Antituberculosis Drugs and Hepatotoxicity

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General Aspects

The three key anti-tuberculosis drugs, viz isoniazid, pyrazinamide and rifampicin, are potentially hepatotoxic.[1] Deaths due to fulminant liver necrosis have been reported, albeit rare in occurrence. With the changing demographics and clinical characteristics of tuberculosis patients in many parts of the world, hepatotoxicity is of increasing concern in the treatment of this disease.

A meta-analysis has shown an incidence rate of liver toxicity of 2.6% with isoniazid and rifampicin co-administration, but only 1.1% with rifampicin alone, and 1.6% with isoniazid alone.[2] Despite earlier controversies, more recent studies suggest an important hepatotoxic potential of pyrazinamide among various components of the short-course antituberculosis drug regimen. As the hepatotoxicity incurred by pyrazinamide is likely to be dose-related, several authorities now recommend the use of lower daily or thrice-weekly dosages of the drug.[1,3] With its possibly lower potential for hepatotoxicity, the American Thoracic Society / Centers for Disease Control and Prevention / Infectious Disease Society of America (ATS/CDC/IDSA) currently recommend rifampicin to be restarted first, after recovery from antituberculosis chemotherapy-induced hepatitis.[3]

In contrast to the treatment of active disease, single drugs or simple 2-drug combinations are generally employed in the treatment of latent tuberculosis infection (LTBI). However, hepatotoxicity remains an important concern, especially for the use of 2 months of rifampicin plus pyrazinamide in the treatment of LTBI among individuals not infected with HIV.[4] For unknown reasons, the reported hepatotoxicity rates were often higher than those reported in the historical short-course treatment trials involving the concomitant use of isoniazid, rifampicin and pyrazinamide. Such rates of major side-effects are unacceptable for a prophylactic therapy. The revised ATS/CDC recommendations now state that rifampicin plus pyrazinamide should generally not be offered to persons with LTBI.[5]

Mechanisms and Immunogenetics

The pathogenesis of drug-induced hepatotoxicity is still not entirely clear for most offending agents. While a dose-related toxicity may exist, a direct correlation between serum drug levels and hepatotoxicity has not been well reported. Thus, the clinical relevance of therapeutic monitoring of serum rifampicin and isoniazid concentrations in managing antituberculosis drug-associated toxicity is still being explored. Hypersensitivity to antituberculosis drugs may be a possibility in some cases of drug-induced hepatitis, especially when patients present with concomitant skin rash, fever, arthralgia and eosinophilia. An altered profile of anti-oxidants with increased lipid peroxidation may suggest that isoniazid- and rifampicin-induced hepatotoxicity are mediated through oxidation damage. One possible mechanism for the additive or synergistic hepatotoxicity of isoniazid and rifampicin is through liver enzyme induction in the hydrolase system enhancing the toxicity of some of the isoniazid metabolites. Antituberculosis drug-induced hepatitis has also been found to be associated with acetylator phenotypes and other genetic polymorphisms, including cytochrome P450 2E1 and glutathione S-transferase M1, and certain Major Histocompatibility Complex Class II associated HLA-DQ alleles.

Risk Factors

Clinical risk factors for drug-induced hepatotoxicity during treatment of tuberculosis include old age, extensive tuberculosis disease, malnutrition, alcoholism, chronic viral hepatitis B and C infections, and HIV infection. One recently published prospective cohort study from Spain[6] has shown the incidence of antituberculosis drug-induced hepatotoxicity (serum transaminase >3 times the upper limit of normal) to be significantly higher in the group with risk factors (18.2%) than in the group without (5.8%). Severe hepatotoxicity (serum transaminase >10 times the upper limit of normal) occurred in 6.9% of the risk factor group and in 0.4% of the group without risk factors. Patients with chronic viral hepatitis infections or HIV infection are subject to 3 to 5 times the risk of drug-associated hepatic dysfunction or toxicity. Chronic hepatitis B and C are of particular relevance in many parts of Asia, and HIV infection is also soaring in some Asian countries. A few studies have shown that the female gender is at an increased risk, but the underlying mechanism has yet to be unravelled. Organ transplant recipients are also at risk, and one possibility seems to be the additive toxic effects of immunosuppressive drugs administered concomitantly. Other examples of interactive toxicity with antituberculosis drugs include acetaminophen and anticonvulsants, particularly in those regimens including isoniazid.

Management Issues

Before commencement of antituberculosis chemotherapy, a detailed history should be obtained to identify possible risk factors for hepatotoxicity. Liver function tests should be performed to provide baseline values for comparison in due course. The patient should be advised to refrain from alcohol use, and both physicians and patients must be prudent in the co-administration of other medications.

To minimise the risk of hepatotoxicity, all patients should be thoroughly educated about the symptoms of hepatitis, and advised to report them promptly for early evaluation. Close clinical monitoring is essential. Although there is some controversy regarding whether routine liver chemistry assessment should be carried out, those patients with risk factors for hepatotoxicity should have regular monitoring biochemically.[3,7] Patients with underlying hepatic abnormality pose a significant problem. Fluctuations in biochemical indicators of liver function can confound monitoring for drug-induced hepatitis,[3] and compromised liver reserve would also increase the risk for hepatotoxicity. Drug regimens with fewer potentially hepatotoxic agents might be beneficial for these patients. However, tuberculosis involvement of liver, usually in the form of microgranulomata, can occasionally cause abnormal baseline liver function tests, and these would in fact improve with effective antituberculosis treatment.[3] Most drug-induced hepatitis occur within the initial 2 months of therapy. Closer monitoring, at weekly / biweekly intervals for example, is therefore recommended during the initial 2 months, followed usually by more widely spaced assessments all through the rest of treatment, for patients with significant underlying liver disease or otherwise at risk of major hepatotoxicity.

