HEPATOTOXICITY IN PATIENTS USING DOT THERAPY IN BANNU, KHYBER PAKHTUNKHWA, PAKISTAN

Mohammad Shoaib Khan[1], Sajid Khan[2], Amjad Mustafa[3], Mohammad Zohaib Khan[4], Ikram ul Haq[5], Mohammad Shoaib Khan[6]

ABSTRACT

Background: Tuberculosis is an infectious and serious major health problem that leads to approximately three million deaths every year throughout the developing world. Although, ATT drugs have been used globally to control tuberculosis. Yet, it is reported as one of the causes of hepatotoxicity.

Objective: Hepatotoxicity in TB patients using DOT therapy in District Bannu, Pakistan.

Methods: This cross-sectional comparative study was conducted in DHQ teaching Hospital Bannu, Khyber Pakhtunkhwa, Pakistan, in one year period from February, 2015 to Jun 2019.

Result: In this study of total 100 cases, male were 42% and female were 58% with male to female ratio was 0.72. Illiterates were 79% and educated were 21%. The commonest age group was 44-48 years. 37% patients showed no hepatotoxicity, 57% were with mild LFT alteration while 6 % developed marked hepatotoxity. The values of ALT before and after using ATT were compared by applying paired t-test and the statistical analysis(p-value) showed significant differences.

Conclusion: This study show high Hepatotoxicity in district Bannu especially very high prevalence in rural areas when compared to urban areas. Also the ratio is high in females as compared males and the commonest age group involved were 21 -40 years.

Key Words: Mycobacterium tuberculosis, DOTs therapy, Hepatoxicity.

INTRODUCTION

TB caused by pathogenic microorganism *Mycobacterium Tuberculosis*, is a chronic Granulomatous inflammation of any organ of the body[1] and globally is still most prevalent disease affecting 08 million new cases annually, of which about 3.5 million cases have pulmonary tuberculosis[2].

Tuberculosis can be treated using group of antibiotics; mostly used are Rifampicin and Isoniazid antibiotics. Eradiation & control of drugs resistant Tuberculosis especially multi drugs resistant TB is global challenge[3]. For that purpose, DOTS, started in 1970s by Tuberculosis Research Centre and then WHO started STP to overcome the global tuberculosis emergency[4]. TB is socioeconomic and infectious disease present almost in the entire world, globally 9.4 million new TB cases have been reported in 2009, of which 95% were in less developed areas including Asia, Middle east, Latin America etc.[5]

Liver injury may result by excessive use or unnecessary use of drugs, which can lead to transplantation of liver followed by death[6,7]. The hepatic intoxication leading to liver injury is the most notable manifestation of drug abuse includes stages started with no signs to hepatic enzyme elevation due hepatic failure[8].

Globally ATTs drugs have controlled tuberculosis. Anti-tubercular therapy (ATT) is the main cause of hepatotoxicity[9-11]. British thoracic society indicate the stoppage of drugs as when there is much elevation in ALT, AST and serum bilirubin, the course may be initiated again when these enzyme comes to normal , but this is only possible if early detection of ATT induced hepatotoxicity is identified and demonstrated[12].

The exact mechanism of the hepatotoxicity of ATT is not known but the nutritional conditions, alcoholism, liver abnormalities, reduce albumin levels, inappropriate and inadequate drug use, sex and age all have some sort of contribution in liver toxicity and liver damage[13,14]. There is much negative effect of ATT regimen like isoniazid, pyrazinamide and Rifampicin by the drug induced hepatotoxicity, immunodeficiency has increase effect

1Department of Biochemistry, Bannu Medical College, Bannu (KP),Pakistan.
2Department of MLT, Bannu college of Medical Technologies & Khalifa gulnawaz Teaching Hodpital Bannu, (KP),Pakistan.
3Department of Pharmacology, KMU, IMS, Kohat (KP),Pakistan.
4Department of Forensic Medicine, Peshawar Medical College, Peshawar (KP),Pakistan.
5Principal scientific Officer/Director technical, National Institute of Health, Islamabad
6Department of Surgery, Bannu Medical College, Bannu (KP),Pakistan

Address for correspondence:
Prof. Dr. Mohammad Shoaib Khan
HoD, Biochemistry Bannu Medical College, Bannu, Pakistan.
E-mail: mshoaibkhan2003@yahoo.com

on the tuberculosis so these patients are more hepatotoxic susceptible[15,16]. Beside this, there is no proper documented proof as weather to continue ATT or not, or when to reintroduce these drugs[17]. Keeping these in mind the present study was aimed with the objective to find out the hepatotoxicity risks associated with the use of ATT drugs in TB patients in district Bannu.

