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Side effects due to primary antituberculosis drugs during the initial phase of therapy in 1149 hospitalized patients for tuberculosis ☆

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Summary
Objective: Side effects of the most commonly used primary antituberculosis (anti-TB) drugs may be mild as well as fatal. The aim of this study was to evaluate the side effects of and the risk factors for developing side effects against anti-TB drugs.
Patients and methods: Records of 1149 patients with established tuberculosis who initially received anti-TB therapy were evaluated retrospectively. The major side effects, which resulted in a definitive termination from 1 or more drugs related to anti-TB therapy, and the risk factors associated with these side effects, were analyzed.
Results: Ninety-five patients (8.3%), constituting 104 cases in total, experienced side effects. Although the frequency of drug reactions were increased from 0.6% at ages <20 to 5.2% at ages 20–40, no gender or age differences were observed between patients who did and did not have side effects. While asymptomatic liver function disturbance was established in 56 of the patients (4.9%) with initiation of anti-TB therapy, the rate of hepatotoxicity was found to be 2.4% in this present study. No age or gender differences were observed among those who had hepatotoxicity and who had not. The major side effects were ototoxicity (1.7%), hepatotoxicity (0.8%), neuropsychiatric manifestations (0.7%), and hyperuricemia (0.6%).
Conclusions: It must be remembered that severe side effects associated with anti-TB drugs were encountered with different frequencies especially among patients

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hospitalized for pulmonary tuberculosis, and these patients should be followed up by closer monitoring for side effects related to anti-TB drugs.

Introduction

Incidence of active pulmonary tuberculosis is estimated to as high as 8 million new cases per year worldwide as well as approximately 2 million deaths per year. More than one-third of the world's population is infected with *Mycobacterium tuberculosis*. In addition, developed countries are experiencing a resurgence of tuberculosis, whereas tuberculosis has been a major challenge for health care providers in developing countries for a long time. There are several chemotherapeutic agents that exist to treat *mycobacterial* infections. However, the necessity of utilization of multidrug regimens has been associated with increased incidence of side effects. These side effects may be mild as well as fatal. A severe side effect against 1 of the primary antituberculosis (anti-TB) drugs, which leads to the discontinuation of that drug, has several complications including an increased morbidity and mortality. At the same time, use of alternative agents may result in greater problems of toxicity and compliance. As a result, the risk of treatment failure and relapses are higher.[1–4] Therefore monitoring is crucial, but 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 current incidence of side effects and the risk factors related to anti-TB drugs for side effects, with a large number of hospital-admitted tuberculosis patients over a time period of 15 years.

Material and methods

Records of patients with active tuberculosis who were admitted to the Respiratory Ward of a University Clinic between 1984 and 2001 were analyzed retrospectively.

Demographical features, radiological extension of the disease, treatment modalities, history of diabetes mellitus (DM), hepatitis, chronic renal failure and history of alcohol consumption, in addition to states of pregnancy or postpartum were recorded.

The diagnosis was made either histologically or microbiologically, or improvements in the clinical status of the patients after completing a full course of multidrug treatment for tuberculosis as evaluated by their physician were also noted.

Radiological extension was defined as described elsewhere: The disease was considered extensive if cavities totaled $\geqslant$15 cm in diameter and/or moderately dense infiltrates involved $\geqslant$75% of lung fields on chest X-ray.[5]

Treatment was planned as recommended by our national tuberculosis program; total treatment period was 9 months. Patients first received primary anti-TB drugs including a combination of 3 or 4 drugs [Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA), Ethambutol (EMB), or Streptomycin (SM)] during an initial phase of 2 months, followed by a continuation phase of 7 months consisting of INH and RIF. Treatment was given daily, and at least the initial phase administered during hospitalization. Drug dosages are presented in Table 1.

