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The clinical characteristics of anti-tuberculosis drug induced liver injury in 2457 hospitalized patients with tuberculosis in China

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Anti-tuberculosis drug induced liver injury (ATDILI) ranks the first in all kinds of drug-induced liver injuries. ATDILI causes not only economic loss of public health system and patients, but also mental burden of patients, and often leads to treatment interruption or drug resistance. To investigate the clinical characteristics and predisposing factors of ATDILI, the clinical characteristics of 2457 hospital-admitted cases treated with anti-tuberculosis (TB) drugs during 2005 and 2009 and their correlative factors were retrospectively analyzed. The incidence of ATDILI among 2457 TB patients who were treated for the first time was 10.9% (267/2457), that is 13.6% (148/1085) in female and 8.7% (119/1372) in male. Female TB patients were more prone to have ATDILI as compared to male TB patients (P<0.05). The incidence of ATDILI in TB patients who were not treated with liver protectants (13.8%, 80/581) was significantly higher than that in patients who were treated with liver protectants (10.0%, 187/1876, P<0.05). 13.2% (139/1050) patients treated with isoniazid (H), rifampin (R), and pyrazinamide (Z)/ethambutol (E) (HRZ/E) regime had ATDILI, which was significantly higher than that in TB patients treated with HRE (9.1%, 128/1407, P<0.05). Susceptible patients of ATDILI should take appropriate preventive measures to avoid the occurrence of drug-induced liver injury.

Key words: Liver injury, anti-tuberculosis drugs, clinical characteristics, predisposing factor.

INTRODUCTION

It is estimated that 550 million people were infected with *Mycobacterium tuberculosis* in China. The incidence of pulmonary tuberculosis (TB) is 459 per 100,000 population, the incidence of smear-positive or culture-positive pulmonary TB is 66 per 100,000 population (The Ministry of health in China, 2011). The high incidence of TB in China, which is the second highest in the world, only next to India, is accompanied by high incidence of anti-TB drug induced liver injury (ATDILI). Studies have shown that the incidence of liver injury induced by the multidrug anti-TB regimens is the highest among all drug-induced liver injuries (Zhou et al., 2007; Wang et al., 2009). ATDILI not only leads to delay in chemotherapy, but also affects the control of TB, which consequently seriously endangered the lives of patients. Therefore, the monitoring ATDILI is crucial.

In this study, 2457 hospital-admitted TB cases in China from 2005 to 2009 and the clinical features of 267 ATDILI cases were retrospectively analyzed to understand the general characteristics and the risk factors of ATDILI, and

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to guide prevention and treatment of ATDILI.

MATERIALS AND METHODS

General information

2457 clinically diagnosed TB patients (except those with TB in the central nervous system due to a high dose of isoniazid) who were admitted to Institute of Tuberculosis Research, the 309th Hospital of Chinese PLA, China, from 2005 to 2009 and accepted the chemotherapeutic regimen according to conventional protocol for TB treatment were included in this retrospective analysis.

Anti-TB treatment

Patients were treated for 6 to 9 months as recommended by our national TB program. They were given anti-TB drugs such as isoniazid (H), rifampin (R), and ethambutol (E) or pyrazinamide (Z) daily in the first two or three months and then followed treatment with HR or HRE for 4 to 7 months. The drug dosages were adjusted based on the body weights of patients except for those who were 60 years and above and had viral hepatitis or alcoholic cirrhosis, were given 2/3 of the normal dosage. Owing to drugs, H, R and Z can cause potential liver damage; the patients were divided into two groups: one group was treated with HRZE or HRZ (HRZ/E); the other was treated with HRE.

The liver protectants chosen were not designed beforehand, because this study was retrospective; the use of liver protectants (for example, reduced glutathione, glucurolactone, or compound glycyrrhizin tablets composed of mono-ammonium glycyrrhizinate, glycine and methionine) was depended on the patients' economic condition or doctors' custom. All patients with liver damage were treated with liver protectants.

