

## RISK FACTORS OF DRUG-INDUCED HEPATITIS IN TB PATIENTS

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## ABSTRACT

**Objectives:** The aim of this research study is to diagnose various factors of risks of ATDH (Anti-TB Drug-induced Hepatitis) in the patients suffering from the disease of TB (Tuberculosis). **Methodology:** In this retroactive research work, we reviewed that clinical records of 194 diagnosed patients of TB in the Nishtar Hospital Multan. We also analyzed the data about the ATDH. The duration of this research was five years from January 2019 to June 2019. The patients of TB who were fulfilling the standard of NTP (National Tuberculosis Program) were the part of this research study. SPSS V.16 was in use for the statistical analysis of the research work. We also used Chi-square and Exact Fisher tests in this research work. **Results:** There were total 194 registered patients of ATDH during treatment and the follow up duration in which 30.78% (n: 63) were female & 65.18% (n: 131) were male patients with an average age of 41.18 years were the participants of this research work. There were statistically significant disparities between the infection of HIV and drug injections in vessels in the patients of ATDH & non-ATDH patients. **Conclusion:** All the previous recognized risk factors for the incidence of ATDH, infection of HIV & IVDU were available with high significance.

**KEYWORDS:** Drug-Induced, Injections, Significance, Tuberculosis, Hepatitis Ethambutol, Incidence, Pyrazinamide.

## INTRODUCTION

Tuberculosis is very serious issue of health in the whole world.<sup>[1]</sup> This is an estimation that 1/3<sup>rd</sup> population of the world has got infection due to Mycobacterium tuberculosis and eight to nine million fresh patients of tuberculosis appear each year.<sup>[2]</sup> In our country Pakistan, it is an important reason of morbidity as well as mortality.<sup>[3]</sup> The basic management of tuberculosis in NTP (National Tuberculosis Program) is the six month course of rifampicin, ethambutol, isoniazid & pyrazinamide which has two phase division.<sup>[4]</sup> Hepatotoxicity is very serious side effect of these drugs that can be the cause of many reactions in the duration of antituberculosis treatment.<sup>[5]</sup> Research work of the past observed the transient rise of the hepatocellular enzymes of serum as ALT & AST in about ten percent patients who got the standard anti-tuberculosis treatment including isoniazid & rifampicin, among these 1% to 2% patients got withdrawal from therapy because of extreme hepatotoxicity which caused fulminant hepatitis.<sup>[6,7]</sup> Majority of the hepatic reactions were depending upon the dose; some were the result of hypersensitivity.<sup>[8]</sup> Some of the risk factors for ATDH are elder age, alcoholism, infection of HIV, infection HBV & HCV and acetylates phenotype.<sup>[6,7]</sup>

Some other factors which can enhance the danger of ATDH are advance stage of TB, Ethnicity of Asia, female gender and improper use of medicines.<sup>[7]</sup> The dysfunction of ATDH normally occur in just some weeks after the start of intensive phase of antituberculosis treatment.<sup>[6,8]</sup> The training of the patient about the different factors of risk for the improvement of the outcome of the treatment in the patients.<sup>[2,9]</sup> The aim of this research work as to determine the risk factors of ATDH in the patients suffering from tuberculosis to improve the out outcome of the treatment.

## METHODOLOGY

In this retrospective research work, we reviewed the records of about 196 patients of TB from January 2019 to June 2019 in the Nishtar Hospital Multan and then assesses the data about ATDH. The patients of Tb diagnosed by the NTP standard were the part of this research work. Patients with minimum two positive sputum smears for SSP-AFB or a radiology of chest suggesting TB with at least one positive sputum culture for the presence of M. tuberculosis & one SSPAFB were necessary for pulmonary tuberculosis as positive (PTB+). Negative patients were available with negative results in all of these results. The identification of the ATDH was

depending upon the clinical outcome and findings of laboratory of increased ALT.

The diagnosis of the patients suffering from ATDH carried out if there was not any visible reason for elevated tests of liver function and if patients was available with one of the following conditions as an increase of 5 times in the upper value of the normal levels of ALT of serum or no sign or some symptoms of the viral infection of hepatitis. We selected three non-ATDH controls for every patient of ATDH. We collected all the information about demography and risk factors in the patients on a well-organized Performa. SPSS V. 16 was in use for the statistical analysis of the collected information. Ethical committee of the hospital gave the permission to conduct this research work.

