Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity

Rohit Singla, Surendra K. Sharma, Alladi Mohan**, Govind Makharia†, V. Sreenivas‡, Brajesh Jha, Sanjeev Kumar, Pawan Sarda & Sarman Singh§

Departments of Medicine, †Gastroenterology, ‡Biostatistics & §Laboratory Medicine, All India Institute of Medical Sciences, New Delhi & **Department of Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati, India

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Background & objectives: Antituberculosis (anti-TB) drug-induced hepatotoxicity (DIH) 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. Several risk factors for hepatotoxicity have been suggested in previous studies. We undertook a prospective case-control study to assess the role of these putative risk factors in the development of DIH in patients receiving anti-TB treatment.

Methods: One hundred and seventy five consecutive cases with a diagnosis of anti-TB DIH were compared with 428 consecutive controls who took anti-TB drugs for the full duration of chemotherapy without clinical or biochemical evidence of hepatitis. Cases positive for markers of acute viral hepatitis were carefully excluded. Cases and controls were compared with respect to age, sex, site of tuberculosis, radiological extent of disease on chest radiograph, body mass index (BMI), mid-arm circumference (MAC) and liver function at baseline which included serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum total protein and serum albumin.

Results: Univariate logistic regression revealed that the risk of developing DIH was greater in older patients. Significantly greater percentage of cases had extrapulmonary tuberculosis (TB) (P<0.01). Also, a significantly higher percentage of cases had moderate to far advanced disease severity on chest radiograph (P<0.01). On multivariate logistic regression, the adjusted odds were significant (P<0.01) for age >35yr, MAC <20cm and hypoalbuminaemia (albumin <3.5 g/dl).

Interpretation & conclusions: Older age, poor nutritional status including baseline hypoalbuminaemia were independent predictors of occurrence of anti-TB DIH. Clinicians should be vigilant for occurrence of hepatotoxicity in this high risk group.

Key words Alanine aminotransferase - albumin - alkaline phosphatase - aspartate aminotransferase - body mass index - drug-induced hepatotoxicity - HIV - mid-arm circumference - tuberculosis
In 1993, the World Health Organization (WHO) declared tuberculosis (TB) to be a ‘global emergency’ with more than a third of the world’s population infected. Globally, 8.9 million new cases of TB occur annually, of which 1.8 million (20%) occur in India. Anti-TB chemotherapy containing isoniazid (H), rifampicin (R) and pyrazinamide (Z) has proven to be highly effective but hepatotoxic. Anti-TB drug induced hepatotoxicity (DIH) is the most common side-effect leading to interruption of therapy. Risk of anti-TB DIH is increased when these drugs are combined.

Wide variations have been found in the reported incidence of hepatotoxicity during short-course chemotherapy. From an analysis of pooled data from four prospective Indian studies, the risk of clinical hepatitis was calculated to be 11.5 per cent (95% CI 9.51 to 13.51), whereas meta-analysis of 14 published studies from west found the risk to be 4.28 per cent (95% CI 3.38 to 5.28). Several risk factors for hepatotoxicity have been suggested such as advanced age, sex, poor nutritional status, liver disease, inappropriate use of drugs, infection with hepatitis B virus (HBV), hepatitis C virus and human immunodeficiency virus (HIV), acetylator status, and high alcohol intake. We report here the findings of a prospective case-control study done to assess the role of these putative risk factors in the development of hepatitis in patients receiving anti-TB treatment.

**Material & Methods**

*Patients and controls:* This prospective case-control study was performed on patients with a diagnosis of DIH attending the out-patient department or admitted to the Medicine Wards of the All India Institute of Medical Sciences hospital, New Delhi and Sri Venkateswara Institute of Medical Sciences, Tirupati. A total of 175 consecutive patients who developed clinical and/or laboratory evidence of DIH while on anti-TB drugs, between 2004 and 2009, were included. These patients met the following diagnostic criteria for DIH: (i) a rise of five times the upper limit of the normal levels (50 IU/l) of serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) on one occasion or more than three times (> 150 IU/l) on three consecutive occasions; (ii) a rise in the level of serum total bilirubin level > 1.5 mg/dl; (iii) any increase in serum AST and or ALT above pre-treatment values together with anorexia, nausea, vomiting and jaundice; (iv) absence of serological evidence of infection with hepatitis viruses A, B, C, or E; and (v) improvement in liver functions (serum bilirubin < 1 mg/dl, AST and ALT <100) after withdrawal of anti-TB drugs. DIH was diagnosed if any one of the criteria 1, 2 or 3 was present along with criteria 4 and 5.

