Anti-tuberculosis Drug Induced Hepatotoxicity

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***Abstract*—Mycobacterium tuberculosis causes tuberculosis, a progressive granulomatous disease. A 6-month regimen of isoniazid, rifampicin, and pyrazinamide is the cornerstone of tuberculosis treatment. Compliance is crucial in tuberculosis treatment. Antituberculosis drugs can produce hepatotoxicity, a severe adverse reaction that can result in considerable morbidity and, in rare cases, death. This type of toxicity may alter how certain tuberculosis patients respond to treatment. Adverse effects frequently have a negative impact on compliance because they frequently need a change in treatment, which can have a poor impact on treatment result. In this study, we cover the metabolism and mechanisms of toxicity of isoniazid, rifampicin, and pyrazinamide, as well as risk factors and management of antituberculosis drug-induced hepatotoxicity. Hepatotoxicity is one of the furthermost serious adverse effects of anti-tuberculosis drugs (ATD). Although many risk factors have been associated with ATD-induced hepatotoxicity, their effect on hepatitis severity has not been studied systematically.**

***Index Terms*—anti-tuberculosis; hepatotoxicity; drug induced liver injury (DILI).**

I. INTRODUCTION:

Despite the fact that very effective treatment has been available for decades, tuberculosis (TB) is still a significant worldwide health issue. When TB was predicted to have 7-8 million new cases and 1.3-1.6 million deaths annually in 1993, the World Health Organization (WHO) deemed the disease a global public health emergency. In India, TB is a major public health matter with an estimated occurrence of 256 per 100,000 population and 26 per 100,000 population dying of TB [1]. Although roughly 85% of TB cases are effectively treated, significant morbidity is caused by adverse treatment-related events, such as hepatotoxicity, skin responses, gastrointestinal, and neurological diseases, which reduces the efficiency of therapy. The most frequent side effect resulting in treatment cessation in 11% of patients receiving isoniazid, rifampicin, and pyrazinamide is hepatotoxicity [2].

One of the most prevalent causes of idiosyncratic hepatotoxicity worldwide is anti-TB medication [3][5]. Depending on the features of the specific cohort, the treatment regimens utilized, the threshold used to express hepatotoxicity, monitoring and reporting procedures, and more, the occurrence of anti-TB medication-induced hepatotoxicity varies greatly. Between 5% and 28% of those on anti-TB medications have reported experiencing hepatotoxicity as a result of their treatment [5].

However, determining how many of these fit into a more present international consensus case definition of drug-induced liver injury is problematic [5]. To define hepatotoxicity, the majority of reports employed an increased alanine or aspartate transaminase of 3 time's upper limit of normal range with symptoms (abdominal pain, nausea, vomiting, unexplained lethargy or jaundice) attributed to liver injury or 5 times ULN of ALT or AST without symptoms [6].

II. Risk factors related with hepatotoxicity:

Drug Associated Factors:

Due to the fact that most patients receive a combination of medications over the duration of their anti-TB therapy, it is challenging to determine the frequency of hepatotoxicity brought on by specific medications. While isoniazid, rifampicin, and pyrazinamide have been associated to hepatotoxicity, ethambutol and streptomycin are not. Isoniazid (INH) with rifampicin hepatotoxicity information [7]. And pyrazinamide [8][9] are based on findings reported during latent TB monotherapy or when these treatments were combined with other, seemingly non-hepatotoxic drugs. Rifampicin-induced DILI has been well-documented when used to treat pruritus in patients with primary biliary cirrhosis [10]. This may be an overestimate, and the heightened risk may be brought on by the liver illness that is underlying. In other studies, there was little risk of DILI caused by rifampicin when it was used alone as prophylaxis for the treatment of latent TB [11][12].

