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Original article

Reintroduction regimens in anti-tubercular therapy-induced hepatitis in extra-pulmonary tuberculosis patients – A pilot study

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ABSTRACT

Background: Anti-tubercular therapy-induced hepatotoxicity (AIH) is associated with a significant mortality. Reintroduction of anti-tuberculosis drugs in patients with AIH has never been studied systematically. The present study was planned to see the best reintroduction regimen in patients of AIH.
Methods: The trial was conducted on 32 patients (divided into three groups) of extra-pulmonary tuberculosis who developed AIH. In group 1 – Isoniazid (INH) and Rifampicin (RIF) were given from day 1. In group 2 – RIF was given from day 1 and INH from day 8. In group 3 – INH was given from day 1 and RIF from day 8. Pyrazinamide was added when above regimens were tolerated.
Results: The incidence was found to be highest in patients with tubercular meningitis (41%) followed by abdominal, pericardial, disseminated, spinal, and lymph nodes. In the study, 21% patients had recurrence of AIH with majority of patients having tolerated the reintroduction of drugs. The success rate of group 1 came out to be 60%, 72.72% in group 2 and 100% in group 3.
Conclusion: The recurrence rate of hepatotoxicity was statistically insignificant between the three groups ($p > 0.05$), and thus all three hepatotoxic drugs can be reintroduced safely in patients developing AIH.

1. Introduction

Tuberculosis continues to remain a significant infectious disease across much of the developing world. It exacts a significant socioeconomic burden on the individual and society. Treatment of tuberculosis (TB) involves several drugs in combination for six or more months. Many of the commonly used anti-tuberculosis drugs are associated with significant potential of causing hepatotoxicity resulting in substantial morbidity and mortality and diminishes treatment effectiveness.[1] Approximately 20% of the global populations with tuberculosis (3.32 million) live in India.[2] Therefore, number of patients with anti-tuberculosis induced hepatotoxicity (AIH) in India may be substantial. While the occurrence of drug induced hepatitis is difficult to predict, it has been observed that certain patients are at higher risk of developing drug induced hepatitis during the course of anti-TB chemotherapy. These include patients with pre-existing liver diseases, particularly those associated with chronic viral infection due to hepatitis B, hepatitis C, and HIV, the alcoholics, the elderly and the malnourished.[3–5]

A meta-analysis of anti-tuberculosis therapy (ATT)-associated hepatotoxicity reported that the frequency of overt clinical hepatitis caused by isoniazid, rifampicin, or both together was 0.6%, 1.1%, and 2.6%, respectively.[6] The spectrum of ATT-induced hepatotoxicity is diverse, ranging from asymptomatic rise in aminotransferases (to fivefold) in 2.3–28% to acute liver failure (ALF) in approximately less than 0.01% of the individuals.[7–10] However, the frequency of ATT-induced hepatotoxicity among Indians seems to be higher (11.5%) than that for the white population (4.3%).[6]

Anti-TB-induced hepatotoxicity is associated with a mortality of 6–12% if these drugs are continued after the onset of symptoms.[11] The risk of hepatotoxicity is increased when the drugs are combined.

The exact role of regular monitoring of liver function tests in patients receiving anti-TB drugs remains controversial. Certain guidelines only emphasize the need of clinical monitoring without mentioning regular biochemical monitoring.[12,13] Transient changes in alanine transaminase and bilirubin level are relatively

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common during anti-TB chemotherapy and do not signify true hepatotoxicity. However progressive rise in alanine transaminase and bilirubin levels is much more ominous.

Hepatotoxicity among patients with pulmonary tuberculosis is 25.7%, 55.4% in extra-pulmonary tuberculosis and 18.9% in disseminated or miliary tuberculosis.[14]

Worldwide, different reintroduction regimens have been advocated, but no consensus guidelines are available. Reintroduction of anti-tuberculosis drugs in patients with ATT-induced hepatotoxicity has never been studied systematically. Also there is lack of any data suggesting ATT-induced hepatotoxicity in patients with extra-pulmonary tuberculosis. We aim to compare the safety of three different reintroduction regimens of anti-tuberculosis drugs in patients with ATT-induced hepatotoxicity in extra-pulmonary tuberculosis. The present study was planned to see the clinical profile of these patients of ATT induced hepatotoxicity and the response to reintroduction of therapy.

2. Methods

A randomized controlled trial was conducted on 32 patients in the Department of Internal Medicine, Maulana Azad Medical College and associated Lok Nayak Hospital, a tertiary care referral centre in New Delhi, India. The study was approved by Institutional Ethical Committee and a written informed consent was obtained from all patients prior to their inclusion in this study.

To detect a difference a 7% between Isoniazid + Rifampicin vs Isoniazid alone at a 95% confidence and 80% power, the sample size would be 1000. The study was done as a pilot and enrolled 32 subjects.

Block randomization was done, which was computer generated offsite and placed in opaque sealed envelopes.

Study subjects included patients with extra-pulmonary tuberculosis who developed ATT-induced hepatitis on anti-tuberculosis treatment.

