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CASE REPORT

Risk factors of acute hepatic failure during antituberculosis treatment: two cases and literature review

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ABSTRACT

Hepatotoxicity is a well-known side effect of antituberculosis treatment (ATT). If not recognised in time, drug-induced hepatitis can develop, which may rapidly progress to acute liver failure. We describe two patients with acute hepatic failure caused by ATT, whose pretreatment liver function had been normal. Both patients successfully underwent liver transplantation. Possible risk factors predisposing towards ATT-induced hepatic failure were evaluated, and at least four risk factors were present in these patients. Although available guidelines do not advocate routine monitoring of liver function during ATT unless baseline values are elevated or in the case of pre-existent liver disease, this is nevertheless common practice. Liver function should always be measured in patients who develop symptoms during ATT, and rising liver function parameters should prompt immediate action to prevent the occurrence of liver failure. This report underscores that regular monitoring of liver function parameters and adherence to guidelines is especially important in patients with risk factors for ATT-induced liver disease. An evaluation of chronic viral hepatitis in risk groups before starting ATT could be worthwhile.

KEYWORDS

Acute liver failure, case report, drug-induced liver disease, hepatitis, liver transplantation, *Mycobacterium tuberculosis*, risk factors

INTRODUCTION

Tuberculosis is still a major problem worldwide. The incidence of tuberculosis in the Netherlands is 10 per 100,000 inhabitants per year, with more than half of all cases occurring in risk groups for tuberculosis, such as asylum seekers and immigrants. In countries where tuberculosis is not endemic, as the Netherlands, knowledge and experience in treating tuberculosis has diminished. Drug-induced liver disease is a well-known side effect of several drugs that are used for the treatment of active tuberculosis or latent tuberculosis infection. Mild hepatic dysfunction, defined as an increase in serum transaminases to less than five-fold the upper limit of normal levels in the absence of clinical symptoms occurs in about 10 to 20% of patients receiving antituberculosis treatment (ATT).[1,2] This is usually reversible even if treatment is continued.[1,3-5] More serious liver disease induced by ATT occurs in 1 to 3% of patients.[4,6] Higher incidences have been reported in India ranging from 8 to 39%.[6] If not recognised in time, ATT-induced liver disease can progress to acute hepatic failure and may result in death unless liver transplantation can be performed.

Several risk factors for ATT-induced hepatic dysfunction have been described, including age, sex, race, pre-existing liver disease, extent of tuberculosis, alcohol consumption, low body mass index, acetylator status, use of hepatotoxic drugs, and a high dosage of ATT in relation to body weight.[7-16] Available guidelines advocate baseline testing of liver function in all patients before starting ATT, while routine measurement of hepatic function during treatment is indicated in patients with baseline abnormalities or those with documented hepatitis B or C virus infection or alcohol abuse.[1,17,18] We describe two patients who developed liver disease and acute liver failure during ATT. Both

successfully underwent liver transplantation, one with a temporary auxiliary graft, the other orthotopically. In both patients, baseline liver function tests had been normal, there was no alcohol abuse and no information on viral hepatitis before starting ATT. However, several other risk factors for development of ATT-induced liver failure were present. The clinical course in these patients suggests that an evaluation of all potential risk factors before starting ATT could guide the monitoring of liver function tests during ATT. Moreover, these cases illustrate that strict adherence to the guidelines during treatment remains important to recognise ATT-induced liver dysfunction in time and prevent progression to acute liver failure.

