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Review Article

Recent progress in genetic variation and risk of antituberculosis drug-induced liver injury

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Abstract

Antituberculosis drug-induced liver injury (ATDILI) is the most prevalent hepatotoxicity in many countries. All of the three first-line antituberculosis drugs, isoniazid, rifampicin, and pyrazinamide, may induce hepatic damage, especially isoniazid. The major drug-metabolizing enzyme of isoniazid is *N*-acetyltransferase (NAT). Other possible enzymes are CYP2E1, glutathione *S*-transferase (GST) and manganese superoxide dismutase (MnSOD, SOD2). There is evidence that variations of the genes that encode these enzymes may influence the activity of the corresponding drug-metabolizing enzymes. Recent studies have demonstrated that these genetic variations may be associated with the risk of ATDILI. Among them, NAT acetylation status has been most studied. The proposed risk-associated genotypes are *NAT2* slow acetylator (without wild-type *NAT2*4* allele), *CYP2E1 *1A/*1A* (homozygous wild type), homozygous null *GSTM1* genotype and *MnSOD* mutant C allele. Although the available data in the field are complex and inconsistent, meta-analyses disclosed that *NAT2* slow acetylator status possesses the highest association (odds ratio = 3.18). There are associations of *CYP2E1 *1A/*1A* and homozygous null *GSTM1* genotype with ATDILI by meta-analyses, but the odds ratios were lower than that of *NAT2*. Of note, there was an ethnic difference in this association. The ATDILI in East Asians seems to have a higher correlation with genetic variations of *NAT2*, *CYP2E1* and *GSTM1*. However, the meta-analyses could not validate these associations in Caucasians, although some showed positive correlations. To mitigate the crucial ATDILI, this review article underlines the importance of this pharmacogenetic endeavor to identify high-risk patients.

Keywords: arylamine acetyltransferase; cytochrome P450 2E1; drug-induced liver injury; genetic variation; glutathione *S*-transferase; isoniazid; toxic hepatitis; tuberculosis

1. Introduction

Owing to the increasing prevalence of drug-resistant mycobacterium tuberculosis (TB) strains and patients with acquired immunodeficiency syndrome (AIDS), TB has been a growing public health burden and challenge. The three common first-line drugs for TB are isoniazid, rifampicin and pyrazinamide, which have the potential to induce liver damage.[1] This antituberculosis drug-induced liver injury (ATDILI) ranges from mild to severe forms, and can even be fatal. The incidence of ATDILI depends on different antituberculosis regimens, definitions of liver injury, and ethnic populations. Generally, 10–20% of patients may have elevation of serum aminotransferase during administration of these drugs. Approximately 1% of patients may develop overt hepatitis, defined as symptomatic hepatotoxicity with jaundice, and significant elevation of serum aminotransferase.[1] The mortality rate of patients with overt hepatitis is estimated to be around 10%. ATDILI is the most prevalent drug-induced hepatotoxicity in Taiwan, China, South Africa and many other areas, which may both threaten patients' health and

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hinder the treatment of TB.[2] Attempts to ameliorate this potentially grave drug-induced liver injury (DILI) are crucial.

2. Characteristics of antituberculosis drug-induced liver injury

Among the antituberculosis drugs, isoniazid is the drug which most frequently induces hepatotoxicity.[1] The latent period of ATDILI ranges from 1 week to 12 months, with the median being around 8 weeks.[1] The clinical course may be insidious, without significant symptoms or signs. However, some cases may have nonspecific manifestations, such as anorexia, nausea, vomiting, poor appetite, upper abdominal discomfort, yellowish discoloration of skin and tea-colored urine. Liver tests often revealed typical hepatocellular pattern, with elevated serum aminotransferase levels, but with normal or near-normal serum alkaline phosphatase. Pathology of the liver is characterized by zonal, submassive, or massive necrosis in the hepatic lobules. Recovery usually occurs if drugs are withdrawn before severe liver injury happens. Of note, liver function may resume to normal in some patients with mild liver injury, even though the anti-TB drugs are continuously administered. This is believed to be an "adaptation" of the liver to dispose of the drugs and metabolites more efficiently.[1] Metabolic intermediates of isoniazid are incriminated in induction of liver injury (Fig. 1).[2] The immunological reaction may play a small role in ATDILI.