The side effects were recorded in the files of the patients. Basal levels of transaminases and bilirubin and a complete blood count were ordered for all tuberculosis patients prior to the onset of the anti-TB chemotherapy in our hospital. Regular laboratory monitoring including serum transaminases and bilirubin levels was performed in hospitalized patients. As part of our clinical practice, serum transaminases and bilirubin levels were measured twice a week in the first 2 weeks, weekly in the following 2 weeks and 2 times during the second month of initial therapy unless no findings or symptoms of hepatitis were observed in the hospital. All side effects were observed during the hospital-stay of the patients including the first 6–8 weeks of the anti-TB chemotherapy. A major side effect was defined as any adverse reaction that led to the discontinuation of 1 or more drugs included in the standard therapy.

An elevation in liver function tests, which do not require drug cessation, is defined as ''functional liver disturbance''. While receiving anti-TB treatment, an increase in AST and/or ALT of more than 3 times the upper normal limit in the presence of symptoms such as anorexia, nausea, vomiting or abdominal pain, or in transaminases of more than 5 times the upper normal limit without symptoms, and/or in total bilirubin to $>$2 mg/dl was accepted as ''hepatotoxicity''.[1] Definitive termination of 1 of

Table 1 Characteristics of patients treated for active tuberculosis between years 1984 and 2001.

Age (years)	*n* (%)	
Mean (range)	36.1(13–92)	
<20	84 (7.3)	
20–40	686 (59.7)	
40–60	270 (23.5)	
>60	109 (9.5)	
Sex		
Male	876 (76.2)	
Female	273 (23.8)	
Method of detection		
Microbiological or histological	1092 (95)	
Clinical diagnosis	57 (5)	
Site of disease		
Pulmonary TB (11 miliary)	1080 (93.9)	
Pleural TB	52 (4.5)	
Larynx TB	9 (0.8)	
Lymph node TB	8 (0.7)	
Drugs		
Isoniazid	5 mg/kg per day	(max 300 mg/day)
Rifampicin	10 mg/kg per day	(max 600 mg/day, weight < 50 kg; not exceed 450 mg per day)
Pyrazinamide	25 mg/kg per day	(max; 2 g/day)
Ethambutol	15 mg/kg per day	(max; 1500 mg/day)
Streptomycin	15 mg/kg per day	(max: 1 g/day, ⩾60 year max; 750 mg/day)
Comorbid conditions		
Diabetes mellitus	82 (7.1)	
COPD	23 (2)	
Cor pulmonale	8 (0.7)	
Chronic renal failure	8 (0.7)	
HBsAg (+)	4 (0.3)	
Epilepsy	5 (0.4)	
History of alcohol consumption	3 (0.3)	
Presence of malignant tumor	13 (1.1)	
Presence of extensive disease	552 (48)	

3 standard drugs related to therapy was considered as "severe hepatotoxicity". Risk factors for hepatotoxicity such as gender, age, hepatitis, alcohol consumption, and presence of additional disease were also analyzed.

While receiving anti-TB treatment, an increase in uric acid levels of more than 8 mg/dl was accepted as "hyperuricemia" that is a well-known side effect of PZA.[6] Patients with hyperuricemia and/or arthralgia related to therapy were analyzed for renal disease, concomitant use of loop-inhibiting diuretics. Persistent hyperuricemia despite adequate hydration, appropriate diet, and use of nonsteroidal anti-inflammatory agents, and/or arthralgia leading to being handicapped were accepted as valid causes for quitting administration of the drug.[1]

The number of patients with "ototoxicity" including auditory (e.g., tinnitus and high-frequency hearing loss) and vestibular (e.g., vertigo, ataxia, and loss of balance) damages related to SM was recorded.[1] Patients' files were searched for the day of ototoxicity and modification related to this side effect. The relationship between the development of ototoxicity and risk factors such as age, concomitant diseases or use of drugs such as loop-inhibiting diuretics were also searched.

INH-related neuropsychiatric manifestations including psychosis, obsessive–compulsive neurosis, dysphoria, memory loss, and inability to concentrate were recorded.[1] The risk factors for psychiatric changes such as diabetes, old age, alcohol consumption, hepatic or renal insufficiency were also analyzed in these patients.

Cutaneous reactions such as pruritus with or without rash and transient morbilliform rash were recorded during the therapy.[1]

All other types of side effects such as flu-like syndrome and retrobulbar neuritis causing loss of visual activity and red–green color discrimination related to EMB had been recorded by physicians.

