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Risk Factors and Pattern of Changes in Liver Enzymes Among the Patients With Anti-Tuberculosis Drug-Induced Hepatitis

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Background: Hepatotoxicity is one of the most frequent adverse events that occurs during tuberculosis treatment and is associated with mortality of 6% - 12% if drugs are continued after the appearance of symptoms. In most of the cases, hepatitis is evident within three months after induction of anti-tuberculosis treatment.

Objectives: The current study aimed to define the pattern of changes in liver transaminases and the associated risk factors among the patients with anti-tuberculosis drug-induced hepatitis who admitted to Boo-Ali Hospital in Zahedan, Southeastern Iran.

Patients and Methods: The current descriptive cross-sectional study reviewed all files of the patients with anti-tuberculosis Drug-Induced Hepatitis (DIH) who referred to Boo-Ali Hospital in Zahedan, Southeastern Iran, in five years. All patients were above 14 years, and were treated with the standard regimen (a combination of isoniazid, rifampin, pyrazinamide, and ethambutol ± streptomycin). Hepatotoxicity was defined when the liver transaminases were more than five, the Upper Limit of Normal (ULN), or had clinical symptoms with an increase of liver transaminases ≥ 3 ULN.

Results: Among the 946 patients with tuberculosis disease (44% men; 56% women), 52 (5.5%) cases had drug-induced hepatotoxicity. Only 25% of the patients with anti-tuberculosis drug-induced hepatitis were below 52; 50% of the cases occurred within the first two weeks after the treatment onset.

Conclusions: Anti-tuberculosis drugs-induced hepatotoxicity caused treatment interruption in 5.5% of the patients with tuberculosis. The majority of the patients with DIH were above fifty, and 50% the cases occurred during the first two weeks after treatment onset. Physicians must carefully and closely monitor such patients.

Keywords: Liver; Drugs; Hepatotoxicity; Tuberculosis

1. Background

Employing multidrug regimens such as the combination of isoniazid, rifampin and pyrazinamide (INH, RIF and PZA) to treat Tuberculosis (TB) is associated with an increased incidence of drug-induced hepatitis (DIH) (1-3). Risk factors of hepatotoxicity progression due to anti-tuberculosis (anti-TB) treatment include chronic liver disease, active alcohol use, extensive pulmonary tuberculosis (PTB), old age, and genetic factors (3). Infection with hepatitis B and C viruses are common causes of chronic liver disease frequently observed in populations at risk for TB infection (1-3). The mechanisms of drug-induced hepatotoxicity from anti-TB agents are thought to involve direct cytotoxicity (by the drugs or their metabolites) and an immune-related component especially by two main drugs(INH and RIF) (4). According to different populations, the incidence of acute liver injury during standard anti-TB treatment is reported, varying from 1% to more than 31% (3-9).

2. Objectives

The current study aimed to estimate the incidence of DIH in Zahedan (Southeastern Iran), where the prevalence of TB is high.

3. Patients and Methods

The current descriptive cross-sectional study reviewed medical history records of the patients with Tuberculosis (pulmonary and extra pulmonary) admitted to Boo-Ali Hospital in Zahedan, Iran, from April 2006 to March 2008 and from April 2011 to March 2014. Tuberculosis was diagnosed through bacteriological and histopathological methods. Bacteriological testing was based on three sputum samples or if the patient could not give the sample, three gastric aspiration samples were examined. The sputum and gastric aspiration samples were evaluated for Acid Fast Bacilli (AFB) by Zeil-Nelson staining and Lowenstein-Jensen medium was used to culture *Mycobacterium tuberculosis*. Patients with Extra Pulmonary Tuberculosis

were evaluated bacteriologically or histopathologically. All patients were treated with the standard regimen (a combination of IND, RIF, PZA and ethambutol (ETB) ± streptomycin). Drug related hepatotoxicity was defined as increase in serum alanine aminotransferase ≥ 3 ULN with symptoms of hepatitis, or more than five times of ULN with or without symptoms of hepatitis. The risk factors and other co-morbidities such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV) infection, diabetes, and use of other hepatotoxic drugs, and clinical course of drug hepatitis were also studied. When the patients showed DIH, their drugs were discontinued and according to the national protocol for the treatment of DIH, all drugs were gradually resumed. The statistical analysis of the results was carried out using SPSS version 17 to evaluate the significant differences; $P \leq 0.05$.

