

**Comprehensive review of anti-tubercular treatment induced liver injury****Nandhini Mohan<sup>1</sup>, Jitendra Kumar<sup>2</sup>, Avinash Chakrawarty<sup>3</sup>, Piyush Ranjan<sup>1\*</sup>**<sup>1</sup>Department of Medicine,  
All India Institute of Medical  
Sciences, New Delhi, India,<sup>2</sup>Department of Pediatrics,  
All India Institute of Medical  
Sciences, New Delhi, India,<sup>3</sup>Department of Geriatric  
Medicine, All India Institute of  
Medical Sciences, New Delhi,  
India**Received:** 17 March 2015**Revised:** 19 March 2015**Accepted:** 24 April 2015**\*Correspondence to:**Dr. Piyush Ranjan,  
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commercial use, distribution,  
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medium, provided the original  
work is properly cited.**ABSTRACT**

The challenge in the management of tuberculosis is further compounded by the liver injury associated with anti-tubercular treatment (ATT) drugs. The problem of drug-induced liver injury (DILI) associated with ATT drugs is significant in the developing countries because of high disease burden, limited monitoring due to scarce resources and lack of awareness. There is heterogeneity in the pharmacokinetics and pharmacodynamics of the various first line ATT drugs. There are various genetic and environmental factors that affect DILI. Various guidelines have been proposed to treat and monitor DILI. This article reviews the problem, risk factors, mechanism, and management strategies of the DILI associated with ATT.

**Keywords:** Drug-induced liver injury, Anti-tubercular treatment, Anti-tubercular treatment induced hepatotoxicity**INTRODUCTION**

Tuberculosis (TB) is a prominent health problem in many developing countries including Indian subcontinent. The challenge in the treatment of TB lies in the necessity of long duration of the treatment, multiple drug administration, and toxicities related to them. One of the important complications, associated with anti-tubercular treatment (ATT) is drug-induced liver injury (DILI). This article strives to provide a comprehensive review of diagnosis and probable management strategies for efficient management of this global problem of ATT-induced DILI.

**DILI IN ATT THE PROBLEM STATEMENT**

DILI is not an uncommon accompaniment of ATT. Its significance is more so in the Indian subcontinent where TB is a major epidemiological problem. South-East Asian region reports the largest number of new cases and deaths from TB.<sup>1</sup> India contributes more than 20% of the world's TB burden with 3.4 million cases.<sup>2</sup> In addition to the agent factor, the morbidity and mortality in TB increases further as a result of ATT-induced hepatotoxicity. In India, 11 out of 12 deaths due to DILI is as a result of ATT therapy.<sup>3</sup> About 10-25% people develop abnormalities in liver

function tests (LFTs) and 3% develop hepatitis as a result of ATT.<sup>4</sup>

## MECHANISM OF INJURY

DILI can be broadly classified into the idiosyncratic type of liver injury or due to dose dependent hepatocyte damage. Dose dependent hepatotoxicity, as the name explains, is the type in which increase in dose results in increased hepatocellular damage. It is the idiosyncratic mechanism of hepatotoxicity, which is difficult to predict and can occur independent of the drug dose used and differs among different individuals. Different classes of drugs are consistent in the pattern of injury produced.<sup>5</sup>

