Review Article

Anti-tuberculosis Drug-induced Hepatitis

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Abstract:

Among the first line anti-TB drugs, INH, Rifampicin and Pyrazinamide are considered to be the most hepatotoxic drugs and cause drug induced hepatitis. Pyrazinamide causes both dose-dependent and idiosyncratic hepatitis whereas Isoniazid and Rifampicin induced hepatotoxicity are considered to be idiosyncratic. There are several risk factors for hepatotoxicity such as old age, malnutrition, genetic predisposition, HIV infection as well as chronic Hepatitis B and C infections. Anti-TB drug induced hepatitis usually occurs within 2 months after starting treatment. Patient may present with mild symptoms to severe acute hepatitis or even acute liver failure. Various guidelines have been published regarding the management of ATT and restarting anti TB drugs. This article reviews the incidence, risk factors, mechanism, diagnosis and management strategies of anti-TB drug induced hepatitis.

Keywords*: Hepatotoxicity, Drug induced liver injury (DILI), anti-tubercular (Anti-TB)*

Introduction:

Tuberculosis (TB) is a major public health problem and continues to be a risk for mortality and morbidity in developing countries. In 1993, World Health Organization (WHO) declared TB a global public health emergency.[1] Despite being a treatable disease, each year an estimated 8.8 million new cases and 2 million deaths occur due to TB worldwide.[2] The underlying causes of this high mortality are unknown. It may be due to associated HIV co-infection, multiple drugs resistant tuberculosis (MDR-TB) or may be due to inadequate management. According to WHO Global TB report 2016, in Bangladesh nearly about 73,000 people die each year from tuberculosis.[3] Although highly efficacious treatment for TB is available, treatment related adverse effects possess threat not only to patients, but also to physicians. Among all the adverse effects caused by anti-TB therapy (ATT), hepatotoxicity is the commonest side effect which leads to discontinuation of drugs in 11% of patients treated with 1st line Anti-TB drugs.[4] The National guidelines for the management of tuberculosis recommend the use of the five first line anti-TB drugs: Isoniazid(INH), Rifampicin (R), Ethambutol (E), Pyrazinamide (P) and Streptomycin(S). Off these, INH, Rifampicin and Pyrazinamide are considered to be the most hepatotoxic drugs and cause drug induced hepatitis.

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Incidence of Anti-TB drug induced hepatitis:

The incidence of anti-TB drug induced hepatitis varies from country to country. Very few data are available regarding toxicity rates of anti TB drug induced hepatitis because liver function tests are not routinely done in many countries in patients on anti TB therapy. From different studies, it has been reported that 5%-28% of patients treated with anti-TB drugs developed drug induced hepatitis.[5] Among the first line anti-TB drugs, pyrazinamide causes more hepatotoxicity than isoniazid or rifampicin. In one study it was observed that up to 15% of patients receiving pyrazinamide developed sign-symptoms of liver disease.[6] With isoniazid monotherapy, significant transaminase elevations were reported in about 0.5% of all patients[7,8] and with prophylactic rifampicin monotherapy, hepatotoxicity was observed in about 1-2% of patients.[8,9]

Risk factors:

There are several risk factors that are proven to be useful to predict the occurrence of drug induced liver injury (DILI). Therefore, close monitoring could be done in this selected group of patients for the occurrence of hepatotoxicity.

Age: Several studies suggested that advanced age was associated with increased risk of TB DILI.[10,11] Contrary to this, in a meta-analysis higher incidence of clinical hepatitis (6.9%) was reported in children receiving INH and rifampicin, compared to adults (2.7%).[12] In a retrospective analysis of various DILI registries showed that hepatitis was a major form of liver injury in young adults, whereas cholestatic type of DILI was more common in elderly patients.[11]

Gender: Several studies have implicated that women are more susceptible to DILI from anti-TB therapy.[13]

Nutritional Status: Malnutrition also contributed to increased incidence of DILI. There is a significant correlation of low BMI for the increased risk of developing a moderate degree of DILI.[14,15]

Genetic factors: Gene polymorphisms at loci of genes coding for cytochrome P450 2E1 and for glutathione S-transferase have also been associated with hepatotoxicity.[16] Several studies from India have shown that presence of HLA DQB1*0201 allele is an independent risk factors for anti-TB drug induced hepatotoxicity.[17]

