IJHRMLP
ISSN 2394–806X (Print), ISSN 2454-5139 (Online)

International Journal of Health Research and Medico-Legal Practice

RESEARCH PAPER

Clinical profile of antitubercular drugs induced liver injury in patients receiving treatment under the national tuberculosis elimination program in a tertiary care centre

Article ID: 574

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Article received: 08-03-2022
Received (revised): 11-05-2023
Editorial approval: 11-07-2023
Checked for plagiarism: Yes
Peer-reviewed article: Yes
Editor who approved:
Prof. AJ Patowary

ABSTRACT

Background and aims: Tuberculosis, including India, remains a significant infectious disease worldwide. The mainstay of drugs in treating tuberculosis includes isoniazid, rifampicin, pyrazinamide, and ethambutol. Antitubercular drug-induced (ATD) liver injury is a leading cause of drug-induced liver injury and acute liver failure in India and much of the developing world. This paper aims to study the clinical profile of patients developing antitubercular drugs induced liver injury while receiving treatment under the National Tuberculosis Elimination Programme (NTEP) in a tertiary care centre.

Methods: A hospital-based, observational study was conducted on 389 patients admitted to the Department of Medicine, Gauhati Medical College and Hospital (GMCH), Guwahati, Assam. All patients underwent pretreatment clinical and laboratory evaluation, including haemoglobin level, serum albumin, Liver Function Test (LFT), ultrasonography (USG) of the abdomen, hepatitis B, C, and HIV status. LFTs were repeated weekly in the first month, then at the end of the second and third weeks. Collected data were analyzed by applying the chi-square test.

Results: 53(13.62%) out of 389 patients developed hepatotoxicity with a male-to-female ratio of 1.8:1, the highest number of patients aged 40-49 years. 66.04% of patients were symptomatic. 88.23% of patients developed an initial rise of bilirubin in 2nd week, and 90.56% developed elevated Alanine Transaminase (ALT) in 2nd week.

Conclusion: A significant number of patients develop hepatotoxicity during treatment with antitubercular drugs. Most patients developed LFT derangements in the first two weeks of treatment and were symptomatic, all recovered completely by the next six to eight weeks, and there was no mortality.

Keywords: Antitubercular drugs; hepatotoxicity; serum bilirubin; alanine transaminase.

Cite this article: *Dutta S, Medhi J, Phukan A. Clinical profile of antitubercular drugs induced liver injury in patients receiving treatment under the national tuberculosis elimination program in a tertiary care centre. Int J Health Res Medico Leg Prae 2023 Jan-Jun;9(1):x-y. Doi: 10.31741/ijhrmlp.v9.i1.2023.5*

INTRODUCTION

Tuberculosis remains a significant infectious disease across much of the developing world. According to the World Health Organization (WHO), India is one of the three countries bearing the largest share of the global burden of tuberculosis (TB) cases.[1] The mainstay of drugs used in treating tuberculosis includes the first-line drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol.[2] The liver plays a significant role in drug metabolism, and liver injury is a possible consequence of ingesting any xenobiotic, including industrial toxins, pharmacologic agents, and Complementary and Alternative Medications (CAMs).[3] Antitubercular drug-induced liver injury is a leading cause of drug-induced liver injury and acute liver failure in India and

much of the developing world. Its clinical spectrum includes asymptomatic elevation in liver tests to acute hepatitis and acute liver failure.[4] Antitubercular drugs induced hepatitis is defined according to the American Thoracic Society as:[5]

A) Presence of at least one of the following:

1) A rise to more than five times the upper limit of normal (ULN) level of liver enzymes

2) Any increase in more than three times the upper limit of the normal level of liver enzymes above pretreatment levels, together with anorexia, nausea, vomiting, jaundice, and

B) Normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of all antitubercular drugs.

