Risk Factors for Liver Injury with an Elevated Serum Bilirubin Concentration Caused by Antituberculous Drugs

Hideaki Kato¹, Nobuyuki Horita¹, Naoki Miyazawa², Takashi Yoshiyama³, Atsuhisa Ueda¹ and Yoshiaki Ishigatsubo¹

Abstract

Objective No studies have so far sufficiently investigated the risk factors for drug-induced liver injury (DILI) with an elevated serum bilirubin concentration.

Methods We conducted a historical cohort study observing inpatients admitted to two hospitals in Japan. A decreased level of activities of daily living (ADL) was defined as a Barthel Index score of <80. The patients were treated with standard regimens under a directly observed treatment short-course strategy.

Results The cohort of 356 patients comprised 244 men (68.5%) and 112 women (31.5%), with a mean age of 63.8±20.2 years. Compared with the patients who did not experience DILI with a bilirubin level of ≥2.0 mg/dL, the patients who experienced DILI with a bilirubin level of ≥2.0 mg/dL more often had a decreased level of ADLs, were more likely to suffer from chronic cardiac disease, had lower serum albumin levels and were less often treated with four-drug regimens involving pyrazinamide (PZA). In a logistic regression analysis in which these five factors acted as independent variables, a decreased level of ADLs was the strongest predictor for DILI with a bilirubin level of ≥2.0 mg/dL, with an odds ratio of 16.5 (95%CI: 1.7-159; p=0.015), followed by chronic cardiac disease, with an odds ratio of 4.0 (95%CI: 1.2-12.6; p=0.020).

Conclusion A decreased level of ADLs and chronic cardiac disease are strong risk factors for DILI with a bilirubin level of ≥2.0 mg/dL resulting from the use of antituberculous drugs. Physicians should pay close attention to the possibility of DILI with a bilirubin level of ≥2.0 mg/dL when treating tuberculosis patients with a decreased level of ADLs and/or chronic heart disease.

Key words: adverse effects, antibacterial agents, bile conjugation, performance status, pulmonary tuberculosis

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Introduction

Although the global incidence of tuberculosis peaked around 2003 and now appears to be in slow decline, the worldwide incidence of new cases is estimated to be nine million every year and the disease is responsible for 1.5 million deaths each year (1). The current standard treatment regimens comprising three or four drugs cure most tuberculosis patients and facilitate reduction of transmission to others in the community (2). Unfortunately, however, antituberculous medications have various adverse effects, one of which is drug-induced liver injury (DILI). DILI is usually related to changes in treatment regimens, the use of less effective second-line treatments and prolonged hospitalization (3).

The presence of an elevated serum bilirubin concentration or bile conjugation in patients with acute liver disease often provides clinically meaningful information. This is because an increased serum bilirubin concentration reflects greater histologic evidence of hepatocellular damage (4), a longer course of the disease (4) and a poorer prognosis (5-7). Many
previous studies have evaluated the risk factors for DILI and how to identify patients at risk of developing DILI. However, to the best of our knowledge, no studies have investigated the specific risk factors for DILI with an elevated serum bilirubin concentration. Therefore, in this study, we researched the risk factors for DILI with an elevated serum bilirubin concentration.

Materials and Methods

Ethics statement

We conducted a historical cohort study reviewing inpatients admitted to two hospitals familiar with tuberculosis in different prefectures. This study was approved by the Institutional Review Board of Yokohama City University Hospital and Institutional Review Board of Fukujuji Hospital. These boards waived the requirement for informed consent due to the observational nature of the study design and the protection of the patients’ anonymity.

Patients

The medical charts of the patients at the two hospitals (Yokohama City University Hospital, Yokohama, Japan (638 beds, including 16 isolation beds for tuberculosis) and Fukujuji Hospital, Tokyo, Japan, a community-based teaching hospital (339 beds, including 60 isolation beds for tuberculosis]) were reviewed. All consecutive patients admitted to the tuberculosis isolation wards of the two hospitals with a primary diagnosis of lung tuberculosis were screened using the following inclusion criteria. The patients treated at the Yokohama City University Hospital were reviewed between January 2008 and November 2011, whereas those treated at Fukujuji Hospital were reviewed between January 2009 and December 2009, on an admission date basis. The inclusion criteria were as follows: (i) lung tuberculosis confirmed with positive sputum smears and cultures, (ii) newly diagnosed lung tuberculosis (i.e., patients who had already started treatment at another hospital were excluded), (iii) an age ≥ 20 years and (iv) treatment with one of the two standard regimens mentioned below with full susceptibility.

