Original Research Article

Study of anti-tuberculosis drug induced hepatotoxicity in tubercular patient under treatment

Hema Malathi[1],Abhishek Rath[2*], Arindam Rath[3] , Satyabrata Sengupta[4]
[1]Clinical Tutor, NRS Medical College & Hospital, Kolkata,West Bengal, India
[2]Clinical Tutor, General Medicine, College of Medicine and JNM Hospital, Kalyani, India
[3]Director, Apollo Infertility Centre, Kolkata,West Bengal, India

Received: 01-11-2020 / Revised: 16-12-2020 / Accepted: 05-01-2021

Abstract

Aims: To find out the frequency of hepatotoxicity in recipients of the anti-tubercular drugs, predictive and risk factors and Methods to continue anti tubercular therapy in patients who are developing features of hepatotoxicity.

Materials and methods: It is a prospective study included a total of 120 patients suffering from pulmonary and extra pulmonary tuberculosis. 100 patients (68 male and 32 female) completed the study (January 2014 to September 2015). 15 patients were lost to follow up and 5 patients died (1 due to fulminant hepatic failure and other 4 due to non-hepatological causes). **Results**: The prevalence of hepatotoxicity in our study was 3% (3/100).The maximum prevalence of toxicity (3.77%) was found in 20 -39 years age group. The prevalence of hepatotoxicity was found more in females than in males (3.12% vs 2.94% respectively). All the ATD hepatotoxicity occurred in patients having BMI <17.9 (5.66%). These 3 patients also had low serum albumin level. So, it appears that low BMI and low serum albumin level which are pointers of under nutrition and poor socioeconomic status are risk factors for development of hepatotoxicity.Clinical parameters like nausea, vomiting, jaundice, ascites, edema, encephalopathy and coagulopathy are the main presenting features of drug induced liver disease. All the three patients having ATD hepatotoxicity had pulmonary tuberculosis and received CAT I DOTS under RNTCP. But in our study there was a short number of cases of extra pulmonary tuberculosis (2/100) and only 27% CAT II.**Conclusion:**Considering the low prevalence of hepatotoxicity in our study; DOTS under RNTCP may be implemented successfully without much fear for hepatotoxicity.

Keywords: Hepatotoxicity, Anti-tubercular drugs, patient.

Introduction

Hepatotoxicity is liver injury caused by drugs and other chemicals[1]. It is one of the most frequent concerns in drug therapy and is the most common cause of post marketing withdrawal of drugs. The significance of hepatotoxicity and mode of prevention/reduction, therefore, is an issue that involves clinicians involved in patient care as well as scientists involved in drug development. Liver is particularly vulnerable to drug induced injury in view of the fact that it functions as the gateway of entry of most foreign substances including drugs, before they can reach their sites of action in an innocuous form. Hepatotoxicity , as are the adverse drug reactions involving the liver are coined, are mostly infrequent , unpredictable events, frequency of which depends on many factors- both genetic and acquired. The significance of the event, both for the patient and the drug, also varies and a spectrum of outcomes exist – ranging from asymptomatic enzyme elevations to progressive and often fatal liver disease. Early detection and prompt withdrawal of the offending drug is the only intervention required . Adverse drug reactions that affect the liver are more difficult to define and often escape detection unless late, as there are no specific biomarkers to define drug induced liver injury, it resembles clinically , morphologically and biochemically liver disease due to other causes and the biochemical tests used to detect liver injury may also be elevated as an adaptive response to drug. In general, however, liver injury is present when abnormalities of liver test include an increase to more than twice the upper limit of normal of serum alanine amino-transferase (ALT), aspartate amino-transferase (AST) or bilirubin levels[1].

