A Guide to the Management of Tuberculosis in Patients with Chronic Liver Disease

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Tuberculosis remains one of the 'Captains of the Men of Death' even today, particularly in the developing world. Its frequency is increased 14-fold in patients with chronic liver diseases (CLD) and liver cirrhosis, more so in those with decompensated disease, probably due to the cirrhosis-associated immune dysfunction syndrome, and case-fatality rates are high. The diagnosis of tuberculosis, particularly the interpretation of the Mantoux test, is also fraught with difficulties in CLD, especially after previous BCG vaccination. However, the greatest challenge in the patient with CLD or liver cirrhosis and tuberculosis is managing their therapy since the best first-line anti-tuberculosis drugs are hepatotoxic and baseline liver function is often deranged. Frequency of hepatotoxicity is increased in those with liver cirrhosis, chronic hepatitis B and chronic hepatitis C, possibly related to increased viral loads and may be decreased following antiviral therapy. If hepatotoxicity develops in those with liver cirrhosis, particularly decompensated cirrhosis, the risk of severe liver failure is markedly increased. Currently, there are no established guidelines for anti-tuberculosis therapy (ATT) in CLD and liver cirrhosis although the need for such guidelines is self-evident. It is proposed that ATT should include no more than 2 hepatotoxic drugs (RIF and INH) in patients with CLD or liver cirrhosis and stable liver function [Child-Turcotte-Pugh (CTP) ≤ 7], only a single hepatotoxic drug (RIF or INH) in those with advanced liver dysfunction (CTP 8–10) and no hepatotoxic drugs with very advanced liver dysfunction (CTP ≥ 11). A standard protocol should be followed for monitoring ATT-related hepatotoxicity and for stop rules and reintroduction rules in all these patients, on the lines proposed here. It is hoped that these proposals will introduce uniformity and result in streamlining the management of these difficult patients. (J CLIN EXP HEPATOL 2012;2:260–270)

The incidence of tuberculosis has been on the wane in the developed world with advances in public health, better standards of living and improvement in the nutritional status of the general population. Better diagnosis and improved healthcare facilities have resulted in higher detection rates and the development of effective anti-tuberculosis drugs (ATD) over the last six decades. The outbreak of the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) pandemic in the decades of the 1980s and 1990s led to an upsurge in the incidence of tuberculosis in the West and around the globe but this has now been checked with the widespread use of highly active anti-retroviral therapy

(HAART). However, tuberculosis remains a common problem in the developing world, especially in countries like China and India. As more and more patients with liver disease and cirrhosis get evaluated for liver transplantation in these parts of the world, the number of patients detected to have tuberculosis in the presence of liver disease is likely to increase.

CIRRHOSIS—A RISK FACTOR FOR TUBERCULOSIS

Although the *tubercle bacillus* can infect anyone, certain factors increase risk of the disease. Mainly, these are factors that cause immune-suppression in some form or the other and include HIV/AIDS, diabetes, end-stage kidney disease, cancer chemotherapy, drugs to prevent rejection of transplanted organ, some drugs used to treat rheumatoid arthritis, Crohn's disease and psoriasis, malnutrition, advanced age, etc. End-stage liver disease is also considered to be an independent risk factor for tuberculosis.¹ In a recent Danish study incidence of tuberculosis among patients with liver cirrhosis was increased 14-fold, being 168.6 per 100,000 person years compared to 7.8 per 100,000 person years in the general population.¹ The highest incidence rate of 246 per 100,000 person years of risk was among men above 65 years of age. The 30-day case-

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Abbreviations: HIV: human immunodeficiency virus; AIDS: acquired immune deficiency syndrome; ATD: anti-tuberculosis drugs; ATT: anti-tuberculosis therapy; ALT: alanine aminotransferase; HAART: highly active anti-retroviral therapy

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fatality rate was 27.3% and the 1-year case-fatality rate was 47.7%.¹ These data demonstrate that not only are patients with liver cirrhosis at increased risk of tuberculosis but also that their prognosis is poor. Similar observations have been reported from a study in western India.² In a recent study from Mumbai, Baijal et al² found that the prevalence of tuberculosis in patients with liver cirrhosis was fifteen times higher than in the general population, and was significantly higher in alcoholics. However, Wu et al³ found that patients with liver cirrhosis did not have an increased risk of pulmonary tuberculosis.