Most commonly, antitubercular drugs induced liver injury is due to metabolic idiosyncrasy due to the metabolites released or accumulated during the metabolic process.[3] Interaction between genetic, host, and environmental factors contribute towards developing antitubercular drugs induced liver injury. The critical factors to be considered are:[4] age, gender, organ involvement/extent of tuberculosis, malnutrition, the influence of alcohol, viral hepatitis (B and C), dosing schedule, and the role of HLA and genetic polymorphism on drug-induced liver injury. As studies regarding this are not very common in the Northeastern region of the country, and most of the studies are conducted in other parts of India, therefore, this study is conducted in our hospital to study the occurrence and probable predisposing factors associated with drug-induced liver injury among patients receiving antitubercular medications.

MATERIALS AND METHODS

It was a prospective, hospital-based observation study conducted for one year, from Jul 1, 2021, to Jun 30 2022, on indoor and outdoor patients in GMCH receiving first-line antitubercular therapy under NTEP and fulfilling the inclusion and exclusion criteria.

Inclusion criteria

Patients prescribed to receive first-line antitubercular drugs for pulmonary or extra-pulmonary tuberculosis under the NTEP schedule containing hepatotoxic Antitubercular Treatment (ATT) and patients above 12 years of age were included in our study.

Exclusion criteria

Patients not receiving first-line or hepatotoxic ATT drugs, patients with preexisting liver disease, patients with baseline transaminases more than twice the upper limit of normal, patients with a previous history of hepatotoxicity due to ATT, and patients who have not completed 12 years of age were excluded.

All the patients had pretreatment evaluation clinically, especially for evidence of liver disease, history of alcohol intake or concomitant drug therapy, and systemic illness in a prepared proforma, a copy of which is annexed. Baseline laboratory evaluation was done for all patients, including haemoglobin levels, serum albumin, LFTs, a USG of the abdomen, and hepatitis B, C, and HIV status. LFTs were repeated weekly for the first month and then at the end of the second and third months. If the patients developed evidence of hepatotoxicity, viral markers (hepatitis A, B, C) were again performed to rule out acute viral hepatitis. The collected data were organized, tabulated in a master chart, and statistically analyzed using IBM SPSS. For statistical analysis, the chi-square test was applied.

Inform consent was obtained from all the participating patients, and the institutional ethical clearance from the ethics committee of GMCH, Guwahati vide ref no: MC/190/2007/pt-11/April- 2021/TH-9.

RESULTS

A total of 389 patients were included in the study. Of them, 223(57.33%) were male, and 166 patients (42.67%) were female. The age of the patients ranged from 14-93 years, and the mean age was 37±14 years. 225(57.84%) patients were suffering from pulmonary tuberculosis and 166(42.16%) were from extrapulmonary tuberculosis.

It was found that 53(13.62%) out of 389 patients receiving ATT developed hepatotoxicity. The clinical profile and results of LFT of the patients developing hepatotoxicity are mentioned below.

Out of 53 patients who developed hepatotoxicity, 34(64.15%) were male and 19(35.85%) were female.

The highest number of patients developing hepatotoxicity belonged to the age group 40-49 years (28.30%) (**Table 1**).

IJHRMLP
ISSN 2394–806X (Print), ISSN 2454-5139 (Online)

Table 1 Age distribution of patients on Antitubercular Treatment who developed hepatotoxicity

Age (years)	Number of patients, N (%)
<30	13(24.53%)
30-39	4(7.55%)
40-49	15(28.30%)
50-59	11(20.75%)
e"60	10(18.87%)
Total	53(100.00%)

Out of 53, 35(66.04%) were found to be symptomatic and 18(33.96%) were asymptomatic .

In 30(88.23%) patients initial rise of bilirubin was seen in 2nd week since starting ATT, and in 4(11.11%) patients initial rise of bilirubin was seen in 4th week since starting ATT (**Table 2**).

Table 2 Onset of initial rise of bilirubin in patients receiving Antitubercular Treatment (ATT)

Time since starting ATT	Number of patients, N(%)
Week 0	0(0.00%)
Week 2	30(88.23%)
Week 4	4(11.77%)
Week 12	0(0.00%)

Of 53 patients, 33(62.26%) had a maximum serum bilirubin level between 3 - 10 times the upper limit of the normal level (**Table 3**).

