HEPATOTOXICITY RELATED TO FIRST-LINE ANTI-TUBERCULOSIS DRUGS AND FACTORSIMPLICATED IN IT: A REVIEW

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ABSTRACT

Isoniazid (INH), rifampicin (R), and pyrazinamide (P), the first-line anti-tuberculosis medications, are all hepatotoxic and raise the risk of hepatotoxicity when combined. Hepatotoxicity is a frequent side effect of treating TB patients with anti-tuberculosis drugs. Once hepatotoxicity occurs, anti-tuberculosis medications should be stopped, and following recovery, they should be gradually reintroduced. The slow acetylator phenotype/genotype of the N-acetyltransferase 2 (NAT2) gene and INH-induced hepatotoxicity are the best-documented risk factors for hepatotoxicity. Other risk factors include being of Indian or Asian descent, old age, malnutrition, hypoalbuminemia, co-infection with hepatitis B and C viruses (HBV and HCV), or HIV infection.Hepatotoxicityaid burdens in morbidity & mortality in patients of tuberculosis.All patients taking anti-tuberculosis drugs should be told to report all new illnesses, especially when associated with vomiting. Careful anti-tuberculosis regimen adjustment and routine liver transaminases monitoring are required for high-risk patients.

KEY-WORDS: Hepatotoxicity;First-Line Anti-Tuberculosis Drugs; Risk Factors; Drug-induced Hepatotoxicity

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INTRODUCTION

Tuberculosis is the primary worldwide cause of death due to infectious disease.[1]In 2020, TB claimed the lives of 1.5 million persons worldwide (including 214000 people with HIV). After COVID-19, TB is the second most common infectious killer in the world and the 13th largest cause of death overall.[2]TB is one of the foremost public health problems in India, causing a significant burden of morbidity and mortality.[3] The treatment regimens for TB patients recommend the use of the five first lines anti TB drugs Isoniazid (INH), Rifampicin (R), Ethambutol (E), Pyrazinamide (P) and Streptomycin (S).[4] Among the drugs,isoniazid, rifampicin, pyrazinamide are hepatotoxic. So, these aid burdens in morbidity & mortality in patients of tuberculosis.[5]

Hepatic dysfunction may be defined as an increase in alanine transaminase (ALT) levels to 1.5 times above the upper limit of normal and for patients with increased pre-treatment ALT the elevation had to be greater than 1.5 times the base line.[6] Transient changes in ALT and bilirubin levels are relatively common during ATT and do not signify true hepatotoxicity. However, the progressive rise in ALT and bilirubin levels is much more dangerous. But the recommendations for the modification of treatment regimen and the cut-off level of liver dysfunction have not been standardized. Some authors recommend stopping the hepatotoxic drugs if the ALT level increases by three times or more compared to that of normal, while others recommend five times.[7]

Hepatotoxicity is consistently the most common seriousadverse reaction in patients taking anti-tuberculosis drugs.Hepatic necrosis is the most important adverse effect offirst-line anti-tuberculosis drug therapy.[8] Asymptomaticrises in transaminases are common and are not by

themselvesjustification for withdrawing medication, since theysettle spontaneously in most patients while treatmentcontinues. All patients taking anti-tuberculosis drugsshould be told to report all new illnesses, especiallywhen associated with vomiting.[8]

ANTI-TUBERCULOSIS DRUGS AND THE LIVER

EFFECT OF FIRST-LINE ANTI-TUBERCULOSIS DRUGS ON THE LIVER

Isoniazid

Initially the hepatotoxic potential of isoniazid was not recognized. In 1969, Scharer and Smith reported that 10.3% of patient receiving isoniazid developed liver function abnormality.[9] After the early reports, United State Public Health Service (USPHS) conducted a large multicentre prospective study in patient receiving isoniazid for chemoprophylaxis to find out the incidence of isoniazid induced hepatotoxicity.[10] In 13,838 patients, the overall incidence of isoniazid induced hepatotoxicity was found to be 1% with a mortality rate of 0.06%. In addition to clinical hepatitis, a large proportion of patients have developed asymptomatic elevation of transaminases.[10] Usually, isoniazid induced hepatitis gradually resolve within one to four weeks after stopping isoniazid. However, if drug is continued, patients may develop severe hepatitis including fulminant hepatic failure.[11] The pathogenesis of isoniazid induced hepatotoxicity is not well understood. Both dose related toxicity and hypersensitivity reaction have been considered. The histopathological picture resembles that of viral hepatitis and shows hepatocyte necrosis, ballooning degeneration and inflammatory infiltrate.[12] These findings may suggest dose related toxicity. Hypersensitivity is considered unlikely because of delayed onset of isoniazid induced hepatotoxicity, absence of symptoms of hypersensitivity. However, in some patients, there is circumstantial evidence of hypersensitivity to drug. In these patients, eosinophils are prominent in liver biopsy and hepatotoxicity recurs on re-challenge.[13]

