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Original Research Paper

Pulmonary Medicine

A STUDY TO DETECT ASSOCIATION OF BODY MASS INDEX AND HYPERBILIRUBINEMIA AS WELL AS BODY MASS INDEX AND LIVER ENZYMES AMONG PATIENTS ON FIRST LINE ANTI-TUBERCULAR DRUGS FROM RNTCP DURING THE COURSE OF ANTI-TB TREATMENT

Dr. Rupam Kumar Ta Associate Professor. Department of Pulmonary Medicine. Burdwan Medical College, Burdwan

Dr. Saugata Bhaumik* 3rd Year Junior Resident, Department of Pulmonary Medicine. Burdwan Medical College, Burdwan *Corresponding Author

Dr. Pronoy Sen 1st year Junior Resident, Department of Pulmonary Medicine. Burdwan Medical College, Burdwan

ABSTRACT

BACKGROUND: Globally, estimated 10.0 million people developed Tuberculosis in 2017. Side effects and toxicity of the first line anti-tubercular drugs were hepatotoxicity, skin rash, and joint pain. Poor nutritional status has been considered to be one of the factors contributing to a higher incidence of DIH induced by short-course chemotherapy for TB in the developing countries. Hence this study was conducted to find out the association between Body Mass Index and hyperbilirubinemia as well as Body Mass Index and liver enzymes among patients on first line anti-tubercular drugs from RNTCP during the course of Anti-TB treatment.

METHODS: 116 patients who were diagnosed to have Pulmonary (PTB)/ Extrapulmonary (EPTB) tuberculosis at Outpatient & In-Patients of Department of Chest Medicine, Burdwan Medical College & Hospital for eleven months after fulfilling the inclusion and exclusion criteria. Treatment was given as per guidelines by Revised National TB Control Program.

RESULTS: Significant association was observed between BMI<18.5 kg/m2 and hyperbilirubinemia and BMI>=18.5 and elevation in SGPT level at 2nd week of treatment.

CONCLUSION: Hyperbilirubinemia is a common occurrence during the course of anti-TB treatment in patients with low BMI. Most patients show tolerance to anti-TB drugs and get adjusted after transient rise in liver enzymes. Clinicians should be vigilant for occurrence of hyperbilirubinemia in this high-risk group.

KEYWORDS : Hyperbilirubinemia, Sgpt, Bmi, Tuberculosis.

BACKGROUND

Human Tuberculosis, a known historical disease, as per genetic and archaeological data Mycobacterium tuberculosis complex (MTBC) may have co-existed with humans for 15,000 years.[1] It's etiology was discovered by sir Robert Koch in March 24th 1882.[2] Globally, estimated 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017: 5.8 million men, 3.2 million women and 1.0 million children.[3] Although witha running programmeto control tuberculosis for almost more than 50 years TB continues to be India's one of the leading health hazard. Almost 480,000 persons die per year and more than 1,400 every day due to tuberculosis in India. Many cases are lost to follow up or inadequately treated in private sector.[4]

Side effects and toxicity of the first line anti-tubercular drugs (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Streptomycin) are a hurdle to the physician and the patients for continuation of treatment.[5]The most severe side-effects leading to interruption of treatment were hepatotoxicity (11%), skin rash (6%), and joint pain (2%).[5] Drug induced injury to liver with first line drugs is a serious challenge during the treatment as well as significant hazard while re-introduction of the same regimen.[6] Incidence of hepatotoxicity in Indian population is around 11.5%, compared with 4.3% in western population, with mortality of 6-12% when continued even after the onset of symptoms. Some responsible factors for hepatotoxicity are older age, female population, poor nutritional status, high alcohol intake, existing liver disease, hepatitis B carriage, increased prevalence of viral hepatitis in developing countries, hypoalbuminemia and advanced tuberculosis, and inappropriate use of drugs.[7,8] Asymp tom atic elevation of transaminases is common, around 20%.[9,10] Clinical presentation of anti-tuberculosis drug induced hepatitis usually resembles acute viral hepatitis and resolves spontaneously following withdrawal of the anti-tuberculosis drugs.[9,10] Many mechanisms were suggested for drug-induced liver damage such asidiosyncratic damage, dose-dependent toxicity, induction of hepatic enzymes, drug-induced acute hepatitis and allergic reactions.[9,10]It takes around 16 weeks (Range 6 weeks-6 months) from treatment initiation to development of clinical symptoms.[10]

