table 2**). Among patients with liver enzyme test results at 1 month, 1 of 199 (0.5%) isoniazid

Table 1. **Baseline Characteristics of 589 Patients Assigned To Receive Rifampin and Pyrazinamide or Isoniazid To Treat Latent Tuberculosis Infection**

Variable	Rifampin and Pyrazinamide Group (*n* = 307)	Isoniazid Group (*n* = 282)
Age > 35 y, *n (%)*	99 (32)	114 (40)
Men, *n (%)*	174 (57)	154 (55)
Mean body weight ± SD, *kg*	71.4 ± 15.3	70.5 ± 15.3
Born outside the United States, *n (%)*	253 (83)	249 (88)
Asia or Pacific Islands	114	113
Latin/South America	55	51
Africa	38	43
Europe	33	24
Caribbean islands	12	18
Indication for treatment, *n*		
New arrival to the United States	197	189
Contact with infectious case	49	48
Tuberculin converter	38	28
Health care worker	18	11
Medical risk factor	5	6

Table 2. **Hepatotoxicity in 411 Patients for Whom Follow-up Liver Enzyme Test Results Were Available***

Hepatotoxicity†	Rifampin and Pyrazinamide Group (*n* = 207)	Isoniazid Group (*n* = 204)
	n (%)	
Grade 1	29 (14)	27 (13.2)
Grade 2	9 (4.3)	3 (1.5)
Grade 3	7 (3.4)	0 (0)
Grade 4	9 (4.3)	2 (1.0)
Total	54 (26.1)	32 (15.7)
Discontinuation of study medications owing to hepatotoxicity	12 (5.8)	2 (1.0)

* The unit of analysis is the patient.
† Grade 1 hepatotoxicity was defined as a serum alanine aminotransferase (ALT) level of 51 to 125 U/L, or 1.25 to 2.5 times normal; grade 2 as serum ALT level 126 to 250 U/L, or 2.6 to 5.0 times normal; grade 3 as serum ALT level 251 to 500 U/L, or 5.1 to 10.0 times normal; and grade 4 as serum ALT level >500 U/L, or >10 times normal, or >250 U/L if accompanied by compatible symptoms. Criteria are based on those in reference 15.

recipients and 16 of 207 (7.7%) recipients of rifampin plus pyrazinamide had ALT levels of 250 U/L or greater, consistent with grade 3 or 4 hepatotoxicity (odds ratio, 16.6 [95% CI, 2.52 to 699]; $P < 0.001$). Among patients who had liver enzyme testing at 1 or 3 months, the proportion with ALT levels of 250 U/L or greater on at least one test increased to 2 of 204 (1%) patients in the isoniazid group. In the rifampin plus pyrazinamide group, liver enzymes were measured at 1 month only (odds ratio, 8.46 [CI, 1.94 to 76.5]; $P = 0.001$). No patient had more than one episode of hepatotoxicity.

Treatment with rifampin and pyrazinamide was more likely than treatment with isoniazid to be discontinued because of hepatotoxicity (odds ratio, 5.19 [CI, 1.11 to 49.1]; $P = 0.033$). No patient in either group was hospitalized for hepatitis, and all patients had resolution of hepatic abnormalities after discontinuation of therapy with medications. The maximum ALT concentrations of patients with grade 4 hepatotoxicity ranged from 695 to 1187 U/L. Approximately 70% of isoniazid-associated hepatotoxicity of any grade was discovered by liver enzyme testing after the first month of treatment, and both cases of grade 4 hepatotoxicity in patients receiving isoniazid occurred during the first 2 months of treatment. No patient who developed grade 3 or 4 hepatotoxicity had evidence of active hepatitis B or C viral infection.

Confirmatory Analyses

In the confirmatory exact analysis that was stratified by quintile of the propensity score, therapy with rifampin plus pyrazinamide was strongly associated with increased risk for grade 3 or 4 hepatotoxicity (odds ratio, 7.75 [CI, 1.74 to 71.3]; $P = 0.003$) and any hepatotoxicity (odds ratio, 1.77 [CI, 1.04 to 3.04]; $P = 0.033$) compared with isoniazid therapy (**Table 3**). The multiple imputation estimates were consistent with the exact results for both grade 3 or 4 hepatotoxicity (odds ratio, 8.57 [CI, 1.93 to 38.0]; $P = 0.005$) and any hepatotoxicity (odds ratio, 1.53 [CI, 0.95 to 2.47]; $P = 0.08$) (**Table 3**). There was little evidence of heterogeneity of the treatment effect on any grade of hepatotoxicity ($P > 0.2$) and no evidence of clustering by site.

