Inactive Hepatitis B Surface Antigen Carrier State and Hepatotoxicity During Antituberculosis Chemotherapy*

Byoung Hoon Lee, MD; Won-Jung Koh, MD; Moon Seok Choi, MD; Gee Young Suh, MD; Man Pyo Chung, MD; Hojoong Kim, MD, FCCP; and O. Jung Kwon, MD

Study objectives: To determine whether inactive hepatitis B surface antigen (HBsAg) carriers are at a higher risk of drug-induced hepatotoxicity than control subjects during antituberculosis treatment with standard short-course regimens of isoniazid, rifampin, ethambutol, and/or pyrazinamide.

Design: Retrospective case-control study.

Setting: Tertiary university medical center.

Patients: One hundred ten inactive HBsAg carriers with newly diagnosed active tuberculosis who had been treated with isoniazid, rifampin, ethambutol, and/or pyrazinamide were included in the study population. Inactive HBsAg carriers were defined as follows: (1) positive for HbsAg; (2) negative for hepatitis B e antigen (HBeAg), positive for antibody to HBeAg; (3) < 10^5 copies per mL of serum hepatitis B virus DNA; and (4) normal pretreatment aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels. Ninety-seven HBsAg-negative patients who received standard antituberculosis medication were selected as control subjects.

Results: The baseline characteristics of the 110 inactive HBsAg carriers were similar to those of the 97 noncarriers. A total of 85% of persons in both groups had received an initial treatment regimen that included pyrazinamide. Thirty-eight inactive HBsAg carriers (35%) and 19 control subjects (20%) exhibited elevated liver enzyme levels during antituberculosis treatment (p < 0.016). Drug-induced hepatotoxicity, which was defined as a liver transaminase level of ≥ 120 IU/L, occurred more frequently in HBsAg carriers (9 of 110 carriers; 8%) than in control subjects (4 of 97 control subjects; 4%), although this was not a statistically significant discrepancy (p = 0.230). More importantly, HBsAg carriers (n = 9; 8%) who received antituberculosis therapy evidenced a higher proportion of moderate-to-severe drug-induced hepatotoxicity when compared with the control subjects (n = 2; 2%; p = 0.05). Isoniazid and rifampin were reintroduced as therapy after AST/ALT levels returned to baseline values in 10 patients (6 HBsAg carriers and 4 control subjects) among the 13 patients exhibiting drug-induced hepatotoxicity, and these retrials proved to be successful in 7 patients (5 HBsAg carriers and 2 control subjects).

Conclusions: Tuberculosis treatment in HBsAg-positive and HBeAg-negative inactive carriers could be pursued in the usual manner, using standard short-course regimens of isoniazid, rifampin, ethambutol, and/or pyrazinamide, with the condition that monthly liver function tests are performed.

CHEST 2005; 127:1304–1311

Key words: hepatitis B virus; hepatitis B surface antigens; hepatitis B e antigens; isoniazid; pyrazinamide; rifampin; toxic hepatitis; tuberculosis

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus

Tuberculosis remains a major health concern both in developing and developed countries. Modern short-course chemotherapies based on the combination of isoniazid and rifampin have proven to be highly effective tuberculosis treatments. However, drug-induced hepatotoxicity associated with first-line drugs such as isoniazid, rifampin, and pyrazinamide is a well-known adverse effect, and may limit their use. Advanced age, female gender, alcohol use, malnutrition, and the presence of underlying chronic liver disease have been shown to bear an increased risk of developing drug-induced hepatotoxicity during antituberculosis treatment.

Although chronic liver disease has been known to increase the risk of drug-induced hepatotoxicity, the relative risks of the various etiologies of chronic liver
Subjects with chronic hepatitis B (n = 43) were excluded from the study, although they received first-line antituberculosis medications. The other excluded cases were as follows: an underlying malignancy that might have caused confusion with regard to the interpretation of the liver function test results due to possible liver metastasis (n = 31); initial regimens including second-line antituberculosis drugs due to multidrug-resistant tuberculosis or abnormal baseline liver function test results (n = 25); acute hepatitis B (n = 2); no follow-up liver function test results (n = 2); positivity for anti-HIV antibody (n = 2); and death not attributable to drug-induced hepatotoxicity, including a cerebral hemorrhage in one patient, and bacterial pneumonia and empyema in another (n = 2). Finally, 110 patients who were inactive HBsAg carriers and had received standard antituberculosis medication were included in the study group. HIV antibody tests were performed on 57 of the 110 HBsAg carriers (52%), and none of these patients were positive for HIV.

