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Original Research Article

Anti-tuberculosis drug induced hepatotoxicity: a study from Himalayan region

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ABSTRACT

Background: Tuberculosis (TB) is the infection of global health concern. The management of TB is a 6-month course of anti-TB drugs. Compliance is crucial for curing TB. Adverse effects often affect the compliance negatively. One of the adverse effects affecting TB treatment outcome is anti-TB drug induced hepatotoxicity (DIH). Therefore, the purpose of this study was to assess the incidence of anti-TB DIH and its associated factors among newly diagnosed TB patients.
Methods: A single centre prospective study was conducted from January-December 2020. All patients who were newly-diagnosed for TB, started anti-TB medication and diagnosed with drug-induced liver injury during anti-tubercular treatment included in the study.
Results: Total of four hundred and ninety-two (492) TB patients taking anti-TB drugs were involved in this study with male predominance and maximum in the age group of 30-45 years. Smear-positive pulmonary TB accounted for 66.9% of all cases. During the study period, 9.3% TB patients developed anti-TB DIH. Among the cases of anti-TB DIH, female patients account for 52%. Patients with extra-pulmonary TB (n=23), low BMI (n=16), alcohol consumption (n=21) had developed anti-TB DIH. The time interval from the initiation of treatment to the onset of hepatotoxicity was 16-45 days.
Conclusion: The chances of hepatotoxicity among TB patients taking anti-TB drugs are always there. Thus, it is necessary to monitor liver function in patients receiving anti-TB drugs routinely.

Keywords: TB, Compliance, Adverse, Hepatotoxicity, Incidence

INTRODUCTION

Tuberculosis (TB) is the infection of global health concern due to the burden of high incidence, co-infections, drug resistance, and medical expenses.[1] TB is a chronic infection caused by bacteria *Mycobacterium* TB, and pathologically characterized by the granuloma formation. Lung is the most common site of infection, but other organs may be involved.[2]

The standard management of TB is a 6-month course of anti-TB drugs in intensive and continuous phase. Isoniazid, rifampicin, pyrazinamide, and ethambutol are taken for 2 months in the intensive phase followed by a continuous phase for four months with isoniazid and rifampicin. Compliance is crucial for curing TB. Adverse effects often affect the compliance negatively, because they require a change of treatment frequently, which may have negative impact on treatment outcome. Anti-TB drug induced hepatotoxicity (DIH) is one of the adverse effects affecting TB treatment outcome.[3]

Hepatotoxicity is usually presented and diagnosed with jaundice or a high concentration of liver function marker proteins like alanine aminotransferase (ALT)/aspartate aminotransferase (AST), total bilirubin or alkaline phosphatase (APT). Treatment should be suspended and generally an alternative or modified regimen should be used for those with ALT elevation more than 5 times the upper limit of normal (ULN) in the absence of symptoms or 3 times the ULN in the presence of hepatitis symptoms. For hepatocellular injury an increase in serum ALT is more specific than an increase in AST which can also signify abnormalities in heart, muscle, or kidney.[4] Therefore, this study was done with the purpose to assess the incidence of anti-TB DIH and its associated risk factors among newly diagnosed TB patients.

METHODS

A single centre prospective study was conducted from January-December 2020 in the govt. medical college, Hamirpur, a tertiary institute in Himalayan region. Ethical clearance was obtained from the ethical review committee of the institute. Four hundred and ninety-two (492) patients, who were newly-diagnosed for TB, started anti-TB medication and diagnosed with drug-induced liver injury during anti-tubercular treatment included in the study after obtaining the informed consent. Patients taking antiretroviral therapy (ART), patients who had baseline AST and ALT values greater than two times the ULN (i.e., ULN>37 U/L and 40 U/L respectively), positive for hepatitis C and/or B virus were excluded from the study.

The socio-demographic and clinical data was collected from each participant. Screening for hepatitis C and B virus was done using rapid test kits. Before the initiation of anti-TB treatment, the baseline measurements of AST, ALT, and total bilirubin were performed. The patients were examined after the initiation of anti-TB treatment, physically as well as biochemically every two weeks for 2 months.

