A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases

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Abstract

Purpose Identification of risk factors associated with antituberculosis drug-induced hepatotoxicity (anti-TB-DIH) is important, especially in endemic area for TB and liver disease. This study assessed the incidence and risk factors of anti-TB-DIH in upper Egyptian patients treated for active pulmonary and extra-pulmonary TB.

Methods A total of 100 consecutive TB patients were prospectively followed up both clinically and biochemically before and during their course of anti-TB therapy with daily doses of isoniazid, rifampin, ethambutol, and pyrazinamide, or streptomycin.

Results Anti-TB-DIH developed in 15 (15%) patients within 15–60 days (median: 30 days) from the onset of therapy. Liver function normalized in 10 (60%) patients within 2 weeks from cessation of therapy. No recurrence of DIH was observed after reintroduction of therapy. Only 1 patient died from fulminant hepatic failure despite discontinuation of all anti-TB drugs. By univariate analysis, patients with anti-TB-DIH had more pre-existing liver disease ($P = 0.024$; OR: 3.60; 95% CI: 1.16–11.18), lower body mass index (BMI; $P = 0.037$; OR: 3.73; 95% CI: 1.04–10.56), lower serum albumin ($P = 0.035$; OR: 3.31; 95% CI: 1.04–10.56), and more extensive disease ($P = 0.033$; OR: 3.50; 95% CI: 1.11–11). Age, gender, raised baseline transaminases level, inclusion of pyrazinamide, and inactive hepatitis B or C carrier state were not significant risk factors of DIH. Using multivariate regression analysis, only pre-existing liver disease and lower BMI of 20 kg/m$^2$ or less were independent predictors of DIH ($P = 0.024$ and $P = 0.047$, respectively).

Conclusion Anti-TB-DIH is not uncommon, needs early recognition and treatment, and is more in patients with pre-existing liver disease and low BMI.

Keywords Drug-induced liver disease · Drug-induced hepatitis · Side effects · Adverse reactions · Pulmonary tuberculosis · Risk factors

Abbreviations

ALT Alanine transaminase
anti-TB-DIH Antituberculosis drug-induced hepatotoxicity
AST Aspartate transaminase
CI Confidence interval
DIH Drug-induced hepatotoxicity
EMB Ethambutol
HBV Hepatitis B virus
HCV Hepatitis C virus
INH Isoniazid
$n$ Number
OR Odds ratio
PZA Pyrazinamide
RIF Rifampin
SD Standard deviation
TB Tuberculosis
Introduction

Tuberculosis (TB) is endemic in developing countries, including Egypt, and is increasingly recognized in developed countries, especially in immune-compromised patients [1]. Despite the efficacy of anti-TB agents, hepatotoxicity from first-line drugs—isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA)—may result in drug(s) discontinuation, de novo liver disease, or exacerbation of pre-existing ones [2–6]. Anti-TB drug-induced hepatotoxicity (DIH) ranges from nonspecific transaminasitis to fulminant hepatic failure [5, 6].

The exact factors associated with anti-TB-DIH are unknown. However, alcohol abuse, increasing age, pre-existing liver disease, slow acetylators, and severe malnutrition have been reported as risk factors [4, 7]. Recent studies suggested that polymorphism and reduced activity of hepatic N-acetyl-transferase-2 genes and glutathione-S-transferase contribute to DIH [8].

The incidence, pattern, and predictors of anti-TB-DIH have not been prospectively studied before in Egypt, where chronic liver diseases secondary to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and/or schistosomiasis are prevalent. Anti-TB-DIH in such endemic areas is difficult to evaluate and need to be differentiated from exacerbation of pre-existing diseases and from de novo infections. Therefore, the aims of this study were to determine the incidence and pattern of anti-TB-DIH in patients with active pulmonary and extra-pulmonary TB and to assess the independent risk factors associated with DIH in these patients.

