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Management of and risk factors related to hepatotoxicity during tuberculosis treatment

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ÖZET

Tüberküloz tedavisinde hepatotoksisite risk faktörleri ve yönetimi

Giriş: *Hepatotoksisite, tüberküloz tedavisi sırasında gelişen ve tedaviye uyumu, tedavi sonuçlarını etkileyen en sık yan etkilerden biridir. Bu çalışma, tüberküloz tedavisi sırasında gelişen hepatotoksisite risk faktörlerini ve yönetimini değerlendirmek amacıyla planlanmıştır.*

Hastalar ve Metod: *Bu çalışma, Süreyyapaşa Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesinde, Ocak 2004-Aralık 2007 tarihleri arasında yatarak tedavi gören hastalarda planlanmıştır. Dünya Sağlık Örgütüne göre antitüberküloz tedavisi alan tüberküloz hastalarında hepatotoksisite prevalansı ve risk faktörleri değerlendirildi. Hepatotoksisite, eşlik eden semptomlarla birlikte herhangi bir karaciğer fonksiyon testinde yükselme olarak tanımlandı. Yaş, cinsiyet, önceki tüberküloz tedavi öyküsü, radyolojik olarak yaygın tutulum, eşlik eden hastalıklar ve ilaç direnci hepatotoksisite gelişimi ve tekrarlayan hepatotoksisite gelişiminde risk faktörleri olarak değerlendirildi.*

Bulgular: *Toplam olgu 1443 (yaş ortalaması: 38.37 ± 16.74; %64'ü erkek) hastadan, 106'sında tedavi başlanmasından ortalama 20 gün sonra hepatotoksisite başladı ve ortalama 14 gün sürdü. Hastaların %78.3 (n= 83)'ünde bir kez hepatotoksisite gelişirken, birden fazla hepatotoksisite hastaların %21 (n= 23)'inde gelişti. Hepatotoksisite gelişenlerin %76.4 (n= 81)'ünde tam doz tüm antitüberküloz ilaçlar karaciğer enzimleri normale döndükten sonra devam edildi. Tekrarlayan hepatotoksisitede, basamaklı antitüberküloz tedavisine sorumlu ilacı çıkararak, devam tedavisi tekrardan başlandı. Hepatotoksisite gelişen hastaların %79.2'sinde Dünya Sağlık Örgütü tedavi rejimine modifiye edilmeden, tedavi verildi. Pirazinamidten 15 olguda, rifampisinden sadece bir olguda vazgeçildi. İzoniazid, etambutol ve streptomisin üçlü rejimi altı olguda verildi. Kinolon sadece bir olguda eklendi. Eşlik eden hastalığın varlığı, hepatotoksisite gelişiminde risk faktörü olarak değerlendirildi. OR= 3.093 (%95 GA 1.95-4.89; p= 0.000), önceki antitüberküloz tedavisi tekrarlayan hepatotoksisite için risk faktörü olarak değerlendirildi (p= 0.027). Mortalite saptanmadı.*

Sonuç: *Bizim bulgularımız göstermiştir ki, çoğu tüberküloz hastasında, hepatotoksisite, ikinci sıra ilaç eklemesine gerek duyulmadan başarılı biçimde yönetilebilir.*

Anahtar Kelimeler: *Hepatotoksisite, tüberküloz tedavisi, yönetim, risk faktörleri.*

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SUMMARY

Management of and risk factors related to hepatotoxicity during tuberculosis treatment

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Introduction: *Hepatotoxicity is one of the most frequent adverse events occurring during tuberculosis treatment that may negatively affect treatment compliance, clinical outcome. This study was designed to evaluate management, risk factors related to hepatotoxicity during tuberculosis treatment.*

Patients and Methods: *Hospitalized patients for tuberculosis treatment at Sureyyapasa Chest Diseases, and Chest Surgery Training and Research Hospital were included, between January 2004 and December 2007. Prevalence of hepatotoxicity, risk factors were evaluated among tuberculosis patients under anti-tuberculosis treatment according to World Health Organization (WHO) guideline. Hepatotoxicity was defined any elevated liver function tests with accompanying symptoms. Age, gender, past history of anti-tuberculosis treatment, extensity of radiological findings, co-morbid disorders and drug resistance were the risk factors evaluated in terms of development and recurrence of hepatotoxicity.*

