Original Article

Drug induced liver injury due to anti tuberculous chemotherapy in directly observed daily therapy in fifty patients : a retrospective study in Western India

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Drug induced liver injury (DILI) is the most common adverse drug reaction leading to interruption of treatment in tuberculosis (TB). There are limited guidelines and treatment strategies on DILI due to anti TB drugs. (1) To study whether rapid reintroduction of drugs in DILI has any adverse outcome. (2) Rates of recurrent drug induced hepatitis. (3) Does DILI predispose a patient for drug resistant TB. Case record forms (CRFs) of 2113 patients were analyzed for the incidence of DILI. A total of 148 patients were diagnosed with hepatotoxicity and after careful exclusion 50 patients were diagnosed with DILI. All patients were reintroduced with all the drugs together once the hepatitis was resolved. A written informed consent was taken. Incidence of hepatotoxicity was 7%. Incidence of DILI was 2.4%. Female predominance was seen (68%). Majority of patients were suffering from pulmonary TB (72%). A mean of 14.2 days were lost before reintroduction. Recurrent DILI was seen in ten percent of patients (n=5). Six patients developed drug resistant tuberculosis due to interruption of treatment. (p value 0.031). Rapid reintroduction of drugs was well tolerated with recurrence rates of 10%. DILI predisposes a patient to develop MDR TB.

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Key words **: Hepatitis, anti tuberculosis treatment, multi drug resistant tuberculosis.**

Drug induced liver injury (DILI) is the most common adverse drug reaction leading to interruption of treatment in tuberculosis (TB). DILI may sometimes be fatal. The incidence of DILI is increasing steadily. However there are limited guidelines and treatment strategies on hepatotoxicity due to anti TB drugs. DILI remains one of the most challenging disorders faced by pulmonologists during the course of treatment for tuberculosis. The biochemical mechanism and pathogenesis of DILI due to anti TB medications is not entirely clear. It is very difficult to predict which patient will develop DILI. Idiosyncratic DILI is less common as compared to intrinsic DILI and has inconsistent dose response relationship and is more varied in its presentation. Metabolic idiosyncratic reactions appear to be responsible for most responsible for most DILI from anti TB medications. The tuberculosis control program in India has defined DILI as an area which requires priority research. Guidelines for management of DILI due to anti TB medications have been published by the American Thoracic Society (ATS)[1], the British Thoracic Society (BTS)[2] and the Task Force of the European Respiratory Society, the World Health Organization (WHO)[3] and the International Union Against Tuberculosis and Lung Disease[4]. However, there aren't any consensus guidelines or Cochrane reviews on the reintroduction strategies.

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Aim :

(1) Rates of recurrent drug induced hepatitis.

(2 To study whether the rapid reintroduction of drugs in patients with DILI has any adverse outcome.

(3) Does DILI predispose a patient for drug resistant tuberculosis ?

Materials and Methods

A retrospective observational study from a Tuberculosis (TB) outpatient department was conducted in two tertiary care private clinics in the city of Mumbai and Thane. The duration of the study was from March 2010 to December 2016. Patients diagnosed with tuberculosis were put on a weight based standard four drug regimen consisting of isoniazid(H), rifampicin(R), pyrazinamide(Z) and ethambutol(E) as per WHO guidelines. All patients were monitored for liver enzyme (LFT) derangements after the initiation of the drugs with the onset of symptoms of nausea and vomiting and repeated subsequently whenever they had symptoms or routinely weekly after the initiation of the anti – TB drugs. Once a patient was detected to have deranged LFTs, then H, R and Z were stopped. These drugs were withheld till the time liver enzymes returned to less than twice the upper normal limit. Once the enzymes came back to normal, all the three drugs, viz H, R and Z were reintroduced at the full dosage on day one itself[5]. This reintroduction regimen was chosen based on the findings

of a randomized trial published in 2010[5].

