Science Press

Journal homepage:
www.jcimjournal.com/jim
www.elsevier.com/locate/issn/20954964
Available also online at www.sciencedirect.com.

• Review

Clinical and experimental research in antituberculosis drug-induced hepatotoxicity: a review

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ABSTRACT

Drug-induced liver injury is the common adverse effect seen in patients receiving antituberculosis drugs (ATDs). There are several risk factors associated with the development of hepatotoxicity in such patients. Though there have been appreciable efforts taken by carrying out studies investigating the efficacy of several natural and synthetic compounds in minimising this effect, the only choice available for clinicians is withdrawal of drugs. This review would give a precise idea of ATD-induced hepatotoxicity, its underlying mechanisms and alternative therapies for the same.

Keywords: antitubercular agents; isoniazid; rifampicin; pyrazinamide; oxidative stress; complementary therapies

Citation: Baskaran UL, Sabina EP. Clinical and experimental research in antituberculosis drug-induced hepatotoxicity: a review. *J Integr Med*. 2017; 15(1): 27–36.

1 Introduction

Drug-induced liver injury (DILI) is the major concern in treating microbial infections. Several toxins, herbs and therapeutic drugs including timicrobials found to be hepatotoxic.[1–4] Most antimicrobial drugs associated with hepatotoxicity exhibit a wide range of severity and found to be idiosyncratic.[5,6] Tuberculosis (TB) is one of the major health threats in recent years in conjunction with the rising human immunodeficiency virus (HIV) epidemic.[7,8] High burden of TB infection in HIV-infected individuals and increased resistance of *Mycobacterium tuberculosis* to most commonly used antituberculosis drugs (ATDs) pose therapeutic challenge in the prevention, diagnosis and elimination of TB infection.[9,10] Commonly used ATDs include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol. Adverse side effects of these drugs vary and may range from mild to severe and are related to factors such as dosage, old age, nutritional status, HIV co-infection, alcoholism, impaired liver and/or liver function. INH-induced hepatotoxicity has been well studied in animal models and also human subjects.[11,12] RIF is an effective inducer of a number of drug-metabolising enzymes of the liver. Induction of drug-metabolising enzymes such as the cytochrome P450 (CYP450) superfamily of enzymes results in increased rate of metabolism of several drugs. Hence, concomitant administration of RIF with other drugs may lead to drug interactions and adverse side effects.[13,14]

2 Risk factors for ATD–induced hepatotoxicity

2.1 Demographic factors

The prevalence of risk factors in individuals receiving ATDs may vary in different regions of the world. Several major risk factors for ATD-induced hepatotoxicity have been reported so far.[15] Advanced age (>60 years old), malnutrition and female sex are the common risk

http://dx.doi.org/10.1016/S2095-4964(17)60319-4
Received June 30, 2016; **accepted** September 27, 2016.
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factors for ATD-induced hepatotoxicity.[16] The ability of an individual's liver to carry out the metabolism and clearance of xenobiotics decreases with advancing age.[17] Hence, they are more susceptible to ATD-induced hepatotoxicity. A study about the effect of age and gender on the activity of human hepatic cytochrome P3A (CYP3A) showed that CYP3A activity is slightly increased in females compared to males.[18] Therefore, female gender could also be a risk factor for ATD-induced hepatotoxicity. The influence of diet and nutritional status on drug metabolism has been well studied.[19,20] Dietary regulation of CYP450 in turn has the effect of bioactivation and metabolism of several drugs.[21,22]

2.2 HIV co-infection

It is well known that individuals with HIV infection may be immunocompromised or immunodeficient. TB is one of the major opportunistic infections seen in HIV-infected patients.[7] In addition, the prevalence of altered patterns of drug metabolism in such patients further explains their increased risk for ATD-induced hepatotoxicity. The concomitant use of highly active antiretroviral therapy and ATDs in HIV-infected individuals further increases the risk of hepatotoxicity.[9,23] Nevirapine, a commonly used non-nucleoside reverse transcriptase inhibitor has been found to be highly hepatotoxic.[24,25] This is a major interruption during the treatment of HIV and TB coinfection leading to withdrawal of drugs.[26]