While acetaminophen is the most common agent in the western world causing drug induced liver injury, in India anti-tuberculosis drugs, particularly isoniazid (INH), are the most common cause of clinically significant drug induced liver disease. The clinical expression of anti-tuberculosis drugs induced hepatotoxicity is varied from asymptomatic liver enzyme abnormalities disappearing on subsequent continuation of therapy to symptomatic acute hepatitis, often leading to fulminant hepatic failure.The incidence of anti-tuberculosis drug induced hepatitis ranges from 1% to 36%,

**Correspondence*

Dr. Abhishek Rath
Clinical Tutor, General Medicine, College of Medicine and JNM Hospital, Kalyani,India
E-mail: drabhishekrath77417@gmail.com

depending on different regimens and definitions of hepatic injury.Alcohol consumption, advanced age, acetylator status, and existing chronic liver disease have been reported to increase the risk of anti-tuberculosis drug induced hepatitis. However, the exact mechanism for this hepatotoxicity remains unclear[2]. Recently, in India there had been a change in approach to tuberculosis treatment with patients receiving intermittent observed therapy with standard drugs. Very little data is available on the frequency of hepatotoxicity with this regimen. Although DOTS programme was initiated to improve compliance, it remains to be seen whether the prevalence of hepatotoxicity in DOTS regimen differ from that observed in daily regimen earlier. This research work has been planned to find out the exact prevalence, modifying factors and outcome of ATD induced hepatotoxicity in patients suffering from both pulmonary and extrapulmonary tuberculosis. In our study, drug induced hepatitis has been defined as an increase in serum ALT level to more than two times a normal level (0 to 40 IU/L), and bilirubin to more than 2 mg/dl or both with clinical symptoms and signs after taking anti-tuberculosis drugs, provided they had normal pre-treatment value.

Materials and methods

This is a prospective study on antituberculotic drug induced hepatotoxicity (AIH) is a prospective , observational study . A total of 120 cases (suffering from pulmonary and extra-pulmonary tuberculosis) were enrolled during the study period of January 2014 to September 2015.The patients were put on ATD after proper categorization (I, II). Treatment was planned according to RNTCP and the patients were given DOTS. ADR were assessed both clinically and biochemically and the patients were followed up accordingly.A detail comparison and discussion will be made considering all the leading studies on AIH.

Inclusion Criteria

All patients diagnosed to have either pulmonary or extra pulmonary tuberculosis and were given DOTS by RNTCP guidelines irrespective of the liver status (except that mentioned in exclusion criteria) were included in the study.

Exclusion Criteria

Patients with clinically decompensated chronic liver disease, Defaulters of DOTS, Patients who had to be changed from one category to another during therapy, Alcoholic liver disease, other medications which can produce hepatotoxicity, below 13 years of age.

Increase in serum ALT levels to more than two times the normal level (0-40 IU/L),Serum bilirubin to more than 2 mg/dL are considered for patients .

N.B: Either of the above two criteria or both should be fulfilled to define ATD induced hepatotoxicity. There should also be normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti TB drugs.

Each subject will have ALT determination at the initiation, 15th day, 30th day and 60th day. However, if symptoms like nausea, vomiting, jaundice, skin rashes, oliguria etc. Develops at any point of time during the first two months of treatment, serum ALT and bilirubin was determined to look for hepatotoxicity.

Table 1:Points and calendar of events

CALENDAR OF EVENTS				
POINTS	**DAY 0**	**DAY 15**	**DAY 30**	**DAY 60**
Symptoms	√	√	√	√
Physical Examination	√	√	√	√
Chest X-ray	√			
ALT/serum bilirubin	√	√	√	√

In case of development of symptomatic hepatotoxicity serum ALT, serum bilirubin, serum albumin, serum ceruloplasmin, HBsAg, IgM anti HbcAg, anti HCV, IgM anti HAV, IgM anti HEV, HIV 1,2 (ELISA) will be done.

Liver biopsy is being planned in selected cases. In patients having asymptomatic elevations of serum ALTor bilirubin ; the drugs will be continued and they will be followed up both clinically and biochemically.

Statistical analysis: Data were represented as Mean + 3SD where applicable. Non-parametric data are expressed as percentage.

