RISK FACTORS FOR DRUG INDUCED HEPATITIS UNDER DOTS PROGRAMME IN GENERAL POPULATION

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ABSTRACT

Background: Short course chemotherapy containing rifampicin and isoniazid in combination has proved to be highly effective under DOTS regimens in the treatment of tuberculosis, but one of its adverse effects is hepatotoxicity. Little however has been published regarding drug induced hepatitis (DH) under general programme conditions. In this study, we aimed to determine the prevalence of drug induced hepatitis and the risk factors associated with the development of hepatitis over a period of 5 years.

Methodology: This was a prospective study done from 2007 to 2011 in a tertiary care hospital. A total of 116 patients were included in the study that presented with hepatitis due to short course chemotherapy and were being treated under various categories of drug regimens. Fourty cases were being followed up and other 76 were seen at the hospital for the first time after the development of hepatitis. The diagnostic criteria's for drug-induced hepatitis were made according to the ATS criteria's. Various risk factors were analyzed for the development of DH.

Results: The prevalence of DH in the present study was 3.6%. It was observed that DH patients were older and their serum albumin levels were lower. Regular alcohol intake, more extensive disease radiologically and female gender were observed to be independent risk factors for the development of DH. No other risk factors analyzed had any significant association with DH.

Conclusion: Of the various risk factors analyzed, advanced age, hypoalbuminaemia, regular alcohol intake and advanced nature of the disease were independent risk factors for the development of DH. The risk of hepatitis in the presence of one or more of these risk factors may be increased.

Key words: Chemotherapy, DOTS, Drug Induced Hepatotoxicity, Tuberculosis.

INTRODUCTION

Tuberculosis (TB) causes a great deal of ill health in the populations of most low-income countries, and due to this world adopted DOTS strategy for TB control though the national TB control programs worldwide and is making good progress. In India, DOTS strategy has been implemented since 1996 and has already reduced the number of deaths. Short course chemotherapy containing rifampicin and isoniazid in combination with ethambutol and pyraziname has proved to be highly effective in the treatment of tuberculosis[1], but one of its adverse effects is hepatotoxicity. The reported incidence of hepatotoxicity in controlled trials of antituberculosis chemotherapy which included INH, RMP and PZA ranged from 0.6 to 3%.[2-4] Little, however, has been published regarding TB drug-induced hepatitis (DH) under general programme conditions.

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However, if serious side-effects do occur and treatment with one of the three drugs must be finally terminated, the patient no longer receives the best treatment available and might be at a higher risk of treatment failure and possibility of development of drug resistance. It has been very important to draw attentions of all health workers towards side effects of anti-tuberculosis drugs since side effects can be harmful to the patients. Hepatotoxicity is one of the important side-effects of anti-TB drugs especially during the initial intensive period, and monitoring is crucial during this period, but may be costly. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug related adverse effects. In this study, we aimed to determine the prevalence of drug induced hepatitis and the risk factors associated with the development of hepatitis over a period of 5 years.

METHODOLOGY

This was a prospective study done from 2007 to 2011 in a tertiary level care KLES Dr. Prabhakar Kore Hospital and MRC at Belgaum, Karnataka, India. All the patients were being treated under various categories of DOTS regimens. The patients who were registered under Category I, II and III were included in study. Thus, a total of 3221 patients who were registered under these regimens, during the above period were included in this study. A total of 116 patients who presented with hepatitis due to the short course anti-tuberculous therapy to the department of Pulmonary Medicine were included in the analysis. Fourty cases were being followed up and the other 76 were seen at the hospital for the first time after the development of hepatitis. All these 116 cases have been analyzed in detail.

Diagnosis of Drug induced Hepatitis (DH): The diagnostic criteria for drug-induced hepatitis were as follows[5]: (1) A rise of five times the upper limit of normal levels (50 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT); (2) A rise in the level of serum total bilirubin >1.5 mg/dl; (3) Any increase in AST and/or ALT above pre-treatment levels together with anorexia, nausea, vomiting, and jaundice; (4) Absence of serologic evidence of infection with hepatitis virus A, B, C, or E. Viral hepatitis markers (HBsAg, IgM anti-HAV, IgM anti-HBc, and anti-HCV second generation antibodies) were analysed using ELISA immunoassay kits. The presence of any one of the first three criteria's along with absence of viral hepatitis was considered to be having drug-induced hepatitis (DH). Patients with associated chronic illnesses such as cirrhosis of the liver, chronic hepatitis, acute viral hepatitis, gastro-intestinal, renal or cardiac diseases were excluded.

