CLINICAL PROFILE OF ANTI TUBERCULAR DRUGS INDUCED LIVER INJURY IN PATIENTS RECEIVING TREATMENT UNDER NATIONAL TUBERCULOSIS ELIMINATION PROGRAMME (NTEP) IN A TERTIARY CARE CENTER

ABSTRACT:

Background and objectives: Tuberculosis continues to remain a significant infectious disease across the developing world including India. The mainstay of drugs in the treatment of tuberculosis include isoniazide, rifampicin,pyrazinamide and ethambutol. Anti tubercular 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. This paper aims at studying the clinical profile of patients developing anti tubercular drugs induced liver injury while receiving treatment under National Tuberculosis Elimination Programme (NTEP) in a tertiary care center. Materials and methods:A hospital based, observation study conducted on 389 patients who were admitted to the Department of Medicine, Gauhati Medical College and Hospital, Guwahati, Assam. All patients underwent pretreatment clinical and laboratory evaluation including hemoglobin level, serum albumin,liver function test,ultrasonogram of abdomen, hepatitis B, C and HIV status .LFTs were repeated weekly in the first month, then at the end of second and third week. Collected data were analysed applying chi-square test. Results : 53 (13.62%) out of 389 patients developed hepatotoxicity with male:female ratio 1.8:1, highest number of patients belonging to the age group 40-49 years. 66.04% patients were symptomatic. 88.23% patients developed initial rise of bilirubin in 2nd week and 90.56% developed elevated ALT in 2nd week. Conclusion : A significant number of patients can develop hepatotoxicity during treatment with antitubercular drugs. Majority of patients developed LFT derangements in the first two weeks of treatment and were symptomatic, all recovered completely by next six to eight weeks and there was no mortality.

KEYWORDS: Anti tubercular drugs; hepatotoxicity; serum bilirubin ; alanine transaminase.

INTRODUCTION

Tuberculosis continues to remain a significant infectious disease across much of the developing world. According to the World Health Organization, 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 the treatment of tuberculosis includes the first line drugs which include isoniazid, rifampicin, pyrazinamide and ethambutol[(2)]. The liver plays a major role in metabolism of drugs and liver injury is a possible consequence of ingestion of any xenobiotic , including industrial toxins, pharmacologic agents, and complementary and alternative medications (CAMs) [(3)]. Anti tubercular 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)]. Anti tubercular drugs induced hepatitis is defined according to American Thoracic Society as [(5)]: A) Presence of at least one of the following: 1) A rise to more than 5 times the upper limit of normal (ULN) level of liver enzymes 2) Any increase in more than 3 times the upper limit of normal level of liver enzymes above pretreatment levels together with anorexia, nausea, vomiting, and jaundice, and B) Normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-tubercular drugs. Most commonly anti tubercular 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 development of anti tubercular drugs induced liver injury. The important factors to be considered are: [(4)] age, gender ,organ involvement/extent of tuberculosis ,malnutrition ,influence of alcohol, viral hepatitis (B &C) , dosing schedule and the role of HLA and genetic polymorphism on drug induced liver injury. As studies regarding this is not very common in the North Eastern 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 drugs induced liver injury among patients receiving anti tubercular medications.

MATERIALS AND METHODS

It was a prospective, hospital based observation study conducted for a period of one year from 1st July, 2021 to 30th June, 2022 on both indoor and outdoor patients in Gauhati Medical College and Hospital receiving first line anti tubercular therapy under National Tuberculosis Elimination Programme (NTEP) and fulfilling the inclusion criteria and exclusion criteria.

INCLUSION CRITERIA

Patients who were prescribed to receive first line anti tubercular drugs for pulmonary or extra pulmonary tuberculosis under the NTEP schedule containing hepatotoxic ATT drugs 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 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 which included hemoglobin levels, serum albumin, liver function tests and ultra sonogram of the abdomen and hepatitis B, C and HIV status . LFTs were

repeated weekly for the first month then at the end of second and third month . 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 was organized, tabulated in a master chart and statistically analysed using the IBM SPSS. For statistical analysis, chi-square test was applied.

RESULTS

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

Clinical profile and results of liver function tests of the patients developing hepatotoxicity are as follows:

In our study 53(13.62%) out of 389 patients receiving ATT developed hepatotoxicity .Out of these 53 patients, 34 (64.15%) were male and 19(35.85%) were female. 15 (28.30%) out of 53 patients belonged to the age group 40-49 years. 35 (66.04%) patients were found to be symptomatic and rest 18 (33.96%) patients were asymptomatic. In 30(88.23%) patients initial rise of bilirubin was seen in 2nd week since starting ATT and in 4 (11.77%) patients , initial rise of bilirubin was seen in 4th week since stating ATT. 33(62.26%) patients had a maximum total serum bilirubin level between 3 - 10 times upper limit of normal level. 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. 51(96.23%) patients had a maximum serum ALT level between 5 - 20 times upper limit of normal reference range.

