ORIGINAL ARTICLE

COMMON RISK FACTORS FOR THE DEVELOPMENT OF ANTI TUBERCULOSIS TREATMENT INDUCED HEPATOTOXICITY

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Background: Tuberculosis is a global pandemic which affects millions of people every year. The treatment of tuberculosis consists of simultaneous use of a number of drugs for a prolonged period of time, therefore anti-tuberculosis treatment induced toxicity is a real problem. Many risk factors which make a tuberculosis patient prone to the development of hepatotoxicity associated with the anti-tuberculosis treatment have been identified. The aim of this study was to determine common risk factors responsible for precipitation of hepatotoxicity following treatment with anti-tuberculosis drugs. **Methods**: This cross-sectional study was conducted in the Department of Pulmonary Medicine, Ayub Teaching Hospital, Abbottabad from 20th April 2013 to 19th March 2014. Patients who were newly diagnosed cases of tuberculosis in whom treatment of tuberculosis with first line anti-tuberculosis drugs was initiated and were 20 years or older, were included. The precipitation of drug induced hepatotoxicity was diagnosed with detailed history taking and physical examination followed by laboratory investigations, i.e., Liver Function tests (LFT). **Results**: Of the total 179 patients included in this study, 100 (55.8 %) were males and 79 (44.2 %) were females. Out of them 23 (12.85%) developed hepatotoxicity. Drug induced hepatotoxicity was observed in the older patients. No relationship was found with the sex, body mass index (BMI), and pre-existing liver disease. **Conclusion**: The study showed that the risk of development of drug-induced hepatotoxicity following treatment with first line anti-tuberculosis treatment increased with the age of the patient.

Keywords: Tuberculosis, Anti-Tuberculous Therapy, Liver disease, Body Mass Index, Hepatotoxicity

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INTRODUCTION

Tuberculosis (TB) is a global pandemic and one third of its prevalent cases are present in the South East Asia region.[1] The annual incidence of tuberculosis has been estimated to be 80,00,000 or 8 million cases with an annual TB-related mortality of about 20,00,000 deaths. The incidence of tuberculosis is increasing. The reason is not exactly known, though it has been suggested that this increase could be due to the emergence of multiple drug resistance TB and its ineffective management in some cases as well as association of tuberculosis with HIV.[2] The exact data of its prevalence in Pakistan is unknown however it has been stated to be 263 cases per million population and its incidence is placed at about 181 cases per million population per year.[3] Anti-TB chemotherapy consists of simultaneous use of a number of drugs and is complicated by the presence of anti-tuberculosis treatment induced hepatotoxicity in many patients. Although it is occasionally predictable and dose dependent, this side effect is commonly idiosyncratic. Most anti-tuberculosis drugs are lipid soluble: their effects in the body are eliminated via biotransformation metabolic reactions carried out in the liver by the specific phase-I and phase-II hepatic enzymes which convert these drugs into water-soluble compounds so that they can later be excreted easily.[4]

The anti-tuberculosis drug Isoniazid (INH) is reported to be the most common anti-TB drug responsible for precipitation of hepatotoxicity and this risk is increased when it is given in combination with other anti-TB drugs.[5] Introduced in 1952 INH is still used in the treatment of TB along with Rifampicin, Pyrazinamide and Ethambutol.[6] Acetylation in the liver is the main metabolic process responsible for elimination of action of INH and compared with the slow acetylators. The rapid acetylators of INH have a greater risk of developing hepatotoxicity. In a study it was found that 60% of female volunteers and 62% of male volunteers were rapid acetylators in Pakistan.[7] Another study reports a 50% distribution of rapid and fast acetylators in subject population in Pakistan.[8] The response of individuals to administration of anti-TB drugs is variable and hepatotoxicity can occur any time from within a week of administration of these drugs to a year later, though most cases occur during first 1–2 months.[9]

Rifampicin is another very useful drug known to cause hepatitis especially in the elderly, alcoholics or patients of Chronic Liver Disease

(CLD). It acts by inducing liver enzymes thus transiently elevating their levels.[9] Anti-TB drugs induced hepatotoxicity presents in any form: increased liver enzymes in blood, acute hepatic injury, chronic active hepatitis on one end of the spectrum to life threatening acute liver failure necessitating liver transplantation on the other end of spectrum.[5]