Measurements

Baseline patient data were obtained as of the date of admission. The presence of bilateral infiltration was evaluated on X-rays according to the agreement of at least four pulmonologists who were in charge of each patient, independent of this study. The existence of bilaterality was always noted, according to the recommendations of the Japanese guidelines for the assessment of bilateral infiltration on X-rays. Habitual alcohol drinkers were defined as patients who consumed alcohol ≥3 days a week. The level of activities of daily living (ADL) was measured based on the Barthel Index (range: 0-100 points), which comprises the following variables: the ability to feed oneself; the ability to get out of a wheelchair; the ability to perform activities related to personal hygiene, such as going to the toilet and bathing; the ability to walk on level ground; the ability to climb stairs; the ability to dress oneself; and the ability to maintain bowel and bladder control (8). In this study, a decreased level of ADL was defined as a Barthel Index score of <80, while a normal level of ADLs was defined as a Barthel Index score of ≥80 (9). We used this cutoff value based on the findings of a previous article (8). We also evaluated the cutoff value using a receiver operating characteristic curve. Chronic heart disease, renal disease, cerebrovascular disease and musculoskeletal disease (compression fractures of the spine followed by fractures of the extremities were most often observed) are not usually considered risk factors for DILI. However, we evaluated these factors in this study, as these diseases are often related to a decreased level of ADLs.

Treatments

A directly observed treatment short-course strategy was provided immediately after admission to the two tuberculosis isolation wards reviewed in this study. One of the following two daily combined regimens was used for the first two months: (i) isoniazid (INH; 5 mg/kg/day; max 300 mg/day), rifampicin (RFP; 10 mg/kg/day; max 600 mg/day), pyrazinamide (PZA; 25 mg/kg/day; max 1,500 mg/day) and ethambutol (15-20 mg/kg/day; max 1,000 mg/day); or (ii) INH, RFP and ethambutol at the same dosages. The four-drug regimen with PZA was used as a first-line regimen, while the three-drug regimen without PZA was primarily prescribed for patients with possible decreased drug tolerance. The treatment choice was made by the physicians treating each patient (2). Patients treated with standard regimens including streptomycin were excluded from this study because streptomycin regimens were usually avoided in order to remove the burden of intramuscular injection and were used in a very limited number of patients in our hospital.

Outcomes

We reviewed the treatment course of each patient for 60 days because PZA and ethambutol were withheld after two months of treatment and because previous studies have shown that most cases of DILI resulting from antituberculous drugs occur within the first two months (10-13). DILI was defined as the change or withdrawal of treatment due to liver injury caused by antituberculous agents judged according to the agreement of at least four pulmonologists in charge of each patient. The judgment was principally based on criteria described in the guidelines (3): a serum transaminase concentration of more than three times the upper limit of the normal range (120 IU/L) with jaundice and/or symptoms of hepatitis; a serum transaminase concentration of more than five times the upper limit of the normal range (200 IU/L); or a total bilirubin level of ≥2.0 mg/dL, regardless of the level of transaminase. Elevation of the transaminase level that was not accompanied by a change in or...
withdrawal of treatment was not regarded as DILI for the purpose of this study. Although elevated serum transaminase concentrations can theoretically be explained by other causes, such as biliary calculus or recent alcohol consumption, these possibilities were discounted by checking the patients’ charts. We classified DILI into "DILI with a bilirubin concentration of ≥2.0 mg/dL measured on the day of DILI diagnosis (14)."

The observation was censored if one of following events occurred: (i) withdrawal or change of the treatment regimen due to a cause other than DILI, (ii) discharge of the patient alive and (iii) death during admission.

