The Egyptian Journal of Hospital Medicine (July 2013) Vol. 52, Page 740–751

Effects of Anti-Tuberculous Drugs on Liver Function Profile in Libyan Patients with Tuberculosis

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ABSTRACT

The present prospective study was designed to conduct a local survey on patients under anti-tuberculosis therapy hospitalized in Abo-Seta hospital, Tripoli, Libya from the safety point of view. The study was carried out on 75 inpatients. The effects of the used drugs on some hematological parameters and liver function biomarkers were monitored for six-month period of treatment. Our survey showed that tuberculosis affects people with low and medium levels of education and with no job. The frequency of adverse effects related to treatment with Abo-Seta hospital regimen were decreases in WBCs count (-38.7%), RBCs count (-32.1%), platelets count (-33%) and hemoglobin concentration (-35.5%). However, in most of the cases, it was not necessary to modify the treatment regimen because of such side effects. Some parameters showed spontaneous recovery as RBCs count (+22.1%) and hemoglobin level (+20.1%). Combined therapy of ethambutol, isoniazid, pyrazinamide, and rifampicin has been used in Abo-Seta hospital, as a regimen for tuberculosis infection, may be associated with a high risk of hepatic toxicity during first month of treatment. However, during the remaining five months there was a good recovery of liver enzymes profile. Upon the data obtained from the present study, it could be concluded that TB patient after 6 month of treatment didn't develop multi-drug resistant tuberculosis (MDR-TB)

Key words: Tuberculosis, anti-tuberculosis therapy, safety profile.

INTRODUCTION

Tuberculosis (TB) is one of the most common infectious diseases caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) **(1)**. Tuberculosis is still a major cause of death from an infectious agent in developing countries, and constitutes a serious threat in large cities of industrialized countries **(2)**. Environmental characteristics such as crowding and social factors had a large impact on exposure to the disease **(3)**. In 1990, approximately, 1.7 billion humans were estimated to be infected worldwide (about one-third of the world's population) **(4)**. Tuberculosis has reemerged as an important public health problem in past as well at recent time in Libya. At 2008 about 1000 TB cases had been reported **(5)**. Also, in Libya, there were a few studies on such serious problem; one of these studies shows the number of Libyan patients whom tuberculosis has been bacteriological confirmed **(6)**, table 1.

Table (1): Numbers of Libyan confirmed TB cases during 1990-2009 (6).

Year	1990	1996	1999	2003	2005	2009
Incidence of TB / 100.000	41	40	23	20	18	16

M. tuberculosis was first isolated in 1882 by the German physician Robert Koch who received the Nobel Prize for this discovery. TB spreads most commonly by airborne transmission and can affect any part of the body but most often the lungs **(5)**. TB, which occurs scattered throughout the body, is referred to as miliary TB. Extra-pulmonary TB is more common in immunodeficiency persons and in young

DOI:10.12816/0000611

children **(7)**. The classic symptoms of TB are a chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. Infection of other organs causes a wide range of symptoms. Only 5% of people who are infected but not sick have latent TB infection. Those who have a latent infection are a symptomatic and do not feel sick. The diagnosis relies on radiology (chest X-Ray), tuberculin skin test, blood tests, as well as microscopic examination and microbiological culture of body fluids **(8)**.

If not treated TB properly, it can be fatal **(9)**. Today, persons with pulmonary TB can be cured with different types of regimens of antibiotics. One of these regimen followed by the Libyan National Center for Disease Control (NCDC), which is proposed by WHO as direct observed therapy for short period (DOTS). The protocol of this regimen is a 6-month course of antibiotics that includes isoniazid, rifampin, pyrazinamide, and ethambutol during the first 2 months. For our knowledge a combination of drugs may develop side effects on the body organs and the most related organ is liver, which is the metabolizing organ for all the received drugs. These side effects may differ from a patient to another due to the behavioral and cultural factors. Moreover, extensively drug-resistant tuberculosis is an emerging health problem that threatens TB control worldwide, since a perfect treatment for this disease has not yet been found.