Four hundred and twenty eight consecutive patients diagnosed to have TB and treated with anti-TB drugs for the full duration of chemotherapy without clinical or biochemical evidence of hepatitis formed the controls for this study. Controls were observed during the same study period with regular follow up of liver function tests. The patients and controls were in the age group of 16-65 yr. Subjects outside this age range were excluded. Written informed consent was obtained from all patients. Institutional Ethics Committees of both the institutions approved the study protocol.

*Study design:* The site of TB, method of establishing the diagnosis of TB, history of chronic liver disease, history of concomitant intake of other hepatotoxic drugs and alcohol intake were recorded. The details of anti-TB drugs (nature of drugs, dosages, duration of treatment and patient’s compliance) were noted. The radiological extent of disease on chest radiograph was recorded and categorized as minimal, moderately and far advanced as described by the National Tuberculosis Association of USA. Past and family history of TB was also recorded. The nutritional status was estimated by calculating the body mass index (BMI (kg/m²)) and mid-arm circumference (MAC (cm)). Patients with BMI range of 18.5 - 24.9 kg/m² were considered to have normal nutritional status. Time interval from initiation of anti-TB drugs to occurrence of DIH was taken as the latent period.

Laboratory investigations including haemogram, blood biochemistry with detailed liver functions (serum bilirubin, AST, ALT, alkaline phosphatase (ALP), serum total protein, serum albumin) were performed in all patients using standard laboratory procedures.

Markers of acute viral hepatitis [immunoglobulin (Ig) M anti-hepatitis A virus (Immuno LISA Organics, Israel), IgM anti-hepatitis B core antigen and/or hepatitis B surface antigen (Microelisa System, BIOMERIEUX, Netherland), IgM anti-hepatitis C virus antibodies (Microelisa System, BIOMERIEUX, Netherland) and IgM anti-hepatitis E virus (Immuno LISA, Organics, Israel)] were performed in all patients who developed features suggestive of DIH while on anti-TB drugs. Serological testing for evidence of HIV 1, 2 infection (enzyme linked immunosorbent assay) was also done. Abdominal ultrasonography was done in all patients.
to rule out fatty liver or chronic liver disease. Those patients whose sera tested positive for markers of viral hepatitis and/or were receiving other potentially hepatotoxic drugs or had ultrasonography evidence of chronic liver disease were excluded from study. HIV positive patients, chronic alcoholics who consumed >48 g of alcohol/day for at least 1 year were excluded. Patients receiving other potentially hepatotoxic drugs (e.g., methotrexate, phenytoin, valproate, fluconazole), pregnant women and subjects not giving written informed consent were also excluded from the study.

Patients with DIH satisfying the exclusion criteria were enrolled into the study. The hepatotoxic drugs H, R and Z were immediately stopped. Patients were started on a regimen consisting of non-hepatotoxic anti-TB drugs, consisting of ethambutol, streptomycin, and one of the flouroquinolones. Patients were subsequently followed up at weekly intervals until clinical and biochemical parameters of acute liver injury stabilized, i.e., absence of vomiting and pain abdomen, both AST and ALT <100 IU/l and serum bilirubin < 1.0 mg/dl. Time interval between stopping H, R, Z and achieving the above mentioned parameters was taken as normalization period.

Statistical analysis: Cases and controls were compared using the Student’s t-test for continuous variables and the Chi-square test for dichotomous variables. Cornfield 95 per cent confidence limits were computed. Univariate logistic regression was performed on all clinical and baseline laboratory parameters to calculate odds ratio and then multivariate logistic regression was performed on all significant (P<0.1) parameters to calculate adjusted odds ratio. Age, BMI, MAC and serum albumin were converted into categorical variables while performing logistic regression. Statistical software package STATA 9.2 was used for data analysis.

