Section: Respiratory Medicine

Original Research Article

APPROACH TO DIAGNOSIS AND TREATMENT OF PATIENTS WITH ANTI TUBERCULAR THERAPY-INDUCED HEPATITIS

Venkateswara Rao Teela[1], Bhima Bhanu Prakash Avanapu[2], Surampalli Koutilya[3], Akasapu Ayyappa[4], Suresh Malla[5], Salapu Saranya[6]

[1]Associate Professor, Department of Respiratory Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.
[2]Assistant Professor, Department of Respiratory Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.
[3]Assistant Professor, Department of Respiratory Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.
[4]Professor and Head, Department of Respiratory Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.
[5]Professor and Head, Department of Pharmacology, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.
[6]Post Graduate, Department of Respiratory Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.

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Corresponding Author:
Dr. Surampalli Koutilya,
Assistant Professor, Department of Respiratory Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Vizianagaram, Andhra Pradesh, India.
Email: surampallikoutilya@gmail.com

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ABSTRACT

Background: Tuberculosis (TB) is a major global health concern caused by Mycobacterium tuberculosis. First-line anti-tubercular drugs (ATT) are highly effective in treating TB, but their use is frequently associated with drug-induced hepatotoxicity, which may lead to treatment interruption, non-adherence, and potential development of drug-resistant TB. **Aim:** This study aims to evaluate the approach to diagnosing and managing patients with anti-tubercular therapy (ATT)-induced hepatitis, focusing on identifying risk factors and providing effective treatment strategies.
Materials and Methods: This prospective observational study was conducted over a 24-month period, involving 300 patients diagnosed with TB. Among the study population, 180 patients had pulmonary TB, 100 had extrapulmonary TB, and 20 had multidrug-resistant (MDR) TB. Of the 300 patients, 270 did not develop hepatitis, while 30 experienced hepatotoxicity. The onset of hepatitis was predominantly observed at 3 weeks following the initiation of ATT. Patients' liver function was closely monitored through regular serum transaminase and bilirubin level assessments.
Results: The incidence of ATT-induced hepatotoxicity was found to be significant, with 10% of patients developing hepatitis. The onset of liver dysfunction typically occurred around 3 weeks after starting ATT. Hepatotoxicity was more prevalent in elderly patients and those with pre-existing comorbid conditions such as diabetes and hepatic dysfunction.
Conclusion: ATT-induced hepatotoxicity remains a common complication in TB treatment, necessitating close monitoring of liver function, especially in high-risk groups. Regular monitoring of liver enzymes, particularly in older patients or those with comorbidities, is crucial to prevent severe liver damage and to ensure effective management of TB.
Keywords: Tuberculosis, ATT-induced hepatitis, Transaminases, Bilirubin.

INTRODUCTION

Tuberculosis, a chronic bacterial infection caused by the Mycobacterium Tuberculosis complex, most commonly by Mycobacterium Tuberculosis. It can affect any organ in the body like bones, kidneys, intestine, and lymph nodes but the lung is the most common site of infection.[1] The treatment of TB

includes a 6-month course of using ATT, where isoniazid, rifampicin, pyrazinamide, and ethambutol are given for 2 months [Intensive phase] followed by 4-months use of isoniazid, rifampicin, ethambutol [Continuous phase]. Various adverse drug reactions were identified with ATT like Hepatotoxicity, gastrointestinal and neurological disorders which reduced the compliance, efficacy of the treatment and increased the mortality rate.[2]

Hepatotoxicity is the most commonly encountered ADR in patients using anti-tubercular drugs like Isoniazid, Rifampicin, and Pyrazinamide, Pyrazinamide being the most hepatotoxic followed by isoniazid and rifampicin.ATT-induced hepatotoxicity is suspected when in the absence of symptoms, elevation of transaminases upto 5 times upper limits of normal and in the presence of symptoms upto 3 times ULN or twice ULN of bilirubin, provided other causes like acute viral hepatitis, autoimmune hepatitis, and other liver diseases should be ruled out.[3]

Drug induced Liver injury can be hepatocellular or cholestatic or autoimmune of infiltrative type. Hepatocellular ATT-induced hepatotoxicity results from a metabolic idiosyncrasy brought on by metabolites generated or accumulated throughout the metabolic process. Genetic variations or polymorphisms in the enzymes that metabolise drugs can help with this. Anti-TB-DIH side effects can vary in severity, with less than 0.01% of patients experiencing severe liver failure and 2.3–28% of individuals experiencing asymptomatic elevations in transaminase.[4,5,6] Advanced age, female gender, pregnancy, comorbidities like obesity, diabetes, and underlying liver disease, genetic factors like acetylator polymorphism, concurrent viral infections like HIV, hepatitis B and C, and underlying nutritional status like malnutrition/hypoalbuminemia are some of the risk factors for DILI caused by anti-tubercular drugs.[7]

The degree of severity of hepatotoxicity was assessed by the peak level of serum transaminases and classified according to the WHO Toxicity Classification Standards.Hence the present study is undertaken to evaluate the approach to diagnosing and managing patients with anti-tubercular therapy (ATT)-induced hepatitis, focusing on identifying risk factors and providing effective treatment strategies.