The idiosyncratic pattern of liver damage has a variable period of development of hepatotoxicity. It can range from 1-week to 1-year or even more.<sup>6</sup> A drug or foreign metabolite that undergoes detoxification in the body via cytochrome p450 passes through three phases namely, transformation (Phase 1), conjugation (Phase 2), and transport into bile canaliculus (Phase 3). The drug can cause hepatotoxicity due to abnormalities in any one of these phases. The covalent binding of the toxic compound or its metabolite with host proteins and the resultant oxidative stress is one of the main mechanism in causing liver injury.<sup>7</sup> Such stressors cause disturbance in intracellular calcium homeostasis resulting in reduction of cellular adenosine triphosphate (ATP) resulting in activation of apoptotic pathways and cell death. Bile canicular damage can result due to disruption of canicular membrane or interference or damage to the canicular multidrug resistance protein (involved in drug transport across the canicular membrane). Canicular damage results in cholestasis. Mitochondrial mechanisms of liver injury are gaining more significance in DILI pathogenesis.<sup>5</sup> The major mechanism is a disruption of electron transport chains as a result of free radical generation, the release of caspases and apoptotic cell death. This can occur as a result of any one of the following steps - the drug in itself or its toxic metabolite disrupting mitochondrial membrane or inhibiting its function, inhibition of beta-oxidation of fatty acids, disruption of electron transport chain or destruction of mitochondrial DNA. All these processes result in a decrease in cellular ATP thereby resulting in cell death. New drug molecules should be screened for possible mitochondrial effects.<sup>8</sup> Allergic mechanism of cell damage results due to drug-protein adduct formation and its presentation on the cell surface. It can also cause an increase in fat accumulation. Hence, idiosyncratic mechanism of liver damage can occur as direct hepatocellular damage, cholestatic pattern of liver injury, steatosis/steatohepatitis, granulomatous hepatitis, autoimmune hepatitis, fibrosis, oncogenesis, immunoallergic and vascular collapse.<sup>5</sup>

## HEPATIC ADAPTATION

Hepatic adaptation requires special mention in DILI. Hepatic adaptation means there is a transient rise in serum aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) levels which resolve on its own even when the drug is continued in the same dosage. Transient rise in an asymptomatic patient of serum AST and ALT levels without bilirubin elevation may not indicate significant injury of the liver. Isoniazid, tacrine, troglitazone, the statins, ximelagatran, and heparin are the common drugs that cause hepatic adaptation. Hepatic adaptation due to isoniazid has been described in a study where patients even showed transient elevations of AST more than thrice upper limit of normal but resolved subsequently with no manifestations of liver injury.<sup>9,10</sup>

## ANTI TUBERCULAR DRUGS AND HEPATOTOXICITY

The major drugs referred to as the first line regimen in treating TB include isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin. Of these, isoniazid, rifampicin, and pyrazinamide are considered to be the major hepatotoxins.

Depending on the time elapsed between drug introduction and development of DILI, it is said that DILI occurring earlier (within 15 days of start of treatment) is due to rifampicin, the prognosis of which is excellent. Whereas delayed DILI occurring 1-month later is due to pyrazinamide with bad prognosis.<sup>11</sup>

### *Isoniazid*

Isoniazid causes hepatotoxicity by an idiosyncratic mechanism resulting in a hepatocellular type of injury. Intermediate metabolite acetyl-hydrazine is implicated in the development of DILI. Further proof that a metabolite of isoniazid is responsible for hepatotoxicity arises from the indirect evidence that concomitant use of both increases the hepatotoxicity of former. This is due to the fact that rifampicin induces the metabolism of isoniazid.<sup>12</sup> A study showed development of hepatotoxicity in 0.6% patients with Isoniazid alone and 2.7% with combined therapy including rifampicin.<sup>13</sup>

### *Rifampicin*

Rifampicin rarely causes serious liver damage. It leads to increase in serum conjugated bilirubin levels due to interference in the transport process.<sup>14</sup> Importance of this drug in DILI lies in the fact that it is used in combination with isoniazid where rifampicin induces the metabolism of isoniazid thereby resulting in increased toxicity.

### *Pyrazinamide*

Pyrazinamide is most hepatotoxic first line drug. In a large study, a regimen containing pyrazinamide found to have

least number of relapses.<sup>15</sup> It causes both dose-dependent and idiosyncratic hepatitis. Mechanism of injury is by induction of free radicals.<sup>16</sup> About 8% people treated with pyrazinamide develop hepatitis. However, the recent regimens, which prescribe lower doses of pyrazinamide has reduced the incidence of pyrazinamide induced hepatotoxicity.<sup>1</sup>

### **Fluoroquinolones**

The majority of the fluoroquinolones is metabolized by the liver. Hence, some amount of hepatotoxicity is an expected side effect. The importance lies in the fact that fluoroquinolones are the drugs used to tide over crisis while awaiting resolution of elevated liver enzymes as a result of ATT-induced hepatotoxicity. Fluoroquinolones can cause hepatotoxic, cholestatic, and mixed liver injury patterns in equal proportions.<sup>17</sup> A population-based study in the older population aged 65 years and more revealed that moxifloxacin and levofloxacin caused an increase in liver failure risk in comparison with clarithromycin.<sup>18</sup> The same study revealed that ciprofloxacin showed no such increase in liver failure risks.

