Initial Experience on Rifampin and Pyrazinamide vs Isoniazid in the Treatment of Latent Tuberculosis Infection Among Patients With Silicosis in Hong Kong*

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Objective: To compare the adverse effects and treatment adherence between 2 months of rifampin plus pyrazinamide (2RZ) and 6 months of isoniazid (6H).

Background: Patients with silicosis in Hong Kong are at high risk of acquiring tuberculosis. A previous study showed that treatment with 6H reduced the risk of silico-tuberculosis by one half.

Method: Patients with silicosis and a Mantoux skin test reaction > 10 mm were randomized to receive either 2RZ or 6H daily. Liver function testing was done monthly during the initial 2 months. The adverse effects and treatment adherence were compared between the two regimens.

Results: Forty patients (mean age, 61.6 ± 9.1 years) and 36 patients (mean age, 57.6 ± 9.7 years) were randomized to the 2RZ and 6H arms, respectively (p = 0.05). Baseline characteristics were comparable. Nineteen patients in the 2RZ arm had peak alanine transaminase (ALT) levels > 1.5 times the upper limit of normal (ULN) in comparison with only five study subjects of the 6H arm (47.5% vs 13.9%, p < 0.01). Fourteen patients (35%) in the 2RZ arm and 1 patient (2.8%) in the 6H arm had peak ALT levels more than five times the ULN (p < 0.001). Only seven patients had symptoms suggestive of hepatitis; none of the patients had jaundice. All recovered after withholding treatment. In the 2RZ study arm, none of the baseline characteristics predicted hepatotoxicity. Other adverse effects were generally mild and comparable between both study arms. Treatment was stopped prematurely in 45% and 36.1% of patients in the 2RZ and 6H arms, respectively (p = 0.43). The main reasons were hepatotoxicity for the 2RZ arm and voluntary withdrawal after experiencing other minor adverse effects for the 6H arm.

Conclusion: A higher incidence of hepatotoxicity was associated with rifampin plus pyrazinamide than isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong.

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Key words: isoniazid; pyrazinamide; rifampin; silicosis; tuberculosis

Abbreviations: ALT = alanine transaminase; BCG = bacille Calmette-Guérin; HBsAg = hepatitis B surface antigen; LFT = liver function test; LTBI = latent tuberculosis infection; ULN = upper limit of normal; 2RZ = 2 months of rifampin and pyrazinamide; 6H = 6 months of isoniazid

Silicosis is an important occupational lung disease in Hong Kong. Despite the ban of hand-dug caisson, and the introduction of various protective measures, there are still 100 confirmed new cases every year.1 The tuberculosis notification rate among the general population was 113.7/100,000 in 2000.1 Patients with silicosis are at high risk of acquiring tuberculosis, and the estimated risk is approximately 3 to 7% per annum in Hong Kong.2,3 A previous, randomized controlled study2 showed that treatment with 6 months of isoniazid (6H) among patients with silicosis reduced the incidence of silico-tuberculosis.

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by one half. However, routine use of isoniazid in the
treatment of latent tuberculosis infection (LTBI)
among patients with silicosis in the nonstudy setting
has resulted in only fair-to-poor acceptance and
adherence. The reported success of treatment with 2
months of rifampin and pyrazinamide (2RZ) in the
treatment of LTBI among patients with silicosis
has raised our interest to see if this shorter regimen
is a better alternative to the 6H regimen. A shorter
course of treatment is attractive, as it may potentially
improve acceptance and adherence. A prospective,
randomized controlled trial was therefore conducted
to compare the efficacy and safety of 2RZ vs 6H in
the treatment of LTBI among patients with silicosis.
The study was approved by the Ethics Committee
of the Department of Health of the Hong Kong
Special Administrative Region. The initial experi-
ence, especially in relation to adherence and adverse
reactions, is presented in this report.

