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STUDY OF LIVER FUNCTION ABNORMALITIES IN THE TUBERCULOSIS PATIENTS UNDERGOING RNTCP- DOTS IN TB CLINIC MADURAI

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ABSTRACT

Introduction: India accounts for nearly one fifth of the global burden of tuberculosis. India has more new TB cases annually than any other country in the world. The obstacles to success to include poor patient compliance, drug resistance, insufficient duration, and irregular therapy and last but not the least Drug induced Hepatotoxicity. DIH is the most unwanted side effect of ATT. Unfortunately almost all the chemotherapeutic agents used in tuberculosis cause hepatotoxicity by single or multiple mechanisms. **Aims and Objectives:** The aim of the study is to analyse the incidence of hepatotoxicity in patients taking anti-tuberculous drug therapy under the RNTCP short course schedule in Madurai district and also to analyse the various risk factors for development of hepatotoxicity. **Materials and Methodology:** A prospective study was conducted among 166 patients selected from amongst those who were registered in the Revised National Tuberculosis Control Programme (RNTCP) of Madurai medical college from June 2007 to June 2008 among which 156 were followed up for 6 months. **Results and Discussion**: Patients above 18 years with sputum positive tuberculosis and patients coming from within and nearby areas of Madurai were included in the study. Out of 156 patients who were followed up for 6 months, 88 were males and rest were females. The age group most commonly had disease was 15-39 yrs with mean age of 36.6years. Out of 156 patients who completed treatment 24 patients had increase in serum enzymes. Eight patients had symptomatic hepatitis. Patients in older age group, malnutrition and cavitary pulmonary tuberculosis disease had symptomatic hepatitis. **Conclusion**: Direct correlation existed between increasing ages, malnutrition, anaemia, advanced disease with sputum positivity and hypoproteinemia. Correction of the modifiable risk factors can lead to decrease in hepatotoxicity. Hepatotoxicity is usually self-limiting and treatment need not be discontinued permanently. Serial monitoring of liver function tests will help in early identification of drug induced hepatotoxicity and prevention of fulminant hepatic failure.

KEYWORDS: Anti tubercular treatment (ATT), drug induced hepatotoxicity (DIH), liver function tests.

INTRODUCTION

Tuberculosis is still one of the world –wide public health problem though the actual fact is that the causative organism was discovered more than centenary ago and also in spite of availability of highly effective drugs and vaccine. India accounts for nearly one fifth of the global burden of tuberculosis. India has more new TB cases every year than any other country globally. Every year approximately 18 lakh persons develop tuberculosis of which about 8 lakh are new smear positive & highly infectious cases and around 4.17 lakh patients die of tuberculosis every year.[1] The hindrances to success of treatment include poor patient compliance, drug resistance, insufficient duration, and irregular therapy and last but not the least drug induced hepatotoxicity (DIH). DIH is the most unwanted side effect of ATT. Unfortunately almost all the chemotherapeutic agents used in tuberculosis cause hepatotoxicity by single or multiple mechanisms. The absence of obvious jaundice, the degree of subclinical hepatotoxicity has to be determined by monitoring the biochemical changes in blood using the liver function tests (LFT). Reports available from various studies conducted previously to assess the hepatotoxicity of Short Course Chemotherapy (SCC) regimens from western as well as many of the Indian studies have shown a high incidence of hepatitis due to short course chemotherapeutic regimens. In view of these variable reports on incidence of drug induced hepatotoxicity during SCC, The aim of the study is to analyse the incidence of hepatotoxicity in patients taking anti-tuberculous drug therapy under the RNTCP short course schedule in Madurai district and also to analyse the impact of various risk factors for development of hepatotoxicity.

MATERIALS AND METHODS

The study was conducted on patients coming to the chest clinic in Govt. Rajaji hospital, Madurai. Approval from

ethical committee was obtained. The study was a prospective study conducted for a period of one year between June 2007-2008. Patients prescribed to receive ATT for confirmed pulmonary or extra pulmonary tuberculosis under the RNTCP schedule who were coming from in and around Madurai city, were included in our study to minimize the rate of dropouts. Patients not receiving isoniazid or rifampicin as a part of therapy, Patients with pre-existing acute or chronic liver disease, Patients with fatty liver as diagnosed by ultrasound examination of the abdomen. If the baseline transaminases more than twice the upper limit of normal, chronic alcoholics, Patients with previous history of hepatotoxicity due to ATT were excluded from the study.

