ORIGINAL ARTICLE

A Prospective Evaluation of Predictive Risk Factors, Severity of Liver Injury and Course of Anti –Tubercular Treatment Induced Hepatotoxicity

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ABSTRACT

Background: Hepatotoxicity is an established complication of Anti-tubercular treatment. However, there is limited information on the incidence, possible predictive risk factors and course of anti- tubercular treatment induced hepatotoxicity.

Objective: The study was planned to evaluate incidence, possible predictive risk factors and course of anti-tubercular treatment induced hepatotoxicity (ATTIH) .

Methodology: The present prospective study was conducted with Newly diagnosed pulmonary and extra-pulmonary tuberculosis patients admitted from may 2014 to may 2016.A sample size of 150 patients were put on ATT ranging from 6 months to 12 months depending on type of Tuberculosis. Their pretreatment clinical, biochemical and radiological parameters were recorded. These parameters were compared between cases and controls by appropriate statistical methods. Patients with abnormal base line LFT'S, Treatment defaulters, failure, MDR cases and patients with NASH, cirrhosis ,acute viral hepatitis &/or renal or cardiac disease were excluded from this study.

Results: Out of 150 patients 22 patients (14.7%) developed ATTIH. Among 22 patients 15 (68.2%) were females and 7 (31.8%) were males. Higher incidence of ATTIH was seen in patients with low BMI of 18.99kg/m^2(45.16%), pretreatment low serum albumin <2.5gm(65.21%), Corrected calcium < 7.9gm/dl(58.8%), Serum cholesterol < 200mg/dl (59.1%), Extra pulmonary TB(69.3%), concomitant paracetamol intake(77.7%). Age and consanguinity were statistically insignificant. In this study 18 patients (81.81%) developed ATTIH within 2 weeks of starting ATT with average of 9 days and severity of liver injury ranged from mild with ALT (51-250IU/L) in 12(54.5%), intermediate (251-500IU/L) in 7 (31.8%) and severe (ALT >500IU/L) in 3(13.6%). Normalization of LFTs after ATTIH was seen within first 2 weeks in 11(50%) patients with average of 11 days. ATTIH was associated with prolongation of expected treatment duration in 16 (72.7%) patients. Recurrence of ATTIH was not seen in any patient on reintroduction of treatment. Among 22 patients, 19(86.36%) were cured, 2(9.1%) expired and 1 patient lost follow up.

Conclusion: Early identification of predictive risk factors, modification of treatment with close monitoring and hospitalization are required for reducing morbidity, mortality and treatment completion in ATTIH.

Key words: Tuberculosis, Anti-tubercular treatment induced hepatitis (ATTIH), Prolongation of treatment.

INTRODUCTION

Tuberculosis is a global emergency. More than 90% of global tuberculosis cases and deaths occur in developing world. An effective control has been achieved by wide spread use of anti-tubercular drugs. Hepato-toxicity is well known with, anti-tubercular Treatment[1,2,3], severity of which ranges from mild alteration in liver enzymes to hepatitis and occasionally complicated by liver failure carrying high mortality unless transplanted. Drug induced hepatotoxicity is potientially serious adverse effect of currently used regimens containing isoniazid, rifampicin and pyrazinamide[1,2,3]. Single agent prophylaxis in TB with Isoniazid resulted in transaminitis in 20% patients but only 1% had severe liver necrosis requiring withdrawal of drug [4]. Several types of drug induced liver damages have been described; 1). Idiosyncratic damage, 2) Dose dependent toxicity, 3). Induction of liver enzymes, 4). Drug induced acute hepatitis, 5). Allergic reactions[5,6,7]. Factors implicated in the development of ATTIH are; 1) Advanced age, 2) Female sex, 3) Alcoholism, 4) Underlying liver disease, 5) Acetylator phenotype, 6) N- acetyl transferase activity, 7) Glutathione S transferase activity, 8) HIV infection, 9) Extensive disease, and 10) Malnutrition[8].