MATERIALS & METHODS

Study design

Cross sectional comparative study

Study population & Period

Patient referred to DHQ Teaching hospital for DOT therapy in 0ne year period i,e. from February, 2019 to February, 2020.

Inclusion & Exclusion criteria

All the patient of any age and sex advised sputum for AFB and Patients prescribed to receive ATT for confirmed pulmonary or extra pulmonary tuberculosis under the Revised National Tuberculosis Control Program schedule were included, While, patients not receiving isoniazid or Rifampicin as a part of therapy or patients with pre-existing acute or chronic liver disease/ fatty liver, Chronic alcohol intake and Patients with other chronic illnesses like malignancy and not willing person etc were excluded.

Sample collection & analysis

Sputum & blood samples were collected in standard manner as prescribed by WHO and processed as per standard protocol.

Statistical analysis

The results obtained were subjected to statistical analysis by using SPSS version 20 and level of significance were calculated.

RESULTS

The results of the study are tabulated at tables 1-3 & graphs 1.1.

The tuberculosis patient was categorized according to their gender. Out of total 100 patients, the male patients were 42% while female patients were found 58% having male to female ration of 0.72. When the tuberculosis patients were categorized according to the level of education, the results showed that most of the patients in our study population were illiterates with overall percentage of 79%, while the percentage of educated patients were found to be 21%. Similarly, the patients were also categorized according to the level of their social status vs poor and medium. Most of the patients were poor status with overall percentage of 71% while, the percentage of medium social level patients was found 29%.

When tuberculosis patients were categorized according to the change in ALT level vs No- hepatotoxicity, Mild LFT alteration and marked hepatotoxicity. The results of our study showed that 37% patients were with No-hepatotoxicity, 57% were with mild LFT alteration while 6 % developed marked hepatotoxicity(Table 1 & Figure 1.1). The values of ALT before and after using ATT were compared by applying paired t-test and the statistical value were considered based on p-value as less than $\alpha = 0.05$. Our obtained value 0.003 is less than 0.05 which indicate that ATT affect the LFTS and is responsible for hepatotoxicity in patients using ATT (Table 2).

Table 3 depicts biochemical profiles of various parameters as comparing their median values with standard deviation before starting ATT in different categories. The patients who suffered hepatotoxicity had significantly lower median values. Total protein values before and after use of ATT shows slight alteration.

DISCUSSION

The different study's findings show that imbalance nutrition and prolong disease condition are prominent risk factors for anti-tubercular drug induced hepatotoxicity (ATT-DIH). Subclinical elevations and change in ALT and AST liver enzyme levels with co-existence of poor nutrition and prolong disease should give alarm for hepatotoxicity. For those Patients which have elevated baseline level of enzyme profile should be advised non-hepatotoxic ATT. Abrupt declines in Renal function gives signals of increased risk for ATT-DIH. Mild Liver enzyme alteration has been reported in 20% of patients[18,] which is an agreement to our study, however it may possible to reverse this damaging or altering liver enzyme function by proper evaluation of patients[19].

Study showed that 1 to 3% of patients undergo severe liver impairment, but in India this rates are even

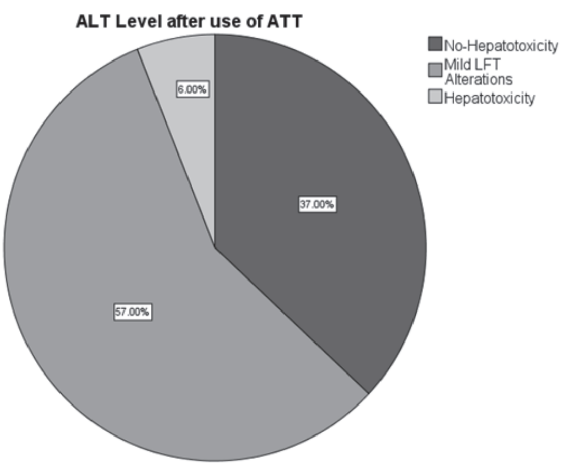

Figure 1.1: Graph showing change in ALT after use of Anti Tubercular Therapy

Table 1: Anthropometric and hepatotoxicity characteristics of studied individuals

Parameters		Subjects	Analysis	
			% age	Overall
	N	100	-	-
Gender	Male	58.0	58 %	100
	Female	42.0	42 %	
Social status	Poor	71.0	71 %	100
	Medium	29.0	29 %	
Educational Status	Illiterate	79.0	79 %	100
	Educated	21.0	21 %	
Hepatoxicity	No hepatotoxicity	57.0	57%	100
	Mild hepatotoxicity	37.0	37%	
	Marked hepatotoxicity	6.0	6 %	

Table 2: Paired Samples Statistics & paired sample test

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ALT Before use of ATT	31.8700	100	12.45003	1.24500
	ALT After use of ATT	68.7200	100	123.22477	12.32248

