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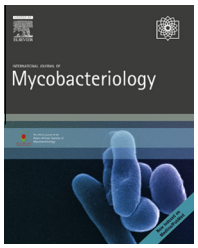

Antituberculosis drugs and hepatotoxicity among hospitalized patients in Jos, Nigeria

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ABSTRACT

Background: Tuberculosis (TB) could be fatal if left untreated, however, adverse effects of anti-TB medications (anti-TBs) themselves may limit treatment. We determined the incidence and clinical characteristics of hepatotoxicity in hospitalized patients receiving first-line anti-TB treatment.

Methods: A retrospective cohort study of patients aged ⩾18 years seen at the medical wards of the Jos University Teaching Hospital from January 2013 to June 2013 was carried out. Data were retrieved for 110 patients who were prescribed anti-TBs. Their demographic and clinical characteristics were described, and the incidence of symptomatic hepatotoxicity determined. The incidence of hepatotoxicity by strict American Thoracic Society criteria (symptomatic hepatotoxicity plus alanine transaminase in IU/L levels >3 × upper limit of normal) was also determined.

Results: Twenty patients developed symptomatic hepatotoxicity, giving an incidence of 18.2%. Furthermore, 18 (16.4%) patients had hepatotoxicity according to the American Thoracic Society criteria. Those with symptomatic hepatotoxicity unexpectedly had lower baseline alanine transaminase interquartile range (IQR) (35 [16–63] vs. 67 [4–226]; $p = .04$) and bilirubin (μmol/L): total IQR (15.3 [10.2–74.8] vs. 20.4 [20.4–20.4]; $p = .01$) and conjugated IQR (7.6 [5.1–34.8] vs. 10.2 [10.2–10.2]; $p = .004$). However, there were no significant differences in age, sex, body mass index, and duration of anti-TB treatment, human immunodeficiency virus infection status, antiretroviral therapy status, alcohol consumption, and the presence of hepatitis B surface antigen or hepatitis C virus antibody.

Conclusion: Hepatotoxicity due to first-line anti-TBs, whether based on clinical features alone or backed by liver chemistry, is common among hospitalized patients in our environment. Studies to determine the predictors of hepatotoxicity to guide clinical interventions aimed at the prevention or timely identification of cases are needed.

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Introduction

Tuberculosis (TB) is one of the most common infectious diseases and there were an estimated 9 million incident cases worldwide according to the global tuberculosis report of 2014 [1]. Since the scale-up of nationwide directly observed treatment (DOTS) in 2002 in Nigeria, a total of 640,113 of all forms of TB have been registered, with 90,447 notifications (400/100,000 population) in 2008 alone [2]. The first line regimen which requires administration of a combination of anti-TB medications (anti-TBs) for 6–9 months achieved a treatment success rate of about 84%, a death rate of 5%, and a defaulter rate of 8% in Nigeria [2]. The DOTS program, which has established or strengthened linkages with tertiary hospitals in recent years, is the major provider of TB treatment using the standard short course chemotherapy [2].

Adverse drug reactions to anti-TBs could lead to treatment interruptions with resultant poor outcomes, including the risk of drug resistance [3]. Hepatotoxicity is one of the most important adverse drug reactions associated with anti-TBs [4], and depending on the definition of hepatotoxicity, the incidence range is from 2% to 28% [5]. Although it may be challenging to predict when hepatotoxicity will occur, it is known that certain patient characteristics put them at higher risk. These include hepatic abnormalities, like chronic hepatitis B virus and hepatitis C virus (HCV), disseminated TB, Asian ethnicity, female sex, significant alcohol use, concurrent administration of other hepatotoxic medications, being elderly, and being malnourished [6–9]. Although human immunodeficiency virus (HIV)/AIDS is significantly associated with development of hepatotoxicity [10], the reason for this association is obscure. However, this may be as a result of excessive immune activation leading to less efficient handling of oxidative stress and detoxification of drug metabolites [11].

The advantage of regular monitoring of liver function test (LFT) in patients receiving anti-TBs, especially in countries where health budgets are meagre, has not been clearly established. However, the prevention or early detection of hepatotoxicity is important as morbidity and mortality can be substantial among those with symptomatic hepatotoxicity. Some guidelines only emphasize clinical monitoring while others additionally recommend routine biochemical monitoring at varying frequencies among the high risk groups [12,13]. Although there are attempts to improve the quality of patient care under DOTS, data on anti-TB hepatotoxicity in Nigeria, whether clinical or biochemical, are scarce. We describe the incidence and the clinical and laboratory characteristics of hospitalized patients receiving anti-TBs who developed hepatotoxicity at the Jos University Teaching Hospital (JUTH), Jos, Nigeria.

Materials and methods

This was a retrospective cohort study of new TB cases aged ⩾18 years seen at the infectious diseases wards of JUTH from January 2013 to June 2013 who were receiving first line anti-TBs. Data were retrieved from the case notes of all of the 110 patients seen in that period who met the inclusion criteria. Usually, all patients starting anti-TBs have baseline LFT done, however, it is only repeated in those who developed hepatotoxicity or if there are other indications. The data collected included: socio-demographic data (age, sex, and alcohol consumption), features of symptomatic hepatotoxicity (including fatigue, loss of appetite, nausea, vomiting, right hypochondrial pain/tenderness, fever, and jaundice), pulmonary or extrapulmonary TB, HIV status, combination antiretroviral therapy (cART) status, and body mass index (BMI; kg/m^2). Laboratory data included alanine transaminase (ALT; IU/L), aspartate transaminase (IU/L), total and conjugated bilirubin (μmol/L), total serum protein and albumin (g/L), hepatitis B surface antigen (HBsAg), and HCV antibody (anti-HCV).

Diagnosis of TB was based on Ziehl–Neelsen sputum smear microscopy, GeneXpert assay, or any combination of clinical and radiological/pathological evidence. Hepatotoxicity was defined as: (1) any combination of newly developing or worsening features of symptomatic hepatitis with a temporal relationship to anti-TB initiation without an apparent alternative explanation; (2) a stricter increase in serum ALT >3 times upper limit of normal (ULN) together with features of symptomatic hepatitis according to the American Thoracic Society (ATS) [13]. This is a part of the ATS definition which also considers ALT >5 times ULN in the absence of symptoms as hepatotoxicity. Our laboratory normal reference for both ALT and aspartate transaminase was <40 IU/L, and <17 μmol/L for total bilirubin. All admitted patients are routinely reviewed and the diagnosis of hepatotoxicity was made by at least a specialty registrar.

We also excluded those who were not prescribed a standard anti-TB regimen or who were already on anti-TBs before hospital admission. Standard anti-TB regimen is: isoniazid, rifampicin, ethambutol, and pyrazinamide with dosages decided according to the weight of the patient [2]. Ethical approval was obtained from the JUTH Ethics Committee.

Statistical analyses

Analyses were carried out using Stata software version 10.0 (Stata Corporation, College Station, TX, USA). The main outcome variable was hepatotoxicity (symptomatic hepatitis ± ALT >3 × ULN).

Baseline characteristics of the 110 patients were described and the characteristics of patients with symptomatic hepatitis were compared with those without. Continuous variables were presented as mean (standard deviation [SD]) or as median (interquartile range [IQR]) while the categorical variables were presented as proportions. Chi-square test or Fisher's exact test was used to determine the association between each categorical variable and the outcome. Comparisons between two means or between two medians were done using unpaired *t* test or Mann–Whitney test. A p value <.05 was considered significant for all tests.