For purposes of comparison, 170 consecutive patients with newly diagnosed tuberculosis who were negative both for HBsAg and hepatitis C virus antibody, and who had been treated for > 3 months with antituberculosis drugs were also identified at the same hospital by computer-assisted searches over the 6-month period between January and June of 2002. Patients with abnormal baseline liver transaminase levels (n = 15) and those subjects receiving initial drug regimens, including second-line antituberculosis drugs (n = 18), were excluded from the study. In addition, subjects with underlying malignancies (n = 38) or those with no available follow-up liver function test results (n = 2) were also excluded after reviewing their medical records. Finally, 97 noncarriers of HBV and hepatitis C virus who had received standard antituberculosis medication were allocated to the control group. Sixty of these 97 control subjects (62%) were tested for the HIV antibody, and all were negative.

We excluded HBsAg-positive patients who were lost to follow-up (n = 10) and those who had been transferred to other institutions, usually to their referring institutions (n = 11), having been treated for < 3 months at our hospital. We applied identical criteria to the control group, excluding the patients who were lost to follow-up (n = 8) and those who had been transferred to other institutions (n = 17), after having been treated for < 3 months at our hospital. Hepatotoxicity was not detected in these 21 HBsAg-positive and 25 control patients during their stay at our hospital.

Definitions

An inactive HBsAg carrier state was defined according to the guidelines issued by the American Association for the Study of Liver Diseases, as follows15: (1) positive for HBsAg; (2) negative for hepatitis B e antigen (HBeAg) and positive for the antibody to HBeAg; (3) < 10^5 copies per mL serum HBV DNA; and (4) normal pretreatment aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels. Chronic hepatitis B was diagnosed according to the following criteria15: (1) positive for HBsAg; (2) > 10^5 copies per mL of serum HBV DNA; and/or (3) elevated AST/ALT levels before undergoing antituberculosis treatment.

The following criteria, which were based on common clinical practices and the recommendations of many studies and authorities, were used to define transient transaminase elevation and drug-induced hepatotoxicity.16,17 Transient transaminase elevation was diagnosed if AST/ALT levels were increased, but was still less than three times the upper normal limit (120 IU/L), but resolved spontaneously despite continued antituberculosis medications. Drug-induced hepatotoxicity was defined when liver transaminase levels exceeded 120 IU/L. If the AST/ALT levels were < 200 IU/L, drug-induced hepatotoxicity was defined as mild. AST/ALT levels of 200 to 500 IU/L indicated moderate

Materials and Methods

Patients and Control Subjects

All patients who were treated for newly diagnosed active tuberculosis at the Samsung Medical Center (Seoul, South Korea) between September 1994 and December 2002, who were positive for HBsAg and negative for hepatitis C virus antibody, were identified by a computer-assisted search of medical records. Two hundred seventeen patients who had been treated for > 3 months with antituberculosis drugs were identified, and their medical records were retrospectively analyzed.

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This study was supported by a grant 00-PJ1-PG1-CH03-0001 from the Korea Health 21 R&D Project, the Ministry of Health & Welfare, Republic of Korea.

Manuscript received March 30, 2004; revision accepted November 29, 2004.

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hepatotoxicity, and AST/ALT levels of ≥ 500 IU/L were considered to indicate severe hepatotoxicity.

