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Original Article

Antitubercular therapy induced liver function tests abnormalities in human immunodeficiency virus infected individuals

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ABSTRACT

Background: Both antitubercular therapy (ATT) and antiretroviral therapy (ART) can cause drug induced liver injury (DILI) in tuberculosis (TB) and human immunodeficiency virus (HIV) coinfection. The aim of this research was to study ATT-induced liver function test (LFT) abnormalities in HIV-infected patients.

Methods: HIV-infected patients diagnosed with TB were evaluated with baseline LFT and CD4 counts. ATT regimen was modified if baseline LFT was significantly abnormal. Patients on protease inhibitors were given rifabutin instead of rifampicin. In patients on nevirapine-based ART, efavirenz was substituted for nevirapine. In ART-naive patients, the timing of introduction of ART was according to CD4 cell counts. LFT were repeated fortnightly or as clinically indicated for 10 weeks.

Results: We studied 100 patients with HIV ([M – 67, F – 23], mean age: 40.05 ± 10.75 years, mean CD4 cell count: 239.157 ± 228.49 cells/dL). Sixty-one patients were on ART prior to diagnosis of TB. Baseline LFT abnormalities ($n = 40$) were similar in ART and non-ART group (28/61 vs 12/39, $p = 0.13$). After starting ATT, derangement of LFT was observed in majority of patients (99/100). However, liver sparing ATT was required only in 15 patients. Bilirubin >2.5 mg/dL was seen only in 9 patients. Significant rise in transaminases was commoner in patients on concurrent ART and ATT ($p = 0.044$) and with baseline LFT abnormalities ($p = 0.00016$). There was no case of acute liver failure or mortality.

Conclusion: Mild LFT abnormalities are common in HIV-infected individuals on ATT. Concomitant use of ATT and ART and baseline LFT abnormalities increase the risk of significant DILI. However, with closer follow-up, serious liver injury can be prevented.

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Introduction

Mycobacterium tuberculosis (MTb) is the commonest opportunistic infection in human immunodeficiency virus (HIV) infected persons.[1] We have effective antiretroviral therapy (ART) for HIV infection which has brought a substantial decrease in deaths related to acquired immunodeficiency syndrome (AIDS),[2–4] but it has also increased the drug induced liver injury (DILI) related to ART.[5,6] The reported incidence of ART-related severe DILI is approximately 10%, and life-threatening events occur at a rate of 2.6 per 100 person-years.[7,8] We also have very effective antitubercular therapy (ATT) for MTb infection but again three out of four first-line anti-TB drugs (isoniazid [H], rifampicin [R] and pyrazinamide [Z]) are associated with hepatotoxicity. While concomitant administration of ATT increases the risk of ART related severe DILI[9]; HIV infection and concurrent ART are important predictors of ATT related liver dysfunction.[10,11] The other risk factors associated with ART/ATT related DILI are Hepatitis B/C co-infection, poor nutrition status, low albumin levels, low CD4 cell count, pre-existing chronic liver disease, abnormal liver function tests (LFTs) at baseline, age >35 years, female gender and significant alcohol consumption.[8–12]

This study was carried out with an aim to study the LFT abnormalities in ATT naive HIV positive patients who were started on ATT and to study the pattern of liver dysfunction in these patients.

Materials and methods

This observational study was carried out at an ART Centre of Pune, Maharashtra and was conducted from August 2015 to October 2016. Pregnant and lactating women were excluded. Written informed consent was taken from all patients. The study was approved by the institutional ethics committee. We studied 100 ATT naive adult HIV patients who were diagnosed to have MTb infection and were started on ATT during the study period.

Evaluation included clinical examination, history regarding alcohol consumption and medication including ART, co-trimoxazole and other potentially hepatotoxic drugs. The diagnosis of MTb infection was clinical, radiological and histopathological examination of specimen (when available). Excessive alcohol use was defined as more than 20 g ethanol per day for men and more than 10 g ethanol per day for women. Baseline investigations including complete blood count, CD4 cell count, Hepatitis B surface antigen (HBsAg), antibodies against Hepatitis C virus (anti-HCV antibodies), and LFTs were done in all patients. The LFTs included serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum alkaline phosphatase (SAP), serum albumin and globulin. Grading of LFT abnormalities was done as under.

Grades of transaminitis

- Grade 1: 1–2× upper limit of normal (ULN) (40–80 IU/L)
- Grade 2: >2–3.0× ULN (81–120 IU/L)
- Grade 3: >3–5.0× ULN (121–200 IU/L)
- Grade 4: >5× ULN (>200 IU/L)

Grades of hyperbilirubinemia

- Grade 1: 1–1.5 mg/dL
- Grade 2: 1.6–2.5 mg/dL
- Grade 3: 2.6–5 mg/dL
- Grade 4: >5 mg/dL

Significant LFT abnormalities was defined as AST/ALT > 3 times the ULN, i.e., >120 IU/L and/or serum bilirubin >2.5 mg/dL. For defining the pattern of liver injury in those with significant DILI, we used ratio of serum ALT to SAP levels as multiple of their ULN (R = [ALT/ULN]/[ALP/ULN]).[14]

Pattern of DILI

- R ≤ 2: cholestatic pattern of DILI
- R > 2 and <5: mixed pattern of DILI
- R ≥ 5: hepatocellular pattern of DILI

Introduction of ATT

Patients without significant baseline LFT abnormalities (except those on protease inhibitors) were started on standard ATT (isonazid [H], rifampicin [R], pyrazinamide [Z] and ethambutol [E]). The patients who were on protease inhibitors based therapy were prescribed rifabutin instead of rifampicin. Patients with significant baseline LFT abnormalities were given liver sparing ATT (streptomycin [S], ethambutol [E], levofloxacin [L]).

ART

Details of ART prior to starting ATT were noted. The ART experienced patients who were on nevirapine based ART, were shifted to efavirenz based therapy. ART naïve patients were started on tenofovir, lamivudine and efavirenz (TLE) as per 2015 World Health Organization (WHO) guidelines for treating HIV-tuberculosis (TB) co-infection. Those with CD4 cell count <50 cells/dL were concurrently started on ATT and ART at first visit; patients with CD4 cell count between 50 and 350 cells/dL were given ART after 2 weeks of ATT; and the patients with higher CD4 cell count (>350 cells/dL) were prescribed ART after 8 weeks of ATT.

Follow-up of patients and ATT modification

All patients were followed up fortnightly for 10 weeks. Patients who had significant LFT abnormalities at baseline or who developed significant LFT abnormalities during follow-up were monitored more frequently, i.e., every 3 days as per American Thoracic Society (ATS) guidelines.

ATT was modified to liver sparing ATT if patients became icteric, became symptomatic with AST/ALT > 3× ULN or if transaminases rose to >5× ULN in asymptomatic patients. The standard ATT was re-introduced sequentially as per the ATS guidelines[11] once the ALT was less than 2× ULN.

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