Results: *Of 1443 patients (38.37 ± 16.74 years; 64.5% were males), 106 (7.3%) was identified to develop hepatotoxicity on an average of 20 days after beginning treatment and lasting an average of 14 days. Hepatotoxicity for once in 78.3% (n= 83) of patients and more than once in 21.7% (n= 23) patients. All anti-tuberculosis drugs was continued at full dosage after the normalization of liver enzyme in 76.4% (n= 81). In recurrence a step-by-step treatment was re-started by exclusion of responsible drug/s. Treatment was administered without modification of WHO regimes in 79.2%. Pyrazinamide was omitted in 15 cases while rifampicin only in one patient. Triple drug regimen with isoniazid, ethambutol and streptomycin was used in six cases. Quinolon was added to treatment only in one patient. Presence of a co-morbidity was determined to be significant predictor of hepatotoxicity development OR= 3.093 (CI= 1.95-4.89; p= 0.000) past history of anti-tuberculosis treatment was significantly associated with recurrence (p= 0.027). There was no hepatotoxicity dependent mortality.*

Conclusion: *Hepatotoxicity can be successfully management of hepatotoxicity without second line tuberculosis drugs in ongoing treatment regime.*

Key Words: *Hepatotoxicity, tuberculosis treatment, management, risk factors.*

INTRODUCTION

Nearly one-third of the global population, i.e. two billion people, has been considered to be infected with *Mycobacterium tuberculosis* and at risk of developing the disease. More than eight million people were reported to develop active tuberculosis every year and about two million to die (1).

The first-line drugs considered to be the most effective and well-tolerated treatment options available for the treatment of tuberculosis and include isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. These drugs have been associated with fewer adverse reactions or side effects besides being least expensive. As a result, the use of other drugs is not justified without first using these five first-line drugs (2).

Distinguishing drug-induced liver injury (DILI) accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant hepatic failure (3). DILI has replaced viral hepatitis as the most apparent cause of acute liver failure (4). Overall, the risk of tuberculosis DILI reported in diverse studies ranges from 5 to as high as 33% (5).

Adverse effects during tuberculosis treatment may negatively affect treatment compliance and outcome with hepatotoxicity being one of the most frequent side effects encountered during tuberculosis treatment.

It seems difficult to reach definitive conclusions regarding risks of individual regimens based on the use of multiple drug regimens in vastly different study populations with varying definitions of hepatotoxicity and different monitoring and reporting practices in the management of hepatotoxicity. The present study was de-

signed to evaluate management of and risk factors related to hepatotoxicity during tuberculosis treatment in a 3-year cohort.

PATIENTS and METHODS

Study Population

A total of 1443 tuberculosis patients [mean (SD) age: 38.37 ± 16.74 years; 64.5% were males] hospitalized for tuberculosis treatment at Ministry of Health Sureyyapasa Chest Diseases and Chest Surgery Training and Research Hospital were included in this study conducted between January 2004 and December 2007. The prevalence of hepatotoxicity and related risk factors were evaluated retrospectively among tuberculosis patients under anti-tuberculosis treatment according to World Health Organization (WHO) guideline.

Data Collection

The data on patient demographics, index cases, comorbidities and prescribed treatments were obtained from medical records. Chest radiography findings were evaluated to determine the extent of the disease. Extensive disease was defined as total bilateral infiltrations ≥ 75% or total cavity diameter ≥ 15 cm. Hemogram, urine analysis, and electrocardiography were performed and hepatitis and human immunodeficiency virus (HIV) markers were evaluated. Control visits were performed twice a week in case of detection of abnormal liver enzymes and abnormal bilirubin level.

