

Frequency of Hepatotoxicity in Pulmonary Tuberculosis Patients taking Anti-Tuberculosis Therapy

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Abstract

Background: Tuberculosis is a global pandemic which affects millions of people every year. The treatment of tuberculosis consists of simultaneous use of several drugs for a prolonged period of time, therefore anti-tuberculosis treatment induced toxicity is a real problem. It is the most common side effect leading to interruption of therapy. Wide variations have been found in the reported incidence of hepatotoxicity during short-course chemotherapy. This study was conducted to determine the frequency of ATT induced hepatotoxicity in pulmonary TB patients.

Methodology: This descriptive, cross-sectional study was conducted at Gulab Devi Chest Hospital Lahore from November 2015 to January 2016. Total 137 pulmonary TB patients were included in this study according to inclusion and exclusion criteria. Data of patients was collected by Questionnaire. Blood samples were taken and LFTs were done. Data was analyzed by using SPSS version 16.

Results: Data of 137 patients was taken in the study. Out of which 60 (43.8%) were male and 77 (56.2%) were female. The mean age was 40.59 ± 16.57 . 45 (32.8%) patients out of 137, develop hepatotoxicity while 92 (67.2%) shows normal patterns of liver function. 22 (16.1%) patients out of 137 showed elevation of serum bilirubin levels.

Conclusion: ATT induced hepatotoxicity is a frequent complication in Pulmonary Tuberculosis patients. So, all patients put on ATT must be followed up for at least the initial month. The patients and the treating physicians must be well-educated about the adverse effects of the ATT, its early recognition and management.

Keywords: Anti-tuberculosis treatment, pulmonary tuberculosis, liver function tests, hepatotoxicity

Introduction:

One of the major causes of death from a curable infectious disease is the Tuberculosis (TB). Largest number of both new cases and deaths from TB has been reported from South-East Asian region (1). The *Mycobacterium tuberculosis* has the ability to persist in host tissues, so drugs are required prolonged administration to destroy the organism (2). There is increase in the occurrence of tuberculosis recent years. In most of the infected patients, immune system prevents the disease. T

cells (both CD4+ and CD8+), cytokines, including IFN- γ , IL-12, TNF- α , and IL-6, and macrophages play this important role (3). Most of the drugs that are used as anti-TB drugs are more or less hepatotoxic, especially when several anti-TB drugs are used in combination (4). Treatment with anti-tuberculosis drugs cause adverse reactions seldomly but in some patients they cause hypersensitivity reactions and in some they may cause hepatotoxicity or neurotoxicity as well (5). Hepatotoxicity is one of the most important adverse drug

reactions associated with anti-tuberculosis drugs that may limit their use. There are transient elevations of serum hepatocellular enzymes (e.g. ALT and AST) in approximately 10% of patients who received chemotherapy including isoniazid and rifampicin (6). Isoniazid and pyrazinamide are the principal antituberculosis drugs that cause hepatotoxicity (7). The studies revealed that formation and accumulation of reactive metabolites contribute the hepatocytic injury (8). The production and elimination of the toxic metabolites depends on the activities of several enzymes, such as *N*-acetyl transferase 2 (NAT2), cytochrome P450 oxidase (CYP2E1) and glutathione *S*-transferase (GSTM1). DNA sequence variations or polymorphisms at these loci could modulate the activities of these enzymes and, hence, the risk of hepatotoxicity (9). The frequency of hepatotoxicity varies from 2 to 28% in different populations. The variation is large due to different definitions of hepatotoxicity and differences between the populations studied (10). Antituberculosis drug-induced hepatotoxicity (ATDH) is a serious complication that can be fatal if therapy is not interrupted in time (1).

There are many drug strategies which are used to treat TB, one of them is DOTS strategy (11). The key component of DOTS strategy is the standard anti-TB short course chemotherapy regimen, which is a drug combination of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S). It is a continuous course of 6–9 months (12). Several anti-tuberculosis agents have been implicated as being hepatotoxic. Isoniazid, particularly in association with rifampicin and pyrazinamide cause liver dysfunction more frequently instead ethambutol and

streptomycin (13). Liver function tests should be carried out before initiation of ATT and should be repeated twice weekly for the first two weeks followed by weekly monitoring till the end of two months and then monthly investigations till the end of the treatment (14).