Patients with liver cirrhosis who develop tuberculosis are generally decompensated, the majority having Child-Turcotte-Pugh (CTP) grade B or C liver function. Although they are at a higher risk of developing both pulmonary and extra-pulmonary tuberculosis,⁴ extra-pulmonary forms, especially tuberculous peritonitis and disseminated tuberculosis, are commoner than in those without cirrhosis. The bacterium is more virulent and the risk of developing multi-drug-resistant tuberculosis is also high.³ Tuberculous peritonitis in cirrhotic patients is more frequently associated with extra-peritoneal tuberculosis, an insidious onset, and less advanced disease at onset.⁵ Adenosine deaminase level analysis is useful in the detection of tuberculous peritonitis in patients without cirrhosis; however the presence of cirrhosis reduces its sensitivity to 30%.⁶ Laparoscopic biopsies and ultrasound or CT-guided fine needle aspiration cytology provide definitive diagnosis of tuberculous peritonitis.^{7,8}

CIRRHOSIS—A STATE OF IMMUNE SYSTEM DYSFUNCTION

Patients with chronic liver disease have suboptimal immune function with relative derangements of cell-mediated immunity. Cirrhosis-associated immune dysfunction syndrome is a multi-factorial state of systemic immune dysfunction in which the ability to clear cytokines, bacteria, and endotoxins from circulation is decreased.⁹ The liver contains 90% of the cells of the reticuloendothelial system that are central to clearing bacteria, such as Kupffer cells and sinusoidal endothelial cells.⁹ Porto-systemic shunting and reduced RE cell mass in patients with cirrhosis allow more bacteria and endotoxins to bypass the liver and enter the systemic circulation. There is reticuloendothelial system dysfunction in patients with cirrhosis; monocyte spreading, chemotaxis, bacterial phagocytosis, and bacterial killing are significantly reduced in cirrhosis compared with controls.⁹ Patients with cirrhosis show decreased neutrophil mobilization and phagocytic activity, a phenomenon that correlates with severity of liver disease. Hyperammonemia and hyponatremia affect neutrophil cell volume and impair phagocytosis.¹⁰ Cirrhosis-associated immune dysfunction is also complicated by factors such as malnutrition, immunosuppressive medications and alcohol intake. Chronic and acute alcohol consumption is associated with a decrease in T cells,

B cells, natural killer cells, monocytes and an increase in proinflammatory cytokines.¹¹

HEPATIC DRUG DISPOSITION IN CIRRHOSIS

Altered handling and clearance of drugs is expected in patients with liver diseases. However ATD hepatotoxicity is thought to result via genetic or acquired polymorphisms in cytochrome P450 cytochromes, acetylator status or other metabolic pathway(s).^{12,13} It is not known if hepatic impairment increases the risk for most drugs acting through unpredictable, idiosyncratic mechanisms leading to reactive metabolites or other potentially hepatotoxic intermediaries.¹⁴ For now, clinical judgment, combined with biochemical monitoring, remains the mainstay of drug use in this setting, pending the development of a sensitive biomarker to predict drug-induced liver injury in patients with cirrhosis of liver.¹⁴

DIAGNOSIS OF TUBERCULOSIS IN END-STAGE LIVER DISEASE

A large number of patients are detected to have latent tuberculosis by tuberculin testing, and most patients have asymptomatic tuberculosis which is not apparent clinically. The interpretation of a Mantoux test is difficult in the setting of liver cirrhosis, since most patients have deficiencies in their immune function.⁹ Also, most patients in India and the south Asian subcontinent will have been vaccinated against tuberculosis with a BCG vaccine. After BCG vaccination the interpretation of a tuberculin test is fraught with uncertainties in the presence of liver cirrhosis. Although a vast majority of transplant candidates are anergic, tuberculin reactivity has been documented in 20–25% of these patients¹⁵ and identifies a subgroup at risk for developing tuberculosis after transplantation.^{16,17} The optimal management of tuberculin skin test-positive patients with end-stage liver disease continues to pose a dilemma for care providers. PPD has been traditionally used to screen tuberculosis. Although effective, it is sometimes inconvenient for evaluating patients who live far from a medical center. Interferon-gamma release assay is an alternative to PPD testing. The test requires only a single contact with a patient. In addition, unlike the PPD, which is subject to interpretation bias, interferon-gamma release assays are machine read and have single cutoffs. Thus, there is little subjectivity to the reading of results. Interferon-gamma release assays have been tested and found to perform reasonably well in healthy populations as well as in patients with end-stage liver disease.^{16–19}

ANTI-TUBERCULOSIS THERAPY

The treatment of tuberculosis in patients with significant liver disease is challenging for several reasons. The ability

to tolerate anti-tuberculosis therapy (ATT) and its potential hepatotoxicity are major concerns in patients with advanced cirrhosis or end-stage liver disease since most of the first-line ATD may demonstrate hepatotoxicity as an adverse effect and can result in treatment discontinuation due to associated morbidity. Firstly, in the presence of preexisting liver disease, the likelihood of drug-induced hepatitis may be higher.^{1,20,21} Secondly, the outcome of drug-induced hepatitis in patients with marginal hepatic reserve may be serious, even fatal. Thirdly, monitoring of drug-induced hepatitis may be confounded in the presence of underlying liver disease due to fluctuating liver function tests related to the preexisting liver disease. Lastly, derangement in liver function tests caused by tuberculosis may improve with ATT.^{21–23} There are no data related to safe use of ATD in patients with underlying chronic liver disease. Park et al found that independent risk factors for ATT drug-induced liver injury were female gender, number of hepatotoxic ATD administered and baseline ALP levels