Evaluation of Tuberculosis

Tuberculosis was defined bacteriologically or histopathologically. Bacteriological testing was based on three sputum samples per patient or, if the patient could not produce sputum, a gastric aspiration sample. The sputum and gastric aspiration samples were evaluated for AFB by EZN and Löwenstein-Jensen medium was used to culture *M. tuberculosis*. Patients who had extrapulmonary tuberculosis were evaluated bacteriologically or histopathologically.

Categorization and Corresponding Treatment Regimens in Tuberculosis Patients

Categorization and corresponding treatment of tuberculosis patients was performed according the WHO guideline (6). Category I tuberculosis patients was defined to be new smear-positive patients, new smear-negative pulmonary tuberculosis with extensive parenchymal involvement and severe forms of EPTB. Category II tuberculosis patients was defined to be previously treated sputum smear-positive PTB patients and patients with relapse and treatment failure. Category III tuberculosis patients was defined to be new smear-negative PTB (other than in Category I) and less severe forms of EPTB. Category IV patients was defined to be chronic and MDR-TB cases (still sputum-positive after supervised re-treatment).

Category I treatment regime composed of two phases including initial phase of 2-month [isoniasid (H), rifampicine (R), pyrazinamide (Z), ethambutol (E)] with direct observation followed by the continuation phase of 4 month HR with self-administration. Category II treatment regime composed of two phases including initial phase of 2-month [HRZES (streptomycine) + 1 month HRZE] under direct observation followed by continuation phase of 5-month HRE with self-administration. Category IV treatment regime was defined as standardized treatment regime with second-line drugs (7).

In case of a failure in category I treatment, category II treatment was strated while in case of a failure in category II treatment, the selected treatment regimen was category IV treatment.

Bacteriological evaluation was repeated in every patient on a monthly basis and category I, category II and category IV patients were hospitalized until they had sputum conversion.

Evaluation and Management of Hepatotoxicity

Hepatotoxicity was defined (1) as a rise of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) to three times of the normal upper limit (2) a rise in the level of serum total bilirubin > 1.5 mg/dL; (3) any increase in AST and/or ALT compared to pre-treatment levels accompanied with anorexia, nausea, vomiting, and jaundice; (4) absence of serologic evidence of infection with hepatitis virus.

Episodes of hepatitis were considered drug induced if transaminases were normal before therapy, increased during therapy, and returned to normal after discontinuation of the responsible drug.

In cases of hepatotoxicity, 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 150 mg 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.

Evaluation of Risk Factors Related to Hepatotoxicity

Age, gender, past history of anti-tuberculosis treatment, extensity of radiological findings, co-morbid disorders and drug resistance were the risk factors evaluated in terms of associations to the development and recurrence of hepatotoxicity.

Statistical Analysis

Statistical analysis was made using computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). Data were analyzed by chi-square (χ^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.

RESULTS

Mean (SD) age was determined to be 38.37 ± 16.74 years. Males composed 64.5% of the overall population. Of 1443 patients, 106 (7.3%) was identified to develop hepatotoxicity (6.9% of males and 8.2% of females) occurring on an average of 20 days after hospitalization and lasting an average of 14 days (Table 1). Hepatotoxicity was determined to develop for once in 78.3% (n= 83) of patients while recorded for more than once in 21.7% (n= 23) patients.

Risk Factors Related to Development of Hepatotoxicity in the Overall Population (n= 1443)

Patients ≤ 40 years of age composed 58.8% of the overall population with development of hepatotoxicity in 6.1% while patients > 40 years of age composed 41.2% of the overall population with development of hepatotoxicity in 9.1%. The development of hepatotoxicity

Table 1. The impact of demographic features and risk factors of patients on development of hepatotoxicity (n= 1443).