PATIENTS AND METHODS

Selection of Patients

From October 1, 2000, all patients with silicosis without a
history of tuberculosis attending the Pneumoconiosis Clinic
under the Department of Health were offered a Mantoux skin
test with 2 U of purified protein derivative RT23. Those with a
positive reaction, defined as an induration \( \geq 10 \) mm,
were informed of the indication for treatment of LTBI and invited to
join the study. Treatment of LTBI with 6H under service setting
would still be offered to eligible patients who refused to partic-
ipate in the study. All recruited subjects must have radiographic
profusion of small opacities of category \( \geq 1 \) according to the
International Labor Office classification. Exclusion criteria in-
cluded the presence of active pulmonary and/or extrapulmonary
tuberculosis at the time of recruitment, history of receiving
\( \geq 2 \) months of antituberculous treatment, intolerance to study med-
ications in the past, poor general condition, and presence of gouty
arthritis, cirrhosis, symptomatic hepatitis, or liver dysfunction
with alanine transaminase (ALT) levels \( > 1.5 \) times the upper
limit of normal (ULN). Active tuberculosis was excluded by
clinical assessment, at least two negative sputum smears and
cultures for Mycobacterium tuberculosis, and stable chest radi-
ographic features over a period of 6 months.

Chemotherapy Regimens

The study subjects were randomized into two study arms (2RZ
vs 6H) by a random number table. For the 2RZ arm, a 2-month
course including 60 doses of rifampin and pyrazinamide was
administered. For those weighing \( < 50 \) kg, the daily dosages
of rifampin and pyrazinamide were 450 mg and 1,000 mg, respec-
tively; the corresponding daily dosages for study subjects \( \geq 50 \) kg
were 600 mg and 1,500 mg. The regimen for the 6H arm
included a 6-month course of isoniazid administered in a daily
dose of 300 mg. There were 180 doses in total. The first dose was
administered in the clinic for observation of any side effects.
The remaining medications were administered monthly with a ran-
dom number of surplus doses. A drug calendar was given to study
subjects for recording their adherence to treatment at home.

Excess medications were to be returned on follow-up to counter-
check the treatment adherence. Adherence was calculated as
the percentage of doses actually received among the expected
number of administered doses.

Initial Investigation and Subsequent Monitoring

Before enrollment, chest radiography, tuberculin tests, blood
tests including complete blood picture, liver function tests
(LFTs), renal function tests, hepatitis B surface antigen (HBsAg),
spot sugar, and urate were done. HIV antibody test was checked
after counseling and consent. Two sputum samples collected on
two different days were sent for direct microscopy and culture of
mycobacteria. Urinalysis for glucose and albumin was also per-
formed.

The study subjects were educated on the potential adverse
effects of the medications and advised to report any suspicious
symptoms promptly. For those assigned to the 2RZ arm,
follow-up was arranged at the first, second, and sixth months, and
every 6 months thereafter. For the 6H arm, follow-up was
monthly for the first 6 months and then every 6 months
thereafter. In both study arms, LFTs were repeated monthly for
the first 2 months and on clinical suspicion of hepatitis. Sputum
examination for mycobacteria and chest radiography were re-
peated at months 2, 6, and 12, and then yearly up to 10 years.

Liver dysfunction was defined as an increase in ALT level to
\( > 1.5 \) times ULN on at least two occasions 2 weeks apart.
Symptomatic hepatitis was defined as the presence of clinically
significant symptoms in association with liver dysfunction. Study
medications were withheld in symptomatic hepatitis or if ALT
was greater than five times ULN. After withholding treatment,
LFTs would be repeated weekly until ALT levels returned to
normal. Treatment would be restarted unless the peak ALT level
was greater than five times ULN, or if there had been clinically
significant symptoms with ALT levels greater than three times
ULN. Treatment would be terminated if patients had any major
or potentially life-threatening adverse effects.

Protocol Modification

The protocol was modified after December 2001 in line with
the updated recommendations by the American Thoracic Society
and Centers for Diseases Control and Prevention, which were
issued after a series of case reports of fatal and severe liver
injuries in association with 2RZ. Habitual drinkers with regular
alcohol intake for \( \geq 5 \) d/wk were excluded from the study.
Patients were also monitored more closely with LFTs every 2
weeks instead of monthly in the first 2 months. The daily dosage
of pyrazinamide was reduced to 20 mg/kg and rounded off to the
nearest and lower 0.25 g.

