Journal of Pharmaceutical Care
jpc.tums.ac.ir

Prediction Model of Drug-Induced Liver Injury in Patients with Pulmonary Tuberculosis: Evaluation of the Incidence and Risk Factors

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Received: 2015-04-13, Revised: 2015-06-14, Accept: 2015-07-19, Published: 2015-08-01

ARTICLE INFO

Article type:
Original article

Keywords:
Tuberculosis
Drug-Induced Liver Injury
Risk Factors

ABSTRACT

***Background*:** Tuberculosis (TB) still remains a major health concern both in developing and developed countries. The rate of the liver injury due to anti-TB drugs in developed countries has been reported up to 4%. The goal of this study is to assess the rate and risk factors for anti-tuberculosis drug-induced liver injury (DILI). Also, a model has been designed to predict DILI in patients with pulmonary tuberculosis.

Methods: We conducted an observational study. The investigation was carried out in the National Research Institute of Tuberculosis and Lung Disease, Tehran, Iran. Anti-tuberculosis drug treatment course and patients' demographic data, medical and drug history, and social habits were extracted from their medical records. DILI was defined as an increase in serum alanine aminotransfrase (ALT) or aspartate aminotransfrase (AST) greater than three times of the upper limit of normal (ULN), with symptoms of liver injury, or five times of the ULN without symptoms.

Results: In this study, 87 patients (33 male, 54 female, mean age 54.3 ± 21.8 years) with tuberculosis diagnosis were followed. Anti-tuberculosis induced liver injury was detected in 14 (16.1%) patients. Concomitant use of hepatotoxic drugs (Isoniazid, Rifampin and Pyrazinamide) and the abnormal baseline serum liver enzyme levels before the initiation of therapy were found as risk factors for anti-tuberculosis induced liver injury.

Conclusion: Anti-tuberculosis induced liver injury is a major problem in tuberculosis patients which lead to treatment interruption in 14 (16.1%) patients. Due to the lack of evidence regarding the mechanism of this side effect, we recommend to monitor anti-tuberculosis drug levels in order to study their probable correlations with DILI.

J Pharm Care 2015;3(3-4):44-48.

► Please cite this paper as:
Dastan F, Dasht Bozorg B, Goodarzi A, Salamzadeh J, Tabarsi P, Kobarfard F, Fahimi F. Prediction Model of Drug-Induced Liver Injury in Patients with Pulmonary Tuberculosis: Evaluation of the Incidence and Risk Factors. J Pharm Care 2015;3(3-4):44-48.

Introduction

Tuberculosis (TB) still remains a major health concern both in developing and developed countries. According to the WHO report in 2002, 38.7 TB cases per 100000 people have been recorded in Iran, ranking the country in the 52nd position among 147 countries regarding the prevalence of TB (1).

For decades, it has been well documented that first-line anti-TB drugs such as isoniazid, rifampin, and pyrazinamide

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Table 1. Summary of clinical and laboratory characteristics of patients.

Variable	Frequency	Drug-induced Hepatotoxicity	
		positive	negative
Sex	Male: 54	7	47
	Female: 33	7	26
Age (year)	86	58.29 ±17.61	53.51 ± 22.53
Weight (kg)	81	52.00 ± 9.39	56.06 ± 12.74
Smoking	Smoker: 13	3	10
	Non-smoker: 74	11	63
Drug abuse	Positive: 9	3	6
	Negative: 78	11	67
Isoniazid (dose/kg)	81	5.08 ± 0.45	4.83 ± 0.62
Rifampin (dose/kg)	81	9.89 ± 1.34	9.52 ± 1.37
Pyrazinamide (dose/kg)	81	19.82 ± 3.63	20.12 ± 3.52
Ethambutol (dose/kg)	78	15.86 ± 2.90	14.80 ± 3.16
AST baseline level	86	30.71 ± 19.44	21.32 ± 9.36
ALT baseline level	86	28.21 ± 25.25	18.09 ± 12.03
ALP baseline level	86	250.71 ± 66.46	268.94 ± 123.34
Bilirubin baseline level	84	0.61 ± 0.36	0.65 ± 0.55

ALT: Alanine aminotransfrase, **AST:** Aspartate aminotransfrase, **ALP:** Alkaline phosphatase.

can cause adverse effects on the liver, ranging from mild transient elevations in aminotransferases, which occur in approximately 10% to 20% of patients, to overt hepatitis, occurring much more rarely (2-4). Considering different demographics and clinical characteristics of tuberculosis patients in many parts of the world, liver injury is of increasing concern in the treatment of this disease and might be an important factor causing treatment failure and relapse (5, 6).