Criteria[9] for ATTIH includes at least one of them; 1) A rise of 5 times the upper limit of normal levels of AST/ALT. 2) A rise in the level of serum total bilirubin >1.5mg/dl. 3) Any increase in ALT/AST above normal levels with nausea, vomiting, anorexia and jaundice. If the transaminase levels are < 5 times upper limit, toxicity was considered mild, 5-10 times moderate and > 10 times as severe[9]. The present study was planned to evaluate incidence, possible predictive risk factors and course of anti-tubercular treatment induced hepatotoxicity (ATTIH)

METHODOLOGY

The study was conducted in department of general medicine of Sheri Kashmir institute of medical sciences (SKIMS) Srinagar, Kashmir. A total of 150 Newly diagnosed pulmonary and extra-pulmonary tuberculosis patients admitted from May 2014 to May 2016 were studied. All patients were put on ATT ranging from 6 months to 12 months depending on type of TB. Patients who developed ATTIH were considered as cases and those not, as controls. All patients had pre treatment evaluation for the evidence of liver diseases, body weight & BMI, history of alcoholism or concimitant drug therapy and laboratory evaluation including complete hemogram, albumin levels, serum cholesterol, LFTs and USG abdomen. Malnutrition was defined as BMI of < 18.99kg/m^2. Viral markers were considered to exclude viral hepatitis. Presence of fatty liver was excluded on the basis of USG. These parameters were compared between cases and controls. Patients with abnormal base line LFT'S, Treatment defaulters, failure, MDR cases and patients with NASH, cirrhosis ,acute viral hepatitis &/or renal or cardiac disease were excluded from our study.

Statistical Analysis: Statistical software SPSS version 20.0 and Microsoft excel were used to carry out the statistical analysis of the results obtained from the study. Data was analyzed by means of descriptive statistics viz, mean, standard deviation, percentages and presented by means of bar diagrams . For parametric data Students independent t-test was employed. Chi square test or Fishers exact test, which ever appropriate was used for non- parametric data. P – value of less than 0.05 was considered statistically significant.

RESULTS

A total of 150 Newly diagnosed pulmonary and extra-pulmonary tuberculosis patients were studied, 73 (48.7%) were males and 77 (51.3%) were females, out of 150 patients 22 (14.7%) developed ATTIH. Higher incidence of ATTIH was seen in females 15(68.2%), thus female gender was statistically significant risk factor for ATTIH (p <.05)

Table 1: Incidence and Pretreatment characteristics with predictive value of ATTIH

Variables	cases	controls	p value
Total patients	22(14.70%)	128(85.3%)	
Sex M:F	7:15	66:62	<0.05
Age	32 ±11.2	34 ±14.5	0.068
BMI ratio (M±2SD)	17.22 ±2.75	21.50 ±2.31	<0.05
Albumin (M±2SD)	2.8 ±1.12	4.1 ± 8	<0.05
Calcium (M±2SD)	7.2±1.6	9.8 ±1.2	<0.05
Cholesterol (M±2SD)	175 ±17.34	252 ±18	<0.05

Table 2: Alteration of liver function tests in patients of ATTIH

Patients with ATTIH	N (n= 22) (%)
ALT	
< 5 times	12 (54.5)
5 -10 times	7 (31.6)
>10 times	3 (13.6)
ALP	
150 – 250	3 (13.6)
251- 350	5 (27.3)
> 350	14 (63.6)
Bilirubin	
1.5 – 2	3 (13.6)
2-4	14 (63.6)
>4	5 (22.7)
Deranged	
1-1.5	16 (71.3)
>1.5	6 (32.7)

Table 3: Frequency of USG findings in ATTIH cases

USG findings in ATTIH	Cases (%)
Narrowing of hepatic veins	2 (8.6)
Reactive GB wall thickening	2 (8.6)
Hypo-echoic echo-texture	3 (13.5)
Peri-portal cuffing	6 (27)
Enlarged liver span with smooth borders	7 (34.6)

Table 4: pattern of normalization of LFTs

Duration for normalization of LFT	Cases with ATTIH (%)
6 days	6 (27.3)
7 to 14 days	11 (50)
15 to 21 days	2 (9)
36 days	1 (4.5)

Table 5 Side effects other than ATTIH were:

Other side effects	Cases (%)
Gastritis	13(8.7)
Rash	1(0.67)
Thrombocytopenia	1(0.67)
Hyper-uricemia	4(2.6)

In this study 18 patients (81.81%) developed ATTIH within 2 weeks of starting ATT with average of 9 days. Follow up USGs in all 150 patients was done and out of 22 ATTIH cases, 14 had acute hepatitis like picture.