In Libya, there is a huge gap between researches on anti-tuberculosis drugs and their effects on body functions during treatment period. Therefore, we designed this study to conduct a local survey on patients under anti-tuberculosis therapy hospitalized in Abo-Seta hospital, Tripoli, Libya from the safety point of view. The effects of the used drugs on the hematological parameters and liver function biomarkers are monitored for six-month period of treatment.

SUBJECTS AND METHODS

Subjects:

Seventy-five patients were inpatients, in 2009, in Abo-Seta hospital, in the west north of Libya, diagnosed as newly infected by TB. All patients were diagnosed as pulmonary tuberculosis by chest X-Ray, medical history and sputum analysis. Some patients had normal liver function while others had abnormal due to positive hepatitis. Prior-therapy samples were taken as controls.

Clinical monitoring:

Complete history background was taken from all patients via questionnaires involving name, sex, nationality, occupation, social status, smoking, residence, education, number of family members, number of rooms, previous treatment, first symptoms, fever, sweating, chest pain, weakness, anorexia, weight, other diseases and any other information, if any. Directly observed treatment (DOT) were also recorded according to **CDC (2000) (8)**.

Methods of treatment:

Patients received the following therapeutic regimen: isoniazid 50 mg once a day, rifampicin 10 mg once a day, pyrazinamide 25 mg once a day, ethambutol 15 mg once a day and/or streptomycin 0.75 g once a day. All patients were treated for 6 months.

Laboratory monitoring:

1. Monitoring of hematological parameters:

Complete blood count (CBC) with more emphases regarding the effects on red blood cells (RBCs) count, white blood cells (WBCs) count were been determined using an automated hematology Sysmex (KS-21N; Sysmex corporation, (Kobe, Japan)), in Libyan National Center for Infectious Disease Prevention and Control (NCDC). Anti-HIV, anti-HBV, anti-HCV antibodies were detected by ELISA. For CBC, blood samples of 5 ml were collected in special heparinized tubes to prevent clotting of the samples; additional 10 ml were collected without anticoagulant for detection for HIV, HBV and HBV antibodies.

2. Monitoring of the drug effect on liver functional parameters:

Patients' liver functions; alanine amino-transferase (ALT) and aspartate amino-transferase (AST) were determined by automatic biochemical analytic apparatus using a spectrophotometer (APPLIED

BIOSYSTEMS BTS 310, Biosystems of New England, Inc. (Waltham, Massachusetts, USA)) at the Libyan National Center for Infectious Disease Prevention and Control, when the patients had empty stomachs. Liver function of the patients was examined repeatedly every 4 weeks till 6 months after therapy. Test tubes without anti-coagulant agent used and filled every time with 10 ml of blood.

3. Monitoring hepatic adaptation:

It was detected by automatic biochemical analytic apparatus using a spectrophotometer APPLIED BIOSYSTEMS BTS 310, Biosystems of New England, Inc. (Waltham, Massachusetts, USA)) at the Libyan National Center for Infectious Disease Prevention and Control. The same previous test tube sample was used for this detection.

Statistical Analysis:

Data was analyzed by using statistics package for social sciences (SPSS Statistics 17.0.1) computer software package for statistical analysis (IBM Corporation, IBM Software Group's Business Analytics Portfolio (USA). Results were expressed as mean ± standard deviation (SD). Statistical test used was student's unpaired *t*-test, P value < 0.05 was considered statistically significant.

RESULTS

1. Clinical monitoring: Characteristics of different patients (questionnaire analysis):

Considering the seventy five TB inpatients, analysis of the questionnaire replies **(table 2)** revealed that age group 30-39 years is more affected by tuberculosis more than other age groups; single patients are more affected by tuberculosis more than married patients (70.7% vs. 29.3%); the smokers are more susceptible to TB infection than non-smokers (69.3% vs. 30.7%); highly educated patients are less affected (2.6%) when compared to medium- and low-leveled educated ones (78.6%). Jobless people were with higher exposure to pulmonary tuberculosis (58.6%) than employees (41.4%). Within the examined group of patients, many patients were infected with other disease conditions as HIV (32%), HBV (3%), and HCV (27%).

Six months after anti-TB therapy, all the inpatients suffered from different symptoms, including fatigue, decreased appetite, dizziness, nausea … etc.