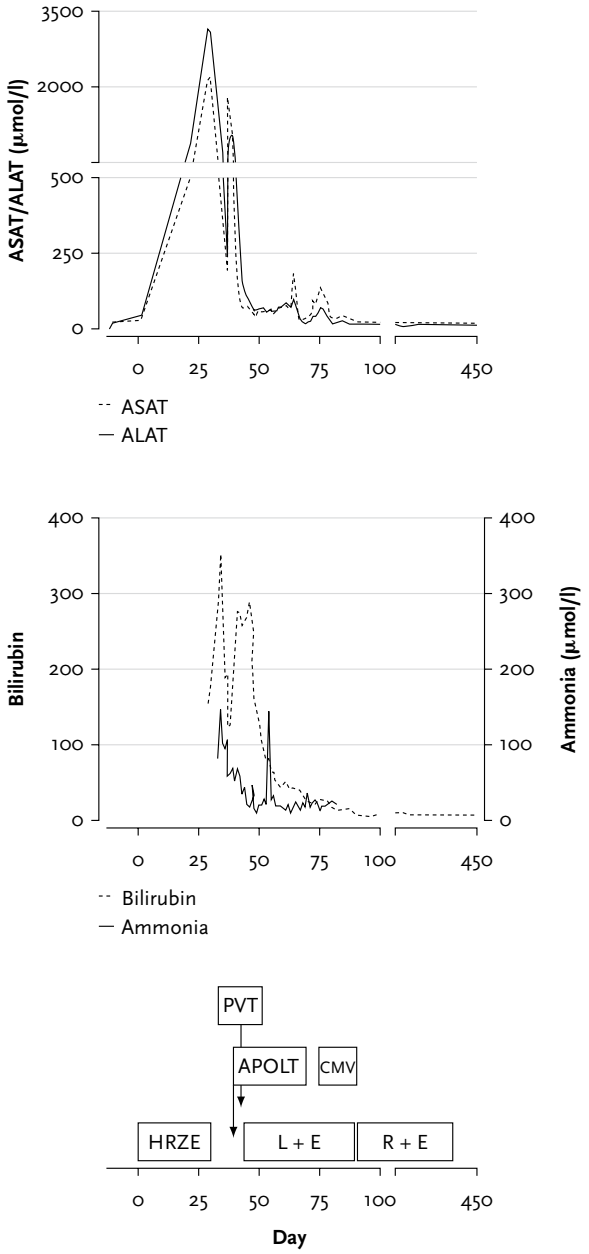
CASE REPORT

Case 1

In July 2003, tuberculous lymphadenitis of the right axilla was diagnosed in a 25-year-old woman of Philippine origin (patient A) in another hospital after a recent visit to the Philippines. A chest X-ray showed no signs of pulmonary tuberculosis. Baseline values of liver function tests (normal values between parentheses) were normal: aspartate aminotransferase (ASAT) 23 U/l (<45 U/l), alanine aminotransferase (ALAT) 19 U/l (<45 U/l), bilirubin 3 μmol/l (14 μmol/l), gamma-glutamyl-transferase (γ-GT) 18 U/l (5-35 U/l), alkaline phosphatase (AP) 59 U/l (40-120 U/l), and lactate dehydrogenase (LDH) 235 U/l (150-400 U/l). She was treated with a combination of rifampin 600 mg/day, isoniazid 300 mg/day, ethambutol 1200 mg/day and pyrazinamide 1500 mg/day (day 0). Her body weight was about 50 kg (110 lbs). On day 14, she developed fever up to 40°C lasting for three days. On day 22 she presented with an extremely itchy rash, which was ameliorated by menthol cream. The patient also complained of upper right abdominal pain, anorexia and nausea without vomiting. Liver function tests in the referring hospital showed the following abnormalities: ASAT 499 U/l (<45 U/l), ALAT 837 U/l (<45 U/l), γ-GT 28 U/l (5-35 U/l), AP 61 U/l (40-120 U/l), and LDH 788 U/l (150-400 U/l). Serum level of bilirubin and clotting parameters were not determined.

Due to a communication problem, the ATT was continued despite these findings. The symptoms worsened in the course of the following week. In addition, she became jaundiced, started vomiting and the vomit and urine were orange coloured. On day 29, isoniazid and rifampin were discontinued when progressive liver function disturbances were found: ASAT 2046 U/l, ALAT 3010 U/l, total bilirubin 156 μmol/l, AP 104 U/l, and γ-GT 71 U/l. The time course of the laboratory results is depicted in *figure 1*. One day later she presented to the other hospital with malaise. She was admitted with a diagnosis of drug-induced liver disease caused by ATT and all medication was stopped. During the next few days, her condition deteriorated with development of hepatic encephalopathy grade I/II as defined by the West Haven criteria.[19] Acute liver failure was suspected since the encephalopathy had developed within two weeks of the onset of jaundice.[20] On day 34, she was transferred to the intensive care unit of Leiden University Medical Centre (LUMC), a centre for liver transplantation.