Clinical Data :

Accurate history of medication exposure and onset and course of liver biochemistry abnormalities was noted. History of other drug reactions as certain cross-reactivities may exist (eg, anti-epileptics). History of other liver disorders for eg, chronic viral hepatitis, nonalcoholic steatohepatitis, hemochromatosis, alcoholic liver disease, primary sclerosing cholangitis, primary biliary carcinoma, liver cancer was noted. Time interval from initiation of anti-TB drugs to occurrence of DILI was taken as the latency period. The R -value was defined as serumalanine aminotransferase / upper limit of normal (ULN) divided by serum alkaline phosphatase / ULN. Time interval from stopping is oniazid, rifampicin and pyrazinamide and achieving these parameters was taken as the normalization period. Patients were continued with ethambutol (E) and fluoroquinolones (FQ) till the transaminase levels returned to less than twice the upper normal limits[6]. Patients who developed recurrence in liver enzyme elevation after reintroduction of the drugs were again subjected to safe anti TB medications, viz E and FQ, and H, R, Z were sequentially reintroduced to determine the offending agent. All the patients were followed closely for any further increase in tuberculosis symptoms and development of multi drug resistant TB (MDR TB). Liver biopsy was performed in patients in which the elevated transaminase levels (more than 50% from the baseline values) persisted in spite of stopping the offending drug at the end of sixty days[7,8].

Laboratory Data Collection :

Tests to detect markers of acute viral hepatitis (Immunoglobulin M [IgM] anti–hepatitis A virus, Hepatitis B surfaceantigen [HBsAg], IgM anti–hepatitis C virus antibodies, and IgM anti-hepatitis E virus) were performed for all patients who developed features suggestive of DILI while receiving anti-TB drugs[1].An enzyme-linked immunosorbent assay (ELISA) to test for HIV type1 and type 2 was also performed. An abdominal ultrasonography was obtained for each patient to rule out fatty liver or chronicliver disease.

The Diagnostic Criteria for DILI were as follows :

(1) An increase of more than five times the upper limit of the normal levels (>250 IU/L) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) on 1 occasion without symptoms or more than thrice the upper limit of normal (>150 IU/L) with symptoms of anorexia, nausea, vomiting, and jaundice.

(2) An increase in serum total bilirubin more than 1.5 mg/dL[1,6].

During reintroduction of anti-TB drugs, liver function testing was done every fourth day after all the drugs were reintroduced[2]. After the successful reintroduction of anti-TB drugs, regular monitoring of liver function was performed by determination of serum bilirubin level, AST level, ALT level, and serum ALP level every week for the first month. From the second month, laboratory measurement was performed only when patient had recurrence of symptoms.

Exclusion Criteria :

Exclusion criteria observed were serological evidence of acute viral hepatitis, evidence of chronic liver disease on ultrasonography, human immunodeficiency virus (HIV) infection, longterm alcoholism [defined as consumption of more than 48 g of alcohol per day for at least 1 year[9]], concomitant consumption of other potentially hepatotoxic drugs (eg, methotrexate, dapsone, phenytoin, valproate, and fluconazole), pregnancy, and up to three months postpartum.

Statistical Data :

Chi square and paired T test was used. Medcalc version 17.1 was used with the help of a statistician.

Results :

