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Research Article

**FREQUENCY OF FIRST LINE ANTITUBERCULOSIS DRUG
INDUCED HEPATITIS**¹Mahnoor Munir Alvi, ²Ushna Khalid, ³Rimsha Riaz

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Abstract:

Tuberculosis is one of the most important communicable diseases worldwide. Its Antituberculosis therapy (ATT) has multiple side effects, out of which ATT induced hepatitis is important one, as it can force the Physicians to modify the treatment.

Objective: To determine the frequency of first line Anti Tuberculosis drugs induced hepatotoxicity during intensive phase of treatment.

Subject and Methods: This was a descriptive case series study conducted at multicenter during July 2018 to December 2018. In this study, 150 patients of either gender with age range of 15 to 60 years were selected by non-probability consecutive sampling after fulfilling the inclusion and exclusion criteria. They were started on category 1 of ATT. They were then followed for two months for the development of ATT induced hepatitis, which was monitored with the help of clinical symptoms and liver enzymes.

Results: In present study, there were total 150 cases out of which 80 were male and 70 females with mean age of 34.28 ± 15.28 years. There were 115 cases suffering from PTB and 35 from EPTB. ATT induced hepatotoxicity was found in 17 out of 150 patients (11.33%). Among these 17 hepatotoxic patients 10 were males and 7 were females ($p=0.63$). ATT induced hepatitis was more seen in cases of PTB where it occurred in 15 cases ($p=0.14$) and among the PTB, the highest was seen in far advanced TB (47.8%), which was statistically significant ($p=0.026$). Highest incidence of hepatotoxicity (22.5%) was found in age group of 49 to 60 years, which was statistically significant ($p=0.036$). Majority (13 out of 17) developed it within first 30 days.

Conclusion: ATT induced hepatitis is a common side effect. About one in every nine case develops it. Old age and Pulmonary disease, especially far advance disease is associated with higher risk of hepatotoxicity.

Key Words: Tuberculosis, Hepatitis, First line ATT.

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INTRODUCTION:

Pulmonary Tuberculosis (PTB) still remains one of the most devastating infectious issue in the world leading millions of people to miseries. It is cited second in the leading causes of death amongst infectious diseases after the notorious Human Immunodeficiency Virus (HIV). About 8.6 million new cases of Tuberculosis were reported in 2012 worldwide while 1.3 million led to death in the same year. Developing world is being proved the graveyard for most of the tuberculosis patients accounting more than 90% deaths. Pakistan ranks 6th in high burden countries worldwide and has an incidence rate of 231/100,000 population [1].

All first line anti tuberculosis therapy (ATT) drugs i.e Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), except Ethambutol (E) are reported to be hepatotoxic. Pyrazinamide is thought to be the most culprit with the hepatotoxicity rate of 9% followed by Isoniazid with 3% and Rifampicin 1% [2]. Rifampicin is less hepatotoxic but it potentiates the toxicity of other drugs like Isoniazid. Ethambutol is considered liver friendly [3]. Therefore, when these above mentioned four drugs used in combination during the intensive phase, hepatotoxicity is likely to be higher. In studies from various countries, it ranged from 5 to 31% [3,4], while in Pakistan multiple studies show 5 to 11% only [5-8]. It has also been found that age, malnutrition, alcoholism, slow acetylators, chronic viral infections like Hepatitis B (HBV), Hepatitis C (HCV) or HIV expose the patients to more hepatotoxicity of ATT drugs [9]. Tuberculosis (TB) can be categorized on the basis of radiological findings into Normal (Extra Pulmonary), Minimal (M), Moderately Advanced (MA) and Far Advanced (FA) [10]. Extent of disease is also a strong predictor for hepatotoxicity. In patients with Far Advanced pulmonary tuberculosis, hepatotoxicity was seen in 16.66% which was very high as compared to Minimal (7.14%) and Moderately Advanced (2.17%) [7]. Patients with age more than 35 years are more vulnerable to hepatotoxicity of ATT as compared to their younger counterparts [11]. In one study conducted recently in Liaquat University of Medical and Health Sciences, Jamshoro in 2012 showed that out of their 500 patients, 55 (11%) developed hepatitis which was supported by development of jaundice besides upper abdominal pain, nausea and vomiting. In 40 (8%) hepatitis resolved within 6 weeks without any sequel. Serious complications were noted in 15 (3%) among which 10 (2%) developed hepatic encephalopathy, 5 (1%) ended up in chronic hepatitis and 5 (1%) died [8]. One study conducted at Lahore reported that majority of the patients (72.7%) suffering from ATT induced

