Original Research Paper

Volume - 13 | Issue - 09 | September - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Respiratory Medicine

MANIFESTATION OF 1ST LINE ATT INDUCED HEPATOTOXICITY: AN EVALUATION OF THE CLINICAL SPECTRUM, DETERMINING FACTORS AND ADVERSE DRUG REACTION ANALYSIS

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ABSTRACT **Objectives:** Antitubercular treatment (ATT)-induced liver injury has been one of the major causes of drug-induced liver injury (DILI). It is associated with multiple attributable risk factors. The study was planned to determine the various risk factors associated with ATT-induced liver injury and to perform causality analysis for suspected adverse drug reactions. **Methods:** The observational follow-up study was done in Himalayan Hospital, Dehradun from 2018 to 2019. Patients were taken on modified ATT and follow-up was done weekly with LFT. Later, 1st line ATT was re-challenged to evaluate for offending drug. **Results:** A total of 180 patients developing symptoms following 1st line ATT intake were evaluated. Loss of appetite, nausea and vomiting were the most common symptoms. Re challenging with first-line ATT was tolerated by 85% of patients. Pyrazinamide was the most common offending ATT causing DILI. Advanced age, hypoalbuminaemia and underlying Liver disease had a significant association with ATT-induced DILI. Upon causality analysis, 65.6% of patients were classified as probable according to the WHO-UMC scale. **Conclusion:** Elderly (≥60 years), hypoalbuminaemia and underlying Liver disease were significant risk factors for ATT-induced DILI. Pyrazinamide was the most common drug to cause ATT-induced DILI.

KEYWORDS : ATT, hepatotoxicity, DILI

Antitubercular treatment (ATT)-induced Liver injury has been amongst the primary causes of drug-induced Liver injury (DILI) and drug-induced acute Liver failure (DIALF) in India (1). DILI has been a concern in the treatment of Tuberculosis (TB) infection (2). The spectrum of ATT-induced liver injury ranges from non-specific transaminitis to fulminant hepatic failure (3).

Adverse drug reactions (ADR) to 1st line ATT may lead to significant morbidity and mortality. The global prevalence of ADR with 1st line ATT is 8-85% based on multiple studies conducted worldwide whereas in the Indian scenario, it varies from 2.3% - 17%. ADR manifestation with 1st line ATT can have a wide spectrum of clinical presentations. Gastrointestinal side effects and Liver injury are the commonest of ADR caused due to 1st line ATT (4).

TB-DILI is the most common cause leading to treatment interruption of Tuberculosis (5). Determining the strength and relationship between the particular drug in a clinical setting and its associated adverse event is done by using Causality analysis. This study attempted to assess various risk factors associated with ATT-induced liver injury and to determine the suspected adverse drug reactions with the usage of 1st line ATT.

MATERIAL AND METHODS:

This observational follow-up study was conducted over a period of one year from December 2018 to December 2019. In this study, 180 patients on 1st line ATT who developed symptoms of ATT-induced hepatitis were recruited by using the purposive sampling method.

A standardised case reporting form was used to collect baseline information. LFTs, serum Creatinine, serum Uric acid and serum Albumin test were used to assess the clinical data. WHO- UMC adverse drug reaction classification was used to perform causality analysis for suspected adverse drug reactions.

After taking ethical approval, objectives and procedures were explained to each participant. Written informed consent was obtained before starting data collection.

RESULTS

Categorical variables like age, gender, symptoms, clinical findings, risk factors and causality assessment for adverse drug reactions were represented in the form of frequencies and percentages (Table 1). Quantitative variables like age, height, weight and BMI were represented in the form of mean ± SD (Table 2). The significance of withholding 1st line ATT and introducing modified ATT was done by comparing initial and follow-up AST/ ALT values using paired T-test (Table 3). Comparison between two sample proportions of the study population was done by Z test in two proportions (Table 4). The association of various risk factors with the occurrence of ATT-induced DILI was done by Chi-square test (Table 5). The value of $p < 0.05$ was considered statistically significant.