Drug Regimens:

The drug regimens used were as follows:

Category 1($2R_3H_3E_3Z_3/4R_3H_3$): rifampicin, isoniazid, ethambutol and pyrazinamide given thrice weekly for two months followed by rifampicin plus isoniazid thrice weekly for four months.

Category 2 (2S3R3H3E3Z3/1R3H3E3Z3/5R3H3): streptomycin, rifampicin, isoniazid, ethambutol and pyrazinamide given thrice weekly for two months followed by four drugs for another 1 month of intensive phase and then rifampicin and isoniazid given thrice weekly daily for five months.

Category 3 ($2R_3H_3Z_3$/4R3H3): same as regimen 1 except for deletion of ethambutol. The regimen is given for total duration of 6 months.

Category 4: Drug resistant cases. Here the second line drugs were given according to the AFB culture and sensitivity testing. Hence the drug regimen was individualized to each patient.

Category 4 patients were neither considered for the final analysis, nor for the calculation of DH. Thus, only the first three regimens were studied for the DH.

Drug Dosages:

The drug dosages were calculated in relation to the weight of the patients as follows:

(1) Streptomycin: 0.75 gm IM (< 50 years) and 0.50 gm (> 50 years)

(2) Rifampicin: body weight < - 450 mg/day; > 50 kg - 600 mg.

(3) Isoniazid: 600 mg (10 – 15mg/kg).

(4) Ethambutol: 1200 mg (30 mg/kg).

(5) Pyrazinamide: 1500 mg (30 – 35mg/kg).

Study Design: Data on patient demographics, co-morbidity, use of concomitant medications, alcohol consumption, body weight, baseline transaminases/ bilirubin and treatment regimen were recorded for all the patients. All the baseline investigations were performed including HIV status. In addition to the patients' data and treatment data, the following information on risk factors were analysed: alcohol abuse (>40 g·day-1); i.v. drug abuse; history of hepatitis; hepatic damage at admission (liver enzymes at admission ≥2 times normal values); history of diabetes mellitus; HIV infection and concomitant therapy with other hepatotoxic drugs (Table 1). The incidence of DH was determined, and the patient and treatment characteristics of those who developed DH were compared with the rest of the cohort. The clinical course and treatment outcome of the patients with DH were also studied. All patients had baseline serum transaminase and bilirubin levels measured prior to starting treatment, and were routinely advised to report immediately should they experience symptoms of hepatitis such as nausea, vomiting or abdominal pain. Monitoring of serum transaminase/ bilirubin levels was carried out in high-risk patients (e.g., history of liver disease or alcohol abuse), or if symptoms or signs suggestive of hepatitis occurred. Chest radiography was performed in all the patients with DH to know the extent of the disease radiologically. It was our operating policy that if a patient developed hepatitis according to the above criteria, TB treatment would be temporarily stopped, even in the absence of symptoms. All drugs were stopped and liver function tests were conducted twice a week. Once liver functions were returned to normal, the drug regime was restarted with all drugs at the same time and full-doses. If hepatotoxicity recurred, the drugs were reintroduced in stages as follows: first EMB at the maximum dosage of 1500 mg and INH at 100 mg. The INH dosage was increased by 100 mg/day to the maximum dosage of 300 mg on the third day. RIF was re-introduced from the fourth day starting at 150 mg and increasing by 150mg on alternate days until the maximum dose of 600 mg was achieved. Once RIF had been re-introduced to its maximum dosages, PZA was started at 500 mg and the dosage increased by 500 mg on alternate days until the maximum dosage of 1500 mg was achieved.

The risk factors for the development of DH were analyzed in details: age, gender, past history of anti-tuberculosis treatment, extensive nature of radiological disease, co-morbid disorders and drug resistance for the development and recurrence of hepatotoxicity. The INH acetylation status was not analysed in this study as we do not have the facility for the same. Ethical clearance was taken from the institutional ethical committee.

Data Analysis: Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago). Data were analyzed by chi-square ($\chi 2$) test and logistic regression analysis. Data were expressed as "mean (standard deviation; SD)", minimum-maximum and percent (%) where appropriate. $p< 0.05$ was considered statistically significant. Continuous variables (ALT and AST) that failed in the assumption of normality and homogeneity of variance were compared across the groups using the Mann-Whitney test. Binary logistic regression was used to calculate the adjusted odds ratio for the significant risk factors of DH. Logistic regression univariate analysis was preformed to analyze the risk factors associated with DH. Furthermore, to remove the confounding variables, we did multivariate Logistic regression analysis to assess the role of independent risk factors for development of DH.