Statistical Analysis

\( \chi^2 \) test and Fisher exact test were used for comparison of
categorical variables as appropriate. Independently, a two-sample
t test was used for comparison of numerical variables; \( p < 0.05 \)
was considered statistically significant.

RESULTS

From October 1, 2000, to September 30, 2002, 517 patients with silicosis and no history of tubercu-
losis were interviewed. Three of them were excluded because of inconclusive diagnosis after review of the
chest radiograph. Three hundred seventeen patients refused tuberculin testing, as they would not consider treatment of LTBI even if test results were positive. Of the remaining 197 patients, 164 were tuberculin positive with an induration ≥ 10 mm. Among these 164 patients, only 77 agreed to participate in the study. Twenty-four patients refused to join the study but agreed to treatment with 6H, and 63 patients refused any form of treatment of LTBI.

Forty patients and 37 patients of the recruited study subjects were randomly assigned to receive 2RZ and 6H, respectively. All of them were Chinese by ethnic origin. One patient in the 6H arm was excluded after randomization, as he later revealed a history of antituberculosis treatment of LTBI. One patient in the 6H arm was excluded after randomization, as he later revealed a history of antituberculosis treatment of LTBI. Six patients in the 2RZ arm had symptoms that could be suggestive of hepatitis; these were generally mild and included malaise, nausea, and anorexia. None had jaundice or elevation of bilirubin level. Serology for acute viral hepatitis A, B, C, and E was not regularly performed, but all these test results were negative among the four patients with screening ordered by their attending physicians. None required hospitalization, and all fully recovered, including those with ALT levels more than five times ULN or symptomatic hepatitis after withholding the medication. Adverse effects other than hepatotoxicity were comparable between the two regimens, and none of them were severe enough to justify termination of treatment on their own.

Table 3 lists the clinical parameters for those with and without significant hepatotoxicity (either peak ALT levels more than five times ULN or symptomatic hepatitis) in the 2RZ arm. There were no significant differences in age, body weight, body mass index, HBsAg status, habitual alcohol use, other medications, baseline ALT, bilirubin and albumin levels, rifampin and pyrazinamide dosage, as well as treatment adherence. Table 4 lists the clinical data of the 16 patients in the 2RZ arm who had significant hepatotoxicity. The number of doses received varied from 17 to 60 doses. Study subjects 1 and 2 completed treatment before they were found to have deranged LFT results by the end of the second month. Hepatotoxicity was found after receiving > 30 doses in three fourths of the patients. None of them had comorbid illnesses, and only two pa-

Table 2—Adverse Reactions in the 2RZ and 6H Treatment Arms*

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>2RZ (n = 40)</th>
<th>6H (n = 36)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &gt; 1.5 × ULN†</td>
<td>47.5</td>
<td>13.9</td>
<td>0.01</td>
</tr>
<tr>
<td>ALT &gt; 3 × ULN</td>
<td>40.0</td>
<td>11.1</td>
<td>0.01</td>
</tr>
<tr>
<td>ALT &gt; 5 × ULN</td>
<td>35</td>
<td>2.8</td>
<td>0.00</td>
</tr>
<tr>
<td>Skin rash</td>
<td>10</td>
<td>5.6</td>
<td>0.67</td>
</tr>
<tr>
<td>Itchiness</td>
<td>32.5</td>
<td>16.7</td>
<td>0.18</td>
</tr>
<tr>
<td>GI upset</td>
<td>20</td>
<td>16.7</td>
<td>0.78</td>
</tr>
<tr>
<td>Joint pain</td>
<td>0</td>
<td>2.8</td>
<td>0.47</td>
</tr>
<tr>
<td>Gout</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other symptoms</td>
<td>20</td>
<td>16.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Data are presented as %.
†ULN; normal range, ≤ 54 U/L.
‡Fisher exact test.
patients were receiving other medications (terbutaline and theophylline), which were unlikely to be the cause of hepatitis. Only one patient was HBsAg positive, and two patients had history of the cause of hepatitis. Only one patient was and theophylline), which were unlikely to be

Patients 4 and 16 stopped treatment themselves; blood tests were done when they reported 11 days