but not cirrhosis itself.²⁴ Different ATD have varying hepatotoxicity, and different regimens of ATD may be used depending upon severity of liver disease. Padmapriyadarsini et al²⁵ observed that an increase in hepatic transaminase values to more than 2 times the upper limit of normal (>80 IU) occurred in 24% of HBV and 20% of HCV co-infected patients who received concurrent ATT either as preventive regimen or as treatment regimen for tuberculosis, which is far higher than the hepatotoxicity seen in patients without liver disease.

Anti-Tuberculosis Drugs

ATT consists of first-line and second-line drugs (Table 1). Among the first-line drugs, isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) are associated with hepatotoxicity and may result in additional liver damage in patients with preexisting liver disease. Considering the efficacy of these drugs, however (particularly INH and RIF), it is generally recommended that they be used if

Table 1 Anti-tuberculosis drugs.

Anti-tuberculosis drugs	Comments
First-line drugs	
Isoniazid	<ul style="list-style-type: none"> • Profound early bactericidal activity against rapidly dividing cells • Inhibits the synthesis of mycolic acids in the bacterial cell wall
Rifampicin	<ul style="list-style-type: none"> • Profound early bactericidal activity against rapidly dividing cells and also against semi-dormant bacterial populations • Inhibits bacterial DNA-dependent RNA polymerase
Pyrazinamide	<ul style="list-style-type: none"> • Weakly bactericidal • Its active form, pyrazinoic acid, disrupts the bacterial membrane and inhibits membrane transport functions • Exert greatest activity against the population of dormant or semi-dormant organisms contained within macrophages or the acidic environment of caseous foci
Ethambutol	<ul style="list-style-type: none"> • Prevents arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase, thus disrupting the arabinogalactan synthesis resulting in the inhibition of mycolyl-arabinogalactan-peptidoglycan complex that leads to increased permeability of the cell wall. • Included in initial treatment regimens primarily to prevent emergence of RIF resistance when primary resistance to INH may be present
Second-line drugs	
Streptomycin	<ul style="list-style-type: none"> • Bactericidal • Protein synthesis inhibitor; it binds to the small 16S rRNA of the 30S subunit of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit
Amikacin/Kanamycin/Capreomycin	<ul style="list-style-type: none"> • Bactericidal, protein synthesis inhibitor • Used for treating patients with drug-resistant tuberculosis • There is nearly always complete cross-resistance between the two drugs, but most streptomycin-resistant strains are susceptible to both
Cycloserine	<ul style="list-style-type: none"> • Bacteriostatic • Used for treating patients with drug-resistant tuberculosis • May also be used on a temporary basis for patients with acute hepatitis in combination with other non-hepatotoxic drugs
Ethionamide	<ul style="list-style-type: none"> • Bactericidal • Used for treating patients with drug-resistant tuberculosis
Fluoroquinolones: ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin	<ul style="list-style-type: none"> • Bactericidal • Used for treating patients with drug-resistant tuberculosis
Para amino salicylic acid (PAS)	<ul style="list-style-type: none"> • Bacteriostatic

possible, even in the presence of preexisting liver disease. Of all these drugs RIF is least likely to cause hepatocellular damage, although rarely it is associated with cholestatic jaundice. Of the three agents, PZA is probably the most hepatotoxic.

First-Line Drugs

Isoniazid

INH is a bactericidal drug, which is effective against both intra- and extra-cellular organisms since it inhibits the synthesis of mycolic acids in the bacterial cell wall. It is an important and integral part of most anti-mycobacterial regimens. In the early 1970s it became apparent that severe hepatic injury leading to death may occur in some individuals receiving INH.²⁶ Additional studies in adults and children have confirmed this, the characteristic pathological process being bridging and multilobular necrosis. INH-induced hepatotoxicity is seen mainly as hepatocellular steatosis and necrosis, and it has been suggested that toxic INH metabolites may bind covalently to cell macromolecules.²⁷ Approximately 0.5% of all patients treated with INH monotherapy develop clinically important increases in aminotransferase levels.²⁸ In patients who are receiving combination therapies that include INH but not RIF, the incidence of hepatotoxic effects is around 1.6%; the corresponding value for regimens containing both INH and RIF is 2.5%.²⁹

INH itself is not hepatotoxic; toxicity is mediated through its metabolite, hydrazine. INH is metabolized in the liver through two main pathways. Acetyl hydrazine, a non-toxic metabolite, is formed when metabolism proceeds along the N-acetyltransferase 2 (NAT 2) pathway while hydrazine, the toxic metabolite, is formed when it proceeds along the amidase pathway.²² These enzymes are stimulated by RIF and other enzyme inducers that potentiate the hepatotoxic effects of INH.²³