RESULTS

The risk of development of drug induced hepatitis (DH) in the present study was 3.6% (116 patients out of total cohort of 3221 patients). We have analyzed these 116 patients who developed DH in detail. The detail baseline characteristics of the patients who developed DH are shown in Table 1. The mean age was 47 ± 7.2 years. Majority of the patients were above the age of 60 years (39.6%). Males composed of 63.1% of patients. The average duration of development of DH was 20 days after starting anti-tubercular therapy and lasted for average of 14 days. Hepatotoxicity was observed to develop for once in 81.9% (n= 95) of patients while it recurred for more than once in 18.1% (n= 21) patients. Majority of the patients had pulmonary tuberculosis (54.3%), followed by pleural tuberculosis (17.3%). Most of the patients had associated co-morbid conditions, with the commonest being COPD (41.4%), followed by diabetes mellitus (21.6%). Forty nine patients (42.2%) had history of alcohol consumption, with more than half being drinking almost on daily basis.

RNTCP Category I patients contributed to 65.5% of the patients, while another 10.3% were under Category II, and rest 24.1% were under Category III regimen. It was observed that the prevalence of DH was almost the same in all the categories of the patients (Table 2).

The rise in ALT and AST was almost 5 times the upper limit of normal (ULN), while the bilirubin was raised to > 2.0 mg/dl, with some patients being raised up to 10mg/dl (Table 3). There were some cases where ALT and AST were raised to 3 times ULN along with symptoms of hepatitis, and we had to stop the therapy.

Table 1. Patient's characteristics at Baseline (N =116 who developed DH)

Age (Years)	No.	(%)
Mean (Range)		
< 20 years	12	10.3
20– 40 years	28	24.1
40 – 60 years	30	25.8
> 60 years	46	39.6
Males	65	56.1
Females	51	43.9
Site of disease		
Pulmonary TB	63	54.3
Pleural TB	20	17.2
Larynx TB	3	2.6
Lymph node TB	12	10.3
Abdominal TB	10	8.6
CNS TB	6	5.2
Bone/Joints TB	2	1.7
Comorbid conditions		
Diabetes mellitus	25	21.6
COPD	48	41.4
Cor pulmonale	10	8.6
Chronic renal failure	6	5.2
HbsAg (+ve)	2	1.7
Epilepsy	3	2.6
History of alcohol consumption	49	42.2
History of malignant disease	3	2.6
Presence of extensive disease	41	35.3
Category of patients		
Category –I	76	65.5
Category –II	12	10.3
Category –III	28	24.1
Total cases	**116**	**100**

Table2. Drug induced hepatitis (DH) among different categories

Category Regimen	Total No. of Patients	DH Patients	%	p value
Category I	2083	83	3.6	NS
Category II	336	12	3.6	NS
Category III	802	28	3.5	NS

p value is calculated by comparing category I with II and III, and category II with III.

Table 3. Pre-treatment and post-treatment liver function tests in 116 DH patients (Data presented of all 116 cases that had developed DH)

	Pretreatment (Mean ±SD)	Post-treatment [median (range)]
Ser Bilirubin, mg/dl	0.5 (0.1)	2.3 (0.7 -11.0)
AST, IU/L	50 (21)	346 (71 -1112)
ALT, IU/L	41 (27)	415 (45 -1421)
Ser Alkaline phosphatase	78 (70)	319 (219 -758)
Ser proteins, gm/dl	6.8 (1.2)	6.9 (5.4 – 9.1)
Ser albumin, gm/dl	2.0 (0.8)	2.2 (1.9 – 5.2)
Ser globulin, gm/dl	3.5 (0.6)	3.6 (1.8 – 6.6)

Risk factors for development of DH: Elderly patients (>60 years) were observed to be at higher risk of developing DH. It was observed that DH was lower among younger age group (<20 years) (10.3%), while it was observed to be present in 39.5% of patients > 60 years of age group. Hepatotoxicity was identified in 9.2% of patients with limited disease while in 35.3% of patients had radiological extensive disease. The development of hepatotoxicity was significantly more common in patients with extensive disease (p= 0.003; Table 3). Co-morbid disorder was evident in 77 cases in the present study. The development of hepatotoxicity was significantly more common in patients with associated co-morbid conditions (Table 1). Past history of anti-tuberculosis treatment was present in 10.3% (n=12) of the cases. Hepatotoxicity was identified in 19.1% of these cases. Alcohol consumption was common especially among the younger age group, and these patients developed DH in 42.2% of the cases. It was also found to be an independent risk factor for the development of DH. About 12 patients had previous history of hepatitis, this may be viral hepatitis with jaundice, and these patients were at higher risk of development of DH

following anti-TB therapy. A lower serum albumin level was also found to be associated with DH. The mean serum albumin level in patients with DH was 2.0gm/dl.

