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Research Article

A PROSPECTIVE STUDY ON ABNORMAL LIVER FUNCTION TEST PATTERNS IN PATIENTS RECEIVING ANTI-TUBERCULOSIS THERAPY

VIJAYALAKSHMI A*, THANMAYI G, JAYAKUMARI S

Department of Pharmacognosy, School of Pharmaceutical Sciences, VISTAS, Vels University, Pallavaram, Chennai, Tamil Nadu, India.
Email: aviji_1975@rediffmail.com

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ABSTRACT

Objective: Identification of risk factors associated with anti-tuberculosis drug-induced hepatotoxicity (anti-TB-DIH) is important, especially in an endemic area for TB and liver disease. This study assessed the incidence and risk factors of anti-TB-DIH. Hence, the present study was designed to evaluate the abnormal liver function test (LFT) in antitubercular therapy.

Methods: A total of 100 consecutive TB patients were prospectively followed up both clinically and biochemically before and during their course of anti-TB therapy with daily doses of isoniazid, rifampin, ethambutol, and pyrazinamide, or streptomycin.

Results: In the study, 18-30 years 17 (17%), 31-50 years 28 (28%), 51-70 years 37 (37%), and 71-80 years 18 (18%) aged patients were found where 63 (63%) are males and 37 (37%) are females. Comparison between before treatment and 2 months treatment showed a significant increase in the level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), *viz*., 51.6±3.92, 42.7±3.21, and 129±3.2 (U/L), respectively, as compared to pre-treatment levels. Comparison between before treatment and 2 months treatment showed a significant increase in the level of AST, ALT, and ALP, *viz*., 51.6±3.92, 42.7±3.21, and 129±3.2 (U/L), respectively, as compared to pre-treatment levels. Comparison between before treatment and after treatment (6 months) revealed a significant increase in the level of AST, ALT, ALP and gamma glutamyl transpeptidase (GGT) viz., 59.9±3.12, 51.6±3.66, 131.6±3.2, and 61±3.2 (U/L) respectively. The total bilirubin and direct bilirubin were found between 2.1±0.9 and 0.6±0.3 mg/dL respectively, when compared with before treatment.

Conclusion: Anti-TB-DIH is not uncommon, needs early recognition and treatment and is more in patients with pre-existing liver disease and lower body mass index.

Keywords: Anti-tuberculosis, Liver function test, Hepatotoxicity.

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INTRODUCTION

Tuberculosis is one of the most rampant communicable and a serious global health issue that remains out of control in many developing countries. It is an infectious disease caused by *Mycobacterium tuberculosis* and is the second leading infectious cause of death in the world [1]. In particular, it is a major public health problem in India. India accounts for one-fifth of the global TB incident cases and topping the list among high burden countries [2]. The overall goals for a successful treatment of TB are to cure the individual patient and to minimize the transmission of *M. tuberculosis* to other persons [3].

The treatment strategy is directly observed treatment (DOT), where the regimen is also referred as short course chemotherapy (SCC). The regimen comprises a combination of isoniazid (INH) (H), rifampicin (RIF) (R), pyrazinamide (PZA) (Z), ethambutol and streptomycin (S) for 6-9 months. According to Revised National TB Control Programme (RNTCP), treatment consists of 2 phases - an initial intensive phase and a second continuation phase. The total duration of treatment is 6-9 months. Sputum microscopy is done regularly to monitor the response to treatment. The intensive phase lasts for 2-4 months. Treatment is given thrice a week on alternate days, and every dose is directly observed. The continuation phase lasts for 4-5 months depending on the patient's response to treatment. The drugs used for the duration of the intensive phase and in treatment may vary within SCC programs [4].

The most undesired side effect of antitubercular therapy is drug-induced hepatotoxicity (DIH). Unfortunately, almost all the chemotherapeutic agents that are used for TB may result in additional liver damage in patients with the pre-existing liver disease by one or several mechanisms. The absence of overt jaundice, the degree of subclinical hepatotoxicity has to be determined by monitoring the biochemical changes using liver function tests (LFTs) [2]. It is vital to consider drugs as a cause of LFT abnormalities. Test results patterns across several parameters are usually more useful than single parameters [5].