The most common drug associated with toxicity is INH. Four large population-based observational studies found that the incidence of isoniazid hepatotoxicity ranged from 0.1% to 0.56% when administered as monotherapy (in the treatment of latent infection) [13][14][15][16]. According to an assessment based on data from the U.S. Food and Drug Administration (FDA), preventive medication based on INH causes 23.2 per 100,000 deaths.(17In a meta-analysis, isoniazid was more likely to be linked to hepatotoxicity even in the absence of rifampicin (odds ratio (OR) 1.6), but the combination of these two drugs was linked to a higher risk of hepatotoxicity (OR 2.6) when compared to each drug alone [18]. Daily dosage regimens have not been linked to a higher risk of hepatotoxicity than three-times-week regimens [19].

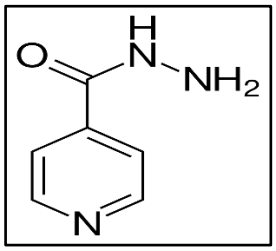
Drug Biotransformation, Detoxification and Elimination:

The formation of reactive metabolites has been linked to a variety of clinical toxicities, including a majority of those categorized as 'idiosyncratic' DILI. Electrophiles are the most common reactive metabolites. When they avoid detoxification, they react with

nucleophilic groups on cellular proteins like lysine and cysteine. Cellular proteins that have been covalently changed can either be fixed or destroyed. If these mechanisms fail, drug-metabolite adduct formation affects critical cellular function, resulting in target organ damage. Potential immune-mediated harm can arise from the synthesis of reactive metabolites followed by covalent protein binding.

High levels or increased activity of the enzymes involved in the biotransformation of a drug into a reactive metabolite, which are commonly phase I cytochrome P450 enzymes involved in oxidation, reduction, or hydrolysis, may be the cause of high levels of reactive metabolite formation in an individual. The detoxification of reactive metabolites, which is usually carried out by phase II enzymes through the processes of glucuronidation, sulfation, acetylation, or glutathione conjugation, may also be impaired in some individuals. Transporter molecules or proteins that support the excretion of water-soluble substances into bile or systemic circulation mediate phase III of drug disposition. The majority of first-line anti-TB medications are lipophilic, and their biotransformation involves being changed into molecules that are water soluble and then being eliminated. Instead of being a direct result of the parent medication, hepatotoxicity seems to be caused by the accumulation and production of reactive metabolites [20][21].

Isoniazid



Structure No 1 : Isoniazid

The liver is the primary organ for INH metabolism and elimination. The risk of hepatotoxicity is governed by two essential enzymes in the metabolic pathway: cytochrome P4502E1 (CYP2E1), a microsomal enzyme, and acetyltransferase 2 (NAT2). Isoniazid is converted to acetyl isoniazid, which is then hydrolyzed to produce acetyl hydrazine, as shown in Figure 1. This process is carried out by NAT2. The latter may undergo oxidation by CYP2E1 to produce N-hydroxy-acetyl hydrazine, which subsequently dehydrates to produce acetyl diazine. Acetyl diazine may be a hazardous metabolite in and of itself or may decompose into reactive acetyl radicals, acetyl ions, and ketene, which may bind covalently with hepatic macromolecules and cause damage to the liver.

Additionally, acetyl hydrazine is further acetylated by the enzyme NAT2 to provide the non-toxic compound diacetyl hydrazine. Therefore, delayed acetylation causes monoacetyl hydrazine as well as the parent molecule to accumulate. INH itself inhibits acetylation of acetyl hydrazine even more. In addition, hydrazine is produced via the direct hydrolysis of INH without acetylation, which may harm the liver [23]. Slow acetylators have a ten-fold enhanced rate of INH metabolism through this little route, particularly when combined with rifampicin [22].

