ORIGINAL ARTICLE

Anti-Tuberculosis Treatment Induced Hepatitis – A Study of Incidence of Recurrence of Hepatitis and Treatment Outcome after Reintroduction of Anti-Tubercular Drugs

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ABSTRACT

BACKGROUND AND OBJECTIVES: Antituberculosis drug-induced hepatotoxicity (ATDH) causes substantial morbidity and mortality and diminishes treatment effectiveness. Asymptomatic transaminase elevations are common during antituberculosis treatment, but hepatotoxicity can be fatal when not recognized early and when therapy is not interrupted in time. Retreatment is started only when all biochemical markers of liver injury have returned to normal levels. This study was undertaken to study the incidence of recurrence of hepatitis and treatment outcome after reintroduction of anti-tubercular drugs. **METHODS:** The study will include patients receiving anti tubercular treatment with deranged liver function tests; attending OPD and indoor facility of Tuberculosis & Respiratory Diseases Department from August 2014 to September 2015 in a tertiary care hospital. The study pattern was Prospective Cohort study with statistical application of Chi-square test. The data was collected using pre tested questionnaire, which elicited demographic and clinical information. **RESULTS:** In present study, patients receiving anti tubercular treatment with deranged liver function tests were included. The incidence of anti-tuberculosis drug induced hepatotoxicity was found high in old age with equal incidence in both males and females, high in alcoholics and in patients on CAT-1 AKT and those with extrapulmonary tuberculosis. All the patients with tuberculosis infection taking AKT (Anti Koch's Treatment) with deranged liver function tests (LFT) from OPD as well as indoor admissions were enrolled and subjected to liver function tests imbibing SGPT, SGOT, Total (direct and indirect) bilirubin. All the subjects were scheduled for weekly follow up and LFT assays until the normal enzymatic range was achieved. **CONCLUSION:** It was observed that recurrence of hepatitis after the reintroduction regimen was more in the older age group. There was no significant difference between both the sexes. Recurrence of hepatitis after the reintroduction regimen was more in patients on category 1 AKT and extra-pulmonary tuberculosis. The majority symptoms having anti-tuberculosis treatment induced hepatitis were vomiting, abdominal pain and nausea. History of any liver disease in the past may increase the risk of drug induced hepatitis.

Keywords: Hepatotoxicity, LFT, ATDH, AKT

INTRODUCTION

The pathogenesis of tuberculosis is determined by distinctive features of the bacilli and host factors. Tubercle bacillus has three important features which distinguish it from most other pathogens and also determines the course of the disease. These are

1. Slow generation time
2. High lipid content of the bacillus
3. Lack of either exotoxin or endotoxin.

The hallmark of TB lesion is caseating necrosis with varying degrees of exudation, Langerhans giant cells, tubercle formation and fibrosis. [3] The obstacles to success include poor patient compliance, high cost of medicines, drug resistance, insufficient duration, irregular therapy and last but not the least **Drug-Induced Hepatitis (DIH).** Antituberculosis drug-induced hepatotoxicity (ATDH) causes substantial morbidity and mortality and diminishes treatment effectiveness. Asymptomatic transaminase elevations are common during antituberculosis treatment, but hepatotoxicity can be fatal when not recognized early and when therapy is not

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interrupted in time. Adverse effects diminish treatment effectiveness, because they significantly contribute to non-adherence, eventually contributing to treatment failure, relapse or the emergence of drug-resistance. Isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic drugs. These drugs are metabolized by the liver. No hepatotoxicity has been described for ethambutol or streptomycin. Metabolism is crucial in ATDH and toxic metabolites play a central role. Hepatotoxicity is the most common adverse effect of anti-TB treatment that leads to interruption of therapy. [6] Retreatment is started only when all biochemical markers of liver injury have returned to normal levels. Although the reintroduction of isoniazid, rifampicin, and pyrazinamide therapy after hepatic injury does involve the risk of additional morbidity, the compelling rationale for doing so is grounded in the fact that non-isoniazid and non-rifampicin anti-TB treatment regimens require a longer duration of administration and lack of proof of clinical efficacy. Individuals with long-term alcoholism, patients with chronic liver disease, and patients who were concomitantly receiving other hepatotoxic drugs were excluded. All of the above characteristics are established risk factors for DIH[11]. Also, treating TB in HIV-infected patients is a complicated matter. These patients generally require antiretroviral drugs, which are potentially hepatotoxic and are associated with multiple drug-drug interactions. Also, hepatitis in these patients may be attributable to an opportunistic infection. Therefore, to simplify matters, HIV-infected patients were excluded from the present study. Furthermore, all patients were investigated for markers of acute viral hepatitis and were carefully excluded from the study. In view of these variable reports on incidence of drug induced hepatotoxicity during Short course chemotherapy (SCC/DOTS), a prospective study was undertaken on 100 patients receiving short course chemotherapy under RNTCP-DOTS and having anti-tubercular drug induced hepatotoxicity.