Rifampicin may induce hepatocellular type liver damage as isoniazid.[1] However, it may also interfere with the uptake and excretion of bilirubin and cause isolated direct or indirect hyperbilirubinemia, without elevation of serum aminotransferase. In addition, rifampicin may augment the activities of amidase and CYP2E1, and enhance the hepatotoxicity of isoniazid (Fig. 1).[2]

Pyrazinamide is known as a dose-dependent hepatotoxin and causes hepatocellular injury like isoniazid.[1] However, little is known about the risk factors and genetic predisposition of pyrazinamide or rifampicin-induced liver injury, because most studies were undertaken with the combination therapy of anti-TB agents.

3. Risk factors of antituberculosis drug-induced liver injury

A better understanding of the risk factors and mechanisms of ATDILI may help us to prevent and mitigate this important adverse drug reaction. Elderly, female, African American, Asian, malnutrition, low body weight, alcoholism, pre-existing liver disease, chronic hepatitis B and C infections, AIDS, pregnancy, co-administration of hepatotoxic agents, abnormal baseline liver function and genetic factors have been reported to increase the risk of ATDILI.[1] Pharmacogenetic or pharmacogenomic approaches to the genetic variations of drug-metabolizing enzymes (DMEs) and immunological reaction have recently gained global attention.[2] Variations of the encoding genes may influence the activity of the corresponding DMEs, and then increase or decrease the susceptibility to ATDILI. Although there have been many reports from different ethnic populations in this field in the past decade, most were small in sample size, and with different definition of DILI.[2] Therefore, the results are intricate and complex, and should be interpreted with caution. Owing to many pharmacogenetic meta-analyses in recent years, we have the chance to re-evaluate the association of genetic factors and ATDILI more objectively.

4. Genetic variation and susceptibility to ATDILI

4.1. N-acetyltransferase

Isoniazid is first metabolized to acetylisoniazid via *N*-acetyltransferase (NAT), followed by hydrolysis to acetylhydrazine (Fig. 1).[3] Acetylhydrazine can be oxidized to many hepatotoxic intermediates by cytochrome P450 2E1 (CYP2E1)[4] or acetylated to nontoxic diacetylhydrazine. Another metabolic pathway to generate toxic metabolites is

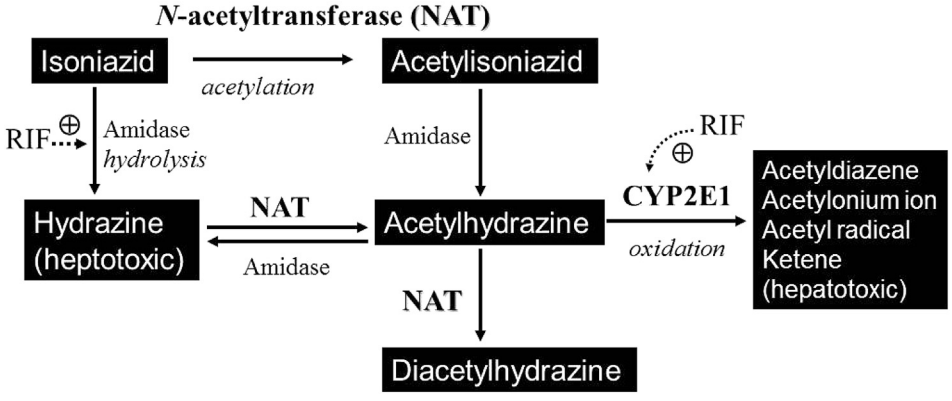

Fig. 1. The metabolic pathway of isoniazid. Isoniazid is first metabolized to acetylisoniazid via *N*-acetyltransferase (NAT), followed by hydrolysis to acetylhydrazine by amidase. Acetylhydrazine can be oxidized to many hepatotoxic intermediates by CYP2E1, or acetylated to nontoxic diacetylhydrazine. Another metabolic pathway to generate toxic metabolites is the direct hydrolysis of isoniazid to toxic hydrazine via amidase. Rifampicin may augment the activities of amidase and CYP2E1, and enhance the hepatotoxicity of isoniazid. CYP = cytochrome; NAT = *N*-acetyltransferase; RIF = rifampicin.