	Development of hepatotoxicity			
	Absent (n= 1337)	Present (n= 106)	Total	p value
Gender				
Male	867 (93.1)	64 (6.9)	931 (64.5)	0.399
Female	470 (91.8)	42 (8.2)	512 (35.5)	
Age groups				
< 40 years	796 (93.6)	52 (6.1)	848 (58.8)	**0.04**
≥ 40 years	541 (90.9)	54 (9.1)	595 (41.2)	
Radiological findings				
Limited	954 (91.8)	85 (8.2)	1039 (86.5)	**0.053**
Extensive	141 (87.0)	21 (13.0)	162 (13.5)	
Co-morbid disorder				
Absent	1107 (94.6)	63 (6.4)	1170 (81)	**0.000**
Present	230 (84.2)	43 (15.8)	273 (19)	
Past history of tuberculosis treatment				
Absent	1076 (93.1)	80 (6.9)	1156 (80.1)	0.208
Present	261 (90.6)	26 (9.1)	287 (19.9)	
Smoking history				
≤ 20 years	1009 (92.8)	78 (7.2)	1087 (75)	0.840
≥ 21 years	327 (92.4)	27 (7.6)	354 (25)	
Drug resistance				
Absent	1108 (92.6)	89 (7.4)	1197 (82.9)	0.577
Present	213 (93.8)	14 (61.7)	227 (15.7)	
Missing	-	-	19	

Data are shown as n (%).

was significantly more common in older patients (p= 0.04; Table 1).

Radiological evaluation of the extent of the disease revealed limited radiological lesions in 1039 (86.5%) of 1201 cases evaluated while extensive disease in 162 (13.5%) cases. Hepatotoxicity was identified in 8.2% of patients with limited disease while in 13.0% of patients with extensive disease based on radiological evaluation. The development of hepatotoxicity was significantly more common in patients with extensive disease (p= 0.05; Table 1).

Co-morbid disorder was evident in 19.0% (n= 273) of the overall population while no-co-morbid disorder was identified in 81.0% (n= 1170). Hepatotoxicity was identified in 15.8% of patients with co-morbid disorder while in 6.4% of patients lacking co-morbidity. The development of hepatotoxicity was significantly more common in patients with co-morbidity (p= 0.000; Table 1).

Past history of anti-tuberculosis treatment was present in 19.9% (n= 287) of the overall population while absent in 80.1% (n= 1156). Hepatotoxicity was identified in 9.1% of patients with past history of treatment while in 6.9% of patients lacking treatment history (Table 1).

Data on drug resistance was evident in 98.7% (n= 1424) of the overall population, with resistance to all anti-tuberculosis drugs in 15.7% (n= 227) and no resistance in 82.9% (n= 1197). Hepatotoxicity was identified in 61.7% of patients with drug resistance while in 7.4% of patients without drug resistance (Table 1).

Being > 40 years old (p= 0.04), presence of extensive radiological lesions (p= 0.05) and co-morbidity (p= 000) were the risk factors determined to be significantly associated with hepatotoxicity development. Presence of a co-morbidity was determined to be significant predictor of hepatoxicity development OR= 3.093 (CI= 1.95-4.89; p= 0.000).

Risk Factors Related to Recurrence in Patients Who Developed Hepatotoxicity (n= 106)

Of 106 patients developing hepatotoxicity, 23 (21.7%; 20.3% of males and 23.8% of females) developed recurrence.

Patients ≤ 40 years of age composed 49.1% (n= 52) of the population having hepatotoxicity with development of recurrence in 6.1%, while patients > 40 years of age composed 50.9% (n= 54) of the population having hepatotoxicity with development of recurrence in 24.1% (Table 2).

Radiological evaluation revealed limited disease in 79.2% (n= 84) of the population having hepatotoxicity with development of recurrence in 16.7%, while patients with extensive disease composed 20.8% (n= 22) of the population having hepatotoxicity with development of recurrence in 40.9% (Table 2).

Co-morbid disorder was present in 40.6% (n= 43) of the population having hepatotoxicity with development of recurrence in 23.3%, while absent in 59.4% (n= 63) of the population of the population having hepatotoxicity with development of recurrence in 19.0% (Table 2).

Past history of anti-tuberculosis treatment was present in 24.5% (n= 26) of the population having hepatotoxicity with development of recurrence in 38.5%, while absent in 75.5% (n= 80) of the population having hepatotoxicity with development of recurrence in 16.2%. The development of recurrence was significantly more common in patients with past history of anti-tuberculosis treatment (p= 0.027; Table 2).