Many risk factors that have been reported to precipitate anti-tuberculosis treatment induced hepatotoxicity include: older individuals (61% more chance of developing drug-induced hepatotoxicity with age between 35-65 years)[10], female sex (32.9% in one study population), poor nutritional status (an increase in risk of 14% for each unit reduction in BMI)[11], a high consumption of alcohol, presence of concomitant liver disease (8.1%)[4], hepatitis B & C carrier state, hypoalbuminemia, advanced stage of tuberculosis, inappropriate dose of anti-tuberculosis drugs, and the acetylator status.[5] Other risk factors that have been reported include overweight/obesity, anaemia, MDR-TB medication, and tobacco smoking. These factors were found to be independently associated with the development of adverse drug reactions in patients with tuberculosis.[12] Gender is a factor in INH induced hepatotoxicity as it has been reported that females develop INH induced hepatotoxicity more than males.[3,13,14]

A varying incidence of anti-tuberculosis treatment induced hepatotoxicity has been reported from different regions of the world, despite the fact that the regimens used are similar. In developing countries, higher incidence rates ranging from 8–39 per cent are reported in developing countries, compared to developed countries at 3–4%. The tuberculosis patients belonging to India were reported to have an incidence of anti-tuberculosis treatment induced hepatotoxicity of 11.5%, which was higher when compared with 4.3% incidence in the developed countries.[1] Poor nutritional status and increased prevalence of concomitant hepatitis due to viral aetiology in the developing countries may contribute in this difference.[5] This study was designed to determine the common risk factors leading to anti-TB hepatotoxicity among patients put on anti-tuberculosis treatment for pulmonary tuberculosis in our region For this purpose, newly diagnosed pulmonary tuberculosis patient was defined as a patient who had been confirmed to have tuberculosis for the first time on the basis of history and investigations including presence of Acid Fast Bacilli (AFB) in sputum (3 early morning sputum samples), and/or chest x-ray findings (consolidation or exudative lymphocytic plural effusion). Drug-induced hepatitis was defined as a serum Alanine Aminotransferase (ALT) more than 3 times Upper Limit of Normal (ULN) (50 UL/L) 8th week after initiation of anti-tuberculosis treatment. Furthermore, the common factors leading to drug induced hepatotoxicity which were studied included advanced age defined as age more than 50 years, Low BMI defined as adult body mass index of <18.5kg/m.^{2} and pre-existing liver disease defined as Hepatitis B or Hepatitis C (as diagnosed by ELISA) already present in patients who were recently diagnosed with pulmonary tuberculosis.

MATERIAL AND METHODS

This cross-sectional study was conducted in the Department of Pulmonary Medicine (Internal Medicine), Ayub Teaching Hospital, Abbottabad from 20th April 2012 to 19th March 2013. The study included 179 consecutive patients of either gender and above 20 years of age who presented to the Medical as well as pulmonology outpatient department of Ayub Teaching Hospital, Abbottabad. The diagnosis in these patients was confirmed by the presence of AFB in sputum. Once patients were confirmed to be tuberculous, informed consent was taken from the patients before including them in the study.

Patients with the following characteristics were excluded from the study: (1) clinical evidence of hepatitis before initiation of ATT as evidenced by anorexia, nausea, vomiting, fever, pain right hypochondrium, tender hepatomegaly, high-colored urine and jaundice. (2) deranged base-line liver function tests (i.e., serum bilirubin more than 20 U/L, Alanine Transaminase (ALT) level more than 40 U/l and Alkaline Phosphatase (ALP) level of more than 280U/l before or at the time of initiation of Anti tuberculosis treatment. (3) evidence of other causes of hepatitis e.g., chronic liver disease as evidenced by presence of jaundice, clubbing, plamar erythema, spider naevi, Dupytren's contracture, asterixis, scratch marks, xanthelasmas, oedema feet, abdominal tenderness, hepatomegaly, splenomegaly and ascites. (4) History of previous episodes of jaundice, transfusions, operations, dental procedures or intravenous drug abuse. (5) presence of non-specific predisposing factors of liver dysfunction that is use of alcohol, contraceptive pills, steroids, cytotoxic drugs, hormone replacement therapy, intravenous drug abuse and use of acetaminophen in high doses.