Table 3—Comparison of Clinical Parameters for Those With and Without Significant Hepatotoxicity in the 2RZ Treatment Arm*

<table>
<thead>
<tr>
<th>Clinical Parameters</th>
<th>Hepatitis</th>
<th>No Hepatitis</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>60.1 (9)</td>
<td>62.7 (9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>65.1 (8.4)</td>
<td>62.1 (8.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.8 (3.0)</td>
<td>24.1 (3.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>% Habitual alcohol use</td>
<td>12.5</td>
<td>20.8</td>
<td>0.68‡</td>
</tr>
<tr>
<td>HBsAg carrier</td>
<td>12.5</td>
<td>12.5</td>
<td>1.00‡</td>
</tr>
<tr>
<td>Comorbid illnesses</td>
<td>0</td>
<td>12.5</td>
<td>0.26‡</td>
</tr>
<tr>
<td>Other medications</td>
<td>12.5</td>
<td>12.5</td>
<td>1.00‡</td>
</tr>
<tr>
<td>Baseline ALT, U/L</td>
<td>21 (12)</td>
<td>22 (10)</td>
<td>0.79</td>
</tr>
<tr>
<td>Baseline albumin, g/L</td>
<td>38.6 (2.3)</td>
<td>38.4 (2.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Dosage of pyrazinamide, mg/kg</td>
<td>23.2 (3.5)</td>
<td>23.4 (3.1)</td>
<td>0.87</td>
</tr>
<tr>
<td>Dosage of rifampin, mg/kg</td>
<td>9.3 (1.3)</td>
<td>9.7 (1.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Adherence, %</td>
<td>89.2 (15.5)</td>
<td>79.3 (32.7)</td>
<td>0.21</td>
</tr>
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*Data are presented as mean (SD) or %.
†Peak ALT > 5× ULN or symptomatic hepatitis.
‡Fisher exact test.

Figures 1 and 2 summarize the overall treatment outcome of the study patients. Treatment completion rates were relatively low in both study arms (55% for 2RZ vs 63.9% for 6H, \( p = 0.43 \)). There was no significant difference in the mean age between those successfully completing treatment and those not completing treatment (60.4 years vs 58.7 years, \( p = 0.47 \)). Treatment was stopped in one patient in the 6H arm because of tuberculosis cervical lymphadenitis, which was discovered during follow-up at 1 month. Treatment was terminated in more patients in the 2RZ arm than in the 6H arm (35.0% vs 5.6%, \( p < 0.01 \)) for significant hepatotoxicity according to the study protocol. Ten patients in the 6H arm voluntarily withdrew before treatment completion in comparison with only 4 patients in the 2RZ arm, but the difference failed to reach statistical significance (27.8% vs 10%, \( p = 0.07 \)). Twelve of these 14 withdrawals (85.7%) were preceded by adverse drug reactions, although none of them were severe enough to justify termination of treatment on their own.

Patients in both study arms had received, on average, slightly more than 70% of the total course (72.0% for 2RZ vs 72.9% for 6H, \( p = 0.92 \)). For those patients with early termination of treatment according to protocol, a higher percentage of the

and 14 days later, respectively. The severity of hepatotoxicity in these two patients may have been underestimated. Only 5 of these 16 patients had a mild overshoot of ALT levels after stopping the drugs, and they all recovered by 19 to 60 days.

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<td>9.3 (1.3)</td>
<td>9.7 (1.2)</td>
<td>0.40</td>
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Table 4—Characteristics of the Patients With Significant Hepatotoxicity in the 2RZ Treatment Arm*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Baseline Risk Factors</th>
<th>ALT.b, U/L</th>
<th>Dosage of Pyrazinamide, mg/kg</th>
<th>Doses Received</th>
<th>Time of Onset, mo‡</th>
<th>Symptoms</th>
<th>ALT.s, U/L</th>
<th>ALT.p, U/L</th>
<th>Days to Recover†</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>Habitual drinker</td>
<td>13</td>
<td>29.4</td>
<td>53</td>
<td>&gt; 2</td>
<td>Malaise</td>
<td>390</td>
<td>390</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>Habitual drinker</td>
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<td>481</td>
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<td>19</td>
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<td>3</td>
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<td>28</td>
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<td>34</td>
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<td></td>
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<td>412</td>
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<tr>
<td>4</td>
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<td>HBsAg+</td>
<td>48</td>
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<td>18</td>
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<td>7</td>
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<td>50</td>
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<td>GI</td>
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<td>185</td>
<td>185</td>
<td>31</td>
</tr>
</tbody>
</table>

