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Original Article

Novel risk factors and early detection of anti tubercular treatment induced liver injury—Looking beyond American Thoracic Society Guidelines

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ABSTRACT

Introduction: ATT remains the standard treatment for tuberculosis. Drug-induced liver injury (DILI) has been a long-standing concern in the treatment of tuberculosis (TB) infection.
Aims and objectives: To study the occurrence and risk factors of DILI in patients on ATT by regular clinical and biochemical monitoring.
Materials and methods: 200 patients, in whom ATT was started, were enrolled in the study. None of the patients with established risk factor for DILI as recognized by ATS guidelines was included in our study population. Regular clinical and liver function test monitoring was done at the commencement of ATT and then at 2, 4, and 8 weeks in the intensive phase subsequently at 4 and 6 months.
Results: DILI developed in 16 patients. Among those, 10 patients (62.5%) developed early DILI and 6 patients (37.5%) developed late DILI. Female gender and extrapulmonary tuberculosis were found to be associated with increased risk of ATT-induced DILI, whereas age, BMI, and serum albumin were not found to significantly increase DILI risk.
Conclusion: DILI is a common problem among patients on ATT in our population. Early detection not only reduces the risk of developing Hepatic Failure but also prevents mortality.

1. Introduction

Tuberculosis [TB] is a common, and in many cases lethal, infectious disease caused by various strains of mycobacterium, usually *Mycobacterium tuberculosis*. One-third of the world's population is thought to have been infected with *M. tuberculosis*.[1] In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people). It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB. India alone accounts for 26% of total cases in the world. Most cases continue to occur in the most productive age-group of 25–54 years.

Antituberculosis treatment (ATT) remains the standard treatment for tuberculosis. The most frequent adverse effects

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of ATT are hepatotoxicity, skin reactions, gastrointestinal, and neurological disorders. Drug-induced liver injury (DILI) has been a long-standing concern in the treatment of tuberculosis (TB) infection. The liver has a central role in drug metabolism and detoxification, and is consequently vulnerable to injury.[2] ATT-related hepatotoxicity ranges from hepatic adaptation to hepatocellular injury to acute hepatic failure.[2] Asymptomatic transaminase elevations are common during ATT, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time.[3–5] Another aspect of DILI is that it decreases treatment effectiveness, because it significantly contributes to noncompliance, ultimately contributing to treatment failure, relapse or the emergence of drug-resistance.

Understanding of ATT-related DILI has been hampered by differences in study populations, definitions of hepatotoxicity, monitoring, and reporting practices.[6–9] Literature reveals that rate of DILI during standard multidrug treatment range from 2.3% to 28% world over.[10] Indian studies reveal that rate of ATT-induced DILI is 11.5%.[11,12] No significant difference in the hepatotoxic effects between thrice weekly regimen and daily basis regimen has been found.[13] Isoniazid, rifampicin, and pyrazinamide carry hepatotoxic potential. Pyrazinamide appears to be the most likely to induce hepatotoxic effects.[14] No hepatotoxicity has been described for Ethambutol or Streptomycin.[15]

The most accepted and detailed document on ATT-induced DILI is provided by American Thoracic Society (ATS). ATS recognized risk factors that predispose patients to develop ATT-induced DILI include:

1. Chronic ethanol consumption
2. Viral hepatitis
3. Pre-existing liver disease
4. Pregnancy/3 months post-partum
5. Concomitant hepatotoxic medications
6. Baseline abnormal ALT/AST/Bilirubin
7. Concomitant HIV
8. Age >35 years.

In such situations, alanine aminotransferase (ALT) monitoring is recommended and treatment should be interrupted and, generally, a modified or alternative regimen used for those with ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms. The usual approach as suggested by ATS includes:

1. After ALT returns to less than two times the ULN, Rifampin may be restarted with or without Ethambutol.
2. After 3–7 days, isoniazid may be reintroduced, subsequently rechecking ALT.
3. If symptoms recur or ALT increases, the last drug added should be stopped.
4. For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampicin and isoniazid, rechallenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to 9 months, although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity.

However, these risk factors do not explain fully why only few patients develop ATT-induced liver injury. Hence, lot of research has been done to identify other unrecognized risk factors which may warrant more frequent liver function tests and close monitoring to detect liver injury at the earliest in order to reduce incidence of ATT-induced liver injury and allow completion of treatment in patients of tuberculosis. Besides, some low risk patients may have asymptomatic liver injury that may go unrecognized while following ATS guidelines and prove fatal if ATT is continued in such patients. Thus, early and more frequent monitoring may be required to detect ATT-induced liver injury. Since tuberculosis is endemic in developing countries like India and ATT-induced liver injury complicates treatment and promotes drug resistance, more studies should come from Indian Subcontinent to formulate guidelines regarding monitoring of patients on ATT. In this regard, we conducted a study in Department of Internal and Pulmonary Medicine of our hospital, Sheri Kashmir Institute of Medical Sciences, J & K India, one of the busiest tertiary care institutes of North India.

2. Aims and objectives

1. To determine possible risk factors associated with ATT-induced liver injury apart from ATS recognized risk factors.
2. To determine the frequency of LFTs to detect ATT-induced liver injury at the earliest.
3. To determine the relevance of early detection of ATT-induced liver injury.

3. Materials and methods

All inpatients and outpatients who met inclusion criteria were put on daily regimen of anti tubercular treatment and drugs were given based on their body weight (isoniazid 5 mg/kg; rifampicin 10 mg/kg; pyrazinamide 25 mg/kg; and ethambutol 15 mg/kg). All these patients underwent routine assessment with serum ALT levels at baseline then at 2, 4 and 8 weeks in the intensive phase and 2 monthly thereafter up to 6 months of ATT. Patients who were diagnosed as cases of DILI, treatment was stopped with close clinical and biochemical monitoring and weekly ALT levels were done and hepatitis viral serology was done to rule out infective cause. Treatment was resumed once there was clinical and biochemical resolution of DILI according to ATS guidelines. Cases with infective cause were excluded from the study. Informed consent was obtained from each participant.

Exclusion criteria included:

1. Multi-drug-resistant [MDR] tuberculosis.
2. Extensively drug-resistant [XDR] tuberculosis cases.
3. Patients with known ATS recognized risk factors.
4. Patients who develop hepatitis during anti tuberculosis treatment and are found to have serological evidence of infectious hepatitis.
5. Patients not compliant with biochemical monitoring as devised for this study.

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