Factors influencing drug induced hepatotoxicity includes age, ethnicity, gender, nutritional status, underlying liver and renal diseases, pregnancy, duration and dosage of drug, drug-to-drug interaction (15). Presence of HBV infection or an underlying silent chronic liver disease was found to significantly increase the risk of developing ATT-induced hepatotoxicity. Continuation of ATT after development of jaundice was associated with a high fatality rate. It was possible to re-introduce isoniazid in 96% and rifampicin in 88% of patients with ATT induced hepatotoxicity. Discontinuation of ATT leads to rapid recovery in most cases and drugs can safely be introduced after recovery in most of cases (16).

The rationale of current is to find out the frequency of hepatotoxicity in patients taking anti-TB therapy and to assess the risk factor in developing hepatotoxicity.

Material & Methods:

This cross-sectional study was conducted at Gulab Devi Chest Hospital, Lahore on patients with pulmonary tuberculosis diagnosed by positive AFB smear or culture.

Non-probability (purposive) sampling was employed to study 137 individuals

Inclusion criteria: Only pulmonary tuberculosis admitted patients who are taking ATT from one month with normal baseline LFTs.

Data was collected by questionnaire (Supplementary File 1). Data was analyzed by SPSS of version 16.0.

Operational Definitions:

Hepatotoxicity: The following WHO criteria were used to define hepatotoxicity.

Mild hepatotoxicity (grade1) was diagnosed if AST/ALT levels were increased but were still less than three times the upper normal limit (125 IU/L).

Grade 2 mild hepatotoxicity was defined when liver transaminase levels were from 125 to 250 IU/L.

If the AST/ALT levels were from 250 to 500 IU/L, it indicated **grade 3** moderate hepatotoxicity.

AST/ALT levels \geq 500 IU/L were considered to indicate **grade 4** severe hepatotoxicity.

Methodology: 137 patients of pulmonary tuberculosis diagnosed by sputum positive AFB smear or culture and receiving anti-tuberculosis therapy (4 drugs regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol) from 1 month were taken into this cross-sectional study. This study was conducted in Gulab Devi Chest Hospital, Lahore from November 2015 to January 2016. A questionnaire was designed to collect the data from the patients regarding their clinical findings and lab results. Patients were selected according to inclusion and exclusion criteria. Blood samples were collected from the patients and serum was separated. The liver enzymes Alanine transaminase (ALT), Aspartate transaminase (7) and Bilirubin analysis were done. The ALT and AST were analyzed by kinetic method using semi auto analyzer and bilirubin was analyzed by color endpoint method using semi auto

Table 1. Similarly, 23 (16.8%) patients out of 137 showed mild (grade 1) increase in

analyzer. The control sample was also used for monitoring each step of procedure and analyzer machine.

Data Analysis:

The data was analyzed using SPSS version 16.0. The qualitative data was presented in the percentages and frequencies in the form of graphs and tables. The quantitative data was presented in the form of mean, range and standard deviation by simple descriptive analysis. Pie chart, bar chart and cross tabulation is also given for categorical data.

Results:

Data of 137 patients was taken in the study. Out of which 60 (43.8%) were male and 77 (56.2%) were female. Minimum age of the patient in this study was 17 years and the maximum was 75 years. The mean age was 40.59 ± 16.57 . Most patients taken in the study was from low economic class (89.1%), 10.2% were from middle class and 0.7% from upper class.

Out of 137 patients, 45 (32.8%) develop hepatotoxicity while 92 (67.2%) shows normal patterns of liver function. 22 (16.1%) patients out of 137 showed elevation of serum bilirubin levels while 115 patients had no elevation in serum bilirubin level. 19 (13.9%) had serum bilirubin level between 1.1-2.0mg/dl and 3 (2.2%) had serum bilirubin level more than 2.0mg/dl. Figure 1 described distribution of serum bilirubin levels in study population. Similarly, 92 (67.2%) patients showed normal ALT level while 22 (16.1%) had mild (grade 1) elevation of ALT, 15 (10.9%) had mild (grade 2) elevation of ALT and 8 (5.8%) had moderate (grade 3) elevation of ALT levels. No one presented the severe hepatotoxicity as showed in

serum AST level, 15 (10.9%) had mild (grade 2) increase and 7 (5.1%) had

moderate (grade 3) increase in AST level **Table 2**. Meanwhile, 23 (16.8%) patients out of 137 had abnormal parameters of serum ALP and remaining 114 (83.2%) had normal serum ALP level **Table 3**.