MATERIALS AND METHODS

Study Design: This was a prospective observational study.

Study Setting: The study was conducted at the Outpatient Department (OPD) and Medical Ward, RICU, Maharajah's Institute of Medical Sciences, Nellimarla. Informed consent was obtained from all patients before the commencement of the study.

Sample Size: A total of 300 patients were included in the study.

Study Period: The study was carried out from January 2022 to January 2024.

Study Population:

Inclusion Criteria

Patients with newly diagnosed tuberculosis (TB) aged >18 years.

Both male and female patients.

Liver Function Test (LFT) abnormalities:

Any rise in Bilirubin levels.

ALT >3 times the upper limit of normal (ULN) and AST >3 times ULN in symptomatic patients.

ALT >5 times ULN and AST >5 times ULN in asymptomatic patients.

Exclusion Criteria

Age <18 years.

Patients currently using Anti-Retroviral Therapy (ART).

Individuals with a history of viral hepatitis (Hepatitis A, B, C, D, or E) who tested positive at the time of presentation.

Patients with pre-existing chronic liver disease or history of chronic alcohol consumption.

Materials

Sputum for Cartridge-Based Nucleic Acid Amplification Test (CBNAAT).

Routine investigations:

Complete Blood Profile (CBP)

Bleeding Time (BT)

Coagulation Time (CT)

Liver Function Test (LFT)

Renal Function Test (RFT)

Ultrasound (USG) abdomen & pelvis

Chest X-ray (Posteroanterior view)

Viral markers: HIV, HCV, HBsAg

Statistical Analysis:

Descriptive statistics were used to summarize patient demographics, clinical characteristics, and laboratory results. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables were presented as frequencies and percentages.

Chi-square or Fisher's exact test were used for comparison of categorical variables between groups. Independent t-test or Mann-Whitney U test were used for continuous variables, depending on the data distribution. Logistic regression was performed to assess factors independently associated with LFT abnormalities in TB patients. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, USA) or equivalent software.

Ethical Considerations: Ethical approval for the study was obtained from the Institutional Ethics Committee (IEC) of Maharajah's Institute of Medical Sciences, Nellimarla. Informed written consent was obtained from all participants before enrollment in the study. Participants were fully informed about the nature, purpose, and potential risks of the study. Patient confidentiality was strictly maintained, and all data were anonymized to ensure privacy. The study adhered to the ethical principles

outlined in the Declaration of Helsinki, ensuring that the rights and well-being of the participants were prioritized throughout the study. Any adverse events or complications arising during the study were promptly reported and addressed according to the institution's protocols.

RESULTS

In the study sample of 300 patients, 180 (60%) were males and 120 (40%) were females. Mean age is 38 years. Of these 140 (46.7%) belonged to Lower middle class and 95 (31.7%) belonged to Lower class and 65 (21.7%) belonged to Middle class.

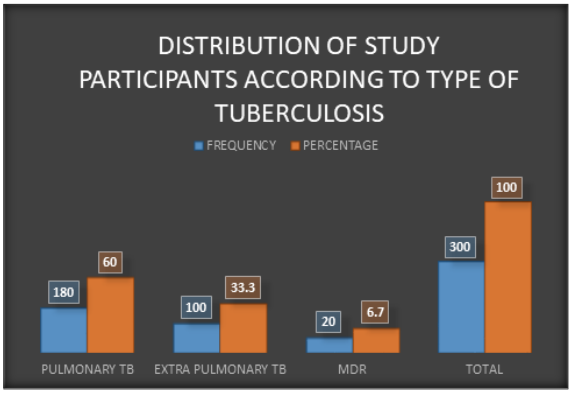

Figure 1: Distribution of study participants according to type of tuberculosis

Among the sample size of 300 patients, 180(60%) had Pulmonary TB and 100(33.3%) had Extrapulmonary TB and 20 (6.7%) had MDR TB.

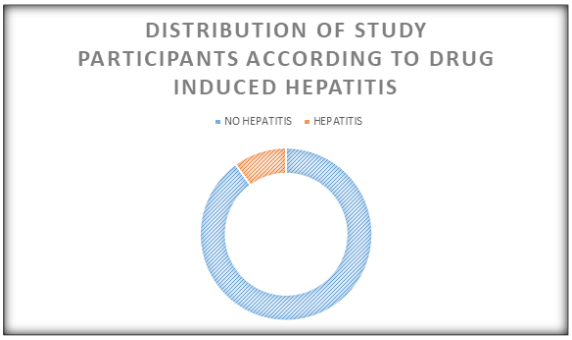

Figure 2: Distribution of study participants according to drug induced hepatitis

Among study participants, 270 (90%) did not develop Hepatitis, and 30(10%) developed Hepatitis. Incidence of Drug-induced Hepatitis was 10%Among the patients with drug induced hepatitis, 25 (8.3%) were Diabetics and 75 (25%) had history of Alcohol intake.