Data on drug resistance was evident in 97.2% (n= 103) of the population having hepatotoxicity, with resistance to all anti-tuberculosis drugs in 13.2% (n= 14) and no resistance in 84.0% (n= 89). Recurrence was identified in 42.9% of patients with drug resistance while in 18.0% of patients without drug resistance (Table 2).

Past history of anti-tuberculosis treatment was the only risk factor determined to be significiantly associated with recurrence (p= 0.027; Table 2).

Co-Morbidities in Patients with Respect to Hepatotoxicity with or without Recurrence

Co-morbidity was identified in 43 of 106 cases with hepatotoxicity including diabetes mellitus (23.3%), hepatitis (11.6%), cancer (7%) and other disorders 58.1(%) such as coronary artery disease, hypertension and CCD (Table 3).

Co-morbidity was identified in 10 of 23 cases with recurrence including diabetes mellitus (20%), and other disorders (80%) such as coronary artery disease, hypertension and CCD (Table 3).

Management of Hepatotoxicity

Anti-tuberculosis treatment was continued at full dosage after the normalization of liver enzyme levels in 76.4% (n= 81) of patients with hepatotoxicity. In recurrent hepatotoxicity a step-by-step anti-tuberculosis treatment was re-started by exclusion of responsible drug/s from the treatment regime. In 79.2% (n= 84) of patients with hepatotoxicity, treatment was administered without modification of WHO treatment regimes. Pyrazinamide was omitted in 15 cases while rifampicin in one case. Triple drug regimen with

Table 2. The impact of demographic features and risk factors on recurrence of hepatotoxicity in patients with hepatotoxicity (n= 106).

	Recurrence of hepatotoxicity			
	No (n= 83)	Yes (n= 23)	Total	p value
Gender				
Male	51 (79.7)	13 (20.3)	64 (60.4)	0.810
Female	32 (76.2)	10 (23.8)	42 (39.6)	
Age groups				
≤ 40 years	42 (80.8)	10 (19.2)	52 (49.1)	0.640
> 40 years	41 (75.9)	13 (24.1)	54 (50.9)	
Radiological findings				
Limited	70 (83.3)	14 (16.7)	84 (79.2)	0.171
Extensive	13 (59.1)	9 (40.9)	22 (20.8)	
Co-morbid disorder				
Absent	51 (81)	12 (19)	63 (59.4)	0.812
Present	33 (76.7)	10 (23.3)	43 (40.6)	
Past history of tuberculosis treatment				
Absent	67 (83.8)	13 (16.2)	80 (75.5)	**0.027**
Present	16 (61.5)	10 (38.5)	26 (24.5)	
Drug resistance				
Absent	73 (82)	16 (18)	89 (84)	0.759
Present	8 (57.1)	6 (42.9)	14 (13.2)	
Missing	-	-	3 (2.8)	

Data are shown as n (%).

Table 3. Co-morbid disorders and categorization of patients with hepatotoxicity with or without recurrence.

		Hepatotoxicity	
	Total cohort (n= 1443) n (%)	Overall (n= 106) n (%)	Recurrent (n= 23) n (%)
Comorbidity			
Diabetes mellitus	110 (3.9)	10 (23.3)	2 (20)
Hepatitis	23 (8)	5 (11.6)	0
Cirrhosis	3 (1.1)	0	0
Cancer	28 (9.8)	3 (7)	0
Other	123 (48.9)	25 (58.1)	8 (80)
Total	287	43	10
Categorization			
Category I	839 (58.1)	63 (59.4)	11 (47.3)
Category II	266 (18.4)	23 (21.7)	10 (43.5)
Category III	317 (22)	17 (18)	2 (8.7)
Category IV	21 (1.5)	3 (2.8)	0 (0)

isoniazid, ethambutol and streptomycin was used in six cases. Quinolon was added to treatment only in one patient.

DISCUSSION

The frequency of hepatotoxicity, one of 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 India (8-10%) while lower in Western countries being < 1% in US, 4% in UK, and 3.3% in Barcelona (8). Hepatotoxicity incidence in our country was reported to range from 0.8 to 18.0% (9).