Statistical analyses

For the univariate analysis, we used the Wilcoxon rank-sum test for continuous variables and the chi-square test for contingency (with the Yates correction, if needed). A logistic regression analysis was used to predict bivariate variables. Receiver operating characteristics curves and Youden’s Index were used to evaluate the cutoff values. A rejection region of 0.05 was adopted. Continuous variables are presented as the arithmetic mean ± SD. The data analyses were performed using the Excel Toukei (SSRI, Tokyo, Japan) and GraphPad Prism ver. 5.0 (GraphPad Software Inc., San Diego, CA, USA) software programs.

Results

The cohort of 356 patients comprised 166 patients (46.6%) from Yokohama City University Hospital and 190 patients (53.4%) from Fukui University Hospital. There were 244 men (68.5%) and 112 women (31.5%), with a mean age of 63.8±20.2 years. Table 1 provides a summary of the patient characteristics. Of the 356 patients, 215 (60.4%) had a normal level of ADLs (Barthel Index ≥80) and 141 (39.6%) had a decreased level of ADLs (Barthel Index <80) (Table 1). A cutoff value between 75 and 80 yielded the best Youden’s index (sensitivity + specificity - 1) of 0.57, which indicates that this cutoff is the most useful (Fig. 1). Age and the incidence rates of chronic heart disease, chronic respiratory disease, chronic renal disease, cerebrovascular disease and musculoskeletal disease were significantly different between the patients with a normal level of ADLs and those with a decreased level of ADLs. In our cohort of 356 patients, 316 (88.8%) did not experience DILI, 24 (6.7%) experienced DILI with a bilirubin level of <2.0 mg/dL and 16 (4.5%) experienced DILI with a bilirubin level of ≥2.0 mg/dL. The average duration from admission to occurrence of DILI with bile conjugation in the 16 patients was 42±11 days on average. Of these 16 patients, eight were discharged alive after negative infectivity was confirmed and eight died during admission for the following reasons according to the death certificates: six due to tuberculosis, one due to liver cirrhosis and one due to pneumonia. The duration between the onset of DILI and death in the eight patients who died was 42±43 days on average.

Compared with the 24 patients who experienced DILI with a bilirubin level of <2.0 mg/dL and 16 (4.5%) experienced DILI with a bilirubin level of ≥2.0 mg/dL. The average duration from admission to occurrence of DILI with bile conjugation in the 16 patients was 42±11 days on average. Of these 16 patients, eight were discharged alive after negative infectivity was confirmed and eight died during admission for the following reasons according to the death certificates: six due to tuberculosis, one due to liver cirrhosis and one due to pneumonia. The duration between the onset of DILI and death in the eight patients who died was 42±43 days on average.

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with a bilirubin level of <2.0 mg/dL, the 16 patients who experienced DILI with a bilirubin ≥ 2.0 mg/dL exhibited a higher rate of a decreased level of ADLs (93.4% vs 54.2%, p=0.020) and low serum albumin levels (2.5±0.5 mg/dL vs. 3.1±0.9 mg/dL, p=0.037). Other baseline characteristics were not significantly different between the two groups. The average duration from the start of treatment with antituberculous agents to DILI diagnosis was 16±11 days among the patients who experienced DILI with a bilirubin level of ≥2.0 mg/dL and 22±22 days among those who experienced DILI with a bilirubin level of <2.0 mg/dL, which was not significantly different.

Compared with the 340 patients who did not experience DILI with a bilirubin level of <2.0 mg/dL, the 16 patients who experienced DILI with a bilirubin level of ≥2.0 mg/dL more often had a decreased level of ADLs, were more likely to suffer from chronic cardiac disease, had higher aspartate transaminase (AST) and lower serum albumin levels and were less often treated with four-drug regimens involving PZA (Table 2). In a logistic regression analysis in which these five factors acted as independent variables, a decreased level of ADLs was found to be the strongest predictor of DILI with a bilirubin level of ≥2.0 mg/dL, with an odds ratio of 16.5 (95%CI: 1.7-159; p=0.015), followed by chronic cardiac disease, with an odds ratio of 4.0 (95%CI: 1.2-12.6; p=0.020) (Table 3).