MATERIALS AND METHODS

STUDY TYPE:

Prospective Cohort Study

STUDY SETTING:

OPD and indoor facility of department of Tuberculosis and Respiratory Disease, Surat Municipal Institute of Medical Education and Research, Surat City.

STUDY PERIOD:

Study was conducted for period of 1 year and 2 months from August 2014 to September 2015, which included 10 months for data collection and four months for data entry and data analysis.

SAMPLE SIZE:

All those patients having diagnosis of tuberculosis with ATT induced liver injury were included in the duration of 1 year and 2 months from August 2014 to September 2015.

CASE DEFINITION:

Drug induced hepatitis-

Three-fold increase in ALT over the upper normal limit in patients reporting jaundice and/or hepatitis symptoms such as nausea, vomiting, abdominal pain, unexplained fatigue OR Five-fold increase in ALT over the upper normal limit in the absence of symptoms.

SELECTION OF SUBJECTS:

Study included the patients on ATT with hepatotoxicity and normal liver in outpatient setting as well as indoor setting of pulmonary Medicine Department in SMIMER. Participants giving written informed consent were included in this study.

DATA COLLECTION:

Data was collected using predesigned, structured and pretested questionnaire.

Variables: the information was collected about the socio demographic profile, clinical symptomatology, family and personal history of patient, laboratory examination, liver function profile, sputum examination, ultrasound examination, anti-tubercular treatment and other treatment and investigation details. The details of follow up investigations was recorded at

reintroduction of drug, increasing the doses and adding other drugs. The reports was also collected and recorded at fixed intervals for each patient according to the protocol.

Inclusion criteria:

All patients above 18 years of age.
Patient receiving ATT exhibiting hepatotoxic effects

Exclusion criteria:

Patient on other medications (such as ART).
Patient having other coexistent lung disease.
Patients with known case of cirrhosis and hepatitis

METHOD

The study included patients receiving anti tubercular treatment with deranged liver function tests; attending OPD and indoor facility of Tuberculosis & Respiratory Disease Department from August 2014 to September 2015. Informed written consent for allowing their clinical data to be used for study purpose was obtained from the patient. Detailed History and clinical evaluation, as per the annexed proforma was obtained. All the patients with tuberculosis infection taking AKT with deranged liver function test from OPD as well as indoor admissions were enrolled. Enrolled patients were subjected to liver function tests imbibing SGPT, SGOT, Total (direct and indirect) bilirubin. All the subjects were scheduled for weekly follow up and LFT assays until the normal enzymatic range was achieved. Subsequently, patients were divided into 2 groups through random assignment. Group A received reintroduction regimen of Isoniazid (H), Rifampicin(R) and Pyrazinamide (Z) at maximum doses from day 1. Group B was given reintroduction regimen as follows-R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15. Both the groups received modified anti-tuberculosis treatment as well, which includes drugs that do not have hepatotoxic potential-

Tablet Ethambutol 800 mg once a day
Tablet levofloxacin 750 mg once a day
Intramuscular injection streptomycin 0.75 gm once a day (0.5 gm once a day for patients with age more than 50 years or body weight less than 30 kg)Patients underwent radiological examination, sputum examination for AFB, and LFT assays were conducted regularly. Data was extrapolated and interpreted from all the groups using ANOVA and applicable statistical tools.

