Hepatotoxicity in tuberculosis treatment: A review

Musa AKM

Introduction

Tuberculosis is a chronic bacterial infection caused by Mycobacterium tuberculosis. Tuberculosis is among the top ten causes of global mortality and affects low income communities. The incidence of tuberculosis varies from 9 cases per 1,00,000 population per year in the USA to 110-165 cases per 100,000 population in the developing countries of Asia and Africa.

Currently more than one third of the world’s population is infected with M. tuberculosis & 8 million new cases and approximately 2 million deaths are expected each year. Effective antitubercular therapy is an important step in the prevention of tuberculosis. Yet all are potentially hepatotoxic. At least 1-2% of patient develop hepatitis, which causes difficulty in management may lead to discontinuation of therapy leading to defaulter; Defaults lead not only to treatment failure but also the emergence and transmission of drug resistant organism. This article review the potential hepatotoxic effect of tuberculosis chemotherapy in patients with or without pre-existing liver disease.

Classification of drugs

<table>
<thead>
<tr>
<th>A. Hepatotoxic</th>
<th>B. Non-hepatotoxic</th>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>Ethambutol</td>
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<tr>
<td>Rifampicin</td>
<td>Streptomycin</td>
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<td>Pyrazinamide</td>
<td>Kenamycin, Amikacin</td>
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<tr>
<td>Ethionamide</td>
<td>Cycloserine</td>
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<tr>
<td>Para-aminosalicylic acid</td>
<td>Fluoroquinolones</td>
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</tbody>
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Isoniazid (INH)

INH is one of the main drug in tubercular chemotherapy (bactericidal), first introduced in 1950s. Reports in the late 1960s suggested that INH causes hepatitis. The largest and most comprehensive study of INH hepatitis was conducted by us public health services during 1971-1972. 14,000 persons receiving INH preventive therapy was monitored for development of hepatitis. Summary of this study shows that-

(i) Overall rate of probable INH hepatitis were 1% but was clearly age related with no cases among those under 20 years and highest rate of 2-3% among those over 50 years.
(ii) Hepatitis was 4 times higher among those consuming alcohol daily than those who do not drink.
(iii) Rates are lower among blacks and higher among whites.
(iv) Increased hepatotoxicity among women who are pregnant in 3rd trimester and immediate post partum period with co-administration of acetaminophen.

In a recent study, the relative risk of hepatotoxic side effects from Isoniazid was elevated more than 1 fold in the presence of active hepatitis (HBsAg+ve). The proinflammatory environment induced by actively replicating Hepatitis B may increases the idiosyncratic toxicity of Isoniazid.

Sub clinical liver injury as indicated by elevated ALT occur in 12-18% of those receiving INH.
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While most elevated hepatic enzymes will normalize during continued use of INH, a few patient progress to overt disease, with hepatic necrosis. Progression is associated with symptoms like anorexia, vomiting, abdominal discomfort, weakness and fatigue. These symptoms should be closely monitored and prompt discontinuation is warranted. If jaundice develops there is 10% mortality.2

Rifampicin

Introduced as a first line antituberculosis drug in 1960 and became the most vital component of short course chemotherapy in 1970s. Because it acts through P-450 enzymatic pathway its drug interaction are an important consideration in planning maintenance therapy.

- Transient elevation of ALT occur in about 1-4% of patient.
- Liver dysfunction associated with Rifampicin is of either hypersensitivity or cholestatic type.
- In the presence of liver disease it may be necessary to reduce the dosage of Rifampicin and monitor serum concentration to avoid hyperbilirubinemia. In the presence of cholestatic jaundice further dose reduction is required.2,3,7,8,11

Pyrazinamide (PZA)

Pyrazinamide is a derivative of nicotinamide and is included in first line drug because of its particular ability to kill persisters that is mycobacteria that are semi dormant often within cells. PZA is potentially hepatotoxic drug but it is a dose related phenomenon with doses of 40-50 mg/kg/day 15% develop drug induced hepatitis where as 2-3% of patient develop hepatitis with doses of 20-30 mg/kg/day. Clearly the use of Isoniazid, Rifampicin and Pyrazinamide may pose serious problem in patient who have tuberculosis and pre-existing liver disease or in whom hepatic dysfunction develops either clinically or chemically after initiation of tuberculosis treatment. Patients with underlying liver disease are subject to a higher incidence of drug related idiosyncratic or hepatotoxic reactions. It is important therefore to identify high risk patient (table II) who may require closer surveillance for symptoms of clinical and biochemical hepatitis.2,3,13,14