Results

Two hundred and thirty seven consecutive patients who developed features suggestive of DIH while on anti-TB drugs, were observed. Four of them died (3 due to acute liver failure and one due to progressive pulmonary tuberculosis leading to acute respiratory failure). Fifty eight patients were excluded for various reasons; 11 were chronic alcoholics, 5 were on hepatotoxic drugs (mainly phenytoin), and 17 were HIV seropositive. Serological evidence confirmed recently acquired acute viral hepatitis in 25 patients, of whom 4 (16%) had hepatitis A, 4 (16%) had hepatitis B, 3 (12%) had hepatitis C and 14 (56%) had hepatitis E. Remaining 175 patients formed DIH cases for the present study. Of these, 12 (6.9%) were asymptomatic, diagnosed by transaminitis alone whereas 158 of them suffered from nausea (90.2%), pain abdomen 49 (28%), vomiting 115 (65.7%) or jaundice 76 (43.4%). Only 25 (14.3%) of the 175 DIH cases had received DOTS (three-weekly intermittent treatment) in accordance with the Revised National Tuberculosis Control Programme guidelines. The remaining 150 (85.7%) patients were on daily treatment with the standard 4-drug regimen as prescribed by their physicians. Among DIH cases, the median latent period for occurrence of DIH was 23 days [interquartile range (IQR) 14 to 44 days] and median normalization time was 18 days (IQR 14 to 28 days).

Age was significantly higher in DIH cases (P<0.01) as compared to controls. MAC, pre-treatment serum protein (P<0.01) and serum albumin (P<0.001) were significantly lower among cases as compared to controls.

### Table I. Comparison of clinical and baseline laboratory parameters between cases and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n=175)</th>
<th>Controls (n=428)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.1 ± 13.55</td>
<td>30.22 ± 12.91</td>
</tr>
<tr>
<td>Females (%)</td>
<td>45.79</td>
<td>51.43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.37 ± 3.10</td>
<td>19.79 ± 3.71</td>
</tr>
<tr>
<td>MAC (cm)</td>
<td>21.78 ± 3.40</td>
<td>23.68 ± 3.90</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>0.69 ± .26</td>
<td>0.67 ± .14</td>
</tr>
<tr>
<td>Serum total proteins (g/dl)</td>
<td>7.59 ± 0.69</td>
<td>7.79 ± 0.90</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.85 ± 0.63**</td>
<td>4.27 ± .74</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>36.18 ± 11.40</td>
<td>36.18 ± 15.02</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>34.81 ± 12.84</td>
<td>32.08 ± 18.11</td>
</tr>
<tr>
<td>Serum ALP (IU/l)</td>
<td>183.32 ± 80.82</td>
<td>183.47 ± 113.68</td>
</tr>
</tbody>
</table>

Values are given as mean ± standard deviation; BMI, body mass index; MAC, mid-arm circumference; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

### Table II. Maximum derangement of liver functions in cases with anti-TB drug induced hepatotoxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum serum bilirubin (mg/dl)</td>
<td>2.45 ± 2.30</td>
<td>1.8 (0.5 - 16.5)</td>
</tr>
<tr>
<td>Maximum AST (IU/l)</td>
<td>333.98 ± 305.56</td>
<td>235 (56 - 1934)</td>
</tr>
<tr>
<td>Maximum ALT (IU/l)</td>
<td>331.48 ± 280.67</td>
<td>239 (52 - 1618)</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.56 ± 0.75</td>
<td>3.47 (1.8 - 5.4)</td>
</tr>
<tr>
<td>Maximum serum ALP (IU/l)</td>
<td>274.73 ± 148.24</td>
<td>232 (32 - 883)</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase
controls (Table I). However, in both cases and controls, pretreatment values were within the acceptable levels for serum total proteins (>7.5 g/dl) and serum albumin (>3.5 g/dl). Table II shows the peak derangement of liver function at the time cases were diagnosed with DIH.

Pulmonary TB was present in 45 (25.7%) DIH cases and 204 (47.6%) controls. Extrapulmonary TB was observed in 97 (55.4%) cases and 144 (33.6%) controls; and miliary/disseminated TB was present in 33 (18.9%) cases and 80 (18.7%) controls. The site of TB was significantly different between cases and controls with more cases having extrapulmonary TB ($P < 0.01$). Also, a significantly higher percentage of DIH cases had moderate to far advanced disease severity on chest radiograph ($P < 0.01$). Furthermore, patients with greater disease severity on chest radiograph were more likely to develop anti-TB DIH. Anand et al have reported similar findings. Hence, regular monitoring of liver function tests should be deemed mandatory in this group of patients. Previous studies have also shown an increased risk of DIH in women [21, 23, 28, 29]. However, female gender was not found to be a predictor for the development of anti-TB DIH in the present study.