Detailed history of the patients was taken including history of present illness, socioeconomic history, drug history and past history of illness. Presence of anorexia, nausea, vomiting, undue fatigue, pain right hypochondrium, high-coloured urine or abdominal distention was specifically asked for and noted so as to exclude presence of hepatitis at initiation of therapy.

Past history of hepatitis, tuberculosis,

malignancy, blood transfusions, and admissions for serious illnesses or operations was recorded. Imaging studies were also used to exclude causes of liver pathology at base-line. Patients administered INH, Rifampicin and Pyrazinamide were carefully monitored and interviewed at the follow up visits. For persons aged 20 years and older, liver functions were measured prior to starting treatment with the standard WHO regime. At the follow-up visit after 8 weeks of anti-tuberculosis treatment, a detailed medical history was taken and physical examination was done and liver function tests were repeated. Data was entered in SPSS version 20.0. Categorical variables were described as frequencies and percentages whereas quantitative variables were described as mean±standard deviation.

RESULT

This study enrolled 179 patients. Of these 179 patients, 100 (55.8%) were males and 79 (44.2%) were females with 22 (12.3%) patients developing drug induced hepatotoxicity, including 13 males and 10 females. Age played a significant role in development of anti-tuberculosis induced hepatotoxicity; there was an increase in the incidence of hepatotoxicity with increasing age. There was no female preponderance in development of ATT-Induced Hepatitis. The mean age was 36.51±9.5 years (20–59). Out of total 131 (73.2%) had no pre-existing liver disease, 32 (17.9%) were positive for Hepatitis B and 16 (8.9%) for Hepatitis C. Patients who had a BMI of above 25 were 37 (20.7%) and below 18 there were 20 (11.2%). Mean baseline ALT levels were 27.13±4.7 IU/L. Mean follow-up ALT levels were 56.75±51.9 IU/L. Table-1 and table-2 shows data of ALT by gender and age. Effect of MI on ALT levels is shown in table-3.

Table-1: Distribution of severity according to gender

	Follow-up ALT levels after 8 weeks				Total
	Less than 50 IU/L	ALT 51-100 IU/L	ALT 151-200 IU/L	ALT 201-250 IU/L	
Male	84	3	10	3	100
Female	59	10	7	3	79
Total	143	13	17	6	179

Table-2: Distribution of severity of ATT induced Hepatitis according to age

Age group (Years)	Follow-up ALT levels after 8 weeks				Total
	Less than 50 IU/L	ALT 51-100 IU/L	ALT 151-200 IU/L	ALT 201-250 IU/L	
20–30	46	2	2	1	51
31–40	60	9	4	2	75
41–50	25	1	7	2	35
>51	10	3	4	1	18
Total	144	13	17	6	179

Table-3: Effects of BMI on development of hepatotoxity

BMI	Follow-up ALT levels after 8 weeks				Total
	Less than 50 IU/L	ALT 51-100 IU/L	ALT 151-200 IU/L	ALT 201-250 IU/L	
Less than 18.5	16	2	1	1	20
18.5–24.99	99	7	11	4	121
25–30	28	2	4	1	35
31 and above	0	2	1	0	3
Total	143	13	17	6	179

DISCUSSION

Tuberculosis is a cause of disease, disability and death across the globe. Tuberculosis infected 8.7 million people in 2011, and 13% of these people had already been diagnosed with HIV infection. In the same year tuberculosis resulted in the death of 1.4 million people who had tuberculosis of any kind. These deaths, when broken down according to the HIV status, included 4,30,000 HIV positive people.[15] Anti-tuberculosis therapy induced hepatotoxicity is one of the major and common side effects. It therefore is important for the physicians to keep a low threshold for timely detection of liver injury due to drug use. Identifying such episodes at an early stage plays a major role in decreasing the severity and extent of liver injury by allowing for discontinuation of the drug. Drug Induced hepatotoxicity presents variable symptoms and signs. There can be no symptoms at all in some cases and others can present with sudden-onset liver failure. In our region, one study was carried out a few years ago to determine the prevalence of drug induced hepatotoxicity that focused on development of hepatotoxicity in tuberculosis patients. Risk factors in causing anti-tuberculosis induced hepatotoxicity in newly diagnosed TB patients were not studied.[9]

In our study 12.84% patients developed drug induced hepatotoxicity. Over all 36 (20.11%) patients showed deranged ALT levels after 8 weeks of therapy. Total number of males with deranged ALT levels was 16 (16%) and of females, 20 (25.31%) showed deranged ALT levels with statistically no significant difference. Three males out of 100 (3%) and 3 females out of 79 patients (3.80%) developed severe hepatotoxicity and their ALT levels were recorded to be more than 200 IU/L. It was noted that the incidence of drug induced hepatotoxicity increased with the increasing age of the patients.

