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Incidence and Clinical Profile of Antituberculosis Treatment-Induced Hepatitis in a Tertiary Care Hospital in Southern India

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ABSTRACT

Introduction: Tuberculosis (TB) is a major health problem. After the widespread use of Antituberculosis Treatment (ATT) effective control has been achieved. As with any drug ATT has its own side effects among which hepatitis is of main concern as it can cause significant morbidity and mortality.

Aim: To assess the incidence of hepatitis in patients receiving ATT as per Revised National Tuberculosis Control Programme (RNTCP) and to know the possible risk factors for the development of drug-induced hepatotoxicity.

Materials and Methods: This study was done on 318 presumed and confirmed cases of TB patients with baseline bilirubin, liver enzymes (transaminases) and albumin values. Out of these 48 lost follow-up and remaining 270 were followed-up and repeat bilirubin, liver enzymes and albumin were done at two weeks or even earlier in patients with symptoms after starting ATT. ATT was reintroduced in a stepwise manner as per American Thoracic Society guidelines. Results were analysed using MS Excel.

Results: Out of the 270 cases, 30 (11.1%) developed ATT-induced hepatitis, among which 26 (86.67%) were followed-up and 4 (13.33%) lost to follow-up. Among 26, 3 (11.53%) developed hepatitis after reintroduction of ATT, two patients with Rifampicin and one with Isoniazid (INH) hence they were treated with alternative regimen and cured. According to this study, CNS tuberculosis had higher incidence of ATT-induced hepatitis. Old age and alcoholism were the independent risk factors. ATT-induced hepatitis commonly developed within two weeks of start of treatment. Average time for resolution of symptoms and restart of ATT was one month. There was no mortality in the study.

Conclusion: The incidence was comparable to other studies. Alcoholism, old age and CNS tuberculosis needs caution when starting ATT. Patients usually require follow-up of two weeks after starting ATT. Caution is required while reintroducing ATT and it is advisable to introduce in a stepwise manner.

Keywords: Antituberculosis drug-induced hepatotoxicity, Liver enzymes, Tuberculosis

INTRODUCTION

Tuberculosis (TB) has proved to be a menace for the human population especially in developing countries. WHO has declared that TB is a global emergency [1]. The global incidence of TB was 9 million in 2013. The incidence of TB in India was around 2.1 million according to 2013 census [2]. It comprises various forms of TB which includes pulmonary and extrapulmonary TB. Extrapulmonary includes TB lymphadenitis, pleural TB, genitourinary TB, skeletal TB, meningeal TB, tuberculoma, gastrointestinal TB, pericardial TB, miliary TB and others [3]. Every year more than 74% of people are diagnosed with TB. More than 18.9 million are started on ATT and 0.24 million die due to TB in India [2]. An effective control has been achieved by the widespread use of ATT. Globally in 2013, the treatment success rate for new cases of TB was 86% [2]. The standard chemotherapy regimen recommends a combination of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) HRZE for two months, followed by HR for four months (2HRZE/4HR). However, despite their efficacy, superadded problems have to be faced due to long duration of treatment. There are varied adverse effects of ATT which include hepatotoxicity, hyperuricaemia, optic neuritis, peripheral neuropathy, autoimmune thrombocytopenia, gouty arthritis amongst which hepatotoxicity is the commonest [3]. Hepatotoxicity is high with INH, Rifampicin, Rifabutin, Pyrazinamide as these drugs are metabolised in the liver. The incidence of hepatotoxicity was more with Indian patients when compared to western population [4]. Though the reasons are unclear, it could be due to the increased incidence of TB in Asian population. A better understanding of this adverse drug reaction may lead to individualised treatment.

A major adverse reaction to first line ATT results in discontinuation of the drug and has several implications. When it comes to ATT-induced hepatitis, there may be increased morbidity, even mortality due to liver failure. This may lead to increased financial burden due to frequent outpatient visits, repeat blood investigations and in some instances prolonged hospitalisation. Alternate regimens have its own problems like need for repeated injectable in place of oral formulations, toxicity, and often less effectivity prolonging the duration of treatment, which creates poor compliance. As a result of which, treatment failure and relapses are higher. So, early recognition of risk factors with close follow-up of patients receiving ATT and subjecting them to repeated liver function tests will help identifying the problem early thus, reducing morbidity and mortality and improving the treatment efficacy [5-7].