Acetylator Status: NAT2 gene (N-acetyl-tranferase 2) which codes for enzyme acetyl-tranferase causes acetylization of INH which is turned into acetyl-isoniazid and then further hydrolyzed to acetylhydrazine and finally oxidized by cytochrome P 450 2E1 to diacetylhydrazine. In patients with slow acetylator response, drug is slowly detoxified and therefore oxidation time for forming the toxic reactive metabolites is increased.[18] Though acetylation rate on isoniazid hepatotoxicity was controversial yet significant correlation was found between slow acetylators and moderate degree of DILI in some studies.[19]

Associated infections: The presence of hepatitis B and/or C co-infection significantly increased the risk of development of ATT induced hepatotoxicity.[20] The chance of hepatotoxicity increased four fold with concomitant HIV infection.[21] It was observed that individual infected with both hepatitis C and HIV, treated with anti-TB drugs, the risk of hepatotoxicity increased to 14.4 folds.[22]

Pathophysiology:

The exact mechanism of anti-TB drug induced hepatitis is unknown. Both Isoniazid and Rifampicin induced hepatotoxicity are considered to be idiosyncratic whereas Pyrazinamide causes both dose-dependent and idiosyncratic hepatitis.

Idiosyncratic drug reactions may be metabolic or immune mediated. In cases of metabolic idiosyncratic hepatitis, abnormalities occur in any one of the phases of drug metabolism, so reactive drug metabolites are formed in increased amount which act as inducing agent for production of excessive reactive oxygen species (ROS) leading to lipid peroxidation and cell death.[1]

Reactive metabolites also covalently bind with cellular enzymes, lipid or nucleic acids and may induce oxidative stress and cause liver injury.[23]

The role of mitochondrial permeability transition (MPT) in the pathogenesis of anti-TB drug induced hepatitis has been reported. The drug or its toxic metabolite causes disruption of mitochondrial membrane, inhibition of mitochondrial respiratory chain resulting in depletion of cellular ATP causing cell death.[1]

In immune mediated DILI, drugs or metabolites covalently bind to cellular protein (haptenization), presented on cell surface which elicit both humoral and cellular immunity causing liver damage.[18]

Anti-tubercular drugs and hepatotoxicity:

Among the first line anti-tubercular drugs, isoniazid, rifampicin, and pyrazinamide are considered to be the major hepato-toxins.

Isoniazid: In the liver, metabolism of INH occurs by liver enzyme N-acetyl-transferase2 (NAT2) to acetylisoniazid, which is further hydrolyzed to acetyl-hydrazine. Acetyl-hydrazine is oxidized by cytochrome P4502E1 (CYP2E1) to form hepato-toxic intermediates, which destroy hepatocytes resulting in liver injury.[24]

Rifampicin: Rifampicin causes hepatocellular pattern of DILI. In the liver, metabolism of rifampicin occurs by des-acetylation to microbiologically active product des-acetyl rifampicin and hydrolysis occurs in a separate pathway producing 3-formyl rifampicin. But these metabolites are non-toxic.[1]

Rifampicin is an inducer of CYP2E1 iso-enzymes and plays a significant role in metabolizing INH and thus produces toxic metabolites.[24]

Pyrazinamide: Pyrazinamide causes both idiosyncratic and dose dependent hepato-toxicity with a higher dose at 40-50 mg/kg than the usual dose of 25-35 mg/kg.

Pyrazinamide, a nicotinic acid derivative, is de-amidated to pyrazinoic acid in the liver and subsequently oxidized to 5-hydroxy-pyrazinoic acid by xanthine oxidase. These two reactive metabolites of PZA are considered to cause hepatotoxicity.[1]

Pyrazinamide also causes injury to liver by generating free radicals.[1]

Diagnosis:

Anti-TB drug induced hepatitis usually occurs within 2 months after starting treatment. Clinical presentations of TB DILI are diverse and nonspecific and range from mild symptoms with increased transaminases to severe acute hepatitis or even acute liver failure.[25] Most of the Anti-TB drug induced patients present with anorexia, nausea and vomiting. Some patients may present with hypersensitivity reactions like fever, rash or eosinophilia. Some cases may present with features of acute hepatitis or features of cholestasis like jaundice, pruritus and an increase in serum alkaline phosphatase, with a mild increase in serum ALT.[18] Outcome of acute liver failure caused by anti-TB therapy has poor prognosis in comparison to ALF caused by acute viral hepatitis.[1]