Statistics

All statistical analyses were performed using the SPSS 11.0 statistical program (SPSS Inc., Chicago, IL, USA). Values are expressed as medians with 95% CI unless otherwise indicated. A *P*-value of less than 0.05 was considered significant. χ^2 and Fisher's exact test were utilized in the analysis of data.

Results

Among the 1149 patients that were evaluated, 876 (76.2%) were male. Characteristics of patients treated for active tuberculosis are shown in Table 1. All patients included in this study were Caucasian. Patients with 20–40 years of age accounted for 59.7% of the total. We ensured that the doses recommended by World Health Organization (WHO) for anti-TB drugs were used in all patients.

Eleven patients died during treatment. However, none of the deaths were attributed to side effects of anti-TB drugs. They were ascribed to respiratory failure and cor pulmonale (4 patients), metastatic lung cancer (3 patients), coronary artery disease (2 patients), massive hemoptysis (1 patient) and acute renal insufficiency (1 patient).

Ninety-five patients (8.3%) had side effects, 9 of which experienced a second adverse reaction. All side effects observed during anti-TB treatment are shown in Table 2. Although the frequency of drug reactions were increased from 0.6% at ages <20 to 5.2% at ages 20–40, no gender or age differences were observed among those who did and did not have side effects ($P = 0.450$ and 0.425, respectively) (Fig. 1).

Table 2 Any side effect occurred during anti-TB treatment.

Side effect	*n* patients (%)
Total patients	95 (8.3)
Total events	104 (9.0)
Hepatotoxicity	
Functional liver disturbance	56 (4.9)
Hepatotoxicity	28 (2.4)
Severe hepatotoxicity	9 (0.8)
Hyperuricemia ($\pm$arthralgia)	31 (2.6)
Ototoxicity	19 (1.7)
Psychiatric changes	8 (0.7)
Cutaneous reactions	7 (0.6)
Flu-like syndrome	3 (0.3)
Gluteal abscess	2 (0.2)
Fever	2 (0.2)
Peripheral neuropathy	1 (0.1)
Changes in visual acuity	1 (0.1)
Hemolytic reaction	1 (0.1)
Change in glucose tolerance	1 (0.1)
Severe side effects	51 (4.4)

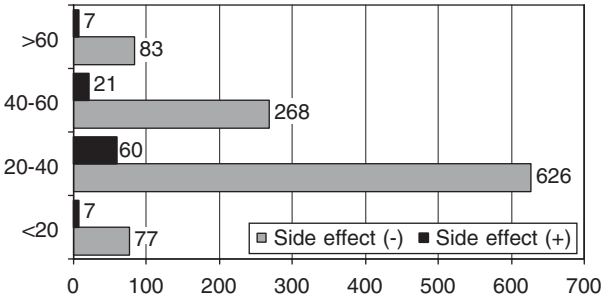

Figure 1 The distribution of the patient's number with side effects positive according to age groups.

Hepatotoxicity

It is well known that INH, RIF, and PZA are the most common potential drugs that cause hepatic injury. In our study, among 84 patients who had increased in liver function tests only 28 eventually experienced hepatotoxicity urging the cessation of the treatment. Severe hepatotoxicity leading to final termination of at least 1 of the 3 standard drugs was observed in 9 patients (0.8%).

Hepatotoxicity occurred in 28 patients (2.4%) during anti-TB treatment, representing 2.5% of all female patients, and 2.3% of all male patients. Of these, all had normal pretreatment liver transaminase levels. Although there was no statistically significant difference in gender in those patients who developed hepatotoxicity compared with who those who did not (OR 1.071; 95%CI, 0.450–2.548; $P = 0.876$), it was shown that male gender implied 1.07-fold more risks for developing hepatotoxicity.