The distribution chart of the levels of bilirubin and AST on diagnosis of DILI is shown in Fig. 2. This figure shows that a patient with a normal level of ADLs rarely experienced DILI with a bilirubin level of ≥2.0 mg/dL and that a very limited number of patients experienced elevation of both AST and bilirubin (very few plots are located in the

Table 2. Comparison of Baseline Characteristics between Patients who Did and Did Not Experience Drug-induced Liver Injury (DILI) with Bilirubin ≥2.0 mg/dL.

<table>
<thead>
<tr>
<th></th>
<th>DILI with bilirubin ≥ 2.0 mg/dL</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(+) n = 16</td>
<td>(-) n = 340</td>
</tr>
<tr>
<td>Age (year)</td>
<td>70.1 ± 17.6</td>
<td>63.5 ± 20.3</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>6 (37.5%)</td>
<td>112 (32.9%)</td>
</tr>
<tr>
<td>Decreased activities of daily living</td>
<td>15 (93.8%)</td>
<td>141 (41.5%)</td>
</tr>
<tr>
<td>Chronic cardiac disease</td>
<td>7 (43.8%)</td>
<td>37 (10.9%)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1 (6.3%)</td>
<td>26 (7.7%)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>3 (18.8%)</td>
<td>17 (5.0%)</td>
</tr>
<tr>
<td>Hepatitis B virus infection</td>
<td>0 (0.0%)</td>
<td>4 (1.2%)</td>
</tr>
<tr>
<td>Hepatitis C virus infection</td>
<td>2 (12.5%)</td>
<td>16 (4.7%)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>2 (12.5%)</td>
<td>26 (7.7%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (12.5%)</td>
<td>81 (23.8%)</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>0 (0.0%)</td>
<td>23 (6.8%)</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>0 (0.0%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5 (31.3%)</td>
<td>73 (21.5%)</td>
</tr>
<tr>
<td>Musculoskeletal disease</td>
<td>2 (12.5%)</td>
<td>56 (16.5%)</td>
</tr>
<tr>
<td>Habitual alcohol drinker</td>
<td>2 (12.5%)</td>
<td>87 (25.6%)</td>
</tr>
<tr>
<td>Use of immunosuppressant</td>
<td>3 (18.8%)</td>
<td>27 (7.9%)</td>
</tr>
<tr>
<td>Number of systemic medications</td>
<td>3.3 ± 2.9</td>
<td>2.7 ± 2.6</td>
</tr>
<tr>
<td>Aspartate transaminase (IU/L)</td>
<td>45.1 ± 25.7</td>
<td>35.1 ± 42.1</td>
</tr>
<tr>
<td>Alanine transaminase (IU/L)</td>
<td>30.4 ± 27.4</td>
<td>26.6 ± 33.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.5 ± 0.5</td>
<td>3.1 ± 0.8</td>
</tr>
<tr>
<td>Bilateral infiltration on X-ray</td>
<td>14 (87.5%)</td>
<td>245 (72.1%)</td>
</tr>
<tr>
<td>Four-drug regimen with pyrazinamide</td>
<td>9 (56.3%)</td>
<td>289 (85.0%)</td>
</tr>
</tbody>
</table>

Wilcoxon rank sum test and chi-square test were used.

Table 3. Logistic Regression for Predicting Drug-induced Liver Injury (DILI) with Bilirubin ≥2.0 mg/dL.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio [95%CI]</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Decreased activities of daily living</td>
<td>16.5 [1.7-159]</td>
<td>0.015</td>
</tr>
<tr>
<td>Chronic cardiac disease</td>
<td>4.0 [1.2-12.6]</td>
<td>0.020</td>
</tr>
<tr>
<td>Aspartate transaminase (AST) (10 IU/L increase)</td>
<td>0.99 [0.89-1.1]</td>
<td>0.890</td>
</tr>
<tr>
<td>Albumin (1 g/dL increase)</td>
<td>0.90 [0.36-2.3]</td>
<td>0.828</td>
</tr>
<tr>
<td>Four-drugs regimen with pyrazinamide</td>
<td>0.76 [0.24-2.4]</td>
<td>0.646</td>
</tr>
</tbody>
</table>

