Hepatotoxicity of Rifampin and Pyrazinamide in the Treatment of Latent Tuberculosis Infection in HIV-Infected Persons: Is It Different Than in HIV-Uninfected Persons?

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(See the editorial commentary by Saukkonen on pages 566–8)

Background. In 2000, results of a multinational trial demonstrated that a 2-month course of rifampin and pyrazinamide (RZ) was as effective as isoniazid (INH) in reducing tuberculosis in human immunodeficiency virus (HIV)–infected individuals with latent tuberculosis infection (LTBI). After the release of new guidelines, the Centers for Disease Control and Prevention received reports of severe hepatotoxicity associated with the use of the RZ regimen for the treatment of LTBI in the general population. To better understand the occurrence of hepatotoxicity in an HIV-infected population, we conducted a more detailed analysis of the liver function test results obtained in the multinational trial of RZ.

Methods. At study entry, patients were required to have a bilirubin level of ≤2.5 mg/dL and both an aspartate aminotransferase (AST) level and an alkaline phosphatase level of ≤5 times the upper limit of normal. Patients with acute hepatitis were excluded. At months 1 and 2 of the study, all patients had bilirubin and AST levels measured.

Results. There was no difference between the RZ and INH groups with regard to AST level or bilirubin level at baseline. An increase in the AST level of ≥40 U/L was associated with the use of INH and older age; and an increase in the bilirubin level of ≥0.5 mg/dL was associated with the use of RZ, male sex, and nonwhite race (P < .05). An absolute AST level of >250 U/L occurred in 12 of 745 INH recipients and in 15 of 721 RZ recipients (P = .56), and an absolute bilirubin level of >2.5 mg/dL occurred in 5 of 743 INH recipients and 13 of 718 RZ recipients (P = .06).

Conclusions. These data demonstrate very little liver injury associated with either INH or RZ in the HIV-infected subjects, leaving unclear the reasons for serious RZ-related liver damage in the general population.

Targeted treatment of latent tuberculosis infection (LTBI) is an important component of the tuberculosis (TB)–control programs in the United States and in many regions of the world [1]. Although isoniazid has been proven to be effective in reducing reactivation of LTBI, the long duration of treatment (6–9 months) and its associated morbidity and mortality [2] have prompted research into alternative therapies.

In 2000, results of a multinational clinical trial demonstrated that a 2-month course of daily rifampin and pyrazinamide was as effective as isoniazid therapy in reducing TB in HIV-infected individuals with LTBI [3]. Two additional trials demonstrated that a twice-weekly regimen of rifampin and pyrazinamide was also effective in reducing TB in HIV-infected persons [4, 5]. On the basis of these studies, in 2000, the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) issued new guidelines
that stated that a 2-month regimen of daily doses of rifampin and pyrazinamide was a preferred regimen (category A) for HIV-infected persons with LTBI and was an acceptable alternative regimen (category B) for HIV-negative persons with LTBI [1].

After the release of these new guidelines, the CDC received reports of severe and fatal hepatotoxicity associated with the use of the rifampin and pyrazinamide regimen for the treatment of LTBI in the general population [6, 7]. Although these individual case reports did not allow an estimate of the risk of hepatotoxicity with rifampin and pyrazinamide, several research groups have since studied the hepatotoxicity of this regimen in controlled and noncontrolled studies in largely HIV-negative persons at risk for TB [8–12]. Most of these studies demonstrated a rate of hepatotoxicity substantially higher (3.5%–13%) than the rates reported in the trials of HIV-infected persons [3–5]. On the basis of these reports and of retrospective surveillance data indicating a high rate of hospitalization and death due to hepatotoxicity, the ATS/CDC guidelines for treatment of LTBI now recommend that rifampin and pyrazinamide “should generally not be offered” (category D) [13].

To better understand the occurrence of clinically significant hepatotoxicity in an HIV-infected population, we did a more detailed analysis of the liver function tests obtained in the large multinational trial of daily rifampin and pyrazinamide. Those data are reported here.

METHODS

The methods of the trial have been reported in detail elsewhere [3] and are summarized here. Eligible patients were ≥13 years of age and were required to be both HIV infected and to have a documented positive tuberculin skin test result (induration, ≥5 mm). At study entry, patients were required to have a bilirubin level of ≤2.5 mg/dL and both an aspartate aminotransferase (AST) level and an alkaline phosphatase level of ≤5 times the upper limit of normal. Patients with acute hepatitis were excluded.