Table 3 Maximum total serum bilirubin levels in patients with hepatotoxicity

Normal	>11.5(>1.3 1.95mg%)	>1.5-3.0(>1.95-3.9mg%)	>3.0-10(>3.9-13mg%)	>10(>13mg%)
N(%)	N(%)	N(%)	N(%)	N(%)
19(35.85%)	0	0	33(62.26%)	1(1.89%)
Week 4				4(11.77%)
Week 12				0(0.00%)

Normal total serum bilirubin level = 0.20-1.30mg%

48(90.56%) out of 53 patients developed elevated ALT in 2nd week whereas rest 5(9.44%) patients developed ALT abnormality in 4th week (**Table 4**).

Table 4 Onset of initial rise of alt in patients receiving Antitubercular Treatment (ATT)

Maximum ALT levels in multiples of ULN	
Time since starting ATT	**Number of patients developing elevated ALT, N (%)**
Week 0	0(0.00%)
Week 2	48(90.56%)
Week 4	5(9.44%)
Week 12	0(0.00%)

ULN- Upper limit of the normal range; ALT-Alanine Transaminase

Out of 53 patients, 51(96.23%) had a maximum serum ALT level between 5 - 20 times the upper limit of normal level (**Table 5**).

Table 5 Maximum alanine transaminase levels in patients with hepatotoxicity

Maximum ALT levels in multiples of ULN				
Normal	**>13.0 (>50-150U/l)**	**>3.05.0(>150-250U/l)**	**>5.020(>250-1000U/l)**	**>20(>1000U/l)**
N(%)	N(%)	N(%)	N(%)	N(%)
0	0	2(3.77%)	51(96.23%)	0

ULN- Upper limit of the normal range; Normal Alanine Transaminase (ALT) level= 4-50U/l

It was found that total serum bilirubin and ALT levels in the patients developing hepatotoxicity started to improve within 2 weeks after stopping ATT. All the patients with hepatotoxicity recovered completely by the end of week 12 and there was no mortality.

DISCUSSION

Presence of hepatotoxicity in patients receiving ATT

In our study, it was found that 13.62% of patients receiving ATT developed hepatotoxicity. Various studies have reported different incidence rates of hepatotoxicity due to antitubercular therapy globally. A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts.[4] For example, the risk of hepatotoxicity based on pooled data from four prospective Indian studies was 11.5% compared with 4.3% in Western publications.[6]

The incidences of hepatotoxicity reported by various researchers like Kamat et al.,[7] as 18%, Sivaraman et al.,[8] as 7%, Juganya et al.,[9] as 11.1%, Singhal et al.m,[10] as 10%, Abera et al.,[11] as 8%, Song et al.,[12] as 11.9%, Anand et al.,[13] as 10.1%, and Mahmood et al.,[14] as 19.76%. Huang et al.,[15] conducted a study on Hong Kong Chinese patients where 13% of patients who received ATT eventually developed hepatotoxicity.

Gender distribution of patients on ATT who developed hepatotoxicity

Out of 53 patients who developed hepatotoxicity, 34(64.15%) were male, and 19(35.85%) were female. The male is to female ratio is 1.8:1. In a study conducted by Juganya et al.,[9] on patients from South India reported 19(63.3%) male patients and 11(36.7%) female patients who developed ATT-induced hepatotoxicity.

Age distribution of patients on ATT who developed hepatotoxicity

It was found that 15(28.30%) out of 53 patients belonged to the age group 40-49 years, implying that the highest number of patients developing hepatotoxicity belonged to the age group 40-49 years. Studies conducted by Huang et al.,[15] and Dufour et al.,[16] reported an increase in hepatotoxicity ranging from 22 to 33% in patients older than 35 compared with a range from 8 to 17% in those younger than 35.