We performed logistic regression analysis to predict DILI with bilirubin ≥ 2.0 mg/dL. Parameters which were significantly different between patients who experienced and those who did not experience DILI with bilirubin ≥ 2.0 mg/dL (Table 3) are included in this model.
the effects of RFP on the bile flow were biphasic: low-dose RFP increased the bile duct flow, while high-dose RFP decreased the bile duct flow (17). In this scenario, high-dose RFP increases the serum concentrations of RFP and serum bilirubin, which may result in a vicious cycle. In fact, DILI caused by RFP is often accompanied by an elevated serum bilirubin concentration (14). Given this, we hypothesized that cytotoxic DILI, primarily caused by INH, and bile congestion DILI, primarily caused by RFP, have different risk factors. In fact, DILI with and without bilirubin elevation had different risk factors in the current study.

The impact of a decreased level of ADLs on DILI has been previously reported (8). However, it is as yet to be determined why DILI with a bilirubin level of ≥2.0 mg/dL occurs almost exclusively in patients with a decreased level of ADLs. Patients with a decreased level of ADLs may have either an impaired catabolism or may be excreting RFP, while they may also be vulnerable to RFP at the same serum concentration. In addition, patients with a decreased level of ADLs may have increased re-uptake of RFP via the enterohepatic circulation. However, there is, as yet, insufficient evidence to support these hypotheses.

Chronic cardiac disease is not usually regarded to be a risk factor for DILI caused by antituberculous drugs. However, any cause of right-sided heart failure can result in hepatic congestion, including constrictive pericarditis, mitral stenosis, tricuspid regurgitation and cor pulmonale. Some studies have reported that right-sided heart failure leads to jaundice and biliary obstruction (18-20). These mechanisms may be associated with DILI with a bilirubin level of ≥2.0 mg/dL. The strength of our study is that it detected the relationship between cardiac disease and DILI supported by the senility of the cohort and the mean age of 63.8±20.2 years. More than 10% of our patients had chronic heart disease and were possibly at risk of right-sided heart failure.

Although we know that RFP, a decreased level of ADLs and chronic cardiac disease are often associated with DILI with a bilirubin level of ≥2.0 mg/dL, clinicians cannot avoid using RFP in the treatment of tuberculosis patients with a decreased level of ADLs and/or chronic cardiac disease because RFP is regarded as being one of the most effective antituberculous agents (2). Therefore, clinicians must be on the lookout for DILI with a bilirubin level of ≥2.0 mg/dL when treating patients with a decreased level of ADLs and/or chronic cardiac disease.

The current study is associated with some limitations. First, this study was designed as a historical cohort study. Nonetheless, we believe that the study’s strengths reside in the clear presentation of the inclusion criteria and outcomes. Second, our cohort did not include a sufficient number of patients with established risk factors for DILI, such as chronic liver disease, chronic renal disease and coinfection with human immunodeficiency virus and the hepatitis B and C viruses (Table 1). These risk factors were not associated with DILI with a bilirubin level of ≥2.0 mg/dL in this study. Nonetheless, we cannot deny the impact of these factors on
DILI with a bilirubin level of ≥2.0 mg/dL in our study due to the insufficient power resulting from the small number of patients with these factors. Similarly, no parameters listed in Table 3 differed between the 332 patients who did not experience DILI with a bilirubin level of <2.0 mg/dL and the 24 patients who experienced DILI with a bilirubin level of <2.0 mg/dL. This is most likely due to the small sample size.

In conclusion, a decreased level of ADLs and chronic cardiac disease are strong risk factors for the development of DILI with a bilirubin level of ≥2.0 mg/dL caused by the use of antituberculous drugs. Physicians should pay close attention to the possibility of DILI with a bilirubin level of ≥2.0 mg/dL when treating tuberculosis patients with a decreased level of ADLs and/or chronic heart disease.

The authors state that they have no Conflict of Interest (COI).

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References