Figure 1. *Liver function parameters in patient A, the X-axis denotes days after starting antituberculosis treatment*



APOLT = auxiliary partial orthotopic liver transplantation; HRZE = isoniazid (H), rifampin (R), pyrazinamide (Z), ethambutol (E); L + E = levofloxacin plus ethambutol; R + E = rifampin plus ethambutol; CMV = treatment for primary cytomegalovirus infection; PVT = portal vein thrombosis.

Other possible causes of liver failure were evaluated but not found. Apart from the ATT, the patient had not been on any other prescribed or self-administered drugs, besides acetaminophen 500 mg once on day 33. She and her family denied alcohol and substance abuse. IgM antibodies to hepatitis A virus, antibodies to hepatitis C virus, hepatitis B surface antigen, antibodies to hepatitis B core antigen, IgM and IgG antibodies to cytomegalovirus and antibodies to human immunodeficiency virus were all negative. There was no indication of autoimmune disease. Tests for antinuclear, antimitochondrial and antismooth muscle antibodies were negative. The ceruloplasmin level was 0.24 g/l (0.20 to 0.60 g/l), α-1 antitrypsin was 1.19 g/l (0.85 to 2.13 g/l), serum iron was 32 μmol/l (10 to 25 μmol/l) and transferrin saturation was 80%. Abdominal ultrasonography showed a normal liver and spleen. There was no ascites. Thus, the diagnosis of ATT-induced acute liver failure with grade II encephalopathy, progressive hyperbilirubinaemia and deteriorating clotting parameters was made. Based on the King's College criteria for liver transplantation as shown in *table 1*, the patient was placed on the high urgency waiting list for liver transplantation following national guidelines.[21-23] Supportive treatment was initiated, including mild cooling (35°C), administration of antibiotics and lactulose, and albumin dialysis with the Molecular Adsorbent Recirculating System, an experimental method for temporary support of liver function.

On day 38, four days after admission to the ICU, a donor liver became available. On laparotomy the recipient's liver was found to be collapsed. Histologically, the liver showed mainly centrilobular necrosis with preservation of the pre-existing architecture, without fibrosis and with a vital aspect of the remaining parenchyma. The biomarker expression of proliferation index Ki-67 showed proliferation of hepatocytes. Together, this indicated the possibility of regeneration. It was thus decided to reduce the graft to an extended left graft (segments 2, 3 and 4) for auxiliary partial orthotopic liver transplantation (APOLT). Only segment 1 of the native liver was resected. Immunosuppressive treatment consisted of basiliximab (monoclonal antibodies inhibiting the effect of interleukin-2 on lymphocytes), (methyl)prednisolone and tacrolimus. The postoperative course was complicated by partial graft portal vein thrombosis on day 39, which was treated with anticoagulation, and by primary cytomegalovirus infection diagnosed on day 72 and treated with ganciclovir. There were no episodes of rejection.

After transplantation, renewed treatment of tuberculosis was indicated because the initial treatment had been inadequate, while the immunosuppressive regimen for prevention of graft rejection is associated with a high risk of progressive tuberculosis.[24] In order to avoid toxicity and difficulties in interpreting liver function parameters, isoniazid, rifampin and pyrazinamide were avoided and nonhepatotoxic antituberculosis drugs were chosen, knowing that their effectiveness may not be optimal. On day 44, five days after APOLT and the start of immunosuppression, ethambutol at 1200 mg/day and levofloxacin at 500 mg/day were started. After recovery of the native liver, the graft could be removed on day 66. The removed graft was reused in another patient, as described in another report (submitted for publication).