The mean age was 36.8 ± 17.2 years (16–80 years, 95% CI 30.1–43.4 years) in patients with hepatotoxicity. No age difference was observed among those who had hepatotoxicity and who had not (OR 1.003; 95%CI, 0.978–1.028; $P = 0.814$). None had a history of alcohol use and none were pregnant or postpartum. Radiological extension did not show any impacts of hepatotoxicity (OR 0.807; 95% CI 0.378–1.721; $P = 0.579$). The odds ratio was 0.476

for the presence of DM (95% CI 0.064–3.544; $P = 0.468$). Only 1 patient with HBsAg positivity had hepatotoxicity.

Median days for evolving hepatotoxicity were 15 ± 7.1 days (95% CI 13.3–18.8 days). Liver function tests returned normal in all patients when medications were discontinued. After laboratory findings had returned to normal levels, the same drug regimens with the same doses were restarted in 18 patients, while challenge dosages of the original anti-TB drugs were added into the treatment regimen gradually, in the order: INH, RIF and PZA in 10 patients with daily monitoring of the patient's clinical condition and liver function. Median interval between detection of hepatotoxicity and restart to the therapy was 14.5 ± 7.7 days (7–38 days, 95% CI 11.5–17.4 days). However, 11 patients had a second hepatotoxicity with retreatment, but the treatment regimens of only 9 patients had to be modified according to relapsed hepatotoxicity.

Severe hepatotoxicity was noted in 5 patients (27.8%), who were re-administered anti-TB treatment with the same drug regimen and same doses after hepatotoxicity. In patient group with anti-TB drugs added into the treatment gradually, severe hepatotoxicity was observed in 4 patients (40%). Although rate of occurrence of severe hepatotoxicity in the re-treatment of tuberculosis was in higher in the gradual reintroduction group (OR 1.73, 95% CI; 0.339–8.867), there was no distinction between different re-treatment protocols and the risk of developing severe hepatotoxicity ($P = 0.677$).

Severe hepatotoxicity was observed in 9 patients. The most common drug, which had to be terminated due to hepatotoxicity, was PZA. PZA was ceased in 7 patients, whereas RIF was stopped in only 2 patients. Severe hepatotoxicity was more frequent among younger patients ($P = 0.038$). While we determined that all patients with severe hepatotoxicity were in the 20–40 years age group, severe hepatotoxicity was not observed among patients <20 years. Although there was no statistically significant difference between severe hepatotoxicity and gender (OR 2.5; 95% CI 0.312–20.1; $P = 0.695$), we determined that male gender was associated with increased risk of severe hepatotoxicity.

Ototoxicity

Ototoxicity, the most important adverse reaction caused by SM, was the main severe side effect observed in this present study. While ototoxicity was observed in 19 patients (%1.7) (mean age: 27.1 ± 6.9 years; male/female: 15/4), the real incidence of ototoxicity was 3.2% in the patients group who received SM (19/578). Ototoxicity appeared on 25 ± 8.1 day of treatment (14–46 days, 95% CI 22.7–30.4 days). Tinnitus (in 9 patients), dizziness/vertigo (in 5 patients), loss of balance (in 3 patients) and hearing disturbance (in 2 patients) were recorded in the ototoxicity group. All patients with ototoxicity had received an anti-TB treatment including SM. In all patients, SM was discontinued immediately after ototoxicity had been discovered. Besides, none of these patients had a history of renal insufficiency.

Ototoxicity was noted to be more common among patients aged between 20 and 39 years. There was no significant distinction between ototoxicity and gender (OR 1.172; 95% CI 0.386–3.560; $P = 0.780$).

Hyperuricemia

It is well known that anti-TB therapy with PZA may affect the uric acid levels and lead to polyarthralgia. In our study, uric acid levels higher than 8 mg/dl were observed in 31 patients (2.7%). During anti-TB treatment, termination of PZA due to hyperuricemia had become necessary in 7 patients (0.6%). Arthralgia not responding to non-steroidal anti-inflammatory drugs (NSAID) was accompanied with hyperuricemia in 4 of the cases (0.3%). Median days for developing hyperuricemia were 17.6 days (5–30 days, 95% CI 15.7–19.6 days).

There were no significant differences in age ($P = 0.233$) or gender (OR 0.765; 95% CI 0.311–1.884; $P = 0.672$) in those patients who developed hyperuricemia compared with those who did not. None of these patients had history of diuretic usage.