Results

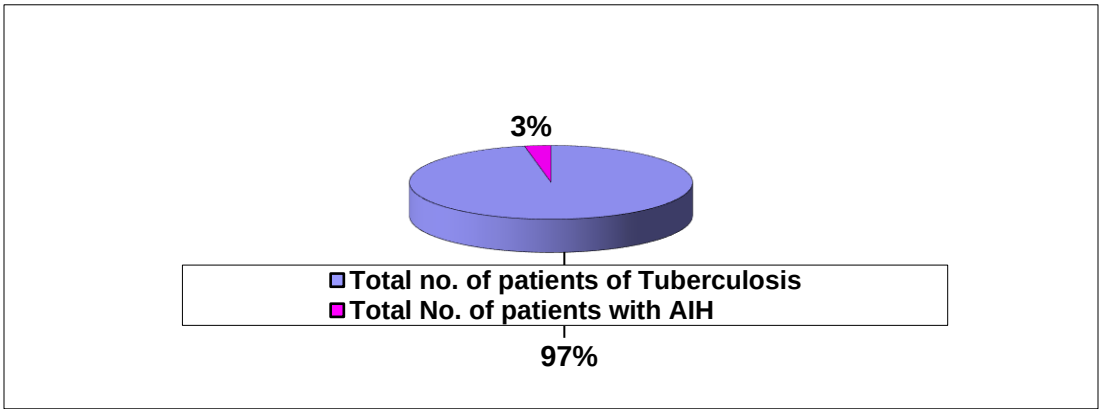

Fig 1: Prevalence of hepatotoxicity

Prevalence of hepatotoxicity in our study is 3% which is lower than other studies of regular 4 drug regimen (2-36%)

Table 1: Demographic details in study

Age in Years	Total Patients / Male / Female	Patients with AIH
13 – 19	11 / 7 (63.63%) / 4 (36.37%)	Nil
20 – 39	54 /35 (64.81%) / 19 (35.18%)	2 (3.77%)
40 – 59	29/21 (72.41%) / 8 (27.59%)	1 (3.44%)
60 – 79	6/5 (83.33%) / 1 (16.67%)	Nil

In this study the maximum prevalence of TB was found in the age group of 20 – 39 years, probably due to highest no. of patients in this group. Females have higher percentage of hepatotoxicity than males**.**

Table 2: Nutritional Status (assessed by BMI and serum albumin)

BMI	Total patients	Patients with AIH
<17.9	53 (53%)	3 (5.66%)
18 – 24.9	45 (45%)	Nil
25 – 29.9	2 (2%).	Nil

It is observed that all three patients had BMI below the mean BMI(17.82)

All toxic patients had serum albumin below the normal range (3.5-5.5gm%). As BMI and serum albumin are pointers of malnutrition , so probably malnutrition is a predisposition factor for hepatotoxicity.

Table 3: Per capita income of patients in study

Name	Monthly income (Rs)	No. of family members	Mean income (per capita) (Rs)
K. S.	1000	3	333.33
M. D.	1500	8	187.5
A. D.	1000	5	200

Two cases had mean per capita income below and one case had above the total mean per capita income (Rs 237) .

Table 4: Clinical Features of patients in study

Parameter	Total patients	Patients with AIH
Nausea	4	3 (75%)
Vomiting	3	2 (66%)
Ascites	1	1 (100%)
Jaundice	4	3 (75%)
Oedema	1	1 (100%)
Encephalopathy	1	1 (100%)
Coagulopathy	1	1 (100%)

The clinical features present in patients who developed AIH were nausea, vomiting, jaundice, ascites, oedema, encephalopathy and coagulopathy. Nausea, vomiting, ascites, jaundice, oedema, encephalopathy and coagulopathy are associated with hepatotoxicity. These 3 patients were not alcoholic nor they had any history of long drawn drug intake.

