Safety and Completion Rate of Short-Course Therapy for Treatment of Latent Tuberculosis Infection

Paul P. Cook, Ricardo A. Maldonado, Connie T. Yarnell, and Don Holbert
1Brody School of Medicine and 2Department of Biostatistics, East Carolina University, and 3Pitt County Health Department, Greenville, North Carolina

Background. Nine months of isoniazid therapy is the recommended regimen for treatment of latent tuberculosis infection, but low completion rates are a serious problem. The search for shorter regimens, compared with the standard isoniazid regimen, is of vital importance. We describe our experience using short-course regimens for the treatment of latent tuberculosis infection.

Methods. We conducted a nonrandomized, observational study of 459 patients in a county health department from June 2000 to January 2006. Short-course therapy was defined as pyrazinamide and rifampin taken daily or twice weekly for 2 months or rifampin taken daily for 4–6 months. Conventional therapy consisted of a 9-month regimen of isoniazid. Liver function testing was performed for both groups in accordance with clinical guidelines. Treatment completion and hepatotoxicity (according to the World Health Organization classification) were determined for the short-course and conventional therapy groups.

Results. Treatment was completed by 241 (77.7%) of 310 patients in the short-course group and by 98 (65.8%) of 149 patients in the isoniazid group (P = .009). Moderate to severe hepatotoxicity (grades 3 and 4) occurred in 6.1% of patients receiving short-course therapy and in 2.0% of patients receiving isoniazid (P = .09). The hepatotoxicity observed in the short-course group was confined to patients receiving pyrazinamide and rifampin daily and was self limited in all cases after the medications were discontinued.

Conclusions. The rate of treatment completion was significantly higher with short-course regimens, compared with the isoniazid regimen. Although the overall risk of hepatotoxicity in patients receiving pyrazinamide and rifampin daily for the treatment of latent tuberculosis infection was higher, liver functions returned to normal after the medications were discontinued.

Preventing active tuberculosis by treating latent tuberculosis infection is a major element of the national strategy for eliminating tuberculosis in the United States. Targeted treatment for persons who are at the highest risk for the reactivation of tuberculosis is needed to achieve this goal [1]. Current American Thoracic Society guidelines recommend a 9-month regimen of isoniazid taken daily for patients with latent tuberculosis who are at high risk for reactivation of the disease [2]. Compliance with treatment is a concern for patients taking isoniazid, because completion rates range from 30% to 64% [3–5]. Shorter regimens with improved completion rates are needed.

The combined regimen of pyrazinamide and rifampin (PZA-RIF) has been associated with severe hepatotoxicity [6–8]. In a recent national survey, the Centers for Disease Control and Prevention (CDC) found that rates of liver injury, hospitalization, and death associated with PZA-RIF therapy exceed rates reported to be associated with isoniazid therapy [9]. As a result of this study, the CDC no longer recommends PZA-RIF for the treatment of latent tuberculosis infection [9]. In a later publication, the CDC described the onsite investigations of all cases of hospitalization or death attributed to the treatment of latent tuberculosis infection with PZA-RIF reported since the regimen was recommended in 1998 [10]. The study suggested that some fatal cases of liver injury occurred despite monitoring. We describe our experience of 5 years with...
short-course regimens of either PZA-RIF for 2 months or rifampin alone for 4–6 months, compared with a 9-month regimen of isoniazid.

**METHODS**

Patients were enrolled at the Pitt County Health Department (Greenville, NC) from June 2000 to January 2006. Candidates were required to have a positive purified protein derivative result, as defined by current American Thoracic Society criteria [11]. Patients with clinical or radiographic evidence of active tuberculosis infection were excluded. Children <3 years old did not receive the PZA-RIF regimen. Patients were offered PZA-RIF unless they had contraindications (i.e., they had active hepatitis or were receiving medications metabolized through cytochrome P450) or if isoniazid was preferred (e.g., for contact lens users, jail inmates, and oral contraceptive users unwilling to switch contraceptive methods). Written informed consent was obtained from all patients or guardians after the potential benefits and risks of each regimen were explained to them. The patient or guardian was given the right to choose isoniazid or rifampin, even if the individual met our criteria for treatment with PZA-RIF. Treatment compliance was assessed by patient interviews conducted by the tuberculosis nurse (C. T. Y.).