Results also revealed that there is a statistically significant difference between AST Dates 1-2 and between ALT dates 1-2. Date 1 refers to the initial presentation and date 2 refers to the 1st follow-up following the introduction of the modified ATT regime. It means that the method of withdrawing ATT and introducing modified ATT improved Liver injury.

Patients with pre-existing Liver disease, hypoalbuminaemia and older age group (≥60 years) had a significant association with ATT-induced Liver injury.

On causality assessment, the majority of patients were implicated as probable (table 1).

DISCUSSION

The purpose of the current study was to evaluate risk factors implicated in the causation of ATT-induced Liver injury. The clinical profile and progression of the disease were recorded. Early detection of ATT-induced Liver disease was vital to avoid serious and fatal complications like acute/ chronic liver failure in susceptible population.

Mean days for LFT values to return to normal levels following transaminitis was 20.68 ± 6.16 days and a median of 7 days. The findings in our study are comparable to a study done in Egypt by Makhlouf et al who reported normalisation of Liver function test parameters within 2 weeks of cessation of therapy (3).

The most common symptom of ATT induced Hepatitis in our study was loss of appetite (70.6%). Least common symptom was skin manifestations. Icterus was the most common clinical finding. Findings in our study are comparable to study done by Abbara et al who determined nausea and vomiting as the most common symptoms (6).

Eighty Five percent patients out of 154 tolerated re-challenge with 1st line ATT. Nine patients tolerated Isoniazid and Rifampicin and in these patients, Pyrazinamide could not be re challenged owing to various reasons. Reasons for not reintroducing Pyrazinamide were Hyperuricaemia, any underlying liver disease or the patient was already previously started on continuous phase of ATT regime. In our study, ATT induced Hepatitis was found to be in 10.5% of subjects on

re-challenging. Pyrazinamide was the most common drug leading to ATT induced Hepatitis in 11 (6.1 %) of patients and Isoniazid caused ATT induced Hepatitis in 1.6 % of patients. Rifampicin-induced Hepatitis was seen in 2.8 % patients. Two patients were kept on modified ATT in view of persistent LFT derangement. Cause of persistent LFTs derangement can be due to underlying pre-existing Liver diseases or idiosyncratic drug reaction to 1st line ATT. These findings were comparable to studies done by Gaude et al who reported incidence of ATT induced hepatotoxicity upon rechallenging at 18.1% and by Costiniuk et al from South Africa who reported an incidence of 12 % (7) (8).

Advanced age, alcoholism, Hepatitis, HIV, malnutrition are various known risk factors of ATT induced Hepatitis (9). Among the various attributable risk factors leading to ATT induced Hepatitis, two different proportions of population were compared. This means that whether occurrence of ATT induced Hepatitis was significantly different in two different population proportion/risk factors. The results concluded that there was significant proportion difference/ non equal manifestation of ATT induced Hepatitis among men and women. Similarly, manifestation of ATT induced Hepatitis was significantly different/ non equal among HIV positive and Non-HIV patients, Diabetics and non-Diabetics. Manifestation of ATT induced Hepatitis was significantly different among populations having pre existing liver disease and no pre-existing liver disease.

Occurrence of ATT induced Hepatitis differed significantly among smokers and non-smokers, age groups (below and above 60 years), alcoholics and non alcoholics, pulmonary disease and extra pulmonary disease patients, between populations having past history of ATT intake and no past history of ATT intake and between patients having hypoalbuminaemia and normal Albumin levels. Very limited studies are available as per our knowledge that have compared proportion differences in manifestation of ATT induced Hepatitis among different population groups. A comparable study done by Makhlouf et al found no statistically significant difference between incidences of ATT induced Hepatitis between Pulmonary and Extra pulmonary TB patients (3).

Study justifies withholding ATT upon derangement of Liver function tests and starting modified ATT. Hence there is a temporal relationship between time since ATT administration and occurrence of ATT-induced Hepatitis.

We found that pre-existing liver disease, old age (≥ 60 years) and hypoalbuminaemia had significant associations with ATT-induced Hepatitis. Other factors such as gender, HIV, Diabetes, smoking and, alcoholism were not associated with ATT induced Hepatitis. The findings in our study are similar to study by Hwa Song et al in South Korea which concludes advanced age and chronic liver disease to be associated with ATT-induced Liver injury (10). Studies done by Makhlouf et al, Anand et al and Mani et al determined Liver disease as an independent risk factor for ATT-induced Hepatitis (3) (4) (11) . On the contrary, study done by Singh et al did not find underlying Liver disease as an associated risk factor (12).