*ALT.b = baseline ALT; ALT.s = ALT when treatment was stopped; ALT.p = peak ALT; normal range ≤ 54 U/L.
†Time of onset of relevant symptoms or first documented liver function impairment, whichever earlier.
‡Days to recover to baseline ALT after stopping treatment.
total course was received in the 2RZ arm than in the 6H arm (55.6% vs 20.6%, p < 0.01). Treatment adherence before termination of treatment was satisfactory in both study arms (82.4% for 2RZ vs 88.8% for 6H, p = 0.29).

**Discussion**

Despite the well-documented high risk of tuberculosis among patients with silicosis in Hong Kong, only 19.5% of a total of 517 patients interviewed finally agreed to some form of treatment of LTBI. Such a low degree of acceptance partly reflected the general difficulty in persuading apparently well patients to accept treatment, and partly reflected the prolonged duration required for treatment of LTBI. The majority of patients undergoing tuberculin testing had a reaction ≥10 mm, although few had received bacille Calmette-Guérin (BCG) vaccination. This finding is in line with a previous study in Hong Kong, and would be expected from the relatively old age distribution of patients with silicosis under study and the high past burden of tuberculosis in Hong Kong.

Notwithstanding the difficulty in recruitment and the consequential small sample size, highly significant differences were found in the rates of hepatic reactions between the two regimens. There was a much higher proportion of patients with peak ALT levels more than five times ULN in the 2RZ arm than in the 6H arm (35% vs 2.8%), with a chance occurrence of < 1 in 1,000. One recently reported, multicenter clinical trial of short-course rifampin and pyrazinamide vs isoniazid in the treatment of LTBI in immunocompetent adults also showed a substantially increased risk of hepatotoxicity in those receiving rifampin and pyrazinamide.

The hepatotoxicity rate for the 2RZ regimen in this randomized controlled trial was probably among the highest reported in literature for both immunocompromised and immunocompetent patients. As shown in Table 3, none of the factors of HBsAg carriage, alcoholism, comorbidities, concomitant medications, body mass index, low serum albumin, baseline liver function, dosage of rifampin or pyrazinamide, or adherence to treatment could have accounted for such phenomenon. Sporadic occurrence of viral hepatitis was an unlikely explanation in
the absence of common source exposure, even though viral hepatitis markers had not been checked in every case. The mean age of study subjects in this trial was probably higher than all other similar trials in the literature. It would be tempting to ascribe such a high incidence of liver dysfunction to the relatively advanced age of this study group. In a case-control study on the risk factors for hepatotoxicity from antituberculous drugs, only advanced age, hypoalbuminemia, high alcohol intake, slow acetylator phenotype, and extensive disease were the risk factors for the development of hepatotoxicity. In a previous study of antituberculosis drug-related liver dysfunction in Hong Kong, age was found to be the only predictor of drug-related liver dysfunction after stratifying the patients according to HBsAg status. In a retrospective study on tuberculosis in older people in Hong Kong, the incidence of liver dysfunction among those patients aged ≥65 years was found to be 17.7%, in contrast with only 9.2% among younger patients. It should be noted that, while the patients in that study were receiving treatment for active tuberculosis, some elderly patients were not administered pyrazinamide, and biochemical monitoring was not regularly performed. In a prospective study of isoniazid–rifampin–pyrazinamide–induced liver injury on Chinese patients in Taiwan, 26% of patients acquired antituberculous drug-induced liver injury (ALT levels greater than ULN). The incidence of drug-induced liver injury was as high as 33% in patients aged ≥35 years. The recent study by Jasmer et al on the treatment of LTBI also found that patients >35 years old had a higher risk of grade 3 or 4 hepatotoxicity.