Though there are controversies regarding hepatotoxicity with alternate day regimen and daily regimen. Some studies are of opinion that there is no difference in hepatotoxicity incidences among daily and alternate day regimen.[11] Therefore, monitoring should be done after starting of Anti-tuberculosis drugs every 2 weeks interval to get a chance to avoid undue disruption in treatment, fatal complications and better patient counselling.[12]

Various studies have shown that Anti-TB drugs are common cause of hepatotoxicity worldwide.[13,14,15] The incidence of anti-TB drug induced hepatotoxicity varies with the characteristics of the populations, drug regimens involved, upper limit used to define hepatotoxicity, monitoring and reporting pattern. Overall, hepatotoxicity due to anti-TB drugs has been reported in 5%–28% of people treated with anti-TB drugs.[14] Many of these may not fit into a more recent international case definition of drug-induced liver injury (DILI). Majority of the reports have used an elevated alanine (ALT) or aspartate transaminase (AST) of 3 times upper limit of normal range (ULN) with symptoms (Abdominal pain, nausea, vomiting, unexplained fatigue or jaundice) attributable to liver injury or 5 times ULN of ALT or AST without symptoms to define hepatotoxicity.[16] Combination therapy develop transient asymptomatic elevation in liver enzymes, which comes to normal level with continuation of the drug.[17,18] The median interval from treatment initiation of drug to development of clinical symptoms is 16 weeks.[19,20]

Poor nutritional status has been considered to be one of the factors contributing to a higher incidence of DIH induced by short-course chemotherapy for TB in the developing countries. Drug metabolism pathways including acetylation pathways have been shown to be deranged in states of protein energy malnutrition.[29]

Therefore, in a country like India where malnutrition is very common it is very important to consider the nutritional status of patients on Anti-TB drugs and provide nutritional care.

Due to paucity of studies in this respect, this study was conducted to find out the association between Body Mass Index and hyperbilirubinemia as well as BMI and Liver enzymes among patients on first line anti-tubercular drugs from RNTCP during the course of Anti-TB treatment.

METHODS

Aprospective observational study after taking proper written consent from the patients wasconducted in Outpatient Department (OPD) & In-Patients of Department (IPD) of Burdwan Medical College, Department of Pulmonary Medicine after they were diagnosed with tuberculosis either clinically or microbiologically as pulmonary or extra-pulmonary during the period of 11months.

Base line data were collected such as history, detailed clinical examination, body mass index, residence, occupation, smoking and alcoholic status, sputum microscopy and CBNAAT, pleural fluid analysis (in cases of pleural effusion), lymph node fine needle aspiration for cytology and CBNAAT (in lymphadenopathy), Chest X-ray, and routine blood along with base line liver function test. All the patients were put on fixed dose combination (FDC) daily regimen with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol as per RNTCP guidelines and according to body weight.

Blood samples were drawn for assessment of bilirubin, SGPT, SGOT and alkaline phosphatase (ALP) on follow-up at 2 weeks interval during the Intensive Phase (IP) and 1-month interval during Continuation Phase (CP). During each follow up visit detailed history and clinical check-ups were done and duly put down on preformed data sheet.

Patients were educated about the signs and symptoms of hepatitis and hepatotoxicity such as nausea, vomiting, abdominal pain and yellowish discoloration of skin and eyes. If any of the mentioned features observed then they were tested for hepatitis (viral) profile, prothrombin time, bilirubin, SGPT, SGOT and alkaline phosphatase test. Also, patients were tested for other organ involvement such, urea and creatinine.