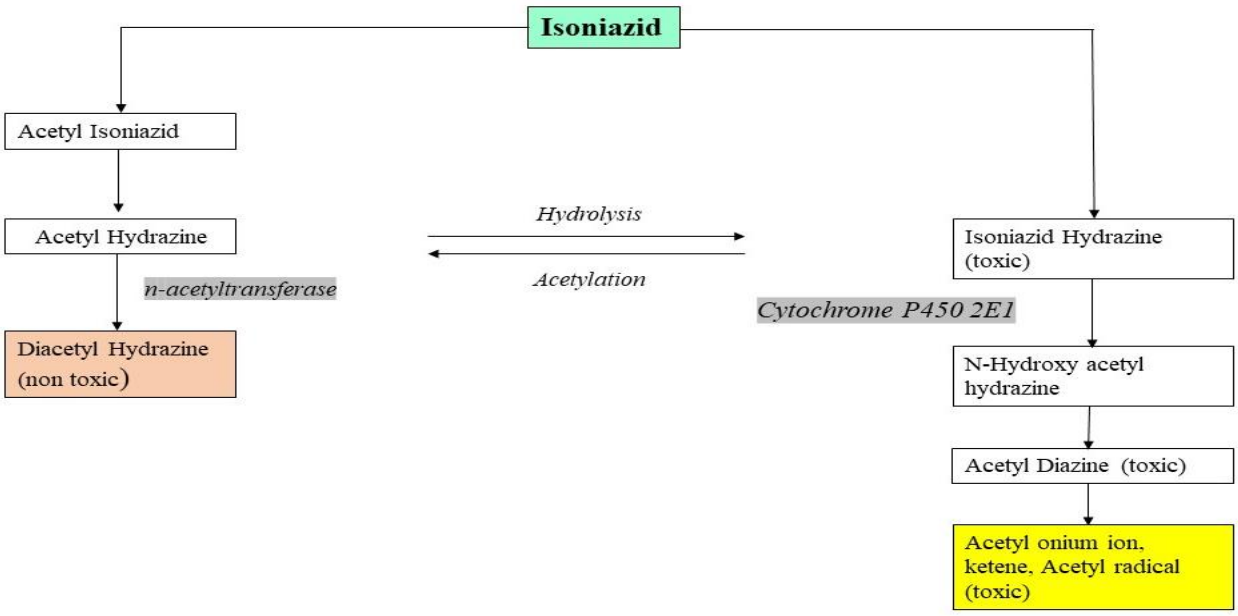
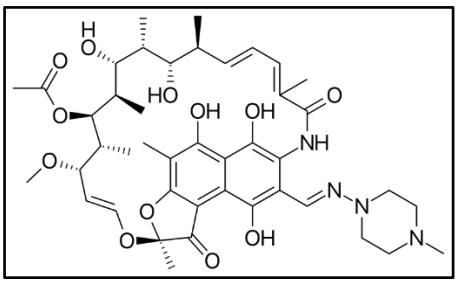


Figure 1 : Pathway involved in the metabolism of Isoniazid.

A novel review on the mechanism of INH hepatotoxicity highlights the role of immune-mediated idiosyncrasy as a mechanism defined by the adaptive responses of the liver to INH and the heterogeneity of the clinical presentation of INH hepatotoxicity [22].

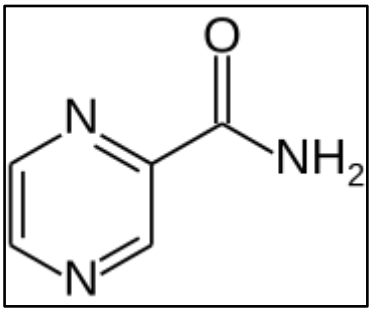
Rifampicin



Structure No 2 : Rifampicin

Rifampicin is quickly absorbed from the stomach and bio-transformed into desacetyl rifampicin in the liver via desacetylation, with a distinct hydrolysis pathway producing 3-formyl rifampicin [25][26][27][28]. The microbiologically active desacetyl rifampicin is more polar than the parent molecule. The majority of the antibacterial action in bile is attributed to this molecule. Both bile and urine are virtually equally excreted with rifampicin. These metabolites don't cause any harm. Rifampicin is linked to the hepatocellular pattern of DILI and frequently increases the toxicity of other anti-TB medications on the liver [25][26][29][30][31]. In research involving patients receiving anti-TB and anti-retroviral medication (ART), the proportion of individuals with the homozygous ABCB1 3435TT genotype who had DILI was three times greater [32].