Patients in the PZA-RIF group received 15 mg/kg of pyrazinamide per day (maximum, 2 g per day) and 10 mg/kg of rifampin per day (maximum, 600 mg per day) or 50 mg/kg of pyrazinamide (maximum, 4 g per day) and 10 mg/kg of rifampin (maximum, 600 mg per day) 2 times per week for 2 months. Patients in the rifampin group received 10 mg/kg of rifampin (maximum, 600 mg per day) for 4 months (6 months for children <15 years old). Patients in the isoniazid group received isoniazid (5 mg/kg per day for adults, and 10 mg/kg per day for children [maximum, 300 mg per day]) and 50 mg of pyridoxine per day for 9 months. Daily medications were self administered; twice-weekly medications were administered under direct observation. Patients receiving PZA-RIF daily were seen every 2 weeks; patients receiving isoniazid or rifampin were seen at monthly intervals. Patients in the PZA-RIF group underwent liver function testing at baseline (enrollment) and at 2, 4, 6, and 8 weeks. In the isoniazid group, patients underwent liver function testing at baseline and monthly thereafter. Patients receiving rifampin underwent liver function testing at baseline and monthly thereafter if baseline liver function test results were abnormal. If baseline liver function test results were normal, repeat liver function tests were performed if patients developed symptoms of hepatitis. Clinical symptoms of hepatitis (i.e., nausea, vomiting, anorexia, jaundice, and fatigue) were assessed by the tuberculosis nurse at each visit. Hepatotoxicity was defined according to the World Health Organization classification [12] and was determined by means of aspartate aminotransferase level: grade 1, an aspartate aminotransferase level 1.25–2.5 times the upper limit of the normal range; grade 2, an aspartate aminotransferase level 2.6–5 times the upper limit of the normal range; grade 3, an aspartate aminotransferase level 5.1–10 times the upper limit of the normal range; and grade 4, an aspartate aminotransferase level >10 times the upper limit of the normal range. Beginning in 2004, patients in the PZA-RIF group who had grade 1–3 elevations in aspartate aminotransferase level but who were not symptomatic (i.e., did not have nausea, vomiting, anorexia, or jaundice) were offered to continue therapy with rifampin alone or to stop both drugs. These patients were seen weekly until their liver function test results returned to baseline values. Patients who stopped pyrazinamide but continued rifampin and completed 4 months of therapy were counted as having completed the short-course regimen. Medications were discontinued for all patients who developed nausea, vomiting, anorexia, or jaundice, as well as for all patients who developed grade 4 hepatotoxicity, regardless of symptoms. Patients were screened for

---

**Figure 1.** Outcome of patients who received short-course regimens. A total of 291 patients were initially treated with pyrazinamide (PZA) and rifampin (RIF). Thirteen of these patients switched to RIF only after developing hepatotoxicity. Twenty-six patients receiving the PZA-RIF regimen dropped out because of noncompliance. Twenty-two patients dropped out because of hepatotoxicity. Seventeen patients dropped out for other reasons, including nausea, rash, and itching. Four of the 32 patients treated with RIF dropped out because of noncompliance.
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short-course therapy group (n = 310)</th>
<th>Isoniazid therapy group (n = 149)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>39.3</td>
<td>37.6</td>
<td>NS</td>
</tr>
<tr>
<td>Female sex</td>
<td>148 (48)</td>
<td>68 (48)</td>
<td>NS</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79 (25)</td>
<td>37 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Black</td>
<td>177 (57)</td>
<td>79 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic</td>
<td>38 (12)</td>
<td>18 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Asian</td>
<td>17 (5)</td>
<td>14 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>71 (22.9)</td>
<td>29 (19.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless indicated otherwise. NS, not significant.

evidence of HIV infection; they were not screened for viral hepatitis. Statistical analysis was performed using the χ² test or Student’s t test, as appropriate.