hepatitis developed it early in the course of treatment [6].

OBJECTIVE:

To determine the frequency of first line Anti Tuberculosis drugs induced hepatotoxicity during intensive phase of treatment.

OPERATIONAL DEFINITIONS:

- FIRST LINE ATT:** Isoniazid (5mg/kg body wt), Rifampicin (10mg/kg body wt), Ethambutol (15mg/kg body wt), Pyrazinamide (25mg/kg body wt) [12].
- HEPATOTOXICITY:** Presence of all or any one of the following:
 - Development of yellow discoloration of eyes (jaundice).
 - Presence of symptoms like nausea, vomiting, upper abdominal pain and loss of appetite.
 - Elevation of liver markers i.e Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP) three times above their normal limit (ALT \leq 40 IU/L, AST \leq 20 IU/L, ALP = 32-92 IU/L) with symptoms as mentioned above.
 - Elevation of liver markers five times above normal with or without symptoms.
 - Serum Bilirubin $>$ 1.5 mg/dl (Normal 0.3-1.0mg/dl) or Serum Albumin $<$ 3.0 g/dl (Normal 3.5-5.5g/dl) [13].
- INTENSIVE PHASE:** First 2 months of antituberculosis treatment containing all four above mentioned ATT drugs

MATERIALS AND METHODS:

In this descriptive cases series study that was conducted at a multicenter during July 2018 to December 2018. There were 150 cases enrolled through non probability consecutive sampling according to the following selection criteria.

Inclusion Criteria:

All patients of either sex with pulmonary and extra pulmonary tuberculosis taking first line ATT during intensive phase of treatment with age $>$ 15 and $<$ 60 years.

Exclusion Criteria:

- Patients with any acute or chronic viral hepatitis i.e HBV, HCV (acute or chronic) or HIV.
- Any other acute or chronic liver disease like alcoholic hepatitis.
- Drug resistant TB cases.
- Pregnancy.

All these patients, fulfilling the criteria were checked for their base line liver enzymes, Ultrasonography (USG) abdomen and viral hepatitis i.e HBV, HCV and HIV to exclude any other pre existing liver disease. After ruling out other preexisting case, the cases fulfilling the inclusion criteria were followed every week during intensive phase and were checked at laboratory of Sheikh Zayed Hospital, Rahim Yar Khan Demographic data like age, sex, weight etc and clinical data like vomiting, abdominal pain, loss of appetite, rise in liver enzymes were also collected.

Data was analyzed with the help of SPSS version 17. Quantitative variables like age was presented in terms of mean \pm SD (Standard Deviation). Frequency & percentages were calculated for gender, site and extent of TB and outcome variable i.e. ATT induced hepatotoxicity seen (yes/no). Effect modifier were controlled through stratification and post stratification apply Chi-Square test taking P-value \leq 0.05 as significant.