Pyrazinamide



Structure No 3 : Pyrazinamide

A nicotinic acid derivative is pyrazinamide. It is deamidated to pyrazinoic acid. This is further oxidized to 5-hydroxy pyrazinoic acid by xanthine oxidase [33][34].The kidneys are used to eliminate the metabolites. Compared to isoniazid and rifampicin, pyrazinamide has a longer half-life, and it is further prolonged when used with allopurinol and other medications that block xanthine oxidase and when there is underlying liver disease. Pyrazinamide toxicity is dose-dependent, with levels utilized in current regimens (25–35 mg/kg) being associated with a higher frequency of hepatotoxicity than those at 40–50 mg/kg. In murine models, pyrazinamide reduced CYP450 activity and changed NAD levels in conjunction with hepatotoxicity caused by free radical species [35][36].

III. Host Associated Risk Factors:

Age

A higher risk of DILI has been linked to ageing. In one study, age beyond 60 years was linked to a 3.5-fold risk of DILI in 519 individuals taking regular anti-TB drugs [2]. In a different study with 430 patients, those over the age of 60 had a 2.6-fold higher incidence of pyrazinamide-related adverse events, including DILI [52]. The frequency of DILI was greater in patients who were 50 years of age or older in a cohort of nearly 3000 patients receiving INH monotherapy [13]. After the age of 50, INH hepatotoxicity has been reported to be more severe and to cause higher risk of death [20][17]. Patients in a case-control study who experienced DILI while taking anti-TB medications were older (39 years) than those who did not (32 years) [53]. In a different trial, patients under the age of 35 had a 17% incidence of hepatotoxicity, whereas patients above the age of 35 had a 33% incidence; in a multivariate analysis, age >35 years was the only independent predictor for predicting anti-TB DILI [54]. Age-related changes in medication distribution and metabolism, as well as decreased liver blood flow, may reduce the efficiency with which medicines are cleared from the body. In contrast to these, a meta-analysis found that children receiving INH and rifampicin had a higher incidence of clinical hepatitis (6.9%) than did adults (2.7%) [18]. However, the inclusion of three small studies—each with 22–60 patients—that reported a very high frequency of "clinical hepatitis" in 25%–52% of all patients is mostly responsible for the high frequency of DILI in children.

Gender

With a reported 4-fold risk, women are more vulnerable to DILI following anti-TB therapy [52][55][56]. Females have higher CYP3A activity, making them more vulnerable to hepatotoxicity [58]. In the third trimester and the first three months following delivery, there has been a tendency toward an increase in the incidence of INH hepatotoxicity in pregnant women [59].

Alcohol Intake

Alcohol has the capacity to generate enzymes and damage the liver. Numerous studies have shown that alcohol prolongs the hepatotoxicity brought on by anti-TB medications. Even in individuals receiving rifampicin as a prophylactic medication, this danger has been proven [39][40].

IV. Genetic Susceptibility:

Even when parameters like treatment regimen and environmental conditions are taken into consideration, anti-TB DILI still remains unpredictable. Hepatotoxicity occurs during the early phase of anti-TB therapy in the great majority of cases, which neither the drug-related factors nor the concurrent risk factors can fully explain. Additionally, findings like the fact that Asian men have isoniazid hepatitis at a rate that is twice that of white men and approximately 14 times that of black men suggest that genetic susceptibility may play a significant role in the development of hepatotoxicity [13].

V. Herbal Hepatoprotectants: to prevent hepatotoxicity due to anti-tuberculosis treatment:

Liver disease is still a global health issue. Unfortunately, traditional or synthetic medications used to treat liver problems are insufficient and can have serious adverse effects [60]. In the lack of a reliable liver protective agent in modern medicine, Ayurveda recommends a range of herbal remedies for the treatment of liver problems [61]. For decades, Ayurvedic and other traditional medicine practitioners have maintained that plant extracts can effectively treat multiple kinds of liver diseases. In ethnomedical practices and traditional systems of medicine in India, numerical medicinal plants are utilized for hepatoprotective activity. Many herbs have been discovered in India, as well as in tropical and subtropical places around the world. Table 1 shows the plants and plant parts that have hepatoprotective effect [62].