Diagnostic and grading criterions for ATDLI

ATDILI was diagnosed according to the Chinese criterion (Xiao et al., 2009) and base on other reports (Turktas et al., 1994; Saukkonen et al., 2006; Aithal et al., 2011), an elevation in the serum concentration of alanine aminotransferase (ALT) and/or total bilirubin (TBIL) exceeding 2 times of the upper normal limit (UNL) was noticed. Then, ATDILI was divided into 3 types as follow: (1) simple liver cell injury, defined as serum ALT level, is more than 2 times of UNL, and alkaline phosphatase (ALP) level is normal but ALT to ALP ratio is greater than or equal to 5; (2) cholestatic liver injury, defined as serum ALP level is more than 2 times of UNL, and ALT level is normal but or ALT to ALP ratio is less than 2; (3) mixed liver injury, defined as both ALT and ALP level is more than 2 times of UNL, and ALT/ALP ratio is between 2 to 5. Except the following liver dysfunction conditions: (1) malnutrition; (2) alcoholic liver disease or habitual drinking; (3) hepatitis B or C infection, liver disease, systemic diseases and/or treatment with non-anti-TB drugs that can induce hepatotoxicity; (4) severe TB or cardiac dysfunction that may cause liver dysfunction; and (5) transient increase in ALT, AST or TBIL, the severity of hepatotoxicity was classified according to the WHO Toxicity Classification Standards (Tostmann et al., 2008; Aithal et al., 2011). ATDILI was classified into 3 grades: (1) mild ATDILI, defined as serum ALT level is 2 to 5 times of UNL and normal TBIL level; (2) moderate ATDILI, defined as serum ALT level is 5 to 10 times of UNL, or serum ALT or AST level is less than 5 times of UNL and TBIL level is 2 to 5 times of UNL; (3) severe ATDILI, defined as both ALT or AST and TBIL level is more than 5 times of UNL, or TBIL lever is more than 2 times of UNL with ascites and/or encephalopathy or other organ failure.

Treatment of patients with ATDILI

Patients with mild ATDILI were continuously treated with anti-TB drugs after treatment with liver protectants. Patients with moderate ATDILI were provided with detoxification, liver protectants and ALT reducing treatment such as orally taking glucurolactone, liver protectant tablets, intravenously infusing diammonium glycyrrhizinate, reduced glutathione, etc., and not further treated with anti-TB drugs. Patients with severe ATDILI were treated as follow: (1) immediately stopped taking all anti-TB drugs in order to remove the cause of the disease; (2) started taking ursodeoxycholic acid as early as possible for short period to accelerate the jaundice disappearing; (3) intravenously administrated diammonium glycyrrhizinate, S-adenosyl methionine, essentiale, reduced glutathione, etc., to accelerate liver detoxification and promote liver cell repair; (4) intravenously administered vitamin, branched-chain amino acids and albumin; (5) given other symptomatic treatment.

Data analysis

The correlations of age, gender, history of liver disease and liver protectants and anti-TB regimes with ATDILI were analyzed using χ^2 test with SPSS statistical software package. The difference of ATDILI incidence between the HRZ/E and HRE groups was analyzed statistically in the first two months during the treatment. A P value less than 0.05 was considered statistically significant.

RESULTS

Sample characteristics

Among 2457 TB patients, 1372 cases (55.8%) were male and 1085 cases (44.2%) female. They were between 15 and 95 years old with average of 44.2±15.3. 897 patients were 60 years and above, accounting for 36.5%, 1560 were younger than 60 years, accounting for 63.5%.

Liver function of all the 2457 TB patients was normal before receiving anti-TB drug treatment. But 358 patients had type B viral hepatitis, fatty liver and alcoholic liver diseases, accounting for 14.6%. 2099 patients had no previous history of liver disease, accounting for 85.4%, among them, 1876 cases (76.4%) were additionally treated with liver protectants and 581 cases (23.6%) were not treated with liver protectants after treatment with anti-TB drugs. Total 267 cases (10.4%) had ATDILI. The injury occurred within the first 2 months of treatment in 201 cases, accounting for 75.2%, of which 28 cases (10.5%) occurred within 2 weeks of treatment. The injury occurred between 2 and 6 months of treatment in 54 cases (20.2%) and occurred after 6 months of treatment in 12 cases (0.4%).

Among these patients, 134 (50.2%) had mild ATDILI, 87 (32.6%) had moderate ATDILI, 46 (17.2%) had severe ATDILI; 184 (68.9%) had simple liver cell injury, 31 (11.6%)

had cholestatic liver injury, and 52 (19.5%) had mixed liver injury.

Clinical manifestations

Among the 267 patients with ATDILI, 14 (5.2%) patients had no obvious clinical manifestations, and 253 (94.8%) had obvious clinical manifestations, in which 246 (92.1%) had fatigue, anorexia, nausea, abdominal distension, diarrhea and other gastrointestinal symptoms; 57 (21.3%) had jaundice; 12 (5%) had hepatomegaly; 3 (1.1%) had hepatic encephalopathy; 187 (76.0%) had malaise; 10 (3.7%) had ascites; 47 (17.6%) had skin rash; and 34 (12.7%) had fever. All the 3 patients with hepatic encephalopathy had severe ATDILI. All patients with severe ATDILI had clinical symptoms.

Blood test results

Among the 267 patients with ATDILI, 33 (12.4%) patients had increased blood eosinophils, in whom 93.9% (31/33) were associated with skin rash; 19 (7.1%) had increased leucocytes; 59 (22.1%) had reduced leucocytes; and 28 (20.7%) had decreased thrombocytes.