All the patients had pre-treatment evaluation clinically especially for evidence of liver disease, history of alcoholism or concomitant drug therapy and systemic illness. Baseline laboratory evaluation was done for all patients which included haemoglobin levels, serum albumin, liver function tests and USG of the abdomen and HIV status. Body mass index (BMI) was calculated. Presence of fatty liver was excluded on the basis of ultrasonography. The patients were categorized into various regimens in RNTCP according to the type of disease. Every effort was taken to maintain compliance to the drug therapy. Patients were informed about the side effects of medications and were asked to report immediately if they developed any of these symptoms. Patients with minor symptoms were treated symptomatically. Those with major symptoms suggestive of hepatotoxicity were hospitalized and evaluated.

Diagnosis of Drug Induced Hepatotoxicity

Hepatotoxicity was defined as the presence of at least one of the following criteria: (1) Appearance of jaundice. (2) a rise of at least five times the upper limit of normal levels (40 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) or >250IU/L on any one occasion without symptoms or more than three times ULN with symptoms. (3) A rise in the level of serum total bilirubin > 1.5mg/dl.[2]

LFTs were repeated weekly for the first month then at the end of second month and after the completion of ATT (six months). If the patients developed evidence of hepatotoxicity, viral markers (hepatitis A, B, C) were again performed to rule out acute viral hepatitis. Data analysis was done SPSS software Version 18.Using this software, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskal Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

The study group was divided into various age groups which ranged between 15 and 78 years. A total of 166 patients were included in the study of which 156 patients were followed up till six months of treatment. Total number of dropouts from the study at the end of six months was 10 out of which seven patients dropped out at the end of two weeks and three at the end of three weeks. Most patients were from in and around Madurai city.

The mean age of the population was 36.6$\pm$13.8 years. Out of 156 patients, 88 were male (56.5%) and 68 were female (43.5%). Most of the patients were in the ages between 15 and 39 years (66%). There was a higher proportion of pulmonary tuberculosis (n=90) than the extra pulmonary form (n=66). Pleural effusion was the most common form of extra pulmonary tuberculosis seen in 31 patients (19.9%) followed by neurotuberculosis in 16 patients (10%). Coming to the category to which the patients belong 99 were registered under category I ATT (59%) followed by 52 patients in category III (32%) and 14 patients in category II (9%) as shown in table-I. Eighty six patients were sputum positive (55%) out of which 56% were males and 44% were females. The mean BMI was 20.5$\pm$3.1kg/m^2. Body mass index was <18.5kg/m^2 in 35 patients (22.4%).

Table 1: General characteristics.

	No of patients	Percentage
SEX		
MALE	88	56.50%
FEMALE	68	43.50%
TYPE		
PULMONARY TB	90	57.70%
EXTRAPULMONARY TB	66	42.30%
CATEGORY		
II	90	57.70%
II	14	9%
III	52	33.30%
SPUTUM AFB		
POSITIVE	86	55%
NEGATIVE	70	45%
BODY MASS INDEX		
< 18.5	35	22.40%
18.5-24.9	106	68%
>25	15	9.60%

Coming to other relevant biochemical investigations, the mean haemoglobin values were 10.4±1.8gms/dl. It was found that 49 patients (31.4%) had a haemoglobin level of <9.9grams/dl, signifying moderate to severe anaemia. Serum albumin levels were < 3.5 grams/dl in 37 patients (23.7%). The mean albumin values were 3.88±0.73grams/dl. Also 19 patients (12%) had systemic disease in the form of diabetes mellitus or chronic renal failure. Twenty two patients (14.1%) of patients were found to be positive when we screened for HIV.