In the view of the above, present study was undertaken not only to calculate the incidence of hepatitis in patients receiving ATT as per RNTCP but also to assess the risk factors, the clinical profile, the timing of incidence and resolution of hepatitis and the drugs causing hepatitis on reintroduction.

MATERIALS AND METHODS

Study Design

This observational cross-sectional study was conducted in Meenakshi Mission Hospital and Research Centre, Lake Area, Melur Road, Madurai, Tamil Nadu, India, a Tertiary Care Hospital for one and half years from 1st August, 2016 to 31st January, 2018 after getting approval from Institutional Ethics Committee (Reg no: ECR/398/Inst/TN/2013/RR-19) and informed consent. The study population included both presumed and confirmed cases of newly diagnosed tuberculosis patients at Meenakshi Mission hospital, Madurai, Tamil Nadu, India.

Inclusion Criteria: The study included all cases of TB diagnosed by:

A. Confirmatory methods like:

1. Sputum AFB positive.
2. Biopsy specimen showing caseating granulomas.
3. TB-PCR (Gene expert) positive for AFB and

B. Presumed cases of TB based on a clinical picture suspicious for TB (eg- prolonged fever/anorexia with weight loss/chronic cough) supported by any one of the following:

1. Pleural fluid, Ascitic fluid, CSF favouring TB.
2. Radiological findings:
   - X-Ray-Apical lobe cavities and opacities, Unilateral hilar/paratracheal LN enlargement.
   - CT Chest-Thick walled cavity, Cavity with surrounding consolidation, Miliary nodules.
   - CT Abdomen- Mesenteric lymphadenopathy, Asymmetrical Ileocaecal thickening, abnormal peritoneal enhancement.

Exclusion criteria:

- Patients having preexisting liver disease.
- Patients having coexisting HIV, Hepatitis B, Hepatitis C.
- Multidrug Resistant (MDR) and Extensively Drug Resistant (XDR) TB patients.

Sample Size

Population (N):244

Adverse Drug Therapy (ADT) (p): 14.3%±5

Confidence limits as % of 100 (absolute±%) (d): 5%

Design effect [for cluster surveys-Design Effect (DEFF]: 1

Confidence Level (%): 95%

Sample Size (n) for various confidence levels

$n= \{DEFF*Np(1-p)\}/ \{(d^2/Z^21-\alpha/2*(N-1)+p*(1-p)\}$

Sample size was calculated as above from OpenEpi, Version 3, based on the article Ambreen K et al., [8].

Data Collection

A total of 318 cases of TB, chosen as per inclusion criteria, were studied. Forty-eight patients, that missed follow-up, were excluded from the study. Risk factors like age, gender, Body Mass Index (BMI), albumin, haemoglobin, high alcohol intake were collected for analysis. High alcohol intake was defined as person drinking more than six units (48gm ethanol) per day for more than one year. Baseline bilirubin, liver enzymes and albumin were done for patients before the start of treatment and then the patients were started on ATT- daily regimen with weight-based INH, ethambutol, rifampicin and pyrazinamide according to RNTCP guidelines. Patients were followed-up weekly and repeat bilirubin, liver enzymes and albumin were done at the end of two weeks of start of treatment for all asymptomatic patients. Repeat bilirubin, liver enzymes and albumin were done even earlier for patients who had symptoms like loss of appetite, nausea, vomiting, abdominal pain, jaundice, itching and dark coloured urine.

Patients who developed hepatotoxicity were diagnosed based on Drug-Induced Liver Injury (DILI) expert working group criteria which are as follows (for labelling DILI any one of the following criteria should be met) [9]:

- Rise in Alanine Aminotransferase (ALT) more than or equal to fivefold increase from Upper Limit of Normal (ULN).
- Twofold or more than twofold rise in Alkaline Phosphatase (ALP) along with more than or equal to twofold elevations in concentrations of 5 nucleotidase or γ-glutamyl transpeptidase above the ULN without known bone pathology.
- More than or equal to three threefold rises in ALT concentration and concurrent elevation of bilirubin concentration surpassing two times of the ULN.