## **RISK FACTORS**

Many phenotypical and genotypical risk factors have been identified. These risk factors prove to be useful to predict the occurrence of DILI thereby requiring more close monitoring for the occurrence of DILI in these select individuals.

### **Age**

Advanced age has routinely been noticed to be associated with increased risk of DILI in various studies so far.<sup>19,20</sup> A case-control study showed increased incidence of DILI in the age group of 35-65 as opposed to the younger population.<sup>21</sup> Furthermore, the difference in the pattern of liver injury based on age has also been revealed in a retrospective analysis of various DILI registries. Hepatitis is the major form of liver injury in youngsters, whereas old age population are more affected by cholestatic pattern of liver injury.<sup>20</sup>

### **Sex**

Many studies have implicated female sex to be at increased risk for DILI as also shown from data analysis of various international registries for DILI.<sup>20,22</sup> Some studies have found evidence against increased incidence of DILI in female gender.<sup>21</sup>

### **Malnutrition**

Nutritional status is one of the areas of concern in South-East Asian regions. Malnutrition also contributes to increased incidence of DILI. Measures of malnutrition

such as skinfold thickness, body mass index, and mid-arm circumference did not significantly predict DILI. Malnutrition measured in terms of hypoalbuminemia (serum albumin levels <3.5 g/dl) predicted two-fold higher incidence of DILI.<sup>21</sup>

### **TB site and stage**

It has been noted that extrapulmonary TB, most commonly abdominal TB, also caused increased risk of DILI. This finding can probably be because of subclinical liver involvement in abdominal TB patients.<sup>21</sup> Severity of TB also was an independent predictor of DILI. Higher the severity of TB infection, higher the incidence of DILI.<sup>23</sup>

### **Associated conditions**

The occurrence of DILI during TB therapy is further confounded by the presence of chronic hepatitis B and C co-infection. Patients with hepatitis B and C co-infection had higher baseline transaminase levels than those not infected.<sup>24</sup> Hepatitis B seropositivity in a study, was not found to be associated with increased incidence of ATT-induced hepatotoxicity though when patients developed DILI the transaminase elevation were higher and duration of illness longer.<sup>25</sup> The same study showed that the presence of Hepatitis C increased chances of hepatotoxicity in patients receiving ATT. HIV co-infection also increased the risk of ATT-induced hepatotoxicity four-fold. When both Hepatitis C and HIV-infected individuals received ATT the risk of hepatotoxicity was 14.4 fold.<sup>26</sup> These results prove the necessity of screening individuals for hepatitis B and C and HIV co-infection in TB patients thereby selecting individuals requiring close monitoring and frequent follow-up. This co-infection also poses confusion in the diagnosis of DILI. Differentiation between reactivation of hepatitis viruses and ATT-induced hepatotoxicity as the cause of elevation in transaminase levels is still undefined. The concentration of toxic metabolic intermediates is increased by the fact that ethanol is also an enzyme inducer.<sup>5,27,28</sup>

### **Genetic factors**

Multiple factors from enzymes to human leukocyte antigens (HLA) have been studied, and some have shown significant association in the development of hepatotoxicity. The study based on genotyping of N-acetyl transferase 2 (NAT2) showed that slow acetylators had increased the risk of hepatotoxicity than rapid acetylators. Furthermore, slow acetylators had more severe hepatotoxicity in comparison with rapid acetylators. This basis can be explained by the fact that slow acetylators also convert the toxic intermediate monoacetyl hydrazine to diacetyl hydrazine slowly.<sup>29</sup> Similarly, mutations and different allelic expression of other enzymes involved in drug metabolism have also shown association with hepatotoxicity.