Psychiatric changes

We observed neuropsychiatric manifestations such as psychosis ($n = 3$), anxiety damage ($n = 2$), crying attack ($n = 1$), behavioral change ($n = 1$), and suicidal tendency ($n = 1$) related to INH in 8 patients (mean age: 35.8 ± 13.3 years; male/female: 7/1). These side effects occurred on the 35.8 ± 13.3 days of the anti-TB treatment (17–60 days, 95% CI 24.7–44.0 days). No gender (OR 0.456; 95% CI 0.056–3.726; $P = 0.688$) or age ($P = 0.841$) differences were observed among patients who had and had not neuropsychiatric problems related to INH. None of these patients had any previous history of seizures. In addition, no risk factors could be identified for the termination of drug therapy due to psychiatric changes such as

diabetes, alcohol consumption, hepatic or renal insufficiency.

Severe side effects

Fifty-one patients (4.4%) had severe side effects, and 6 patients experienced a second major adverse reaction, constituting a total of 57 (4.9%) events, leading to final termination of 1 of the standard drugs.

The major severe side effects were ototoxicity (1.7%), hepatotoxicity (0.8%), neuropsychiatric manifestations (0.7%), and hyperuricemia (0.6%). The frequency of severe side effects was highest for SM (1.9%), followed by PZA (1.5%) and INH (0.8%) (Table 3). The median period of time between the onset of therapy and detection of severe side effect was 25.3 ± 11.2 days (7–55 days, 95% CI, 22.1–28.5 days).

Although all severe side effects were more frequent among male patients, no statistically significant differences were seen between male and female patients for severe adverse effects (OR 1.47; 95% CI, 0.710–3.075; $P = 0.399$). Patients in the severe side effects group were significantly younger than those in the non-severe side effects group. There was a statistically significant distinction in age of those patients who had severe adverse effect compared with those who had not ($P = 0.035$).

Other side effects

While cutaneous lesions were observed in 7 patients (0.6%) during the anti-TB treatment, a definitive termination of any 1 of the drugs due to cutaneous reactions was determined in 4 patients (0.3%). The drug most responsible for developing a cutaneous reaction and severe cutaneous side effects was SM. Other drugs were RIF and PZA.

Flu-like syndrome was observed in 3 cases, in 2 of which RIF therapy was discontinued. The interval between the onset of treatment and flu-like syndrome was 11.6 days (7–21 days). Two patients had drug fever and the final cessation of PZA was necessary in 1 of them. There were 2 patients who developed gluteal abscess due to SM. EMB was terminated due to changes in visual activity in 1 patient. INH was discontinued due to peripheral neuropathy in 1 patient, RIF was discontinued in 2 distinct patients because of the occurrence of hemolytic reaction and changes in glucose tolerance.

Discussion

The results of this study indicate that intolerance of anti-TB standard therapy due to the side effects of anti-TB drugs is still a serious problem in the hospital-treated patients with tuberculosis. In our study, we found that the current incidence of side effects was 8.3%, in a total of 104 events. Although the major severe side effects were ototoxicity, hepatotoxicity, neuropsychiatric manifestations, and hyperuricemia, the incidence of severe side effects was not as high as in the other studies (range 5.1–23%)[4,7,8]: total complication rate due to anti-TB drugs were 57 events, with low life-threatening complications.

Table 3 Number of severe side effects due to INH, RIF, PZA, SM, EMB (57 events in 51 patients).