**Treatment and Monitoring**

During the study period, it was our policy to perform assessments of liver chemistry, HBsAg, and hepatitis C virus antibody before commencing the initial antituberculosis treatment. Patients who were positive for HBsAg were also tested for HBeAg, the antibody to HBeAg, and HBV DNA. In South Korea, a 6-month regimen consisting of 2 months of therapy with isoniazid, rifampin, ethambutol, and pyazinamide, followed by 4 months of therapy with isoniazid, rifampin, and ethambutol has been strongly recommended by the National Tuberculosis Program.\textsuperscript{\textcopyright,\textcopyright} Alternatively, a 9-month regimen of therapy with isoniazid, rifampin, and ethambutol can be administered.\textsuperscript{\textcopyright,\textcopyright} Therefore, most patients at our hospital initially took daily self-administered therapy including isoniazid (300 mg), rifampin (450 to 600 mg), ethambutol (800 to 1,200 mg), and pyazinamide (1,500 mg). However, the decision to include pyazinamide in the initial treatment regimens was made by clinicians on a case-by-case basis. The decision to administer ethambutol to new patients in the continuation phase was based on the high rates of primary drug resistance in South Korea, although no studies have yet been performed to determine whether the inclusion of ethambutol actually improves outcomes in drug-resistant cases.\textsuperscript{\textcopyright,\textcopyright} The majority of patients were treated at an outpatient clinic. Liver chemistry tests were performed on a monthly basis after the inception of treatment.

If any liver chemistry abnormalities were detected, monitoring was performed more frequently (ie, at least weekly or biweekly). Treatment after the development of hepatotoxicity was undertaken in the generally accepted manner.\textsuperscript{\textcopyright,\textcopyright} Patients exhibiting mild increases in liver transaminase levels, but without clinical symptoms, were carefully observed with no changes in treatment. In the case of a patient who exhibited symptoms suggesting drug toxicity, who also showed markedly increased liver transaminase levels, it was our policy to withdraw therapy with all hepatotoxic drugs. These drugs then were replaced with nonhepatotoxic drugs, such as ethambutol, cycloserine, quinolones, and aminoglycosides. After liver transaminase normalization, the hepatotoxic drugs were serially reintroduced. Rifampin therapy was reintroduced first, at progressively increasing dosages. The targeted treatment regimen usually included isoniazid, rifampin, and ethambutol, without pyazinamide, and therapy continued for > 9 or 12 months. If symptoms recurred or liver transaminase levels increased during the reintroduction of therapy with hepatotoxic drugs, the offending drug was withdrawn, and nonhepatotoxic drug therapy was maintained. In most patients in whom drug-induced hepatotoxicity developed during antituberculosis treatment in the present study, tests to check the presence of the antibody to hepatitis A virus IgM, HBeAg, the antibody to HBeAg, and the antibody to hepatitis B core antigen IgM, and the serum levels of HBV DNA were not performed.

**Statistical Analysis**

Values were expressed as the mean ± SD, or as numbers (percentages) in the text and tables. Differences with regard to numeric values between the inactive HBsAg carrier and control groups, or between the drug-induced hepatotoxicity and nonhepatotoxicity groups, were analyzed using the Student t test for variables with a normal distribution, or the Mann–Whitney U test for those individuals lacking normal distribution. Nominal variables were assessed using the χ\textsuperscript{2} test or the Fisher exact test, as appropriate. A p value of < 0.05 was considered to be statistically significant. A statistical software package (SPSS, version 11.0; SPSS, Chicago, IL) was used for the analysis throughout.

**RESULTS**

**Baseline Characteristics**

The baseline characteristics of the 110 inactive HBsAg carriers in the study group were similar to those of the 97 noncarriers in the control group (Table 1). Age, sex, body mass index, baseline liver function test results, and tuberculosis sites were similar between the two groups. In the 68 patients with pulmonary tuberculosis in the HBsAg carrier group, 32 patients (47%) were smear-positive and culture-positive, and 13 patients (19%) were smear-negative and culture-positive. In the control group, the 68 patients with pulmonary tuberculosis in-