A total of 2113 patients' case record forms were reviewed. Majority of our cohorts were in the age group less than 35 years (65%, n=1370). Of these, 148 patients had hepatitis during the course of the disease (7%). After careful exclusion, 2.4% patients were diagnosed as drug induced liver injury (DILI) (n=50). Mean age was 37.18 (SD 17.62). Age range was 16 to 84 years. Sixty percentage of our study patients were below the age of 35 years (n=30). Percentages of DILI were 2.2 in age less than 35 years and 2.7 in persons more than 35 years (p value 0.42). Female predominance was seen in our study. Two thirds of the participants were females(n=32, 68%). Pulmonary tuberculosis was seen in 72% (n=36) of cases. Only one disseminated TB was seen. Rest 26 % (n=13) were extra pulmonary TB. Of these extra pulmonary TB cases, 90% (n=11) were cervical lymph node tuberculosis. Rest two, were spine TB and abdominal TB, one each. Latency period varied between 02 to 120 days, the average being 18.12 days. (SD 21.03). All patients (n=49) had a latency period within a span of two months. Only one patient had a delayed latency period (120 days). R value was greater than five in 76% of the patients (n=38), between 2 and 5 in 12% of patients (n=6) and less than 2 in 12% of patients (n=6) (Fig 1). The average ALT was 336.16 (SD 303.95), AST was 422.12 (SD 384.48) and total bilirubin was 2.11. In 56% of the patients (n=28), the highest total bilirubin was less than 2.0 g/dL. In these patients, the mean AST

was 519 and ALT was 385. The rate of decline of AST was faster as compared to ALT (Fig 2). The rate of decline of bilirubin was the slowest as compared to all the liver enzymes. The normalization period varied between 05 to 90 days, the average being 14.2 days (SD16.98). Only two patients took more than two months for the liver enzymes to normalize. Of these, one underwent liver biopsy and died during the course of illness. Patients in whom the R value was less than 2 (cholestatic type) took a longer time for the enzymes to come back to normal. Recurrence of DILI was seen in 10 % (n=5) of patients in whom the drugs were reintroduced. Of these, three patients developed MDRTB subsequently. A total of six patients developed MDRTB (12%). Analysis revealed a statistically significant chance of developing MDRTB in patients with DILI as compared to those without DILI (p value 0.031). Death was seen in one patient.

Discussion

Hepatotoxicity during the course of treatment with Anti TB medications may be multi factorial. Factors like alcoholism; viral hepatitis and HIV are amongst commonest confounding causes in any study on DILI. Of all the patients diagnosed with hepatotoxicity (n=148) in our cohorts, only 35% (n=50) were included in the study. The incidence rates varied between 2% to 28% in various studies[10,14]. Majority of our study group were below the age of 35 years (60%) as TB is known if affect the younger productive age group population in developing countries, more so in India. Most of the studies and literature suggest that DILI increases with increasing age. As in our study, none of the studies have demonstrated any statistical significance[11,12,13]. Most of the studies have quoted female predominance. In the Singaporean study by Teleman et al, the risk of hepatotoxicity was four times in women as compared to the male cohorts[11]. The extent of tuberculosis including cavitory disease, multi-bacillary TB and extra-pulmonary organ involvement have been incriminated as positive predictors for TB DILI by some authors[15] while others have failed to note any significant association[16]. In our study, the majority of the patients were pulmonary tuberculosis. This may be due to referral bias.

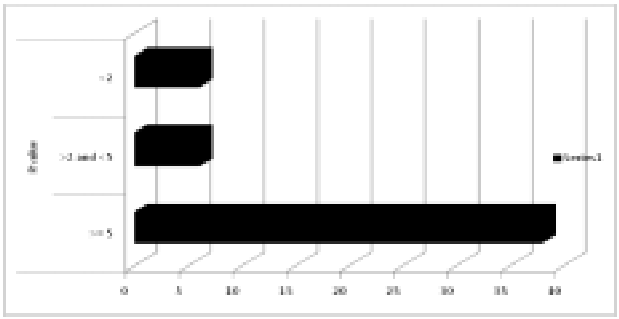

Fig 1 — Number of patients classified according to the R value.
X axis : Number of Patients