Studies have also shown increased risk of hepatotoxicity in individuals carrying manganese superoxide dismutase mutant c allele and glutathione-S transferase M1 null genotype.<sup>30</sup> Many diseases have established a relation to specific HLA alleles. Risk of DILI has been found to be increased fourfold in DQA1\*0102 and two-fold in individuals carrying DQB1\*0201.<sup>23</sup>

It also has been noted that ATT-induced hepatotoxicity is more common in the Asian population in comparison with the west.<sup>30</sup> This difference probably has its basis in the following factors. (1) TB being an endemic problem higher chances of old age people getting affected, (2) undernutrition being more prevalent in the South-East Asian regions than the west, (3) Specific genotypes such as NAT2\*6/\*6 and NAT2\*6/\*7 that causes slow acetylation and pose increased risk of hepatotoxicity being more frequently present in Asian population.

## DIAGNOSIS

Diagnosis of DILI is basically a diagnosis of exclusion. Clinical presentation ranges from asymptomatic elevation of serum transaminases to acute liver failure.<sup>5</sup> As there are no specific symptoms, signs, laboratory markers to implicate drugs as a cause of liver injury,<sup>31</sup> exclusion of common hepatotoxins like acute viral hepatitis and expert opinion is often required to establish the diagnosis. Many diagnostic criteria have come into play for helping in the diagnosis of DILI, though many fail to have adequate reliability for its widespread use. The following criteria is most widely used to define patients with hepatotoxicity due to anti-tubercular drugs.<sup>32</sup>

After exclusion of viral hepatitis by serological testing and patients with no known prior chronic liver disease having either one of the following criteria can be taken to be having DILI.

1. Asymptomatic serum transaminase elevation to more than 5 times upper limit of normal
2. Serum bilirubin level >1.5 g/dl
3. Serum transaminase elevation in association with symptoms such as anorexia, nausea, vomiting, abdominal discomfort and increased fatigability.

Nonetheless careful evaluation and expert opinion in patients presenting with elevated transaminases during ATT treatment is the backbone of diagnosis.

## MANAGEMENT OF ATT-INDUCED DILI

### General measures

Stoppage of all hepatotoxic first line drugs is recommended at the first sign of symptomatic hepatitis. For mild cases, mere withdrawal of hepatotoxic drugs resulted in clinical and biochemical improvement in terms of normalization of elevated transaminase levels.

Severe cases presenting with acute liver failure should be managed with N-acetyl cysteine (NAC). Beneficial effect of NAC has been proved in various non-acetaminophen induced liver injury. The US acute liver failure group studied survival benefit of NAC as a continuous infusion for 72 hrs in acute liver failure.<sup>33</sup> The study group also included patients with DILI. This study revealed that transplant free survival in DILI was 58% for NAC in comparison with placebo. The transplant free survival benefit was present in patients with Grade I-II hepatic encephalopathy (52% in NAC and 30% in placebo) but not in Grade III-IV patients. As NAC is non-toxic, usage of NAC is justified.

Preventive effect of NAC in the development of DILI, when used in combination with anti-TB drugs, was established in another study.<sup>34</sup> This study randomized patients into two treatment arms - one with standard first-line regimen without NAC (32 patients) and the second arm contained patients treated with standard first line and NAC (28 patients). There were 12 cases of hepatotoxicity in group one and none in group two. Hence, the use of NAC significantly prevented ATT-induced hepatotoxicity.

### Liver transplantation in ATT-induced DILI

Liver transplantation is a tricky decision in the management of ATT-induced hepatotoxicity. Liver transplantation has gained significance as the only life-saving measure in patients with severe acute liver failure. Standard first-line anti-TB therapy has been shown to be more hepatotoxic in patients post liver transplantation.<sup>35</sup> Re-introduction of first line hepatotoxic drugs has many moral implications. Rapid dissemination of TB post-transplant is also a concern.<sup>36</sup> Efficacy of treatment with second line less effective agents for TB receiving immunosuppressive treatment post-transplantation requires further study. The duration of treatment required for TB with second-line non-hepatotoxic drugs post-transplant is also unknown. Idilman et al. reported a case of liver transplantation in a patient with ATT-induced hepatotoxicity and subsequent treatment with second line anti-TB agents.<sup>15</sup> Spanish doctors reported a case of successful treatment of a patient who developed fulminant hepatic failure as a result of ATT started for vertebral TB with liver transplantation and post-transplant treatment with ciprofloxacin, ethambutol, and streptomycin. Such case reports provide an avenue for further research into liver transplantation as a viable treatment option.<sup>37</sup>