Side effects	INH* *n* (%)	RIF* *n* (%)	PZA* *n* (%)	SM* *n* (%)	EMB* *n* (%)	Total *n* (%)
Hepatotoxicity	—	2 (0.2)	7 (0.6)	—	—	9 (0.8)
Ototoxicity	—	—	—	19 (1.7)	—	19 (1.7)
Psychiatric changes	8 (0.7)	—	—	—	—	8 (0.7)
Hyperuricemia	—	—	7 (0.6)	—	—	7 (0.6)
Cutaneous reactions	—	1 (0.1)	1 (0.1)	2 (0.2)	—	4 (0.3)
Fever	—	—	2 (0.2)	—	—	2 (0.2)
Flu-like syndrome	—	3 (0.26)	—	—	—	3 (0.26)
Peripheral neuropathy	1 (0.1)	—	—	—	—	1 (0.1)
Gluteal abscess	—	—	—	1 (0.1)	—	1 (0.1)
Hemolytic reaction	—	1 (0.1)	—	—	—	1 (0.1)
Change in glucose tolerance	—	1 (0.1)	—	—	—	1 (0.1)
Changes in visual acuity	—	—	—	—	1 (0.1)	1 (0.1)
Total event	9 (0.8)	8 (0.7)	17 (1.5)	22 (1.9)	1 (0.1)	57

Values are present as event of side effect number.
*INH: Isoniazid, RIF: Rifampin, PZA: Pyrazinamide, SM: Streptomycin, EMB: Ethambutol.

The incidence rate of side effects other than hepatotoxicity was especially low and in accordance with published rates. However, hyperuricemia was found to be the most frequent side effect caused by anti-TB drugs in the present study. Although we observed elevated uric acid levels in 2.7% of our patients, this rate was 40–47% in previously published 2 series.[9,10] In another study, while hyperuricemia was detected in 44 of 51 patients who were initiated PZA for tuberculosis; non-gouty arthralgia was observed in only 9 patients.[6] Also, it was accepted that the importance of arthralgia or drug-induced hyperuricemia in the initial intensive phase of treatment was controversial[1,3]; PZA was discontinued due to persistent arthralgia with hyperuricemia in 7 (0.6%) patients in our study. Incidence of arthralgia that resulted in the discontinuation of PZA similar to that reported in other series (0.2%, 2%).[3,7]

Ototoxicity that manifested itself either as auditory or vestibular damage was found to be the most frequent severe side effect (1.7%) in the present study. All patients with ototoxicity used SM for at least 14 days and gender was not found to be associated with ototoxicity as in the study of De Jager and Van Altena,[11] which investigated the ototoxic and nephrotoxic effects of long-term use of aminoglycosides for anti-TB therapy. None of the patients had used loop-inhibiting diuretics associated with an increased ototoxicity risk,[1] and SM was discontinued immediately after the development of ototoxicity.

While asymptomatic liver function disturbance was established in 56 patients (4.9%) on anti-TB therapy, rate of hepatotoxicity was 2.4%. It is important to note that an asymptomatic increase in serum liver function tests occurs in nearly 20% of the patients on anti-TB therapy and in the absence of symptoms, treatment should not be altered.[9] However, it must also be remembered that hepatotoxicity is an important side effect related to anti-TB drugs. Hepatotoxicity causes significant morbidity and mortality, and modification of the drug regimen may be required.[12] For this reason, identification of patients associated with increased risk for hepatotoxicity is necessary. It was determined that the incidence of hepatotoxicity varied between 4.3% and 19% in published studies from various countries.[3,4,8,12–17] Despite the efforts spent for defining the exact risk of developing hepatotoxicity during anti-TB therapy, factors predicting the development of hepatotoxicity are still controversial. Besides, it is difficult to assess the real incidence of hepatotoxicity in selected patient groups from the published data, because different definitions are used for hepatotoxicity. Reported risk factors for hepatotoxicity include old age, female sex, history of hepatitis, high alcohol intake, concomitant intake of other hepatotoxic drugs, poor nutritional status, advanced disease, pre-existing liver disease, and acetylator status in literature.[3,18–20]

In contrast to multiple published studies,[3,7,8,12,16,19,20] there was no increased risk of hepatotoxicity among elderly patients in this present study. On the other hand, there are some similar studies in the literature, which have shown that there is no relationship between the risk of hepatotoxicity and age.[13,15,21–23] We thought that it could be associated with the average age, and low number of patients $\geqslant$60 years compared to the other study. Besides, the relationship between the risk of developing hepatotoxicity and age in the present study was similar to that reported in a series with a total 786 of patients.[13,15,21,22]

In our study, although there was no equal distribution of gender, we found that the risk of hepatotoxicity was slightly higher in male patients, but this was not significant. However, there were some studies reporting a higher risk of hepatotoxicity in female patients,[3,4,7,8,15,16,21,22,24,25] and also, some other studies that show no differences between the,two genders for the risk of developing hepatotoxicity.[12,19,21,23,26] two Similarly, radiological extension and history of alcohol consumption could not be suggested as risk factors for hepatotoxicity in our study. These results may have been limited by the small number of patients with hepatitis B carriers and alcohol consumption.