A total of 21 patients developed recurrence of DH. It was observed that the factors that contributed for the development of DH were: previous hepatitis episode, previous ant-TB treatment, age > 60 years, extensive disease on radiology, hypoalbuminaemia and alcohol consumption. Past history of anti-tuberculosis treatment was the only risk factor determined to be significantly associated with recurrence (p= 0.027).

On univariate analysis, the factors that were significantly associated with DH were prior history of hepatitis, age > 60 years, female sex, alcohol consumption, previous ant-TB therapy, hypoalbuminaemia, extensive nature of disease and diabetes mellitus (Table 4). On multivariate analysis, the significant risk factors that were associated with DH were female sex, prior history of hepatitis, alcohol consumption, hypoalbuminaemia, age > 60 years and extensive nature of disease radiologically (Table 5).

Table 4. Univariate analysis of Risk factors for DH (N =116)

	OR	95% CI	p value
History of hepatitis	2.5	1.4 – 3.6	(0.001)
Age > 60 years	2.0	3 – 4.3	(0.005)
Female sex	2.1	0.7 – 4.3	(0.002)
HIV infection	1.9	0.5–7.2	(0.45)
Alcohol abuse	0.9	0.6–3.7	(0.05)
Hepatic disease at admission	1.12	0.4–2.8	(0.70)
Concomitant hepatotoxic drugs	1.22	0.7 – 3.1	(0.15)
Hypoalbuminemia	2.1	1.4 -3.7	(0.005)
Previous anti-TB therapy	2.4	1.1 – 3.6	(0.01)
Extensive disease	2.7	2.3 -4.7	(0.003)
Diabetes mellitus	1.8	0.8 – 2.5	(0.05)
COPD	2.3	1.1 – 3.3	(0.89)

Table 5. Multivariate analysis of Risk factors for DH (N =116)

		OR	95% CI	Likeli-hood p value
Independent Variables associated with DH				
Age > 60 years	3.1	1.6 – 7.6	7.5	0.002
Female gender	1.6	1.0 – 2.5	3.5	0.03
Alcohol abuse	2.2	1.9 – 5.3	4.6	0.005
Hypoalbuminemia	3.2	1.4 -5.4	6.6	0.002
Extensive disease	2.3	2.1 – 4.9	4.3	0.002
History of hepatitis	1.5	1.6 - 4.3	4.2	0.01
Dependent Variables associated with DH				
Abnormal baseline transaminases/ bilirubin	1.2	0.2 – 1.5	1.4	0.27
Previous anti-TB therapy	1.3	0.3 – 2.1	0.3	0.56
Diabetes mellitus	1.1	0.6 – 2.3	0.4	0.35

Management of Hepatotoxicity: Anti-tuberculosis treatment was continued at full dosage after the normalization of liver enzyme levels in 82.7% (n= 96) of patients with hepatotoxicity. In recurrent hepatotoxicity a step-by-step anti-tuberculosis treatment was re-started and patients could tolerate all the drugs successfully. Thus, it was possible to administer the treatment regimen to all the patients without modification of WHO treatment guidelines.

DISCUSSION

The presence of drug induced hepatotoxicity (DH) in the present study was observed to be 3.6%. the prevalence of DH was observed to be same among all the three different categories. The drug resistant cases that were on category IV were not included in the study, and hence they were not analyzed for DH. The frequency of DH, which is the most important side effects of tuberculosis treatment, varies in different countries varies ranging from 1% to 10%. Depending on factors such as race, socio-economical condition and geographical location, the frequency was determined to be highest in developing countries (8% - 10%) while lower in

Western countries being < 1% in US, 4% in UK, and 3.3% in Barcelona[6]. Meaningful comparison of the incidences of reported hepatotoxicity across different treatment centres is often not possible, as hepatitis has not been consistently defined in the literature. Definitions have ranged from asymptomatic elevation of transaminases of 2 X ULN, to symptomatic, jaundiced individuals with AST >150 U/L[7]. The relatively higher incidence of hepatotoxicity in the developing countries has been attributed to various factors such as older age, higher alcohol intake, malnutrition, intestinal parasitism, past history of jaundice, chronic liver disease, indiscriminate use of drugs, and viral hepatitis[8]. There is no consensus as to which one of these factors, whether alone or in combination, is involved in the development of drug-induced hepatitis and whether anyone could be used as markers to identify patients at higher risk.

