Severe Hepatotoxicity Associated with Rifampin-Pyrazinamide Preventative Therapy Requiring Transplantation in an Individual at Low Risk for Hepatotoxicity

D. Kunimoto,[1] A. Warman,[2] A. Beckon,[2] D. Doering,[2] and L. Melenka[2]

[1]Division of Infectious Diseases, Department of Medicine, University of Alberta, and [2]Capital Health TB Clinic, Edmonton, Alberta, Canada

We report a case of severe hepatotoxicity associated with rifampin-pyrazinamide preventative therapy that required liver transplantation in a closely monitored, human immunodeficiency virus–uninfected individual who had no risk for hepatotoxicity. Because hepatotoxicity associated with this treatment appears to be idiosyncratic, we recommend closer monitoring of liver enzyme levels than do the Centers for Disease Control and Prevention guidelines, as well as at least temporary interruption of treatment during any elevation of liver enzyme levels greater than the normal value.

Two months of short-course rifampin and pyrazinamide treatment for latent tuberculosis infection (LBTI) has been demonstrated to be efficacious among HIV-infected patients [1, 2]. The rifampin-pyrazinamide regimen may be useful when completion of longer treatment courses is unlikely, and it has also been recommended as an alternative to isoniazid therapy for HIV-uninfected patients [3]. More recently, 21 cases of severe hepatotoxicity that resulted in 5 deaths have been reported [4]. This has resulted in the development of modified recommendations, including the recommendation against administering rifampin-pyrazinamide treatment for LBTI to persons with underlying liver disease. We report a case of severe rifampin-pyrazinamide–associated hepatotoxicity in an individual with no underlying liver disease and monitored according to the most recent (Centers for Disease Control and Prevention [CDC]) guidelines.

Case report. The patient was a 37-year-old man from El Salvador who immigrated to Canada in 1986 and who was employed at an inner-city business. He underwent a tuberculin skin test (TST) in March 2002 as part of an investigation of an inner-city outbreak of tuberculosis, and the result was positive (induration, 23 mm). It was subsequently discovered that he had previously tested positive (induration, 10 mm) in 1986 but had not received preventative therapy. He was taking no medications, he had no allergies or history of liver disease, and he consumed 1 drink of alcohol every 2–3 months. He had a history of gastroplasty, which had been performed a few years earlier for the purpose of weight loss. Baseline laboratory work performed in April 2002 revealed a normal complete blood cell count and differential, a normal urate level, an aspartate aminotransferase (AST) level of 26 U/L, negative results of a serological test for HIV infection, and negative results of a hepatitis B surface antigen test. The hepatitis C virus (HCV) antibody enzyme immunoassay revealed low titers twice, and the results of a Chiron RIBA 3.0 Strip Immunoblot Assay were indeterminate twice. This was followed by a qualitative HCV PCR test, the results of which were negative. The patient denied having any risk factors for hepatitis C. The results of chest radiography were normal, and 3 sputum specimens were negative for acid-fast bacilli on smear and culture.

On the basis of the patient's positive TST result and his history of probable recent contact with $\geqslant$2 persons with smear results positive for *Mycobacterium tuberculosis,* he was offered a course of preventative, daily, directly observed therapy with rifampin-pyrazinamide. He accepted this recommendation, and, on 15 April 2002, he started receiving a course of rifampin (600 mg) and pyrazinamide (1500 mg; 18.5 mg/kg) under direct observation 5 times per week, with monitoring of the complete blood cell count and differential, the AST level, and the urate level every 2 weeks. The patient had missed several doses until 5 July 2002, at which time the patient had taken 42 doses of rifampin-pyrazinamide over 59 days. His AST level, which had been normal to slightly elevated, was 162 U/L on 5 July, at which time rifampin-pyrazinamide therapy was stopped (table 1).

The patient was asymptomatic until 19 August, when he began complaining of fatigue, nausea, and myalgias. Since starting rifampin-pyrazinamide therapy, he had not been receiving any other medications, had consumed no alcohol, had worked as a clerk at an inner-city agency, and had no known exposure to other hepatotoxins. He was referred to a hepatologist on 21

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Reprints or correspondence: Dr. Dennis Kunimoto, Div. of Infectious Diseases, Dept. of Medicine, 2F1 Walter Mackenzie Health Sciences Centre, University of Alberta Hospital, 8440-112 St., Edmonton, Alberta, Canada, T6G 2B7 (Dennis.Kunimoto@ualberta.ca).

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Table 1. Results of laboratory tests for 37-year-old man who had hepatotoxicity associated with rifampin-pyrazinamide therapy.