When anti-TB therapy was discontinued, liver function tests returned to normal in all of the 28 patients with hepatotoxicity. Anti-TB medications were reintroduced one by one in gradually increasing doses to 10 patients, and the same doses were administered to the remaining 18 patients whenever liver functions returned to normal level. Eleven patients developed recurrent hepatotoxicity that required the cessation of 1 or more anti-TB drugs due to severe hepatotoxicity in 9 of them. Although Tahaoglu et al.[5] showed that re-treatment with a full-dose anti-TB regimen caused more hepatotoxicity in their study, we did not have a significant variation between the development risk of severe and/or recurrent hepatotoxicity and 2 distinct retreatment protocols as in the study of Sharma et al.[12] The incidence of severe hepatotoxicity related to the anti-TB drugs was 0.8% and PZA most the frequently terminated drug for hepatotoxicity in our study. Our results are in agreement with those of 4 series[3,4,7,8] and PZA was the most frequent causative agent for hepatotoxicity in these studies too.

In our study, the ratio of severe hepatotoxicity was quite different from most previously published studies (range 2.7–11%).[3,7] There are some reasons related to this rate; *firstly*, we thought that the low number of patients with risk factors for hepatotoxicity such as alcohol intake, i.v. drug abuse, or concomitant use of other hepatotoxicity drugs, and comorbid conditions like pre-existing liver diseases and human immunodeficiency virus (HIV) infection, could be effective in the low rate of severe hepatotoxicity. *Secondly*, the patient groups did not include young children who may imply totally different risk factors. Interestingly, severe hepatotoxicity was more frequent in younger patients and male gender was also associated with increased risk for severe hepatotoxicity in our study. A similar occurrence rate of severe hepatotoxicity in male patients was found as in the study of Ohkawa et al.[22]

The rate of neuropsychiatric events related to INH was 0.7% in our study. While Schaberg et al.[3] found the rate of neuropsychiatric problems as 1.5% in their study, it was higher (30–37%) in different series that included specific risk groups such as patients with chronic renal failure, multi drug resistance TB.[27,28] No high cutaneous adverse reaction rates with anti-TB drugs were identified, as reported in 3 other series (respectively; 6%, 6%, 30.4%, 4.8%).[3,7,23,29] In our study, visual toxicity due to EMB occurred in only 1 patient (0.1%) as reported in the study of Yee et al. (0.2%).[7]

There are some parts that may be improved in our retrospective study. The results obtained in this study are clearly not representative of all tuberculosis patients, for instance, the outcomes of outpatients are not included and the side effects related to anti-TB drugs include only those that evolved in the initial phase of anti-TB therapy, not inclusive of the entire treatment duration. Another limitation is that there were few patients with extra-pulmonary disease in this study, thus limiting interferences to this group of patients who might tolerate therapy differently. Finally, there is the issue of deficient patient records. Despite all, the results of our hospital are valuable in order to manage the treatment of patients with pulmonary tuberculosis.

Management of active tuberculosis includes the initiation and the completion of anti-TB therapy, and also the interference of side effects related to anti-TB drugs. In conclusion, it must be kept in mind that severe side effects with anti-TB drugs are common especially among patients hospitalized for pulmonary tuberculosis and they should be followed up by closer monitoring for the side effects related to anti-TB drugs.