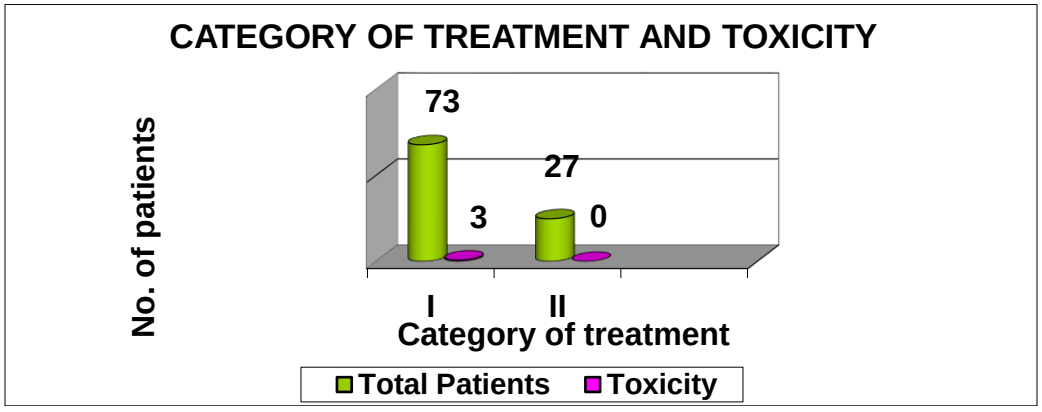

Fig 2: Category of Treatment of patients in study

From this study it is observed that toxicity is found in Category I only. It can be explained by the fact that; in category I all the patients are naive whereas in category II (although having 5 drugs) toxicity is less as these patients have had received ATD previously before getting Cat II and are thus not naive patients.Although all cases of AIH was

noticed in pulmonary TB; yet the association of type of TB and AIH cannot be definitely concluded from this observation alone because of discrepancy between case load of two types of TB. (98% in PTB and 2% in EPTB) observed in our centres of study. Out of the 3 patients developing hepatotoxicity, all 3 had increased serum bilirubin levels and one had increased serum ALT levels. One patient died after 35 days of initiating ATD out of fulminant hepatic failure. It is observed that increase in serum bilirubin is an important marker of hepatotoxicity.ATD were introduced sequentially as isoniazid, rifampicin and pyrazinamide within a span of 3 weeks and no further toxicity developed in two patients. One patient died after 35 days due to fulminant hepatic failure and ATD could not be reintroduced in this case.

Discussion

The population selected for the study were 100 cases of pulmonary and extra- pulmonary tuberculosis. They were put on DOTS regimen according to RNTPC. All the patients were followed up both clinically and biochemically and observed for signs and symptoms of hepatotoxicity. In case of development of symptomatic hepatotoxicity with biochemical manifestations, the drugs were stopped and introduced gradually according to following order – INH, Rifampicin and Pyrazinamide. Patients who developed asymptomatic hepatotoxicity (as defined by serum ALT>80) at any point of time were followed up both clinically and biochemically without stoppage of any drugs and it was found the serum ALT became normal in subsequent samples.Out of the 3 patients developing symptomatic AIH; one patient died out of fulminant hepatic failure. Reintroduction of drugs was possible in other two patients without difficulty. In our study, only 3 patients out of 100 patients developed hepatotoxicity. So, the prevalence of AIH was found to be 3%. The prevalence obtained is much lower than previous studies using regular 4 drug regimen from USA and UK of 3% and 4% respectively[3]. Steele, et al undertook a metanalysis to estimate the prevalence of ATD hepatotoxicity[4]. A total of 34 clinical studies (22 adults and 12 children) published between 1966 and 1989 were analysed. They found that the incidence of clinical hepatitis in adults with isoniazid alone was 0.6%, while multidrug rifampicin and not isoniazid 1.1%. The incidence of clinical hepatitis in 6105 patients taking isoniazid and rifampicin combination was 2.6% which was significantly higher than the incidence in patients taking multiple drugs containing isoniazid without rifampicin and those taking multiple drugs containing rifampicin without isoniazid.A Japanese study investigated on total number of 77 patients, found that incidence rate of 18.25% patients developing adverse hepatic reactions in the first month of INH and RMP treatment. The risk of hepatotoxicity based on data from 4 prospective Indian Studies was 11.5% compared with the 4.3% in 14 published studies from the West[5]. The incidence of hepatotoxicity has been reported to be higher in developing countries, and factors such as acute or chronic liver disease, poor nutrition, widespread parasitism, chronic infections, indiscriminate use of various drugs, ethnic factors, severity of the disease, chronic alcoholism or genetic predisposing may play a role individually or collectively. So, considering various leading studies of regular drug therapy ; the prevalence of hepatotoxicity is much lower in our study group using DOTS regimen.In our study population : the prevalence of toxicity was found to be nil in 13- 19 years, 3.77% in 20 – 39 years, 3.45% in 40 – 59 years and nil in 60 – 79 years. Many authors have studied age as a putative factor in the development of AIH. According to USPHS study report of Kopanoff and Workers[6], of13,838 patients on prophylactic isoniazid therapy, hepatitis was very uncommon in patients younger than 20 years and occurred in 0.3% of patients aged 20 – 34 years, 1.2% of patients aged 35- 49 years, and 2.3% of patients aged 50-64 years. In an uncontrolled study by the USPHS, the relative risk of isoniazid hepatotoxicity was found to be 0/1000 in patients younger than 20 years of age, compared to the relative risk of 19.2/1000 observed in patients 50-64 years of age.In a case-control study, Pande, et al[7] observed that ATD induced hepatotoxicity was more frequent in older patients.However, in another Indian study, it was observed that age has no co-relation with anti-tuberculosis treatment induced hepatotoxicity. In a study conducted by Van Hest. R, et al[9] showed preventive treatment with rifampin-pyrazinamide caused severe hepatotoxicity more often than did preventive treatment with isoniazid , especially in patients <25 years old.Our observational study supports the work done by Kopanoff and coworkers[6] ; but fails to support other studies which states that ATD induced hepatotoxicity is more common in older populations.In our study population of 100, 68 (68%) were male and 32(32%) were female patients out of which toxicity developed in 2.94% of male and 3.12% of female patients. Studies of Taneja DP, Dalip K[10] revealed then adverse hepatotoxic reactions to ATD are not influenced by the sex of the patient. R. Shakya, BS Rao, et al study found female gender as another independent predictor of anti TB drugs–induced hepatotoxicity[11]. Though frequency of drug- induced liver injury was found to be higher in female, severity of hepatotoxicity was found to have no role upon gender.Our study supports the study of R. Shakya et. al. but does not match with study of Tanja DP et.al. regarding sex as a factor for hepatotoxicity[10,11].