Asymptomatic, self-limited increase in aminotransferase levels is observed in the majority of patients treated with INH, which does not progress to more serious forms of liver injury.²⁷ Presence of jaundice, encephalopathy and the presence of severe hepatitis (aminotransferase levels >10-fold) are associated with a poor outcome.³⁰ Approximately 5–10% of patients who have clinical symptoms of severe hepatitis including jaundice develop acute liver failure.³¹ Age appears to be the most important factor in determining the risk of INH-induced hepatotoxicity. Hepatic damage is rare in patients less than 20 years old; it is observed in 0.3% of those in the 20–34 years age group, increasing to 1.2% in the 35–49 years age group and 2.3% in those older than 50 years of age.^{26,27,32–34} Up to 12% of patients receiving INH may have elevated plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities.^{32,33} Recent treatment studies have reported significant transaminase elevation in 1–4% of those treated with INH

for latent tuberculosis infection.^{33–36} A meta-analysis of six studies estimated the rate of clinical hepatitis in patients given INH alone to be 0.6%.²¹ A large survey estimated the rate of fatal hepatitis to be 0.023%, but more recent studies suggest the rate is substantially lower.^{36–38}

Hepatotoxicity due to INH therapy seems to be idiosyncratic in most patients and does not recur with rechallenge, hence can be reintroduced after complete clinical recovery. A few cases may be due to allergic-type hypersensitivity reactions with prominent eosinophilia and rash.^{39,40}

While testing baseline and follow-up serum ALT and bilirubin levels before beginning INH therapy is desirable in all patients, it is strongly recommended for patients with an underlying liver disorder such as chronic hepatitis B and C, alcoholic hepatitis and cirrhosis, in patients who regularly consume alcohol, those with HIV infection being treated with HAART, pregnant women, and those who are up to 3 months postpartum.⁴¹ INH should be discontinued when jaundice and/or hepatitis symptoms are reported and ALT is at least three times the ULN, or if ALT is at least five times the ULN in the absence of symptoms.⁴² Most hepatitis occurs 4–8 weeks after the start of therapy. INH should be administered with great care to those with preexisting hepatic disease.

Rifampicin

RIF is a bactericidal agent which inhibits mycobacterial DNA-dependent RNA polymerase. RIF is primarily metabolized by acetylation and glucuronidation; metabolites are excreted in the bile. Hepatotoxicity associated with RIF is usually idiosyncratic.³¹ RIF may occasionally cause dose-dependent interference with bilirubin uptake due to competition with bilirubin for clearance at the sinusoidal membrane, resulting in mild, asymptomatic unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. Conjugated hyperbilirubinemia probably results from RIF inhibiting the major bile salt exporter pump, impeding secretion of conjugated bilirubin at the canalicular level.⁴³ This may be transient and occurs early in treatment or in some individuals with preexisting liver disease.^{44,45} Occasionally RIF can cause hepatocellular injury and can potentiate hepatotoxicity of other ATD.⁴³ In patients with primary biliary cirrhosis, in whom baseline transaminases were significantly elevated, clinically significant hepatitis was attributed to RIF in 7.3 and 12.5% of patients.⁴⁵ RIF can cause hepatocellular changes such as centrilobular necrosis, associated with cholestasis. Histopathological findings range from spotty to diffuse necrosis with more or less complete cholestasis. Bridging necrosis, lymphocytic infiltration, focal cholestasis, increased fibrosis, and micronodular cirrhosis have been seen in patients with RIF- and PZA-induced hepatotoxicity.²³

Idiosyncratic hypersensitivity reaction to RIF, manifested as anorexia, nausea, vomiting, malaise, fever, mildly elevated ALT, and elevated bilirubin, usually occurs in the

first month of treatment initiation.⁴⁶ Published tuberculosis-related studies have assessed RIF alone for treatment of latent tuberculosis, and all these studies confirm the low rate of hepatotoxicity of RIF, chiefly manifested as asymptomatic elevation of transaminases. Chronic liver disease, alcoholism, and old age appear to increase the incidence of severe hepatic problems when RIF is given alone or concurrently with INH.⁴¹

Pyrazinamide

PZA, a nicotinic acid derivative, is deamidated to pyrazinoic acid, which is the active form of PZA that disrupts the bacterial membrane and inhibits membrane transport functions.⁴⁷ Hepatotoxicity is the most serious side effect of PZA. When administered in a dose of 40–50 mg/kg orally, signs and symptoms of hepatic disease appear in about 15% of patients, with jaundice in 2–3% and death due to hepatic necrosis in rare instances.²³ Elevations of plasma ALT and AST are the earliest abnormalities produced by the drug. Doses employed currently (15–30 mg/kg per day) are much safer.