Normal range taken as for liver function tests were as follow bilirubin <1.2mg/dl, SGPT<40 IU/L, SGOT<40 IU/L, ALP 40-120 IU/L, GGT <60 IU/L, Albumin >3mg/dl.

Hepatotoxicity was considered as per American Thoracic Society guidelines - as 1) rise in serum ALT above 5 times from baseline, 2) serum ALT above 3 times with symptoms like nausea, vomiting, pain abdomen and jaundice.

In cases with hepatitis patients were admitted in our indoor department and symptomatic treatment given. ATD were stopped for 2 weeks or until SGPT and SGOT comes down to less than 2 times the upper normal limit in cases with hepatitis. Re-introduction with ATD were done with same regimen in full doses after 2 weeks.

And patients were closely observed for any further hepatitis. If symptomatic hepatitis develops or liver enzymes start raise alarmingly then patient were planned for shift the current regimen to hepato-safe regimen.

Serial increase or decrease in liver function were recorded and patients were counselled not to take any hepatotoxic drugs or alcohol during the treatment period.

Every patient's sputum samples were tested as per RNTCP guidelines.

Those who were not responding to ATD regimens were further investigated for drug resistance.If any of the patients found to be a case of DRTB (Drug Resistance Tuberculosis) then he/she was excluded from the study. Statistical analysis was done by SPSS version 20.

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Continuous variables are expressed as Mean, Median and Standard Deviation and compared over time using Wilcoxon Signed Ranks Test. Association between continuous variables are captured using Spearman's Rank Correlation Coefficient.

RESULTS

Table 1. Demographic Chart of TB Patients included in the Study

Characteristics		No(n)	Percentage (%)
Age (years)	11-20 yrs.	27	23.7
	21-30 yrs.	39	34.2
	31-40 yrs.	21	18.4
	41-50 yrs.	4	3.5
	51-60 yrs.	17	14.9
	61-70 yrs.	6	5.3
Gender	Male	59	51.8
	Female	55	48.2
Patient registered at	IPD	56	49.1
	OPD	58	50.9
Address	Rural	73	64
	Urban	41	36
Marital Status	Married	94	82.5
	Unmarried	20	17.5
Smoking status	Smoker	43	37.7
	Non-smoker	71	62.3
Alcohol Intake	Yes	42	36.8
	No	72	63.2
Sputum smear	Positive	41	36
	Negative	73	74
Diagnosis	Microbiologically	77	67.5
	Clinically	37	32.5
CBNAAT	MTB Detected	77	67.5
	MTB not Detected	37	32.4
Family/Contact H/O PTB	Present	64	56.1
	Absent	50	43.9
Chest X-Ray	Normal	57	50
	Abnormal	57	50
Case Type	Newly Diagnosed	94	82.5
	Previously Treated	20	17.5

Out of 114 treated cases 5 patients developed hepatitis and we re subjected to interruption in treatment, whereas rest of the patients continued treatment without any symptoms. Among the 5 patients 4 male and 1 female. 4 PTB and 1 EPTB. 2 patients developed hepatitis 4 weeks after treatment, 1 developed after 2 weeks, and other 2 patients developed after 4 months of treatment. 2 patients had BMI < 18.5 kg/m2 and other were >18.5 kg/m2. 3 patients were age below 40 years and 2 of the patients were above 40 years. All of them were newly diagnosed cases. Among the 5 cases 3 had SGPT and SGOT levels above 3 times but below 5 times and had symptoms like nausea vomiting and abdominal pain and jaundice. On the other hand, 2 cases had SGPT and SGOT above 5 times and they also presented with symptoms like

