Original Article

Anti Tuberculousis Drugs Induced Hepatitis

Prevalence of Anti Tuberculousis Drug Induced Hepatitis in Patients on Anti Tuberculous Drug in Mardan Medical Complex

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ABSTRACT

Objective: To determine the frequency of anti tuberculousis drugs induced hepatitis in Mardan Medical Complex.
Study Design: Descriptive / cross sectional study
Place and Duration of Study: This study was conducted at the chest OPD and TB centre of Mardan Medical Complex, Mardan from November 2018 to July 2019.
Materials and Methods: Diagnosed 309 cases of TB both pulmonary and extra pulmonary were taken. Among these only category I TB patients were selected and followed up for the development of ATT induced hepatitis.
Results: Study included a total of 309 patients in which 170 (55.01%) were male patients and 139 (44.98%) were female patients. Ages of the patients ranged between 15 and 80 years with a mean age of 34.8 years among male while 14 and 80 years with an mean age of 38.40 years among female. Out of 309 patients only 56 (18.12%) patients developed ATT induced hepatitis.
Conclusion: ATT induced hepatitis is an important and common side effect of anti tuberculous therapy and needs early recognition and treatment to avoid non compliance to ATT and treatment failure.
Key Words: Hepatitis, ATT, anti tuberculous drugs.

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INTRODUCTION

Tuberculosis is a health problem worldwide that is both preventable and curable. About one-third of world's population is infected by tuberculosis[1]. If an active case of TB is left untreated then each active case can infect 10 to 15 people in one year[1]. Pakistan is 5th amongst 22 countries with highest burden of TB[2]. The currently recommended first line treatment for Cat-1 TB is a regimen of isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and pyrazinazmind (PZA) for intial two months(intensive phase) and for next four months(continuation phase) INH and RMP[3]. Three first line drugs that are INH, RMP, and PZA are metabolized by liver and are hepatotoxic. Drug-induced hepatotoxicity associated with first-line drugs such as isoniazid, rifampin, and pyrazinamide is common, as with the use of many other therapeutic agents that causing hepatotoxicity,[4,5] this side effect of ATT drug is predictable and depend on dose of drug but for most it is idiosyncratic and dependent on parameters such as dosage, age, gender, and body mass index (BMI).[6]

The occurrence of ATT induced hepatitis is different among different countries that is the incidence is higher in the developing countries with rates ranging between 8% to 39% compared to developed countries at 3%-4%, despite similar regimens used.[7-10] As a specific example, a higher risk of 11.5% has been reported in Indian patients, compared to 4.3% in published studies from the developed countries.[1,12,13] One recent study from Singapore reported an incidence of 5.3%.[14] Higher incidence of ATT induced hepatitis in developing countries is due to risk factor like severity of the disease, nutritional status, wrong diagnosis and the effect of Hepatitis B and Hepatitis C positive serology.[15-18] One prospective cohort study from Spain has shown the incidence of anti tuberculosis drug-induced hepatotoxicity to be significantly higher in the group with risk factors (18.2%) than in the group without (5.8%).[19] In Pakistan about 19.76% of the patients developed anti tuberculosis drug induced hepatotoxicity. It usually occurs in the initial few weeks of the intensive phase of anti- tuberculosis chemotheraphy.[20]

MATERIALS AND METHODS

This was a prospective study carried out at Mardan Medical complex which is a tertiary care teaching

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hospital, from 1st November 2018 to 1st July 2019. Mardan medical complex having a chest OPD and a TB centre where diagnosed cases of tuberculoses are treated.

In our study we enrolled a total of 309 diagnosed cases of both pulmonary and extra pulmonary cases, including only category I TB patients. Approval for the study was obtained from ethical committee of the hospital. Written informed consent was taken from the patient for enrolment in study. After proper diagnosing according to the National and WHO guide lines patients were started on anti-TB drugs and followed up according to national TB treatment guidelines. The patients were also counselled to come to OPD if they developed signs and symptoms of hepato toxicity like anorexia, nausea, vomiting and yellow discolouration of the sclera and urine. Patients presenting with the above mentioned symptoms were subjected to liver functions tests (ALT, AST, ALP and serum bilirubin). Those patients fulfilling the criteria given below [23] were labelled as cases of anti-TB drug induced hepatitis. 1) ALT > 5 times normal irrespective of the signs and symptoms of hepatitis. 2) ALT >3 times normal with signs and symptoms of hepatitis. 3) Serum billirubin bilirubin to > 1.5 mg/dl.