After discharge from hospital on day 88, ATT with levofloxacin and ethambutol was changed to rifampin 450 mg/day and ethambutol 800 mg/day. Liver function parameters remained stable, but the patient experienced itching and gastrointestinal problems. The measured peak serum level of rifampin was 13.0 mg/l. Peak serum levels of 3 mg/l are considered adequate. After reduction of the rifampin dose to 300 mg/day all symptoms subsided. Serum levels at 0, 3 and 6 hours after intake were undetectable, 5.7 mg/l and 3.3 mg/l, respectively. She completed nine months of treatment without further complications and has fully resumed her former activities.

Case 2

In April 1996, a 54-year-old male of Chinese descent (patient B) started coughing without sputum production. In October 1996, smear-positive pulmonary tuberculosis was

Table 1. *Assessment of patients A and B according to King's College criteria for liver transplantation*

	Patient A, day 34	Patient B, day 249
PT >100 s *or*	No	No
INR >6.5 *or*	No	No
≥3 of following criteria:	Yes	Yes
• Jaundice >7 days before encephalopathy	Yes	Yes
• Age <10 *or* > 40 year	No	Yes
• PT >50 s *or* INR >3.5	Yes (PT 67.9 s; INR 5.9)	No (PT 26.1 s; INR 2.7)
• Bilirubin > 300 μmol/l	Yes (337 μmol/l)	Yes (613 μmol/l)
• Aetiology: non-A, non-B, halothane or (non-acetaminophen) drug-induced	Yes	Yes
Number of criteria present	4	4

The complete criteria include separate criteria for patients with liver failure associated with acetaminophen intoxication.[21] PT = prothrombin time; INT = international normalised ratio.

diagnosed at another hospital and therapy with isoniazid 300 mg/day, rifampin 600 mg/day, and pyrazinamide 2000 mg/day was started (day 0). His body weight was 78 kg, length 1.67 m. Pretreatment liver function parameters were normal (ASAT 12 U/l, ALAT 19 U/l, bilirubin 12 μmol/l). Three months later, there was a transient rise in the liver enzymes ASAT and ALAT. ATT was continued without modifications. Diagnostic tests for viral hepatitis were not performed at that time.

On day 208, patient B was admitted to hospital with complaints of pain in the epigastric region, anorexia, exhaustion, dizziness and a slight jaundice. ASAT was 320 U/l, ALAT 577 U/l, AP 86 U/l, γ-GT 29 U/l, LDH 363 U/l and bilirubin 27 μmol/l. The ATT was discontinued and tests were performed to determine the cause of the hepatitis. IgG antibodies to hepatitis A were positive, IgM negative. Hepatitis B surface antigen was positive, anti-HBs was negative, anti-HBc was positive with anti-HBc IgM negative, HBe Ag was negative, anti-HBe was positive, all consistent with chronic hepatitis B virus (HBV) infection. IgG antibodies to Epstein-Barr virus and to cytomegalovirus were positive. The patient was negative for human immunodeficiency virus, hepatitis C and hepatitis D antibodies.

During the ensuing weeks, ASAT and ALAT rose to 2000 U/l. Bilirubin rose to 550 μmol/l. Liver synthetic function was affected, as reflected by decreased albumin, increased prothrombin time; arterial ammonia was 46 μmol/l. He developed oedema for which diuretics were given. No other specific therapy was prescribed.

On day 242, patient B was released from the referring hospital in good clinical condition. At that time, liver function was stable, albeit grossly abnormal. On day 249 he returned to hospital complaining of increasing drowsiness. The ASAT was 124 U/l, ALAT 136 U/l, bilirubin 613 μmol/l and ammonia 68 μmol/l. The international normalised ratio was elevated at 2.7. Serum creatinine was 114 μmol/l (68-115 μmol/l), while it had been 65 μmol/l one week earlier, suggestive of developing hepatorenal syndrome. The differential diagnosis consisted of acute liver failure caused by ATT with inactive chronic HBV infection or acute liver failure due to a flare of chronic HBV infection. Patient B was transferred to the LUMC. Ultrasonography of the abdomen showed a small but homogenous liver with a normal flow in the portal vein and a normal-sized spleen. Results of repeated serology for HBV infection were identical to those reported above. HBV DNA in the serum was undetectable, so ATT-induced acute liver disease in a patient with a currently inactive chronic HBV was considered likely. Besides ATT, patient B had not taken any other drugs in the recent past. He smoked 10 to 15 cigarettes a day and the patient and his family denied alcohol abuse. The King's College criteria for liver transplantation were met (*table 1*).