4. Results

The current study reviewed all files of the patients with anti-TB drug-induced hepatitis admitted to Boo-Ali Hospital in Zahedan during five years. Among the 946 patients with TB (44% men; 56% women) 52 patients (27 males, 25 females, and mean of age 15 - 89 years) were hospitalized due to anti-TB drug-induced hepatitis. Of the 52 patients with anti-TB drug-induced hepatitis, 75% were above 52 years; 50% of the cases occurred within the first two weeks after the treatment onset. Time range for developing DIH was 3 - 150 days after the patients received anti-TB drugs. Three patients had positive serology markers for HBV (positive result for HBs Ag and PCR-HBV tests). Nobody was positive for HCV or HIV. Five patients had diabetes mellitus. Among the patients with DIH, five patients were treated with five anti-TB drugs because of relapse or treatment failure; 45% had ALT, AST ≥ 6 times of ULN. These patients had loss of appetite (86%), icterus (46%), nausea (86%), vomiting (57%), malaise (24%), right upper quadrant tenderness (24%), and loss of consciousness (5.7%). Liver enzyme levels were normal after four to 30 days. No death was occurred. The mean of hospitalization duration was 13 days.

5. Discussion

The current study showed that 5.5% of the patients with TB treated with anti-TB drugs faced hepatotoxicity. Drug-induced hepatotoxicity is one of the most important side effects of anti-TB treatment, which varies in different countries and the incidence various from 1% to 31% (4-9). Frequency is higher in countries like India (10%) and turkey (18%), while it is lower in Western countries (< 1% in USA, 3.3% in Spain, and 4% in UK) (3-9). Published reports from Iran show that DIH is higher among Iranian patients (Sistanizad 28% (8), and Khalili 31% (9)). Depending on the factors such as geographical location, genetic factors, age, race, poor nutritional status, high alcohol use, extensive disease, pre-existing liver disease, hepatitis B and C, hepatitis B carriage, hypoalbuminaemia and acetylated status, the frequency was demonstrated to be different (3-5). Higher incidence of hepatotoxicity in older age may be secondary to the increased prevalence of co morbid disorders as well as use of related additional drugs in this age group (1-4). In the current study, 75% of the patients were more than 52 years. It was reported that the administration of rifampicin in a multidrug treatment regimen increased the incidence of significant hepatotoxicity among adults from 1.6% to 2.55% (2, 7). Pyrazinamide also contributed to increased incidence or severity of hepatotoxicity (2). In the current study patients received the standard regimen (combination of Isoniazid, rifampicin, pyrazinamide, and ethambutol ± streptomycin). Extensive Tuberculosis itself may be a risk factor for Tuberculosis DIH (5-7). Based on medical records, nearly one-third of the patients with hepatitis also show an Extensive Tuberculosis on chest X-ray. In such situation, close follow-up is required during treatment with periodical clinical controls and laboratory tests. It is recommended that patients with TB be evaluated for hepatotoxicity by medical history, physical examination, laboratory tests, and they should also be aware of hepatotoxicity and hepatitis symptoms such as loss of appetite, nausea, vomiting, icterus, and abdominal pain and precautions for use of alcohol and other hepatotoxic drugs (10-14). According to the World Health Organization (WHO) recommendations, if the diagnosis is drug-induced hepatitis, the anti-TB drugs should be stopped until the normalization of the liver function tests (1-3). In the present study treatment was re-initiated only after normalization of liver enzymes. In the clinical practice, in drug related hepatotoxicity a step-by-step treatment approach was re-started by exclusion of responsible drug/s from the treatment regimen. Although, higher recurrence rate of hepatotoxicity in the retreatment of TB with a full-dose regimen including pyrazinamide is higher than regimen without this drug (13, 14), the current study attempted to re-start all four drugs if possible; the purpose is mainly to observe Multiple Drug Resistance (MDR) and pre-extensively drug-resistant TB in this region (15).

Although the frequency of DIH in the current study was lower than those of other studies in this area, similar to other reports, most of the TB cases in which hepatotoxicity developed occurred in the subjects above 52 years old and a lot of them occurred after the first month of treatment. It should be considered that these cases require careful clinical and laboratory monitoring. Priorities for future studies include basic studies to define genetic risk factor, the mechanism of anti-TB drug-induced hepatotoxicity, and the development of safer TB drug regimens.

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Authors' Contributions

Study concept and design: Batool Sharifi Mood, Maliheh Metanat; acquisition of data: Mohammad Rakhshani; statistical analysis and interpretation of data: Masoud Salehi; drafting of the manuscript: Maliheh Metanat, saeideh Metanat; critical revision of the manuscript for important intellectual content: Batool Sharifi Mood.

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