PZA may exhibit both dose-dependent and idiosyncratic hepatotoxicity and should be used with added caution in patients on other ATDs.²¹ Due to its excess risk of hepatic injury, PZA is not recommended for prophylaxis according to *Centers for Disease Control and Prevention (CDC)*, Atlanta, regardless of the underlying liver disease.⁴⁸ There may be shared mechanisms of injury for INH and PZA, because there is some similarity in molecular structure. PZA may induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis.⁴¹

Ethambutol

EMB is a bacteriostatic antibiotic approved for the treatment of mycobacterial infections. It works by preventing the formation of the bacterial cell wall. Mycolic acids attach to the 5'-hydroxyl groups of D-arabinose residues of arabinogalactan and form mycolyl-arabinogalactan-peptidoglycan complex in the cell wall. EMB disrupts arabinogalactan synthesis by inhibiting the enzyme arabinosyl transferase. Disruption of the arabinogalactan synthesis inhibits the formation of this complex and leads to increased permeability of the cell wall. Hepatotoxic effects of this agent are not of major concern.

Second-Line Drugs

They can be used if either hepatotoxic effects or multidrug resistance develop during first-line therapy. *Streptomycin* is a bactericidal aminoglycoside antibiotic, which is considered safe to use in patients with an underlying liver disease. *Capreomycin*, like streptomycin, is not metabolized by the liver and is eliminated unchanged through the kidneys. They are considered safe for use in patients who have an underlying liver disease and as a second-line therapy if hepatotoxic effects develop in patients treated with first-line

anti-tuberculosis drugs. *Cycloserine* also has no reported hepatotoxic effects. However, in patients with alcoholic hepatitis, an interaction between alcohol and cycloserine can lead to an increased risk of seizures.⁴⁹

Quinolones (levofloxacin, moxifloxacin, ofloxacin and gatifloxacin) are currently considered fairly safe, and their pharmacokinetics does not seem to be altered in patients who have advanced liver disease.^{50–52} Hepatotoxic effects associated with quinolones are usually mild and reversible.⁵³

Anti-Tuberculosis Therapy in Liver Disease

The severity of drug-induced liver injury, when it occurs, may be greater in patients with underlying liver disease, likely reflecting a summation of injuries.⁵⁴ The ATDs have their own hepatotoxic potential but when used in combination with each other the overall hepatotoxicity may be cumulative. Also, combining these drugs can considerably increase the global risk of hepatotoxicity in the presence of liver disease. RIF is an enzyme inducer and increases the risk of hepatotoxicity of INH and reduces the time between the initiation of INH and onset of hepatitis. Moreover, the severity of INH hepatitis is increased; however there is no information on a possible increase of the liver toxicity of PZA by RIF.

The management of patients with liver disease who develop tuberculosis varies from center to center since no guidelines have been proposed for the use of ATT in the presence of preexisting liver disease. The need for such guidelines is beyond dispute. Once established and accepted, they will help to introduce uniformity in the management of tuberculosis in liver diseases, and in the management of patients with latent and overt tuberculosis infection awaiting liver transplantation. Agreement on uniform management of tuberculosis in liver diseases is also an essential requirement for collaborative studies.

We hereby propose certain guidelines which may be useful for managing tuberculosis in patients with liver diseases. We have combined our clinical experience with data from the existing guidelines for the treatment of tuberculosis.

Acute Hepatitis

Patients with acute hepatitis rarely need to be treated for tuberculosis on an urgent basis. Since ATT can be delayed, it should be deferred until acute hepatitis has resolved.

Once there is evidence of acute hepatitis in a patient receiving ATT, it is essential to immediately stop all potentially hepatotoxic drugs such as INH, RIF, and PZA till complete clinical and biochemical resolution of hepatotoxicity. In the interim period, at least three non-hepatotoxic drugs viz. EMB, streptomycin and quinolones such as ofloxacin, levofloxacin, etc. can be used after checking renal function and visual acuity.⁵⁴ Most ATD can be safely restarted in a phased manner after complete resolution of transaminitis.

Chronic Hepatitis B Virus Infection

Hepatitis B virus (HBV) infection has been reported to be a significant risk factor for hepatotoxicity related to ATT.⁵⁵ Isoniazid monotherapy is safe in patients with HBV infection⁵⁶ while multidrug ATT is associated with significant incidence of hepatotoxicity. Multidrug therapy for tuberculosis is also associated with fulminant disease, increased mortality and later onset of hepatotoxic effects in these patients.^{55,57} Amongst 110 inactive HBsAg carriers and 97 controls without HBV infection, 38 inactive HBsAg carriers (35%) and 19 control subjects (20%) developed elevated liver enzyme levels during ATT ($P = 0.016$).⁵⁷ A higher proportion of inactive HBsAg carriers who received ATT evidenced moderate-to-severe drug-induced hepatotoxicity when compared with the control subjects (8 vs. 2%; $P = 0.05$).⁵⁷ The liver injury was also more severe by histologic assessment in the hepatitis B carriers when compared to non-carriers ($P = 0.008$).⁵⁵