17 (37.8%) out of 45 patients developed jaundice (fig.4) and 7 (15.6%) developed hepatomegaly (fig.5). Fever was a symptom in 41 patients out of 45 (who develop hepatotoxicity), 34 had nausea, 14 had vomiting and 40 had loss of appetite as presenting symptoms of hepatotoxicity (table.6-9).

Discussion:

Tuberculosis is a major cause of preventable infectious disease induced death in the world. Timely diagnosis and proper chemotherapy are the mainstays of treatment. The hepatotoxic side effect of ATT has been under extensive discussion and studies to confirm their frequency and outcome in patients, all over the world. However, it is a surprising fact that most of this research work has been done in the west and in the more developed nations of the world. All available data is based on studies conducted in regions having better socio-economic conditions, awareness of impact of disease and having better patient education about possible side-effects and follow-up facilities as well as better patient compliance thus resulting in lesser frequency of hepatitis.

This study was conducted to determine the frequency of ATT induced hepatotoxicity. As per the results in this study, it was found that among 137 ATT taking patients 45 (32.8%) had abnormal parameters with the elevation of serum bilirubin level, AST level and ALT level. Bilirubin is found to be elevated in 16.1% of the patients and 32.8% of the patients have raised ALT and AST levels. It showed that drug induced

hepatotoxicity due to anti TB drugs is relatively higher among the low-income status. The probable causes behind these findings could be poor nutrition.

Similarly, in a study conducted by Khoharo, K. et al in 2010 at Muhammad Medical College Hospital, Mirpurkhas and Liaquat University Hospital Jamshoro, ATT induced hepatotoxicity developed in 26% patients with minor, moderate and severe alanine transaminase (ALT) rise noted in 52.75%, 43.95% and 3.3% cases respectively. (17) Malnutrition, female sex, and older age were noted as the risk factors. Like this study, a study conducted in Bhaktapur, Nepal by Khadka, J. et al in 2009 reported the same results as this study. It reported 35% ATT induced hepatotoxicity with elevation of serum bilirubin, ALT and AST. The facts associated behind these findings are probably poverty, malnourishment, alcohol consumption, illiteracy of people and poor health management system. (18)

A study conducted by Mahmood, K. et al in 2007 at Medical Unit-V and OPD department of Civil Hospital Karachi, reported the 19.76% incidence of ATT induced hepatotoxicity which is lower than our study. This is because our study is done on AFB smear positive patients only rather than on both positive or negative as in former study. The former study also revealed the frequency of ATT induced hepatotoxicity is more common in smear positive patients than smear negative. (19)

Conclusion:

Hepatotoxicity due to ATT is quite a significant and common problem, being more prevalent in the elderly. All efforts must be made to identify such cases as soon as possible through regular clinical assessments and biochemical monitoring. It is worthwhile to appreciate that more

stress must be laid on case identification during the initial two months of therapy.

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Table 1. Serum ALT Levels in study population

Alanine aminotransferase	Frequency	Percent
normal (below 50)	92	67.2
Grade 1 (51 to 125)	22	16.1
Grade 2 (126 to 250)	15	10.9
Grade 3 (251 to 500)	8	5.8
Total	137	100.0

Table 2. Serum AST level in study population

Aspartate aminotransferase	Frequency	Percent
normal (below 50)	92	67.2
Grade 1 (51 to 125)	23	16.8
Grade 2 (126 to 250)	15	10.9
Grade 3 (251 to 500)	7	5.1
Total	137	100.0

Table 3. Serum ALP levels in study population

Alkaline phosphatase	Frequency	Percent
Normal	114	83.2
Abnormal	23	16.8
Total	137	100.0