Those patients with hepatitis while taking some other hepatotoxic drugs along with anti tuberculosis drugs were excluded from study to prevent bias because we were not known which one was the cause of hepatitis. Similarly Patients with acute hepatitis whose signs and symptoms and liver function tests did not normalize after stopping anti -tuberculosis drugs for 7 days were also excluded as they warranted further investigations for an alternative diagnosis. Also those patients who were taking second line drugs for multi drug resistant tuberculosis and those with inadequate medical records to allow complete analysis, were excluded from study.

All patients were interviewed with a questionnaire to obtain clinical data like age, sex, alcohol intake, current clinical symptoms (anorexia, nausea, vomiting and jaundice) with duration, detailed history of tuberculosis and the drug history of not only anti tuberculosis drugs but drugs for any other medical or surgical disease. All laboratory investigations were done in the Pathology Department while chest X-ray and ultrasound abdomen in the Radiology Department of Mardan medical complex. All patients with anti-tuberculosis drugs induced hepatitis were managed according to the standard guidelines. The above mentioned clinical, biochemical and historical data collection was documented on Performa and was analyzed statistically. All the information / data were kept confidential because the disease is still considered to be a social stigma. Statistical analysis was performed by using SPSS version 15.0. Frequencies / Percentages were calculated for different study variables.

RESULTS

In our study we have included a total of 309 patients in which 170 (55.01%) were male patients and 139 (44.98%) were female patients. Out of 309 patients only 61 patient developed ATT induced hepatitis but only 56 (18.12%) patients were eligible according to our inclusion criteria and remaining 5 (1.61%) patients were excluded according to our exclusion criteria. Those excluded were either active hepatitis C or hepatitis B cases, or due to non-specific pre-treatment hepatitis, and incomplete medical records. Ages of the patients ranged between 15 and 80 years with an mean age of 34.8 years among male while 14 and 80 years with an mean age of 38.40 years among female.

DISCUSSION

Tuberculosis is the disease which currently infects about 1/3rd of the world population [1] and our country Pakistan came at No 5 in the list of 22 courtiers having highest numbers of tuberculosis patients [2]. Treatment of tuberculosis patients by use of first line anti-TB drug which is a regimen of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinazmind (Z) for two months, and isoniazid (H), rifampicin for next four months. Anti tuberculous drugs are most effective against active cases of TB but due to one of the major and serious side effect which is ATT induced hepatitis patients taking anti-TB should be regularly evaluated for hepatotoxicity.

Early diagnosis of anti-TB drug hepatitis and discontinuation of anti-TB play crucial role in decreasing severity of disease and limits extend liver injury. Presentation of Drug Induced hepatotoxicity is very variable that is there may be no symptoms in some cases and others may present with sudden-onset liver failure. Therefore physicians should regularly evaluate patients taking anti tuberculosis drug for hepatotoxitiy by routine follow-up visit and doing laboratory investigation and by looking for sign and symptoms of ATT induced hepatitis. Risk factor for ATT induced hepatitis play important role in developments of anti-TB drugs induced hepatitis and may help identify those at risk. Although in this study we mainly focused only on the prevalenceof ATT induced hepatitis. However in one of my previous studies conducted in lady reading hospital Peshawar we indentified the frequency of risk factor in patient with anti-TB drug induced hepatitis. In that study we have found that frequency of risk factors in ATT induced hepatitis is significantly high.

The prevalence of anti tuberculosis induced hepatitis in this study was 18.12% which is comparable with study (19.8%) done in Karachi Pakistan [21]. The reported prevalence of ATT induced hepatitis in developing countries is higher than developed countries. In developing countries the rates of ATT induced hepatitis range between 8% to39% compared to developed

countries at 3%-4%, despite similar regimens used [7-10]. One possible reason of higher prevalence in our study may be due to presence of risk factor for ATT induced hepatitis. higher incidence of ATT induced hepatitis in developing countries is due to risk factor like age, sex, severity of the disease, nutritional status, alcoholism, wrong diagnosis and the effect of Hepatitis B and Hepatitis C positive serology [15-18].

CONCLUSION

In conclusion ATT induced hepatitis is an important side effect of anti tuberculous therapy and may lead to non compliance to ATT and treatment failure. Therefore this side effect needs vigilance, early recognition, treatment and proper counselling to improve adherence to ATT and treatment out come.

Author's Contribution:

Concept & Design of Study:	Nabi Rehman
Drafting:	Sajjad Ali, Shah Zeb
Data Analysis:	Muhammad Abbas, Naveed Khan, Rehman ud Din
Revisiting Critically:	Nabi Rehman, Sajjad Ali
Final Approval of version:	Nabi Rehman

Conflict of Interest: The study has no conflict of interest to declare by any author.

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