2.3 Pre-existing liver disorders

Patients with pre-existing liver disease have an increased risk of developing ATD-induced hepatotoxicity. Alcoholism and liver cirrhosis are also risk factors for ATD-induced hepatotoxicity. Studies have shown that patients with alcoholic fatty liver due to chronic consumption of alcohol present with low levels of plasma and hepatic glutathione and hence such individuals possess an increased risk of developing drug-induced hepatotoxicity.[27] Furthermore, hepatitis B and C are opportunistic infections seen in HIV patients which add to the risk of developing ATD-induced hepatotoxicity.[28]

2.4 Genetic polymorphisms as risk factors

Polymorphisms in drug-metabolising enzymes are responsible for the variation in drug metabolism among individuals.[29] Genetic polymorphisms in these enzymes affect their activity thereby leading to accumulation of toxic metabolites. *N*-acetyltransferase 2 (*NAT2*) polymorphism acts as a susceptibility risk factor for ATD-induced hepatotoxicity.[30–32] Based on the polymorphisms in *NAT2* gene, the individuals on INH medication may be classified as rapid or slow acetylators. A study among Japanese patients with TB showed that *NAT2 6A,* a haplotype of the *NAT2* gene could be used as biomarker in predicting the risk of ATD-induced hepatotoxicity. CYP2E1 c1/c1 genotype may be a risk factor for ATD-induced hepatotoxicity, and the concomitant presence of the slow acetylator *NAT2* genotype may further increase this risk.[33] These two genotypic patterns serve as one of the important risk factors associated with INH-induced hepatotoxicity in Asian population. Polymorphisms in glutathione-S-tranferases (GSTs) observed in individuals lead to inter-individual variations in drug metabolism. A study evaluating the association and frequency of *CYP2E1*, *NAT2*, *GSTM1* and *GSTT1* polymorphisms in ATD-induced hepatotoxicity showed that frequency of *NAT2* slow acetylator profile was found to be higher than that of *GSTM1* and *GSTT1*.[34] A case-control study carried out in Indian population showed that *GSTM1* and *GSTT1* null genotypes were not associated with ATD-induced hepatotoxicity.[35]

Genetic polymorphisms are associated with RIF metabolism in several studies. A study in TB patients co-infected with HIV revealed that high frequency of *SLCO1B1* (rs4149032) gene polymorphism is associated with low concentrations of RIF.[36] Another study showed that *CES2* gene polymorphism is associated with variations in plasma RIF concentrations and also the metabolism of the drug.[37] Such polymorphisms are known to be associated with RIF resistance in tuberculosis patients.

A study on Korean patients treated with first-line ATDs showed that polymorphisms in *TNF-α* gene are associated with ATD-induced hepatitis. This study also showed that *TNF-α* polymorphism –308G/A may be a risk factor for ATD-induced hepatitis.[38]

2.5 Role of orphan nuclear receptors

Orphan nuclear receptors are a superfamily of nuclear receptors involved in the induction of several genes including CYP450 enzymes.[39] The major orphan nuclear receptors involved in xenobiotic metabolism are constitutive androstane receptor and (CAR) pregnane X receptor (PXR).[40,41] They belong to the subfamily nuclear receptor 1. PXR has been found to play a significant role in DILI as it is predominantly present in liver.[37] It regulates the expression of enzymes involved in hepatic drug clearance. Li et al.[42] showed that PXR modulates INH- and RIF-induced hepatotoxicity. RIF-mediated PXR activation has been found to enhance the progression of DILI.[43]

3 Mechanisms of liver injury in ATD–induced hepatotoxicity

3.1 INH

INH is a first-line drug used in TB treatment. It is a synthetic derivative of nicotinic acid and has a relative molecular mass of 137.14 g/mol. Though its mechanism of action is not yet clearly understood, it appears to