RESULTS

A total of 310 patients were treated with a short-course regimen. Two hundred ninety-one patients received PZA-RIF, and all but 13 of these patients received daily therapy. Nineteen patients were initially treated with rifampin; 13 additional patients in the PZA-RIF group switched to rifampin after developing increases in levels of liver transaminases (figure 1). One hundred forty-nine patients received isoniazid. Baseline characteristics of the study groups are shown in table 1. Both groups had similar distributions of sex, race, age, and reported alcohol use. Two patients in each group were found to have HIV infection; 1 patient in each group was known to have a history of chronic hepatitis C.

Treatment was completed by 241 (77.7%) of 310 patients in the short-course group and by 98 (65.8%) of 149 of patients in the isoniazid group (P = .009) (figure 1). Noncompliance with medications (26 patients) was the most common reason for not completing therapy in the short-course group. Twenty-two patients in the short-course group did not complete therapy because of hepatotoxicity. In the isoniazid group, noncompliance with the regimen was the major reason for failure to complete the course of therapy, accounting for 88% of hepatotoxicity cases (45 cases) of noncompletion. Hepatotoxicity was the reason for not completing therapy with isoniazid in only 6% of cases. Noncompliance was a much more common reason for noncompletion in the isoniazid group, compared with the short-course group (P < .0001), whereas hepatotoxicity was a more common reason for noncompletion in the short-course group, compared with the isoniazid group (P = .0012).

Patients with hepatotoxicity. Overall hepatotoxicity (table 2) was documented in 57 (18.4%) of 310 patients in the short-course group and in 17 (11.4%) of 149 patients in the isoniazid group (P = .077). There was a higher incidence of grade 3 or 4 hepatotoxicity in the PZA-RIF group, compared with the isoniazid group (6.1% vs. 2.0%; P = .08) (table 2). Male sex and alcohol use were not associated with the development of hepatotoxicity in either of the treatment groups. Alcohol use was felt to be a contributing factor in 2 of 58 patients who experienced hepatotoxicity in the PZA-RIF group and in 1 of 17 patients in the isoniazid group. Patients who developed grade 3 or 4 hepatotoxicity in the short-course group were older than patients who did not develop liver enzyme abnormalities (mean age, 47.2 years vs. 38.9 years; P = .056). Of the 19 patients with grade 3 or 4 hepatotoxicity, only 3 were symptomatic (i.e., they had a history of nausea, vomiting, or anorexia). None of the patients who developed hepatotoxicity died, and none required a liver transplant. Liver enzyme levels returned to normal in all patients when their medications were discontinued.

Of the 57 patients who had hepatotoxicity in the PZA-RIF group, 37 (65%) completed therapy. Thirteen patients who developed hepatotoxicity in the PZA-RIF group completed 4 months of treatment with rifampin alone for latent tuberculosis infection after discontinuing pyrazinamide (figure 1). One patient in the PZA-RIF group was hospitalized for hepatitis. This patient had a grade 4 elevation in liver enzyme level and was discharged from the hospital in stable condition after 4 days; the patient’s liver enzyme level returned to normal within 4 weeks. Among the 17 patients who developed hepatotoxicity in the isoniazid group, 14 (82%) completed therapy. None of the patients in the isoniazid group with hepatotoxicity were hospitalized.

Fifty (88%) of 57 of patients who developed hepatotoxicity in the PZA-RIF group had initial increases in liver function test results by the fourth week (figure 2). Of patients who developed grade 3 or 4 hepatotoxicity, 17 (89%) of 19 patients

Table 2. Hepatoxicity associated with each treatment group.

<table>
<thead>
<tr>
<th>Hepatotoxicity grade</th>
<th>Increase in ALT level</th>
<th>No. (%) of patients, by treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ULN</td>
<td>Short-course</td>
</tr>
<tr>
<td>1</td>
<td>1.25–2.5 × ULN</td>
<td>20 (6.5)</td>
</tr>
<tr>
<td>2</td>
<td>2.6–5 × ULN</td>
<td>18 (5.8)</td>
</tr>
<tr>
<td>3</td>
<td>5.1–10 × ULN</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10 × ULN</td>
<td>9 (2.9)</td>
</tr>
<tr>
<td>Total&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>57 (18.4)</td>
</tr>
</tbody>
</table>

NOTE. Short-course therapy consisted of a regimen of pyrazinamide and rifampin or a regimen of rifampin only. ALT, aspartate aminotransferase; ULN, upper limit of the normal range.