A case can be made for decreasing viral load using antiviral therapy against HBV with high-potency, high genetic barrier drugs such as entecavir and tenofovir in patients with HBV infection needing ATT to prevent the development of liver dysfunction. Hepatotoxicity related to ATT was more common in HBV positive patients who were seropositive for hepatitis B e antigen (HBeAg) than among those who were seronegative for HBeAg (relative risk [RR] = 11.38, CI = 5.49–23.59, $P < 0.001$).⁵⁸ Most episodes of liver dysfunction were usually preceded by an increase in HBV-DNA levels.⁵⁵ At least one case report describes that treatment with lamivudine enabled isoniazid and rifampicin treatment in a patient with pulmonary tuberculosis and hepatitis B co-infection.⁵⁹ However, more data need to be generated before a firm recommendation can be made on this issue.

Chronic Hepatitis C Virus Infection

Although not as extensively documented as with HBV infection, increased risk for hepatotoxicity related to ATT has been noted in patients infected with HCV. While the risk of developing ATD-induced hepatitis is not increased with isoniazid monotherapy, it is increased 5-fold during multidrug therapy,^{60,61} 4-fold if the patient is HIV positive and 14-fold if a patient is co-infected with both HCV and HIV, indicating that infection with HCV and HIV are independent and additive risk factors for the development of drug-induced hepatitis during ATT.⁶¹

Kwon et al⁶² demonstrated that drug-induced hepatitis occurred more frequently in HCV-seropositive patients (13%) than in control subjects (4%). ATD reintroduction after the liver transaminase level returned to baseline was safe and successful. These findings suggest that treatment for tuberculosis in HCV-seropositive patients could be pursued in the usual manner, using standard short-course regimens, with the condition that monthly liver function tests are carefully performed.^{62,63}

Antiviral combination therapy for HCV with pegylated interferon and ribavirin may be used to reduce ATT-related toxic effects in selected patients and may also allow the reintroduction of ATD in those who previously developed hepatotoxicity when exposed to these drugs.^{61,64}

Cirrhosis

Most authorities suggest that PZA is contraindicated in the presence of liver disease although some authors believe that PZA is well tolerated in these patients.^{65–69} Current recommended dose of 15–30 mg/kg has significantly less risk of hepatotoxicity. The frequency of hepatotoxicity in patients who received PZA in doses of 25–35 mg/kg along with RIF and INH was found to be similar to those who received only RIF and INH.^{66,67}

Dhingra et al⁶⁹ recommended that, in patients with cirrhosis of liver, treatment may be started with an aminoglycoside, a quinolone and EMB. If further addition of drugs is considered necessary RIF may be added. INH may be substituted for RIF, if RIF cannot be given. PZA is best avoided in patients with chronic liver disease.

An important consideration when prescribing ATT in a patient with liver cirrhosis is the risk of liver failure due to hepatotoxicity. While the overall risk for developing hepatotoxicity is increased somewhat in patients with liver cirrhosis, the risk of liver failure and mortality when it does develop is dramatically increased. In a patient with cirrhosis, liver failure occurs when a critical threshold of hepatocellular function is crossed due to progression of liver disease.^{70,71} Any attrition of liver function due to ATD-induced hepatotoxicity in a patient with well-compensated or previously decompensated chronic liver disease may result in severe, acute deterioration, resulting in a clinical picture suggestive of acute or acute-on-chronic liver failure (ALF or ACLF) (Figure 1). With this background in mind, one needs to be circumspect in making recommendations regarding the prescription of ATT in liver cirrhosis (Table 3). Patients with well-compensated chronic liver disease may tolerate an ATT regimen containing two hepatotoxic drugs because, in case of ATD-induced hepatotoxicity, there is a chance of recovery due to preserved liver reserve. However it would be inappropriate to use any hepatotoxic drug in patients with decompensated liver disease because the chance of recovery from ATD-induced hepatotoxicity is remote in these fragile patients with exhausted liver reserve.

Regimens with Two Potentially Hepatotoxic Drugs

Treatment without Isoniazid

Therapy with four drugs (INH, RIF, PZA and EMB) is effective in the control of overt tuberculosis, despite *in vitro* resistance to INH, as long as the initial phase consisted of treatment with four drugs and RIF is used throughout

Figure 1 Deterioration in the liver function due to anti-tuberculosis drugs induced hepatotoxicity in a normal person and in a patient with previously well-compensated or decompensated chronic liver disease.