Symptomatic hepatotoxicity in patients receiving ATT

Of 53 patients who developed hepatotoxicity, 35(66.04%) patients were found to be symptomatic, and the rest 18(33.96%) were asymptomatic. Antitubercular drug-induced liver injury has a broad spectrum of presentations, ranging from the asymptomatic mild rise in liver biochemical tests to acute hepatitis and acute liver failure, and as per various studies conducted globally, symptomatic hepatitis is seen in 1-6% of patients taking isoniazid prophylaxis or combination drugs.[4] However, the finding in our study is in concordance with the studies conducted by Abbara et al.,[17] where 67.6% of patients were symptomatic, and Anand et al.,[13] who in a study conducted on Indian patients reported that 68.1% of patients were found to be symptomatic.

The onset of the initial rise of total serum bilirubin in patients receiving ATT

In 30(88.23%) patients initial rise of bilirubin was seen in 2nd week since starting ATT, and in 4(11.77%) patients,

IJHRMLP
ISSN 2394–806X (Print), ISSN 2454-5139 (Online)

the initial rise of bilirubin was seen in 4th week since starting ATT. In the study conducted by Abera et al.,[11] the time interval from the initiation of treatment to the onset of hepatotoxicity was 13-58 days (median of 26 days). A study conducted by Gaude et al.,[18] in Southern India, reported that the average duration of development of drug-induced liver injury was 20 days after starting antitubercular therapy. In a study by Juganya et al.,[9] it was found that hepatitis got resolved in most patients within 3- 4 weeks after stopping ATT. In another study by Abbara et al.,[17] median time from stopping the treatment to resolving LFT abnormalities was 28 days.

Maximum total serum bilirubin levels in patients with hepatotoxicity

Of 53 patients, 33(62.26%) had a maximum total serum bilirubin level between 3 - 10 times the upper limit of the normal level. A study by Mathur et al.,[19] stated that the total serum bilirubin level peaks in patients with hepatotoxicity were 10±0.91mg%.

The onset of the initial rise of alt in patients receiving ATT

The initial rise of ALT in patients with hepatotoxicity was maximum in 2nd week after starting ATT. 48(90.56%) patients developed elevated ALT in 2nd week whereas rest 5(9.44%) patients developed ALT abnormality in 4th week. It was in concordance with a study by Juganya et al.,[9] who reported initial elevation of liver enzymes to be more common between 8-14 days. Abbara et al.,[17] reported the median time to onset of elevation in liver enzymes to be 12.5 days (range 7-30 days). Studies by Anand et al.,[13] and Singhal et al.,[10] also reported that the resolution of liver enzyme abnormalities was observed within 3 weeks of stopping ATT.

Maximum ALT levels in patients with hepatotoxicity

Of 53 patients, 51(96.23%) had a maximum serum ALT level between 5 - 20 times the upper limit of the normal reference range. A study by Abbara et al.,[17] reported that 87.6% of patients developed ALT levels 5 times the upper standard limit. In a study by Juganya et al.,[9] the peak ALT level in patients with hepatotoxicity was an average of 465.6U/l.

CONCLUSION

The present study concluded that many tuberculosis patients receiving first-line antitubercular drugs can develop drug-induced hepatotoxicity. Most patients with hepatotoxicity in our study developed derangements in liver function within the first two weeks of starting antitubercular drugs and were symptomatic. Liver function abnormalities started to resolve within two weeks after stopping antitubercular therapy in our study's patients who developed hepatotoxicity. All the patients with hepatotoxicity entirely recovered by the next six to eight weeks, and there was no mortality. However, further studies with a longer follow-up and bigger patient pool are required to reach a better conclusion.

Data availability: The data used to support the findings of this study are included in the article.

Conflicts of interest: None declared.

Funding statement: This research did not receive any funding.

Acknowledgements: We acknowledge the department's staff members who have helped us complete this project by providing the department's necessary infrastructures.

Supplementary materials: Nil.

Ethical clearance: Taken from the Institutional Ethics Committee of GMCH.

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