Patients and methods

Patients

This prospective study was conducted in the Chest Outpatient Clinic, Assiut University Hospital, Assiut, Egypt, from October 8, 2004, till January 4, 2005. Inclusion criteria comprised patients with active pulmonary or extra-pulmonary TB, who were going to start anti-TB drug regimen irrespective of their liver disease status. Of 104 consecutive patients registered in the clinic during the study period, 4 patients did not complete their follow-up and were excluded. All patients gave written informed consent and the study was approved by the Faculty of Medicine Research Ethics Committee.

Anti-TB regimen

Total treatment period was 6 months including intensive and continuation phases (2 and 4 months, respectively). The intensive phase comprised INH (5 mg/kg day⁻¹; maximum 300 mg/day), RIF (10 mg/kg day⁻¹; maximum 600 mg/day), EMB (15–20 mg/kg day⁻¹), and PZA (20–25 mg/kg day⁻¹), or streptomycin. The continuation phase comprised daily similar doses of INH and RIF.

Diagnosis of DIH

Anti-TB-DIH was diagnosed according to International Union against Tuberculosis and Lung Disease [9] as follows:

1. Normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-TB drugs, and
2. Presence of at least one of the following:
   i. A rise to more than 2 the upper limit of normal (ULN) level of alanine transaminase (ALT) and/or aspartate transaminase (AST) [10–12].
   ii. A rise in total serum bilirubin to more than 1.5 mg/dl.
   iii. Any increase in AST and/or ALT above pretreatment levels together with anorexia, nausea, vomiting, and jaundice.

Baseline assessment

Pretreatment evaluation included clinical history, physical examination, body mass index (BMI = body weight (kg)/[height (m)]²), chest radiographs, abdominal ultrasonography, complete blood cell count, liver function tests (LFTs), and hepatitis markers. Samples from HBsAg, anti-HB core antibody (anti-HBc), and/or anti-HCV antibody-positive patients were tested for HBV DNA and HCV RNA, respectively. A BMI of less than 20 kg/m² was considered as low. Hypoalbuminemia was defined as serum albumin level of less than 3.5 mg/dl. The ULN in our laboratory is 41 IU/l for ALT and 38 IU/l for AST.

Follow-up

Patients were followed closely in a specialized clinic by a chest physician and a hepatologist fortnightly over the first 2 months, then monthly till the end of the 6-month period. In each visit, patients were assessed clinically (response to therapy, any adverse effects, and nutritional status), and biochemically including LFTs, which were repeated whenever symptoms or signs suggestive of hepatotoxicity (nausea, anorexia, malaise, vomiting, hepatomegaly, or jaundice) occur.

Exclusion of other causes of liver disease

Before attributing hepatotoxicity to anti-TB drugs, other causes of liver diseases were excluded by: IgM anti-
hepatitis A virus antibody, HBsAg, IgM anti-HBe in addition to the HBV DNA if the HBsAg and/or HBeAb are positive, anti-HCV antibody and HCV RNA if the anti-HCV antibody is positive, autoimmune screen (anti-nuclear and anti-smooth muscle antibodies), and abdominal ultrasound to assess for liver abscesses, focal lesions, or biliary obstruction.

Management of DIH

INH, RIF, and PZA were stopped immediately in all patients who developed anti-TB-DIH when serum transaminases levels were more than 3 times the ULN in the presence of symptoms or more than 5 times the ULN with or without symptoms. LFTs were monitored weekly for 2 weeks, and then fortnightly. Two other anti-TB medications without hepatotoxicity, namely, EMB and streptomycin, were used until the cause of the hepatitis is identified. Anti-TB medications (INH, RIF, and PZA) were restarted once transaminases levels return back to less than 2 times the ULN. In patients with elevated baseline transaminases from pre-existing liver disease, drugs were restarted when the enzymes return to baseline levels. Anti-TB drugs were reintroduced with RIF, followed by INH, and then PZA as previously reported [13]. If a patient again develops hepatotoxicity, the causative drug was permanently discontinued [14].