Reported risk factors for hepatotoxicity include older age, child age, female sex, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B carriage, 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 (2,5). In a 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 was also demonstrated to contribute to increased incidence or severity of hepatotoxicity (11).

In line with several studies suggesting increasing age as a risk factor for tuberculosis DILI, development of hepatotoxicity was more common in patients > 40 years old compared with younger patients in our study population (12,13). However, logistic regression analysis revealed presence of co-morbidity as the only risk factor significantly associated with the development of hepatotoxicity (OR= 3.093; 95% CI= 1.95-4.89). Nevertheless, higher incidence of hepatotoxicity in older age may be secondary to increased prevalence of comorbid disorders as well as use of related additional drugs in this age group.

Albeit not significant in our study, women were reported consistently to have risk of hepatotoxicity higher than men (12,14,15).

Extensive tuberculosis disease itself may be a risk factor for tuberculosis DILI, although confounding factors are impossible to exclude (12,16). In our study, hepatotoxicity was markedly higher in patients with extensive disease rather than limited disease (13% vs. 8.2%) while not identified to be a significant determinant in the logistic regression analysis.

There are different recommendations and clinical approaches concerning follow up of patients, timing of the anti-tuberculosis treatment withdrawal and treatment regimen after hepatotoxicity development.

It has been recommended that patients must be evaluated for hepatotoxicity via medical history, physical examination, laboratory analysis, and also should be acknowledged about hepatotoxicity, hepatitis symptoms including loss of appetite nausea/vomiting and abdominal pain and precautions for use of alcohol and hepatotoxic drugs (1,5,17). Routine follow up during treatment has been recommended only in patients with initially abnormal liver function tests and risk factors (5,17). Accordingly, follow up of patients based on clinical signs was considered to be sufficient by WHO and routine laboratory follow up was not recommended unless past history of liver disease, regular alcohol consumption or advanced was evident (1). In our study, laboratory controls were performed twice a week only in patients with initially high levels of liver enzymes while patients with normal laboratory findings lacking clinical complaints were not routinely followed in terms of laboratory tests.

While known to be hepatotoxic drugs, there is no consensus on indications for treatment withdrawal for H, R and Z. ATS recommended that if AST levels are more than five times the upper limit of normal (even if without symptoms) or more than three times the normal in the presence of symptoms, hepatotoxic drugs should be stopped immediately (5). According to BTS, if the liver enzymes were 5 fold of normal levels, all drugs should be discontinued (17). In our clinical practice, hepatotoxicity was considered in case of a rise of three times the upper limit of nomal levels of serum AST and /or ALT; a rise in the level of serum total bilirubin > 1.5 mg/dL or any increase in AST and/or ALT above pretreatment levels together with anorexia, nausea, vomiting and jaundice. Since which drug causes hepatotoxicity is unknown and alteration in treatment regime is quite likely due to drug resistance, treatment withdrawal included all of ongoing tuberculosis drugs in case of development of hepatotoxicity in our patients.

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 (1,17). ATS recommends initiation of the new treatment regime following hepatotoxicity provided that ALT levels are below the two fold of upper normal limits. In our study population, 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. Development of a symptom or elevation in ALT is considered to be indication for the withdrawal of the latest added to the treatment regime. 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 (1).

In our clinical practice, we started the full drug dosages after the normalization of the enzyme values in 81 (76.4%) cases and 23 (21.7%) of 106 cases had recurrent hepatotoxicity. All patients with hepatotoxicity were monitored for the development of recurrence. In recurrent hepatotoxicity a step-by-step treatment approach was re-started by exclusion of responsible drug/s from the treatment regime. Tahaoglu et al. 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 on hepatotoxicity recurrence in tuberculosis patients. They reported higher recurrence rate of hepatotoxicity in the retreatment of tuberculosis with a full-dose regimen including pyrazinamide (18).

