CASE REPORT

Anti-tuberculosis drug-induced hepatitis in renal transplant patient with pulmonary and extra pulmonary tuberculosis

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Abstract  Hepatotoxicity is a major side-effect of the medicines used in tuberculosis therapy. Although the guidelines for the management of antituberculosis drug induced hepatitis have been published from varieties of health institutes and organizations, they are to a great extent highly similar, there are nevertheless some important differences.

We report a case of hepatitis in a renal transplant recipient admitted with pulmonary and extra pulmonary (abdominal) tuberculosis and review the literature on this topic.

The introduction of antimicrobial teams, including specialist pharmacists, microbiologists and infectious disease physicians, is a major factor to improve the quality of care and faces the overcoming of antimicrobial resistance. Reintroducing one antituberculosis drug at a time with close monitoring of liver enzymes seems to be the optimal approach in the management of antituberculosis drug induced hepatitis.

With multi-disciplinary clinical approach the patient has been successfully cured and has returned to normal active life.

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1. Introduction

Tuberculosis (TB) in solid organ transplant recipients occurs mainly by the reactivation of latent disease and has been related to the type of organ transplanted, the level of immuno-suppression, and concomitant opportunistic infections. Hepatotoxicity is one of the main side-effects of the drugs used in tuberculosis treatment. Pharmacists rounding with infectious disease team (ID) play a vital role in improving the antimicrobial therapy process, therapeutic drug monitoring and the management of adverse drug reaction (Wada, 2005; Tahaoglu et al., 2001; Lopez and Schlug, 2010; Weller and Jamieson, 2004; Rapp, 2006) (Table 1).
We report a case of hepatitis in a renal transplant recipient admitted with pulmonary and extra pulmonary (abdominal) TB and review the literature on this topic. The management of hepatitis related to anti-tuberculosis, and the role of clinical pharmacist is discussed. The Medline and Sumsearch databases were included in the literature review stage. The search terms included in the literature review were: hepatitis, hepatotoxicity, tuberculosis, anti-tuberculosis, renal transplantation, infectious disease, and pharmacist.

Although the high rate of hepatitis associated with anti-tuberculosis is well established, there is no consensus on the clinical approach required for cases in which hepatotoxicity has developed (Lopez and Schluger, 2010). Our patient had a renal transplant and was taking immunosuppressants, which made it more complicated. When admitted the patient appeared weak, depressed, and without hope – most likely a shadow of his former self because of previous experience with therapy failure and long hospital stay. However, through multi-disciplinary clinical approach, the patient has returned to normal active life.

2. Patient case presentation

A 28-year-old Omani native female, married, weighing 37 kg, with a history of renal transplantation in 2006. One year after transplantation, she presented to the Emergency Department at the Royal Hospital (Muscat; Oman) with abdominal pain and fever for the last 3 weeks. She was admitted under the nephrology team, and then shifted to ID.

Before admission the patient was on maintenance immunosuppressive regimen of tacrolimus capsule 2.5 mg twice daily, mycophenolate capsule 750 mg twice daily, and prednisolone tablet 7.5 mg once daily.

The patient was not known to have had TB exposure and had no recent travel history, and she was unaware of the results of prior tuberculin skin testing. Tissue specimens obtained from the gastro-intestinal tract revealed granulomatous inflammation with bacilli visible on acid-fast stain. Sputum microscopy detected Mycobacterium tuberculosis by acid-fast stain provide the preliminary confirmation of pulmonary TB. The patient was diagnosed with pulmonary and extra pulmonary (abdominal) TB. She was isolated and Anti-Tuberculosis Therapy (ATT) was initiated under the nephrology team, and included isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (ETH), with immunosuppressives to be continued (see Box 1).