The normal maximum values of AST and ALT were 37 U/L and 40 U/L, respectively. For both men and women, these were the same cut-off points. After 2 weeks of the recovery period, their ALT and/or AST level has been found to be <3 times ULN without the signs and symptoms of hepatotoxicity. Due to reversal of hepatotoxicity manifestations, we believed that anti-TB drugs were the cause for it. SPSS 20 was used for statistical analysis.

RESULTS

Total of four hundred and ninety-two (492) TB patients taking anti-TB drugs were involved in this study. Among them, 294 (59.8%) were males and 198 (40.2%) females. The age of the cases ranged from 15 years to 72 years, with maximum number of participants 194 (39.4%) in the age group of 30-45 years followed by 124 (25.2 %) in the age group of 15-29 years, 112 (22.8%) in the age group of 46-60 years and 62 (12.6%) in the age group of >60 years. The body mass index (BMI) measurement of the majority 419 (85.2%) of the participants was within the normal range (i.e., 18.5-24 kg/m^2), followed by 52 (10.6%) underweight (i.e., <18.5 kg/m^2) and 21 (4.2%) overweight (>24 kg/m^2). Among the 492 participants, 184 (37.4%) were reported to have alcohol intake and 76 (15.4%) were used to smoke (Table 1). Smear-positive pulmonary TB accounted for 329 (66.9%) of all cases, and extra-pulmonary TB accounted for about 163 (33.1%) cases.

Table 1: General characteristics, (n=492).

Variables		N (%)
Gender	Male	294 (59.8)
	Female	198 (40.2)
Age group (years)	15-29	124 (25.2)
	30-45	194 (39.4)
	46-60	112 (22.8)
	>60	62 (12.6)
BMI (kg/m^2)	Normal (18.5-24)	419 (85.2)
	Underweight (<18.5)	52 (10.6)
	Overweight (>24)	21 (4.2)
Alcohol intake	Yes	184 (37.4)
	No	308 (62.6)
Smoking	Yes	76 (15.4)
	No	416 (84.6)

During the study period, 46 (9.3%) TB patients out of 492 developed anti-TB DIH, which was confirmed by clinical examination and liver function test. They showed elevated serum concentrations of ALT, AST, and total bilirubin. Patients with anti-TB DIH had their ALT value >3×ULN + symptoms in 18 (39.1%) patients and >5×ULN with/without symptoms in 28 (60.9%), AST value >3×ULN + symptoms in 21 (45.6%) and >5×ULN with/without symptoms in 25 (54.4%) patients, and bilirubin values >2×ULN in 24 (52%) patients (Table 2).

Table 2: Laboratory data of patients, (n=46).

Parameters	Cut-off value	Patients with DIH (%)
Alanine aminotransferase (ALT) U/L	>3 ULN+symptoms	18 (39.1)
	>5 ULN ±symptoms	28 (60.9)
Aspartate aminotransferase (AST) U/L	>3 ULN+symptoms	21 (45.6)
	>5 ULN ±symptoms	25 (54.4)
Total bilirubin (mg/dL)	>2 ULN	24 (52)

Among the total 46 anti-TB DIH cases, female patients account for the highest number 24 (52%). Most of the patients who had developed ant-TB DIH showed the same signs and symptoms i.e., myalgia, vomiting, nausea,

anorexia and jaundice. The most common symptoms being nausea in 39 (84.8%) and anorexia 37 (80.4%), followed by malaise and jaundice. Patients with extra-pulmonary TB (n=23), low BMI (n=16), alcohol consumption (n=21) had developed anti-TB DIH (Table 3).

Table 3: General characteristics of the patients with DIH, (n=46).

Variables		N (%)
Gender	Male	22 (47.8)
	Female	24 (52.2)
Age group (Years)	15-29	14 (30.4)
	30-45	18 (39.1)
	46-60	9 (19.6)
	>60	5 (10.9)
BMI (kg/m^2)	Normal (18.5-24)	28 (60.9)
	Underweight (<18.5)	16 (34.8)
	Overweight (>24)	2 (4.3)
Alcohol intake	Yes	21 (45.7)
	No	25 (54.3)
Smoking	Yes	20 (43.5)
	No	26 (56.5)
Extent of TB	Pulmonary	23 (50)
	Extra-pulmonary	23 (50)

The time interval from the initiation of treatment to the onset of hepatotoxicity was 16-45 days. Twenty-nine (29) out of the 46 cases had developed hepatotoxicity in the first months of intensive phases of treatment, whereas others had developed hepatotoxicity in the second month. The patients who had developed anti-TB DIH were followed weekly for 3 weeks with liver function test (ALT, AST, and total bilirubin) until their liver-enzyme levels returned to the baseline state or normal.