Table 1 : Plants and plant parts that have hepatoprotective effect.

Botanical name (Family)	**Parts used**
Allium cepa (Alliaceae)	Bulbs
Allium sativum (Alliaceae)	Bulbs
Aphanamixis polystachya (Meliaceae)	Stem, root bark, Seeds
Apium graveolens (Ericaeae)	Seeds
Boerhaavia diffusa (Nyctaginaceae)	Whole plant with root
Calotropis gigantean (Asclepiadaceae)	Leaves
Carica papaya (Caricaceae)	Milky juice
Cynara scolymus (Asteraceae)	Leaves and roots
Daucus carota (Apiaceae)	Fruit and root
Desmodium biflodrum *Linn* (Fabaceae)	Whole plant
Eclipta prostrata (Asteraceae)	Whole plant
Ficus glomerata Roxb (Moraceae)	Seeds
Glycosmis pentaphylla (Rutaceae)	Leaves
Hibiscus lampas cav. (Malvaceae)	Fresh Roots
Iris germanica (Iridaceae)	Rhizomes
Moringa pterygosperma (Moringaceae)	Leaves, stem, root and gum
Phyllanthus emblica (Euphorbiacee)	Roots
Santolina chamaecyparissus (Asteraceae)	Whole plant
Sarothamnus scoparius (Papilionaceae)	Root
Silibum marianum (Asteraceae)	Seeds
Solanum nigrum (Solanaceae)	Leaves
Taraxacum officinale (Asteraceae)	Roots
Terminalia chebula (Combretaceae)	Fruits
Tinospora cordifolia (Menispermaceae)	Fresh stem
Trigonella foenum graecum (Papilionaceae)	Leaves and Seeds
Zingiber officinale (Zingiberaceae)	Rhizomes

VI. Management:

Studies examining DILI lack the scientific rigor, consistent methodology, and sizeable scale to produce the evidence on which recommendations can be founded, despite the enormous worldwide burden of TB and decades of experience in the use of anti-TB drugs. As a result, methods for managing, monitoring, and preventing hepatotoxicity have mostly been focused on retrospective observational research. Recommendations for assessment, selection of an anti-TB drug regimen, patient instruction, clinical intensive care, and interventions in the event of hepatotoxicity have been published by the American Thoracic Society (ATS), British Thoracic Society (BTS), and more recently by the National Institute for Clinical Excellence (NICE), UK. It should be emphasized that many of these suggestions rely only on professional judgement [7][41][42].

Risk Stratification:
Pretreatment evaluations should, wherever practical, include a check for chronic liver disease, as well as a history of excessive alcohol use, intravenous drug misuse, and nutritional examination. Serology for chronic viral infections (HIV, hepatitis B, and C), as well as an proper assessment for underlying liver disease, should be part of the baseline evaluation [41][42]. When considering empirical TB treatment, a risk-benefit analysis is essential because these individuals have been proven to have an increased risk of adverse outcomes [3][43]. Before choosing to treat latent TB, an individual's risk of DILI should be evaluated against their risk of getting active TB.

Choice of Drugs and Regimen:
There is no proof that three-times-per-week dosing schedules have a minor risk of hepatotoxicity than daily dosing schedules [19]. Professional body guidelines offer guidance on the selection of medications, pharmacological combinations, and therapy duration that are thought to be appropriate for certain clinical settings. Cost, accessibility, affordability, efficacy, and related negative consequences should all be taken into account [44][45].When possible, it is preferred to employ isoniazid and rifampicin in the treatment of latent or active TB infection due to their high efficacy. However, monotherapy with either isoniazid or rifampicin is preferred for the treatment of latent TB when a specific individual is at higher risk of hepatotoxicity because combined therapy raises the risk of DILI [18].