2. Laboratory monitoring:

2.1. Determination of hematological parameters:

As shown in table (3), the anti-tuberculosis therapy caused a gradual significant decrease in the number of WBCs count from the beginning of treatment until the end of course (control samples = 9.32 ± 0.88 $x10^3$, after one month = 7.69 ± 0.35 $x10^3$, and after six months = 5.71 ± 0.55 $x10^3$, n = 75; $P < 0.05$), with percentage range of -17.5% to -38.7%, respectively.

Also, RBCs count showed a significant decrease after one month of treatment (5.89 ± 0.36 $x10^6$ in control samples vs. 3.66 ± 0.48 $x10^6$ after one month, $P < 0.05$), with percentage of -32.1%. However, by the end of the course, there was a significant recovery in number of RBCs in the end of the course compared after one of treatment (4.70±0.35$x10^6$, when compared with the value 3.66 ± 0.48 $x10^6$ that was recorded after one months; n = 75; $P < 0.05$) with a recovery percentage of +22.1%.

Table (2): The sociodemographic and clinical characteristics among 75 TB infection inpatients.

Variables	TB patients (n=75)	
	No.	%
Age group (years):		
11-19	3	4.0
20-29	11	14.7
30-39	38	50.7
40-49	17	22.6
50-59	5	6.6
≥ 60	1	1.4
Marital status:		
Single	53	70.7
Married	22	29.3
Educational level:		
High	16	21.4
Medium/low	59	78.6
Job:		
Have no job	44	58.6
Have a job	31	41.4
Smoking status:		
Yes	52	69.3
No	23	30.7
Associated infections:		
HIV	24	32
HBV	2	2.7
HCV	20	26.7

Platelets count exhibited a significant decrease from the beginning of treatment until the end of course (in control samples = 429.6 ± 11.9 $x10^3$, after one month = 330.61 ± 32.69 $x10^3$, after six months = 277.27 ± 15.39 x 10^3; n = 75; P < 0.05) with percentages of -23% and -33%, respectively.

Hemoglobin level exhibited a significant decrease after one month of treatment (14.52 ± 0.45 g/dl in control samples vs. 9.74 ± 1.22 g/dl after one month; n=75; P < 0.05) with percentage of -35.5%. However within the course of treatment there was a spontaneous recovery in hemoglobin level that was significant after 6 months of treatment (12.19±0.15g/dl compared to 9.74 ± 1.22 g/dl that was recorded after one month; n = 75; P < 0.05) and this increase was with a percentage of +20.1%.

2.2. Effect of anti-tuberculous drugs on liver function:

As shown in table (4), ALT level was increased after one month of treatment (36.25 ± 1.39 U/L in control samples vs. 64.6 ± 3.55 U/L after one month of therapy; n = 75; P < 0.05) with an increase percentage of +43.9%. However, there was a significant gradual recovery towards the normal value starting from the 2nd month until the end of course (39.28 ± 1.33 U/L after six months, compared to 64.6 ± 3.55 U/L, the value that was recorded after one month; n = 75; P < 0.05) with a recovery percentage of -39.2%.

Table 3: Show the effect of antituberculosis treatment during 6 month on WBC, RBC, platelets and hemoglobin.

Parameter	Before treatment Mean ± SD	Antituberculosis treatment duration (Month)					
		1st Mean ± SD	2nd Mean ± SD	3rd Mean ± SD	4th Mean ± SD	5th Mean ± SD	6th Mean ± SD
WBC ($x10^3$)	9.32 ± 0.88	7.69 ± 035*	8.25 ± 1.01	7.52 ± 0.60	7.13 ± 0.70	6.30 ± 0.63	5.71 ± 0.55#
RBC ($x10^6$)	5.89 ± 0.36	3.66 ± 0.48*	4.04 ± 0.18	4.29 ± 0.21	4.34 ± 0.16	4.54 ± 0.25	4.70 ± 0.35#
platelets ($x10^3$)	429.60 ± 11.90	330.61 ± 32.69*	317.01 ± 60.75	300.00 ± 38.73	277.75 ± 15.29	283.37 ± 12.65	277.27 ± 15.39#
Hemoglobin (g/dl)	14.52 ± 0.45	9.74 ± 1.22*	10.67 ± 1.01	11.04 ± 1.02	11.41 ± 1.06	12.04 ± 1.03	12.19 ± 0.15#