jaundice, nausea and vomiting. Serum hepatitis virology markers were negative for all the 5 cases and their serum urea and creatinine levels were within normal limit. Prothrombin time and INR was within normal range in all the hepatitis cases. All the case had raised serum bilirubin at the time of hepatitis and were between 3mg/dl and 5 mg/dl. ATT was on hold for an average 2 (10 to 15 days) weeks for all the patients and same regimen of ATT continued. No second episode of symptomatic hepatitis developed later, although 2 patients had SGPT and SGOT above normal range but were below 2 times of upper normal limit. No other symptoms were noted in these cases of DILI. At the end of 6th month all patients with ATT induced hepatitis had normal serum bilirubin, SGPT and SGOT level. Among the 114 patient's bilirubin levels were abnormal in 13.2% after 2nd week, 7.9% after 4th week, 6.1% after 6th week, 5.3% after 8th week, 3.5% after 3rd month, 6.1% after 4th month, 6.1% after 5th month, but all patient had normal bilirubin after 6th month. Mean, median and standard deviation in bilirubin levels during the treatment period were shown in table 2. Statistically significant changes seen compared to bilirubin level at the start of treatment and 2nd week [p-value <0.001], 4th week [p-value 0.020], 4th month [p-value 0.026] and 5th month [p-value 0.016] [Table 2].

Table 2. Statistical Significance of Changes in Bilirubin Levels

	p Value	Significance
Bilirubin (mg/dl) - 2nd Week - Bilirubin (mg/dl) - Day 0	<0.001	Significant
Bilirubin (mg/dl) - 4th Week - Bilirubin (mg/dl) - Day 0	0.020	Significant
Bilirubin (mg/dl) - 6th Week - Bilirubin (mg/dl) - Day 0	0.181	Not Significant
Bilirubin (mg/dl) - 8th Week - Bilirubin (mg/dl) - Day 0	0.426	Not Significant
Bilirubin (mg/dl) - 3rd month - Bilirubin (mg/dl) - Day 0	0.822	Not Significant
Bilirubin (mg/dl) - 4th month - Bilirubin (mg/dl) - Day 0	0.026	Significant
Bilirubin (mg/dl) - 5th month - Bilirubin (mg/dl) - Day 0	0.016	Significant
Bilirubin (mg/dl) - 6th month - Bilirubin (mg/dl) - Day 0	0.065	Not Significant
Wilcoxon Signed Ranks Test		

Table 3. Elevation of Liver Enzymes in Follow Up

Characteristic		No (n)	Percentage (%)
Serum SGPT	Elevated	95	83.3
	Not elevated	19	16.7
Serum SGOT	Elevated	81	71.1
	Not elevated	33	28.9
Serum SGPT&SGOT both	Elevated	76	66.7
	Not elevated	38	33.3
Serum SGPT&SGOT elevated	>5 times	2	1.75
	>3 times but <5 times	3	2.63
Serum SGPT&SGOT elevated > 3 times	Symptomatic	5	4.38
	Asymptomatic	0	0
SGPT Elevated in	No Follow-up	19	16.7
	1 follow-up	45	39.5
	2 follow-ups	28	24.6
	3 follow-ups	12	10.5
	4 follow-ups	8	7
	6 follow-ups	2	1.8
SGOT Elevated in	No Follow-up	33	28.9
	1 follow-up	38	33.3
	2 follow-ups	29	25.4
	3 follow-ups	10	8.8
	4 follow-ups	1	0.9
	5 follow-ups	1	0.9
	6 follow-ups	2	1.8

Table 5: Association of BMI with SGPT

		BMI Kg/M2		Total		
		<18.5	>=18.5		p Value	Significance
SGPT (IU/L) - 2nd Week	Normal	32(68.09)	31(46.27)	63(55.26)	0.021	Significant
	Abnormal	15(31.91)	36(53.73)	51(44.74)		
Total		47(100)	67(100)	114(100)		

Significant association was observed between BMI>=18.5 kg/m2 and elevation in SGPT level at 2nd week of treatment compared to BMI < 18.5kg/m2

Table 6: Association of BMI with serum Bilirubin values in 2nd week

		BMI Kg/M2		Total		
		<18.5	>=18.5		p Value	Significance
Bilirubin (mg/dl) - 2nd Week	Normal	18(40.91)	44(63.89)	62(54.38)	0.033	Significant
	Abnormal	26(59.09)	26(36.11)	52(45.62)		
Total		44(100)	70(100)	114(100)		

Statistically significant number of patients having BMI <18.5have high bilirubin levels. In contrary to that liver adaptive response is higher among the patients with BMI >=18.5 which is also statistically significant.