One week after starting ATT, the patient developed abnormal liver function test (LFT), and a few days later the LFT deteriorated and the patient was jaundiced with macrocytic anaemia (haemoglobin of 5 g/dL, normal range 11–18.0 g/dL). The patient appeared weak, suffered a loss of appetite (weight: 32 kg), and was febrile with a productive cough. She received a blood transfusion, ATT withheld with close LFT monitoring (Table 1). Three days later; the LFT improved and ATT was resumed. Ten days after resuming ATT, the patient again developed abnormal LFT with elevations of alkaline phosphatase to 368 IU/L (normal range 30–125 IU/L) from baseline of 100 U/L, alanine aminotransferase to 264 IU/L (10–60 IU/L), and bilirubin to 240 μmol/L (3–17 μmol/L). RIF was withheld until the bilirubin level became normal. PZA was discontinued. ETH and INH were continued and moxifloxacin was added. The patient’s LFT normalized within two weeks, rifabutin was introduced in the place of rifampicin. Prednisolone and cyclosporine were stopped, and tacrolimus was used as a single immunosuppressant. Insulin was introduced as the patient’s blood glucose level was constantly elevated. At this stage; the patient was febrile, and was shifted out of the isolation room as a result of negative culture. Two weeks later, the patient was discharged with an appointment with nephrology and ID (see Box 2).

3. Discussion

The World Health Organization (WHO) reports on overcoming antimicrobial resistance (WHO, 2000) and the European Union ‘Copenhagen Recommendation’ is that antimicrobial teams, including specialist pharmacists, microbiologists and infectious disease physicians, be established in all the hospitals (Weller and Jamieson, 2004). The Infectious Diseases Society of America’s guidelines on improving the use of antimicrobial agents in hospitals similarly encourages the introduction of such teams (Lopez and Schluger, 2010; Marr et al., 1988).

The role of the ID clinical pharmacist in the UK includes prescription monitoring, taking accurate medication histories, provision of medicines’ information, patient counselling, and regular liaison with the medical or surgical team and daily contact with the patient, educating all grades of healthcare workers and helping to develop policy. Such practice has been shown to improve patient care and provide better, more cost-effective, use of medicines (Schumock et al., 2003). The addition of a dedicated antibiotic pharmacist to an active team has been shown to benefit patients by reducing medication errors and the length of hospital stay, encouraging oral medication and ensuring appropriate drug choice (Weller and Jamieson, 2004). These benefits are achieved in a variety of ways but central to the role of the antibiotic pharmacist is the monitoring and enforcement of hospital antibiotic policy (Lopez and Schluger, 2010; Weller and Jamieson, 2004).

### Box 1  Current medication.

**ATT**
- Pyridoxine 50 mg OD
- Rifampicin 300 mg OD
- Ethambutol 600 mg OD
- INH 300 mg OD
- Pyrazinamide 1200 mg OD

**Immunosuppressants**
- Prednisolone 10 mg od
- Tacrolimus 2 mg od
- Mycophenolate 750 mg BID

### Box 2  Discharge medications.

- Ethambutol 600 mg od
- Moxifloxacin 400 mg od
- Isoniazid 300 mg od
- Rifabutin 300 mg od
- Pyridoxine 50 mg od
- Erythropoietin 30000 Iu twice weekly
- Tacrolimus 4 mg bid
- Insulin biphasic 30 Iu/day
In general, treatment duration of TB totals six months for most cases of fully sensitive disease, usually involving INH and RIF antibiotics, supplemented in the first 2 months with PZA and ETH antibiotics with the exception of TB involving the CNS when treatment should be for one year (Thwaites and et al., 2009). Guidelines for the management of antituberculosis drug induced hepatitis (ATDH) have been published by the American Thoracic Society (ATS), the British Thoracic Society (BTS), the Task Force of the European Respiratory Society, the WHO and the International Union against Tuberculosis and Lung Disease (Blumberg et al., 2003; Joint Tuberculosis Committee of the British Thoracic Society, 1998; Migliori et al., 1999; Navarro and Senior, 2006; Saukkonen et al., 2006). Although the guidelines from the ATS, BTS and the Task Force are to a great extent highly similar, there are nevertheless some important differences (Joint Tuberculosis Committee of the British Thoracic Society, 1998).

Hepatotoxicity is one of the major side-effects of the medicines used in TB therapy (Tost et al., 2004). It seems that INH, RIF and PZA each have hepatotoxic side-effects which increase when the drugs are combined (Tahaoglu et al., 2001). RIF is considered to be of low hepatotoxicity; but due to its enzyme inducer effect it may enhance the toxicity of INH when the two are combined (Tahaoglu et al., 2001). RIF has not been shown to increase the toxicity of PZA, nor to have interfered in its metabolism; however, more cases of hepatotoxicity are observed in regimens containing two months of RIF and PZA in HIV-negative patients than in those with INH (Jasmer et al., 2002; Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent, 2001; WHO, 1992).