-Values are means ±SD, n=75, $P < 0.05$
-* Mean value was significantly different to that at control ($P < 0.05$).
-# Mean value was significantly different to that at First month ($P < 0.05$)

2.3. Hepatic adaptation:

As shown in table (4), AST had been increased after one month of treatment (30.31 ± 1.53 U/L in control samples vs. 47.57 ± 2.98 U/L after one month of anti-TB therapy; n = 75, P < 0.05) with an increase percentage of +36.3%. However, parallel to ALT, there was a significant gradual recovery expressed as gradual decrease starting from the 2nd month until the end of course (35.03 ± 0.55 U/L after six month, compared to 47.57 ± 2.98 U/L, the value that was recorded after one month; n = 75, P < 0.05) with a percentage recovery of -25.8%.

Similarly, ALP showed an initial increase after one month of treatment (156.17 ± 21.35 U/L in control samples vs. 281.83 ± 45.8 U/L after one month of anti-TB therapy, n = 75, P < 0.05) with a percentage of +44.6%. That result was followed by a gradual recovery starting from the second month till the end of the course at 6 months (256.67 ± 34.93 U/L after six month, compared to 281.83 ± 45.8 U/L, the value that was recorded after one month of therapy; n = 75; P <0 .05) with a recovery percentage of -8.9%.

Table 4: Show the effect of antituberculosis with in 6 month on liver function enzyme.

Parameter	Before treatment Mean ± SD	Antituberculosis treatment duration (Month)					
		1st Mean ± SD	2nd Mean ± SD	3rd Mean ± SD	4th Mean ± SD	5th Mean ± SD	6th Mean ± SD
ALT (U/L)	36.25 ± 1.39	64.60 ± 3.55*	58.68 ± 2.66	51.00 ± 1.39	47.55 ± 1.27	42.63 ± 1.63	39.28 ± 1.33#
AST (U/L)	30.31 ± 1.53	47.57 ± 2.98*	39.87 ± 1.87	38.82 ± 0.90	36.67 ± 1.01	36.30 ± 0.74	35.03 ± 0.55#
Alkaline phosphatase (U/L)	156.17 ± 21.35	281.83 ± 45.80*	270.28 ± 30.69	257.78 ± 53.65	248.00 ± 45.94	239.00 ± 39.85	256.67 ± 34.93

- Values are means ±SD, n=75, $P < 0.05$
-* Mean value was significantly different to that at control ($P < 0.05$)
-# Mean value was significantly different to that at First month ($P < 0.05$)

DISCUSSION

The wide prevalence of tuberculosis throughout the world makes it social and economical burden especially for developing countries and the use of anti-tuberculous drugs is an optimistic approach for this problem. However certain reservations associated with its use need to be properly evaluated especially anti-tuberculosis treatment-induced liver injury and the predisposing factors that add to this hepatotoxicity **(10)**.

Our survey shows that tuberculosis in Libya can be related to people with low income, bad habits and low educational level, however, some communities provide a better environment for disease transmission than others. Previous surveys have documented great disparities in rates of tuberculosis among neighborhoods **(11)**. These differences depended, in part, on community-level, ecological risk factors that facilitate transmission-poverty, crowding, and other markers of deprivation have long been associated with increased rates of tuberculosis **(12, 13)**. In addition to ensuring treatment efficiency, countries health departments collect case-specific demographic information (e.g., age, race, foreign-born status) and disease information (e.g., site of infection, drug resistance) **(14)**. Some other studies have supported our finding and the role of ecological risk

factors, such as low income, lack of social capital, and overcrowding, in tuberculosis disease **(15, 11, 16, 17)**. Although genetic differences have been linked to increased mycobacterial susceptibility **(18, 19)**, our study has considered the nationality of the patients under investigation whether they are Libyans or non-Libyans; we found that most of the patients (94.7%) were Libyans; and this may be explained on the basis of most of non-Libyan patients are not recorded, and all foreigners may go to other centers because of cost concern or may leave the country. Our results was explained within the context of recent research on "social capital" as a major factor for tuberculosis in Tripoli area as shown that 70.7% of patients were single, for our knowledge always single people cannot manage their food or habit culture.