Statistical analysis

Data were collected in a specialized Data Collection Form, and then entered in the Statistical Package for Social Sciences (SPSS, version 15.0; SPSS Inc., Chicago, IL) for Windows. Data are expressed as mean ± SD and frequencies as appropriate. Data were compared through Student’s t test and χ² analysis for continuous variables and proportions, respectively. Elevations in serum AST and ALT levels (pretreatment levels vs. peak levels during treatment) were analyzed by paired t test. Risk factors for DIH were evaluated by multivariate logistic regression analyses. Statistical significance was accepted at P < 0.05.

Results

Baseline patients’ characteristics are shown in Table 1. One hundred patients were included in this prospective study, 44 (44%) male and 56 (56%) females, with mean ± SD age 33.60 ± 13.03 years. The mean ± SD BMI was 20.29 ± 4.38 kg/m². A total of 37 (37%) patients had active pulmonary TB and 63 (63%) patients had active extra-pulmonary TB. As shown in Table 2, extra-pulmonary TB involved the pleura in 23 patients (23%), lymph node in 20 patients (20%), the peritoneum in 16 patients (16%), and other sites in the remaining 4 patients (4%).

During the study period, anti-TB-DIH was detected clinically and confirmed biochemically in 15 patients (15%; Fig. 1). The time interval from onset of therapy and the detection of hepatotoxicity ranged from 15 to 60 days (median: 30 days). Twelve patients had alteration in LFTs within 2–4 weeks, whereas the rest (n = 3) showed alteration after 2 months of treatment. The time interval from the onset of hepatotoxicity to normalization of LFTs was 15–45 days (median: 15 days). Almost 60% of patients had normalization of their LFTs within 2 weeks of cessation of anti-TB therapy.

The clinical manifestations of DIH were nausea, anorexia, and malaise in 10 (66.7%) patients, vomiting in 2 (13.3%) patients, jaundice in 5 (33.3%) patients, and encephalopathy in 1 (6.7%) patient (Table 3). Anti-TB therapy was stopped temporarily until their clinical and biochemical profiles normalized. None of the patients had recurrence of hepatotoxicity with the reintroduction of anti-TB drugs.

Death was reported in 1 case because of fulminant hepatic failure that developed 3 weeks after the onset of therapy. This case belonged to a 21-year-old woman with pulmonary TB and positive serology for HCV. Her BMI was 17.53 kg/m² and she was on INH, RIF, PZA, and streptomycin. Her hepatic failure progressed till she died 3 weeks later despite discontinuation of all her anti-TB drugs and supportive measures; liver transplantation was not feasible.

Administration of anti-TB drugs lead to slight, but statistically significant, elevations in transaminases levels in all patients (n = 100; P = 0.02 for ALT and P = 0.00 for AST). All patients developing DIH (n = 15) showed significant rise in ALT and AST levels, which did not exceed 5 times the ULN in all of them. A rise in bilirubin level was detected in 7 patients only, 4 of them had increase of more than 3 mg/dl (Table 4).

There was no statistically significant difference in the incidence of DIH between patients with pulmonary TB and those with extra-pulmonary TB (Table 2). However, patients with pre-existing liver disease (liver cirrhosis, fatty liver, or diffuse hepatic pathology) were found to be at higher risk for anti-TB-DIH (P = 0.02; OR: 3.60; 95% CI: 1.16–11.18; Table 4). Also, patients with BMI of less than 20 kg/m² (P = 0.037; OR: 3.73; 95% CI: 1.04–10.56) and those with serum albumin levels of less than 3.5 mg/dl (P = 0.035; OR: 3.31; 95% CI: 1.04–10.56) were found to be at higher risk for anti-TB-DIH. Seven of the fifteen patients who developed DIH had positive sputum smear for acid-fast bacilli, which may indicate that open pulmonary TB has a probable role in predisposing the patient to DIH (P = 0.033; OR: 3.50; 95% CI: 1.11–11; Table 5). In the
Table 1  Baseline patients' characteristicsa