In those patients diagnosed with hepatotoxicity, INH, rifampicin and pyrazinamide were stopped and they were started on modified ATT with ethambutol, ofloxacin or levofloxacin and streptomycin. These patients were asked to review after one week and a repeat bilirubin and liver enzymes and albumin were done.

If there were resolution of symptoms with normalisation of bilirubin, liver enzymes and albumin, hepatotoxic drugs were introduced one by one and newly added nonhepatotoxic drugs were stopped one by one. First rifampicin was usually introduced followed by INH with withdrawal of streptomycin, finally pyrazinamide was introduced with withdrawal of ofloxacin/levofloxacin as per American Thoracic Society guidelines [10]. Then, the same treatment was continued. In the worst case if hepatotoxicity developed during reintroduction, that particular drug was stopped completely and patient was continued with modified ATT.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel and analysed using Statistical Package for Social Science (SPSS) version 16. Qualitative variables such as gender, type of TB were summarised using proportion and frequencies. Quantitative variables such as age, albumin, haemoglobin, BMI were summarised using mean and standard deviation. Mann-Whitney U test was used to compare Liver Function Test (LFT) parameters among hepatotoxic and nonhepatotoxic group, Chi-square test was used to find association between dependent and independent variables like alcoholism and Antituberculosis drug-induced hepatotoxicity (ATDH), keeping p-value <0.05 as significance.

RESULTS

Among the 270 patients, 30 developed ATT-induced hepatitis with an incidence of 11.1%. The incidence of hepatotoxicity was more in elderly with mean age of 51.9 years (SD±18.7 years) [Table/Fig-1]. Total 12% of females developed hepatotoxicity compared to 10.7% of males but it was not statistically significant [Table/Fig-2]. CNS tuberculosis had higher incidence of ATDH (66.7%) when compared to other forms of TB [Table/Fig-3].

Age group (years)	No. of cases	Hepatitis	
		Yes	No
		Number (%)	Number (%)
Up to 20	15	2 (13.3)	13 (86.7)
21-40	95	7 (7.4)	88 (92.6)
41-60	115	10 (8.7)	105 (91.3)
Above 60	45	11 (24.4)	34 (75.6)
Total	270	30 (11.1)	240 (88.9)
Range (years)		18-89	12–77
Mean (years)		51.9±18.7	44.3±15.3
p-value		0.014	

[Table/Fig-1]: Tabulates the incidence of hepatotoxicity in various age groups.

Sex	Number of cases	Hepatitis	
		Present	Absent
		Number (%)	Number (%)
Male	178	19 (10.7)	159 (89.3)
Female	92	11 (12.0)	81 (88.0)
p-value		0.91 Not significant	

[Table/Fig-2]: Demonstrates the correlation between incidence of hepatitis among males and females.

Type of TB	Total cases	Cases		p-value
		With hepatitis	Without hepatitis	
	Number	Number (%)	Number (%)	
Pulmonary TB Other types	171 99	17 (9.9) 13 (13.1)	154 (90.1) 86 (86.9)	0.547
Pleural TB Other types	33 237	2 (6.1) 28 (11.8)	31 (93.9) 209 (88.2)	0.49
Lymph nodes Other types	11 257	1 (9.1) 29 (11.3)	10 (90.9) 228 (88.7)	0.786
Genito Urinary Other types	17 253	1 (5.9) 29 (11.5)	16 (94.1) 224 (88.5)	0.757
CNS Other types	9 261	6 (66.7) 24 (9.2)	3 (33.3) 237 (90.8)	<0.001
Disseminated Other types	16 254	3 (18.8) 27 (10.6)	13 (81.2) 227 (89.4)	0.554
Skeletal, Abdominal and Miliary. Other types	13 257	Nil 30 (11.7)	13 (100.0) 227 (88.3)	0.393

[Table/Fig-3]: Represents the incidence of hepatitis in various forms of TB.