His condition further deteriorated with development of hepatic encephalopathy grade IV on day 254. He was transferred to the intensive care unit. ASAT was 294 U/l, ALAT 160 U/l, bilirubin 595 μmol/l and ammonia 168 μmol/l. Prothrombin time was 30.5 seconds and international normalised ratio was 2.5. Biopsy of the liver revealed a disrupted architecture without normal liver parenchyma, massive hepatic necrosis, bridging fibrosis, interface hepatitis and cholestasis. On day 256, patient B underwent orthotopic liver transplantation. Intravenous hepatitis B hyperimmune globulin (HBIG) was administered during and after transplantation, at a later stage converted to monthly intramuscular HBIG with oral lamivudine 100 mg daily. HBsAg has remained negative after transplantation. As the patient had been treated for tuberculosis for at least seven months, no further treatment for tuberculosis was given. There has been no recurrence of tuberculosis.

ASSESSMENT OF RISK FACTORS FOR ATT-INDUCED LIVER DISEASE

Patient A had five risk factors for ATT-induced liver disease (*table 2*). The patient was taking three hepatotoxic drugs as part of ATT, she was a woman of Oriental race and had a low body mass index. In addition, the initial dosage of 600 mg rifampin per day may have been too high in relation to her weight of 50 kg (110 lbs). This is the dosage advised for patients weighing ≥50 kg.[24,25] After resuming rifampin at 450 mg/day on day 89, a very high serum concentration was measured, indirectly indicating that the initial dosage had been too high.

Patient B had four risk factors (*table 2*). He was on three hepatotoxic drugs as part of ATT, was of Oriental race, was >35 years and he had pre-existing liver disease,

Table 2. *Risk factors for liver disease induced by antituberculosis treatment in patients A and B*

	Patient A	Patient B
Age >35 years	No	Yes
Female sex	Yes	No
Oriental race	Yes	Yes
Pre-existing liver disease	No	Yes*
Extensive tuberculosis	No	No
Alcohol consumption	No	No
Low body mass index	Yes	No
Hepatotoxic drugs**	Yes	Yes
High dosage in relation to body weight	Yes	No
Acetylator status	Not determined	Not determined
Risk factors present (total)	5	4

*This was not known at the start of treatment. **Hepatotoxic drugs as part of antituberculosis treatment (isoniazid, rifampin and pyrazinamide), prescribed drugs for other indications or self-administered drugs.