Nutritional status of 100 patients were assessed by BMI and serum albumin was done in 3 patients of hepatotoxicity. Poor nutritional status is believed to be predisposing factor for tuberculosis. In our study of 100 patients, 53 (53%) had BMI <17.9; 45 (45%) had BMI of 18 – 24.9 and 2 (2%) had BMI of 25 – 29.9 with a mean BMI of 17.82 $\pm$ 2.60. In patients who had ATD hepatotoxicity; BMI was less than the mean BMI. Two out of three patients had BMI below 3 SD of mean. Again 2 out of the 3 patients had per capita family income less than the mean. Serum albumin was also low as compared to normal value (3.5-5.5 gm%).It appears from our study that low BMI, low per capita income and low serum albumin are associated with hepatotoxicity.The association of malnutrition and hepatotoxicity was studied by several workers.Santra et al showed that low glutathione level is associated with higher ATD hepatotoxicity[12]. In malnutrition, glutathione sources are depleted which makes one vulnerable to oxidative injury. In a malnourished person

liver metabolizes drug at a slower pace. Recently environmental studies have given credence to important contributory role of protein calorie under- nutrition in the development of tuberculosis.Isoniazid metabolism is decreased in the states of malnutrition leading to increased toxicity by metabolites. Our study corroborates with the fact that malnutrition predisposes to drug induced hepatotoxicity.In our study 3 patients who developed hepatotoxicity due to antituberculotic therapy resembled viral hepatitis in its mode of onset. Nausea, vomiting, jaundice, ascites, oedema,coagulopathy and encephalopathy were the presenting features.The clinical profile of patients receiving ATD is variable. Most of the patients tolerate the drugs inspite of presence of prodromal symptoms such as nausea, vomiting, pain in the right upper quadrant of abdomen and asymptomatic elevation of hepatic transaminases. Singh J. Garg PK[13] conducted a prospective study to determine the clinical strategy of reintroduction of ATD. Seventy- two consecutive patients with clinical evidence of ATD – induced hepatotoxicity was included. Jaundice was the presenting symptom in 44(61%) patients; prodromal symptoms were present in 28 (39%). Serious complications developed in 12 (16.6%) patients (fulminant hepatic failure in seven, subacute hepatic failure in four, hepatic encephalopathy in one). Nine patients (three males, six females) died from these complications. The mean duration of treatment before the onset of hepatitis was significantly longer in the group that died (53.22 +/- 36.22 days) than in the rest of the patients (31.07 +/- 30.30 days; p <0.01).A case of fulminant hepatitis in a young Chinese man was reported by Girotto I, Gjonovich A, Preciso G[14]Tost JR, Vidal R et al in Spain determined the frequency of severe hepatotoxicity due to anti-tuberculosis (TB) drugs, and predictors of development of acute liver failure or of death[15]. A retrospective study was conducted by members of the Spanish Society of Pneumology from 18 hospitals during 1997-2001. A case of severe hepatotoxicity was defined as any asymptomatic patient with a ten-fold increase in transaminases or three- fold increase in cholestasis parameters, or, among patients with hepatitis symptoms, any raised hepatic parameters or development of hepatic failure. One hundred and six patients developed severe hepatotoxicity. Of a total of 3510 patients, 90 were treated for active TB (2.56%). Eleven cases (10.3%) presented with acute liver failure, three of which underwent liver transplant. The global case fatality rate was 4.7% (five cases, three associated with alcohol use or hepatotoxic drugs).The predictors of poor prognosis were total bilirubin >2 mg/dl and serum creatinine >1.5 mg/dl. Pereira RM et al[16]study presented a case of a 5- month-old patient who had pulmonary and meningeal tuberculosis and who developed toxic hepatitis