Original Article

Anti-tuberculosis, Drug-induced Hepatitis in Patients of Pulmonary Tuberculosis with Chronic HCV

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ABSTRACT

OBJECTIVE: To determine the frequency of anti-tuberculosis drug-induced hepatitis in patients of pulmonary tuberculosis co-infected with chronic HCV.

METHODOLOGY: This cross-sectional descriptive study was conducted at Liaquat University Hospital after obtaining permission from the ethical review committee. One hundred twenty-four patients, irrespective of gender, aged 20 or greater, were selected through nonprobability convenience sampling from December 2020 to February 2021. Patients of pulmonary tuberculosis (TB) who were sputum positive and co-infected with chronic Hepatitis C Virus HCV with normal Liver Function Test (LFT) were picked. Chronic HCV was evidenced by positive anti-HCV on ELISA. Alcoholics, HBsAG-positive patients, and persons with altered LFT before the start of Anti-tuberculosis treatment (ATT) were exempted from the study. If LFT after one week of treatment displayed a rise in bilirubin greater than 1.5 mg and or increase in Aspartate aminotransferase(AST) and Alanine aminotransferase (ALT) greater than 120 IU/L, then patients were further followed and LFT repeated thrice on the 15th day of holding the ATT. Drug-induced hepatitis was labelled when LFT normalize after two weeks of withholding treatment. All this data was itemized on proforma and analyzed through SPSS 17 software.

RESULTS: Out of 124 patients, 70 were male, and 54 were female. Age varied from 20 to 60 years (mean age was 42.4 years) .37.9% of patients were more than 50 years of age. In this study, only 16.93% of patients developed ATT-induced hepatitis.

CONCLUSION: Anti-tuberculosis-induced liver enzyme elevation is a common incident in inpatients of pulmonary tuberculosis co-infected with chronic HCV.

KEYWORDS: Hepatitis C Virus, Liver Function Test, Ammonia tolerance test, Drug-induced hepatitis, Pulmonary Tuberculosis

INTRODUCTION

Mycobacterium tuberculosis was recognized as an infective agent with high mortality for centuries. Even in this modern world, tuberculosis contributes a lot, causing fatalities[1]. It is one of the deadliest diseases caused by a single infective organism[2]. TB is a tremendous financial and health burden for nations globally, as it still affects 9.27 million new cases annually worldwide[3]. Tuberculosis became the cause of death of over 2,000,000 people annually, universally[2]. Based on these facts, the World Health Organization declared tuberculosis a global emergency[3]. Among the countries that bear the burden of tuberculosis, third-world countries share the foremost portion[3]. Pakistan ranked 7th globally among countries 4 with the highest number of tuberculosis and has an incidence of 275 per 100,000 populations[3]. Apart from the disease burden, anti-ATT -induced side effects are also troublesome and are more marked over the liver, a challenge for treatment[2].

Many first-line drugs may lead to hepatic dysfunction, but the occurrence varied from 1% to 31% [4]. One researcher observed damage caused by ATT to the liver, found in up to 19.67% of patients[2]. Frequency is different in various geographical areas but more common in underdeveloped countries[4].

Although ATT-induced hepatotoxicity is a well-known problem, the situation becomes harder in countries like Pakistan, where liver diseases are prevalent. One of the significant, clinically relevant side effects of the treatment of TB is liver damage manifested as raised liver enzymes, which may lead to discontinuation of the patient's treatment[3]. There is a lack of detailed information about anti-tuberculosis therapy's effects on the liver, particularly in the background of chronic liver diseases.

Pakistan has so many HCV cases that it is among the top afflicted countries[5]. In one study, researchers noted that 22% of patients were co-infected with

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tuberculosis and HCV[5].

About the prevalence of HCV in patients with TB and the impact that the infection has on these patients, few studies have been conducted worldwide, and there is still little validation concerning this topic[4]. Among first-line drugs for treating tuberculosis, Isoniazid and rifampicin may harm the liver by causing changes in the cell wall structure, reduced glutathione level, and activation of CYP2E18[2].

This study evaluated the effect of ATT on the liver in patients with pulmonary tuberculosis who also suffered from chronic HCV, and this would assess whether treating pulmonary Kock's with a standard regime poses a significant danger in patients co-infected with chronic HCV. That would help identify patients who need a change in treatment. This issue is paramount because HCV and pulmonary tuberculosis co-infection cases are abundant.