Major infectious cause of mortality in India and many other developing countries include lower respiratory tract infections, HIV/AIDS, perinatal conditions, diarrhoeal diseases, tuberculosis, and malaria **(20)**; and all these kinds of infectious diseases are related to the low level of education and poverty. This statement agrees with our study, where, 78.6% of monitored patients were found to have low or medium degree of education and 58.6% were jobless and both of these concerns were strongly related to poverty.

Smoking and tobacco uses are usually related in young individuals to infections such as lower respiratory tract infections and tuberculosis and in middle aged and the elderly to cardiovascular diseases, cancer, and chronic lung diseases **(21, 20, 22)**. It is well known in the developed countries that smoking use is most prevalent among the least privileged groups **(23, 24)**. These groups are the unhealthiest and face the largest health in equities in terms of preventive, curative and rehabilitative therapies **(25)**. As shown in our survey, we have found that most of our TB patients are smokers (69.3%); this finding is consistent with other reports; for example, tobacco smoking was associated with a two-fold increased risk of active tuberculosis in a representative cohort of Taiwan's population **(26)**.

Leukopenia may occur in the course of treatment with anti-tuberculosis drugs, but it is not necessary to stop the chemotherapy immediately because of this fact, as the WBCs count recovers spontaneously or remains under stable leukopenic state during the course of chemotherapy in most cases. However, when leukopenia appears, the peripheral blood counts must be checked cautiously, and the chemotherapy should be stopped if the WBCs count progressively decreases. The patients who showed leucopenia due to anti-tuberculosis drugs may have had weaker natural and acquired cell-mediated immunologic response to tuberculosis infection, and more vulnerable bone marrow cells and hepatic cells to anti-tuberculosis drugs than the control. Our result showed leucopenia about -39.83% starting from the beginning of treatment figure. This finding is in agreement with **Nagayama *et al.* (2004) (27)**, who recorded leucopenia due to anti-tuberculous chemotherapy, including rifampicin and isoniazid.

Since RBCs can behave as bioreactors that are able to convert pro drugs to membrane-releasable active drugs, new compounds (AZTpEMB, AZTpEMBpAZT, and AZTp2EMB) comprising both anti retro viral and anti microbial drugs were designed and synthesized. Among these, only AZTp2EMB was hydrolyzed by erythrocyte enzymes and could be encapsulated inside RBCs **(28)**. Our data expressed that RBCs count decreased significantly (-32.1%) after one month of anti-TB treatment; however, from 2nd month, it started to recover. This may be explained on the basis of that initially RBCs undergo deformation to protect itself from drug toxicity.

On the other hand, some other studies indicated that none of the anti-tuberculosis drugs is without adverse reactions but only rarely are the adverse reactions lives threatening. Thrombocytopenia (TCP) is a well-known complication following the administration of certain drugs and is characterized by rapid lowering of the platelet count whenever the offending drug is taken by the sensitized individual. Rifampicin-induced TCP is a rarely reported adverse reaction **(29)**.

To test development of thrombocytopenia in inpatients under anti-

TB therapy, platelet count was included in the study. Although there was a decrease in platelet count after treatment as compared to pre treatment, it was within the normal range. This decrease in platelet count may be due to Rifampicin whose one of the side effects is thrombocytopenia. The result of the present study was in agreement with the study of **Nagayama *et al*. (2004) (27)** that was carried out in Japan. Besides, another study by **Handin (1991) (30)** indicated that many drugs had effect on platelets in the form of reducing their number; however, upon discontinuation of the suspected drug, there will be regain of the platelets number. TCP was also recorded as an adverse reaction associated with intermittent rifampicin regimen by **Toman (1989) (31)**. During using anti-tuberculosis drugs, if purpura occurred, rifampicin should be stopped immediately and should not be given again even in small doses **(32)**. Those previous data are in agreement with these stated in the present study that taking anti-tuberculosis drugs had a significant decreasing effect on the platelets number at a percentage of -35.5%.