Retreatment is started only when all biochemical markers of liver injury have returned to normal levels. In all patients with pre-existing liver disease, frequent clinical and laboratory monitoring are be performed to detect drug-induced hepatic injury. However, due to the effectiveness of these antitubercular drugs, especially (INH and RIF) even in the presence of pre-existing liver disease, should be used if possible [4]. Hepatocyte injury usually results in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation. The AST and ALT are the most commonly used identifying markers of hepatocyte injury. Injury to hepatocytes causes these enzymes to leak into circulation and thus, raising serum levels. Elevation of the ALT is most specific for hepatic cells injury as its concentration in the liver far exceeds that in any other organ. Elevation of AST is less specific as it may occur also due to damage to skeletal muscle, kidney, brain, and red blood cells [5]. Hence, the present study aimed to evaluate the abnormal LFT patterns in proved cases of pulmonary TB in patients on short-term regimen of anti-TB therapy (ATT) as per RNTCP.

METHODS

Patients

This prospective study was conducted in the ESI Hospitals, Ayanavaram, Chennai, Tamil Nadu, India, from September 2015 to April 2016. Inclusion criteria comprised patients clinically diagnosed with active pulmonary or extra-pulmonary TB and using DOTS therapy and non-

resistant TB. Of 102 consecutive patients registered in the clinic during the study period, 2 patients did not complete their follow-up and were excluded. All patients gave written informed consent, and the study was approved by the Faculty of Institution Ethics Committee, approval no. IEC/DOPV/2015/13.

Anti-TB regimen

Total treatment period was 6 months including intensive and continuation phases (2 and 4 months, respectively). The intensive phase comprised INH (5 mg/kg day^{-1}; maximum 300 mg/day), RIF (10 mg/kg day^{-1}; maximum 600 mg/day), ethambutol (EMB) (15–20 mg/kg day^{-1}), and PZA (20–25 mg/kg day^{-1}), or streptomycin. The continuation phase comprised daily similar doses of INH and RIF.

Diagnosis of DIH

Anti-TB-DIH was diagnosed according to the International Union against tuberculosis and lung disease [6] as follows:

1. Normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-TB drugs and
2. Presence of at least one of the following:
   i. A rise to more than 2 the upper limit of normal (ULN) level of ALT and/or AST [7]
   ii. A rise in total serum bilirubin to more than 1.5 mg/dl
   iii. Any increase in AST and/or ALT above pre-treatment levels together with anorexia, nausea, vomiting, and jaundice.

Baseline assessment

Pre-treatment evaluation included clinical history, physical examination, body mass index (BMI = body weight (kg)/[height (m)]^2), chest radiographs, abdominal ultrasonography, complete blood cell count, LFTs, and hepatitis markers. Samples from hepatitis B surface antigen (HBsAg), anti-HB core antibody (anti-HBc), and/or antihepatitis C virus (HCV) antibody-positive patients were tested for hepatitis B virus (HBV) DNA and HCV RNA, respectively. A BMI of <20 kg/m^2 was considered as low. Hypoalbuminemia was defined as serum albumin level of <3.5 mg/dl.

Follow-up

Patients were followed closely in a specialized clinic by a chest physician and a hepatologist fortnightly over the first 2 months, then monthly till the end of the 6-month period. In each visit, patients were assessed clinically (response to therapy, any adverse effects, and nutritional status), and biochemically including LFTs, which were repeated whenever symptoms or signs suggestive of hepatotoxicity (nausea, anorexia, malaise, vomiting, hepatomegaly, or jaundice) occur.

Exclusion of other causes of liver disease

Before attributing hepatotoxicity to anti-TB drugs, other causes of liver diseases were excluded by: IgM antihepatitis A virus antibody, HBsAg, IgM anti-HBc in addition to the HBV DNA if the HBsAg and/or HBcAb are positive, anti-HCV antibody and HCV RNA if the anti-HCV antibody is positive, autoimmune screen (antinuclear and antismooth muscle antibodies), and abdominal ultrasound to assess for liver abscesses, focal lesions, or biliary obstruction.

Management

LFTs were monitored weekly for 2 weeks, and then fortnightly. Blood biochemistry with detailed liver functions serum bilirubin, AST, ALT; alkaline phosphatase (ALP); gamma glutamyl transpeptidase (GGT) were performed in all patients using standard laboratory procedures. If a patient develops hepatotoxicity, the causative drug was permanently discontinued.

Degree of abnormal LFT's

Abnormal levels of liver enzymes are common among persons infected with TB and may be caused by multiple factors including medication toxicity and coinfection with HCV or HBV. We used the consensus criteria set by international drug-induced liver injury (DILI) expert working group for DILI case definition. The ULN liver enzymes level for the study population was set based on the respective mean baseline value after exclusion of the 5% extreme values [8]. Accordingly, the ULN of ALT for men and women were 33 U/L and 29 U/L, respectively, and for AST, ALP, total bilirubin, and direct bilirubin were 41 U/L, 128 U/L, 1.0 mg/dL, and 0.3 mg/dL, respectively.