Rifampicin

The major adverse effect of rifampicin therapy is hepatotoxicity.Abnormalities in liver function tests are common in patients receiving rifampicin and this resolve even while the drug continues to be used. In several published studies, the reported incidence of transaminases elevation and overt clinical hepatitis during rifampicin therapy in the absence of isoniazid varied from 0.6 to2.7.[14] Rifampicin induced hepatotoxicity occurs earlier compared to isoniazid and produces a patchy cellular abnormality with marked periportal inflammation.[15] Rifampicin induced hepatitis has been postulated to occurs as a part of systemic allergic reaction and due to unconjugated hyperbilirubinemia as a result of competition with bilirubin for uptake at hepatocyte plasma membrane.[16]

Pyrazinamide

Liver damage is the most common adverse effect of pyrazinamide. It varies from asymptomatic alteration of liver function detectable only by laboratory tests, through a mild syndrome characterized by fever, anorexia, malaise, liver tenderness, hepatomegaly, and splenomegaly, to more serious reactions with clinical jaundice, and finally the rare form with progressive acute yellow atrophy and death.[16]Earlier pyrazinamide was employed in a dosage of 40 to 50 mg/kg/day for prolonged periods and hepatotoxicity developed in about 15% of the cases leading to the abandonment of pyrazinamide as a first line drug[30]. However, pyrazinamide is presently administered in a dosage of 25 to 35 mg/kg/day. The contribution of pyrazinamide to the development of hepatotoxicity at this dosage

has been controversial.The exact pathogenic mechanism of pyrazinamide induced hepatic damage has not been classified yet.[16]

HEPATOTOXICITY DUE TO COMBINATION THERAPY

Isoniazid and Rifampicin

There is evidence to suggest that hepatotoxicity occurs with greater frequency and may be more severe when isoniazid and rifampicin are administered in combination than when either drug is given alone.[17] Steel et al undertook a meta-analysis to estimate the incidence of anti-tuberculosis treatment induced hepatotoxicity.[17] A total of 34 clinical studies (22 involving adults and 12 involving children) published between 1966 and 1989 were analyzed. They found that incidence of clinical hepatitis in adults with isoniazid alone was 0.6%, with multidrug isoniazid regimen without rifampicin 1.6% and with regimen containing rifampicin and not isoniazid 1.1%. The incidence of clinical hepatitis in 6105 patients taking isoniazid and rifampicin combination was 2.6% which was significantly higher than the incidence in patient taking multiple drugs containing isoniazid without rifampicin and those taking multiple drugs containing rifampicin without isoniazid. Children receiving isoniazid and rifampicin combination had a significant higherincidence of hepatitis (6.9%) compared to those receiving multiple drugs containing isoniazid without rifampicin (1.6%). The authors concluded that isoniazid and rifampicin combination caused more hepatotoxicity than either drug administered alone and the hepatotoxicity effects of these two drugs given together was additive rather than synergistic.[17]

It is not clear as to why is there an increased risk of hepatotoxicity with isoniazid and rifampicin combination. The answer probably lies in the interaction between isoniazid and rifampicin metabolism.[18] The metabolism of isoniazid is influenced by both genetic and intercurrent factors. The principal metabolite of isoniazid, acetyl isoniazid, is converted to monoacetyl hydrazine. This in turn metabolized by microsomal p-450 enzymes to other compounds causing hepatotoxicity and this effect may be enhanced by rifampicin induced enzyme induction. Because acetyl isoniazid formation occurs in large amounts in rapid rather than slow acetylators, it was suggested that rapid acetylators are more prone to hepatotoxicity. There is considerable debate with regard ti whether the hepatotoxicity is due to additive the additive effect of isoniazid and rifampicin or synergistic direct toxic effect of drugs or is a hypersensitivity phenomenon.[19]