Several studies have reported that the risk of anti-TB DIH increases with advancing age [21-26] with a few failing to show it [27]. Our study clearly showed that DIH induced by anti-TB treatment was more frequent in older patients ($P < 0.01$), with 61 per cent more chances to develop DIH in adults in the age range of 35-65 yr as compared to younger adults. Previous studies have also shown an increased risk of DIH in women [21, 23, 28, 29]. However, female gender was not found to be a predictor for the development of anti-TB DIH in the present study.

We observed a disproportionally higher risk of developing DIH in patients with extrapulmonary TB, most of whom had abdominal tuberculosis. This may suggest that this group of patients may have subclinical hepatic involvement also which predisposes them to develop anti-TB DIH. Anand et al have reported similar findings. Hence, regular monitoring of liver function tests should be deemed mandatory in this group of patients. Among the subgroup of patients with pulmonary TB, we observed that patients with greater disease severity on chest radiograph were more likely to develop anti-TB

| Table III. Results of significant variables as observed on univariate and multivariate logistic regression analysis with DIH as outcome variable |
| Variable | Odds ratio (95% CI) | Adjusted Odds ratio (95% CI) | $P$ value |
| Age >35 yr | 2.14 (1.49 - 3.07) | 1.61 (1.24 - 2.08) | < 0.01 |
| MAC < 20 cm | 2.70 (1.72 - 4.16) | 2.56 (1.58 - 4.15) | < 0.01 |
| Hypoalbuminaemia (serum albumin <3.5 g/dl) | 2.80 (1.82 - 4.30) | 1.95 (1.22 - 3.10) | < 0.01 |

DIAH, drug induced hepatotoxicity; CI, confidence intervals.
DIH. This finding was in agreement with observations from a previous study.30

Poor nutritional status has been considered to be one of the factors contributing to a higher incidence of DIH induced by short-course chemotherapy for TB in the developing countries.31,32 Drug metabolism pathways including acetylation pathways have been shown to be deranged in states of protein energy malnutrition33. In our study we evaluated nutritional status with the help of BMI, MAC and serum albumin. Although BMI of cases was lower as compared to controls, the difference was statistically insignificant. MAC < 20 cm and hypoalbuminaemia were recognized as a positive predictor of occurrence of DIH, even after adjusting for other variables in the multivariate logistic regression.

Our present study has several merits. We compared a fairly large number of DIH cases with controls. Such a large sample size has not been studied in previous studies. Also, we carefully excluded patients with acute viral hepatitis by performing markers of acute viral hepatitis in all patients who developed features suggestive of DIH. Besides, we also excluded chronic alcoholics, patients with chronic liver disease and patients concomitantly consuming other hepatotoxic drugs as these conditions can produce changes mimicking DIH. As a result, pre-treatment serum AST, ALT and bilirubin were in the normal range, and also were similar among cases and controls. HIV-infected patients were also excluded as these patients receive potentially hepatotoxic drugs and hepatitis in these patients may also be due to opportunistic infections. A few limitations were also present in this study. Being a case-control study it cannot give accurate risk ratios for the development of hepatitis in patients given anti-TB drugs in the presence of these putative risk factors.

To conclude, anti-TB DIH is a relatively common problem. Acute viral hepatitis should be ruled out, especially in countries like India that are endemic for it. The present study identified age, site of TB, disease severity on chest radiograph, MAC, baseline serum protein and serum albumin as risk factors for anti-TB DIH with age > 35 yr, MAC < 20 cm, baseline hypoalbuminaemia being independent predictors of occurrence of anti-TB DIH on multivariate logistic regression. This high risk group should be clearly identified prior to initiation of anti-TB drugs, and monitored carefully for occurrence of hepatotoxicity.

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References


Reprint requests: Dr S.K. Sharma, Chief, Division of Pulmonary, Critical Care & Sleep Medicine, Professor & Head, Department of Medicine All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029, India
e-mail: sksharma@aiims.ac.in, surensk@gmail.com