Response to treatment was measured by:
Improvement in clinical parameters
Sputum conversion (in case of PTB)
Radiological improvement (in case of PTB or EPTB)

DISCUSSION

1. The mean age of patients in group A who developed recurrence of hepatitis after drug reintroduction was 52.4 years and the mean age of patients in the same group who did not develop recurrence of hepatitis after drug reintroduction was 38.4 years. It was observed that recurrence of hepatitis after the reintroduction regimen was more in the older age group.
2. In this study, there were 24% females and 76% males in group A. In group B, there were 16% females and 84% males. But there was no significant difference in the incidence of recurrence of hepatitis after drug reintroduction between both the sexes.
3. In group A, 44% patients were on Category 1 AKT and 56% patients were on Category 2 AKT. In group B, 54% were on Category 1 AKT and 46% patients were on Category 2 AKT. It was observed that recurrence of hepatitis after the reintroduction regimen was more in patients on category 1 AKT.
4. In group A, 44% patients were suffering from pulmonary tuberculosis and 56% patients were suffering from extra-pulmonary tuberculosis . In

group B, 52% patients had pulmonary tuberculosis and 48% patients had extra-pulmonary tuberculosis. This observation suggests that recurrence of hepatitis after drug reintroduction was more in patients suffering from extra-pulmonary tuberculosis.

5. In group A, 38% patients had their sputum positive for acid fast bacilli (AFB) and 62% patients had their sputum negative for AFB . In group B, 28% patients had sputum positive pulmonary tuberculosis and 72% patients had sputum negative for AFB.
6. In the present study, 16% patients of group A and 18% patients of group B were suffering from extensive or disseminated tuberculosis.
7. In the present study, the majority symptoms in both the groups of patients having anti-tuberculosis treatment induced hepatitis were vomiting, abdominal pain and nausea.
8. In group A, 24% patients were cured of tuberculosis, 14% patients defaulted the treatment, 4% patients died during treatment, 16% patients had treatment failure and treatment was completed in 42% patients. In group B, 12% patients were cured of tuberculosis, 10% patients defaulted the treatment, 6% patients died during treatment, 14% patients had treatment failure and treatment was completed in 58% patients.
9. In group A, 3 patients had past history of liver disease out of which 2 patients developed recurrence of hepatitis after reintroduction regimen. History of any liver disease in the past may increase the risk of drug induced hepatitis.
10. In both the groups of patients with anti-tuberculosis treatment induced hepatitis, the symptoms of hepatotoxicity developed in the early phase of treatment (i.e. within 3-4 weeks of starting AKT)
11. In the present study, in group A, the mean of initial values of total serum bilirubin level and serum alanine transferase (or SGPT) in patients who developed recurrence of hepatitis after reintroduction regimen was 10.18 mg/dl and 821 U/L respectively and in patients who did not develop recurrence of hepatitis after reintroduction regimen, the initial values were 2.98 mg/dl and 370.52 U/L. Thus concluding, the patients with higher serum bilirubin and SGPT levels have increased risk of developing recurrence of hepatitis after drug reintroduction.
12. The mean of S. bilirubin levels of patients who developed recurrence of hepatitis after reintroduction regimen was 4.44 mg/dl in group A and 3.45 mg/dl in group B. This observation shows that the mean of S. bilirubin levels in patients who developed recurrence of hepatitis after the reintroduction regimen was significantly lower than the S. Bilirubin levels before reintroduction regimen. Also, it is observed that the mean of S. bilirubin levels in patients who developed recurrence of hepatitis after the reintroduction regimen in group B (where hepatotoxic drugs are introduced on by one) is lower than those of group A (where all three hepatotoxic drugs are given all at once).
13. The mean of SGPT levels of patients who developed recurrence of hepatitis after reintroduction regimen was 507.4 U/L in group A and 350.25 U/L in group B. This observation shows that the mean of SGPT levels in patients who developed recurrence of hepatitis after the reintroduction

regimen was significantly lower than the SGPT levels before reintroduction regimen. Also, it is observed that the mean of SGPT levels in patients who developed recurrence of hepatitis after the reintroduction regimen in group B (where hepatotoxic drugs are introduced on by one) is lower than those of group A (where all three hepatotoxic drugs are given all at once).