A meta-analysis has shown 2.6% incidence rate of liver toxicity with isoniazid and rifampin co-administration, the rates of Drug-induced Liver injury (DILI) caused by rifampin, and isoniazid monotherapy were 1.1% and 1.6%, respectively (7). The rate of the liver injury due to anti-TB drugs in developed and developing countries has been reported up to 4% and 39%, respectively (8,9).

DILI was observed in 10.7% of patients in a teaching hospital in Iran (10). Anti-tuberculosis DILI is a major problem in Iranian tuberculosis patients and cause treatment interruption in 31.37% of them (11).

Although some risk factors such as advanced age, female gender, alcohol use and malnutrition are known to increase the risk of DILI, the relative risk factors for the various etiologies of this adverse effect remain unclear (12–14).

Since there is a discrepancy between the tolerance of standard therapy reported in other clinical trials and the tolerance we observed in our patients, as the representative of tuberculosis patients in developing countries, we analyzed the current incidence of DILI severe enough to cause intolerance of standard therapy and investigated the risk factors for the occurrence of this adverse effect. As there is not any specific report of this reaction in Iranian TB patients, this study was designed to determine the rate and the probable risk factors of anti-TB induced liver injury in Iranian TB patients.

Methods

This observational study was funded by the research deputy of Shahid Beheshti University of Medical Sciences and was approved by its clinical ethics committee.

Treatment naïve patients who were newly diagnosed with pulmonary TB and received standard anti-TB drugs for at least two days were included in the study. Informed consent was obtained from all participants of the study. Anti-TB drugs were administered based on weight early in the morning. The investigation was carried out between January and October 2012 in the TB and Lung Disease Research Center, NRITLD, Masih Daneshvari Hospital, a university affiliated hospital. Patient data including anti-tuberculosis drug treatment course, their demographic data, medical and drug history, and social habits were extracted and recorded from their medical charts.

The excluded cases were as follows: HIV positives, hepatitis (viral or non-viral), heavy smokers (more than one pack of cigarette per day), regular alcohol consumers, pregnant women, children younger than 14 years old, Multi Drug Resistance (MDR) TB, heart failure, End

Table 2. Assessment of risk factors for drug-induced hepatotoxicity.

Variable	Analysis result
Sex	(p=0.31)
Age (year)	(p=0.46; 95% CI: -7.92 ± 17.46)
Weight (kg)	(p=0.28; 95% CI: -11.47 ± 3.35)
Smoking	(p=0.43)
Drug abuse	(p=0.16)
Isoniazid dose (dose/kg)	(p=0.17; 95% CI: -0.11 ± 0.61)
Rifampin dose (dose/kg)	(p=0.37; 95% CI: -0.45 ± 1.02)
Pirazinamide dose (dose/kg)	(p=0.78; 95% CI: -2.43 ± 1.84)
Ethambutol dose (dose/kg)	(p=0.27; 95% CI : -0.84 ±2.94)
AST baseline level	(p=0.006; 95% CI: -16.08 ± -2.71)
ALT baseline level	(p=0.02; 95% CI: -18.75 ± -1.49)
ALP baseline level	(p=0.59; 95% CI: -49.36 ± 85.82)
Bil baseline level	(p=0.80; 95% CI: -0.27 ± 0.35)

CI: Confidence Interval, **ALT:** Alanine aminotransfrase, **AST:** Aspartate aminotransfrase, **ALP:** Alkaline phosphatase, **Bil:** Billirubin.