Patients with drug induced hepatotoxicity satisfying the criteria mentioned in Table 1 were enrolled into the study. Patients with past history of tuberculosis, any liver illness, and use of hepatotoxic drugs, alcohol, pregnancy, acute viral hepatitis and HIV infection were excluded. Treatment with the hepatotoxic drugs (isoniazid, rifampicin, and pyrazinamide) was stopped once diagnosis of ATT-induced hepatitis was established. Patients were subsequently followed up at weekly intervals until clinical and biochemical parameters of acute liver injury stabilized (i.e., absence of vomiting and abdominal pain, both AST and ALT levels 40 IU/L, and serum bilirubin level 1.0 mg/dL). Time interval between stopping isoniazid, rifampicin and pyrazinamide and achieving these parameters was taken as the normalization period. After stabilization of liver functions, the patients were randomized into 1 of the three groups (Table 2).

Analysis was performed using computer software SPSS for Windows, version 18. Quantitative data were expressed as Mean ± Standard Deviation. Group mean values were analyzed by analysis of variance (ANOVA), and the proportions were compared with use of the Chi-square test and Fisher's exact test. Associations with a p value < 0.05 were considered to have statistical significance.

Table 1
Clinical chemistry criteria for drug-induced hepatotoxicity – any of the following.

- More than or equal to fivefold elevation above the upper limit of normal for alanine aminotransferase
- More than two or equal to twofold elevation above the upper limit of normal for alkaline phosphatase (particularly with accompanying elevations in concentrations of 5′-nucleotidase or gamma-glutamyl transpeptidase in the absence of known bone pathology driving the rise in alkaline phosphatase level
- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of bilirubin concentration exceeding 2 times upper limit of normal

Table 2
Reintroduction therapy would be divided into 3 groups-.

Group 1	Isoniazid and rifampicin at full dosages from day 1
Group 2	Rifampicin at maximum dosage from day 1 and isoniazid at maximum dosage from day 8
Group 3	Isoniazid at maximum dosage from day 1 and rifampicin at maximum dosage from day 8 Pyrazinamide was added if they tolerated the above regimen in 3 weeks and patients were then followed up for another 3 weeks with liver function tests

3. Results

The mean age of presentation in the study was 29.37 ± 13.497 years (Table 3) which is a decade earlier than the western population. A female preponderance (66%) was seen. The incidence was found to be highest in patients with tubercular meningitis (41%) followed by abdominal (19%), pericardial (13%), disseminated (9%), spinal (9%), and lymph node tuberculosis (6%). Approximately 34% patients with AIH were receiving treatment from DOTS as compared to 66% on physician prescription. The mean BMI of patients was in the low normal range i.e.19.53 ± 2.05 kg/m^2 (Table 3), a parameter which has been scarcely studied as a risk factor for development of hepatotoxicity. The mean latent period for development of AIH was 7.84 days ± 6.149 days and the median normalization days for liver functions was 8.81 ± 4.22 days (3–21) (Table 3). The values of maximum derangement of liver function test in the study groups prior to and after reintroduction of anti-tubercular treatment did not show any statistical difference (Tables 4 and 5). In the study, 21% patients had recurrence of AIH with majority of patients having tolerated the reintroduction of drugs. In the present study, an increased severity of the first episode of AIH did not confer an increased risk of recurrence (Table 6). Pyrazinamide was introduced after establishing isoniazid and rifampicin safety, thus emphasizing the role of gradual reintroduction of ATT to avoid the combined effects of hepatotoxicity. Of the 7 patients developing recurrence of AIH, 4 were in group 1, 3 in group 2 and none in group 3 (Table 7). The success rate of group 1 came out to be 60%, 72.72% in group 2 and 100% in group 3. On statistical analysis using ANOVA, fisher exact test and chi-square method, no statistical difference (p-value = 0.07) was found

Table 3
Baseline parameters of the three groups.

Parameters	Group 1 (n = 10)	Group 2 (n = 11)	Group 3 (n = 11)	p-value
Age, years	31 ± 12.93	32.18 ± 15.36	25.09 ± 12.112	0.435
BMI, kg/m^2	19.87 ± 2.44	19.88 ± 1.73	18.86 ± 1.97	0.427
Haemoglobin, gm%	11.13 ± 2.19	11.31 ± 1.34	10.72 ± 1.90	0.745
ESR, mm/h	54.10 ± 26.15	56.64 ± 12.68	69.91 ± 11.75	0.104
S. Albumin, g/dL	3.22 ± 0.49	3.36 ± 0.40	3.23 ± 0.51	0.742
Latency period, days	7.10 ± 3.95	9.27 ± 9.24	7.09 ± 3.78	0.651
Normalization period, median days (range)	10.20 ± 4.82 (4–18)	9.64 ± 5.25 (3–21)	6.73 ± 1.10 (4–8)	0.132

Table 4
Baseline liver function tests in the three groups.

Parameters	Group 1 (n = 10)	Group 2 (n = 11)	Group 3 (n = 11)	p
S. Bilirubin, mg/dL	0.56 ± 0.11	0.55 ± 0.16	0.60 ± 0.14	0.636
S. Albumin, g/dL	3.20 ± 0.4	3.36 ± 0.40	3.23 ± 0.51	0.742
AST, IU/L	29.10 ± 8.5	33.27 ± 9.89	26.91 ± 9.23	0.278
ALT, IU/L	32.10 ± 7.52	33.91 ± 10.47	30.27 ± 9.02	0.651
ALP, IU/L	109.90 ± 55.09	123.45 ± 53.82	94.73 ± 53.30	0.469

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