| Variable        | All patients (n = 100) | Patients without DIH (n = 85) | Patients with DIH (n = 15) |
|-----------------|------------------------|-----------------------------|---------------------------|
| Mean age, years | 33.60 ± 13.03          | 33.16 ± 13.12               | 36.07 ± 12.69             |
| Gender          |                        |                             |                           |
| Men             | 44 (44%)               | 48 (56.5%)                  | 37 (43.5%)                |
| Women           | 56 (56%)               | 8 (35.3%)                   | 7 (46.7%)                 |
| Height, m       | 162.87 ± 9.73          | 162.67 ± 9.71               | 164 ± 10.8                |
| Weight, kg      | 53.61 ± 11.19          | 54.12 ± 11.05               | 50.73 ± 11.97             |
| BMI, kg/m²      | 20.29 ± 4.38           | 20.54 ± 4.37                | 18.88 ± 4.30              |
| Albumin, g/l    | 36.57 ± 7.59           | 37.33 ± 7.44                | 37.33 ± 7.44b             |
| Bilirubin, µmol/l| 7.42 ± 3.87            | 7.14 ± 4.04                 | 7.81 ± 2.71               |
| ALT, U/l        | 17.27 ± 12.38          | 17.53 ± 13.15               | 15.87 ± 6.73              |
| AST, U/l        | 28.50 ± 14.89          | 28.78 ± 15.44               | 27 ± 11.67                |

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DIH, drug-induced hepatotoxicity; n = number

Data expressed as mean ± SD except gender (number (percentage))

b P < 0.05 as compared with non-DIH group

Table 2  Hepatotoxicity among patients with different clinical varieties of tuberculosisa

| Clinical variety | Varieties of tuberculosis | Hepatotoxicity |
|------------------|----------------------------|----------------|
|                  | n  | %  | n  | %  |
| Pulmonary        | 37 | 37 | 8  | 21.6|
| Pleural effusion | 23 | 23 | 4  | 17.4|
| Lymph node       | 20 | 20 | 0  | 0   |
| Abdominal        | 16 | 16 | 2  | 12.5|
| Peritoneal       | 14 | 14 | 1  | 7.1 |
| Intestinal       | 2  | 2  | 1  | 50  |
| Pericardial      | 1  | 2  | 0  | 0   |
| Genital          | 2  | 1  | 0  | 0   |
| Cutaneous        | 1  | 1  | 1  | 100 |

a P = 0.08 by χ² analysis when compared with drug-induced hepatotoxicity in patients with pulmonary TB (n = 37) versus those with extra-pulmonary TB (n = 67)

Table 3  Clinical presentations of anti-TB DIH

| Variable          | Patients with anti-TB-DIH (N = 15) |
|-------------------|------------------------------------|
|                   | n  | %  |
| Nausea            | 10 | 66.7|
| Anorexia          | 10 | 66.7|
| Malaise           | 10 | 66.7|
| Vomiting          | 2  | 13.3|
| Jaundice          | 5  | 33.3|
| Encephalopathy    | 1  | 6.7 |

Note: n, number; DIH, drug-induced hepatotoxicity

Table 4  Alterations in liver function tests in the patients who developed anti-TB DIH

| Variable         | Patients with anti-TB DIH (N = 15) |
|------------------|------------------------------------|
|                   | n  | %  |
| ALT in all the 15 cases |    |    |
| ≤3 times ULN     | 9  | 60.00|
| 3–4 times ULN    | 4  | 26.67|
| >4 times ULN     | 2  | 13.33|
| AST in all the 15 cases |    |    |
| ≤3 times ULN     | 8  | 53.33|
| 3–4 times ULN    | 6  | 40.00|
| >4 times ULN     | 1  | 6.67 |
| Raised bilirubin in 7 cases |    |    |
| 1.5–2 mg/dl      | 2  | 28.57|
| 2–3 mg/dl        | 1  | 14.29|
| >3 mg/dl         | 4  | 57.14|