DISCUSSION

In the present study, we analyzed the incidence, clinical features, risk factors, biochemical characteristics, and outcomes of anti-TB DIH. Four hundred and ninety-two newly diagnosed TB patients who were negative for human immunodeficiency virus, hepatitis B and C virus, and started taking anti-TB drugs were included in this study.

The incidence of anti-TB DIH in the present study was found to be 9.3%, which was consistent with the study conducted by Marzuki et al (9.7%) in Malaysia and Abera et al. (8.1%) in Dawro Zone, South Ethiopia.[5,6] The variation in the incidence of anti-TB-DIH worldwide may be attributed to the differences in patient's characteristics, indiscriminate use of drugs, and the definition criteria of hepatotoxicity.[4]

The time elapsed from the starting of anti-TB treatment to developing anti-TB DIH was ranging from 16-45 days. The finding of this study, regarding the onset of developing drug induced hepatotoxicity after starting the treatment is similar to studies conducted in Dawro zone, South Ethiopia by Abera et al was ranging from 13-58 days, in Nepal by Shakya et al was 12-60 days and by Makhlouf et al was 15-60 days.[6-8]

In our study we found that drug induced hepatocellular injury is more common in females and young patients, similar to the study done in Nepal by Shakya et al., reported that the incidence of anti-TB-DIH was higher in younger patients.[7] However, a report by Devarbhavi et al suggested that males have a higher risk of developing anti-TB-DIH.[9]

Alcohol consumption is a well-established risk factor for anti-TB drug-induced hepatotoxicity, as shown in studies done at Dawro zone, South Ethiopia by Abera et al and also Pande et al reported that the history of chronic alcohol intake was common among the cases.[6,10] In our study, there was association between alcohol consumption and drug-induced hepatotoxicity. On the contrary, a study done in Egypt by Makhlouf et al showed that high alcohol intake had no correlation with the incidence of anti-TB DIH.[8]

In this we found that extrapulmonary-TB and low BMI (<18.5 kg/m^2) were associated with anti-TB DIH. Similar to our study, extrapulmonary organ involvement was reported to be associated with the incidence of anti-TB DIH in a study by Sharma et al and Shakya et al from Nepal, showed that malnourishment had a significant association with the incidence of anti-TB-DIH.[7,11]

Other risk factor associated with anti-TB DIH includes viral hepatitis. Anand et al reported that patients with hepatitis B virus infection had significantly higher incidence of anti-TB DIH than those without infection.[12] The patients enrolled in our study were negative for hepatitis B virus. The results of meta-analysis by Steele et al reported the incidence rate of hepatotoxicity was high with isoniazid followed by pyrazinamide and rifampicin.[13] TB patients who were included in the current study were taking a combination of four anti-TB drugs: isoniazid, rifampicin, pyrazinamide, and ethambutol. Therefore, it was difficult to infer which drug was responsible for the cause of hepatotoxicity.

In the current study, liver function test for monitoring of TB patients was done. Patients having signs and symptoms suggestive of hepatotoxicity were put under close follow-up. Their liver function tests monitored and physical examination done regularly. Fortunately, all of the cases recovered after a few days and treatment completed successfully.

The limitations of the current study are that, TB patients were monitored with liver function test in the initial phase of treatment. As most of the time, anti-TB DIH was expected to happen during the intensive phase of treatment. The present study was not able to assess the

reoccurrence or occurrence of anti-TB DIH in the continuous phase of treatment.

CONCLUSION

The chances of hepatotoxicity among TB patients taking anti-TB drugs are always there especially during intensive phase. So, patients taking anti-TB drugs should be followed biochemically more frequently during the initial phase of treatment. Liver injury can be fatal if diagnosis and treatment are not initiated timely. Thus, it is necessary to monitor liver function in patients receiving anti-TB drugs routinely.

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