Correlation of age with ATDILI

Among the 2457 TB patients, 86 out of 897 (9.6%) patients who were 60 years and above had ATDILI, and 181 out of 1560 (12.0%) patients who were younger than 60 years had ATDILI. The incidence of ATDILI between the two groups was not significantly different ($P>0.05$).

Correlation of gender with ATDILI

Out of 1372 male patients, 119 (9.6%) had ATDILI, whereas 148 out of the 1085 (13.6%) female patients had ATDILI. Compared with male patients, women seem to be more susceptible to ATDILI ($P<0.05$).

Correlation of previous history of liver disease with ATDILI

Among 358 patients who had had hepatitis, fatty liver and other liver diseases, 31 (8.7%) had ATDILI. Among 2099 patients with no history of liver disease, 236 (11.2%) had ATDILI. The incidence of ATDILI was not significantly different between these two groups ($P>0.05$).

Effect of liver protectants on the incidence of ATDILI

Among 1876 patients (76.4%) who were treated with liver protectants, 187 (10.0%) had ATDILI. Among 581 patients (23.6%) who were not treated with liver protectants, 80 (13.8%) had ATDILI, which was significantly higher than that of patients who received liver protectants ($P<0.05$).

Correlation of anti-TB regimes with ATDILI

Among 1050 cases (42.7%) primarily treated with HRZ/E regimen, 139 (13.2%) had ATDILI, in which 104 (9.9%) occurred within the first two months. Among 1407 cases (57.3%) treated with HRE regimen, 128 (9.1%) had ATDILI, in which 97 (6.9%) occurred within the first two months. The incidence of ATDILI in HRZ/E group increased significantly than that in HRE group in the first two months of treatment ($P<0.05$).

Outcome of treatment

Liver function of all patients with mild to moderate ATDILI was recovered after treatment. Among the 46 patients with severe ATDILI, 42 recovered after being treated with liver protectants, 1 did not recover, 3 died of liver failure. Among these 46 patients, 33 (75.0%) patients had liver cell injury and cholestasis, 8 patients had fever, rash, increased eosinophils and other allergic manifestations. All the 4 patients who died or did not recovered after treatment had clinical manifestations of fever and rash. One patient admitted to our Institute 10 days after the onset of fever, rash, and increased blood eosinophils, but not gastrointestinal symptoms, was found having elevated transaminase and bilirubin level, and diagnosed with severe hepatitis; the delay of diagnosis resulted in severe outcome.

DISCUSSION

ATDILI is the most common adverse reactions during the course of regular chemotherapy. It occurred in 0.8 to 34.9% TB patients treated with chemotherapy. The incidence of ATDILI was slightly higher in Asian countries than in Western countries (Gulbay et al., 2006; Sun et al., 2009; Agal et al., 2005; Fernandez et al., 2004; Singanayagam et al., 2012). This study found that 10.4% (267/2457) TB patients had ATDILI, which occurred within 2 months of chemotherapy in 75.2% patients, in consistence with previous reports: Sun et al. (2009) reported that hepatitis occurred in 42 TB patients (16.1%), with 60% of the events in the first 2 months of treatment. Devarbhavi et al. (2013) found that three-quarter ATDILI, and Shang et al. (2011) 71.59% ATDILI occurred within the first 2 months. All of these suggested that the monitoring of liver function was very important in the first two month during the treatment. Among the patients with

ATDILI, 68.9% had liver cell injury, 19.5% had mixed liver injury and 11.6% had cholestasis. The incidence of severe ATDILI is very low, 75.0% of which was mixed ATDILI. Consistent with domestic and oversea researches, this study found that most of ATDILI patients, if found at early stage, could be cured with proper treatment and their liver function could be restored.

This study found that allergic manifestations such as fever (12.7%), rash (17.6%) and increased eosinophils (12.4%) could occur before or accompany at the same time with ATDILI in some patients. Shao et al. (2007) retrospectively analyzed 29 cases with ATDILI and found that up to 11 (37.9%) patients had elevated blood eosinophil percentage. Yin et al. (2008) reported that 2 of 116 cases (1.7%) with ATDILI had fever, joint pain and increased blood eosinophils. These results suggested that allergic factors played an important role in ATDILI. Therefore, when TB patients had allergic manifestations such as fever, rash and increased blood eosinophils, liver function should be examined in time to prevent drug induced-severe liver disease and negative consequences.