Three fourths of the monitored patients suffered from low hemoglobin level so that they may fall in the category of moderate to severe anemia. Nutritional status of our patients was very poor and 61 patients (91%) of them were below 18.5 kg/m^2 BMI; and 27% of the patients showed the hypoalbuminemia and this may be one of the risk factors of anti-TB therapy-induced hepatotoxicity **(33)**. A group of researchers concluded that improvement of hematological status was dependent only on the improvement of the disease process as **Das *et al.* (2003) (34)**. Although a few reports referred to the effect of anti-TB therapy on the hemoglobin level, yet, our study recorded clearly that the used drugs had a lowering effect on the hemoglobin level only in first month in treatment at a percentage of -33%.

The possible explanation of anti-TB therapy-induced hepatotoxicity in malnutrition is the depletion of glutathione stores that makes one vulnerable to oxidative injuries. Our study depicts the same result as a study conducted at India showing three times higher incidence of anti-TB therapy-induced hepatotoxicity in malnourished patients **(35)**. For our knowledge a combination of drugs will develop side effects on the human body organs, and the most related organ is the liver. Anti-tuberculosis medication frequently causes disturbance to liver function tests and may cause serious liver function dysfunction **(36)**. Enzymes for drug metabolism in hepatocyte microcosms may have a congenital defect, malformation, low activity, or be inhibited by drugs, so drug metabolites are very toxic to hepatocytes. Another reason is the hypersensitivity to drugs. The drugs may act as haptens causing allergic reaction by immune mechanism leading to the single ALT increase in clinical situation. Commonly used anti-TB drugs, such as isoniazid, rifampicin, pyrazinamide, ethambutol, etc., are all hepatotoxic, especially when rifampicin and pyrazinamide are used in combination **(37)**. Isoniazid causes hepatic damage either by the toxicity of or hypersensitivity induced by its metabolite-acehydrazide. Rifampicinmay accelerate the metabolism of isoniazid as astrong enzyme inducer resulting in the increase of acehydrazide. Acehydrazide combines with bio macro-molecules in liver leading to hepatocellular damage usually seen in aged patients with excessive drinking, malnutrition or a liver ailment. Pyrazinamide's hepatotoxicity is dose-dependent and the general dose rarely causes hepatic damage. Isoniazid and rifampicin are the first line anti-TB medicines because of their strong bactericidal effects. However, rifabutin, amikacin, ofloxacin, levofloxacin, etc., treatment plan have not been reported with obvious hepatotoxicity **(38, 39)**. It had been reported that rifampin appears to enhance metabolic hepatocellular idiosyncratic reaction in patients receiving isoniazid, perhaps by promoting the formation of toxic isoniazid metabolites **(40)**. The use of multidrug regimens for the treatment of tuberculosis based on the combination of isoniazid, rifampin, ethambutol, and/or pyrazinamide has proven to be a highly effective therapy **(41)**. However, its

effectiveness is offset by the increased incidence of drug-induced hepatotoxicity. The development of drug-induced hepatotoxicity is often of great concern, as it often necessitates the cessation or modification of treatment **(42)**. The occurrence of liver injury during anti-tuberculosis treatment varies, and appears to be much higher in developing countries (up to 39%) than in developed countries (3-4%) **(43)**; despite of the use of similar regimens. The reasons for this higher incidence of drug-induced hepatotoxicity in developing countries remain unclear. It has been suggested that this may be attributable to viral hepatitis, which is particularly prevalent in the developing world **(44)**.

In our study the patients developed anti-TB-induced hepatotoxicities indicated by increasing of all of the three enzymes, 43.9% for ALT, 36.6% for AST and 44.6% for ALK that almost over lap the study conducted in Japan by **Ohno *et al.* (2000) (45)**.