TABLE 1: PRESENCE OF HEPATOTOXICITY IN PATIENTS RECEIVING ATT

HEPATOTOXICITY	NUMBER OF PATIENTS, N(%)
Present	53 (13.62%)
Absent	336 (86.38%)
Total	389(100%)

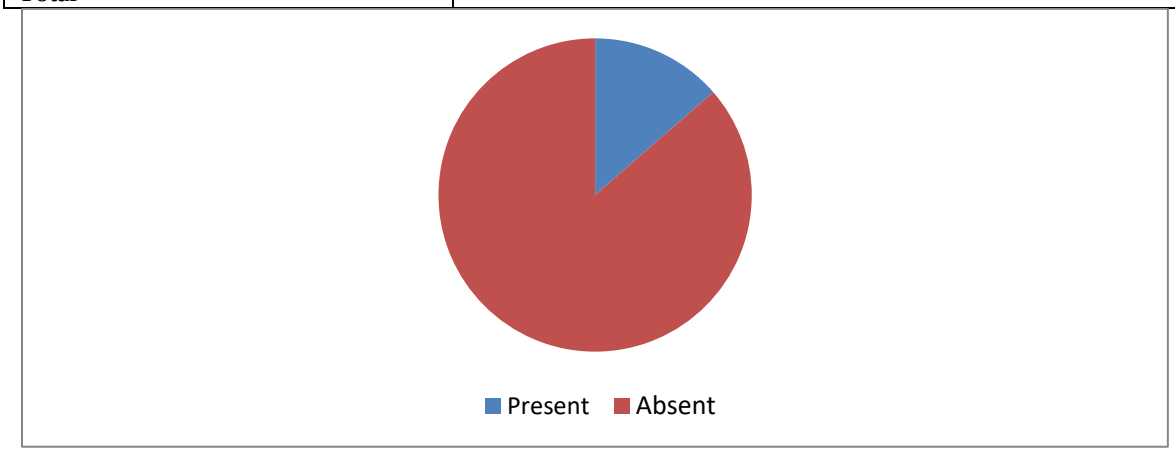

TABLE 2: AGE DISTRIBUTION OF PATIENTS ON ATT WHO DEVELOPED HEPATOTOXICITY

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%)
≥60	10(18.87%)
TOTAL	53(100.00%)

TABLE 3: MAXIMUM TOTAL SERUM BILIRUBIN LEVELS IN PATIENTS WITH HEPATOTOXICITY

MAXIMUM TOTAL SERUM BILIRUBIN IN MULTIPLES OF UPPER NORMAL LIMIT (ULN)				
NORMAL	>1-1.5(>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%)

TABLE 4: MAXIMUM ALT LEVELS IN PATIENTS WITH HEPATOTOXICITY

MAXIMUM ALT LEVELS IN MULTIPLES OF ULN				
NORMAL	>1-3.0(>50-150U/l)	>3.0-5.0(>150-250U/l)	>5.0-20(>250-1000U/l)	>20(>1000U/l)
N(%)	N(%)	N(%)	N(%)	N(%)
0	0	2(3.77%)	51(96.23%)	0

DISCUSSION

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 anti tubercular 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 following is a list of incidence of hepatotoxicity by some workers:

i)Kamat et al [7] : 18%

ii) Sivaraman et al [8] : 7%

iii) Juganya et al [9] : 11.1%

iv)Singhal et al [10] : 10%

v) Abera et al [11] : 8%

vi) Song et al [12] : 11.9%

vii)Anand et al [13] : 10.1%

viii) Mahmood et al [14] : 19.76%

Huang et al conducted a study on Hong Kong Chinese patients where 13% of patients received ATT eventually developed hepatotoxicity[15].

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

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

Out of 53 patients who developed hepatotoxicity, 35 (66.04%) patients were found to be symptomatic and rest 18 (33.96%) patients were asymptomatic. Anti tubercular drug induced liver injury has a wide spectrum of presentations, ranging from 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% patients were symptomatic and Anand et al [13] who in a study conducted on Indian patients reported that 68.1% patients were found to be symptomatic.

In 30(88.23%) patients initial rise of bilirubin was seen in 2nd week since starting ATT and in 4 (11.77%) patients , initial rise of bilirubin was seen in 4th week since stating 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 DILI was 20 days after starting anti-tubercular therapy . In a study by Juganya et al [9] it was found that hepatitis got resolved in majority patients within 3- 4 weeks after stopping ATT. In another study done by Abbara et al.[17], median time from stopping the treatment to resolution of LFT abnormalities was 28 days.

Out of 53 patients 33(62.26%) patients had a maximum total serum bilirubin level between 3 - 10 times upper limit of normal level. In a study done by Mathur et al[19], peak total serum bilirubin level in patients with hepatotoxicity was found to be 10±0.91mg%. 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 studies done be Juganya et al [9] who reported initial elevation elevation of liver enzymes to be more common between 8-14 days. Abbara et al.[17] reported median time to onset of elevation in liver enzymes to be 12.5 days (range 7-30 days). Studies done by Anand et al.[13] and Singhal et al.[10] also reported that resolution of liver enzyme abnormalities was observed within 3 weeks of stopping ATT .

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

CONCLUSION

From the present study , we have come to a conclusion that a significant number of tuberculosis patients receiving first line antitubercular drugs can develop drug induced hepatotoxicity. Majority of the 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 the patients who developed hepatotoxicity in our study. All the patients with hepatotoxicity recovered completely by the next six to eight weeks and there was no mortality.

However, further study with a longer follow up and bigger patient pool is required to come to 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.

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