METHODOLOGY

This cross-sectional descriptive study was conducted at Liaquat University Hospital after obtaining permission from the ethical review committee; 124 patients of either gender, aged 20 or greater, were selected through nonprobability convenience sampling from December 2020 to February 2021. Patients of pulmonary tuberculosis who were sputum for AFB positive and co-infected with chronic HCV with normal LFT were picked. Chronic HCV was evidenced by positive anti-HCV on ELISA. Alcoholics, HBsAg-positive patients, and persons with altered LFT before the start of ATT were exempted from the study. After informed consent, clinical data was noted, and the examination and a chest X-ray posteroanterior (PA) view were obtained, along with another routine blood test. LFT was assessed at baseline and then after one week of initiating treatment. Patients who showed a rise in bilirubin greater than 1.5 mg and or an increase in ALT and/or AST greater than 120 IU/L were further followed, and LFT was repeated thrice on the 15th day of holding the ATT. Drug-induced hepatitis was labelled when LFT normalized in this selected group after two weeks of withholding treatment. All this data was registered on proforma and analyzed through SPSS 17 software.

RESULTS

In this study, a total of 124 patients were registered. Out of them, 70 were male and 54 were female. The age range varied from 20 to 60 years, with a mean age of 42.4. As shown in **Figure I**, most patients (37.9%) were older, i.e., over 50. Out of 124 patients, 14 were lost to follow-up, while only 21 (16.93%) developed ATT-induced hepatitis, as shown in **Figure II.**

Levels of bilirubin, ALT and AST at the start of treatment, end of 1st week, and end of the third week are shown in **Table I**.

FIGURE I: FREQUENCY OF AGE IN GROUPS

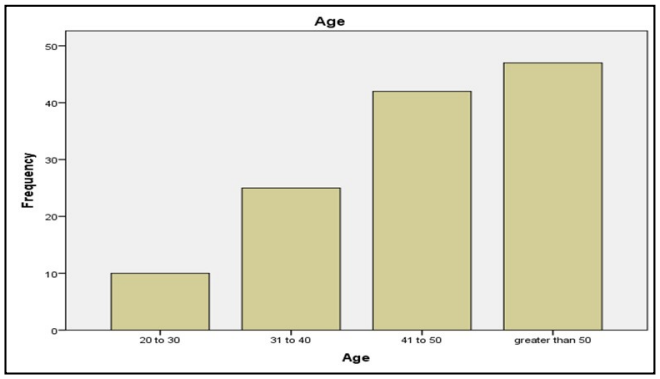

FIGURE II: OUTCOME OF LFT

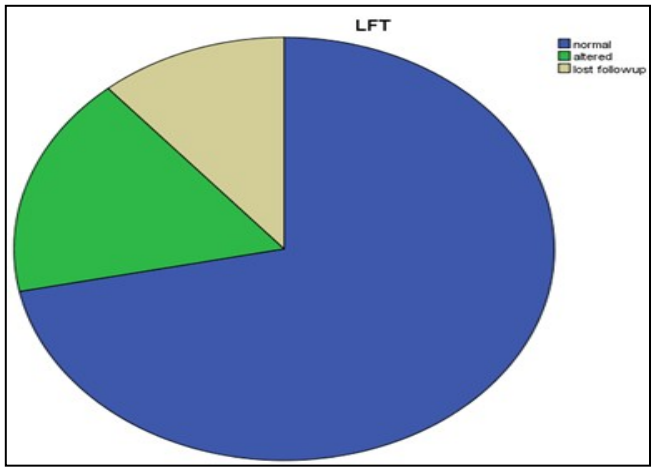

TABLE I: RESULTS OF LFT AT BASELINE, AFTER ONE AND THREE WEEK (n=21)

LFT	Mean±SD	Range
At baseline		
Serum bilirubin(mg/dl)	0.86 ±0.13	0.1 to 1.5
AST(IU/L)	22.0±3.0	≤ 40
ALT(IU/L)	18.0 ±2.19	≤ 40
After one week (n=21)		
Serum bilirubin(mg/dl)	2.36±1.6	>1.5
AST(IU/L)	528± 312	>120
ALT(IU/L)	428±298	>120
After three weeks (n=21)		
Serum bilirubin(mg/dl)	1.38 0±.26	0.1 to 1.5
AST(IU/L)	38.17 ±10.30	≤ 40
ALT(IU/L)	35.91 ±11.43	≤ 40

DISCUSSION

Tuberculosis is among the most disastrous infectious diseases for humankind. According to reports, two billion humans suffer from tuberculosis, with the addition of approximately more than ten million new cases annually[6].

The world is also facing the problem of hepatitis viruses nowadays, including HCV, which was

discovered in 1988[7]. Pakistan stands second in the world for the highest number of HCV cases[8]. According to a systematic review and meta-analyses, every 20th person in our homeland has HCV infections[9]. The situation is worse in Sindh than in other provinces of Pakistan[8]. Tuberculosis patients may also be co-infected with chronic HCV, which creates an additional challenge for treating tuberculosis, bearing in mind drug-induced hepatitis due to antituberculous treatment[10].