The combination of multi drug therapy for tuberculosis has been associated with increased risk of hepatotoxicity when compared with INH mono therapy used for TB prophylaxis **(46)**. The reported incidence of anti-TB-induced hepatotoxicity is different in various countries though not fully understood but could be due to the characteristics and the risk factors of the population studied, the different diagnostic criteria used to define hepatotoxicity, different geographical areas, tests carried out during follow ups and the type of monitoring **(47)**. Parallel studies conducted in Nepal and Hong Kong resulted in increase in hepatic biomarkers with percentages of 8% and 13%, respectively. Four prospective Indian studies documented the risk of anti-TB-induced hepatotoxicity as11.5% compared with 4.3% in fourteen published studies from west **(48)**. Hepatotoxicity occurs generally within weeks to months rather than the days to weeks of onset seen with hypersensitivity reactions **(49)**. In addition, only one study **(50)** has examined the risk of drug-induced hepatotoxicity in standard short-course anti-TB treatment in patients with clinical TB. Studies in the1950s suggested that elevated glutamate pyruvate transaminases occurred in 20%, and overt hepatitis in 8%, of those treated with pyrazinamide, which has some structural resemblance to isoniazid **(1)**. Experience with lower dose regimens, in combination with other agents, suggests that there is only a small risk of hepatocellular injury **(51)**, though cases of fatal hepatic necrosis have been described **(52)**. **Younossian *et al.* (2005) (53)** concluded that combing pyrazinamide and ethambutol for latent tuberculosis infection may be associated with a high risk of hepatic toxicity, and warrants close monitoring. There is clearly a need for alternative preventive treatments for contacts exposed to multidrug-resistant tuberculosis. **Thompson *et al.* (1995) (36)** suggested a protocol for using liver function tests to monitor for liver damage, and give recommendations on what action to take when these become abnormal and same suggestion been supported by other group as **Parthasarathy *et al.* (1986) (42)**. In a study in Hong Kong, 1,386 Chinese patients with sputum smear-positive pulmonary tuberculosis were under treatment for 6 month with combinations of anti-tuberculosis drugs recorded non-significant differences between the regimens with and without streptomycin **(54)**. Even the recovery of the liver is a normal mechanism as the body rebuilds its own cells, which agree with our results for all three liver function enzymes. There are many risk factors of hepatic damage during the course of anti-TB treatment, such as the type of tuberculosis, recurred tuberculosis, HBV infection, alcohol drinking, age, nutrition status, heredity, individual difference and immune status, etc. Scholars outside China reported that most of hepatocytes in HBV carriers without clinical symptoms had changes in histology and spot necrosis in some hepatocytes. One researcher took liver biopsies from 25 pulmonary tuberculosis patients with HBV infection during the course of anti-TB treatment and discovered that all the patients with liver dysfunction suffered from viral hepatitis, even liver cirrhosis. Hepatic damage of the patients with pulmonary tuberculosis during the course of anti-TB treatment was related to HBV infection and pre-existing pathologic changes in liver. Anti-TB medicines only aggravated pre-existing hepatic damage **(55, 56)**. So, HBV infection or pre-existing liver

ailment might be an important risk factor **(57, 58)**. Hepatotoxicity caused by anti-TB medicines was liable to happen in the first 2-3 months of aggressive anti-TB treatment. Hepatic damage of the patients with positive HBV was caused by viral damage over lapped by medicine damage **(59)**. The prevalence of TB was reported to be higher among hepatitis- C virus-infected (HCV) patients than among those without infection **(60)**. However, the relationship between HCV infection and the development of drug-induced hepatotoxicity during treatment for TB is not well defined in literature **(50, 61)**. Percentage of patients which are infected with other kind of disease can be seen in HIV.

In conclusion, we can state that manifestations of side effects related to anti-tuberculosis treatment with our regimen in the population of the tuberculosis inpatient clinic of the Abo-Seta hospital are apparent. However, in the great majority of cases, it was not necessary to modify the treatment regimen due to adverse effects. These results show the importance of the early recognition of these effects and the early initiation of the appropriate approach. It is fundamental to follow the recommendation of the National Health Foundation Guide to Epidemiological Surveillance of Tuberculosis **(62)** that clinical follow-up evaluations of patients be carried out by health professionals at least once a month and includes an interview regarding the possible signs and symptoms related to side effects.

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