## RESULTS

Total 194 patients including 30.78% (n: 63) females & 65.18% (n: 131) males with an average age of 41.18 years were the registered patients for ATDH in the process of treatment as well as period of follow up. There was occurrence of ATDH in 59.8% (n: 119) patients in the duration of 1<sup>st</sup> two months of treatment. Only 2.0% (n: 2) patients met their death because of ATDH. Past viral infections of HBV & HCV were available in 36.89% (n: 75) patients, among these patients, most patients (76.0%) were available with the past background of imprisonment & drug addicted through injections. Some other outcomes in the patients group of ATDH and non-ATDH are present in Table-1.

**Table 1: Demographic characteristics and risk factors for drug hepatotoxicity among TB patients.**

Variables		ATDH (Cases, n=194)		Non ATDH (Control, n=590)		P value	Odds ratio OR, 95% CI
		No	Percent	No	Percent		
Sex	Male	131.0	65.18	354.0	57.88	0.0500	1.38, 0.7-1.7
	Female	63.0	30.78	236.0	38.8		
Age (Year)	>35	143.0	71.18	314.0	51.18	0.0001	2.38, 1.5-3.2
	<35	51.0	24.78	276.0	44.78		
Smoking		77.0	37.88	167.0	26.38	0.0028	1.68, 1.2-2.3
IVDU		107.0	53.00	56.0	7.68	0.0001	9.28, 5.5-14.5
Imprisonment		56.0	27.28	69.0	9.88	0.0001	3.8, 2.1-2.3
Alcohol consumption		6.0	2.00	5.0	1.18	0.0100	3.48, 1.3-7.7
Viral co infection	HBV	14.0	6.8	23.0	2.18	0.0200	2.00, 1.1-3.6
	HCV	59.0	28.78	16.0	1.00	0.0001	12.18, 6.2-22.7
	HIV	12.0	5.8	4.0	1.00	0.0001	5.48, 2.6-17.5
Cavitary TB		55.0	26.78	110.0	16.78	0.0038	1.68, 1.2-2.3

## DISCUSSION

In current research work elder age, cigarette smoking, drug usage through injections, imprisonment, high usage of alcohol, viral infections of HCV & HBV and infection of HIV were the most common risk factors for the complication of ATDH as discovered by previous research works. There was significant amount of infection HCV was available in ATDH patients & non-ATDH patients, the patients with positive HCV were available with high risk as compared to the HCV negative patients. Same findings were the outcome of some other research works.<sup>[6,10]</sup> Very same to the other research works, we discovered relationship between positivity of HBsAg and occurrence of hepatotoxicity.<sup>[11]</sup> The impact of HCV infection was much high as compared to the influence of infection of HBV. Getnet stated very less proportion of the patients who are available as positive for Anti-Hepatitis C virus antibody & HBsAg in his research work.<sup>[2]</sup> The rate of occurrence of positivity of HIV in the patients of ATDH was much high as compared to the cases of non-ATDH. This result proves that patients with HIV infection are available with high risk for the development of ATDH as compared to the HIV negative patients. Ungo in the year of 1998, Pedral- Sampaio in 2004 & Yee in 2003 stated the same

results in their research works.<sup>[10,12,13]</sup> This was due to the usage of various drugs before the identification of the tuberculosis by the patient which can lead to the low immunity in those patients.<sup>[14]</sup> Similar to the many research works of the past the consumption of alcohol is one established factor for the development of ATDH.<sup>[13,15,16]</sup> in this current research work, we also discovered this association. Imprisonment was another risk factor for ATDH but reasons behind this fact are not well clear.

Some research works stated the malnutrition as an independent risk factor for the development of ATDH.<sup>[15]</sup> In this current research work, most of the patients were available with low weight showing some degree of this risk factor of malnutrition in them. Similar to many research works of the past which showed that patients with high age have high danger of acquiring hepatotoxicity.<sup>[10,12]</sup> in current research, we observed the same result. There are some studies which have the opposite opinions about the elder age as a risk factor.<sup>[17]</sup> We also stated cigarette smoking as an impart risk factor. A research work also confirmed this finding.<sup>[6]</sup> There are some limitations of this research work as this was a retroactive work and it did not describe the influence of every risk factor. This study was also unable to describe

the association between different variables. This research work was a single center study and there is need of further research works to consolidate the findings of this research work on general population.