Date	AST level, U/L	Total bilirubin level, μmol/L	Prothrombin time, INR	Comment(s)
10 Apr 2002	26	—	—	Baseline
15 Apr 2002	—	—	—	Patient started rifampin-pyrazinamide therapy
1 May 2002	26	—	—	—
21 May 2002	44	—	—	—
3 Jun 2002	32	—	—	—
17 Jun 2002	50	—	—	—
4 Jul 2002	162	—	—	Rifampin-pyrazinamide therapy stopped; no symptoms
15 Jul 2002	292	—	—	—
2 Aug 2002	473	—	—	—
9 Aug 2002	752	22	1.1	—
14 Aug 2002	926	24		—
19 Aug 2002	1757	63	1.3	Symptoms started
23 Aug 2002	2243	159	1.6	—
26 Aug 2002	2409	274	2.1	Patient admitted to the hospital
28 Aug 2002	1868	287	2.0	—
30 Aug 2002	2087	427	2.9	—
3 Sep 2002	662	391	7.8	—
4 Sep 2002	—	—	—	Liver transplantation performed

NOTE. INR, international normalized ratio.

August, and standard pretransplantation evaluation revealed no evidence of acute viral hepatitis. Specifically, IgM antibody to hepatitis A, Epstein-Barr virus viral capsid antigen, and varicella-zoster virus were absent. The test result for the presence of IgM antibody to cytomegalovirus was indeterminate, but the test result for detection of IgG was positive. Examination of a stored serum specimen obtained on 1 May 2002 yielded the same results. The results of tests for hepatitis B surface antigen, antibody to surface antigen, and antibody to core antigen were all negative. Hepatitis C antibody testing was repeated on 9 and 30 August, and the results remained unchanged, with a low-titer positive result of the enzyme immunoassay and indeterminate results of the immunoblot assay. The patient underwent liver transplantation on 4 September 2002. Liver biopsy performed before transplantation revealed submassive hepatic necrosis.

Discussion. LTBI treatment is difficult to administer because of a perceived lack of immediate benefit, the long duration of therapy, and the immediacy of adverse effects, when present. Treatment is more difficult to administer to an inner-city population, among whom competing problems, such as a lack of food, a lack of housing, personal safety issues, and drug or alcohol use, often have higher priority for individuals than does the risk of acquiring tuberculosis in the future.

Shorter courses of preventative therapy have been recommended as alternatives to 9 months of isoniazid therapy, including rifampin alone for 4 months, but routine use of rifampin is discouraged because of the potential for development of resistance and the numerous interactions with other prescription and nonprescription drugs [3]. Rifampin-pyrazinamide was also shown to be effective in HIV-positive individuals [1, 2], and it is presumed to be equally effective in HIV-negative individuals [3]. Compliance rates are also better for rifampin-pyrazinamide therapy than for 6-month [1, 5] and 9-month [2] courses of isoniazid. This short-course combination therapy was initially recommended with clinical monitoring at weeks 2, 4, and 8 of treatment, as well as with laboratory testing in selected cases at baseline and additional testing for adverse reactions or abnormal baseline values [3]. Twenty-one cases of severe hepatotoxicity that resulted in 5 deaths were reported in August 2001, prompting a recommendation for closer monitoring and a recommendation against use of rifampin-pyrazinamide in populations at higher risk for hepatic complications [4]. An update by the CDC indicated that 40 cases of severe hepatotoxicity with 8 fatalities were identified by 25 September 2002 [6]. The guidelines for rifampin-pyrazinamide use remained essentially unchanged from the earlier report.

The pathophysiology of rifampin-pyrazinamide hepatotoxicity is not clear, but we suspect that pyrazinamide is the primary problem. Pyrazinamide-associated hepatotoxicity tends to occur during the second month of treatment, whereas isoniazid-associated hepatotoxicity occurs predominantly during the first month of therapy [7]. This is consistent with reports of severe hepatotoxicity associated with rifampin-pyrazinamide use that occurred primarily during the second month of treatment, including all 5 deaths due to hepatotoxicity during the second month of treatment [4]. Again, in contrast to isoniazid-associated hepatotoxicity, which is usually quickly reversible by withholding the drug, pyrazinamide-associated hepatotoxicity is slower to reverse and may result in liver failure, even after discontinuation of the drug [7], as occurred in our patient. Therefore, early detection of hepatotoxicity and discontinuation of therapy is the only modality known to prevent severe hepatotoxicity.