Paired Samples Test

		Paired Differences					T	Df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	ALT (Before)	-36.85000	122.64792	12.26479	-61.18601	-12.51399	-3.005	99	0.003
	ALT (After)								

Tables 3: Biochemical findings of liver functions before & after ATT therapy

Parameters	No-Hepatotoxicity	Mild LFT Alterations	Hepatotoxicity
ALT (M ± SD)			
ALT Before use of ATT	33.70 ± 11.68	30.50 ± 12.96	33.50 ± 12.38
ALT After use of ATT	32.08 ± 5.60	55.66 ± 24.46	418.66 ± 367.27
AST (M ± SD)			
AST Before use of ATT	232.16 ± 80.16	204.03 ± 85.46	230.00 ± 82.38
AST After use of ATT	216.21 ± 67.10	236.78 ± 70.43	287.16 ± 73.70
SBR (M ± SD)			
SBR Before use of ATT	0.62 ± 0.12	0.66 ± 0.20	0.66 ± 0.18
SBR after use of ATT	0.84 ± 0.16	1.02 ± 0.34	5.28 ± 2.7
T.Protin (M ± SD)			
T.Protin Before use of ATT	7.19 ± 0.57	7.42 ± 0.49	7.18 ± 0.41
T.Protin after use of ATT	7.34 ± 0.49	7.29 ± 0.59	7.86 ± 0.45
ALBUMIN (M ± SD)			
ALBUMIN Before use of ATT	4.49 ± 0.46	4.59 ± 0.55	4.58 ± 0.34
ALBUMIN after use of ATT	4.45 ± 0.40	4.41 ± 0.47	2.76 ± 0.45

more sever i,e. from 8 to 39%[20]. Therefore, it is highly recommended to make proper evaluation for starting DOTS therapy because if this damaging process of liver goes undetected, liver failure would occur which would proceed to death unless immediate liver transplant surgery is carried out.

The available studies strongly showed emphasis on evaluation of LFT before starting ATT and to adopt the criteria for strict compliance to carry out routine examination of liver function during treatment of patients which has abnormalities and patients with hepatitis B or C either previously infected or currently[21-22]. The results of our study are mimic with these findings and showed that 37% patients developed no hepatotoxicity, 57% were with mild LFT alteration while 6 % developed marked hepatotoxity. Similarly, in our study, when the values of ALT before and after using ATT were compared by applying paired t-test, the p-value showed significant differences, which indicate that ATT affect the LFTS and is responsible for hepatotoxicity in patients using ATT.

Raised ALT levels give signals to investigate viral hepatitis and to see toxicity to any other used drugs and also need frequent monitoring. In those patients which has already abnormal liver function test, ATT should not be started until their LFT become normal with rest, proper balance diet and hepatoprotective therapies.

There is no any proper liver enzyme frequency evaluation procedures, however it is documented by some renowned societies, such as American thoracic society, whereas, it is recommended to evaluate LFTs in every 2 to 4 weeks in patients who are at risk and similarly, JTC-British thoracic society guidelines suggest to evaluate LFTs in every week for first 2 weeks, then every 2 weeks for 2 months[23-24]. In Chinese national program, before starting ATT liver enzyme level are checked and then after every two months the LFTS are checked[25].

Typical approach for prevention of ATT-DIH is to stop INH if level of ALT high as much as 3-fold from normal range, beside with jaundice and also if patients complain with symptoms of hepatic illness. However, if this symptom is not present, rise in ALT level 5 folds is deciding factor[26]. After withdrawal of ATT, if the condition remains the same, proper investigations for such patients like autoimmune disease must be considered. To switch again to ATT depends on risk benefit assessment, and it also needs careful assessment and frequent follow up of patient with continuous monitoring of liver function, due to relapse chance of liver injury.

CONCLUSION

Anti-Tuberculosis Treatment induce hepatotoxicity in certain population, Various risk factors associating ATT-DIH are poor nutritional conditions, smoking and tobacco & pan use, improper use of ATT drugs etc. besides, this females showed more hepatotoxicity than males. So, it is recommended to have regular liver function test investigation before, during and after the DOT therapy and stoppage of ATT drugs if hepatotoxicity is developed.