Stage Hepatic Disease (ESHD), End Stage Renal Disease (ESRD), Cystic Fibrosis (CF), and burnt.

According to current American Thoracic Society, Centers for Disease Control and Prevention and Infectious Diseases Society of America guidelines, DILI was defined as increase in serum alanine aminotransfrase or aspartate aminotransfrase greater than three or five times of the upper limit of normal, with or without symptoms of hepatitis, respectively (15).

Liver transaminases were measured for all patients before the initiation of the anti-TB therapy, and thereafter if symptoms arose. Patients were encouraged to return at any time if new symptoms or problems arose during therapy. Fatigue, weakness, abdominal cramps, nausea/vomiting, jaundice, loss of appetite and pruritus were included as DILI symptoms. In severe cases, edema, ascites, confusion and coma were also mentioned. Since alterations of the serum transaminases would be observed in patients with hepatitis, they were excluded from our study to avoid the interferences with elevated transaminase serum levels associated with DILI. The patients were followed for developing DILI and the records of patients who developed side effects were reviewed in details to find probable risk factors for DILI.

Statistical data were analyzed using the 18th version of SPSS (PAWS) software. Chi-square, T-test, Fisher's exact test and multivariate analysis were used to test for the level of significance. Odd Ratio (OR) and P-values were used to find the significant risk factors.

Variables with $p<0.05$ were considered as potential predictors for DILI.

Results

Basic characteristics of the patients are shown in table1. The total number of 87 patients including 54 males and 33 females, with mean±SD age of 54.3±21.8 years, were admitted to the hospital with the diagnosis of pulmonary TB during the study period.

Nine (10.3%) patients had history of drug abuse. Habitual history results showed that 13 (14.9%) patients were smokers.

Anti-TB induced liver injury was detected in 14 (16.1%) patients. The mean time which was elapsed between starting of anti-TB drugs and elevation of ALT was 14.7 ± 10.8 days.

Assessment of probable risk factors involved in DILI revealed that, concomitant use of hepatotoxic drugs, and abnormal baseline serum ALT and AST levels were significantly correlated with occurrence of DILI ($p<0.0001$; r=0.76).Univariate logistic regression analysis showed that higher levels of AST (p =0.006; 95% CI: -16.08 to -2.71) and ALT (p=0.02; 95% CI: -18.75 to -1.48) could be considered as risk factors for occurrence of anti-TB induced liver injury.

Multivariate logistic regression analysis revealed that the higher baseline levels of AST and ALT as new variables were significantly associated with occurrence of DILI. These results were also confirmed with the Pearson correlation analysis (p=0.28, 95% CI: 1.000 to 1.001). In other words, the patients with the concomitant higher levels of AST and ALT had a greater chance to experience DILI. The final model was determined as follows:

$$P/1\text{-}P = e^{-2.11} \times e^{0.001(ALT \times AST)}$$

P= The probability of the occurrence of drug-induced liver injury

e= The Napierian logarithm base

There were not any significant correlations between

other variables including sex, weight, age, drug abuse, smoking habits and the dose of isoniazid, rifampin, pyrazinamide and ethambutol (dose/kg) as risk factors and the occurrence of liver injury (Table 2).

Discussion

The reported prevalence of TB seems to be higher among patients in Iran than developed countries (16). DILI due to antituberculosis regimens containing isoniazid, rifampin, and pirazinamide is a potentially serious adverse effect and one of the main causes of TB treatment interruption. Prevalence of anti-TB induced liver injury in Iran was reported from 16.1% to 27.7% in previous studies (10, 17). In the present study, statistical analysis showed that the incidence of DILI associated with anti-TB drugs was 16.1%.

A great variability was observed in the incidence of DILI in different countries because of the differences in the studied population and the employed methodologies. The incidence of anti TB DILI was 5% in Spain in a study involving 466 patients (18). Huang YS, et al., in Taiwan, reported an incidence of 14.7% in 224 patients (19). In Nepal and Turkey the incidences were 8% and 8.1%, respectively (20,21). In Germany the incidence was 11% among 519 patients hospitalized with tuberculosis (22). A higher risk of DILI has been reported in Indian patients (up to 11.5%) compared to the Western counterpart ones (up to 4.3%) (23).