Liver Function tests

Overall, 24 patients out of 156 had some abnormality of liver function (15.4%). The most common form of hepatotoxicity was asymptomatic rise in transaminases (n=16) followed by acute hepatitis like picture with jaundice (n=8). All 16 patients who developed increase in enzymes were asymptomatic. Eight patients developed jaundice. There was no incidence of fulminant hepatic failure or chronic hepatitis. All patients who developed liver injury were investigated for viral hepatitis and none of the patients tested positive for any of the viral markers performed namely, IgM antibody for HAV, HbSAg, and anti HCV. Most of the derangements occurred within the first two weeks of starting therapy and subsided spontaneously on stopping the drug within 4-6 weeks. The results are summarized in tables 9, 10 and 11.

Table 2: Bilirubin and Enzyme Abnormalities.

	Bilirubin		Sgot/sgpt	
	<1.5	>1.5	Normal	Abnormal
0 week	156	0	156	0
2 weeks	150	6	136	20
4 weeks	154	2	155	1
24 weeks	156	0	156	0

It was observed that the mean bilirubin levels were 1.01±0.37mg% in the second week and dropped down to 0.85±0.19mg% at the end of four weeks. Six patients had jaundice at the end of two weeks and two patients had persistent jaundice at four weeks that recovered within the next two weeks. The abnormalities in liver enzymes were analysed in relation to the time of onset of enzyme elevation. The patterns of hepatotoxicity were analysed in relation to symptoms and LFT abnormality. It was observed that asymptomatic enzyme elevation was the most common form of hepatotoxicity seen in 16 patients (66.6%) followed by clinical hepatitis with jaundice in eight patients (33.3%). There was near equal incidence of toxicity in males (n=7) and females (n=9). The initial elevation in liver function tests were seen in few patients by second and fourth weeks.

Further analysis of hepatotoxicity in relation to the various risk factor was done and the following observations were made-

Table 3: Factors Affecting Lft.

Factors	Lft abnormalities		P Value
	Present	Absent	
TB CATEGORY			
I (N=90)	13	77	0.012
II (N=14)	6	8	
III (N=52)	5	47	
AGE GROUP			
LESS THAN 30	5	47	0.0027
30-39	2	49	
40-49	8	18	
50-59	4	11	
>60	5	7	
SPUTUM AFB			
POSITIVE (N=86)	19	67	0.0187
NEGATIVE (N=70)	5	65	
HEAMOGLOBIN %			
<9.9 (N=49)	17	32	0.0001
>9.9 (N=107)	7	100	
BODY MASS INDEX			
<18.5 (N=35)	19	16	0.0001
>18.5 (N=121)	5	116	
SERUM ALBUMIN			
<3.5 (N=37)	17	20	0.0001
>3.5 (N=119)	7	112	
HIV			
POSITIVE (N=22)	11	11	0.0001
NEGATIVE (N=134)	13	121	

To start with Category of ATT, It was observed that six patients (42.9%) started on category II developed toxicity in comparison to 13 patients (14.4%) on category I and five patients (9.6%) on category III. Next we correlated with age group where it was observed that five out of 12 patients above the age of 60 years developed abnormalities of LFT (41.7%). This was statistically significant (p=0.0027), implying that the elderly patients were more susceptible to liver damage due to ATT.

Followed by this Sputum AFB was analysed and it was observed that out of 86 patients who were sputum positive, 19 developed hepatotoxicity (22.1%) in comparison with only five sputum negative patients (7.1%). Eighty percent of patients with hepatotoxicity were sputum positive, possibly indicating severe disease as a risk factor for hepatotoxicity. The value was statistically significant (p=0.0187).

Coming to blood parameters out of 49 patients who had moderate to severe anaemia, 17 developed liver function test abnormalities (34.7%). In contrast, only seven patients who had haemoglobin levels above 9.9grams% developed toxicity (6.5%). Also 70% of patients with hepatotoxicity had haemoglobin levels <9.9gm% and the value was statistically significant (p=0.0001). Moderate to severe anaemia directly correlated with hepatotoxicity. Serum albumin was also analysed which showed that 45.9% of patients with hypoalbuminemia (n=17) had toxicity. The value was statistically significant (p=0.0001) as shown in the table above. HIV status of the patients were also correlated where Out of 22 patients who tested positive for HIV, 11 (50%) developed hepatotoxicity. The value obtained was statistically significant (p=0.0001) indicating that HIV infection may be a significant risk factor for ATT induced hepatotoxicity.