| Table 1—Baseline Characteristics of HBsAg Carriers and Control Subjects*
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<tbody>
<tr>
<td>Baseline Characteristics</td>
<td>HBsAg Carriers (n = 110)</td>
<td>Control Subjects (n = 97)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>44.0 ± 15.3</td>
<td>44.0 ± 15.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>58 (53)</td>
<td>58 (60)</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>21.5 ± 3.5</td>
<td>21.6 ± 2.9</td>
</tr>
<tr>
<td>Baseline AST, IU/L</td>
<td>21.3 ± 7.1</td>
<td>19.5 ± 7.0</td>
</tr>
<tr>
<td>Baseline ALT, IU/L</td>
<td>19.3 ± 8.3</td>
<td>17.7 ± 8.5</td>
</tr>
<tr>
<td>Baseline albumin, g/dL</td>
<td>4.0 ± 0.8</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>Site of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>63 (57)</td>
<td>60 (62)</td>
</tr>
<tr>
<td>Pulmonary and extrapulmonary TB</td>
<td>5 (5)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>42 (38)</td>
<td>29 (30)</td>
</tr>
<tr>
<td>Initial treatment regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA</td>
<td>93 (85)</td>
<td>82 (85)</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>17 (15)</td>
<td>15 (15)</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. (%), unless otherwise indicated. TB = tuberculosis; INH = isoniazid; RIF = rifampin; EMB = ethambutol; PZA = pyazinamide.
cluded 29 patients (43%) who were smear-positive and culture-positive and 11 patients (16%) who were smear-negative and culture-positive. In both groups, 85% of patients had received an initial treatment regimen that included pyrazinamide (Table 1).

Incidence of Liver Dysfunction

Elevated liver enzyme levels during antituberculosis therapy were observed more commonly in HBsAg carriers than in control subjects. Thirty-eight inactive HBsAg carriers (34%) and 19 control subjects (20%) exhibited elevated liver enzyme levels, including transient transaminase elevation and drug-induced hepatotoxicity, during antituberculosis treatment (p = 0.016) [Table 2]. However, most of the patients exhibited at least transient elevations of transaminase. Of 38 HBsAg carriers with elevated liver enzyme levels, serum AST/ALT levels were elevated above the upper normal limit but remained below three times the upper normal limit (≥ 40 and < 120 IU/L, respectively) in 29 patients. In these 29 HBsAg carriers with transient transaminase level elevation, asymptomatic AST/ALT elevations resolved spontaneously, despite the continuation of initial antituberculosis regimens. Fifteen of the 25 control subjects with AST/ALT level elevation also evidenced transiently increased transaminase levels, and all patients continued with antituberculosis regimens, during which serum AST/ALT levels normalized spontaneously.

Drug-induced hepatotoxicity during antituberculosis treatment occurred more frequently in HBsAg carriers (9 of 110 carriers; 8%) than in control subjects (4 of 97 control subjects; 4%), although this was not a statistically significant discrepancy (p = 0.230) [Table 2]. In the nine HBsAg carriers with drug-induced hepatotoxicity, however, all patients showed moderate-to-severe hepatotoxicity, exhibiting AST/ALT levels of > 200 IU/L. Conversely, mild hepatotoxicity developed in two patients (50%), and moderate-to-severe hepatotoxicity developed in another two of the four patients with drug-induced hepatotoxicity in the control group (50%). Consequently, HBsAg carriers bore a higher proportion of moderate-to-severe drug-induced hepatotoxicity compared with the control subjects (9 of 110 carrier [8%] vs 2 of 97 control subjects [2%]; p = 0.05) [Table 2]. All 13 patients in whom drug-induced hepatotoxicity developed, including two patients with severe hepatotoxicity, evidenced normal serum bilirubin levels at the time of the detection of liver injury. One 52-year-old female patient in the inactive HBsAg carrier group who was receiving an initial regimen of isoniazid, rifampin, and ethambutol exhibited severe hepatotoxicity after 3 months of antituberculosis treatment.

Factors Associated With Drug-Induced Hepatotoxicity During Antituberculosis Treatment

No significant differences were observed with regard to other variables, such as age, sex, body mass index, and baseline AST, ALT, and albumin levels, or the inclusion of pyrazinamide in the treatment regimens, between those individuals who developed or did not develop drug-induced hepatotoxicity (Table 3).

Management of Drug-Induced Hepatotoxicity

Isoniazid, rifampin, ethambutol, and pyrazinamide were initially administered to all nine inactive HBsAg carriers who developed hepatotoxicity during antituberculosis treatment, with the exception of one patient who did not receive pyrazinamide. Antituberculosis regimens were withheld immediately after the detection of hepatotoxicity and were supplanted by nonhepatotoxic antituberculosis drugs. In three patients, including one patient with severe drug-induced hepatotoxicity, nonhepatotoxic antituberculosis drug therapy was maintained until the end of treatment, without the reintroduction of therapy with isoniazid and rifampin, based on the decisions of individual clinicians. Otherwise, first-line antituberculosis drugs were rechallenged after AST/ALT levels returned to baseline levels in the other six HBsAg carriers. Therapy with isoniazid and rifampin