the course of treatment; results improves when PZA is used throughout the 6 months.⁷² In drug-resistant tuberculosis, failure and relapse were most strongly associated with initial drug resistance. Failure was also associated with shorter duration of RIF therapy and non-use of streptomycin, whereas the rate of relapse was higher with shorter duration of RIF therapy and non-use of PZA.⁶⁵ Thus it is reasonable to employ an initial phase regimen of RIF, PZA and EMB followed by a continuation phase of RIF, EMB and PZA.²⁹ Although this regimen has two potentially hepatotoxic medications, it has the advantage of retaining the 6 months duration.²¹ However, we always prefer to avoid the use of PZA in patients with cirrhosis of liver with compromised liver functions because the liver injury induced by this drug may be severe and prolonged.⁷³ Saigal et al found that substituting ofloxacin for INH in patients with cirrhosis of liver was associated with reduced risk of hepatotoxicity during ATT.⁷⁴

Treatment without Pyrazinamide

PZA can cause a dose-dependent hepatotoxicity and should be used with added caution in patients with liver

disease on other ATD.⁷⁵ Kaneko et al in a recent study concluded that in patients with chronic hepatitis, ATT containing INH and RIF without PZA could be used safely although the inclusion of PZA in the regimen did substantially increase the incidence of drug-induced hepatotoxicity.⁷⁶ They found that 12 of the 13 patients who developed hepatotoxicity in the HRZ group could be treated by an ATT regimen containing INH and RIF but excluding PZA. Although the frequency of PZA-induced hepatitis is slightly less than that occurring with INH or RIF, the liver injury induced by this drug may be severe and prolonged.⁷³ Therefore one might elect to employ a regimen with an initial phase of INH, RIF and EMB for 2 months followed by a continuation phase of INH and RIF for 7 months for a total of 9 months.²¹

Regimens with Only One Potentially Hepatotoxic Drugs

Single drug therapy with either RIF or INH is usually effective for patients with latent tuberculosis infection. Both short- and long-term courses, including 4 months of RIF as well as 9 months of INH have been used.⁷⁷ Generally, it is believed that RIF should be retained for treatment of

Table 2 Clinical hepatitis in persons taking isoniazid and/or rifampicin.

Drug(s)	Clinical hepatitis (%)
INH	0.6
INH plus other drugs but not RIF	1.6
INH plus RIF	2.73
RIF plus other drugs but not INH	1.1
RIF	0

INH, isoniazid; RIF, rifampicin. Source: references 21,29.

Table 3 Treatment regimens of anti-tuberculosis therapy in patient with chronic liver disease.²¹

A. Regimens with only two potentially hepatotoxic drug:
(i) Regimens without INH
(ii) Regimens without PZA
B. Regimens with only one potentially hepatotoxic drug.
C. Regimens with no potentially hepatotoxic drugs.

tuberculosis in liver disease, due to its high efficacy and lower incidence of hepatotoxicity as compared to INH and PZA. Though INH is generally more efficacious in the treatment of tuberculosis, it also is far more hepatotoxic than RIF. Additional agents in such regimens could include EMB, a fluoroquinolone, cycloserine and injectable agents like streptomycin and amikacin. The duration of treatment with such regimens should be 12–18 months, depending on the extent of the disease.²¹

Regimens with No Potentially Hepatotoxic Drugs

In the setting of severe unstable liver disease, where hepatic decompensation and complications of cirrhosis are evident, a regimen with no hepatotoxic agents might be required. In such a situation the scenario is further complicated by the development of complications of cirrhosis, such as, hepato-renal syndrome, hepatic encephalopathy, ascites and coagulopathy. Such a regimen might include injectable agents like streptomycin or amikacin/kanamycin, EMB a fluoroquinolone and another second-line oral drug. There are no data that provide guidance as to the choice of agents or the duration of treatment or that indicate the effectiveness of such a regimen. Expert opinion suggests that a regimen of this sort should be given for 18–24 months. The ATS guidelines advise the use of, then EMB with fluoroquinolone, cycloserine and capreomycin or aminoglycoside for 18–24 months if the patient has liver cirrhosis with encephalopathy.²¹

Thus ATT in patients with chronic liver disease should be used cautiously and the choice of regimen should be based on severity of underlying liver disease (Table 4).

Surveillance

ATD hepatotoxicity manifests as anorexia, nausea, vomiting, and jaundice, and generally occurs 15–60 days after initiation of therapy. Therefore monitoring liver function tests more frequently at the start of therapy is a reasonable way to identify patients with ATD-induced hepatotoxicity. Baseline measurements of serum transaminases, bilirubin, alkaline phosphatase, and creatinine, and a blood platelet count are recommended for all adults beginning treat-

ment. For patients with preexisting severe liver disease, some clinicians also recommend periodic measurement of prothrombin time and INR to assess hepatic synthetic function.⁴¹ We recommend that liver function tests should be done weekly for a month then every 2 weeks for 2 months and every month thereafter in patients with preexisting liver disease.