RESULTS:

In present study, there were total 150 cases out of which 80 were male and 70 females with mean age of 34.28 ± 15.28 years. There were 115 cases suffering from PTB and 35 from EPTB. ATT induced hepatotoxicity was found in 17 out of 150 patients (11.33%) as in figure 1. Among these 17 patients 10 were males and 7 were females (table 1); however, the difference was statistically not significant ($p=0.63$). ATT induced hepatitis was more seen in cases of PTB where it occurred in 15 cases compared to EPTB where it was in 2 cases only ($p= 0.14$) out of their respective groups (table 2). Among the PTB, the highest hepatotoxicity was seen in far advanced TB (47.8%), which was statistically significant ($p = 0.026$). The incidence of hepatotoxicity in rest of the categories was 12% and 1.5% in moderately advanced, minimal subcategory of PTB respectively (table 3). Highest incidence of hepatotoxicity (22.5%) was found in age group of 49 to 60 years, which was statistically significant ($p= 0.036$). In other groups, there was 10.14% hepatotoxicity in age group 15 to 26, 4.76% in age group of 27 to 37 years and no one suffered it in age group of 38 to 48 years (table 4). Table 5 shows the time of development of ATT induced Hepatitis from start of therapy. Majority (13 out of 17) developed it within first 30 days as compared to 4 out of 17 in last 30 days.

DISCUSSION:

ATT induced hepatitis is one of the most important side effects as it can force the physician to modify the treatment to drugs which are less effective and also have more side effects, or it

may lead to overt fulminant hepatitis which may endanger the life.

In this study ATT induced hepatitis was seen in 17 out of 150 cases (11.33%) which is higher than reported in most reviews of literature. There are number of studies conducted in various parts of the world which reported incidence of ATT induced Hepatitis ranging from 1 to 61% 14,15. This wide variation in results might be due to different characteristics of subjects of studies, difference in inclusion and exclusion criteria, variable cut off values for defining hepatotoxicity as well as presence of various confounding factors like acetylator status, prevalence of hepatitis B, C and Alcohol consumption etc. But studies from Pakistan has shown that ATT induced hepatitis was seen in 5 to 11% of the cases^{5,8} which is comparable to this study.

Male gender has been considered as a risk factor for development of drug induced hepatotoxicity¹⁶. In this study, out of total 17 patients who had ATT induced hepatotoxicity, it was seen more commonly in males where 10 out of 80 males developed hepatotoxicity as compared to 7 out of 70 females, out of total 17. The number was slightly higher in males but it was not statistically significant ($p=0.63$). Various other studies also failed to show any significant association between gender and ATT induced hepatitis¹⁷⁻¹⁸.

Site of the disease also remained an important concern for the development of ATT induced hepatitis. It was more frequently observed in patients with PTB than with EPTB. In this study, 15 out of 17 cases that developed ATT induced hepatitis were suffering from PTB. However, when considered the total number of patients in PTB and EPTB groups, this difference was not statistically significant ($p = 0.234$). Various studies published in literature have revealed conflicting results. Some of them found significant association between PTB and hepatotoxicity^{3,7}. While others showed difference which was statistically not significant^{11,19}. There are few small studies which even contradict these results i.e. they found more hepatotoxicity in EPTB⁶. But in those studies TB of the gastrointestinal tract and the liver were contributing a major bulk of EPTB.

Although site of disease (PTB vs EPTB) did not proved to be significant, severity of disease emerged as a risk factor in this study. Eleven out

of seventeen patients who developed ATT induced hepatitis were suffering from far advance PTB. Many studies have shown linear association between the extent of disease and ATT induced hepatotoxicity²⁰⁻²¹. This might be due to involvement of the lung, resulting in hypoxia which can damage liver due to production of toxic free radicals. When considered the total number of patients with far advanced TB group, 11 out of 23 patients had this adverse effect which statistically significant ($p = 0.02$).

It was reported previously that chances of ATT induced hepatitis are higher during initial period of therapy and it reduces thereafter.²² Various possible explanations for it include malnutrition resulting from anorexia, higher chances of allergic/ idiosyncratic reactions in the initial phase of treatment and hypoxia associated with extensive lung involvement etc. Similar trend has been observed in this study. out of total 17

patients who developed this adverse effect, 6 had it during 1st 15 days and 7 during 2nd 15 days period. The incidence fell in next month, 4 developed it during 3rd fortnight and none during the last 15 days of the therapy. This finding is consistent with previous reports.^{6,8}

There are certain **limitations of this study**. Firstly, there was small number of patients in this study. Secondly the patients were observed for only in the intensive phase of therapy i.e. first 2 months. Follow up for full course of treatment may be more revealing.