Rifampicin, Isoniazid and Pyrazinamide

Rifampicin, isoniazid, and pyrazinamide are typically included in standard antitubercular regimens. The challenging question of whether hepatitis is brought on by isoniazid, pyrazinamide, or both emerges when hepatotoxicity takes place. Rifampicin, a potent enzyme inducer, may make isoniazid and pyrazinamide more toxic to the liver. Two types of fulminant liver injury can be seen in patients receiving the drugs isoniazid, rifampicin, and pyrazinamide together.[20] The first pattern is characterised by an early (often within the first 15 days) rise in blood transaminase activity following the start of therapy. This pattern is most likely the result of isoniazid liver damage brought on by rifampicin. In most cases, the prognosis is favourable.The second pattern is defined by a late occurrence of an increase in serum transaminase activity, typically more than one month after the start of therapy. This pattern may be connected to pyrazinamide hepatotoxicity, according to certain theories. This particular hepatitis typically has a terrible prognosis. These distinctions cannot be relied

entirely upon in each individual case, despite the fact that they may be valid in terms of probability. Therefore, it is advised that when severe liver impairment (serum transaminase values >3 times the upper limit of normal) occurs, both isoniazid and pyrazinamide medication should be stopped.[20]

FACTORS IMPLICATED IN THE DEVELOPMENT OF ANTI-TUBERCULOSIS TREATMENT INDUCED HEPATOTOXICITY

The fact that anti-tuberculosis drugs cause hepatotoxicity only in small proportion of patients raises the question about some predisposing factors for the development of anti-tuberculosis treatment induced hepatotoxicity. Certain putative factors have been implicated in the development of anti-tuberculosis treatment induced hepatotoxicity. These are discussed below.

Age

Isoniazid induced hepatotoxicity has been correlated with age. The incidence of serious hepatotoxicity is rare below 20 years of age. It was found to be 0.3% in the age group of 20 to 34 years, 1.2% in 35 to 49 years age group and in patients above the age of 50 years, the risk increased to 2.3%.[21] In a case control study, Pande et al observed that anti-tuberculosis treatment induced hepatotoxicity was more frequent in older patients.[22]

Gender

In some studies, elderly females have been reported to be a higher risk to develop anti-tuberculosis treatment induced hepatotoxicity.[22]

Ethnic and racial variation

In Indian patients, a higher risk of anti-tuberculosis treatment induced hepatotoxicity than in their Western counterparts.[23-24]

Genetic factors

Role of genetic factors has not been fully evaluated in anti-tuberculosis treatment induced hepatotoxicity. Sharma et al recently reported the major histocompatibility (MHC) class II alleles and clinical risk factors for the development of anti-tuberculosis treatment induced hepatotoxicity in 346 north Indian patients with TB receiving anti-tuberculosis treatment.[25]

Acetylator status and hepatotoxicity

There is considerable confusion in the literature regarding acetylator phenotype status and the development of hepatotoxicity. Rapid acetylators have been shown to be more susceptible to isoniazid induced hepatotoxicity hepatitis.[26]

Underlying chronic liver disease

Even though there are reports that patients with known liver disease can be treated with isoniazid and rifampicin containing regimens without undue risk, many workers have reported that patients with underlying liver disease and alcoholics are more prone to develop anti-tuberculosis treatment induced hepatotoxicity. Gronhagen-Riska et al studied predisposing factors in hepatitis due to combined isoniazid and rifampicin treatment and reported that one half of the patients who developed large increase in transaminases (> 150 units/l) were either alcoholics had history of previous liver or biliary disease.[27] The peak transaminases and bilirubin were higher in patients who were hepatitis B virus carriers than who were not.

Malnutrition

The studies have shown that drug metabolizing processes that drug metabolizing processes in the liver including acetylation pathways are deranged in states of protein energy malnutrition. A significant decrease in isoniazid metabolism has been demonstrated in kwashiorkor.[28]

MANAGEMENT OF ANTI-TUBERCULOSIS TREATMENT INDUCEDHEPATOTOXICITY

Diagnosis

The criteria for the diagnosis of anti-tuberculosis treatment induced hepatotoxicity by some of the published international guidelines are listed in Table 1.[29,30]

Table 1: Diagnosis of anti-tuberculosis treatment induced hepatotoxicity:

Guidelines	**Elevation of transaminases**	**Elevation of serum bilirubin**
American Thoracic Society (ATS)/ Centers for Disease Control and Prevention (CDC)/ Infectious Disease Society of America (IDSA)	With jaundice and/ or hepatitis symptoms (nausea, vomiting, abdominal pain, unexplained fatigue):Three-fold increase in alanine aminotransferases (ALT) over the upper normal limit OR Absenceof symptoms:Five-fold increase in ALT over the upper normal limit	Any increase
European Respiratory Society (ERS)/ World Health Organization (WHO)/ International Union Against Tuberculosis and Lung Disease (IUATLD)	Five-fold increase in ALT over the upper normal limit	Any increase

According to WHO classification severity of hepatotoxicity is defined in Table 2.[31]

Table 2: Severity of hepatotoxicity:

Grade	**Serum ALT level**
I	51 to 125 IU/l or 1.25 to 2.5 times normal
II	126 to 250 IU/l or 2.6 to 5.0 times normal
III	251 to 500 IU/l or 5.1 to 10.0 times normal
IV	>500 IU/l or greater than 10 times normal or > 250IU/l if accompanied by symptoms of jaundice

Treatment of Tuberculosis in Patients with Antituberculosis Drug Induced Hepatotoxicity

Once the diagnosis of hepatotoxicity is established, it is essential to first stop all potentially hepatotoxic drugs till complete clinical and biochemical resolution of hepatotoxicity occurs.[32] In the interim period, at least three non-hepatotoxic drugs such as ethambutol, streptomycin and quinolones (moxifloxacin or ofloxacin) can be used after appropriate checks on renal function and visual acuity. After complete resolution of transaminases, most anti-tuberculosis drugs can be safely restarted in phased manner.[29] Regarding the safety and wisdom of re-starting the same hepatotoxic drugs which caused hepatitis, the clinical experience has shown that these drugs can be given safely. The re-introduction of anti-tuberculosis drugs has seldom been systematically studied and a great deal of controversy exists regarding sequence in which the drugs are to be reintroduced, whether the re-introduction should be done

in full dosage or in gradually escalating dosage.[29]

Recommendations for Re-introduction of Treatment in Patient with Anti-tuberculosis Drug induced Hepatotoxicity

According to the guidelines, suspected anti-tuberculosis drugs can be started one at a time once the transaminases levels return to less than two times the upper normal. Rifampicin is to be restarted first. If the liver functions remain normal after one week, isoniazid can be added to the regimen. If the liver functions remain normal after one week, then pyrazinamide is added. If there is recurrence of symptoms or deterioration of liver functions, the last added drug should be stopped.[29] Depending on the number of doses taken, bacteriological status and the severity of the disease, the treatment may have to be individualized and extended. In a recent study in TB patients with serious liver injury, a 12-month regime of ethambutol, and ofloxacin, including streptomycin for the first three months, followed by ethambutol and ofloxacin for the subsequent nine months was well tolerated, and it was effective in 85 percent of patients.[33]

PREVENTION

One of the most important predictors of hepatotoxicityduring anti-tuberculosis drug therapy is an abnormal liverfunction test at baseline. It is reasonable to avoid potentiallyhepatotoxic drugs in the management of patientswith pre-existing liver disease.The use of ofloxacin instead of rifampicin in anti-tuberculosisdrug regimens for patients with underlyingchronic liver disease has been reported to be associatedwith a significantly lower risk of hepatotoxicity.Similar observations have been reported among carriersof hepatitis B and liver transplant recipients by otherinvestigators.[34]

CONCLUSION

Hepatotoxicity caused by first-line anti-TB medications is a major adverse effect that is still an issue everywhere in the world. Hepatotoxicity prevention and early detection efforts are substantially hindered by our incomplete understanding of its pathophysiology. In order to quickly translate the innovative results into practical applications, future studies examining the mechanisms behind the pathogenesis should be carried out utilising human tissue and samples whenever possible. Recent studies on idiosyncratic hepatotoxicity genetic susceptibility have promised the development of sophisticated algorithms that include drug, host, and environmental risk factors that would allow pre-emption of hepatotoxicity and, as a result, allow better medication customization based on precise estimates of risk-benefit ratio. There is unquestionably a critical need for more sophisticated, original, genetic, proteinaceous, and metabolite biomarkers that can identify individuals with a higher risk of hepatotoxicity, aid in an early diagnosis, and monitor for hepatotoxicity throughout treatment.

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