Original Article

Drug induced hepatitis among Iranian patients suffering from tuberculosis

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ABSTRACT

Objectives: To identify the risk factors of anti TB drug induced hepatitis (ATDH) among the patients with tuberculosis.

Methodology: In a retrospective study, medical records of 3960 notified tuberculosis cases over the five year period (2004-2008) in Khuzestan province Health Center, south west of Iran, were reviewed and ATDH data were analyzed. Inclusion criteria were documented TB, diagnosed based on National Tuberculosis Program (NTP). Data of ATDH and non ATDH were analyzed in SPSS 16 system and by chi square and exact fisher tests.

Results: One hundred ninety eight cases including 65(32.8%) female and 133(67.2%) male with mean age of 43.2 year and SD of 9.5 were registered as ATDH during treatment and follow up period. Differences between HIV infection and intravenous drug injection in ATDH cases and non ATDH patients was statistically significant {(p=0.0001, OR: 14.2), (p=0.0001, OR: 7.5) and (p=0.0001, OR: 11.3) respectively}.

Conclusion: Among previously established risk factors for ATDH, HCV infection, IVDU and HIV infection had the most importance.

KEY WORDS: Drug induced hepatitis, Tuberculosis, National anti tuberculosis program.

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INTRODUCTION

Tuberculosis (TB) is a major public health problem worldwide.[1] It is estimated that *Mycobacterium tuberculosis* has infected one-third of the world's population and 8–9 million new TB cases occur each year.[2] In Iran, it is a significant cause of morbidity and mortality.[3] The cornerstone of TB management in National Program against Tuberculosis (NPT) is a standard 6-month course of isoniazid, rifampicin, pyrazinamide and ethambutol, divided in two phases. The intensive phase included two months with four drugs and then continued by second phase with isoniazid and rifampicin.[4] Hepatotoxicity is one of the most serious adverse effects of Isoniazid, pyrazinamide and rifampicin, and can lead to such reactions during anti TB therapy.[5]

Previous studies showed transient elevations of serum hepatocellular enzymes (e.g. alanine aminotransferase (ALT) and aspartate aminotransferase

(AST) in approximately 10% of patients who received a standard anti TB combination therapy including isoniazid and rifampicin, of these 1–2% patients withdrew from the treatment because of severe hepatotoxicity that ultimately led to fulminant hepatitis.[6,7] Most of the hepatic reactions are dose-related; some are, however, caused by drug hypersensitivity.[8] Risk factors for anti TB drug induced hepatitis (ATDH) are acetylates phenotype, old age, malnutrition, alcoholism, HIV infection, as well as chronic hepatitis B and C infections.[6,7]

Other factors that may increase the risk of ATDH are: advanced tuberculosis, Asian ethnicity, female sex, concomitant administration of enzyme-inducers (e.g. barbiturates and anesthetic agents) and inappropriate use of drugs.[7] Drug-induced hepatic dysfunction usually occurs within the initial few weeks of the intensive phase of anti TB therapy.[6,8] Patient training especially those with risk factors on symptoms of hepatitis and laboratory monitoring (ALT and AST) are mandatory to improve the outcomes of patients with drug-induced hepatitis during anti TB therapy.[2,9] Considering lack of epidemiological studies to evaluate the risk factors of ATDH caused by NPT in Ahvaz, the present study was performed, aimed to identify the risk factors of ATDH among the patients with TB treated by NPT regimen.

METHODOLOGY

In a retrospective study, medical records of 3960 notified tuberculosis cases over the five year period (2004-2008) in Khuzestan province Health Center (KHC), south west of Iran, were reviewed and ATDH data were analyzed. Inclusion criteria were documented TB, diagnosed based on National Tuberculosis Program (NTP).