| Table 2—Liver Dysfunction During Antituberculosis Treatment Between HBsAg Carriers and Control Subjects* |
|-------------------------------------------------------|------------------|------------------|------------------|
| Variables                                             | HBsAg Carriers   | Control Subjects | p Value          |
|                                                      | (n = 110)        | (n = 97)         |                  |
| Abnormal liver function during treatment              | 38 (34)          | 19 (20)          | 0.016            |
| Transient transaminase elevation                      | 29 (26)          | 15 (16)          | 0.056            |
| Drug-induced hepatotoxicity                           | 9 (8)            | 4 (4)            | 0.230            |
| Mild                                                  | 0 (0)            | 2 (2)            | 0.218            |
| Moderate                                              | 8 (7)            | 1 (1)            | 0.038            |
| Severe                                                | 1 (1)            | 1 (1)            | 1.000            |

*Values given as No. (%), unless otherwise indicated.
without pyrazinamide was successfully reintroduced in five of these six HBsAg carriers (83%). Only one patient experienced recurrent hepatotoxicity after the reintroduction of isoniazid therapy, and, in this case, the antituberculosis drugs were replaced by a combination of rifampin and nonhepatotoxic drugs. This treatment was continued thereafter.

In the four control subjects who exhibited drug-induced hepatotoxicity, isoniazid and rifampin without pyrazinamide were successfully readministered to two of them, after temporarily withholding the hepatotoxic drugs. In the remaining two control subjects, the reintroduction of therapy with first-line drugs was unsuccessful, and subsequently nonhepatotoxic drug therapy was instituted. No hospitalization or mortality related to drug-induced hepatotoxicity occurred in the inactive HBsAg carrier and control groups.

**DISCUSSION**

The use of multidrug regimens for the treatment of tuberculosis based on the combination of isoniazid, rifampin, ethambutol, and/or pyrazinamide has proven to be a highly effective therapy. However, its effectiveness is offset by the increased incidence of drug-induced hepatotoxicity. The development of drug-induced hepatotoxicity is often of great concern, as it often necessitates the cessation or modification of treatment. The occurrence of liver injury during antituberculosis treatment varies, and appears to be much higher in developing countries (8 to 39%) than in developed countries (3 to 4%), despite the use of similar regimens. The reasons for this higher incidence of drug-induced hepatotoxicity in developing countries remain unclear. It has been suggested that this may be attributable to viral hepatitis, which is particularly prevalent in the developing world.

Due to the varying circumstances of tuberculosis patients and the different drugs used, it remains controversial as to whether patients with chronic HBV infection are subject to greater incidences of drug-induced hepatotoxicity during antituberculosis treatments. In a previous prospective study by Hwang et al., the occurrence of drug-induced hepatotoxicity during antituberculosis treatment was found not to be significantly different between HBsAg carriers and noncarriers (9 of 31 [29%] vs 54 of 209 [26%], respectively). In their study, patients with elevated serum ALT levels prior to receiving treatment were excluded from the study, and drug-induced hepatotoxicity was defined as an elevation of ALT levels above the upper normal limit. Wong et al. reported that drug-induced hepatotoxicity developed more frequently in HBsAg carriers than in noncarriers (15 of 43 [35%] vs 26 of 281 [9%], respectively). In their study, drug-induced hepatotoxicity was defined as an increase in ALT levels to 1.5 times the upper normal limit, and for patients with increased pretreatment levels of ALT the ALT elevation had to be > 1.5 times the baseline level.

In addition, two case-control studies produced inconclusive results as to whether HBsAg positivity is a predictive marker for the development of hepatotoxicity during antituberculosis treatment. As the study designs and, more importantly, the definitions of drug-induced hepatotoxicity differ in studies, direct comparisons of findings appear to be inappropriate. However, we have made some comparisons based on several important observations made during the present study.

First, the present study included > 100 HBsAg carriers, which is a larger study population than previous studies have used, and it revealed that the elevations of liver enzyme levels during antituberculosis therapy were more common in HBsAg carriers (34%) than in the control subjects (20%).