Patients were randomly assigned to receive either a 12-month regimen of isoniazid (300 mg q.d.) or a 2-month regimen of rifampin (600 mg q.d. or 450 mg q.d. if <50 kg in weight) plus pyrazinamide (20 mg/kg q.d.); both regimens were self-administered. Patients were evaluated at 1, 2, 3, 6, 9, and 12 months of study for adverse events, including hepatitis. At months 1 and 2, all patients had measurements of bilirubin and AST levels performed. After the first year of the study, patients were evaluated every 6 months for TB and other clinical events.

Comparisons of outcomes in treatment groups were made using Student’s t test for continuous data and Fisher’s exact test for categorical data. In addition, multiple logistic regression analysis was used to assess the relationship of 4 variables—treatment group, age, sex, and race—with an increase in the AST level of ≥40 U/L or an increase in the bilirubin level of ≥0.5 mg/dL.

RESULTS

As previously reported, [3] a total of 1583 HIV-infected patients were randomized, including 1128 in the United States, 189 in Mexico, 157 in Haiti, and 117 in Brazil. Study participants had a mean age of 37 years, 86% were black or Latino, and 28% were female. The median CD4 cell count was 436 cells/mm³, and only 7% of patients had a prior AIDS diagnosis. A total of 792 patients were assigned to receive rifampin and pyrazinamide, and 791 were assigned to receive isoniazid.

As shown in table 1, baseline bilirubin and AST values were similar in both treatment groups. For both treatment groups, the bilirubin values increased slightly at months 1 and 2 of the study. The mean increase in the AST level from baseline to month 2 in the group receiving isoniazid was 13 U/L, compared with a mean increase of 8 U/L in patients receiving rifampin and pyrazinamide (P = .05).

Of the 791 patients randomized to receive isoniazid, 5 (0.6%) developed a grade III bilirubin level (>2.5 mg/dL) at either the month 1 or month 2 visit, compared with 13 (1.8%) of 718 patients randomized to receive rifampin and pyrazinamide (P = .06). Grade III AST evaluations (>250 U/L) occurred in 12 (1.6%) of 745 patients receiving isoniazid and in 15 (2.1%) of 721 patients receiving rifampin and pyrazinamide (P = .56). The 12 patients who received isoniazid and who developed an AST level >250 U/L had a mean age of 39 years, a mean baseline AST level of 78 U/L, and a mean baseline CD4 cell count of 425 cells/mm³. Maximum AST levels ranged from 268 to 1030 U/L, with only 2 of the patients having grade IV elevations (i.e., >500 U/L). The 15 patients who received rifampin and pyrazinamide and who developed an AST level >250 U/L had a mean age of 37 years, a mean baseline AST level of 54 U/L, and a mean baseline CD4 cell count of 515 cells/mm³. Maximum AST levels ranged from 257 to 1107 U/L, with 4

<table>
<thead>
<tr>
<th>Time</th>
<th>Bilirubin level, mean mg/dL</th>
<th>AST level, mean U/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid recipients (n = 791)</td>
<td>RZ recipients (n = 792)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.64</td>
<td>0.65</td>
</tr>
<tr>
<td>Month 1</td>
<td>0.67</td>
<td>0.69</td>
</tr>
<tr>
<td>Month 2</td>
<td>0.68</td>
<td>0.69</td>
</tr>
</tbody>
</table>

NOTE. RZ, rifampin-pyrazinamide.

* P = .05
patients having a maximum level of >500 U/L. Most of the bilirubin elevations were isolated and not associated with other abnormal liver findings; of the patients in the rifampin and pyrazinamide group, 13 had a grade III bilirubin elevation, and only 3 of the 13 patients also developed an AST level of >250 U/L. There were no hospitalizations or deaths due to use of isoniazid or rifampin and pyrazinamide in this study.

To better understand risk factors associated with bilirubin and AST increases, a multiple logistic regression analysis was performed. As shown in table 2, use of rifampin and pyrazinamide, nonwhite race, and male sex were factors associated with developing an increase in the bilirubin level of >0.5 mg/dL from baseline to either month 1 or 2 of the study. Age was not a significant factor. Hepatocellular toxicity, as evidenced by increases in the AST level of >40 U/L from baseline, was also evaluated using logistic regression analyses for both regimens. As shown in table 2, older age was the only factor associated with this level of increase in the AST value, although there was a trend towards more hepatotoxicity among isoniazid recipients ($P = .055$).