CONCLUSION:

ATT induced hepatitis is a common side effect. About one in every nine case develops it. Old age and Pulmonary disease, especially far advance disease is associated with higher risk of hepatotoxicity.

FIGURE 1: FREQUENCY OF ATT INDUCED HEPATITIS: n=150

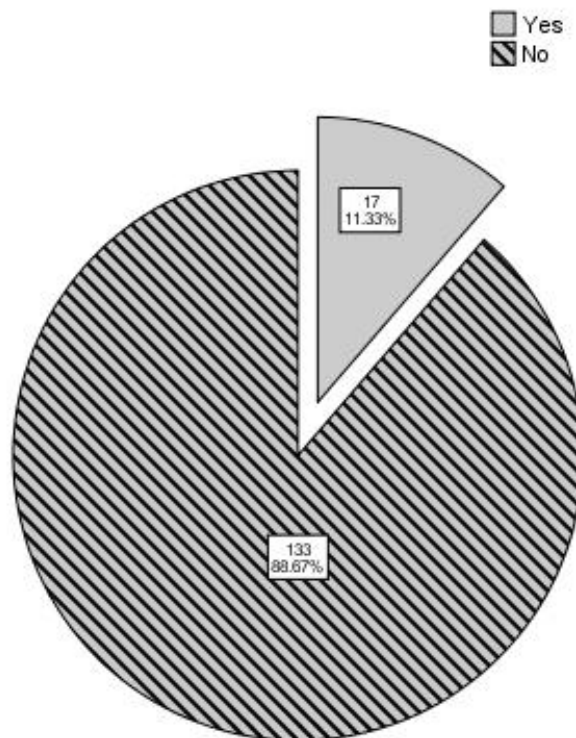


TABLE 1: ATT INDUCED HEPATITIS WITH RESPECT TO GENDER n= 150

ATT induced Hepatitis	Gender		Total
	Male	Female	
Yes	10 (58.82%)	7 (41.18%)	17 (100%)
No	70 (52.63%)	63 (47.37%)	133 (100%)
Total	80 (53.33%)	70 (46.67%)	150 (100%)

p= 0.63

TABLE 2: ATT INDUCED HEPATITIS WITH RESPECT TO SITE OF DISEASE n= 150

Diagnosis	ATT induced Hepatitis		Total
	Yes	No	
PTB	15 (13.04%)	100 (86.96%)	115 (100%)
EPTB	2 (5.71%)	33 (94.29%)	35 (100%)

p= 0.14

TABLE 3: ATT INDUCED HEPATITIS ACCORDING TO RADIOLOGICAL EXTENT OF DISEASE n= 115

Diagnosis	ATT induced Hepatitis		Total
	Yes	No	
Minimal	1 (1.5%)	66 (98.5%)	67
Moderately Advance	3 (12.0%)	22 (88.0%)	25
Far Advance	11 (47.8%)	12 (52.2%)	23

p= 0.026

TABLE 4: ATT INDUCED HEPATITIS WITH RESPECT TO AGE GROUPS n=150

AGE GROUPS (YEARS)	ATT induced Hepatitis		Total
	Yes	No	
15 to 26	07 (10.14%)	62 (89.86%)	69
27 to 37	01 (4.76%)	20(94.24%)	21
38 to 48	00 (00%)	20 (100%)	20
49 to 60	09 (%22.5)	31(77.5%)	40

p= 0.03

TABLE 5: TIME TAKEN TO DEVELOP ATT INDUCED HEPATITIS n= 17

Duration of ATT	ATT induced Hepatitis		Total
	Yes	No	
Less than 15 Days	06 (35.3%)	11 (64.7%)	17
16 to 30 Days	07 (41.2%)	10 (58.8%)	17
31 to 45 Days	04 (23.5%)	13 (76.5%)	17
46 to 60 Days	00 (00.0%)	17 (100%)	17

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