<table>
<thead>
<tr>
<th>Factors</th>
<th>DIH Group (n = 13)</th>
<th>No DIH Group (n = 194)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 35 yr</td>
<td>8 (62)</td>
<td>133 (69)</td>
<td>0.599</td>
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<tr>
<td>Female sex</td>
<td>9 (69)</td>
<td>82 (42)</td>
<td>0.058</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>22.1 (18.1–30.2)</td>
<td>21.3 (14.7–31.6)</td>
<td>0.653</td>
</tr>
<tr>
<td>Baseline AST, IU/L</td>
<td>19 (10–38)</td>
<td>20 (2–40)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline ALT, IU/L</td>
<td>13 (10–40)</td>
<td>16 (6–40)</td>
<td>0.121</td>
</tr>
<tr>
<td>Baseline albumin, g/dL</td>
<td>4.2 (3.2–8.3)</td>
<td>4.0 (1.1–7.2)</td>
<td>0.409</td>
</tr>
<tr>
<td>Initial treatment regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA</td>
<td>12 (92)</td>
<td>163 (84)</td>
<td>0.697</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>1 (8)</td>
<td>31 (16)</td>
<td></td>
</tr>
</tbody>
</table>

*Values given as No. (%) or median (range), unless otherwise indicated. DIH = drug-induced hepatitis. See Table 1 for abbreviations not used in the text.
Also, drug-induced hepatotoxicity, which was defined as an elevation of AST/ALT levels of > 120 IU/L, occurred more frequently in HBsAg carriers (8%) than in control subjects (4%), although this was not a statistically significant discrepancy. More importantly, our study revealed that HBsAg carriers (5%) exhibited higher proportions of moderate-to-severe hepatotoxicity during antituberculosis therapy than the control subjects (2%).

It is important to note that asymptomatic increases in liver enzymes levels occur quite frequently in patients receiving standard short-course regimens.2,28 The definitions adopted for drug-induced hepatotoxicity differ in a somewhat arbitrary manner, ranging from a simple elevation of ALT above the upper limit of normal values2 to clinical hepatitis coupled with jaundice.3,26 In terms of increasing clinical relevance, the presence of a major side effect resulting in the discontinuation of one or more drugs and/or the presence of a side effect directly resulting in hospitalization could be reasonably adopted as the operational definition for an adverse reaction.17 The American Thoracic Society published2 new guidelines in 2003 for the treatment of tuberculosis and recommended that therapy should not be altered in the absence of symptoms, despite modest asymptomatic elevations in transaminase levels. However, if transaminase levels exceed five times the upper normal limit with or without symptoms, or exceed three times the upper normal limit in the presence of symptoms, it was recommended that therapy with hepatotoxic drugs be immediately discontinued.2

In the present study, these recommendations were applied to the definition and identification of drug-induced hepatotoxicity. Furthermore, we think that these criteria are more clinically relevant than the classic criteria. This study revealed that moderate-to-severe hepatotoxicity occurred more frequently in HBsAg carriers during antituberculosis treatment. We think that this is, clinically, a more important thing than the high frequency of abnormal liver function, including the transient elevation of transaminase levels that was observed during antituberculosis therapy in HBsAg carriers.

Second, the present study suggested that the reintroduction of therapy with antituberculosis drugs might be safe and successful, even in HBsAg carriers, after recovery from drug-induced hepatotoxicity. Rechallenge with the drugs ostensibly responsible for the hepatotoxicity, such as isoniazid or rifampin, may constitute a burden for both the physicians and the patients. In a study by Yee et al.,12 only 3 of the 12 patients in whom hepatotoxicity developed were rechallenged with the drugs, and this was not successful in any of those patients. In our study, therapy with isoniazid and rifampin was reintroduced in six of nine HBsAg carriers after the resolution of their hepatotoxicity, and reintroductions was successful in five of those patients (83%). Thus, given careful monitoring, we think that a trial of reintroduction of at least isoniazid and rifampin is feasible, even in HBsAg carriers.