Nonhepatotoxic Adverse Events

The overall occurrence of adverse events not due to hepatotoxicity was similar in the treatment groups (20% among recipients of rifampin and pyrazinamide and 16% among isoniazid recipients [$P = 0.2$]) (**Table 4**). Skin rash was the only nonhepatotoxic adverse effect that occurred more frequently with rifampin plus pyrazinamide (6%) than with isoniazid (2%) ($P = 0.01$). The occurrence of other adverse events did not significantly differ between groups. However, discontinuation of medication use because of nonhepatotoxic adverse events was more common among patients who received rifampin and pyrazinamide than those who received isoniazid ($P = 0.049$). Results were similar among the 525 patients with postenrollment follow-up. Univariate analysis of predictors of nonhepatotoxic adverse events in recipients of rifampin and pyrazinamide for whom follow-up data were available were female sex (odds ratio, 2.35 [CI, 1.33 to 4.15]; $P = 0.003$) and a trend toward recent arrival in the United States (odds ratio, 1.68 [CI, 0.95 to 2.96]; $P = 0.07$). Univariate predictors

Table 3. **Odds Ratios for Incidence of Grade 3 or 4 Hepatotoxicity in Patients Assigned To Receive Rifampin and Pyrazinamide or Isoniazid**

Method of Analysis	Treatment Group	Patients, *n*	Odds Ratio (95% CI)	*P* Value
Observed data	Rifampin and pyrazinamide	207	8.46 (1.9–76.5)	0.001
	Isoniazid	204	Referent	–
Stratified exact*	Rifampin and pyrazinamide	207	7.75 (1.74–71.3)	0.003
	Isoniazid	204	Referent	–
Multiple imputation†	Rifampin and pyrazinamide	307	8.57 (1.93–38.0)	0.005
	Isoniazid	282	Referent	–

* The exact odds ratio, CI, and *P* value are derived from the noncentral hypergeometric distribution of tabulations of grade 3 and 4 hepatotoxicity by treatment assignment, stratified by quintile of the propensity score and conditional on the number of cases of hepatotoxicity in each stratum. Propensity scores were estimated by using a multivariable logistic model that included site, sex, age >35 years, baseline body weight, tuberculin conversion, presence of related medical conditions, and being a health care worker, as well as interactions between site and baseline body weight, sex, and being a health care worker.
† Missing alanine aminotransferase values were simulated in 10 data sets by using SAS Proc IM separately for each arm of the trial. The imputation model for the isoniazid arm included site, sex, age >35 years, baseline weight, birth in the United States, and nonmissing liver enzyme values. The model for the rifampin plus pyrazinamide arm included these covariates plus an indicator for health care workers. Imputed alanine aminotransferase values ≥251 U/L were then classified as grade 3 or 4 hepatotoxicity. One to four cases of hepatotoxicity were imputed among recipients of rifampin and pyrazinamide; no cases were imputed among isoniazid recipients.

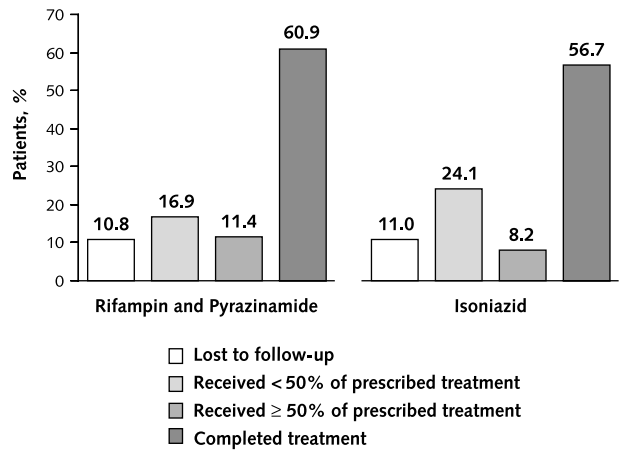
Table 4. **Nonhepatotoxic Adverse Events in the 589 Patients Assigned To Receive Rifampin and Pyrazinamide or Isoniazid To Treat Latent Tuberculosis Infection**