### Table 1: Pharmaceutical care plan for anti-tuberculosis drug-induced hepatitis in renal transplant patient with pulmonary and extra pulmonary tuberculosis.

<table>
<thead>
<tr>
<th>Care issue/desired output</th>
<th>Action</th>
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<tr>
<td>Continuity of relevant medicine on admission/ Ensure no discrepancies/omission from drug chart</td>
<td>Confirm drug history, and ensure continuity of relevant medicine on admission</td>
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| Absence of actual/potential medication problems/ Ensure absence of medicine related problems | Screen patient medication for:  
  - Use renal excreted drugs  
  - Monitor drug-drug interaction between rifampicin and immunosuppressive agents |
| Pulmonary and extra pulmonary (abdominal) TB/ Cure patient and prevent the transmission of Mycobacterium tuberculosis to other persons  
  - Patients with active pulmonary TB are isolated in negative-pressure hospital rooms until they are culture negative and susceptibilities confirm that the organism is susceptible to the treatment | Initial phase: 2-months of:  
  - isoniazid 5 mg/kg (maximum 300 mg/day)  
  - pyridoxine for patients receiving isoniazid to prevent polyneuropathy, 25–50 mg orally daily dose  
  - rifampin 10 mg/kg (maximum 600 mg/day)  
  - pyrazinamide: 40–55 kg: 1,000 mg; 56–75 kg: 1,500 mg; 76–90 kg: 2,000 mg  
  - ethambutol: 40–55 kg: 800 mg; 56–75 kg: 1,200 mg; 76–90 kg: 1,600 mg  
  - The drugs are given once a day for 8 weeks (56 doses)  |
| Anti TB drug induced hepatitis (ATDH)/ Normalize LFT, avoid offending drug and continue ATT | 1. Screen lab results: Elevated LFT  
  2. Stop all ATT until LFT normalized  
  3. Start ATT one by one with close monitoring of LFT  
  4. Start ethambutol and Isoniazid  
  5. Withhold rifampicin until bilirubin level goes back to normal. Rifabutin in place of RIF  
  6. Do not re-start pyrazinamide  
  7. Start Moxifloxacin |
| Post renal transplant on immunosuppressive agents/ To prevent graft rejection with safe and effective drug regimen | Ensure suitable immunosuppressive regimen Rx, avoid excessive immunosuppression  
  - Long-term corticosteroid and cyclosporine can cause DM. Start Insulin  
  - Manage peripheral neuropathy  
  - TDM and dose adjustment to overcome the interaction with rifampicin/rifabutin |
| Anaemia related to renal disease/To correct haemoglobin level | Blood transfusion  
  - Erythropoietin  
  - Dietician input |
| Discharging patient/Compliance with therapy, Response to therapy, ADRs detection and management | Ensure patient knows all changes in drug regimen  
  - Provide written information where possible  
  - Ensure keeping patient record for follow up care |
PZA hepatotoxicity depends on its dose, and the most offending hepatotoxic effect is seen at doses of 30 mg/kg/day. Reintroduction of PZA should be avoided once hepatotoxicity occurs, as it increases the risk of recurrence (Tahaoglu et al., 2001).

The hepatocellular pattern of liver injury, which is seen in INH, RIF, PZA toxicity, has a predominant initial elevation of alanine aminotransferase (Tostmann et al., 2008). Therefore, this biochemical parameter is most often used to monitor the liver function during ATT (Tostmann et al., 2008). In this case, there was abnormal LFT with elevations of alkaline phosphatase to 368 IU/L, alanine aminotransferase to 264 IU/L, and bilirubin to 240 µmol/L. The reintroduction of the same regimen led to the same reaction, which confirms the causality. According to the WHO, a common definition of ATDH is treatment-emergent increase in serum alanine aminotransaminase greater than three or five times the upper limit of normal, with or without symptoms of hepatitis, respectively (WHO, 1992).

Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Some advise starting rifampicin because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent (Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease, 2010; World Health Organization, 2010). After 3–7 days, isoniazid may be reintroduced. In patients who have experienced jaundice but tolerate the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.