accomplished by hepatic failure, while he was being treated with isoniazid, pyrazinamide and rifampicin. The clinical manifestations and the laboratory alterations were detected in the fifth day of treatment and the recovery was fast; and almost complete by the end of the first week, in which the use of isoniazid had been suspended. Our study found similar clinical profile as reported by other studies regarding ATD hepatotoxicity.Coexisting liver disorders like viral hepatitis, alcoholic liver disease, chronic drug (Ayurveda, homeopathic) intake, Wilson's disease with hepatic involvement etc modify ATD induced hepatotoxicity. In our study; one patient who developed ATD hepatotoxicity had HBsAg positive. Two other patients were negative for viral markers. All the 3 patients of hepatotoxicity had negative serology for HIV.All the patients who developed ATD hepatotoxicity were non- alcoholic, nor did they had history of chronic drug intake and did not have any chronic liver pathology. It has been shown that patients with underlying liver disease and alcoholics are more prone to develop anti tuberculosis treatment induced hepatotoxicity. Gronhagen-Riska, et al[17] studied predisposing factors in hepatitis due to combined isoniazid and rifampicin treatment and reported that one half of the patients who developed large increase in transaminase [more than 150 U/1] were either alcoholics or had a history of previous liver or biliary disease. They also observed that the peak transaminase and bilirubin levels were higher in patients who were hepatitis B virus carriers than in those who were not. A study from Europe also showed that concurrent and previous biliary disorders were risk factors for isoniazid hepatotoxicity. Kopanoff et al[9] have reported that hepatotoxicity is more likely to occur in alcoholic patients with pre-existing liver damage than in non- alcoholic patients. However, Girling[18] observed that patients with known liver disease can be treated with isoniazid and rifampicin containing regimens without undue risk. Mc Glynn,et al[19] reported that there is no evidence of increased risk of hepatotoxicity with isoniazid therapy in hepatitis B virus carriers than in non-carriers. Fulminant and subacute hepatic failures were seen more frequently in hepatitis B virus carriers with a significantly higher mortality as compared to non-carriers. In another prospective study, no increased risk for hepatotoxicity was noted in patients with either underlying compensated alcoholic liver disease or hepatitis B carrier state. Retrospective case-control study was carried out on 110 HBsAg carriers with newly diagnosed active tuberculosis who had been treated with isoniazid, rifampin, ethambutol, and/or pyrazinamide. Inactive HBsAg carriers were defined as follows: (1) positive for HBsAg: (2) negative for hepatitis B antigen (HBeAg), positive for antibody to HbeAg: (3) < 10^5 copies per ml of serum hepatitis B virus DNA; and (4) normal pre-treatment aspartate aminotransferase (AST) alanine aminotransferase (ALT) levels. 97 HBsAg negative patients who received standard antituberculotic medication were selected as control subjects. The baseline characteristics of the 110 inactive HBsAg carriers were similar to those of the 97 non-carriers. A total of 85% of persons in both groups had received an initial treatment regimen that included pyrazinamide. 38 inactive HBsAg carriers (35%) and 19 control subjects (20%) exhibited elevated liver enzyme levels during anti tuberculosis treatment (p = 0.016). Drug-induced hepatotoxicity, which was defined as a liver transaminase level of >/=120 IU/L, occurred more frequently in HBs Ag carriers (9 of 110 carriers; 8%) than in control subjects (4 of 97 control subjects; 4%), although this was not a statistically significant discrepancy (p=0.230). More importantly, HBsAg carriers (n= 9.8%) who received anti tuberculosis therapy evidence a higher proportion of moderate- to-severe drug-