Body mass Index (BMI) was analysed and it was observed that 19 out of 35 patients (54.3%) with BMI <18.5kg/m^2 had LFT abnormalities and 80% of patients with hepatotoxicity had BMI values of <18.5kg/m^2 and the value was statistically significant (p=0.0001), implying that malnutrition may be a significant risk factor for toxicity.

DISCUSSION

The wide prevalence of tuberculosis all over the world makes it a social and financial burden especially for developing countries and the use of anti-tuberculous drugs is a positive approach for this problem. However certain reservations associated with its use need to be properly evaluated especially ATT induced liver injury and the predisposing factors that add to this hepatotoxicity. Hence this study was conducted to study the incidence of ATT induced hepatotoxicity in RNTCP clinic, Madurai and to assess the role of age, sex, severity of the disease, nutritional status, hypoalbuminemia,

sputum positivity and HIV status as risk factor for ATT induced hepatotoxicity.

The reported incidence of ATT induced hepatotoxicity is different in various countries though not fully understood but could be due to the characteristics and the risk factors of the population studied, the different diagnostic criteria used to define hepatotoxicity, different geographical areas, tests carried out during follow ups and the type of monitoring.[3] It's not clear why only a few patients who receive ATT develop hepatitis is not clear and several studies searched for host factors, environmental factors or some interaction among various factors. While some papers have focused on genetic factors, such as HLA typing, Cytochrome P450 2E1 or acetylator status, others have primarily studied clinical factors.

In this study of 156 patients, all were administered DOTS therapy under RNTCP and belonged to different treatment categories. Male: female ratio was almost equal (53.5%:48.5%). Age group of the patients ranged from 15-78 years. Various studies report different incidence rates of hepatotoxicity due to anti tuberculous therapy. A higher risk of hepatotoxicity has been reported in Indian patients than in their Western counterparts.[4] the risk of hepatotoxicity based on data from four prospective Indian studies was 11.5% compared with 4.3% in Western publications.[5] similarly in our study 15.4% of the patients developed ATT induced hepatotoxicity that almost overlaps the other studies conducted worldwide. The incidence of hepatotoxicity due to combination chemotherapy ranges from 1-39%. Above incidence is similar to studies done previously by several authors like one done by Schberg et al[6] where the prevalence was 11% and Kamat et al[7] which showed a prevalence of 18%.

In a study done in Pakistan, 19.76% of the patients developed ATT induced hepatotoxicity that almost overlapped the study conducted at Japan.[8,9] A study conducted in Nepal[10] resulted in 8% and 13% in Hong Kong Chinese patients.[11] In the analysis done by Col AC Anand et al, the incidence of hepatotoxicity among patients on ATT was 10.1%,[12]

In our study we analysed the possible predisposing factors for hepatotoxicity induced ATT. A significant proportion of patients older than 60 years developed hepatotoxicity (p=0.0027). Although the number of patients above the age of 60 years receiving ATT was less (n=12), nearly half of these patients developed liver function abnormalities. Some studies have reported that the risk of ATT-induced hepatitis increases with advancing age, the highest incidence being in individuals older than 50 years as shown by Gangadharan et al.[13]

In a study done by Col AC Anand et al in 2006, no significant correlation of age with ATT-induced hepatotoxicity was found. However, once hepatotoxicity developed, fatal outcome was much more likely among the older patients (mean age 47.1 years as compared to 38.9 years in non-fatal cases).[13] Studies from Pande et al and other researchers showed that increasing age is associated with more hepatotoxicity.[14] Similarly in a study done by Khalid Mohammad et al, older age group was affected more as compared to younger one (25.8% vs. 14.4%).[8]

Although previous studies have quoted an increased risk of hepatotoxicity for females, it was found to be almost equal in this study. There was a marginal increase in sub clinical hepatitis in females in accordance with many other studies (nine in females vs. seven in males). Vulnerability of females could be due to variations in pharmacokinetics and slow acetylating enzymatic pattern, resulting in hepatotoxicity. Anand AC et al did not find any difference in the incidence of hepatotoxicity in their study[12] this has also been reported in a study done by Taneja et al.[15]