Alternative regimens depend on which drug is implicated as the cause of hepatitis. Reintroducing one drug at a time is the optimal approach, especially if the patient’s hepatitis were severe (World Health Organization, 2010). In this case; after two trials with full dosage of first line ATT, ID team changed the treatment strategy by introducing one drug at a time. The patient’s LFT normalized within two weeks. INH was started with ETH. RIF was withheld until the bilirubin level became normal. Then rifabutin was introduced in the place of RIF for its lower liver enzymes induction activity. At this stage, the patient was tolerating the new regimen, and LFT was constantly normal. Therefore; the decision of discontinuing PZA was made, and moxifloxacin was added from the second line ATT which has no hepatocellular toxicity, and is among the newer quinolones that has the most in vitro activity against M. tuberculosis, followed by levofloxacin, ofloxacin, and ciprofloxacin (Hu et al., 2003).

In a prospective study, forty five patients with new TB developed hepatotoxicity after the ATT was randomized to a drug regimen consisting of INH, RIF, ETH and streptomycin (STR) administered by gradually increasing the number and dosage of the drugs (group I). Patients in group II were retreated with the same regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) in the same dosages throughout. This study revealed that the rate of recurrence of hepatotoxicity in the retreatment of tuberculosis is less than when pyrazinamide is not included in the regimen (Tahaoglu et al., 2001). In this study, the most common predisposing factor of hepatotoxicity was alcoholism, followed by being a carrier of VHB, and, lastly, taking other hepatotoxic drugs. Another retrospective study recommended in the presence of risk factors, to reduce the dose of PZA to 20–25 mg/kg and not to re-introduce this drug if hepatotoxicity occurs (Hu et al., 2003).

Organ transplantation places patients at an increased chance of contracting TB. In the United States the risk of contracting TB was estimated to be 20–74 times greater in transplanted patient than in the general population (Lopez and Schluger, 2010). In general, transplanted kidney patients should be managed with the standard ATT for 6 months (Menzies et al., 2008).

It is important to exclude other potential causes before concluding that the hepatitis is induced by the ATT. If the patient is severely ill with TB and it is considered unsafe to stop TB treatment, a non-hepatotoxic regimen consisting of streptomycin, ethambutol and fluoroquinolone (moxifloxacin) should be started (Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease, 2010).

ATT interactions with immunosuppressive drugs are vital and can lead to graft rejection. RIF is the drug which mainly interferes with immunosuppressive agents by stimulation of a number of liver enzymes including uridine diphosphate glucuronosyltransferases, monoamine oxidases, glutathione S-transferases and cytochrome P450 (Chang et al., 2007). The daily corticosteroid dose should be stepped up to double the baseline dosage in patients taking RIF. Cyclosporin level can be lowered when combined with RIF, and it should be monitored and the dose modified accordingly. Tacrolimus plasma levels need to be monitored and the dose may be required to be increased (Chang et al., 2007). RIF also interacts with mycophenolate mofetil by the induction of hepatic, renal and gastrointestinal uridine diphosphate glucuronosyltransferases and organic anion transporters with resulting functional inhibition of enterohepatic recirculation of mycophenolate (Tostmann et al., 2008). Once RIF has been stopped, liver enzyme induction usually takes 2 weeks to return to normal. Therefore, the dose of immunosuppressants will need to be reduced to avoid accumulation and toxicity. In this case, RIF was stopped and replaced by Rifabutin which has less liver enzymes induction activity, but dosage modification of immunosuppressants was still indicated. Patient’s blood glucose was continually high, which may be due to the long term administration of prednisolone and cyclosporine. In this case, three clinical factors were indicating high level of immunosuppression: Drug interactions, hyperglycaemia, and multiple immunosuppressive agents. Such high level of immunosuppression is not recommended. Therefore, prednisolone and cyclosporine were stopped, and tacrolimus was used as a single immunosuppressant at a higher dosage.

4. Conclusion

In conclusion: Hepatotoxicity is one of the major side-effects of the medicines used in TB therapy. Reintroducing one drug at a time with close monitoring of LFT seems to be the optimal approach in the management of ATDH. With multi-disciplinary clinical approach, pharmacist rounding with infectious disease team (ID) plays an integral role in improving antimicrobial therapy process, therapeutic drug monitoring and adverse drug reaction management.
References


Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection. MMWR 2001; 50: 733–735.