The difference in the incidence may also related to various definitions for DILI. It is defined, as asymptomatic elevation of transaminases of 2 × ULN, to symptomatic, jaundiced individuals with AST >150 U/L (24). The relatively higher incidence of hepatotoxicity in the developing countries has been associated to various factors such as older age, higher alcohol intake, malnutrition, past history of jaundice, chronic liver disease, illogical use of drugs, and viral hepatitis (25). Factors such as female gender, low body mass index, extra-pulmonary and positive HIV were observed to be risk factors for DILI (26). One study showed that the presence of disseminated TB and malnutrition (BMI < 18.5 kg/m^2) were independent predictors in the development of DILI in TB/HIV co-infected patients (27).

Higher prevalence of anti-TB DILI in Iran might be due to several factors such as, metabolic pathway polymorphism, race, malnutrition, undiagnosed liver diseases, and MDR and XDR TB.[11] The hospital which the study was performed in, is a referral one and complicated patients usually are referred to this center. In our study, we focused on anti-TB DILI closely as a part of clinical pharmacy services and pharmaceutical care adverse drug reaction (ADR) unit. This study was implemented in tuberculosis ward of the hospital and the patients were monitored for 2 weeks and then followed periodically until 6 months.

The involved risk factors in the present study were concomitant use of hepatotoxic anti-TB drugs and elevated baseline serum levels of ALT or AST.

According to our findings, higher baseline levels of liver transaminases were associated with higher incidence of anti-TB induced liver injury which was consistent with other reports (10,17,28).

In this study we achieved a new model to predict anti-TB induced liver injury in the patients which is shown by the following equation:

$$P/1\text{-}P = e^{-2.11} \times e^{0.001(ALT \times AST)}$$

P= The probability of the occurrence of drug-induced liver injury

e= The Napierian logarithm base

By the use of this model, prediction of susceptibility to DILI in TB patients would be possible. As drug-induced hepatotoxicity is a crucial concern in tuberculosis patients and may lead to interruption of medications and death, prevention of this adverse effect by creating a model may have a great clinical value.

Although we could not find any significant correlations between the dose of anti-TB drugs and the risk of DILI, according to some other studies, the risk of liver injury could be minimized through dose adjustment of anti-TB drugs and closer monitoring. This controversy between our results and the outcomes of other studies might be due to the differences in the applied methods or the varieties in sampling (8,11,12,14).

Although it has been reported that advanced age can be a risk factor for DILI (29,30). We could not find any significant correlations between age and incidence of DILI. In the previous studies in Iranian TB patients, advanced age was also not proved to be a risk factor for anti-TB induced liver injury (10, 17) which is supporting our results. However, the higher mean age of the patients (58.29±17.61) in hepatotoxic group showed the necessity of careful surveillance in the elderly population.

In our study other variables including sex, weight, age, drug abuse, smoking habits and the dose of isoniazid, rifampin, pyrazinamide and ethambutol (dose/kg) were not determined as risk factors for anti-TB induced liver injury in Iranian population. Previous studies conducted in Iran also confirmed our results (11, 17)

According to one study, alcohol abuse, extensive nature of disease, and hypoalbuminemia were independently associated with DILI (31) while in another study (32) it was revealed that patients with hypoalbuminemia had a two-fold higher risk of developing DILI. High alcohol intake and advanced TB were also associated with development of DILI (33, 34). In patients with advanced disease, multiple factors such as underlying nutritional status, hypoalbuminemia, alcohol abuse and long-standing disease may play a role in developing DILI (35).

Anti-TB induced liver injury can be one of the important

reasons for noncompliance among the tuberculosis patients. In the present study the incidence of DILI was evaluated as 16.1%.

The higher baseline serum liver enzyme levels before the initiation of therapy were shown to be as major risk factors for anti-TB induced liver injury.

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