The various reported risk factors for hepatotoxicity include older age, child age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B and C infections, extensive disease, hypoalbuminaemia and acetylator status. In all disease groups, close follow-up is required during treatment with periodical clinical controls and laboratory tests.[9] In one meta-analysis, the presence of rifampicin in a multidrug treatment regimen was reported to increase the incidence of significant hepatotoxicity among adults from 1.6% to 2.55%.[10] The pyrazinamide has also been demonstrated to contribute to increased incidence or severity of hepatotoxicity.[11]

Increasing age group was observed to be a significant risk factor for development of DH. Various other studies also have found similar prevalence. Babalik et al[12] has observed that age > 40 years were at higher risk for the development of DH, while another study form India has also observed higher prevalence of DH in > 60 years of age group. The higher incidence of hepatotoxicity in older age may be secondary to increased prevalence of co-morbid conditions as well as use of related additional drugs in this age group. Female gender has been also found to have higher prevalence of DH. Other studies have also reported a female preponderance amongst those developing hepatitis although the exact reason is not known.[14]

On multivariate analysis, other risk factors that were independently associated with significant DH in the present study were alcohol abuse, extensive nature of pulmonary tuberculosis disease, and hypoalbuminaemia. Malnourished children also have been observed to have threefold increased incidence of DH in one study[15], while in another study[4] it was found that patients with pretreatment hypoalbuminaemia had a twofold higher risk of developing DH. Other measures of malnutrition, such as BMI and triceps skin fold thickness, were not predictors of DH. It appears that under-nutrition as identified by hypoalbuminaemia may in itself be a risk factor for drug-induced liver injury. The possibility that hypoalbuminaemia was caused partly by the development of hepatitis itself cannot be ruled out. It was also observed that high alcohol intake and advanced tuberculosis were associated with DH.[5,16,17] Moderately/far advanced pulmonary TB was an independent predictor of DH in many studies.[5,13] High alcohol intake was recorded in 20% of the cases, indicating that consumers of high alcohol are more prone to develop hepatotoxicity. The disease extent was also a significant risk factor for the development of hepatitis. In patients with advanced disease, multiple factors may a role in developing DH. This includes underlying nutritional status, hypoalbuminaemia, alcohol abuse and long standing nature of disease which will lead to undernourishment of an individual.

The addition of pyrazinamide to the regimen increases the risk of DH.[18] But such incidence was not observed in the present study. Another factor that may be responsible for DH is the acetylation status of the patients. But the reported data show no consensus, both fast and slow acetylators have been reported to be more prone to developing hepatotoxicity on short course chemotherapy[19]. Pande et al[13] observed that DH to be more frequent among slow acetylators as compared to the control group. We could not assess the acetylation status of an individual and but one should keep acetylation factor in mind. Certain immunogenetic risk factors have also been studied for DH and it was observed that absence of HLADQA1*0102 , and presence of HLA-DQB1*0201 were independent risk factors for DH.[5]

All patients who developed viral hepatitis during anti-tuberculosis treatment were excluded in this study,

although the possibility that a few of them had viral hepatitis that was not detected by the serological tests used cannot be excluded. Serological markers were evaluated only for hepatitis A, B, and C virus. Kumar et al[20] observed that the reported high incidence of drug-induced hepatitis in developing countries was, to a significant extent, attributable to these viral infections.

According to recommendations, if the diagnosis is drug-induced hepatitis, the anti-tuberculosis drugs should be stopped and the drugs must be withheld until the normalization of the liver function tests[21]. ATS recommends initiation of the new treatment regime following hepatotoxicity provided that ALT levels are below the two fold of upper normal limits. In this study, treatment was re-initiated only after normalization of liver enzymes. There are different opinions about initiation of treatment after normalized liver functions tests. ATS recommends initiation of the therapy with rifampicin monotherapy or combined E + R treatment with addition of H to the treatment regime after 3-7 days if no elevation is evident in ALT levels and addition of Z after 3-7 days with control of ALT levels. WHO recommended re-introduction of all the drugs at once when drug-induced hepatitis was resolved with discontinuation of the latest drug added in case of symptom recurrence or abnormality in liver function tests.[21] In the present study, we started the full drug dosages after the normalization of the enzyme values in all the cases and 21 (18.1%) of 116 cases had recurrent hepatotoxicity. Another study[12] had observed the prevalence of 21.7% risk of DH during reintroduction of the drugs. In recurrent hepatotoxicity, a step-by-step treatment approach was re-started in re-initiation of the drugs. The risk factor associated with recurrent hepatotoxicity was past ant-TB history. Tahaoglu et al[22] compared the efficacy of two different re-treatment protocols including reintroduction of full-dose regime with pyrazinamide and gradual reintroduction of a regimen without pyrazinamide in recurrent hepatotoxicity tuberculosis patients. They reported higher recurrence rate of hepatotoxicity in the retreatment of tuberculosis with a full-dose regimen including pyrazinamide.