Patient Education:
Whenever possible, patients should be reminded during educational sessions about the importance of drug adherence, follow-up appointments for monitoring, and symptoms of hepatotoxicity. Patients who exhibit any symptoms suggestive of hepatotoxicity should be urged to discontinue all anti-TB medications and seek immediate medical assistance. One report from an INH-based chemoprophylaxis program revealed that regular questioning and symptom reporting at monthly visits proved beneficial in preventing major DILI without the requirement for standard liver biochemistry measures [16]. Patients should be instructed to avoid consuming alcohol and to consult with a physician before taking any prescription or over-the-counter medications since these may increase toxicity and result in DILI.

Monitoring:
Directly observed short-course therapy (DOTS) increases the efficacy of treatment and helps assess treatment adherence when conducted on a regular basis with patients. Therapeutic drug monitoring [46][47] has been found to enhance clinical responsiveness, but it has yet to be proven that it can predict hepatotoxicity. Up to 20% of patients may experience transient, asymptomatic ALT elevations during the first few weeks of starting anti-TB therapy. As these elevations spontaneously resolve, it is believed that they are caused by "adaptation" rather than hepatotoxicity; potential mechanisms underlying the former phenomenon are discussed in the literature. As part of a strategy employed by the Seattle-King County Public Health Department to monitor INH therapy, patients were instructed to cease taking their prescription and contact the clinic if they started to have signs of hepatotoxicity [48][49][16]. The prevalence of hepatotoxicity in 11,141 individuals was substantially lower (0.1%-0.15%) than previously anticipated (1%) and there were no fatalities thanks to meticulous clinical surveillance without frequent laboratory investigations [16]. The ATS guidelines advise against routine liver biochemistry testing in those without any obvious risk factors; however, in patients with risk factors for developing hepatotoxicity and in those with abnormal baseline tests, liver biochemistry-based monitoring should be taken into consideration at 2-weekly intervals in the first 2-3 months of therapy.

VII. Future Development:
Hepatotoxicity induced due to anti-tuberculosis drug is a serious adverse reaction and continues to be a universal problem. The lack of knowledge on the pathophysiology of anti-TB DILI substantially hampers efforts at prevention and/or early detection. Future research on the processes underlying the development of anti-TB DILI should be conducted whenever possible utilizing human tissue and samples so that the innovative results can be quickly applied in therapeutic settings. A crucial initial step [50] in research looking to uncover risk factors of DILI in large patient cohorts is to establish clear and uniform phenotypic criteria. Recent studies on genetic susceptibility to "idiosyncratic" DILI have promised the development of sophisticated algorithms that include drug, host, and environmental risk factors that would allow pre-emption of DILI [51] and, as a result, allow better medication customization based on precise assessments of risk-benefit ratio. Undoubtedly, there is a critical need for more sophisticated, original, genetic, proteinaceous, and metabolite biomarkers that can identify patients with a higher risk of developing DILI, aid in an early diagnosis, and monitor for DILI throughout treatment. Anti-TB DILI offers a chance for research that will significantly affect many different sectors, such as drug discovery and development, primary and secondary care.

Conclusion: Idiosyncrasy is a type of adverse drug reaction which causes hepatotoxicity during tuberculosis (TB) treatment. The incidence of hepatotoxicity is relatively high among tuberculosis patients taking first-line anti-tuberculosis drugs i.e., isoniazid, rifampicin and pyrazinamide but isoniazid is a most common drug associated with hepatotoxicity. The risk of drug induced liver injury is also linked with host related factor such as age, gender and alcohol intake. Alcohol damage the liver and in numerous studies have shown that alcohol prolongs the hepatotoxicity by anti-tuberculosis drugs. Environmental condition also takes into consideration, anti-TB DILI is still unpredictable. To prevent hepatotoxicity induced due to anti-tuberculosis medication herbal hepatoprotectant are used.

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