Pyrazinamide has been associated with serious and even fatal hepatitis when administered in large daily doses of 40 to 70 mg/kg and for a prolonged period of time. When pyrazinamide was used in the earlier trials of short-course chemotherapy at a daily dose of 25 to 35 mg/kg for 2 months, no increase in hepatotoxicity was noted. However, in a study on the management of antituberculosis drug-induced hepatotoxicity by Tahaoglu et al, the recurrence rate of hepatotoxicity was higher in the reintroduction of a full-course regimen including pyrazinamide than gradual re-introduction of a regimen without pyrazinamide. In another study of hepatotoxicity of tuberculosis chemotherapy under general program conditions in Singapore, pyrazinamide was withheld from patients deemed at higher risk for hepatotoxicity at the discretion of the treating physicians in one fourth of all patients, and all three patients with fatal drug-induced hepatitis had received pyrazinamide-containing regimens. The high rate of significant hepatic reactions found in the 2RZ arm of this study also suggested the high potential for hepatotoxicity of pyrazinamide-containing regimens, even when pyrazinamide was employed mostly in the daily dosage range of 20 to 25 mg/kg. As the dosage range employed in this study was relatively narrow, it is uncertain whether the incidence of such reactions among the relatively old study subjects could have been reduced by further lowering the dosage of pyrazinamide. Although no age-related difference in the blood level of pyrazinamide was found in a previous study, age-related change in renal clearance could have affected the elimination of its metabolites among the older patients. As much remains unknown about pyrazinamide, one of the most important drugs currently available for the treatment of tuberculosis, further studies are warranted to address these issues.

The majority of study subjects with drug-related liver dysfunction in this study were asymptomatic. It is difficult to predict what would have happened if LFTs were not regularly monitored and treatment continued. In a study by Dossing et al in Denmark, the majority of patients with aspartate transaminase levels more than six times ULN were successfully put back on the full original regimen. While substantial degree of risk may be tolerated for treatment of clinical disease, the level of tolerance for treatment of latent infection is justifiably much lower. Cases of fatality have prompted the American Thoracic Society and Centers for Diseases Control and Prevention to update the guidelines in the treatment of LTBI. Termination of treatment is probably the only option with a drug-related elevation of the ALT level as high as five times ULN in the absence of definite evidence of the safety to continue drug treatment.

The relatively low threshold of tolerance to adverse drug effects also applied to patients. Although the nonhepatic adverse effects encountered in this study were mostly mild and did not justify termination of treatment on their own, many patients refused to continue or resume drug treatment after experiencing these effects, especially for those in the 6H arm. As a result, only 55% of patients in the 2RZ arm and 63.9% in the 6H arm completed treatment. Even if we assume that the protective efficacy for patients with silicosis is 50% as found in a previous local, randomized, controlled study on three different kinds of chemoprophylactic regimens, including 6H, 3 months of rifampin, or 3 months of isoniazid plus rifampin, the overall reduction in the tuberculosis risk among these patients would have been very moderate. Although the majority of those with the 2RZ regimen terminated early had received over one half of the assigned regimen, it would be unrealistic to expect a substantial degree of protection among them. If the low degree of acceptance of treatment
of LTBI among the patients with silicosis is also taken into account, there is certainly a need to look for regimens that are better tolerated and more efficacious than those currently available. Apart from the duration of treatment, hepatotoxicity is another crucial issue. Rifampicin alone appears to be safer than the combination of rifampicin and pyrazinamide. It is uncertain whether the longer elimination half-life of rifapentine offers any advantage apart from the less-frequent administration. The fluoroquinolones are commonly employed in the treatment of multidrug-resistant tuberculosis. They appear to be relatively well tolerated even among the older patients. Their relatively high propensity for development of resistance poses genuine concern with monotherapy. Also, there have been some data on the limited tolerance of the combination of ofloxacin and pyrazinamide in a rather small number of contacts of multidrug-resistant tuberculosis. However, it may still be worthwhile to examine the role of this important class of drug in other combination regimens, eg, in combination with the rifamycins, for the treatment of LTBI.

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