* P = .077
had initial incremental changes in liver function test results by the fourth week.

DISCUSSION

In the United States, 9.5–14.7 million persons have latent tuberculosis infection [13]. The American Thoracic Society recently published performance measures and objectives for tuberculosis control [13]. One of the objectives was to increase the percentage of contacts with persons with acid-fast bacilli sputum smear–positive tuberculosis who complete treatment for latent tuberculosis infection. The most recent national data from the year 2000 indicated that only 56.7% of such patients completed therapy [13]. Of course, most of these patients were treated with isoniazid. In North Carolina, 60%–65% of patients treated for latent tuberculosis infection actually complete therapy (unpublished data). Again, most of these patients were treated with isoniazid. These poor completion rates should be a wake-up call that our current standard of care (a 9-month regimen of isoniazid) is not adequately addressing this serious problem. Our data demonstrate that the short-course regimens are more likely to be completed than the isoniazid regimen.

The frequency of moderate to severe hepatotoxicity (grade 3–4 or an aspartate aminotransferase level >5 times the upper limit of the normal range) in our patients receiving PZA-RIF was comparable to the frequency reported in several other studies [5, 14, 15] and was higher than the frequency reported in other studies [16–18]. Nearly 90% of patients who developed any grade of hepatotoxicity in the PZA-RIF group had initial increases of liver function test results (at least a doubling of the baseline aspartate aminotransferase level or an aspartate aminotransferase level >1.25 times the upper limit of the normal range) by the fourth week of therapy, supporting the practice of intensive monitoring to identify such patients.

Although pyrazinamide and rifampin are potentially hepatotoxic, the regimen with rifampin alone shows a low incidence of hepatitis [19, 20]. We were able to achieve completed therapy with rifampin alone (for 4 months) in 13 patients who developed grades 1–3 hepatotoxicity while receiving PZA-RIF. Liver function test results returned to normal in all 13 patients. Therefore, in agreement with other studies [21–23], we suspect that pyrazinamide is the most likely agent responsible for the hepatotoxicity associated with this regimen.

Recent publications from the CDC discourage the use of PZA-RIF for the treatment of latent tuberculosis infection [9, 10], citing severe liver toxicity in patients who received this regimen. The lack of effective monitoring of those patients may have contributed to their poor outcomes. Our results differed from this retrospective analysis of several sites [10] in which fatal cases of liver injury occurred despite monitoring. The patients in the CDC study were subjected to different standards of monitoring, most of which are considered to be inadequate, compared with today’s standards. Most (42 of 50) patients in the CDC study did not receive the degree of intensive monitoring of liver function that was done in our study. We believe that our study, which incorporated uniform, intensive monitoring of liver enzyme levels for all subjects, provides a more realistic picture of the true toxicity of this regimen. Therefore, we disagree with the authors’ comments that “even if more intense monitoring could improve safety, it would make RZ (rifampin/pyrazinamide) less practical for widespread use” [10, p. 353].

In conclusion, our data demonstrate a much higher completion rate with the short-course regimens, compared with the isoniazid regimen. This higher completion rate may justify the use of short-course therapy for patients who may have difficulty with adherence to therapy. Although hepatotoxicity was more common in the PZA-RIF group, the intensive monitoring allowed for early identification of such patients, so that therapy could be changed, resulting in no serious morbidity.

Acknowledgments

Potential conflicts of interest. P.P.C. has received research funding from Pfizer, Merck, and GlaxoSmithKline and has served on speakers’ bureaus for Wyeth, Sanofi-Aventis, and Merck. All other authors: no conflicts.

References

20. Geiter LJ, Results of a randomized, controlled trial to assess the toxicity and patient adherence with two short course regimens for the prevention of tuberculosis, a two month regimen of rifampin and pyrazinamide or a four-month regimen of rifampin only, in comparison with a control regimen of six-months isoniazid. PhD. (Epi) Thesis. Baltimore: School of Hygiene and Public Health, John Hopkins University, 1997:180.