Malnutrition was assessed in terms of BMI, haemoglobin and albumin levels [Table/Fig-4-6]. According to this study, there was no association between malnutrition and ATDH whereas alcohol intake was associated with ATDH with an incidence of 23.3% in alcoholics [Table/Fig-7]. On analysing baseline and repeat liver enzymes among patients with ATDH and those without ATDH, repeat values were significantly elevated in the ATDH group [Table/Fig-8].

Body mass index kg/m^2	No. of cases	Hepatitis	
		Yes	No
		Number (%)	Number (%)
<15	12	2 (16.7)	10 (83.3)
15-25	195	24 (12.3)	171 (87.7)
25-30	49	4 (8.2)	45 (91.8)
>30	14	Nil	14 (100)
Total	270	30 (11.1)	240 (88.9)
Range		14.38-27.44	12.1-44.85
Median		21.33	21.45
Mean±SD (kg/m^2)		20.94±3.33	22.11±4.77
p-value		0.196	

[Table/Fig-4]: Represents the relationship between BMI and hepatitis.

Haemoglobin% (g/dL)	No. of cases	Hepatitis	
		Yes	No
		Number (%)	Number (%)
<10	18	4 (22.2)	14 (77.8)
10-12	73	10 (13.7)	63 (86.3)
12-15	151	15 (9.9)	136 (90.1)
>15	28	1 (3.6)	27 (96.4)
Total	270	30 (11.1)	240 (88.9)
Range		3.5-17.2	8.2-17.8
Median		12.1	12.5
Mean±SD (g/dL)		11.71±2.48	12.47±1.64
p-value		0.074	

[Table/Fig-5]: Represents the haemoglobin levels in normal and hepatitis patients.

Most of the patients developed hepatitis within 8-14 days (53.3%) of start of ATT with the range of 5-70 days and a mean of 19.9 [Table/Fig-9]. The most common symptom at presentation was vomiting (50%) and loss of appetite (33.3%). Few were asymptomatic (23.3%) and were diagnosed based on alteration in liver enzymes. Rest had yellowish discolouration of sclera, dark coloured urine, itching and abdominal pain. Few cases had more than one illness [Table/Fig-10].

Serum albumin (g/dL)	No. of cases	Hepatitis	
		Yes	No
		Number (%)	Number (%)
<3.5	202	24 (11.9)	178 (88.1)
3.5-5.5	68	6 (8.8)	62 (91.2)
Total	270	30 (11.1)	240 (88.9)
Range		1.8-4.2	1.1-4.4
Median		3.1	3.1
Mean±SD (g/dL)		3.01±0.58	3.07±0.59
p-value		0.61	

[Table/Fig-6]: Shows the relation between pretreatment hypoalbuminaemia and hepatitis.

Alcoholism	No. of cases	Hepatitis	
		Present	Absent
		Number (%)	Number (%)
Present	30	7 (23.3)	23 (9.6)
Absent	240	23 (76.7)	217 (90.4)
p-value		0.024	

[Table/Fig-7]: Shows incidence of hepatitis in alcoholics and nonalcoholics.

Variable	Total		With hepatitis		Without hepatitis		p-value
	Mean	SD	Mean	SD	Mean	SD	
	Baseline liver function test		Repeat liver function test				
Total bilirubin	0.61	0.34	2.8	3.74	0.51	0.25	0.001
Direct bilirubin	0.19	0.14	16.8	79.6	0.17	0.11	0.003
Serum albumin	3.06	0.58	2.88	0.53	3.34	0.53	0.001
SGOT	28.27	15.94	465.6	1114.49	29.08	16.86	0.001
SGPT	25.19	24.04	218.3	368.71	25.90	18.99	0.001
GGT	37.10	31.46	130.48	185.77	35.19	23.25	0.001
ALP	79.04	33.63	117.05	89.98	76.17	27.95	0.001

[Table/Fig-8]: Represents the baseline and repeat liver function test in patients with and without hepatitis.
SGOT: Serum glutamic-oxaloacetic transaminase; SGPT:Serum glutamic pyruvate transaminase; GGT: Gamma glutamyl transferase; ALP: Alkaline phosphatase

Duration after which hepatitis developed (days)	Number of cases (%)
1-7	3 (10)
8-14	16 (53.3)
15-21	2 (6.7)
22-28	5 (16.7)
>28	4 (13.3)
Total	30 (100)
Range	5-70 days
Mean±SD (days)	19.9±14.4

[Table/Fig-9]: Shows the duration after which hepatitis developed in ATDH patients.