Cases with at least two sputum smear positive for acid fast bacillus (SSP-AFB) or, a chest radiography suggestive of tuberculosis plus one SSP-AFB or, sputum culture positive for *M.tuberculosis* and one SSP-AFB were defined as smear positive pulmonary tuberculosis (PTB+). Cases with clinical finding suggestive of TB plus three sputum smear negative AFB (SSN-AFB) after two weeks of antibiotic therapy plus C-X-ray (suggestive TB) were defined as smear negative pulmonary tuberculosis (PTB-). Other diagnostic criteria were cerebro spinal fluid analysis for TB meningitis and CT-scan and microbial study for milliary or extra pulmonary tuberculosis. Diagnosis of ATDH was based on clinical finding and laboratory results of elevated ALT. Patients were diagnosed as ATDH if there was no apparent cause for the raised liver function tests plus if he/she had one of the following: a rise of five times the upper limit of normal levels (40 U/L) of serum ALT and no sign and symptom of hepatitis. Clinical hepatotoxicity was diagnosed if a patient had elevated ALT plus symptoms of ATDH including: nausea, vomiting, weakness and jaundice. Patients with elevated baseline ALT were excluded the study.

For each ATDH case three patients without ATDH were randomly selected as control. Demographic characteristics, medical history, imprisonment, HIV, HBV, HCV serology status, drug addiction, underlying diseases, drug side effects and other medical problems during anti TB treatment of both cases (ATDH patients) and controls were taken from their medical files in Razi Hospital and KHC. Finally data were analyzed in SPSS 16 system and by chi square and exact fisher tests.

In this study according to NPT, tuberculosis patients are followed up during treatment course (at least 6 months) and 12 months after completion of treatment (month 3, 6 and 12). ATDH was recorded over the period of treatment and follow up period.

RESULTS

Out of the 792 studied cases who were treated by NPT regimen, 303 (38.2%) were female and 489 (61.8%) were male. One hundred ninety eight cases (5%) including 65(32.8%) female and 133(67.2%) male with mean age of 43.2 year and SD of 9.5 were registered as ATDH during treatment and follow up period. ATDH in one hundred and twenty one (61.1%) patients occurred during the first two months of therapy. Only four deaths (2.02%) were directly attributed to ATDH. Previous viral hepatitis (B and C) infection was detected in 77 case (38.9%), among them majority (78%) had history of imprisonment and intravenous drug injection. Other results in ATDH (case) and non ATDH (control) are shown in Table-I.

DISCUSSION

In the present study age, smoking, injecting drug addiction, imprisonment, alcohol consumption, viral hepatitis and HIV co infection were considered as risk factors for ATDH. The proportion of HCV infection in ATDH cases and non ATDH patients was statistically significant (p=0.0001, OR: 14.2), indeed, HCV positive patients are at a higher risk than HCV negative ones. Similar findings have been observed in other studies.[6,10] Similar to the other studies we found association between HBsAg positivity and development of hepatotoxicity.[11] Indeed the effect of HBV infection is significantly lower than the effect of HCV. This may be attributed to the routine HBV vaccination as a part

Table-I: Demographic characteristics and risk factors for drug hepatotoxicity among tuberculosis patients under treatment in Khuzestan Health Center.

Variables		*ATDH (Cases, n=198) N (%)*	*Non ATDH (Control, n=594) N (%)*	*P value*	*Odds ratio OR, 95% CI*
Sex	Male	133 (67.2)	356 (59.9)	0.07	1.4, 0.9-1.9
	Female	65 (32.8)	238 (40.1)		
Age (Year)	>35	145 (73.2)	316 (53.2)	0.0001	2.4, 1.7-3.4
	<35	53 (26.8)	278 (46.8)		
Smoking		79 (39.9)	169 (28.4)	0.003	1.7, 1.2-2.3
IVDU		109 (55)	58 (9.7)	0.0001	11.3, 7.7-16.7
Imprisonment		58 (29.3)	71 (11.9)	0.0001	3.1, 2.1-4.5
Alcohol consumption		8 (4.0)	7 (1.2)	0.01	3.5, 1.3-9.9
Viral co infection	HBV	16 (8.1)	25 (4.2)	0.04	2.0, 1.1-3.8
	HCV	61 (30.8)	18 (3.0)	0.0001	14.2, 8.2-24.9
	HIV	14 (7.1)	6 (1.0)	0.0001	7.5, 2.8-19.7
Cavitary TB		57 (28.8)	112 (18.8)	0.004	1.7, 1.2-2.5