**DISCUSSION**

A regimen of rifampin and pyrazinamide given for 2–3 months has been shown to be effective in preventing active TB in HIV-infected persons with LTBI [1–3]. The data presented here support the low level of clinically meaningful hepatotoxicity associated with this regimen in an HIV-infected population. Using AST levels as a marker of hepatocellular damage, the mean AST level did not increase and, in fact, was somewhat lower (49 vs. 55 U/L) at months 1 and 2 of treatment, compared with the isoniazid regimen. Furthermore, the 2 regimens showed similar rates of grade III or higher AST abnormalities. Of the factors associated with an increase in the AST level of >40 U/L, only older age was significant ($P = .026$), although there was a trend to greater increases in the AST level among persons who received isoniazid ($P = .055$). Therefore, using 3 different means of evaluating the impact on the liver, we demonstrated that the rate of hepatotoxicity was equivalent in both groups and certainly was not higher in persons who received rifampin and pyrazinamide. Furthermore, because isoniazid was given for an additional 10 months without routine biochemical testing being performed, patients who received isoniazid may have had somewhat higher levels of liver function abnormalities than we found in this study.

Two other studies of rifampin and pyrazinamide given for the treatment of LTBI support the safety of this regimen in HIV-infected persons (table 3). Halsey et al. [4] randomly assigned 784 HIV-infected persons in Haiti either to receive a twice-weekly regimen of rifampin and pyrazinamide for 2 months or a regimen of isoniazid for 6 months. All patients had AST levels measured at baseline and at months 1 and 2 of treatment. The rates of AST elevations “were very low (1–3%) and did not differ significantly between drug regimens” [4, p. 790], and no patients discontinued treatment as a result of adverse events. Mwinga et al. [5] conducted a 3-arm evaluation of treatments in Zambia: twice-weekly rifampin and pyrazinamide for 3 months, isoniazid for 6 months, and placebo for HIV-infected patients. Patients had AST levels measured monthly and were removed from the study if levels were $\geq 2$ times the upper limit of normal. Only 1 of 360 patients in the rifampin and pyrazinamide group developed an abnormal AST level, compared with 3 of 360 patients in the isoniazid group and 0 of 360 patients in the placebo group. In sum, in the 2 reported controlled trials and in our trial, >1500 HIV-infected persons received rifampin and pyrazinamide for 2–3 months and developed no evidence of excess hepatocellular damage, compared with patients receiving either isoniazid or placebo.

In contrast to the lack of clinically relevant hepatotoxicity in the 3 trials of HIV-infected persons, there have been subsequent case reports [6, 7] and studies demonstrating greater levels of serious hepatotoxicity when rifampin and pyrazinamide were used for the treatment of LTBI in patients at risk for TB, most of whom were HIV negative. In the largest of these comparative studies, Jasmer et al. [8] evaluated 307 persons assigned to receive rifampin and pyrazinamide for 2 months and 282 persons assigned to receive isoniazid for 6 months. Individuals with HIV infection or with alanine aminotransferase (ALT) levels of $\geq 3$ times upper limit of normal at baseline were excluded. At month 1, a total of 16 (7.7%) of 207 patients receiving rifampin and pyrazinamide had ALT levels of $\geq 250$ U/L, compared with 1 (0.5%) of 199 patients who received isoniazid ($P < .001$). In a similar study of 224 patients, McNeill et al. [9] reported that 13% of patients receiving rifampin and pyrazinamide developed an ALT level of $\geq 160$ U/L, compared with 4% of patients receiving isoniazid ($P = .03$). Of patients tested for HIV infection, 3 (1.3%) were noted to be positive.

Four groups have reported rates of toxicity in noncontrolled studies involving 2-month regimens of rifampin and pyrazin-
Table 3. Rates of hepatotoxicity in comparative trials of rifampin and pyrazinamide versus isoniazid for treatment of latent tuberculosis infection.

<table>
<thead>
<tr>
<th>Study population, site</th>
<th>No. of patients</th>
<th>TA threshold, U/L</th>
<th>Treatment group, % of patients with TA levels greater than the threshold</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States, Mexico, Brazil, and Haiti</td>
<td>1583</td>
<td>&gt;250</td>
<td>1.6</td>
<td>2.1 PR</td>
</tr>
<tr>
<td>Haiti</td>
<td>784</td>
<td>&gt;150</td>
<td>1–3</td>
<td>1–3 [4]</td>
</tr>
<tr>
<td>Zambia</td>
<td>720</td>
<td>&gt;90</td>
<td>&lt;1</td>
<td>&lt;1 [5]</td>
</tr>
<tr>
<td>Largely HIV-uninfected patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>San Francisco, CA</td>
<td>589</td>
<td>&gt;250</td>
<td>1</td>
<td>7.7 [8]</td>
</tr>
<tr>
<td>North Carolina</td>
<td>224</td>
<td>&gt;160</td>
<td>4</td>
<td>13 [9]</td>
</tr>
</tbody>
</table>