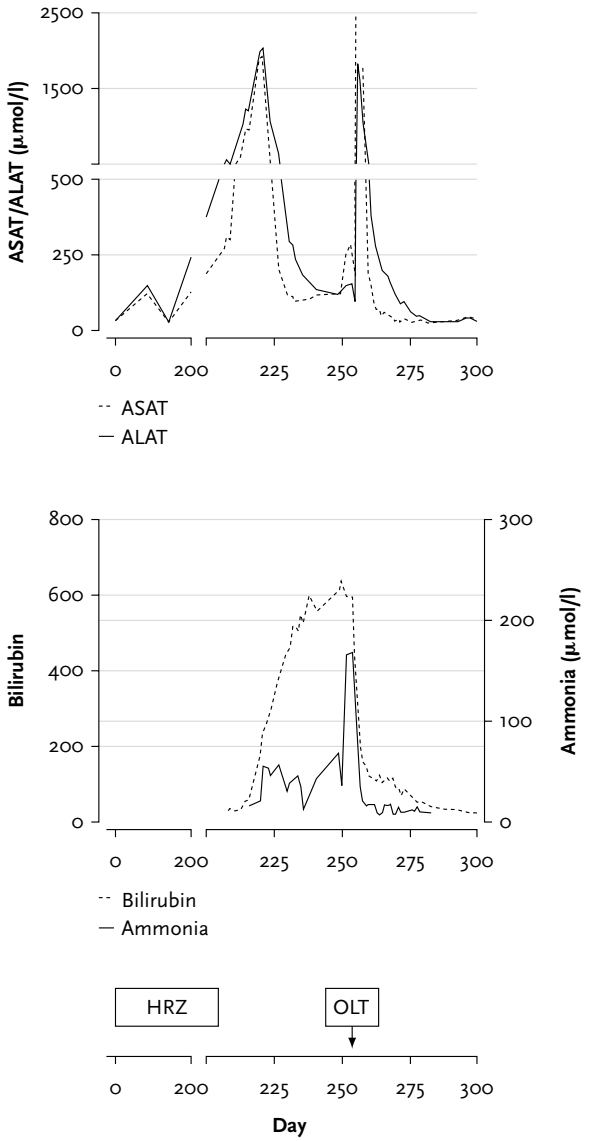
namely chronic HBV infection although the latter was first diagnosed later during ATT. He had been taking pyrazinamide for a relatively long time, considering the recommended therapeutic regimens in national and international guidelines advocate the use of this drug during the initial two months of treatment only.[1,17,18,26]

DISCUSSION

The diagnosis of acute liver failure caused by ATT was made in both the patients described above. Patient A did not have liver disease before starting ATT, while patient B suffered from chronic inactive hepatitis B virus (HBV) infection even though this was first diagnosed at a late stage during ATT and baseline liver functions had been normal. Another difference was the interval between starting ATT and onset of hepatic dysfunction, which was three weeks in patient A, while in patient B this was diagnosed after almost 30 weeks of ATT (*figures 1* and *2*). Rash is another side effect of isoniazid (2%), rifampin (0.8%) and ethambutol (0.5%). Patient A had a rash as well as liver failure but the relation to ATT-induced liver disease is unclear.[27] Patients A and B both underwent liver transplantation, temporary APOLT and orthotopic liver transplantation, respectively. The severity of liver damage precluded APOLT in patient B. The graft could be removed in patient A after regeneration of the native liver had occurred. In both patients, guidelines on the use of ATT were not strictly adhered to and this most likely contributed to the progression to fulminant liver failure. In patient A, all hepatotoxic drugs should have been stopped immediately after the symptoms had developed and liver function was significantly abnormal. In patient B, an evaluation of viral hepatitis at the time of the transient elevation of liver enzymes during ATT would have revealed the presence of HBV infection which should have led to more frequent monitoring of liver functions and to the discontinuation of pyrazinamide.

Prescribed drugs are responsible for 10 to 30% of cases of acute liver failure, and acetaminophen intoxication is the cause in the majority of these cases. ATT represents an important class of drugs that can cause acute liver failure when used in normal dosages, with an incidence of one out of every 10,000 patients taking ATT. The case fatality rate of ATT-induced hepatotoxicity has been estimated at 4.2 per 100,000 patients commencing ATT.[28] A wide disparity exists between the reported incidence of ATT-induced liver disease in India (8 to 39%) compared with reports from Western countries (2 to 3%).[6] The higher incidence in India has been attributed to various factors such as older age, higher alcohol intake, malnutrition, intestinal infections with intestinal parasites, past history of jaundice, high prevalence of chronic liver disease, indiscriminate use of drugs and concomitant viral hepatitis.[15]

Figure 2. *Liver function parameters in patient B*



The X-axis denotes days after starting antituberculosis treatment. HRZ = isoniazid (H), rifampin (R), pyrazinamide (Z); OLT = orthotopic liver transplantation.