Adverse Effect	Rifampin and Pyrazinamide Group (n = 307)	Isoniazid Group (n = 282)	P Value*
	n (%)		
At least 1 adverse effect	62 (20)	46 (16)	0.2
Nausea or vomiting	18 (6)	12 (4)	>0.2
Skin rash	19 (6)	5 (2)	0.007
Epigastric pain	9 (3)	8 (3)	>0.2
Fatigue or malaise	11 (4)	14 (5)	>0.2
Dizziness	3 (1)	5 (2)	>0.2
Headache	5 (2)	4 (1)	>0.2
Fever or chills	1 (0.3)	1 (0.4)	>0.2
Arthralgia	1 (0.3)	5 (2)	0.11
Diarrhea	3 (1)	2 (1)	>0.2
Peripheral neuropathy	0 (0)	1 (0.4)	>0.2
Anorexia/weight loss	3 (1)	1 (0.4)	>0.2
Insomnia	0 (0)	2 (1)	0.2
Pruritus	3 (1)	1 (0.4)	>0.2
Dysmenorrhea	1 (1)	0 (0)	>0.2
Discontinuation of study medication owing to nonhepatotoxic adverse effect	16 (5)	6 (2)	0.053

* Between-treatment differences were assessed by using the Fisher exact test. Results were similar when analysis was restricted to the 525 participants who were not lost to follow-up after the start of the trial.

of nonhepatotoxic adverse events in isoniazid recipients for whom follow-up data were available included age older than 35 years (odds ratio, 1.96 [CI, 1.06 to 3.62]; P = 0.03) and birth in the United States (odds ratio, 3.88 [CI, 1.64 to 9.18]; P = 0.002).

Figure 2. **Completion of therapy for latent tuberculosis infection in patients assigned to receive rifampin and pyrazinamide or isoniazid.**



Patients lost to follow-up were those in whom no follow-up data on adherence were available. Treatment was prescribed for 2 months for patients assigned to rifampin and pyrazinamide and 6 months for those assigned to isoniazid. The proportion of patients who completed treatment did not significantly differ between the two groups, even after adjustment for site, age older than 35 years, sex, place of birth, medical conditions, hepatotoxicity, and other adverse events (odds ratio, 1.32 [95% CI, 0.92 to 1.90]; P = 0.13).

Percentage of Patients Who Completed Treatment

Although the duration of treatment differed in the isoniazid group and the rifampin plus pyrazinamide group, the proportion of patients who completed treatment was similar (160 of 282 [56.7%] patients vs. 187 of 307 [60.9%] patients, respectively; odds ratio, 1.19 [CI, 0.84 to 1.64]; $P > 0.2$) (**Figure 2**). After adjustment for site, age older than 35 years, sex, place of birth, medical conditions, hepatotoxicity, and other adverse events, the odds ratio for completion of treatment in recipients of rifampin plus pyrazinamide compared with isoniazid recipients was 1.32 (CI, 0.92 to 1.90; P = 0.13). Independent risk factors for noncompletion of treatment in the multivariable logistic model were study site 2 (odds ratio, 2.06 [CI, 1.32 to 3.23]; P = 0.002) or 3 (odds ratio, 3.48 [CI, 2.19 to 5.53]; $P < 0.001$), grade 3 or 4 hepatotoxicity (odds ratio, 4.85 [CI, 1.61 to 14.7]; P = 0.005), and adverse events other than hepatotoxicity (odds ratio, 2.90 [CI, 1.83 to 4.58]; P = 0.005). In multivariable analysis, patients who had grade 1 or 2 hepatotoxicity were more likely to complete treatment (odds ratio, 2.81 [CI, 1.45 to 5.45]; P = 0.002).

Patients Older Than 35 Years of Age

Among the 213 patients older than 35 years of age at study entry, those who received rifampin and pyrazinamide had a higher risk for grade 3 or 4 hepatotoxicity than did those who received isoniazid (multiple imputation odds ratio, 12.2 [CI, 1.49 to 100.3]; P = 0.02). In this subgroup, no statistical difference in the occurrence of nonhepatotoxic adverse events was observed between those who received rifampin and pyrazinamide and those who received isoniazid (odds ratio, 1.09 [CI, 0.59 to 2.03]; $P >$

0.2). The percentage of patients in this subgroup who completed treatment was identical (56%) in both treatment groups but slightly lower than that in younger participants (60%). In multivariable analysis, age older than 35 years may predict noncompletion of treatment (odds ratio, 1.38 [CI, 0.95 to 2.02]; $P = 0.09$).