DISCUSSION

In the present study, transient hepatic function derangement was seen in patients initially more in the second week of treatment and the effect seems to fade of later subsequent follow up. All patients were closely monitored during treatment, counselling done to prevent use of any kind of hepatotoxic agents or alcohol. Those who developed hepatitis were also observed not report any kind of hepatic symptoms even after completion of treatment. And all patients completed their treatment successfully without further adverse reactions. So, from our study we can say that ATT can be reintroduced, even after hepatitis develop during treatment, safely after a gap and waiting for the patient to become asymptomatic with normalization of enzymes.[21,22]

In a study by Gulati et al. it was observed that most cases of hepatic enzyme elevations occur in intensive phase of ATT, in our study we have seen that most number patients have abnormal liver enzymes in second and fourth week after treatment.[23] As most anti-TB drugs are metabolized by the liver, therefore, it is the central to detoxification of INH, Rif, and PZA. So poor compliance in the initial phase of treatment is more likely.

In the study by Vijayalakshmi et al drug induced hepatitis cases were reintroduced with hepatosafe regimen of ATT to complete the treatment,[24] but in our case, we stay with the same regimen and started with the full dose in all the 5 cases of hepatitis and didn't observed any further hepatitis in all the cases. A study with full dose re-introduction of all antitu

bercular drugs also had successful completion of ATT course comparable to other safer regimen.[25] Therefore, it can be said that though drug induced hepatitis can occur with the standard four drug regimen initially but on rechallenge same event may not happen. Incidence of drug induced hepatitis was 4.38% in our study which supporting the existing literature. As per the study by Surendra K Sharma et al ATT induced hepatitis was about 5% of all anti-TB treatment for Indian population and only 2% for western populations.[7]

Asymptomatic elevation liver enzymes are noted in various studies to be around 20%.[26,27,28] But our study observes that this figure is much higher in our study population. Near about 76% patients in our study showing abnormal level of liver enzymes (Both SGPT and SGOT). Only 16.7% had no elevation in SGPT and 28.9% had no elevation in SGOT. So adaptive response to Anti-TB medications are much more common in our study population than previous study suggests.

In the study by Singla et al[29]poor nutritional status has been considered to beone of the factors contributing to a higher incidenceof drug induced hepatotoxicity induced by short-course chemotherapy for TBin the developing countries. Similarly, in our study we have found statistically significant association between low BMI and serum hyperbilirubinemia in the 2nd week of receiving ATT.

CONCLUSION

Drug induced liver function abnormality is a common occurrence during the course of anti-TB treatment. Most patients show tolerance to anti-TB drugs and get adjusted after transient rise in liver enzymes. Some patients may develop serious hepatitis and need treatment interruption, but we should always try to stay with the present regimen and see whether reintroduction leads to any further derangement or hepatitis. Asymptomatic rise may be upto 3 times from the baseline value, but that does not need any intervention unless patients develop symptoms. Serum Bilirubin values show statistically significant rise in patients with low BMI on ATT compared to those patients having higher BMI. Hence serum Bilirubin values along with Liver enzymes have to be measured in low BMI group of patients.Abdominal symptoms like pain, nausea, vomiting and jaundice should always be taken seriously and needs intervention by holding the ATT. Risk factors like, age, gender, smoking habits, alcohol intake, tuberculosis disease severity, along with BMI must be studied further to have better understanding in relation to liver function changes. Concomitant use of hepatotoxic agents in low BMI groups should be avoided as far as possible.

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