Factors that have been associated with a higher risk of ATT-induced liver disease include female sex, age >35 years, oriental race, extent of tuberculosis, pre-existing liver disease, alcohol consumption, nutritional status defined by low body mass index and serum albumin level, certain antituberculosis drugs or combinations thereof and the dosage of drugs in relation to body weight.[7-16,29] Before starting ATT in a specific patient, apart from the measurement of baseline liver function, an assessment of all these known risk factors of ATT-induced liver disease could aid in determining the frequency of monitoring liver enzymes.

The drugs most frequently responsible for hepatotoxicity are isoniazid, rifampin and pyrazinamide.[1,4,17,18] The frequency of ATT-induced hepatotoxicity in the Netherlands is not known because this is not registered. The reported incidence of drug-induced liver disease in patients taking isoniazid or rifampin is 1.6 and 1.1%, respectively.[6] When used in combination, isoniazid and rifampin more frequently cause hepatotoxicity (2.6%) than either drug alone,[6] suggesting an additive but not a synergistic effect. The frequency of severe hepatotoxicity in patients treated with a combination of isoniazid, rifampin and pyrazinamide was 3.4%.[30]

The proposed mechanism of isoniazid toxicity is the production of a hepatotoxic metabolite in liver cells.[3,31] Isoniazid is acetylated to acetylisoniazid, which in turn is hydrolysed to yield the free hydrazine derivative that is the main cause of hepatocellular damage. Acetylator status seems to matter, with most evidence pointing towards slow acetylators having a higher risk of isoniazid-induced liver disease.[8-11,32] Large increases in transaminases were observed more often in slow acetylators (72%) than in rapid acetylators (27%),[10,15] reflecting hepatic exposure to higher drug concentrations, but the difference was only observed during the first weeks of treatment. After eight weeks of treatment the risk of ATT-induced liver disease was not different between slow and rapid acetylators.[10]

Patient B received pyrazinamide 2000 mg/day for almost seven months, which probably contributed significantly to the development of acute liver failure. Pyrazinamide hepatotoxicity is dose-dependent, liver disease rarely occurring with the current dosage of 30 mg/kg and when used for two months at the most.[4] The mechanism is unknown. Liver failure due to pyrazinamide usually occurs after long periods of ATT for tuberculosis disease. In contrast, rapidly progressive liver failure has been described during short-course treatment with a combination of rifampin and pyrazinamide (2RZ) for the treatment of latent tuberculosis infection.[30] For this reason, this regimen has now mostly been abandoned. Pyrazinamide coadministration is associated with an increased mortality in patients with (sub)fulminant liver failure due to ATT, compared with patients with the same condition who have not received pyrazinamide.[20] Pyrazinamide should be prescribed with caution to individuals with hepatic dysfunction,[27] and should not be used for longer than two months because pyrazinamide is only active during the intensive phase of treatment: see the review by Mitchison.[33] If used in patients with underlying liver disease, regular monitoring is indicated.[1]

Speculations have been made on how to distinguish which drug in an ATT regimen is responsible for a patient's ATT-induced liver disease. The interval between the start of ATT and the onset of the abnormalities in liver function can help to assess which drug is the most likely cause. Isoniazid-induced hepatotoxicity usually occurs soon after the start of ATT, as was the case in patient A, but can still occur at any later time point during treatment. Continuation of isoniazid despite symptoms has been associated with a severe clinical course and fatal outcome.[34] Pyrazinamide hepatotoxicity usually occurs after longer periods of treatment (patient B), but again this is not a rule. Isoniazid is associated with fulminant liver failure (patient A) while pyrazinamide more often leads to subfulminant liver failure (as occurred in patient B).[20] However, these parameters cannot be used in an individual patient to discriminate which drug was causative. In patients in whom liver function recovers after discontinuation of ATT, the drugs can often be restarted by sequential introduction followed by frequent monitoring of liver function parameters. This may reveal the causative drug, but liver functions more frequently remain normal or rise only insignificantly during re-challenge because the risk of recurrence of ATT-induced liver disease after resumption of ATT following normalisation of liver functions is low. There is no clear explanation for this phenomenon, but it argues against an idiosyncratic or allergic reaction as the cause of ATT-induced liver disease.