The degree of severity of hepatotoxicity was evaluated based on WHO toxicity classification standards [9]. Mild hepatotoxicity is defined as AST and/or ALT elevations of <3-fold the ULN (<121 IU/L); moderate hepatotoxicity as elevations of 3-5-fold the ULN (121-200 IU/L); severe hepatotoxicity as elevations 5-10 times (201-400 IU/L), and very severe hepatotoxicity >10 times the ULN (>400 IU/L) or more than 250 IU/L with symptom of fulminant hepatitis as evidenced by jaundice and/or lethargy.

Mild:
(2-4 × ULN).

Moderate:
(5-10 × ULN).

Severe:
(> 10 × ULN).

Management of drug toxicity and the stopping rule for treatment discontinuation was done according to the WHO guiding principles for the management of antiretroviral drug toxicity based on the severity grade [10].

Statistical analysis

Variables are represented as mean ± standard error mean if normally distributed, and statistical significance was defined as a $p<0.05$. In continuous variables, independent *t*-test was applied. In addition, to compare each TB drug concentration with the grade of hepatotoxicity, ANOVA was applied. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Version 15.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total number of 100 patients have been selected in the study based on inclusion and exclusion criteria. In this, 18-30 years 17 (17%), 31-50 years 28 (28%), 51-70 years 37 (37%), and 71-80 years 18 (18%) were found where 63 (63%) are males and 37 (37%) are females. In the present study, based on social habits the patients were categorized into smoker 37 (37%), non-smoker 22 (22%), alcoholic 28 (28%), and non-alcoholic 13 (13%), family history of TB 23 (23%) and no family history of TB 77 (77%). Among them, newly diagnosed 82 (82%) and relapse 18 (18%), with comorbidities such as hypertension 26 (26%), diabetes (32%), ulcer 10 (10%), and HIV 0 (0%), were found.

During the study period, anti-TB-DIH was detected clinically and confirmed by LFT. About 30 patients showed alteration in AST (serum glutamic oxaloacetic transaminase) level (30%), 22 patients showed alteration in ALT (serum glutamic pyruvic transaminase) level (22%), 21 patients showed alteration in ALP level (21%), 10 patients showed alteration in GGT level (10%), 8 patients showed alteration in total bilirubin level (8%), and 9 patients showed alteration in indirect bilirubin level (9%) (Table 1).

Severity of hepatotoxicity classified based on the level of biochemical derangement according to WHO adverse drug reaction grading system showed that mild hepatotoxicity observed in all patients. Comparison between before treatment and 2 months treatment showed a significant increase in the level of AST 51.6±3.92 ($p<0.05$*), ALT 42.7±3.21 ($p<0.05$*), and ALP 129±3.2 ($p<0.01$**), respectively.

Comparison between before treatment and 6 months treatment showed more significant increase in the level of AST 59.9±3.12

(p<0.01**), ALT 51.6±3.66 (p<0.01**), and ALP 131.6±3.2 (p <0.01**), respectively, and a significant increase in the level of GGT 61±3.2 (p<0.05*), respectively. The results were tabulated in Table 2. In the present study, abnormal LFTs parameters were monitored and revealed mild hepatotoxicity in patients receiving antitubercular therapy.

DISCUSSION

In the present study, the pattern of alteration of liver enzymes was evaluated. Hepatotoxicity is the most common adverse effect of anti-TB treatment that leads to interruption of therapy. Retreatment is started only when all biochemical markers of liver injury have returned to normal levels. Patients were confirmed of anti-TB-DIH both by biochemical test by measuring serum level of ALT, AST, and ALP and also clinical monitoring of their signs and symptoms. Once the hepatotoxicity has occurred, all the drugs are withdrawn, and retreatment is started only when all biochemical markers have returned to normal levels. It is well-accepted fact that the risk of adverse effect must be balanced with the benefits of effective TB treatment. Prolong interruption of treatment may lead to undesired drug resistance and may prolong the therapy. In the present study, mild hepatotoxicity was observed in patients initially in lower doses, which were increased on subsequent days with daily monitoring of patient's clinical and biochemical conditions. All the patients were kept under observation for whole the treatment period. None of the patients had reoccurrence of hepatotoxicity later. They completed their anti-TB treatment successfully without any further complication. So, this study revealed that it is possible to reintroduce potentially hepatotoxic agents easily after recovery [11,12]. Mechanism for this adaptation is not known. It was felt that gradually introducing the drugs by giving them in increasing number and dosage is the reason for the successful retreatment procedure [13]. This effect is believed to be the avoidance of hypersensitivity reaction due to the administration of all the drugs at once in high dose. So, careful dose selection of drugs to be used in retreatment and the pattern of dose increment is of paramount importance.