For diagnosis of anti- tubercular drug induced hepatitis (ATH), many diagnostic criteria have been published so far. But the most widely used criteria for defining patient with ATH are:

Without any evidence of viral hepatitis and without prior chronic liver disease, serum transaminase levels are: 1) greater than three times the ULN with jaundice and/ or hepatitis symptoms; or 2) greater than five times the ULN regardless of hepatitis symptoms.[24]

Management:

Various guidelines regarding the management of ATT and restarting anti TB drugs have been published by The American Thoracic Society (ATS),[24] The British Thoracic Society (BTS),[26] National Institute for Clinical Excellence (NICE),[27] World Health Organization (WHO)[1] and The International Union Against Tuberculosis and Lung Disease.[1]

Patients should be educated about symptoms of hepatotoxicity and advised to stop all anti-TB medications and seek medical advice if any symptoms of hepatotoxicity arise. It should be noted that immediately after the start of anti-TB treatment; up to 20% of patients develop asymptomatic transaminase elevations which resolve spontaneously.[28]

Routine liver biochemistry testing:

The ATS guidelines[24] do not recommend routine liver biochemistry testing for healthy patients, but should be considered in patients with risk factors for developing hepatotoxicity at 2 weekly intervals in the first 2–3 months of therapy.[24] Where as the Task Force[1] and BTS[26] recommend performing baseline liver function testing in all patients.

In general, all ATT medications should be discontinued when patients develop anti TB drug induced hepatitis and should remain stopped until liver function tests become normal or at least ALT falls below 2 times of ULN.[1]

Different guidelines have some variations for restarting the ATT drugs. Both ATS and BTS recommend restarting the anti-TB medications one at a time.

American Thoracic Society recommends reintroduction of full dose of rifampicin followed by isoniazid1-week later and then pyrazinamide after next 1 week. Before introduction of each drug ALT level should be within normal range. If ALT level starts to rise, last introduced drug should be stopped.[24]

British Thoracic Society suggests restarting all drugs at the same time but should be started with smaller doses until full therapeutic dosing is reached. Isoniazid, rifampicin, and pyrazinamide are started at doses of 10 mg/kg/day, 15 mg/kg/day and 25 mg/kg/day, respectively to full therapeutic dosing on day 4.[29]

The WHO as well as the International Union Against Tuberculosis and Lung Disease advice simultaneous reintroduction of all the drugs; if however, patients again develop hepatotoxicity after re-challenge, then the drugs are to be reintroduced one by one.[1] The national TB guidelines of Bangladesh provide information regarding the management of ATT induced hepatotoxicity and the details regarding the starting of TB drugs in patients developing hepatotoxicity.

National recommendations for managing ATT induced hepatotoxicity and restarting the therapy:

- If patient clinically develops jaundice or suspected hepatitis (tender hepatomegaly, icterus, ascites), biochemical test such as SGPT, S. bilirubin should be done.

- In symptomatic patients if SGPT rise to >3 times of ULN or in asymptomatic patient SGPT > 5 times of ULN, ATT drugs are to be stopped.
- Patient should be checked for viral markers.
- If viral markers are negative, then drug induced hepatitis is diagnosed.
- Follow up should be done until biochemical resolution of hepatitis.
- ATT drug should be reintroduced one at a time, initially with INH followed by Rifampicin, with ¼ th dose, then gradually increase to full dose by 72 hours. Then introduce another drug and monitor for hepatotoxicity.

In case of TBM, disseminated TB or miliary TB:

- If patient develops drug induced hepatitis, then the offending drugs should be stopped but treatment should be continued with Streptomycin, Ethambutol and Fluroqunolones till restarting first line drugs after resolution of drug induced hepatitis.
- First line drugs should be restarted one by one with full dose in an interval of 48 to 72 hours, first with INH and then rifampicin but not pyrazinamide.

Conclusion:

Tuberculosis is a major public health problem in Bangladesh and drug induced hepatitis is one of the common adverse effect in patient getting ATT. Drug induced liver injury due to ATD usually occurs within 2 months after administration of ATD. Patients may present with mild symptoms to severe acute hepatitis or even acute liver failure. Among the anti-TB drugs, INH, rifampicin, and pyrazinamide are considered to be hepatoxic. Early detection of anti-TB drug induced hepatitis is very important so that patient could be managed properly.

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