NOTE. PR, present report; RZ, rifampin-pyrazinamide; TA, transaminase.

amid. Bock et al. [10] reported that only 2 of 168 incarcerated persons who started a regimen of rifampin and pyrazinamide developed a grade III or higher transaminase abnormality. In a second study of prisoners, Chaisson et al. [11] reported that only 1 of 589 persons who started a regimen of rifampin and pyrazinamide developed an aminotransferase level of grade III or higher. In both of these prison-based studies, aminotransferase testing was done at baseline and at months 1 and 2 of treatment for persons receiving therapy. The number of HIV-infected persons was noted to be low in these 2 studies. In a report of the use of rifampin and pyrazinamide in a largely homeless population with high rates of substance abuse, Stout et al. [12] found that 4 of 114 persons developed grade III or higher ALT levels; the results of HIV tests were positive for 8 (22%) of 37 persons tested. Routine liver function tests were not performed in this study.

In a retrospective surveillance survey of health departments by the CDC [13], the rate of a grade III or higher elevation in the AST level was estimated to be 2.6% for persons receiving rifampin and pyrazinamide. Seventy-seven percent of subjects received daily therapy, and 23% received twice-weekly therapy [13]. Of greater concern, however, was the finding in this survey that hospitalization resulting from hepatitis occurred at a rate of 3.0 per 1000 treatment initiatives (95% CI, 1.8–4.2), and there were 0.9 deaths per 1000 treatment initiatives (95% CI, 0.2–1.6) among those receiving rifampin and pyrazinamide for treatment of LTBI. Rates of hepatotoxicity by HIV infection status were not reported, but of the 11 persons who died, 2 were known to be HIV infected. There were no hospitalizations or deaths related to use of anti-TB drugs in our study; however, there was inadequate power to detect rare events.

The lack of serious hepatotoxicity associated with the use of rifampin and pyrazinamide in the prospective trials of HIV-infected patients—compared with higher rates detected in the case reports and studies involving other populations—cannot be readily explained. Although it may be that the hepatic damage from rifampin and pyrazinamide is immunologically mediated and is therefore lower in the HIV-infected persons, there is no clear support for this hypothesis. In our trial, patients were not severely immunocompromised (with a mean CD4 cell count at baseline of 440 cells/mm³, only 7% of persons had a prior diagnosis of AIDS).

The rates of hepatotoxicity associated with rifampin and pyrazinamide therapy in HIV-infected patients are similar to those seen when these drugs are given as part of the treatment for active TB. Conversely, in HIV-negative patients, hepatotoxicity was more frequent than what would have been expected on the basis of data from TB treatment studies. In a 1982 summary of TB treatment studies, Girling [14] reported that hepatitis occurred in only 1% of 544 persons treated with regimens containing isoniazid, rifampin, and pyrazinamide, and it occurred in 1% of 485 persons receiving regimens that did not contain pyrazinamide. In US Public Health Service Trial 21, a total of 678 patients received isoniazid plus rifampin for the treatment of TB, and 823 patients received isoniazid, rifampin, and pyrazinamide [15]. Elevations in hepatic enzyme levels were reported for only 1.2% of patients receiving the 2-drug regimen and for 1.6% of patients receiving the 3-drug regimen. In a recent Canadian series of 430 persons treated for active TB with isoniazid, rifampin, pyrazinamide, and ethambutol, 3% developed clinical hepatitis [16]. Other studies, using less defined measures, have reported rates of hepatocellular damage in ≥5% of patients receiving treatment for TB [17, 18]. Therefore, the rates of hepatotoxicity found in the trials of LTBI in HIV-positive persons are in the range reported from most treatment studies, and the rates found in HIV-negative persons receiving rifampin plus pyrazinamide for treatment of LTBI are higher than expected. This raises the question of whether the use of isoniazid provides a protective effect to patients receiving rifampin and pyrazinamide.
The analyses presented here, as well as data from the other 2 comparative trials of rifampin and pyrazinamide, support the safety of the rifampin and pyrazinamide regimen for the treatment of LTBI in HIV-infected persons. The recent CDC surveillance data raise concern over serious and sometimes fatal reactions when rifampin and pyrazinamide are used for chemoprophylaxis. Our data support the use of rifampin and pyrazinamide in HIV-infected patients with LTBI who are not likely to complete a longer regimen. If used, the 2-drug regimen must be administered under close monitoring and supervision, following recently published guidelines [13]. We concur that rifampin and pyrazinamide should generally not be used by HIV-negative patients.

Acknowledgments

Financial support. National Institute of Allergy and Infectious Diseases and Centers for Disease Control and Prevention.
Conflict of interest. All authors: No conflict.

References