Gulati *et al.* [14] have reported as antitubercular chemotherapy is prone to induce hepatic dysfunction as liver plays a central role in the metabolism and detoxification of these agents, this is more likely to occur in the initial intensive phase therapy with four drugs, *viz*., RIF, INH, PZA, and ethambutol. Such a drug-induced liver dysfunction poses a major problem for effective completion of the course of ATT and hence could influence compliance. Poor compliance may result in stoppage of therapy which not only precipitates recurrence of disease but also results in the development drug resistance and multidrug resistance TB. Hepatoprotective agents are, therefore, of great importance with respect to the control of the disease and its effective chemotherapy [15].

Table 1: Distribution based on abnormal liver function tests

LFT	Number of patients (%)
AST (SGOT)	30 (30)
ALT (SGPT)	22 (22)
ALP	21 (21)
GAMMA GT	10 (10)
Total bilirubin	8 (8)
Direct bilirubin	9 (9)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transpeptidase

Table 2: Liver function test patterns

LFT	Before treatment	After 2 months	After 6 months
AST (U/L)	41.4±2.16	51.6±3.92[a]*	59.9±3.12[b]**
ALT (U/L)	29.6±3.10	42.7±3.21[a]*	51.6±3.66[b]**
ALP (U/L)	103±6.1	129±3.2[a]**	131.6±3.2[b]**
GGT (U/L)	40±5.2	49.5±6.2	61±3.2[b]*
Total bilirubin (mg/dl)	0.8±0.6	2.1±0.9	1.9±0.6
Direct bilirubin (mg/dl)	0.4±0.2	0.6±0.3	0.7±0.3

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transpeptidase, [a]Comparison between before treatment and 2 months treatment, [b]Comparison between before treatment and 6 months treatment, All values are mean±SEM. *p<0.05 is statistically significant when compared. **p<0.01 is statistically significant when compared

Al-Salmi [16] has reported that alternative regimens depend on which drug is implicated as the cause of hepatitis. Reintroducing one drug at a time is the optimal approach, especially if the patient's hepatitis were severe. In this case, after two trials with full dosage of first line ATT, infectious disease (ID) team changed the treatment strategy by introducing one drug at a time. The patient's LFT normalized within 2 weeks. INH was started with ethionamide. RIF was withheld until the bilirubin level became normal. Then, rifabutin was introduced in the place of RIF for its lower liver enzymes induction activity. At this stage, the patient was tolerating the new regimen, and LFT was constantly normal. PZA toxicity depends on its dose, and the most offending abnormal effect is seen at doses of 30 mg/kg/day. Reintroduction of PZA should be avoided once toxicity occurs, as it increases the risk of recurrence [6]. Therefore, the decision of discontinuing PZA was made, and moxifloxacin was added from the second line. Anti Tubercular Therapy (ATT) is among the newer quinolones that has no hepatocellular toxicity and has the most *in vitro* activity against *M. tuberculosis*, followed by levofloxacin, ofloxacin, and ciprofloxacin. With multi-disciplinary clinical approach, pharmacist rounding with ID team plays an integral role in improving antimicrobial therapy process, therapeutic drug monitoring, and adverse drug reaction management.

All patients were under close supervision and monitoring of laboratory and vital signs until medication is tolerated. It was showed that upon restarting of anti-TB drugs; two patients developed hepatotoxicity while the rest tolerated the drugs with minimal elevation of liver enzymes and no clinical symptoms were observed. The present study has important limitations. Our findings may not be widely generalizable as the data emanated from relatively few patients who were hospitalized in a single tertiary hospital. The estimation of incidence was based on symptomatic hepatotoxicity. Because LFT is not routinely repeated following initiation of anti-TBs, patients with asymptomatic hepatotoxicity [7] might have been missed. It was, therefore, also not possible to determine if this group of patients was at increased risk of progressing to the more clinically relevant overt hepatotoxicity. Anti-TB-DIH is not uncommon, needs early recognition and treatment, and is more in patients with pre-existing liver disease and lower BMI.

CONCLUSION

Biochemical abnormalities generally occur before clinical symptoms or signs of liver injury develop. Thus, close monitoring of LFTs can detect the liver injury and the optimal approach in the management and serious prevention of antitubercular liver injury and avoid incompliance of anti-TB treatment. Regular clinical evaluation of patients is recommended, and educating patients regarding signs and symptoms of hepatitis should be continually reinforced. Consensus guidelines for the management of patients with anti-TB treatment-induced hepatotoxicity are yet to be evolved. Therefore, more research and efforts are warranted to enhance the diagnosis and the prevention of anti-TB-DIH.

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