Once the offending drugs were stopped, it took around 3-4 weeks in majority (43.3%) for the hepatitis to settle [Table/Fig-11]. There was recurrence of hepatitis in three cases after reintroduction one with INH (3.33%) and two with rifampicin (6.64%).

DISCUSSION

In this study out of 270 patients, 30 patients developed ATT-induced hepatotoxicity with an incidence of 11.1%. According to literature there is a wide variation in the incidence of antituberculous drug-induced hepatotoxicity ranging from 2%-39% [4,11]. Studies done by Steele M et al., and Abera W et al., in Ethiopia showed an ATDH incidence of 8.9% and 8.1%, respectively which is almost similar

Presenting illness	Number of cases (%)
Loss of appetite	10 (33.3)
Dark coloured urine	1 (3.3)
Sclera discolouration	3 (10)
Vomiting	15 (50)
Itching	1 (3.3)
Abdominal pain	1 (3.3)
Asymptomatic	7 (23.3)
Total	30 (100)*

[Table/Fig-10]: Depicts the varied clinical presentation of ATDH patients.
*Some cases had more than one illness

Period within which hepatitis settled (week)	Number of c*Some cases had more than one illnessases (%)
2	3 (10)
3-4	13 (43.3)
5-8	5 (16.7)
>8	5 (16.7)
Lost to follow-up	4 (13.3)
Total	30 (100)

[Table/Fig-11]: Represents the duration within which hepatitis settled.

to this study [11,12]. Asian studies show an incidence ranging from 8.0–19.8% [13,14]. However, the incidence in this study was lower than that from Egypt (15%) [15] and higher than that of the Western world (4.3%) [11]. The variation in the incidence of antiTB drug-induced hepatotoxicity worldwide may be attributed to the differences in patients' characteristics, indiscriminate use of drugs, and the definition criteria of hepatotoxicity and prevalence of TB [10]. The incidence of ATT-induced hepatotoxicity varies worldwide and it has been reported to be higher in developing countries where other factors such as malnutrition, indiscriminate use of drugs, high burden of TB and various other factors are predominant [7].

Patients of both pulmonary and extrapulmonary TB were included in the study. Majority of the patients were diagnosed to have pulmonary TB followed by genitourinary TB, abdominal TB and rest were various other forms of TB. In most of the studies pulmonary TB was the most common indication for starting ATT [5,6]. This might be an explanation for increased number of pulmonary TB patients in the hepatotoxic group. As explained above, out of 30 patients who developed hepatotoxicity 17 patients belonged to pulmonary TB group, but the incidence of hepatotoxicity in pulmonary TB was only 9.9% that is 17 out of 171 patients compared to CNS TB patients who showed increased incidence 66.6% that is 6 out of 9 patients developed hepatotoxicity which was statistically significant (p-<0.001). Mahmood K et al., showed increased incidence of hepatotoxicity in patients diagnosed with abdominal TB that is 46.4% [5]. Certain studies have reported increased incidence of hepatotoxicity in patients with extrapulmonary TB [5,16,17].

In this study, 19 male patients and 11 female patients developed ATT-induced hepatotoxicity which is 63.3% and 36.7%, respectively. Several studies reported more incidence in females when compared to males [5,7,13]. The female predominance was attributed to variations in pharmacokinetics and acetylator status. Female sex have increased CYP3A activity when compared to males making them more vulnerable [18,19]. However, gender predominance neither affected the treatment duration nor caused significant morbidity.

The various risk factors include advanced age, high alcohol intake, hypoalbuminaemia, anaemia, preexisting liver disease, patients living with HIV/AIDS (PLHA), Hepatitis B and Hepatitis C, concomitant use of paracetamol and low serum cholesterol [5]. HIV and TB has increased hepatotoxicity because antiretroviral therapy itself carries individual risk of hepatotoxicity (e.g., Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI), Protease inhibitors). Antifungals (e.g., fluconazole) used as prophylaxis is also a risk factor. Hepatitis B and Hepatitis C are common causes of chronic liver disease and they increase the risk. However, PLHA, Hepatitis B, Hepatitis C and preexisting liver disease were excluded in this study.