Likewise, if patients with prolonged and severe hepatotoxicity tolerated R and H, prolongation of treatment course to 9 months was reported to be a safer strategy than addition of Z to treatment regime in ATS guideline. In WHO guideline, 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol has been suggested if rifampicin is implicated. If isoniazid cannot be used, 6-9 months of rifampicin, pyrazinamide and ethambutol has been indicated to be considered while if pyrazinamide is discontinued before the completion of the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months. In our study, pyrazinamide was omitted in a total of 15 cases while rifampicin only in one case. Isoniazid, ethambutol and streptomycine triple drugs regimen was prescribed in six cases and quinolon was added to treatment regime only in one patient.

Hepatotoxicity has been recognized to occur in about 2% of patients treated with ethionomide or prothionamide and in 0.3% of patients treated with para-aminosalicylic acid. Cycloserine does not appear to be associated with hepatotoxicity, but stated to be used with caution in patients at risk for alcohol withdrawal seizures (5). In our study population, 3 (14.3%) of 21 cases who were treated with second line-drugs standarted MDR treatment had hepatotoxicity. We omitted protionamid from the treatment.

Our finding of past history of tuberculosis treatment to be a significant risk factor for the hepatotoxicity recurrence may indicate the necessity of step by step treatment strategy in the management of hepatotoxicity in previously treated patients with exclusion of the drug responsible for the development of hepatotoxicity from the treatment regime.

It seems difficult to reach definitive conclusions regarding risks of individual regimens based on the use of multiple drug regimens in vastly different study populations with varying definitions of hepatotoxicity and different monitoring and reporting practices in the management of hepatotoxicity.

In our study, patients with hepatotoxicity development were successfully treated without alteration in the standard treatment regime with low rate of recurrence in case of re-introduction of all drugs at once. Our findings seem to indicate the need for closer follow up of patients with co-morbid disorders, past history of tuberculosis treatment and extensive disease in terms of hepatotoxicity development. Based on our clinical practice, adequate management of drug related hepatotoxicity developed during tuberculosis treatment seems quite possible without exclusion of first-line drugs, especially of H and R and with a minor role of the second-line drugs.

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CONFLICT of INTEREST

None declared.

REFERENCES

1. *WHO/HTM/TB/2009.420: Treatment of Tuberculosis: Guidelines for National Programmes. Fourth edition.*
2. *Jose A, Caminero Luna A. Tuberculosis Guide for Specialist Physicians, International Union Against Tuberculosis and Lung Disease 68 boulevard Saint Michel, 75006 Paris - France 2003: 158.*
3. *Larrey D. Epidemiology and individual susceptibility to adverse drug reactions affecting the liver. Semin Liver Dis 2002; 22: 145-55.*

4. *Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, et al; U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137: 947-54.*
5. *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.*
6. *Treatment of Tuberculosis: Guidelines for National Programmes. 3rd ed. World Health Organization-Geneva 2003.*
7. *Guidelines for the programmatic management of drug -resistant tuberculosis.WHO/HTM/TB/2006.361.*
8. *Tost JR, Vidal R. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis 2005; 9: 534-40.*
9. *Kiter G, Coskunol I. Hepatotoxicity during the anti-tuberculosis treatment: a retrospective survey of 5-year-period. Tuberk Toraks 2000; 48: 20-5.*
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. *Døssing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. Tuber Lung Dis 1996; 77: 335-40.*
13. *Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, Chang FY, Lee SD. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology 2002; 35: 883-9.*
14. *Shakya R, Rao BS, Shrestha B. Incidence of hepatotoxicity due to antitubercular medicines and assessment of risk factors. Ann Pharmacother 2004; 38: 1074-9.*
15. *Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002; 6: 699-705.*
16. *Hwang SJ, Wu JC, Lee CN, Yen FS, Lu CL, Lin TP, et al. A prospective clinical study of isoniazid-rifampicin-pyrazinamide-induced liver injury in an area endemic for hepatitis B. J Gastroenterol Hepatol 1997; 12: 87-91.*
17. *Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax 1998; 53: 536-48.*
18. *TahaoGlu K, Ata CG, Sevim T. The management of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2001; 5: 65-9.*