In a study done by Khoharo *et al*, 26% of the study participants developed hepatotoxicity of varying degrees.[3] That particular study identified female sex, older age, malnutrition, acetaminophen use, low serum albumin and low serum cholesterol as the possible risk factors for precipitation of liver injury in patients treated with anti-tuberculosis drugs.

In contrast, our study didn't show any significant association with sex, BMI or the presence of pre-existing liver disease.

A study by Lee *et al*, reported that the incidence of anti-tuberculosis induced liver injury was detected in 9.4% patients.[16] They found that the risk was higher if the patient was a female or had a presumed recent infection with tuberculosis as suggested by a history of contact with a case of tuberculosis or recent conversion of tuberculin skin test (TST). They also reported that the risk of precipitation of anti-TB treatment induced liver injury was not associated with the race of patient, age, use of recreational drugs, dose of pyrazinamide or alcohol consumption.[16]

An incidence rate of 7.35% for drug induced hepatitis due to anti tuberculosis treatment was reported from Turkey by Babalik *et al*.[17] The authors reported an increased incidence of drug induced liver injury in the presence of co-morbidity and increased age especially in those who were older than 40 years at the time of initiation of treatment. Some of these findings are confirmed in our study where among patients older than 40 years of age, the incidence of hepatotoxicity was 24.52% which is quite high. Thus far, findings in our study are in line with other international studies indicating towards a possible role played by increasing age in precipitating hepatotoxicity due to the use of drugs. These findings have been reported by many studies across the world.[12,18,19] A study by Chamorro *et al* noted that ethnicity (having Bolivian ancestry), female sex and a slow acetylator status were important predictors for the development of liver injury after administration of anti-tuberculosis drugs.[13] Similar findings were also reported by Tostmann *et al*. They reported a possible role of HIV infection, slow acetylator status, being female, presence of malnutrition as well as pre-existing liver disease in the causation of anti-tuberculosis treatment induced hepatotoxicity.[4] Shakya *et al* reported that female sex, young age, poor nutritional status and the extent of disease at the time of presentation were important risk factors for the development of drug induced hepatotoxicity.[20] These findings were not proved in our study. Poor nutritional status, concomitant pre-existing liver disease and female sex had no association with development of anti-tuberculosis treatment induced hepatotoxicity. Similarly, Haq *et al* have reported a higher incidence of drug induced hepatotoxicity in females and individuals older than 35 years.[19] A recent study by Chung-Delgado *et al* reported that increased age, especially patients older than 40 years at the time of starting anti tuberculosis treatment, over-weight or obese patients, presence of anaemia, administration of drugs for treatment of multi-drug resistant tuberculosis, and tobacco smoking increased the risk of precipitation of anti-tuberculosis treatment induced liver injury.[12] In contrast to other studies, this study reported that poor nutritional status was not a risk factor for development of liver injury with anti-tuberculosis treatment. In a similar study by Yee *et al* [21], it was reported that age more than 60 years at the time of starting treatment, female sex and having being born in Asia increased the risk of occurrence of major side effects with the treatment in patients. This study correlates partially with our study. Though there were no patients aged 60 or more in our study, the eldest patient was 59 years old, yet the increasing incidence of drug induced hepatotoxicity as the age increased meant that had there been patients older than 60 years of age, they would probably have had an increased risk of precipitation of anti-tuberculosis treatment induced hepatotoxicity.

Limitation of our study was a small sample size and not getting patients of older ages on the sample. Nonetheless most of the findings are in consonance with the literature that creates a local evidence of the phenomenon for use by the relevant quarters.

CONCLUSION

Individual risk factors for liver injury with anti-tuberculosis treatment can be determined easily. However, the presence of these risk factors does not imply that a patient will develop drug induced hepatotoxicity thus making it very difficult to accurately predict who will develop liver injury once anti tuberculosis treatment has been started.

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