International guidelines issued by the American Thoracic Society, the British Thoracic Society and the European Respiratory Society Task Force all state that baseline determination of liver function tests should be carried out before ATT is started in patients with TB disease.[1,17,18] Notably, there are no general data to support the practice of routine measurement of liver function in patients with normal pretreatment liver function and without evidence of pre-existent liver disease, guidelines being based on clinical experience and expert opinion.[18] Elevated liver function tests are not necessarily a contraindication for ATT but alternative regimens with less or no hepatotoxic drugs are available.[1] Regular monitoring of liver functions is advocated in patients with pre-existent abnormalities or known risk factors and in patients developing symptoms.[1,17,18] In patients with latent TB infection, baseline monitoring of liver functions is only advised in selected cases with a history of liver disease, HIV infection, alcoholism or pregnancy or if the combination of rifampin and pyrazinamide is used.[1,35] Repeat measurements are advocated only if baseline values were abnormal.

So, it has not been definitively established whether liver function parameters should always be measured during ATT and how frequently, or whether this can be guided by the symptoms. However, it is generally agreed that liver parameters should be checked at regular intervals, e.g. monthly, in patients with known pre-existing liver disease, in those using comedication with a risk of interaction with ATT or if continued alcohol consumption is suspected. Guidelines for the clinical management of patients with a rise in liver function parameters during

ATT state that all drugs should be discontinued when serum transaminases exceed five times the upper level of normal.[1] In patient A, ATT was not stopped until a week after the high liver function tests were found. This delay may have contributed to the progressive deterioration as the prognosis is related to the time between onset of hepatic dysfunction and discontinuation of ATT.[9,27] Patient B was admitted to the hospital with symptoms suspicious of hepatitis and high liver enzyme values on day 207 after starting ATT. On day 136 his liver enzymes had been within the normal range. More frequent monitoring during this interval of 70 days could have revealed an elevation of liver enzymes at an earlier stage, before symptoms led to the detection of already severe abnormalities.

In patients requiring liver transplantation for ATT-induced liver failure, non-hepatotoxic drugs are preferred for the treatment of tuberculosis after transplantation in order to avoid toxicity and difficulties with interpretation of liver function parameters. In patient A, liver function parameters rose during the occurrence of partial portal vein thrombosis and later during primary CMV infection in the postoperative period. At that time, the non-hepatotoxic drugs levofloxacin and ethambutol were used. When liver function has stabilised, rifampin can generally be resumed under close monitoring. In patient A, this was done without affecting liver function and was tolerated well after adjustment of the dosage to serum levels.

The incidence of elevated liver enzymes was significantly higher in HBV carriers using ATT when compared with non-HBV carriers with such treatment, probably reflecting pre-existent liver disease.[2,30,36,37] Since coinfection with HBV is endemic in many parts of Asia, this could also contribute to the observed higher incidence of ATT-induced liver disease in India and in general to the increased susceptibility of patients from oriental origin to ATT-induced liver disease. The clinical and histological signs of ATT-induced liver disease often resemble viral hepatitis.[3,7,38] Efforts have been made to distinguish hepatitis B from ATT-induced liver disease histologically. Wong *et al*. developed a probability score to evaluate ATT as the cause of liver injury in HBV carriers and noncarriers with liver dysfunction while using ATT.[36] Except for the presence of fibrosis, which is a typical characteristic of (chronic) HBV infection, no marked difference in histopathological pattern could be observed between HBV carriers and noncarriers. It has previously been mentioned that virological tests to exclude coexistent viral hepatitis should be considered before starting ATT.[17]

In conclusion, acute liver failure is a serious complication of ATT. Monitoring of liver function parameters at regular intervals can help to prevent this condition by withdrawal of all hepatotoxic drugs when values of liver enzymes reach critical levels. An assessment of all risk factors for hepatotoxicity before starting ATT may help to determine the frequency of monitoring. Screening for chronic viral hepatitis in risk groups could contribute to the prevention of ATT-induced liver disease, especially in patients originating from regions where HBV and hepatitis C infection are endemic.

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