Transient changes in bilirubin and transaminase levels are relatively common during antituberculosis chemotherapy, and may not signify true organ toxicity. Table 1 depicts the cut-off levels of serum bilirubin and transaminases for withholding therapy among asymptomatic patients, as suggested by various professional authorities.[3, 7, 8] Caution should also be exercised in the presence of a stepwise escalation of transaminase levels and / or a persistent elevation of bilirubin levels. It appears that for patients who are going to develop hepatitis eventually, an elevated enzyme level 3 times the upper limit of normal may easily become 5 times the upper limit of normal in due course. The American Thoracic Society indeed recommends stopping antituberculosis drugs when the serum transaminase level reaches 3 times the upper limit of normal for patients with symptoms suggestive of hepatitis. Symptoms like anorexia, nausea, vomiting, epigastric distension, right upper abdominal discomfort, malaise and weakness are important,[1] and more so are relevant signs such as jaundice and hepatomegaly. Indeed, regardless of the concurrent severity of biochemical dysfunction, presence of definite and relevant symptoms would generally prompt the cessation of all antituberculosis drugs. On the other hand, there are possible limitations in symptom monitoring. Aside from concern over the specificity, symptoms can evolve very quickly in association with rapid deterioration of liver status, symptomatic thresholds may be affected by old age and other socio-epidemiologic factors such as drug addiction, alcoholism or psychiatric illnesses, and prolonged duration of symptoms may also be associated with a poorer overall prognosis.

Diagnosis of drug-induced hepatotoxicity is often based on circumstantial evidences, including the temporal relationship between the introduction of a drug and the onset of liver injury, as well as the resolution of manifestations of such injury following drug withdrawal. Endemic viral hepatitis can fortuitously occur during antituberculosis therapy, and they should be excluded wherever appropriate. Rechallenge with the suspected drug may not be safe or always necessary, unless alternatives do not exist. While some authorities[7,8] found it possible to reinstitute the "full" antituberculosis regimen after recovery from the drug-induced hepatitis, it appears that most often dosage modification is necessary, especially for isoniazid and/or pyrazinamide, unless a predominant co-insulting factor such as alcohol could be totally withdrawn in the presence of very good liver function reserve / recovery.

If the tuberculosis disease is of lesser severity in terms of radiographic extent, bacillary load and infectiousness, it may be possible to withhold therapy until full recovery of liver chemistry. The desirable waiting time also depends on whether hepatotoxicity sets in during the initial, or the continuation phase of therapy, and the amount of therapy received prior to the onset of such toxicity. The patient can then be retreated with a regimen containing fewer potentially hepatotoxic drugs. The ATS / CDC / IDSA have made some suggestions regarding such regimens.[3] Table 2 shows some important examples of drugs with low or little hepatotoxic potential. One possible choice of such regimen embraces the use of streptomycin, ethambutol and isoniazid. Whenever possible, it seems advisable to resume the use of both isoniazid and rifampicin (by slow sequential introduction) so that the total duration of treatment will not be unduly long. Some fluoroquinolones such as ofloxacin / levofloxacin, and perhaps ciprofloxacin, were found to have low hepatotoxic potential in the majority of recipients who developed hepatic intolerance to the first-line antituberculosis drugs. Fluoroquinolone-containing interim regimens are often preferred if hepatotoxicity occurs during the initial intensive phase of chemotherapy, and the anticipated interruption of chemotherapy extends beyond 2 weeks, especially in the presence of severe tuberculosis. As the victim of hepatotoxicity has usually received pyrazinamide for sometime earlier on, this drug, with its significant hepatotoxic potential and putative activity mainly in the initial phase, is generally not suggested to be resumed after the successful reintroduction of both isoniazid and rifampicin for treating drug-susceptible disease. In uncommon occasions, when co-administration of rifampicin and isoniazid proves impossible, then the fluoroquinolone can be incorporated as a component of the final definitive antituberculosis drug regimen.

Table 1 Suggestions on Managing Drug-Induced Hepatitis in Tuberculosis

Authority	Monitoring in presence of risk factors# (especially liver diseases)	Stopping drugs if clinical or symptomatic hepatitis	Cut-off levels for stopping drugs (even when asymptomatic)	
			ALT	Bilirubin
ATS	Yes	Yes	5X$^{\Delta}$	↑
BTS	Yes	Yes	5X	↑
ERS	-	Yes	5X	↑
HKTBS	Yes	Yes	3X*	2X†

Kindly see text for details
Δ AST (aspartate transaminase) generally preferred
∗ progressive escalation
† persistent elevation

ATS = American Thoracic Society
BTS = British Thoracic Society
ERS = European Respiratory Society
HKTBS = Hong Kong Tuberculosis Service
ALT = alanine transaminase

Table 2 Antituberculosis Drugs and Their Comparative Potentials for Hepatotoxity

Greater Potential	Lower (or Little) Potential
Isoniazid	Streptomycin, Kanamycin, Amikacin, Capreomycin
Rifampicin, Rifabutin	Ethambutol
Pyrazinamide	Ofloxacin, Levofloxacin, Ciprofloxacin
Ethionamide, Prothionamide	Cycloserine
Para-aminosalicylic acid	

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