Among the study participants who developed hepatitis 30 (100%) had moderate severity hepatitis, classified according to the WHO Toxicity Classification Standards. Majority 20 (66.6%) patients developed hepatitis at 3 weeks of initiation of ATT.

Symptoms include Nausea seen in 25 (83.3%), Anorexia in 20 (66.6%), Malaise in 15(50%) and Vomitings in 10 (33.3%) patients. Among the 30 patients, only 10 required ICU admission.

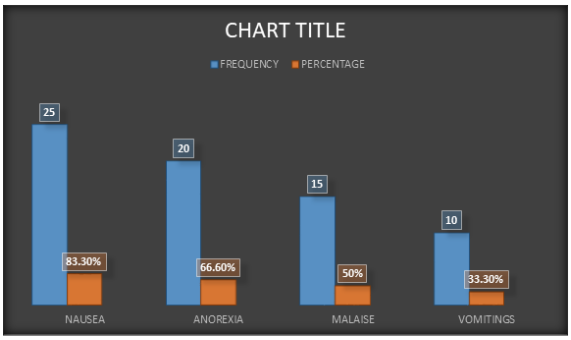

Figure 3: Chart Title

Among these patients who developed hepatitis, in majority of them 15 (50%) symptoms resolved by 4 weeks after stopping att. After the treatment of hepatitis, initially INH was reintroduced in all 100% patients. Rifampicin was reintroduced among 25 (83.3%) patients. Pyrazinamide was successfully reintroduced among only 15 (50%) patients.

No significant difference is noted in between patients with hepatitis and patients without hepaitis in regards to age, type of TB, BMI, DM. A significant difference was noted in patients with history of alcohol intake.

DISCUSSION

In this Prospective Observational study done in MIMS Hospital, Vizianagaram, which is done over a period of 24 months, 300 patients satisfying the inclusion criteria were included. Mean age was 38.08 years. Among the study participants, 180 (60%) were males and 120 (20%) were females. Of these 140 (46.7%) belonged to Lower middle class and 95 (31.7%) belonged to Lower class and 65 (21.7%) belonged to Middle class.

Among the 300 patients, 180 (60%) had Pulmonary TB and 100(33.3%) had Extrapulmonary TB and 20 (6.7%) had MDR TB. Among them, 270 (90%) did not develop Hepatitis, and 30 (10%) developed Moderate severity Hepatitis. The incidence of Anti Tubercular Therapy induced hepatotoxicity in the present study was found to be 10%, comparable to a study conducted in Malaysia,[6] (9.7%). In addition, the incidence is slightly higher than the study done in Dawro Zone, Ethiopia,[7] (8.1%). In addition, incidence was lower than studies done in Pakistan (13%), Spain (12%), Florida (16.4%) and Morocco (24.6%). The cause of discrepancy might be due to less sample size, differences in lifestyle, nutrition status, genetic makeup.

The duration during which ATT induced hepatitis developed ranged between 14 to 28 days of initiation of ATT. similar to this finding, the onset of developing drug induced hepatotoxicity was

reported between 10 – 25 days in a study conducted in Morocco.[8] However, according to the study done in Ethiopia,[9] (8 – 56 days) , the onset of anti TB drug induced hepatotoxicity was not in line with the present study.

Majority 15 (50%) had their hepatitis resolved by 4 weeks and the remaining patients 5(16.7%) each had their hepatitis resolved by 2, and,5 weeks respectively. The mean Duration within which hepatitis was Resolved (weeks) was 3.66 weeks with a SD of 1.03 weeks.

After treating Hepatitis, Isoniazid was reintroduced successfully among 100% of patients, Rifampicin among 25(83.3%), and pyrazinamide was successfully reintroduced among 15 (50%) patients.

No significant difference is noted between patients with hepatitis and patients without hepatitis in regards to age, type of TB, BMI, and DM. This finding was not in line with the study done in Ethiopia,[9] where the incidence of ATT induced Hepatotoxicity was higher in the presence of comorbid medical conditions (12.9 times) and in patients with the age group of 18-49 years (0.85 times). No association was reported between age and drug-induced hepatotoxicity in many studies.[7,10,11] A significant difference was noted in patients with a history of alcohol intake. It is similar to the findings observed in studies conducted at Dawro zone,[7] Southeast Iran,[12] and in Nepalese,[13] population.

CONCLUSION

The incidence of hepatotoxicity is relatively high among TB patients using first line anti-TB drugs. It is necessary to educate the patients about the possible Adverse drug reactions associated with the drugs used in treating TB. Patients must be counselled about the signs and symptoms of hepatotoxicity and should encourage them to report them as soon as possible.

Monitoring Liver function tests among the patients with old age, comorbid diseases and History of alcohol intake during the first 8 weeks of treatment is important

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