ATDH: Anti TB drug induced hepatitis, IVDU: Intravenous drug users, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, OR: Odds ratio, CI: Confidence interval

of Expanded Program of Immunization since 1993 in Iran. Getnet and et al reported small number of patients who are positive for Anti-HCV antibody and HBsAg in their study.[2]

In our study being IVDU was main risk factors for ATDH (p=0.0001, OR: 11.3). We believe that although IDVU is not an independent factor for ATDH, but, because of frequent viral hepatitis in these patients and very hazard materials make them a target for hepatic injuries.[6] The frequency HIV positivity among ATDH cases was significantly higher than non ATDH (p=0.0001, OR: 7.5). This finding confirms that HIV positive patients are at a higher risk for ATDH than HIV negative ones. Ungo and et al (1998), Pedral-Sampaio and et al (2004) and Yee and colleagues (2003) have reported similar findings in their works.[10,12,13] This may be partly explained by the different drugs used by these patients before the diagnosis of TB was made. The other possible reason for this finding could be, since patients with low immunity are more prone to opportunistic infections, this might necessitate consumption of other hepatotoxic drugs leading to sub clinical liver damage and thereby increase susceptibility for hepatic damage while taking anti TB drugs.[14] Like other previously published investigations being alcoholic is one of the well established risk factors for ATDH.[13,15,16] In our study however, we found this association. Although in the region of study patients refuse correct declaration in medical history but, even low frequency of history of alcohol consumption was enough to confirm its effect on hepatotoxicity. The present study showed that imprisonment put the patients at a higher risk for ATDH. The reason for this finding is not clear, but we suppose that being in prison may put the patient at some condition like malnutrition, expose to more virulent strain of mycobacterium, dangerous behaviour such as IVDU, alcohol consumption and smoking. We didn't find the effect of prison as an independent variable in inducing hepatitis in the medical literature. Malnutrition as a risk factor for ATDH was suggested by previous studies.[15] However, in this study because of the larger proportion of study participants having a low weight making comparison of malnutrition as an independent factor difficult. Like previous studies which showed that patients in the older age group are at increased risk for development of hepatotoxicity[10,12], in this study, such a finding was observed. However, there are also studies which support that age is not a risk factor for development of hepatotoxicity in patients taking anti-tuberculosis therapy.[17] We have also observed that patients who smoked concomitantly with the anti-tuberculosis therapy were at risk for the development of hepatotoxicity. This could be because of the synergistic hepatotoxic effect caused by the systemic effect of nicotine on various organs such as the liver. Similar finding was observed by other investigators.[6]

Limitations of the study: Since the design of this study was retrospective definite case control study to show

exact effect of each risk factor was not appropriately possible. As a result it was difficult to make strong association on different parameters such as association of hepatotoxicity with these parameters. Moreover, since the majority of our study participants were underweight it was difficult to see the association between malnutrition and hepatotoxicity. Since the study was conducted only in one health center which was also located in one province there might be a problem of representing the whole country with regard to economic status and ethnic group.

CONCLUSION

Like previous studies age, smoking, injecting drug addiction, imprisonment, alcohol consumption, and viral hepatitis and HIV co infection were considered as risk factors for ATDH, among them HCV infection, IVDU and HIV infection had the most importance. We recommend that TB patients with HIV, HCV co-infection, and those with IVD addictions have initial screening with liver function test and closely monitored with subsequent tests during treatment. We also recommend that further studies should be conducted to explore the detail mechanism as to why these identified risk factors contribute for development of hepatotoxicity and also further asses those risk factors that are not addresses in this study in detailed.

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Conflict of interest: We declare that there is no conflict of interest in this study.

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