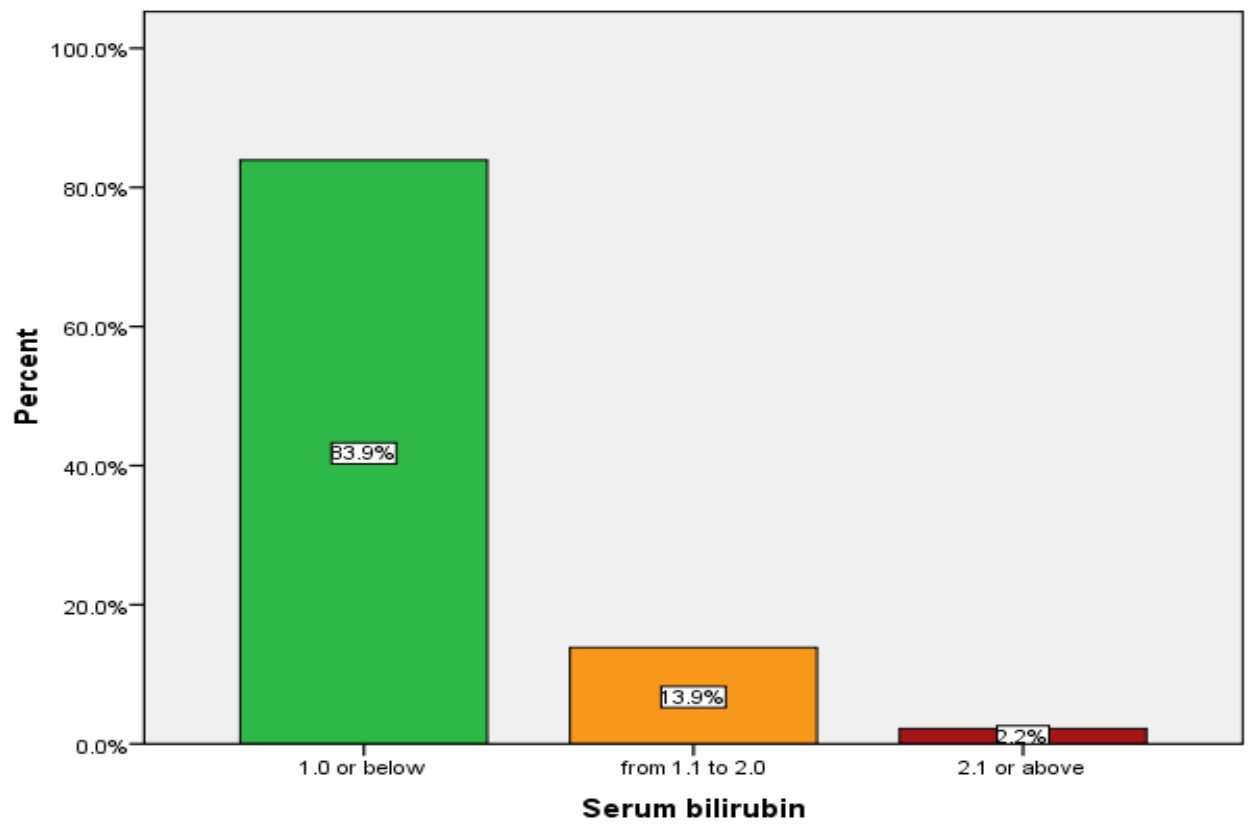


Figure 1. Serum total bilirubin levels in study population

Supplementary File 1:

Frequency of Hepatotoxicity in Pulmonary Tuberculosis patients taking Anti-tuberculosis Therapy

Questionnaire

Name _____ D/O,S/O,W/O _____
 Age/Sex _____ Economic status _____
 Ward _____ Reg# _____

Clinical Features

Jaundice _____ Hepatomegaly _____
 Fever _____ Nausea _____
 Vomiting _____ Loss of appetite _____

Any previous liver problem _____

Drugs addiction _____

On ATT _____ From: _____

Laboratory Findings

Viral hepatitis screening

Tests	Results
Anti-HCV	
HBsAg	

Liver Function Tests

Tests	Results
Bilirubin	
ALT	
AST	
ALP	