Third, the addition of pyrazinamide was not found to be a significant risk factor for the development of drug-induced hepatotoxicity in our study. This finding was consistent with data reported earlier.3,28 The incidence of drug-induced hepatotoxicity in clinical trials,23,24 in which isoniazid and rifampin have been used either with or without pyrazinamide, revealed no increases in drug-induced hepatotoxicity for the three-drug therapy, compared with therapy including only isoniazid and rifampin. However, some studies4,5,17 have indicated that the incidence of pyrazinamide-induced hepatotoxicity was significantly higher than that observed with the other first-line drugs. The role of pyrazinamide in treatment tolerability in HBsAg carriers cannot be determined from our study, because the numbers of the patients who received the various regimens were insufficient for comparing the tolerability of the regimens. Furthermore, the assignment of the treatment regimens was not random, and the safety of various regimens was not part of the study design and goals. Further research is required in order to address the safety of antituberculosis regimens including pyrazinamide in HBsAg carrier patients.

In addition, the strict inclusion criteria adopted by our study are worthy of consideration. Contrary to the observations of earlier studies,8–11 an inactive HBsAg carrier state was strictly defined in the present study, as we excluded patients who were positive for HBeAg, had > 10⁵ copies per mL of serum HBV DNA, and/or had elevated AST/ALT levels before receiving antituberculosis treatment, according to the recently published practice guidelines.15 Also, drug-induced hepatotoxicity developed in < 10% of HBsAg carriers. As previously mentioned, some studies7,8,11 have reported high incidences of drug-induced hepatotoxicity or clinical hepatitis during antituberculosis therapy, or during the treatment of latent tuberculosis infection, in HBsAg-positive patients. In these studies, however, a substantial proportion of the HBsAg-positive patients exhibited increased baseline levels of liver enzymes before treatment, were HBeAg-positive, or had detectable serum levels of HBV DNA. Thus, our study suggested that HBeAg status, rather than simple HBsAg positivity status, might be a more important predictor with regard to the risk of drug-induced hepatotoxicity during the administration of standard antituberculosis regimens or isoniazid pro-

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phyaxis for latent tuberculosis treatment in patients with chronic HBV infection.

Guidelines published in 2003 by the American Thoracic Society recommended that tuberculosis patients with epidemiologic factors suggesting a risk for hepatitis B (eg, injection drug use, birth in Asia or Africa, or HIV infection) should undergo a serologic test for detection of this virus. At this point, our study results indicated that it is important to test for HBeAg and HBV DNA in HBsAg-positive patients. Patients who are HBsAg-positive, HBeAg-negative, and exhibit no detectable serum traces of HBV DNA could be treated with a recommended short-course regimen under careful monitoring, including monthly liver function tests.

The present study has several limitations, which are generally inherent in retrospective analyses. For example, precise information on alcoholism or the use of potentially hepatotoxic drugs such as acetaminophen was unavailable, largely due to the difficulty of obtaining reliable information by medical chart review. Second, the phenotype or genotype of N-acetyltransferase 2, which is largely responsible for isoniazid metabolism, was not tested. Third, in most patients in whom hepatotoxicity developed during antituberculosis treatment in the present study, the antibody to hepatitis A virus IgM, HBeAg, the antibody to HBeAg, the antibody to hepatitis B core antigen IgM, and serum levels of HBV DNA were not assessed. Up to 15 to 20% of HBsAg carriers in the inactive state were found to have experienced exacerbations of hepatitis with or without HBeAg seroconversion; therefore some HBsAg carriers who had been judged to have drug-induced hepatotoxicity in the present study would actually face the possibility of exacerbation or reactivation of their HBV infections.

**Conclusion**

In summary, drug-induced hepatotoxicity during antituberculosis treatment occurred more frequently in HBsAg carriers (8%) than in control subjects (4%), although this was not a statistically significant difference. More importantly, HBsAg carriers (8%) who received antituberculosis therapy had a higher proportion of moderate-to-severe drug-induced hepatotoxicity when compared with control subjects (2%). However, the reintroduction of therapy antituberculosis drugs could be safe and successful, even in HBsAg carriers, after recovery from drug-induced hepatotoxicity. These findings suggested that tuberculosis treatment in HBsAg-positive and HBeAg-negative inactive carriers could be performed in the usual manner, using recommended short-course regimens containing isoniazid, rifampin, ethambutol, and/or pyrazinamide, under the condition that monthly liver function tests be performed.

**References**

15. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2001; 34:1225–1241


28 Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1978; 59:13–32