Note: ULN, upper limit of normal; n, number; DIH, drug-induced hepatotoxicity; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Fig. 1 Incidence of anti-TB drug-induced hepatotoxicity in patients with tuberculosis (n = 100)
multivariate logistic regression analysis, only pre-existing liver disease ($P = 0.024$; OR: 0.259; 95% CI: 0.08–0.83) and BMI less than 20 kg/m² ($P = 0.047$; OR: 0.25; 95% CI: 0.63–0.98) were found to be independent predictors of anti-TB-DIH (Table 6).

As shown in Table 5, there was no significant difference between patients who developed DIH and those who did not regarding other variables, such as age, sex, and raised baseline AST, ALT, or the inclusion of PZA in the treatment regimen. While inactive HBV carriers were not found to be at a higher risk for anti-TB-DIH, inactive HCV carriers appear at a higher risk although it did not reach statistical significance ($P = 0.088$; OR: 3.07; 95% CI: 0.81–11.69).

### Table 5 Risk factors for anti-TB drug-induced hepatotoxicity by univariate analysis

| Variables                  | Hepatotoxicity | OR       | 95% CI     | $P$  |
|----------------------------|----------------|----------|------------|------|
| $n$ | Rate, % |
| Gender                    |                |          |            |      |
| Men ($n = 44$)            | 7              | 15.9     | 0.88       | 0.29–2.65 | 0.821 |
| Women ($n = 56$)          | 8              | 14.3     |            |        |      |
| Age                       |                |          |            |      |
| $>35$ years ($n = 65$)    | 6              | 13.8     | 1.29       | 0.42–3.97 | 0.434 |
| $\leq35$ years ($n = 35$) | 9              | 17.1     |            |        |      |
| Albumin level, g/dl       |                |          |            |      |
| $>3.5$ ($n = 58$)         | 5              | 8.6      | 3.31       | 1.04–10.56 | 0.035 |
| $<3.5$ ($n = 42$)         | 10             | 23.8     |            |        |      |
| Body mass index, kg/m²    |                |          |            |      |
| $>20$ ($n = 44$)          | 3              | 8.6      | 3.73       | 1.04–10.56 | 0.037 |
| $<20$ ($n = 56$)          | 12             | 21.4     |            |        |      |
| Pre-existing liver disease|                |          |            |      |
| No ($n = 66$)             | 6              | 9.1      | 3.60       | 1.16–11.18 | 0.024 |
| Yes ($n = 44$)            | 9              | 26.5     |            |        |      |
| Hepatitis C virus$^a$     |                |          |            |      |
| Negative ($n = 87$)       | 11             | 12.6     | 3.07       | 0.81–11.69 | 0.088 |
| Positive ($n = 13$)       | 4              | 30.8     |            |        |      |
| Hepatitis B virus$^b$     |                |          |            |      |
| Negative ($n = 97$)       | 15             | 15.5     | 0.85       | 0.78–0.92 | 0.611 |
| Positive ($n = 3$)        | 0              | 0        |            |        |      |
| Abnormal baseline transaminases |              |          |            |      |
| No ($n = 88$)             | 14             | 15.9     | 0.48       | 0.06–4.03 | 0.430 |
| Yes ($n = 12$)            | 1              | 8.3      |            |        |      |
| Acid-fast bacilli in sputum |              |          |            |      |
| Negative ($n = 67$)       | 8              | 10.5     | 3.50       | 1.11–11.00 | 0.033 |
| Positive ($n = 24$)       | 7              | 29.2     |            |        |      |
| Severity of disease       |                |          |            |      |
| Minimal ($n = 15$)        | 5              | 31.3     | 0.37       | 0.07–1.85 | 0.201 |
| Moderate/advanced ($n = 21$) | 3           | 14.3     |            |        |      |
| Use of pyrazinamide       |                |          |            |      |
| No ($n = 26$)             | 4              | 15.4     | 0.97       | 0.28–3.33 | 0.587 |
| Yes ($n = 74$)            | 11             | 14.9     |            |        |      |