Age is another independent risk factor stated by many studies [5,20-24]. In this study, patients with age more than 60 years had a higher incidence of hepatitis. This was similar to studies done by Mahmood K et al., Yee D et al., Singh MK et al., [5,20,21]. In a study done by Tariq S et al., hepatitis was common in middle age among 20-30 years but there was no correlation between age and ATDH [22]. The discordance between these findings could be possibly explained by fact that age categorisation for young and old people are different. However, old aged patients are more susceptible as they have decreased clearance of drugs metabolised by CYP450 enzymes, due to changes in liver blood flow, liver size, drug binding or distribution with ageing [25].

High alcohol intake is an independent risk factor. It was ascribed to malnutrition and glutathione store depletion and due to enzyme induction by alcohol [27]. High alcohol intake was considered as a risk factor in few studies [5,21,26,27]. In this study, 7 out of 30 who developed hepatotoxicity were alcoholic, accounting to 23.3%, which was statistically significant. On the contrary, studies done by Fernandez-Villar A et al., Dossing M et al., Altman C et al., and a study done in Egypt [15,28-30] showed no correlation between high alcohol intake and incidence of ATDH. This difference in observation among various studies makes high alcohol intake as a predisposing factor for drug-induced hepatotoxicity controversial.

Nutritional status as an independent risk factor was analysed in various studies [5,12,27] most commonly in developing countries. Drug metabolism pathways including acetylation pathways have been shown to be deranged in states of protein energy malnutrition and depletion of glutathione stores which make the patient more vulnerable to oxidative injuries. It also decreases xenobiotic clearance and higher plasma levels [19].

The nutritional status of patients was studied using various tools like BMI, haemoglobin levels and pretreatment hypoalbuminaemia. They did not affect the incidence of ATDH. The reason for this deviation of finding is that patients in this study had average BMI of 20.94 and they were not malnourished. Majority had pretreatment hypoalbuminaemia which was similar in both hepatotoxic and nonhepatotoxic group but it wasn't statistically significant. ATT-induced hepatotoxicity can manifest in various ways. It can be either asymptomatic with only elevated liver enzymes to symptoms ranging from nausea, vomiting to overt liver failure. In this study, out of 30 patients, 7 patients (23.3%) were asymptomatic. Among the various symptoms, vomiting and loss of appetite were the predominant symptoms. Based on the type of drug-induced reaction the onset of hepatitis may vary. The latency period between the start of the treatment and development of hepatitis may vary and it is important to analyse this as it may help the treating physician for early diagnosis and prevent further progression. The onset of hepatotoxicity ranged from 5 to 70 days of start of treatment and it was more common between 8-14 days. Majority, that is 26 out of 30 patients, developed hepatitis within 28 days and only four patients developed after 28 days.

Among that 30 patients who developed hepatotoxicity 26 patients were cured; four patients lost to follow-up. The hepatotoxicity following reintroduction of drugs was seen in 3 out of 26 patients (11.5%). Among the three, two had hepatotoxicity with rifampicin and one had hepatotoxicity with INH on reintroduction. In this study hepatitis was resolved in majority that is 13 out of 30 patients (43.3%) within 3- 4 weeks. This was similar to study done by Abbara A et al., where median time from stopping the treatment to re-establishing full-dose treatment was 28 days [26]. Fortunately, there was no liver failure or mortality in this study. Patients with predisposing factors

need careful and close follow-up. Reintroduction of ATT should be done in a stepwise manner. After development of hepatitis, immediate withdrawal of hepatotoxic drug should be considered.

Limitation(s)

Acetylator status and genetic polymorphism analysis were not done.

CONCLUSION(S)

Present study shows that ATT-induced hepatitis is a main concern in treating TB patients especially in the country where the TB burden is high. It also emphasises that special caution should be excised in treating alcoholics, elderly people and patients with CNS tuberculosis who are at higher risk. Further studies are needed in hepatitis B, C and HIV/AIDS patients.

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