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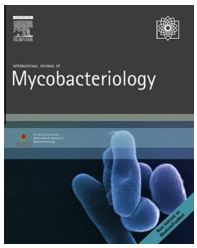

Incidence of antituberculosis-drug-induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: A cohort study

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ARTICLE INFO

Article history:
Received 2 October 2015
Accepted 11 October 2015
Available online 30 October 2015

Keywords:
Anti-TB-DIH
Ethiopia
Incidence
Liver function test
Risk factor

ABSTRACT

Background: Antituberculosis drugs cause hepatotoxicity in some individuals leading to acute liver failure, which results in death. Such phenomena limit the clinical use of drugs, contributing to treatment failure that possibly causes drug resistance. Furthermore, associated risk factors for the development of antituberculosis-drug-induced hepatotoxicity (anti-TB-DIH) are found to be controversial among different study findings.

Methods: A prospective cohort study was conducted from May 2014 to October 2014 in Dawro Zone, Tercha District Hospital Laboratory, South Ethiopia. One hundred and twenty-four new tuberculosis-positive individuals available from Tercha Hospital and five health centers during data collection were consecutively included. The sociodemographic data and anthropometric measurement were obtained. Then, 5 mL of venous blood was drawn from each individual, and the alanine transaminase, aspartate transaminase, and total bilirubin were measured photometrically at baseline, and then continuously monitored by measuring these liver enzymes every 2 weeks for 2 months. Data were analyzed with SPSS version 20 for Windows (SPSS Inc., Chicago, IL, USA).

Results: The incidence of anti-TB-DIH was found to be 8% (10 patients out of 124). Raised serum transaminase and bilirubin level, as well as signs and symptoms of hepatotoxicity (nausea, anorexia, vomiting, malaise, and jaundice), were observed in the cases. The onset of hepatotoxicity ranged from 13 days to 58 days (median, 26 days) after treatment was initiated. Of the various risk factors analyzed, only high alcohol intake was associated with the incidence of anti-TB-DIH (odds ratio = 9.3, 95% confidence interval 1.8–47, $p < .007$). Age, gender, extent of tuberculosis disease, and malnutrition were not significantly associated with anti-TB-DIH.

Conclusion: The incidence of anti-TB-DIH in Dawro Zone was high. The drug responsible for the hepatotoxicity was not known. However, chronic high alcohol intake was associated with the development of anti-TB-DIH.

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Peer review under responsibility of Asian African Society for Mycobacteriology.
http://dx.doi.org/10.1016/j.ijmyco.2015.10.002

Introduction

Tuberculosis (TB) continues to remain a significant infectious disease across much of the world. It poses a formidable socioeconomic burden on the individual and on the society. There were 8.6 million newer TB cases and an estimated 1.3 million deaths that occurred worldwide in 2012 [1]. New cases of TB-infected individuals are treated by a combination of four drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol [2]. However, a variety of adverse reactions of these drugs have been reported; one of the well-known toxic effects is hepatotoxicity [3]. Antituberculosis-drug-induced hepatotoxicity (anti-TB-DIH) may result from the direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and/or liver vasculature [4,5]. Most types of anti-TB-DIH is due to metabolic idiosyncrasy due to the metabolites released or accumulated during the metabolic process. These hypersensitivity or metabolic reactions occur largely independent of the dose [6].

Anti-TB-DIH is confirmed by an elevated level of aspartate transaminase (AST) or alanine transaminase (ALT) to five times the upper limit of normal (ULN), in the absence of jaundice or other symptoms, or up to three times the ULN in the presence of symptoms of hyperbilirubinemia (bilirubin 2 times the ULN) [7]. Although a vast majority of patients tolerate the drugs, some 3–25% develops anti-TB-DIH worldwide. Anti-TB-DIH accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant liver failure [8,9]. The spectrum of anti-TB-DIH is diverse, ranging from asymptomatic rise in transaminase (to fivefold) in 2.3–28% to acute liver failure in approximately <0.01% of the individuals [10].

There are factors that contribute to the development of anti-TB-DIH [2,3,7]. Some studies reported that the history of chronic alcohol intake is a predisposing factor for anti-TB-DIH [11,12]. Several studies reported that old age is a potential risk factor for anti-TB-DIH [3,7,13]. However, a study in Nepal revealed that the incidence of anti-TB-DIH was higher in younger patients [3]. Some studies suggested that female gender is an independent predictor of anti-TB-DIH [3,14]. However, a recent report suggested that males have a higher risk of developing anti-TB-DIH [15]. A study reported that there was no significant association between the extent of TB disease and the incidence of anti-TB-DIH [16]. However, extrapulmonary organ involvement was reported to be associated with the incidence of anti-TB-DIH in studies from India [17,18]. Some studies from Nepal [3], Spain [28], and India [11,18] showed that malnourishment had a significant association with the incidence of anti-TB-DIH.

The risk factors that contribute to the development of anti-TB-DIH are still obscure and controversial. Understanding anti-TB-DIH is restricted by the difference in study population, definition of hepatotoxicity, and monitoring practices. There was no study that determined the incidence of anti-TB-DIH and assessed the risk factors of anti-TB-DIH among TB patients in Dawro Zone. Therefore, this study was aimed to determine the incidence of anti-TB-DIH and identify the possible risk factors of anti-TB-DIH among TB patients in Dawro Zone, South Ethiopia.

Materials and methods

Study setting and study participants

A prospective cohort study was conducted from May 2014 to October 2014 in Southern Ethiopia. One hundred and twenty-four newly TB-infected individuals with negative hepatitis B surface antigen, anti-hepatitis C virus (HCV) antibodies, and human-immunodeficiency-virus test, and having complete recorded data were included in this study consecutively. Patients who had ALT and AST values greater than two times the ULN (i.e., ULN > 42 U/L and 37 U/L, respectively), and patients positive for hepatitis B surface antigen, anti-HCV antibodies, as well as retreatment case of TB were excluded from the study.

Data collection and laboratory testing

The sociodemographic and clinical data were collected using a structured questionnaire and checklist. Then, 5-mL venous blood samples were collected using test tubes that contain separator gels and allowed to clot for 30 min. After retracting the clot, the samples were centrifuged at 3000 g for 10 min. Pure serum samples were transferred to Nunc tubes, and screened for hepatitis B and C virus using rapid hepatitis B surface antigen and rapid anti-HCV test kits, respectively. The baseline measurements of ALT, AST, and total bilirubin were performed photometrically using Mindray BS-200E Chemistry Analyzer machine (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) before the initiation of anti-TB treatment. After the initiation of anti-TB treatment, the patients were examined both physically and biochemically every week for 2 months. The standard operating procedures and manufacturer instructions were strictly followed throughout the procedures, and all reagents were prepared according to the manufacturer's instruction. A quality-control run was undertaken for all laboratory tests in this study.

Statistical analysis

Data were coded, entered, and cleaned using statistical software (EpiData, version 3.1), and then exported to and analyzed with SPSS, version 20 for Windows (SPSS Inc., Chicago, IL, USA). The mean standard deviation (SD) and frequency of variables were calculated. The bivariate and multivariate logistic regression was calculated to evaluate the possible association of the variables, and $p < .05$ was considered as statistically significant.

Ethical consideration

The ethical clearance was obtained from the Jimma University Ethical Review Committee, and an official letter was written to Dawro Zone Health Bureau. For voluntary participation, the research participants signed an informed consent based