**Note:** OR, odds ratio; CI, confidence interval

$^a$ HCV infection was defined as positive serum anti-HCV antibody and HCV RNA by polymerase chain reaction

$^b$ HBV infection was defined as positive serum hepatitis B surface antigen and HBV DNA by polymerase chain reaction

### Table 6 Independent risk factors for anti-TB drug-induced hepatotoxicity by multivariate analysis

| Variables                  | Hepatotoxicity | OR       | 95% CI     | $P$  |
|----------------------------|----------------|----------|------------|------|
| $n$ | Rate, % |
| Body mass index, kg/m²     |                |          |            |      |
| $\geq20$ ($n = 44$)        | 3              | 8.6      | 0.25       | 0.03–0.98 | 0.047 |
| $<20$ ($n = 56$)           | 12             | 21.4     |            |        |      |
| Pre-existing liver disease |                |          |            |      |
| No ($n = 66$)              | 6              | 9.1      | 0.26       | 0.08–0.83 | 0.024 |
| Yes ($n = 44$)             | 9              | 26.5     |            |        |      |

**Note:** OR, odds ratio; CI, confidence interval; $n$, number
Discussion

The use of multidrug regimens for the treatment of TB, such as the combination of INH, RIF, and PZA, has been associated with an increased incidence of hepatotoxicity when compared with INH monotherapy used for anti-TB prophylaxis [5, 15]. The incidence of anti-TB-DIH varies worldwide and has been reported to be higher in developing countries where factors such as acute or chronic liver disease, indiscriminate use of drugs, malnutrition, and more advanced TB have been implicated [16–18]. However, it is unclear if these are independent risk factors for hepatotoxicity. In our study, 15% of the patients developed anti-TB-DIH, an incidence similar to reports from Asia (8.0–19.8%) [14, 19–21], and higher than those from the West (4.3%) [22].

The variation in the incidence of anti-TB-DIH may be related to differences in patients’ characteristics, regimens used, type of monitoring, and the diagnostic criteria defining hepatotoxicity [23]. Despite these variations, the issue of anti-TB DIH remains important, especially in countries that are endemic for both TB and liver diseases as the case in Africa, Asia, and South America, and is expected to increase in the developed countries with the well-known rise of TB in the era of immunosuppressive therapy.

Anti-TB-DIH in our patients manifested as anorexia, nausea, vomiting, and jaundice, and occurred 15–60 days (median: 30 days) after initiation of therapy. This was in agreement with the results of Shakya et al. [20], who reported an interval of 12–60 days (median: 28 days). Similarly, Mahmood et al. [14] reported that the onset of anti-TB-DIH in almost two thirds of their patients (41/67) was within 14 days from the start of therapy. This emphasizes the importance of close and more frequent monitoring of patients in the first 2 months of anti-TB therapy.

In the present study, the interval from the onset of hepatotoxicity to LFTs normalization was 15–45 days (median: 15 days). In almost three fifths of patients, their LFTs normalized within 2 weeks. Also, Mahmood et al. [14] reported that in four fifths of patients, their LFTs normalized within 2 weeks. In addition, Shakya et al. [20] reported that liver enzymes returned to the normal level within few days of cessation of therapy.