14. It is observed in the present study that recurrence of hepatitis when graded in terms of S. bilirubin and liver enzymes, is less severe in group B than in group A, which conveys that the reintroduction regimen given to group B is slightly safer than that given to group A, though the difference in safety is not statistically significant.

CONCLUSION

Out of 50 patients in group A, who received reintroduction regimen of Isoniazid (H), Rifampicin(R) and Pyrazinamide (Z) at maximum doses from day 1, 5 patients developed reccurence of hepatitis. Out of 50 patients in group B, in whom the hepatotoxic drugs were reintroduced one by one, at an interval of 7 days (R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15), 4 patients developed recurrence of hepatitis. According to the tests applied in statistical analysis, it is concluded from the present study that that is no significant difference in rate of recurrence of hepatitis after drug reintroduction in both regimens.

REFERENCES

1. K.Park,Park's textbook of preventive and social medicine.18th edition June 2005 pages 146 –155
2. Govt.of India (20004), Annual report 20003-2004, Ministry of Health and family welfare, New Delhi.
3. AnibranMaitra, Vinay Kumar Robbins basic pathology 7th edition Pg 487
4. Richard J.Wallace, Jr., David E.Griffith.Harrison's Principles of internal medicine, 16th edition 2005, Antimicrobialagents p 946
5. Farcas et al: Adverse drug reactions in clinical Practice: A causality assessment of a case of drug-induced pancreatitis (Farcas and Bojita, 2009)
6. Schaberg T, Rebhan K, Lode H.Riskfactorsforsideeffectsofisoniazidrifampicin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. EurRespir J 1996;9:2026–2030.
7. Dash LA, Comstock GW, Flynn PG. Isoniazid preventive therapy: retrospect and prospect. Am Rev Respir Dis 1980;121:1039–1044.
8. Singh J, Garg PK, Tandon RK. Hepatotoxicity due to anti-tuberculosis therapy: clinical profile and reintroduction of therapy. J ClinGastroenterol 1996;22:211–214.
9. Tahaoglu K, Atac¸ G, Sevim T, et al. The management of anti-tuberculosis drug induced hepatotoxicity. Int J Tuberc Lung Dis 2001;5: 65–69.
10. Agal S, Baijal R, Pramanik S, et al. Monitoring and management of anti-tuberculosis drug induced hepatotoxicity. J GastroenterolHepatol 2005;20:1745–1752.
11. Saukkonen JJ, Cohn DL, Jasmer RM, et al on the behalf of ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: Hepatotoxicity of Antituberculosis Therapy. Am J RespirCrit Care Med 2006;174: 935–952.
12. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom. Thorax 1998;53:536–548.
13. TBC India Web page. Directorate General of Health Services Ministry of HealthandFamilyWelfare.http://www.tbcindia.org.Accessed8February 2010.
14. World Health Organization (WHO). Treatment oftuberculosis:Guidelines

for national programmes. 2nd ed. Geneva, Switzerland: WHO, 1997; 25–39
15. Study of 50 cases of Pulmonary TB with DM. Dr.Prabhakar Singh, November 2005.
16. Marrie TJ, bactremi pneumococcal Pneumonia, a Continuously involving disease. Journal of Infectious Disease, 1992, 24:247-251.
17. Nolan CM, Beauty HN, Bagdade JD, further characterization of impaired bactericidal function of granulocyte in DM. 1978, 1978,27:889-94.
18. Ruiz P. Gomez F. Schnaber Ad, IMPAIRED FUNCTION Of MACROPHAGE Fc Gamma receptor in end stage renal disease, NEng J Med. 1989,322:717-725.
19. Dandapat MC, Mishra BM, Dash SP, Kar PK. Peripheral lymph Node tuberculosis: a review of80 cases. Br J Surg. 1990 Aug;77(8):911-2.
20. Levin-Epstein AA, Lucente FE. Scrofula- - the dangerous masquerader Laryngoscope. 1982;92:938-943.
21. Patel RV, Mehta RT. Short term chemotherapy in TubercululosisIndian Journal Surgery 1987;49:336–41
22. Swai AB, McLast DG, Mugusi F, TB in DM patients in TanzaniaTropDoct1990.20: 147-150.
23. Sharma SK, Mohan A. pulmonary tuberculosis. Indian J Med Res. 2004;120:316-353.

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