The importance in managing patients of ATT-induced hepatotoxicity lies in the fact that only these hepatotoxic first line drugs have maximum efficacy in the treatment of TB. Mere stoppage of drugs and thereby helping in the resolution of hepatotoxicity does not provide a solution to the bigger picture of treating the disease. Management of such patients includes reintroduction of these drugs and careful monitoring for recurrence of hepatitis. The period until reintroduction (till AST/ALT values returns to twice of



ULN) can be covered with streptomycin, ethambutol, and fluoroquinolone.<sup>15</sup> Reintroduction of these drugs do not result in recurrent hepatotoxicity in most of the cases.<sup>19</sup>

### **Guidelines for reintroduction of the drugs**

There are various published guidelines for the reintroduction of ATT drugs. Most commonly used are the following.

#### **American Thoracic Society<sup>19</sup>**

Full dose of rifampicin followed 1-week later by isoniazid followed 1-week later by pyrazinamide (provided next to each drug introduction ALT levels were within normal range. If rising stop last introduced drug).

#### **British Thoracic Society<sup>37</sup>**

They recommend reintroduction of all drugs at the same time but to be started with smaller doses until full therapeutic dosing is achieved. Isoniazid, rifampicin, and pyrazinamide are started at doses of 100 mg/day, 150 mg/day, and 500 mg/day, respectively to full therapeutic dosing on day 4.

#### **Sharma et al. from India**

Full doses of all drugs at once after LFT values have become normal. A study done at All India Institute of Medical Sciences in India, showed that there was no significant difference in recurrence of hepatotoxicity.<sup>38</sup> Thus, in sick patients all three drugs can be reintroduced at the same time, thereby reducing morbidity and mortality.

### **Management in case of recurrence of hepatotoxicity**

If there is a recurrence in hepatotoxicity subsequent to the use of a first-line drug, then that particular drug responsible is stopped, and therapy should be continued with the use of second-line agents in its place. Various regimens have been described without the use of one or two first-line agents.

### **Management in special situations**

Special situations like patients with chronic underlying liver disease deserve special mention. Subsequently management of TB in chronic hepatitis patients with the use of anti-TB therapy as highlighted earlier results in increased risk of hepatotoxicity. A Japanese study showed that such patients with chronic hepatitis had increased the incidence of hepatotoxicity when regimens including pyrazinamide (isoniazid + rifampicin + pyrazinamide) were used as compared to regimens involving isoniazid and rifampicin alone. Besides, the study showed the importance of avoiding alcohol in chronic hepatitis patients, especially use of alcohol >20 g.<sup>39</sup> This study

concluded that isoniazid and rifampicin can be used safely in patients with chronic hepatitis. When pyrazinamide is included increased vigilance for the development of hepatotoxicity is required. Another retrospective analysis from India also confirmed the above finding that anti-TB therapy can be used safely in patients co-infected with hepatitis B, C, and HIV.<sup>40</sup>

### **Monitoring**

It is recommended that baseline LFT values are obtained prior to starting ATT therapy, and they are monitored every 2 weeks for the first 2 months and monthly until regimen is over. Given the limited resources in Indian subcontinent, such monitoring can be restricted to high-risk groups such as alcoholics, Hepatitis B carrier, Hepatitis C infected, HIV-infected, pregnant females, and at extremes of age (<5 and >65).

### **CONCLUSION**

TB and DILI have gained such significance in view of the multiple co-infections. Efficient management calls for greater knowledge and widespread awareness and rapid identification of the problem with a proper referral. Though much has been said and done, there are multiple areas, which require further insight. Liver transplantation and post-transplant treatment options require further study. Efficient management strategies with second line agents or newer non-hepatotoxic first line congeners will help the problem in a long way. As physicians, rapid identification of DILI in itself goes a long way in preventing morbidity and mortality.

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