## CONCLUSION

Similar to the studies of past elder age, cigarette smoking, drug usage through injections, imprisonment, consumption of alcohol, infections of HCV & HBV and infection of HIV are the main factors of risk for ATDH. The findings of this research work recommend the tests for liver function for the patients of tuberculosis. There is also need of future research works to determine the detail processes about the role of the risk factors for the development of the other complications as hepatotoxicity and those further research works will help in the consolidation of the findings of this research study.

## REFERENCES

1. Mirhaghani L, Nasehi M. National tuberculosis program in Iran. Ministry of Health (Nashr-e Seda), 2002; 15-20.
2. Fernandez-Villar A, Sopena B, Fernandez-Villar J, Gallardo RV, Ulloa F, Leiro V, et al. The influence of risk factors on the severity of antituberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis.*, 2004; 8(12): 1499-1505.
3. Fitzgerald DW, Sterling TR, Haas DW. *Mycobacterium tuberculosis*. In: Mandell GL, Bennett JE, Dolin R. (editors). *Principle and Practice of infectious diseases*. 7th ed., USA, Philadelphia; Churchill Livingstone, 2010; 31293163.
4. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R, et al. Antituberculosis drug induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol*, 2008; 23(2): 192-202.
5. Yew WW, Leung CC. Anti-tuberculosis drugs and hepatotoxicity. *Respirology*, 2006; 11(6): 699-707.
6. Patel KJ, Kedia MS, Bajpai D, Mehta SS, Kshirsagar NA, Gogtay NJ. Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral center: a prospective study. *BMC Clin Pharmacol*, 2007; 28(7): 8-16.
7. Pol S, Lebray P, Vallet-Pichard A. HIV Infection and Hepatic Enzyme Abnormalities: Intricacies of the Pathogenic Mechanisms. *Clin Infect Dis.*, 2004; 38: 65-72.
8. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D. Anti-tuberculosis drug-induced hepatotoxicity. The role of hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med*, 1998; 157: 1871-1876.
9. Anand A, Seth AK, Paul M, Puri P. Risk Factors of Hepatotoxicity during Anti-Tuberculosis Treatment. *MJAFI*, 2006; 62: 45-49.
10. Alavi SM, Salami N. The causes of death among patients with tuberculosis in Khuzestan, Iran. *Pak J Med Sci.*, 2008; 24(2): 217-220.
11. Kishore PV, Palaian S, Paudel R, Mishra P, Prabhu M, Shankar PR. Drug induced hepatitis with anti-tubercular chemotherapy: Challenges and difficulties in treatment. *Kathmandu Univ Med J.*, 2007; 5(2): 256-260.
12. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during anti-tuberculosis treatment. *Am J Respir Crit Care Med*, 2002; 166: 916-919.
13. Pan L, Jia Z, Chen L, Fu E, Li G. Effect of antituberculosis therapy on liver function of pulmonary tuberculosis patients infected with hepatitis B virus. *World J Gastroenterol*, 2005; 11: 2518-2521.
14. Yimer G, Aderaye G, Amogne W, Makonnen E, Aklillu E. Anti-Tuberculosis Therapy-Induced Hepatotoxicity among Ethiopian HIV-Positive and Negative Patients. *PLoS ONE*, 2008; 3(3): e1809. doi: 10.1371/journal.pone.0001809.
15. Pedral-Sampaio DB, Alves CR, Netto EM, Brites C, Oliveira AS. Efficacy and safety of Efavirenz in HIV patients on Rifampin for tuberculosis. *Braz J Infect Dis.*, 2004; 8: 211-216.
16. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*, 2003; 167: 1472-1477.
17. Mahmood K, Hussain A, Jairamani KL, Talib A, Abbasi B. Hepatotoxicity with anti-tuberculosis drugs: The risk factors. *Pak J Med Sci.*, 2007; 23: 33-38.