Few studies have reported various contrasting results regarding association of various risk factors with ATT induced Hepatitis. A study done by Saha et al in Vellore found that risk factors like HIV, alcohol consumption, Hepatitis, existing chronic Tuberculosis were not significantly associated with ATT induced Hepatitis whereas other known confounders like age, sex, BMI had poor correlation with ATT induced Hepatitis (13). On the other hand, study done by Gaude et al in Belgaon, Karnataka observed occurrence of ATT induced Hepatitis in elderly, alcoholics, patients with past history of viral Hepatitis, Hypoalbuminaemia, females and Diabetics (7).

WHO- UMC causality analysis for adverse drug reaction was performed in the present study. A majority of patients were categorised as probable as per WHO- UMC scale. Two patients in our study died during the course of follow up. The cause of death can be attributed to other comorbid illnesses in these patients along with ATT induced Liver dysfunction. Two patients lost to follow up. Two patients were not re challenged with 1st line ATT in view of persistent derangement of Liver function test. The cause for deranged Liver function can be attributed to underlying Liver disease or idiosyncratic reaction to 1st line ATT. The findings in our study are similar to a study done by Shang et al in China who reported 61 percent patients as probable.

CONCLUSION

ATT-induced Liver injury is an important complication of Tuberculosis treatment. Common symptoms include loss of appetite, nausea and vomiting. Pyrazinamide was the most common drug followed by Rifampicin and then Isoniazid to cause Liver dysfunction. Elderly (≥60 years), hypoalbuminaemia and underlying Liver disease were significant risk factors for ATT-induced DILI. Study concludes that ATT-induced Liver injury is a burden acting as a hindrance in the treatment of Tuberculosis. There is a need for increased awareness and understanding of ATT-induced Liver injury.

Table 1: Distribution of the study population

Variables	Frequency	Percentage
Age (Years)		
0-12 years	1	0.6
13-18 years	11	6.1
19-59 years	103	57.2
≥60 years	65	36.1
Symptoms (at the time of presentation)		
New onset fever	17	9.4
Recurrent nausea and vomiting	124	68.9
Loss of appetite	127	70.6
Aches and pains	36	20.0
Skin manifestations	13	7.2
Fatigue	50	27.8
Clinical findings		
Pallor	11	6.1
Icterus	24	13.3
Lymphadenopathy	3	1.6
Risk Factors and co-morbidities		
Hypoalbuminemia	131	72.8
Abnormal BMI	96	53.3
Smoking	78	43.3
Alcohol	68	37.8
Diabetes Mellitus	23	12.8
Underlying Liver disease	12	6.7
Hypertension	8	4.4
Hyperuricaemia	7	3.9
HIV	5	2.8
Thyroid disorder	1	0.6
Causality Assessment of adverse drug reactions (WHO-UMC probability scale)		
Certain	18	10
Probable	118	65.6
Possible	25	13.9
Conditional	19	10.5
Past history of ATT intake		
Yes	29	16.1
No	151	83.9
Site of Tuberculosis		
Abdominal	4	2.2
Cervical	1	0.6
Empyema	3	1.6
Genitourinary	1	0.6
Intestinal	1	0.6
Knee	1	0.6
Lymph node	2	1.1
Miliary	4	2.2
Pericardial	2	1.1
Pleural Effusion	20	11.1
Pott's Spine	6	3.3
Pulmonary	126	70
Spondylodiscitis	1	0.6
Meningeal	7	3.8
Wrist joint	1	0.6
Final outcome on re challenging 1st line ATT on study group		
Tolerated	145	80.5
Tolerated Isoniazid and Rifampicin	9	5
Pyrazinamide induced Hepatotoxicity	11	6.1
Rifampicin induced Hepatotoxicity	5	2.8
Isoniazid induced Hepatotoxicity	3	1.6
Rifampicin induced Rash	1	0.6
Lost to follow up	2	1.1