Nutritional status of our patients was very poor. BMI were below 18.5 (kg/m2) in 23% of patients and 23.4% of the patients had hypoalbuminemia. In our study there was a significant relationship of hepatotoxicity to low serum albumin and low BMI as noted in the previous studies done by Pande et al. Nearly 72% of patients with hepatotoxicity had serum albumin <3.5 grams%. Krishnasamy et al says that under nutrition contributes to drug toxicity by various mechanisms.[16] Toxicity and over dosage is much more likely to occur even with normal dosage of medicine in the presence of normal serum albumin.[17] A study from Pakistan shows significant correlation between the two variables.

The possible explanation of ATT induced hepatotoxicity in malnutrition is depletion of glutathione stores that makes one vulnerable to oxidative injuries. Low nutritional status is considered to be one of the factors contributing to relatively high incidence of ATT-related hepatitis in studies from developing countries. Drug metabolism pathways including acetylation pathway have been shown to be deranged in states of protein energy malnutrition.[18] A direct correlation was also obtained between low BMI and hepatotoxicity (p=0.0001) and this was in concordance with the previous studies. A similar significant relationship was noted between haemoglobin levels and hepatotoxicity (p=0.0001). Most of the patients with hepatotoxicity had severe anaemia.

Nineteen patients (80%) were sputum smear positive and they were severely affected indicating the extensiveness of the disease also as a risk factor as noted in previous studies done by Pande et al (p=0.001) and Devoto et al.[19] (p=0.02). Severity of the disease in sputum smear positive patients could be secondary to more tubercular bacilli in smear positive patients as compared to smear negative patients. In our study, there was direct association between sputum positivity and hepatotoxicity (p=0.0187). In the study done by Khalid Mohammad,

forty patients (59.70%) were sputum smear positive and they were severely affected indicating the extensiveness of the disease as a risk factor.

In our study, HIV infection was found to be a significant risk factor for TB DIH (p=0.0001). The patients were not on antiretroviral therapy at the start of ATT, thus ruling out antiretroviral therapy as the cause of liver function abnormalities. This was in concordance with the previous studies done by the European tuberculosis study group where it was found that patients with HIV and TB had significant risk of hepatotoxicity irrespective of whether the patient was on ART or not. None of the patients in this study who developed toxicity had viral hepatitis though there is evidence to indicate that patients with viral hepatitis B or hepatitis C had a higher risk of drug toxicity than general population.[20]

The frequency of self-limiting asymptomatic enzyme elevation raises the question of whether the drugs should be stopped; and if so, at what levels they should be stopped. Mild transient self-limiting transaminase rise occurs early during the course of therapy irrespective of the regimen used and this should not be used as a criterion for stopping therapy. Onset of hepatotoxicity occurred within one month of start of therapy in our study. Usually pyrazinamide produced a delayed onset of hepatotoxicity whereas early toxicity is produced by isoniazid and rifampicin. Parthasarathy et al concluded that acute hepatitis is nearly always associated with jaundice.[21] In our study also, patients who developed jaundice has an enzyme elevation of >200 IU/L. after withdrawing the drugs, all levels returned to normal within four weeks.

Some researchers say it may not be advisable to stop all drugs at a time but since the possibility of fulminant hepatic failure always arises, it is advisable to stop all drugs till enzyme elevation settles down to normal levels. In our study, all drugs were reintroduced according to the British Thoracic society guidelines. None of the patients developed recurrent hepatotoxicity. The onset of drug induced hepatotoxicity cannot be exactly predicted but measures to prevent it can be taken well in advance. High protein diet, abstinence from alcohol and smoking, good supportive medications like vitamin B6 and vitamin C have shown to reduce the incidence of hepatotoxicity. Well educated patients and skilled, alert, treatment supervisor can reduce the hepatotoxicity, fulminant hepatitis and its complications.