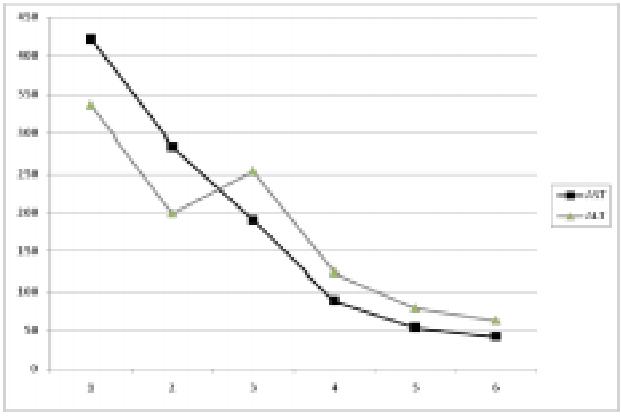

Fig 2 — Enzyme variation over days.
X axis: Number of days. Y axis: Enzyme levels in IU/L. ASt: Aspartate transaminase, ALT: Alanine transaminase

On the basis of the R-value at presentation, DILI can be categorized into hepatocellular,cholestatic, or mixed types. This categorization allows testing for competing etiologiesin asystematic approach[8]. Our study showed majority of the patients being classified as hepatocellular type based on the R value. However, in approximately one fourth of the patients (24%) we could find the other types also suggesting that DILI due anti TB medications had differing presentations. In the study done by Naqvi *et al* in Pakistan, 63% of their patients had hepatocellular pattern while mixed and cholestatic was found in 23 and 13% respectively[17].

Cholestatic DILI takes longer to resolve than the hepatocellular DILI[8].

There are no studies validating the utility of liver biochemical tests in prevention of DILI or assessing its severity. Such monitoring is often seen as inconvenient, expensive and inefficient by both patients and doctors, and thus the monitoring recommendations are poorly followed[18,19]. However, monitoring with liver tests is recommended in the following groups: patients who consume alcohol, individuals with chronic hepatitis B or C, and those on concomitant hepatotoxic drugs, have elevated baseline transaminase levels, and suffer from underlying liver disease and those with HIV[1,19].

In general, persistence of biochemical abnormalities lowers the threshold for liver biopsy. The majority of DILI cases show steady decline in liver biochemistries after the presumed drug is stopped. This observation is often referred to as “washout” or “de-challenge” and is a major factor in DILI diagnostic scoring algorithms[8,20]. Persistence of elevations weakens the case for DILI, thereby strengthening the possibility of other diagnoses[8]. The cut-off time for a significant decrease in alanine aminotransferase is 60 days[20]. For cholestatic injury, lack of significant drop in alkaline phosphatase or bilirubin (>50% drop in peak-ULN or drop to less than twice ULN) at 180 days

is considered significant. Liver biopsy at 60 days for unresolved acute hepatocellular and 180 days for cholestatic DILI is recommended[8].

Various guidelines[1,8] mention avoidance of reintroduction of offending drugs whenever possible. They also advocate complete stoppage of pyrazinamide in the regimen. Considering that first line anti-TB drugs are highly effective and relatively in expensive, benefits of re-challenge must outweigh its risks; it is unwise to discard these drugs from the regimen. Therefore, it is acceptable to attempt reintroduction of these medications[4,21].

In the study by Sharma *et al*, 11%–24% of patients, re-exposure to the same drug regimen led to recurrence of DILI[5] and positivere-challenge was not affected by the degree of initial injury[5]. Our study showed a recurrence of 10%.

Our study also showed higher incidence of MDR TB in patients with DILI, more so in patients with recurrent DILI. Our study showed a statistically significant increased chance of MDR TB in these patients of DILI. We couldn't find any studies which showed increased incidence of MDRTB in patients with DILI.

Drawbacks of the Study:

It was not clear which drug caused the hepatotoxicity as all the drugs were reintroduced simultaneously. It was possible that many study patients might have had hepatic adaptation or indeterminate unrelated hepatic events[22]. In this study, treatment interruption might have been done because of a concern of evolving hepatotoxicity rather than established hepatotoxicity as in the original study[5]. Excluding patients with preexisting liver disease or who were at greater risk for hepatotoxicity could have resulted in some observation bias.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.Written informed consent was obtained from all patients.

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