On modified ATT	2	1.2
Death	2	1.1

Table 2: Demographic and clinical parameters of the study group

Variable	Minimum	Maximum	Mean ± Std. Deviation
Age (years)	1.0	80.0	39.01 ± 25.14
Height (cm)	136.0	180.0	160.106 ± 6.71
Weight (kg)	25.0	84.0	50.37 ± 9.94
Body Mass Index (kg/m^2)	13.14	27.98	19.93 ± 2.77
Mean days of onset of symptoms	0.0(within hours)	34.0	8.78 ± 6.31
Mean days for Liver Function to become normal	2.0	122.0	20.68 ± 6.16

Table 3: Table depicting significance of withdrawing ATT and introducing patients on modified ATT

Paired AST and ALT values before and after introducing modified ATT	Paired Differences			P-value
	Pooled Mean ± Standard Deviation	95% Confidence Interval of the Difference		
		Lower	Upper	
AST date 1 (initial value) - AST date 2 (1st follow up)	234.90 ± 333.31	184.88	284.92	.000*
ALT date 1 (initial value) - ALT date 2 (1st follow up)	136.28 ± 237.35	100.77	171.80	.000*

Table 4: Comparison of two population proportions in occurrence of ATT induced Hepatitis

Variables		Proportion	Z- Value	P-Value
Sex	Female	30.0	-7.58950	<0.001*
	Male	70.0		
HIV	No	97.2	13.567	<0.001*
	Yes	2.8		
Diabetes Mellitus	No	87.2	14.116	<0.001*
	Yes	12.8		
Age	Below 60 years	63.9	5.2747	<0.00001*
	Above/equal 60 years	36.1		
Liver Disease	No	93.3	6.2553	<0.001*
	Yes	6.7		
Smoking	No	56.7	2.54250	0.011*
	Yes	43.3		
Alcohol	No	62.2	4.62960	<0.001*
	Yes	37.8		
Site of disease	Pulmonary	70.0	7.5895	<0.00001*
	Extrapulmonary	30.0		
BMI	Normal	46.7	-1.2523	0.2113
	Abnormal	53.3		
History of ATT intake	Yes	16.1	-12.8641	<0.0001*
	No	83.9		
Hypoalbuminaemia	No	27.2	- 8.652	<0.00001*
	Yes	72.8		

Table 5: Association between various risk factors and ATT induced Liver injury

Variables		Not Tolerated/ On Modified Att		Tolerated		
Gender	Female	7	13.0%	47	87.0%	0.53
	Male	21	16.7%	105	83.3%	
Total	28	15.6%	152	84.4%		
HIV	No	28	16.0%	147	84.0%	0.333
	Yes	0	0.0%	5	100.0%	
Total	28	15.6%	152	84.4%		
Diabetes Mellitus	No	23	14.6%	134	85.4%	0.381
	Yes	5	21.7%	18	78.3%	
Total	28	15.6%	152	84.4%		
Age ≥ 60 years	No	9	7.7%	107	92.3%	0.006*
	Yes	14	21.8%	50	78.2%	
Total	23	12.8%	157	87.2%		
BMI	Abnormal	14	14.5%	82	85.5%	0.954
	Normal	12	14.3%	72	85.7%	
Total	26	14.4%	154	85.6%		
Site of disease	Pulmonary	16	14.5%	110	85.5%	0.480
	Extrapulmonary	9	16.6%	45	83.3%	
Total	25	13.9%	155	86.1%		
Underlying Liver disease	No	23	13.7%	145	86.3%	0.001*
	Yes	5	41.7%	7	58.3%	
Total	28	15.6%	152	84.4%		
Smoking	No	16	15.7%	86	84.3%	0.956
	Yes	12	15.4%	66	84.6%	
Total	28	15.6%	152	84.4%		
Alcohol	No	18	16.1%	94	83.9%	0.806
	Yes	10	14.7%	58	85.3%	
Total	28	15.6%	152	84.4%		
Hypoalbuminaemia	No	12	24. 5%	37	75.5 %	0.019*
	Yes	14	10.7%	117	89.3%	
Total		26	14.5%	154	85.5%	

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