Medications for treating tuberculosis may have harmful effects on the liver, and debate is still going on whether HCV co-infection in tuberculosis patients may worsen or precipitate drug-induced hepatotoxicity. In a study from Nepal, authors found that 20.98% of the people were affected by ATT in the form of liver damage and that it was comparable to other third-world countries' scenario[11]. ATT-induced drug toxicity is more common in our part of the world compared to industrialized nations[12].

Our study focused on first-line ATT-induced liver damage in pulmonary tuberculosis patients co-infected with chronic HCV. We noted that out of 124 patients, only 21 developed liver enzyme alterations. Bartaula B et al. [11] mentioned in their article a study conducted in Florida on 128 persons, which found that 30% of tuberculosis patients co-infected with hepatitis C suffered from elevation in liver enzymes because of drugs used to treat tuberculosis. In contrast, the ratio of hepatitis due to the treatment in non-HCV infected persons was 11%, so they suggested that HCV infection is a risk factor for causing liver enzyme alterations in tuberculosis patients when they use anti-tuberculosis drugs.

In a retrospective study from India, the authors stated that hepatitis C is not ominously linked with drug-induced hepatitis[13], contrary to many others and our study[11,14].

In our study, the mean age of patients was 42.4 years, slightly higher than Ivanova D et al.[14] noted in their research, which was 38 years. The majority, 37.9 of patients, belonged to an age group more significant than 50. Other studies also documented more liver damage in the older age group of 40-60 years[12]. In the research by Metanat M 2015[4] they found that old-aged persons were more likely to develop alteration in liver enzymes due to ATT; most of the participants in their study were older than 50.

Comparable to our study, the research work of Chang TE et al. [15] detected more severe liver damage with high elevation of liver enzymes in persons who were anti-HCV positive, especially those older than 65 years of age. In our study, males were 70 and females were 54, so slight male predominance was noted. In their meta-analysis of 8 years, Behzadifar M et al. reported that TB and HCV were more common in men than women[16].

In a study conducted in Egypt by Agha MA 2015[10], authors found HCV was strongly linked with DIH (drug -induced hepatitis) due to first-line ATT in tuberculosis patients. They also discussed other studies that supported their results. They identified 40 % of their patient from group 1 (tuberculosis and HCV co-infection) exhibited an alteration in liver enzymes. In comparison, only 20.75% of patients from group 11 (tuberculosis without co-infection with HCV) showed elevated liver enzymes. This was a remarkable finding and highlighted noteworthy dissimilarity between both groups. Our study also disclosed a substantial number of cases who exhibited Drug-induced hepatitis (DIH) on first-line drugs for tuberculosis, i.e. 17%. To assess liver damage due to ATT is of utmost value as if it goes unchecked, it may result in mortality of 6% - 12%[4].

In our study, we selected patients with normal baseline LFT; 21 patients developed ATT-induced hepatitis as detected by elevation in bilirubin, AST, and ALT. In our patient, bilirubin was not markedly raised. The mean with a standard deviation of bilirubin AST and ALT levels were 2.36±1.6, 528±312, and 428±298, respectively.

The occurrence of DIH was substantially more significant in the chronic HCV patients alone and patients of chronic HCV co-infection with chronic HBV[17].

How, in the presence of HCV, more hepatotoxicity occurred is not fully understood. Some scientists postulated that HCV core protein amendment in the fat breakdown was a significant liver injury offender because of drugs in the HCV group. Kim WS et al.[17] unveiled that HCV-induced fatty liver may lead to programmed cell death, contributing to hepatitis and sequelae.

We recommend that HCV-positive patients with tuberculosis on treatment should be followed meticulously.

CONCLUSION

This study concluded that drug-induced hepatitis due to anti-tuberculosis treatment is not uncommon in patients with pulmonary tuberculosis who are co-infected with chronic HCV infection. Chronic HCV makes the liver more vulnerable to anti-tuberculosis treatment-induced hepatitis. Elevation in liver enzymes is more common in patients older than 50.

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AUTHOR CONTRIBUTION

Memon N: Concept and design of the work, review, and manuscript drafting.

Humaira M: Manuscript drafting, review, and final approval of the manuscript
Shaikh MA: Expert Opinion, Critical review, and final approval of the manuscript
Bano R: Acquisition, analysis, and interpretation of data and make it suitable for final revision
Anjum S: SPSS Analysis, interpretation of data, and review
Shah M: Data collection and sequencing of the material, grammatical review
Kaka IH: Data collection and review of the manuscript

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