References

1. Centers for Disease Control and Prevention. American Thoracic Society, CDC, and Infectious Diseases Society of America. Treatment of tuberculosis. *Morbidity Mortality Weekly Rep (MMWR)* 2003;**52**(RR-11):1–77.
2. Myers JP. New recommendations for the treatment of tuberculosis. *Curr Opin Infect Dis* 2005;**18**:133–40.
3. 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**: 2026–30.
4. Dossing M, Wilcke JT, Askgaard DS, Nybo B. Liver injury during antituberculosis treatment: an 11-year study. *Tuberc Lung Dis* 1996;**77**:335–40.
5. Tahaoglu K, Atac G, Sevim T, Tarun T, Yazicioglu O, Horzum G, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis* 2001;**5**:65–9.
6. Inoue T, Ikeda N, Kurasawa T, et al. Hyperuricemia and arthralgia during pyrazinamide treatment (Abstract). *Nihon Kokyuki Gakkai Zasshi* 1999;**37**:115–8 [article in Japanese].
7. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003;**167**:1472–7.
8. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tuber Lung Dis* 1996;**77**:37–42.
9. Steele MA, Des Prez RM. The role of pyrazinamide in tuberculosis chemotherapy. *Chest* 1988;**94**:845–50.
10. Papastavros T, Dolovich LR, Holbrook A, Whitehead L, Loeb M. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. *CMAJ* 2002;**167**:131–6.
11. De Jager P, Van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *Int J Tuberc Lung Dis* 2002;**6**:622–7.
12. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factorsfor the development of hepatotoxicity during antituberculosis treatment. *Am J Respir Crit Care Med* 2002;**166**:916–9.
13. Ungo JR, Jones D, Ashkın D, Hollender ES, Bernstein D, Albanese AP, et al. Antituberculosis drug–induced hepatotoxicity the role of hepatitis C virus and the human immunodeficiency virus. *Am J Respır Crıt Care Med* 1998; **157**:1871–6.
14. Turktas H, Unsal M, Tulek N, Oruc O. Hepatotoxicity of antituberculosis therapy (rifampicin, isoniazid and pyrazinamide) or viral hepatitis. *Tuber Lung Dis* 1994;**75**:58–60.
15. Devoto FM, Gonzalez C, Iannantuono R, Sera HA, Gonzalez CD, Saenz C. Risk factors for hepatotoxicity induced by antituberculosis drugs. *Acta Physiol Pharmacol Ther Latinoam* 1997;**47**:197–202.
16. 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.
17. Stout JE, Engemann JJ, Cheng AC, Fortenberry ER, Hamilton CD. Safety of 2 months of rifampin and pyrazinamide for treatment of latent tuberculosis. *Am J Respir Crit Care Med* 2003;**167**:824–7.
18. Thompson NP, Caplin ME, Hamilton MI, Gillespie SH, Clarke SW, Burroughs AK, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. *Eur Respir J* 1995;**8**:1384–8.

19. Pande JN, Singh SP, Khilnani GC, Khilnani Si Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996;**51**:132–1366.
20. Wong WM, Wu PC, Yuen MF, Cheng CC, Yew WW, Wong PC, et al. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. *Hepatology* 2000;**31**:201–6.
21. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 2003; **349**:474–85.
22. Ohkawa K, Hashiguchi M, Ohno K, Kiuchi C, Takahashi S, Kondo S, et al. Risk factors for antituberculous chemotherapy-induced hepatotoxicity in Japanese pediatric patients. *Clin Pharmacol Ther* 2002;**72**:220–6.
23. Lobue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med* 2003;**168**:443–7.
24. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;**17**: 1014–8.
25. Aktogu S, Yorgancıoglu A, Çırak K, Kose T, Dereli SM. Clinical spectrum of pulmonary and pleural tuberculosis: a report of 5480 cases. *Eur Respir J* 1996;**9**:2031–5.
26. Mcneill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis improved completion rates but more hepatotoxicity. *Chest* 2003;**123**:102–6.
27. Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. *Int J Tuberc L ung Dis* 2001;**5**:648–55.
28. Quantrill SJ, Woodhead MA, Hardy CC, Hardy CC, Hutchison AJ, Gokal R. Side-effects of antituberculosis drug treatment in patients with chronic renal failure. *Eur Respir J* 2002;**20**: 440–3.
29. Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med* 2002;**137**:640–7.