Three of the first-line ATD, INH, RIF and PZA can cause drug-induced liver injury. In patients without liver disease and with normal transaminase levels at baseline, potentially hepatotoxic medications should be stopped immediately and the patient evaluated promptly if serum ALT concentrations rise to more than five times the upper limit of normal (ULN) with or without symptoms or to more than three times the ULN with jaundice and/or hepatitis symptoms.⁴¹ If the AST level is less than five times the upper limit of normal, toxicity is considered to be mild, an AST level 5–10 times normal defines moderate toxicity, and an AST level greater than 10 times normal (i.e. greater than 500 IU) is severe. In addition to AST elevation, occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with RIF hepatotoxicity.

The definition of hepatotoxicity in patients with previous liver diseases is much disputed, because it is difficult to define the influence of the natural evolution of the underlying liver disease.⁵⁴ Although it is generally recommended that INH therapy be interrupted when transaminase levels increase to 3–5 times the ULN,⁶⁵ this limit has not been defined in patients with transaminase values already elevated before starting ATT. Schenker et al reported that elevations in the ALT and/or AST levels to 50–100 IU/L more than the baseline levels might define toxicity.⁵⁴ ATT should also be stopped if a rise in serum bilirubin level of more than 2.5 mg/L is observed. Serologic testing for hepatitis A, B, C and E should be performed and the patients questioned carefully regarding symptoms suggestive of biliary tract disease and exposures to other potential hepatotoxins, particularly alcohol and hepatotoxic medications. Drug-induced hepatitis is usually a diagnosis of exclusion but, in view of the frequency with which other possible causes are present, clinching the diagnosis in any given patient may be difficult.

Table 4 Use of anti-tuberculosis drugs in chronic liver disease.

Child-Turcotte-Pugh score	Liver disease	Treatment
≤7	Stable	Recommend treatment with two potentially hepatotoxic drugs, likely to be well tolerated; avoid pyrazinamide
8–10	Advanced	Recommend a regimen with only one potentially hepatotoxic drug; rifampicin is preferred over isoniazid; pyrazinamide should not be used
≥11	Very advanced	Recommend treatment regimen with no potentially hepatotoxic drugs; can use (streptomycin, ethambutol, fluoroquinolones, amikacin, kanamycin) and other second-line oral drugs for 18–24 months.

Reintroduction of Anti-Tuberculosis Drugs

Reintroduction of ATT is contraindicated in those who have experienced life-threatening hepatotoxic effects, including fulminant hepatitis and severe liver failure or have underlying decompensated liver disease. In these patients, recurrence of hepatotoxic effects might be fatal. Suitable non-hepatotoxic medications should be selected on the basis of the severity of the underlying liver disease and Child-Turcotte-Pugh score (Table 4).

It is generally prudent to continue ATT with at least three non-hepatotoxic drugs until the specific cause of hepatotoxicity can be determined and an appropriate longer term regimen begun, given that the schedule for restarting ATD is much more prolonged with drug-induced hepatitis as compared to rash or drug fever.

The implicated ATDs should be restarted one at a time after the AST concentration has returned to less than two times the upper limit of normal. After ALT returns to less than two times the ULN, RIF may be restarted with or without EMB.⁴¹ RIF should be restarted first because it is much less likely to cause hepatotoxicity than INH and is a highly effective agent (Table 2). ATD should be reintroduced in lower doses than were used in the initial therapy, e.g., INH 50 mg and RIF 150 mg and then stepped up (e.g., 50–100 mg for INH and 150 mg for RIF) every 3–4 days gradually to the recommended therapeutic doses. We do not recommend the reintroduction of PZA and should be permanently discontinued. If symptoms recur or ALT increases, the last drug added should be stopped. In patients with elevated baseline ALT from preexisting liver disease, drugs should be restarted when the ALT returns to near baseline levels in the manner described above.

CONCLUSION

In conclusion, it is clear that there is a pressing need to standardize the use of ATD in patients with CLD and liver cirrhosis. The area is bedeviled with problems and difficulties. To sample a few, these difficulties begin with making a diagnosis of tuberculosis in CLD and liver cirrhosis, assessing the presence of occult TB in the prospective transplant recipient with prior BCG vaccination, extend to the lack of strong prospective data on criteria for diagnosing ATD hepatotoxicity in the patient with CLD and previously deranged liver tests, on the efficacy of viral load lowering in CHB and CHC for ameliorating hepatotoxicity, on predicting likelihood of hepatotoxicity and liver failure in the cirrhotic patient being initiated on ATT and culminate with a lack of good data regarding efficacy of 2 hepatotoxic drugs, 1 hepatotoxic drug and no hepatotoxic drug ATT in liver cirrhosis with varying levels of liver dysfunction. The first step in this difficult terrain would be to propose a set of guidelines based on expert opinion which would allow the collection of a prospective database which is the only rational method to unravel this particular Gordian

knot. The present review is a preliminary step in this direction.

CONFLICTS OF INTEREST

All authors have none to declare.

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