induced hepatotoxicity when compared with the control subjects (n= 2; 2% p = 0.05). Isoniazid and revamping were reintroduced as therapy after AST/ALT levels returned to baseline values in 10 patients (6HBsAg carries and 4 control subjects) among the 13 patients exhibiting drug-induced hepatotoxicity, and these retrials proved to be successful in 7 patients (5 HBsAg carriers and 2 control subjects). So, in conclusion; tuberculosis treatment in HBsAg positive and HBeAg negative inactive carriers could be pursued in the usual manner, using standard short- course regimens of isoniazid, rifampin, ethambutol, and/or pyrazinamide, with the condition that monthly liver function tests are performed.So, in our observational study with a small number of 3 patients developing hepatotoxicity (with one being HbsAg positive), it can't be said with certainty whether pre-existing liver disorders play a role in the development of hepatotoxicity.Patients with severe form of tuberculosis have been reported to have a higher incidence of developing hepatotoxicity than those with milder forms of the disease. In our study, hepatotoxicity was found in those 3 cases having pulmonary TB.None of the cases of extra pulmonary TB had hepatotoxicity.Our study does not support the published reports of other studies that ATD hepatotoxicity is more prevalent in extra pulmonary TB. This is because of the fact that only 2/100 patients had EPTB in our study. A larger study with EPTB patients with DOTS is needed to support other studies.All the three patients had elevation of conjugated bilirubin; thus, probably pointing towards cholestatic hepatotoxicity, which may be due to Rifampin. One patient had both conjugated bilirubin and serum ALT raised which probably points towards mixed hepatocellular injury by isoniazid and rifampicin. The patient who had mixed hepatocellular injury died of fulminant hepatic failure within 35 days after starting ATD. The other two patients had subsequent normalization of LFT upon discontinuation of ATD and they could be started with subsequent therapy with ATD without further hepatotoxicity. The drug stoppage period for first patient was from Day 30 to Day 60, whereas in case of second patient the period was Day 3 to Day 60, ATD was introduced sequentially in both the patients within a span of three (3) weeks in the order- isoniazid, rifampicin and pyrazinamide. Shakya R, et al[11] monitored 50 patients of active tuberculosis infection with normal pre-treatment liver function clinically as well as biochemically in a prospective cohort analysis. Four (8%) patients developed drug- induced hepatotoxicity. Jaundice was the presenting symptom in all of them. Time interval for onset of the hepatotoxicity was 12 to 60 days (median 28 days). Antituberculotic drugs were found to be associated with derangement of hepatic function resulting elevation in liver enzyme to a variable extent. 38% patients had 2 times and 30% had more than 3 times elevation of ALT. Similarly, 40% and 29% of patients showed 2 and more than 3 times elevating the AST levels respectively. Another study conducted by Schluger LK, USA[20] , concluded than the incidence of Isoniazid hepatotoxicity increased when the drug was used in conjunction with Rifampicin for the treatment of M. tuberculosis infection. Our study corroborates with the study of Shakya R, et Al[11] regarding the time of onset of ATD hepatotoxicity which is most common in first 2 months of therapy.3 patients (2 male & 1 female) developed asymptomatic hepatotoxicity at any point of time between Day 0 toDay 60, as they had serum ALT >80 IU/L with normal serum bilirubin.ATD was continued in these patients and subsequent serum ALT became normal. This phenomenon can be explained by hepatic adaptation.