DISCUSSION

In a group comprising mostly foreign-born adults without HIV infection, 2 months of therapy with rifampin and pyrazinamide for treatment of latent tuberculosis infection was associated with a statistically significantly higher risk for hepatotoxicity than was 6 months of isoniazid therapy. Because of its association with grades 3 and 4 hepatotoxicity, treatment with rifampin and pyrazinamide was also more likely than isoniazid treatment to be discontinued as a result of hepatotoxicity. Although the proportion of nonhepatotoxic adverse events was similar between the two regimens, treatment was discontinued in statistically significantly more recipients of rifampin and pyrazinamide than isoniazid recipients. In addition, although the duration of treatment with rifampin and pyrazinamide was 4 months shorter than that of isoniazid treatment, the percentage of patients who completed treatment was similar in both groups.

Our results suggest that a 2-month regimen of rifampin and pyrazinamide has similar tolerability and acceptability compared with a 6-month regimen of isoniazid. Whether the rifampin and pyrazinamide regimen would be better tolerated and accepted than the currently recommended 9-month regimen cannot be determined from this study. However, because most of the adverse events in the isoniazid regimen, especially hepatotoxicity, occurred relatively early in the course of treatment, it is unlikely that many more adverse events would occur with an additional 3 months of treatment. The percentage of patients who developed grade 4 hepatotoxicity with isoniazid treatment (2 of 282 [0.7%]) is similar to that observed by Nolan and colleagues (20), who reviewed all cases of isoniazid-related hepatotoxicity over 7 years.

Because we studied adverse events and completion of treatment with rifampin plus pyrazinamide or with isoniazid for latent tuberculosis infection, patients underwent regular testing of liver enzymes, which is not usually recommended as part of routine care (11). As a result, we detected most cases of hepatotoxicity on the basis of liver enzyme measurement, and hepatotoxicity was only rarely accompanied by symptoms (4 of 589 patients).

Of note, mild elevation of liver enzyme levels (up to five times the normal value [grade 1 or 2 hepatotoxicity]) does not necessarily indicate that treatment must be stopped. In our study, 35 of 38 (92%) patients who had mildly elevated liver enzyme levels (that is, grade 1 or 2 hepatotoxicity) completed treatment with rifampin and pyrazinamide. Of greater concern are patients who had elevation of serum aminotransferase levels to more than five times normal (grade 3 or 4 hepatotoxicity), in whom treatment was usually discontinued. Although the frequency with which these patients developed symptomatic hepatotoxicity cannot be predicted, hepatotoxicity would have probably progressed if therapy had been continued. In the few published case reports on hepatotoxicity due to regimens containing rifampin and pyrazinamide (12, 13), a common history has been that therapy was continued despite symptoms of hepatitis. Furthermore, because liver enzymes were not routinely measured after 2 months of treatment with rifampin and pyrazinamide, our study may underestimate the incidence of hepatotoxicity with this treatment. Three recipients of rifampin and pyrazinamide developed elevated levels of aminotransferases to greater than five times the normal value (grade 3 hepatotoxicity) at the completion of the second month of treatment, outside the study protocol.

We also found that among persons older than 35 years of age, a group that is at increased risk for hepatotoxicity due to isoniazid therapy, treatment with rifampin and pyrazinamide was associated with increased risk for grades 3 and 4 hepatotoxicity compared with isoniazid. Thus, therapy with rifampin and pyrazinamide may have no particular advantage over isoniazid therapy in persons older than 35 years of age, and persons of this age may be at increased risk for grade 3 or 4 hepatotoxicity. We conclude that patients receiving rifampin and pyrazinamide therapy for latent tuberculosis infection should be monitored closely for any symptoms suggestive of hepatitis. Our results support revised recommendations (13) to include routine follow-up testing of liver enzymes after treatment has begun to screen for hepatotoxicity and thus prevent progression to severe toxicity.

Although experience with rifampin and pyrazinamide for treatment of latent tuberculosis infection in adults without HIV infection is limited, the percentage of patients in our study with hepatotoxicity markedly exceeded that found by Bock and associates (21), who administered these medications to inmates of an urban jail. However, those investigators administered pyrazinamide at a daily dosage of 15 to 20 mg/kg of body weight. In that study, aminotransferase levels were elevated up to 5 times the normal value in 8 of 168 patients, from 5 to 10 times normal in 1 patient, and more than 10 times normal in 1 patient. In three studies of rifampin plus pyrazinamide to treat latent tuberculosis infection in HIV-infected persons (8–10), abnormal liver enzyme levels were seen collectively in only 1% to 3% of patients, a proportion much smaller than in our study. The reasons for these differences are not clear. Possible explanations may include a higher rate of alcohol consumption, higher dosage of pyrazinamide, and older age among our patients, all of which may have predisposed them to drug-induced hepatotoxicity.