Table I. High risk patients for hepatotoxic reaction to anti tuberculosis drugs

- Persons more than 35 years of age.
- Persons from areas where hepatitis is endemic
- Postpartum African-American and Hispanic women
- Persons with
  - Alcohol induced liver disease on a history of substance abuse.
  - A history of malnutrition or Kwashiorkor
  - AIDS or HIV infection.
  - Active or chronic viral hepatitis.
  - A history of chronic use of enzyme inducing agent or medication causing drug interaction.

Drug induced hepatitis in a recent study in Singapore revealed that the incidence of TB drug induced hepatitis was 5.3% age more than 60 year, abnormal baseline transaminase/bilirubin levels and female sex were risk factor associated with development of TB drug induced hepatitis. The median time of drug induced hepatitis was 38 days.14

Treatment of patients with liver disorder

The patients with the following condition can receive short course chemotherapy regimens provided that there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute hepatitis, excessive alcohol consumption.

Established chronic liver disease

Isoniazid plus Rifampicin plus 1 or 2 non hepatotoxic drugs such as Streptomycin and Ethambutol can be used for a total treatment duration of eight months. An alternative regimen is Streptomycin plus Isoniazid plus Ethambutol in the initial phase followed by INH and Ethambutol in the continuation phase with a total treatment duration of 12 months. Patients with liver disease should not receive PZA. Therefore the recommended regimen are the following- 2SHRE/6HR or 2SHE/1OHE.3,15,17
Treatment of TB during acute hepatitis (Acute viral hepatitis)
It is rare eventually that patient has TB and also at the same time acute hepatitis unrelated to TB or anti TB treatment. Clinical judgment is necessary. In some cases it is possible to defer TB treatment until acute hepatitis has resolved. In other case when it is necessary to treat TB during acute hepatitis the combination of Streptomycin and Ethambutol upto maximum duration of 3 months is safest until the hepatitis has resolved. The patient can receive a continuation phase of six month with Isoniazid and Rifampicin. Treatment of drug induced hepatitis during antitubercular therapy has been described in flow chart.

Monitoring of antitubercular chemotherapy
- It is always recommended that antitubercular drugs should be started after confirmation of diagnosis.
- Those who have established CLD should be close monitored.
- Those whose age is more than 50 years should be closely monitored.
- Base line LFT. e.g. SGPT & S. bilirubin should be done if it is raised HBsAg & Anti HCV should be sent.
- Every patient receiving anti TB should be clinically seen by consultant physician at least once in a month. Patients should be carefully educated about the sign and symptom of drug induced hepatitis (dark urine, loss of appetite, vomiting, abdominal discomfort) should be instructed to discontinue treatment promptly and see their health care providers.
- Pt should be counselled to avoid alcohol completely. Pregnant women should be closely monitored. Ask to avoid analgesic like paracetamol in third trimester.
- PZA should be avoided in patients with abnormal baseline findings on LFT.
- Try to find out offending drug by doing following investigation:
  - S. bilirubin, SGPT, SGOT, Alkaline phosphatase, Serum uric acid, CBC, ESR
  - Disproportionate increase in bilirubin level in relation to liver enzymes levels may be due to the use of Rifampicin, where as abnormal findings on LFT and hyperuricemia with or without arthritis may led the clinician to incriminate Pyrazinamide. During reintroduction of drugs-offending agents should be introduced lastly with close monitoring.

Conclusion
Side effect of most commonly and first line antitubercular drug range for minor gastrointestinal symptom to severe hepatotoxicity, if unrecognised they can lead to increase morbidity and mortality as well as higher healthcare cost Erratic treatment protocols should be avoided. Recognition of the problem and planning and implementation of modified treatment protocols when needed may play a dominant role in treating and controlling tuberculosis and may prevent morbidity and mortality sometimes associated with tuberculosis treatment.
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