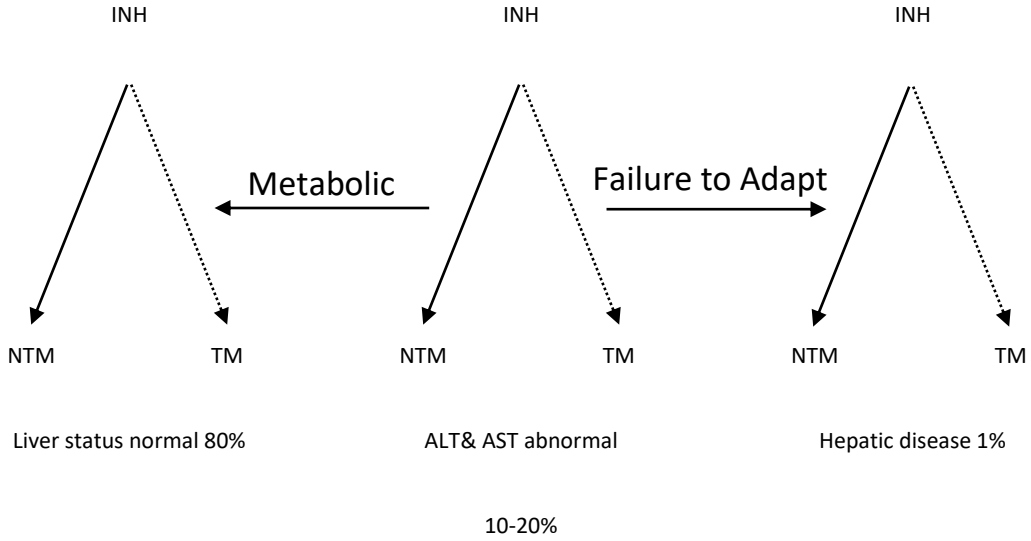

Fig 3: Hypothetical explanation of relationship of frequent (10-20%) abnormality to uncommon (1%) overt hepatic injury
TM = Toxic metabolite ; NTM = Non toxic metabolite

The above figure depicts hypothetical explanation of relationship of frequent (10-20%) abnormality to uncommon (1%) overt hepatic injury. Most patients with abnormal values show improvement or no worsening as administration of the drug is continued, as the result of presumably metabolic adaptation. Failure to adapt leads to overt disease. In this study the phenomenon of hepatic adaptation is seen in 3% of overall cases (3/100); male 2.94% (2/68) and female 3.12% (1/32) This adaptation perhaps involves activation of alternative pathways leading to less toxic metabolites or enhanced detoxification or disposal of the toxic metabolites. So, it is observed from our study that females have a higher adaptation rate than males, probably due to some alternative pathways to detoxify ATD. One died of fulminant hepatic failure due to AIH. 4 died out of malnutrition, anaemia, sepsis (no evidence of clinical or biochemical hepatotoxicity at the time of dying).

Conclusion

ATD hepatotoxicity is one of the most prevalent drug induced liver injuries. Earlier recognition of AIH is needed to reduce significant morbidity and mortality. ATD hepatotoxicity can present as acute, subacute or chronic hepatic dysfunction. In our study one patient died of fulminant hepatic failure due to AIH. In other two patients after AIH developed drug was withdrawn and reintroduced after LFT became normal in a sequential manner without further development of symptomatic hepatotoxicity. Non-hepatotoxic ATD's like FQ were not used in our study. The patients in our study had initial elevation of serum ALT which subsequently became normal even with ATD challenge; probably that they had also tubercle bacilli infiltrating the liver. Considering the low prevalence of hepatotoxicity in our study; DOTS under RNTCP may be implemented successfully without much fear for hepatotoxicity.

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Conflict of Interest: Nil Source of support:Nil