Management of active tuberculosis includes the initiation and completion of the anti-TB therapy, and also interferences of side effects related to anti-TB drugs. The study showed that drug induced is a frequent side effect of anti-TB therapy under DOTS therapy. DH could considerably impact the anti-TB treatment, potentially leading to unsuccessful treatment outcomes and the prolongation of intensive treatment phase. Early diagnosis and identification of the risk factors for DH is important to prevent hepatitis induced mortality. Therefore, more research and efforts are warranted in order to enhance the diagnosis and the prevention of DH.

REFERENCES

1. Parthasarthy R, Raghupati SG, Janardhanam B, Ramachandran P, Santha T, 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.
2. Singapore Tuberculosis Service/British Medical Research Council. Assessment of a daily combined preparation of isoniazid, rifampicin, and pyrazinamide in a controlled trial of three 6 month regimens for smear-positive pulmonary tuberculosis. Am Rev Respir Dis 1991;143:707–12.
3. Myesr JP. New recommendations for the treatment of tuberculosis. Curr Opin Infect Dis 2005;18:133-40.
4. Singapore Tuberculosis Service/British Medical Research Council. Clinical trial of six month and four month regimens of chemotherapy in the treatment of pulmonary tuberculosis: the results up to 30 months. Tubercle 1981;62:95–102.
5. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med 2002;166:916–19.
6. Tost JR, Vidal R. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis 2005;9:534-40.
7. Thompson N P, Caplin M E, Hamilton MI, Gillepsie SH, Clarke SW, Burrough AK, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. Eur Respir J 1995:1384–88.
8. Gangadharan PRJ. Isoniazid, rifampicin and hepatotoxicity. Am Rev Respir Dis 1986;133:963-5.
9. Saukkonen JL, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis

therapy. Am J Respir Crit Care Med 2006;174:935-52.

10. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest 1991;99:465-71.
11. Chang KC, Leung CC, Yew WW, Lau TY, Tam CM. Tuberculosis and chest service, centre for health hepatotoxicity of pyrazinamide cohort and case-control analyses. Am J Respir Crit Care Med 2008;177:1391-6.
12. Babalik A, Arda H, Bakirci N, Agca S, Oruc K, Kiziltas S et al. Management of and risk factors related to hepatotoxicity during tuberculosis treatment. Tuberk Toraks 2012;60:136-44.
13. Pande JN, Singh SPN, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax 1996;51:132-36.
14. Gronhagen RC, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid-rifampicin treatment of tuberculosis. Am Rev Respir Dis 1978;118:461-66.
15. Mehta S. Malnutrition and drugs: clinical implications. Dev Pharmacol Ther 1990;15:159–65.
16. Gronhagen RC, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid rifampicin treatment of tuberculosis. Am Rev Respir Dis 1978;118:161–66.
17. Riaska N. Hepatitis cases in isoniazid treated groups and in a control group. Bull Int Union Tuberc 1976;51:203–06.
18. Teleman MD, Chee CBE, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002;6:699–705.
19. Gurumurthy P, Krisnamurthy MS, Nazareth O, Parthasarthy R, Raghupati SP, Somasundaran PR, et al. Lack of relationship between hepatic toxicity and acetylator. phenotypes in 3000 south Indian patients during treatment with isoniazid for tuberculosis. Am Rev Respir Dis 1984;129:58-61.
20. Kumar A, Misra PK, Mehrotra R, Govil YC, Rana GS. Hepatotoxicity of rifampicin and isoniazid: is it all drug induced hepatitis? Am Rev Respir Dis 1991;143:1350-52.
21. WHO/HTM/TB/2009.420: Treatment of Tuberculosis: Guidelines for National Programmes. Fourth edition, 2009.
22. TahaoGlu K, Ata CG, Sevim T. The management of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2001;5:65-69.