CONCLUSION

Liver function abnormalities occurred in 15% of the study group under RNTCP which is a significant number. Asymptomatic enzyme elevation is the most common abnormality in our study. Direct correlation existed between increasing ages, malnutrition, anaemia, advanced disease with sputum positivity and hypoproteinaemia. Correction of the modifiable risk factors can lead to decrease in hepatotoxicity. Hepatotoxicity is usually self-limiting and treatment need not be discontinued permanently. Serial monitoring of liver function tests will help in early identification of drug induced hepatotoxicity and prevention of fulminant hepatic failure. Further research is needed to find out the exact mechanisms of hepatotoxicity due to ATT and the possible role of hepatoprotective agents.

REFERENCES

1. Govt. of India, Annual report 2003-2004, Ministry of Health and Family Welfare, New Delhi, 2004.
2. Joint tuberculosis committee of British thoracic society. Chemotherapy and management of tuberculosis in UK: recommendations 1998. Thorax, 1998; 53: 536-548.
3. Villor AF, Sopena B, Villor JF. The influence of risk factors on the severity of antituberculosis drug induced hepatotoxicity: Int J Tuberc Lung disease, 2004; 8(12): 1499-1505.
4. Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculous therapy: clinical profile and reintroduction of therapy. J clin gastroenterol, 1996; 22: 211-214.
5. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid And Rifampin: a meta-analysis. Chest., 1991; 99: 465-471.
6. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J., 1996; 9: 2026-2030.
7. Kamat SR, Mahasthur AA, Dubey GR, Goremade. Hepatotoxicity in short course chemotherapy. Lung India, I(6): 256-258.
8. Khalid Mahmood, Akhtar Hussain, Krishan Lal Jairaman, Abu Talib, Badar-uddin Abbasi, S.Salkeen. Hepatotoxicity with Antituberculous Drugs: The risk factors. Pakistan journal of medical sciences, January – March 2007; 23: 1.
9. Ohno M, Yamaguchi I, Yamamoto I, Fukuda T, Yokota S, Maekura R, et al. Slow N-acetyltransferase 2 genotype affects the incidence of INH and RMP-induced hepatotoxicity. Intl J of Tuberc Lung Dis., 2000; 4(3): 256-61.
10. Shakya R, Rao BS, Shrestha B. Evaluation of risk factors for anti tuberculosis drug induced hepatotoxicity in Nep- alese population. Ann Pharmacother, 2004; 38(6): 1074-9.
11. Yi-Shin Huang, Herng-Der Chern, Wei Juin Su, Jaw-Ching Wu, Shinn-Liang Lai, Shi-Yi Yang et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for all antituberculosis drugs-induced hepatitis. Hepatology, 2002; 35: 883-9.
12. Col AC Anand, VSM, Lt Col AK Seth, Lt Col M Paul, Lt Col P Puri. Risk Factors of Hepatotoxicity during Anti-tuberculosis Treatment MJAFI, 2006; 62: 45-49.
13. Gangadharan PRJ. Isoniazid. rifampicin and hepatotoxicity. Am J Respir Dis., 1986; 133: 96.

14. Singh J, Arora A, Garg PK, Thakur VS, Pande JN, Tandon RK. Anti-TB treatment induced hepatotoxicity: role of predictive factors. Postgrad Med J., 1995; 71: 359-62.
15. Taneja DP, Kaur D. Study on hepatotoxicity and other side effects of antituberculosis drugs. J Indian Med Assoc., 1990; 88: 278-80.
16. Krishnaswamy K, Prasad CE, Murthy KJ. Hepatic dysfunction in undernourished patients receiving isoniazid and rifampicin. Trop Geogr Med., 1991; 43: 156-160.
17. Mehta S. Malnutrition and drugs: Clinical implications. Dev Pharmacol Ther., 1990; 15(3-4): 159-65.
18. Buchanan N, Eyberg C, David MD. Isoniazid pharmacokinetics in kwashiorkor. S Afr Med J., 1979; 56: 299-300.
19. Devoto FM, Gonzalez C, Serra HA. Risk factors for hepatotoxicity induced by antituberculous drugs. Acta physiol pharma ther Latin am, 1997; 47: 197-202.
20. Ungo JR, Jones D, Ashkin D, Hollender E, Bernstein D, Albanese A, Pitchenik A. Antituberculosis drug-induced hepatotoxicity: the role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med., 1998; 157: 1871-1876.
21. Parthasarathy R et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle, 1986; 67: 99-108.