Normalization of LFT was seen in 6 patients (27.3%) in 6 days, 11 patients (50%) in 7-14 days with median of 11 days, 2 patients (9%) in 15-21 days, 1 patient took 36 days, 2 patients expired of Acute liver failure. ATTIH resulted in prolongation of expected treatment duration in 12 patients. Out of 22 ATTIH patients 19 were completely cured, 2 Patients died of ALF one patient lost follow-up.

DISCUSSION

The use of multidrug regimens for the treatment of Tuberculosis such as the combination of Isoniazid, Rifampicin and Pyrazinamide has been associated with an increased incidence of hepatotoxicity when compared with Isoniazid monotherapy used as Anti-tubercular prophylaxis[1,10].In our study 14.7% of the patients developed ATTIH, an incidence similar to reports from Asia (8-19.8%)[11,12,13,14] and higher than those from the west (4.3%)[15]. Haung et al[15] reported that in total of 224 patients, 33 patients (14.7%) were diagnosed with ATTIH similar to this study. Similarly, in a study of Hoda et al[16] a total of 100 consecutive TB patients were prospectively followed up both clinically and biochemically before and during the course of anti- Tubercular therapy with daily doses of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide or Streptomycin ATTIH developed in 15(15%) patients.

In this study 59% cases developed ATTIH within 7-14 days (average 9 days).This is in agreement with the results of Mehmood et al[12], who reported that the onset of ATTIH in almost two thirds of their patients (41/67) was within 10-14 days from the start of therapy. Similarly, Shakya et al[13] reported an interval of 12-60 days (median=28 days). This emphasizes the importance of close and frequent monitoring of patients in first 2 mnths of anti tubercular treatment.

In the present study the interval from onset of hepatotoxicity to LFTs normalization was 2-46 days (median= 11 days). In almost 3/5 th of patients, LFT normalized within 2 weeks which is consistent with Mehmood et al[1 2] who reported that in 4/5th of patients, LFTs normalized within 2 weeks. In addition, Shakya et al[13] reported that liver enzymes returned to the normal level within few days of cessation of therapy.

Present study shows increase in the risk of treatment induced hepatotoxicity in females compared to males (19.8 vs 12.5%). Several studies have confirmed the same findings[15,16,17].

The higher vulnerability of females could be due to variations in pharmacokinetics and slow acetylation[18] pattern and lower BMI. Malnutrition may be a risk factor for ATTIH as detected by BMI < 18.99kg/m^2 and serum albumin levels < 3.5mg/dl. This may be due to depletion of glutathione stores, which makes patients more vulnerable to oxidative injuries and the slower pace at which their liver metabolize drugs. This study shows pretreatment low BMI (63.6%), Low Hb (63.2%), low serum cholesterol levels(59.1%) were associated with higher rates of ATTIH with a significant p values. Kumar et al[19] reported similar findings.

In this study, among ATTIH cases concomitant paracetamol ingestion was reported in 77.7%. This factor of indiscriminate drug use may be responsible for higher rates of ATTIH compared to west[20]. Other side effects reported were gastritis (9.8%), Hyperuricemia (2.5%), Rash (0.4%), thrombocytopenia (0.8%) and optic neuritis (0.4%). 12(53.8%) patients had mild transaminitis,

Moderate in 7 (33.2%) patients and severe in 3(13%) patients. It was consistent with study of Iftikhar et al[23]. We were safely able to reintroduce INH and RCIN in all cases after recovery from hepatitis. We introduced ATT in a stepwise manner[21] both with regard to the specific drug and the dosage and this strategy proved to be fairly effective and safe.

0ut of 22 ATTIH patients,20(90.9%) patients with ATTIH were hospitalized. 3 female patients (9.3%) presented with ALF, among them two patients expired despite discontinuation of ATT and one patient was managed in ICU setting with NAC and her LFTs never normalized and was treated with alternate regimen for 24 months. INH was successfully introduced in remaining patients during hospitalization and these patients were discharged after successful re-challenge. Recurrence of ATTIH was not seen on reintroduction. All these findings however need to be studied with greater number of cases for confirmation of results.

CONCLUSION

Anti- tubercular treatment induced hepato-toxicity influences the outcome of tuberculosis. It increases the morbidity and mortality. Early detection and pretreatment risk factor identification, hospitalization and appropriate modification of treatment will definitely reduce the ATTIH and will result in successful completion of ATT and better outcome.

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