Results of previous studies provide some insight into whether rifampin or pyrazinamide might be more likely to

be the cause of drug-induced hepatotoxicity. None of 165 patients with silicosis and latent tuberculosis infection in Hong Kong (22) who received rifampin alone for 12 weeks developed hepatitis, and the proportion of patients with an elevated serum ALT level was similar among rifampin recipients and placebo recipients. In contrast, among 22 persons who had contact with a person with multidrug-resistant tuberculosis and were treated with ofloxacin and pyrazinamide (25 mg/kg daily), 5 had a peak serum ALT level of 1 to 5 times normal and 4 had levels of 5 to 10 times normal (23). The potential for higher doses of pyrazinamide to cause hepatotoxicity was clearly demonstrated in early clinical trials (24). Among patients given isoniazid, pyrazinamide (40 mg/kg of body weight), and para-amino salicylic acid to treat tuberculosis, 6.6% developed severe hepatotoxicity. Although we used a lower dosage of pyrazinamide (20 mg/kg daily), these findings taken together suggest that pyrazinamide may be the primary cause of the increased risk for hepatotoxicity that we observed.

Although other nonhepatotoxic adverse events occurred with similar frequency among patients who received rifampin plus pyrazinamide and those who received isoniazid, the percentage of patients in whom therapy was discontinued was significantly greater among those taking rifampin plus pyrazinamide. This is perhaps because clinicians were less comfortable prescribing and managing adverse events associated with this new treatment for latent tuberculosis infection.

In contrast to studies demonstrating a higher rate of completion of therapy among HIV-infected patients taking rifampin and pyrazinamide to treat latent tuberculosis infection (8–10), we found that the percentage of patients who completed this therapy was similar to that of patients who received isoniazid, even though isoniazid therapy required an additional 4 months of administration. A substantial number of patients in both groups did not complete treatment, but the percentage who completed treatment in our study was still higher than that reported by other public health tuberculosis clinics (25). The reasons for the high number of dropouts are not entirely clear, but this finding emphasizes the need for adherence-promoting measures to improve completion of therapy (26). We intentionally did not use any of these adherence-promoting measures so that we could assess the rate of completion among patients who were typical of those seen in urban tuberculosis clinics in the United States and managed in the standard manner.

Our study has limitations. Liver enzymes were not measured in all patients because of loss to follow-up; thus, potential adverse events and hepatotoxicity were not identified in these patients. However, the rate of loss to follow-up was similar in both groups, and the multiple imputation results in which these missing outcomes were estimated from baseline data and treatment assignment were consistent with results in the 411 participants for whom follow-up liver enzyme values were available. Imbalances between groups at baseline included a greater number of patients older than 35 years of age in the isoniazid group, which may have led to an increased risk for hepatotoxicity among isoniazid recipients. However, the risk for hepatotoxicity was higher in patients taking rifampin plus pyrazinamide, and adjustment for this imbalance by using propensity scores did not change the results. Because our study was not blinded, ascertainment bias may have influenced reporting of adherence and adverse events. Finally, we had limited power to examine heterogeneity of treatment effects and clustering by site. However, results for the 411 participants with complete data do not strongly suggest either difficulty.

In summary, administration of rifampin and pyrazinamide for 2 months to treat latent tuberculosis infection was associated with a significantly higher risk for hepatotoxicity, especially grades 3 and 4 hepatotoxicity, than was 6 months of isoniazid therapy in adults without HIV infection. The occurrence of nonhepatotoxic adverse events was similar between the two groups. Although the duration of treatment with rifampin plus pyrazinamide was shorter than the duration of isoniazid treatment, the proportion of patients who completed therapy was similar between groups. Our findings suggest that rifampin and pyrazinamide should be used with caution and support recommendations for frequent laboratory assessment for liver injury after treatment to document early liver injury and prevent progression to severe toxicity.

APPENDIX: THE SHORT-COURSE RIFAMPIN AND PYRAZINAMIDE FOR TUBERCULOSIS INFECTION (SCRIPT) STUDY INVESTIGATORS

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