The CDC recommends that treatment be stopped and not resumed if any of the following findings are made: an AST level of >5 times the upper limit of the normal range in an asymptomatic person, an AST level greater than the normal range accompanied by symptoms of hepatitis, or a serum bilirubin level greater than the normal range [4]. We stopped rifampin-pyrazinamide therapy before any of these occurred, yet our patient's condition progressed to liver failure. In contrast, a multicenter trial involving 307 patients who received rifampin-pyrazinamide therapy, compared with 282 patients who received 9 months of isoniazid therapy, found no cases of hepatotoxicity requiring hospitalization [8]. Severe hepatotoxicity in the rifampin-pyrazinamide group occurred in 7.7% of patients, but, in all cases, it was reversible. Mild toxicity (liver enzyme levels of <5 times the normal level) occurred in 18.3% of patients; rifampin-pyrazinamide therapy was continued, and the liver enzyme levels were rechecked 2 weeks later. The report did not indicate what proportion of these mild toxicities progressed to severe hepatotoxicity. Another report of preventative therapy with rifampin-pyrazinamide reported severe hepatotoxicity in 9.4% of 148 patients, with 2 patients requiring hospitalization, but no fatalities occurred [9]. Multivariate analysis found that hepatotoxicity was associated with female sex and presumed recent infection, but it was not associated with use of alcohol or illicit drugs, age, race, or pyrazinamide dose.

Severe hepatotoxicity is not limited to rifampin-pyrazinamide therapy for LTBI; it also occurs with treatment of active disease. Teleman et al. [10] reported that hepatotoxicity (defined as an alanine aminotransferase level of >3 times the upper limit of normal) occurred in 5.3% of 1036 patients treated for active tuberculosis. A total of 5.9% of 783 patients who received a regimen that included rifampin-pyrazinamide and isoniazid developed hepatotoxicity, whereas only 3.9% of 228 patients who received a regimen that included rifampin and isoniazid (but not pyrazinamide) developed hepatotoxicity. What is striking is that 3 fatalities occurred as a result of hepatotoxicity in patients who received rifampin-pyrazinamide and isoniazid; one of these patients was 16 years old and had no risk factors for hepatotoxicity, although his dosage of pyrazinamide was 28 mg/kg per day.

On the basis of our experience and that of others noted above, rifampin-pyrazinamide therapy carries some risk, even for persons without underlying liver disease. We had successfully started administering preventative therapy with rifampin-pyrazinamide to 69 other individuals, 39 of whom completed a full course. Of interest, two-thirds of the 69 persons had underlying hepatitis C or alcohol abuse and did not develop severe hepatotoxicity. On the basis of this experience, liver failure associated with receipt of rifampin-pyrazinamide therapy appears to be idiosyncratic. It is not known how closely one must monitor the patient or when to discontinue therapy to be absolutely safe, but prudence dictates that one should error on the side of caution, because, in our opinion, liver failure associated with preventative therapy is an unacceptable outcome. Therefore, we would agree with the recommended monitoring of liver enzyme levels every 2 weeks for the first month of therapy, but we would also recommend intensifying testing by routine weekly monitoring after the first month to try and detect any hepatotoxicity early. Also, temporary discontinuation of rifampin-pyrazinamide therapy would be prudent for any increase in the AST level that is greater than the normal value, with the consideration of restarting treatment, depending on results of subsequent liver tests. Although these suggestions may be overly cautious, we believe they are justified until additional experience determines the optimal monitoring and identification of predictors of hepatotoxicity associated with rifampin-pyrazinamide use in HIV-uninfected populations.

References

1. Halsey NA, Coberly JS, Desormeaux J, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet **1998**; 351:786–92.
2. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs. isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. JAMA **2000**; 283:1445–50.
3. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Morb Mortal Wkly Rep **2000**; 49:1–51.
4. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. MMWR Morb Mortal Wkly Rep **2001**; 50:733–5.
5. Bock NN, Rogers T, Tapia JR, Herron GD, DeVoe B, Geiter LJ. Acceptability of short-course rifampin and pyrazinamide treatment of latent tuberculosis infection among jail inmates. Chest **2001**; 119:833–7.
6. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide treatment for latent tuberculosis infection. MMWR Morb Mortal Wkly Rep **2002**; 51:998–9.
7. Durand F, Jebrak G, Pessayre D, Fournier M, Bernuau J. Hepatotoxicity

of antitubercular treatments: rationale for monitoring liver status. Drug Saf **1996**; 15:394–405.
8. Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med **2002**; 137:640–7.
9. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. Int J Tuberc Lung Dis **2002**; 6:995–1000.
10. Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis **2002**; 6:699–705.