Several studies suggested that increasing age is a potential risk factor for anti-TB-DIH [14, 21, 24–28]. One study reported that the rate of anti-TB-DIH ranges from 2 to 8% as age increases, with an average of 5% [28]. Other studies reported that hepatotoxicity ranges from 22 to 33% in patients older than 35 years compared with a range from 8 to 17% in those younger than 35 years [21, 29]. Also, Mahmood et al. [14] reported that older age group was affected more than the younger age group (25.8 and 14.4%, respectively). In contrast, Shakya et al. [20] reported that the incidence of anti-TB-DIH is higher in younger patients. This might be explained by the fact that the majority of patients enrolled in their study were young. This study and others [30] have showed that age is not a risk factor for the development of anti-TB-DIH.

Several studies reported that females are at increased risk of hepatotoxicity compared with males [24, 25, 31, 32]. However, this difference was not treatment limiting, nor statistically significant [31, 32]. One study did show a 4-fold increase in the risk of treatment-limiting hepatotoxicity in women, but with an overall incidence of only 2% [25]. Mahmood et al. [14] reported higher incidence of anti-TB-DIH in females than males (26.3% vs. 19.7%). The higher vulnerability of females could be due to variations in pharmacokinetics and slower acetylation pattern [33] and/or lower BMI. Other studies, in agreement with ours, showed no increased risk of anti-TB-DIH in women [3, 27, 30, 34–36].

Malnutrition may be a risk factor for anti-TB-DIH as detected by BMI of less than 20 kg/m² and serum albumin levels of less than 3.5 mg/dl. This may be due to depletion of glutathione stores, which makes patients more vulnerable to oxidative injuries, and the slower pace at which their livers metabolize drugs. Indeed, low BMI and hypoalbuminemia were associated with higher rates of anti-TB-DIH in several studies [14, 16, 20, 28, 37–39].

Seven of the fifteen patients who had anti-TB-DIH in this study had positive sputum smear for acid-fast bacilli. This was also reported in another study in which 40 (59.7%) patients were sputum smear positive and were more severely affected [14], indicating that patients with more extensive or open pulmonary TB are at an increased risk for anti-TB-DIH, necessitating more frequent and closer follow-up.

Inclusion of PZA in the regimen did not lead to more hepatotoxicity in our patients. This is consistent with earlier reports [17, 34, 40] and clinical trials [41, 42]. Some studies [6, 43, 44], on the other hand, have indicated that the incidence of PZA-induced hepatotoxicity was significantly higher than that observed with the other first-line drugs.

Similar to the result of others [3, 7], we found that patients with pre-existing liver disease are at higher risk of anti-TB-DIH. Indeed, an increased risk of hepatotoxicity during treatment of TB was observed in patients with abnormal baseline transaminases [45]. In the current study, inactive HBV carrier state was not a risk factor for anti-TB-DIH. However, our study included only 3 inactive HBV carriers. Previous studies showed more anti-TB-DIH in HBV carriers [34, 46, 47], whereas 1 did not [48]. Also, we observed a trend toward more anti-TB-DIH in inactive HCV carriers, although it did not reach statistical significance. A study on has 128 inpatients in Florida, approximately 30% of HCV-
infected individuals developed anti-TB-DIH compared with 11% among uninfected individuals, and hepatitis C was an independent risk factor for the development of hepatotoxicity [49].

In our study, a 21-year-old woman died secondary to fulminant hepatic failure despite discontinuation of all anti-TB drugs. It has been suggested that the severity of INH-induced hepatotoxicity may be worse or even fatal in women [11, 50]. Liver transplantation was the definitive therapy, but unfortunately was not available.

In conclusion, anti-TB-DIH is not uncommon, can be fatal, and is significantly more frequent in patients with pre-existing liver disease, malnourished patients, and those with hypoalbuminemia. Also, extensive or open pulmonary TB may have a role in predisposing patient to hepatotoxicity. Close follow-up, early recognition, and the immediate withdrawal of the causative agent are essential to prevent progression and allow the liver to heal. This topic is of higher importance in the developing countries where both TB and liver diseases are endemic.

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