Many studies have shown that TB patients with viral hepatitis, history of liver disease, or carrying hepatitis virus were independent factors for development of ATDILI, and the elderly and women were prone to have ATDILI (Sun et al., 2009; Fernandez et al., 2004; Shakya et al., 2004; Wong et al., 2000). Col et al. (2006) has reported that patients with hepatitis B virus (HBV) infection had significantly higher incidence of ATDILI (37.5%, 9/24) than those without HBV infection (10.2%, 13/128, $P<0.01$). In China, due to high HBV infection, TB patient concurred with chronic hepatitis B is common in clinic. The study from Guo et al. (2005) showed that among 132 TB cases with HBV infection in China, the incidence of ATDILI was 35.61%, significantly higher than those of 17.02% in 94 TB patients without HBV infection. Yin et al. (2008) found that TB patients with positive hepatitis B surface antigen (HBsAg) and older than 60 years old had higher incidence of ATDILI, which was 32.1% (18/56) and 22.9% (8/35), respectively, compared with that of TB patients with negative HBsAg or younger than 60 years old ($P<0.05$). Fernández et al. (2004) found in a retrospective study that 56 out of 471 TB patients had clinical features of ATDILI, among them, elder TB patients and TB patients with liver disease had increased incidence of ATDILI ($P<0.001$). All of the aforementioned researches have prompted that the elderly and TB patients with liver disease are the high-risk population of ATDILI. The reasons that the elderly are more vulnerable to ATDILI may be weakened drug biotransformation and excretion resulting from less liver blood flow, reduced liver cell function, and decreased liver microsomal enzyme amount and activity. TB patients with liver disease are prone to have ATDILI, which is because they already had liver damage before application of anti-TB drugs. These results are in contrast to a previous report of Gulbay et al. (2006) that retrospective evaluation of 1149 TB patients who initially received anti-TB therapy did not observe age differences in patients with and without hepatotoxicity. The current study did not find TB patients with history of viral hepatitis and other liver diseases and elderly patients are prone to have ATDILI, which may be related to the following factors: (1) decreased anti-TB drug dosage had been clinically taken into account in these patients; (2) application of liver protection drugs reduced the incidence of ATDILI; (3) the liver injury was induced by many factors. it was also found out that TB patients without liver protectant had significantly higher ATDILI incidence (13.8%, 80/581) than that of TB patients with liver protectant (10.0%, 187/1876, $P<0.05$). These results further suggested that susceptible patients of ATDILI should take appropriate preventive measures to avoid the occurrence of drug-induced liver injury. Because this study was retrospective, the liver protectants chosen were not designed beforehand, and the use of liver protectants was depended on the patients' economic condition or doctors' custom. Therefore, we could not further analyze the effect of different liver protectants, which is worthy of further study in the future.

This study found that the incidence of ATDILI was higher in female patients than that in male patients, which is similar to a previous report by Hunt et al. (1992). They proposed that higher incidence of liver damage induced by some non-anti-TB drugs in female may be related to higher CYP3A activity (Hunt et al., 1992), but the relationship of CYP3A activity with ATDILI is unclear. Col et al. (2006) showed that among 69 TB patients with ATDILI and 70 TB patients without ATDILI, the proportion between male and female patients was not significantly different ($P>0.05$). Similarly, Gulbay et al. (2006) also did not observe gender differences in 1149 TB patients with and without hepatotoxicity. However, Shao et al. (2007) reported a contrary result among 29 ATDILI cases, 20 (68.97%) were male and 9 (31.03%) were female. These differences may be associated with case selection and sample number. The relationship between gender and ATDILI requires further study.

The study also found that the incidence of ATDILI in TB patients treated with HRZ/E regimen was significantly higher than that in TB patients treated with HRE regimen ($P<0.05$), which is consistent with the report by Hang et al. (2008) that the incidence of ATDILI was 2.6% significantly higher in patients treated with HRZ/E regimen than that of 0.8% in patients treated with HRE regimen ($P<0.05$). This result indicates that HRZ/E regimen is more toxic to liver than HRE, possibly related to the toxicity accumulation of higher liver toxic pyrazinamide, or the increased liver toxicity of isoniazid and/or rifampin that resulted from the interference of pyrazinamide with the metabolism of isoniazid and/or rifampin. Therefore, TB patients with high ATDILI risk should select treatment regimen strictly according to the condition of individuals.

This study was retrospective. Therefore, there were some

limitations: first, some laboratory variables were missed, which hindered us from studying the relationship between serum albumin and outcome of ATDILI (Devarbhavi et al., 2013); second, owing to the fact that the treatment regimes were not designed in advance, some patients received the treatment with regimes HRZ/E, some patients with regimes HRZ, which might affect the incidence of ATDILI. But we could know the difference of ATDILI incidence between the two regimes.

Conclusively, ATDILI is a common complication during anti-TB chemotherapy, which causes not only economic loss of public health system and patients, but also mental burden of patients, and often leads to treatment interruption or drug resistance. Further study on the molecular mechanism of ATDILI and clinical predisposing factors is vital. For population susceptible to ATDILI, selective anti-TB chemotherapy should be applied for individuals to reduce the incidence of ATDILI.

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