REFERENCES

1. Godreuil S , Torrea G, Terru D, Chevenet F, Diagbouga S, Van de Perre P et al. First Molecular Epidemiology Study of M. tuberculosis in Burkina Faso . JclinMicrobiol,2007; 45 (3) : 921-27.
2. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis- estimated incidence, Prevalence, and Mortality by Country. JAMA 1999.
3. Shinnick T, Good R. Diagnostic mycobacteriology laboratory practices. Clin Infect Dis. 1995; 21: 291-99.
4. World Health Organization. Global Tuberculosis Program. Global Tuberculosis Control WHO,2010.
5. Raviglione MC, O'Brien RJ. Tuberculosis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine. 18 edn. New York: Mc Graw-Hill Medical Publication Division. 2012; 1340-1359.
6. Nilesh Mehta, MD, Lisa Ozick, MD, Emmanuel Gbadehan, MD, 'Drug-Induced Hepatotoxicity'. Meds cape reference, Drugs, Disease and procedure, April 26, 2010. Available at: http://emedicine.medscape.com/article/169814-overview. Accessed July 2014
7. Crofton SJ, Norman H, Miller F. Clinical Tuberculosis. London: MACMILLAN Education Ltd. 1999; 2:8-12.
8. National Guidelines and Operational Manual for Tuberculosis Control. Dhaka: Directorate General of Health Services. 2009: 4:12-15.
9. Mahmood K, Hossain A, Jairamani KL, Talib A, Abbasi BU, Salkeen S. Hepatotoxicity with anti-tuberculosis drugs: the risk factors. Pakistan Journal of Medical Sciences. 2007; 23(1): 56-59.
10. Nahar BL, Hossain AKMF, Islam MM, Saha DR. A comparative study on the adverse effects of two anti-tuberculosis drugs regimen in initial two-month treatment period. Bangladesh J Pharmacol. 2006; 1: 51-57.
11. Reid RT, Innes JA. Respiratory disease. In: College NR, Walker BR, Ralston SH (Eds). Davidson's principles and practice of medicine. Edinburgh: Churchill Livingstone Elsevier Ltd. 2010; 21:641-730.
12. Shakya R, Rao BS, Shrestha B. Evaluations of risk factors for anti-tuberculosis drug-induced hepatotoxicity in Nepalese population. Kathmandu University Journal of Science, Engineering and Technology. 2006; 2(1): 1-8
13. Mahmood, K., Hussain, A., Jairamani, K. L., Talib, A., Abbasi, B. U., & Salkeen, S. Hepatotoxicity with antituberculosis drugs: the risk factors. Pakistan journal of medical sciences, 2007; 23(1), 33.
14. Saha, A., Shanthi FX, M., Winston A, B., Das, S., Kumar, A., Michael, J. S., & Balamugesh, T. Prevalence

of hepatotoxicity from antituberculosis therapy: a five-year experience from South India. Journal of primary care & community health,2016; 7(3), 171-174.

15. Mahashur AA, Prabhudesai PP. Hepatitis and antitubercular therapy. J Assoc Physicians India. 1991; 39:595–596.

16. Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculosis therapy. Clinical profile and reintroduction of therapy. J Clin Gastroenterology. 1996; 22(3):211–214.

17. Steele MA, Burk RF, Desprez RM. Hepatitis with Isoniazid and Rifampicin; a meta-analysis. Chest. 1991; 99:465–471.

18. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, Fujiwara P, Grzemska M, Hopewell PC, Iseman MD, Jasmer RM, Koppaka V, Menzies RI, O'Brien RJ, Reves RR, Reichman LB, Simone PM, Starke JR, Vernon AA; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society: Treatment of tuberculosis. Am J Respir Crit Care Med. 2003; 167(4): 603-62.

19. Tost JR, Vidal R, Caylà J, Díaz-Cabanela D, Jiménez A, Broquetas JM, Study Group for Severe Hepatotoxicity due to Anti-tuberculosis Drug. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis. 2005; 9(5): 534-40.

20. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest 1991; 99(2): 465-71.

21. [No authors listed] Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society, Thorax. 1998; 53(7): 536-48.

22. Migliori GB, Raviglione MC, Schaberg T, Davies PD, Zellweger JP, Grzemska M, Mihaescu T, Clancy L, Casali L. Tuberculosis management in Europe. Task Force of the European Respiratory Society (ERS), the World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) Europe Region, Eur Respir J. 1999; 14(4): 978-992.

23. Agal S, Baijal R, Pramanik S, Patel N, Gupte P, Kamani P, Amarapurkar D. Monitoring and management of antituberculosis drug induced hepatotoxicity. J Gastroenterol Hepatol. 2005; 20(11): 1745-1752.

24. Byrd RB, Horn BR, Solomon DA, Griggs GA, Toxic effects of isoniazid in tuberculosis chemoprophylaxis. Role of biochemical monitoring in 1,000 patients. JAMA 1979; 241(12): 1239-1241.

25. Xia YY, Hu DY, Liu FY, Wang XM, Yuan YL, Tu DH, Chen YX, Zhou L, Zhu LZ, Gao WW, Wang HY, Chen da F, Yang L, He PP, Li XT, He YJ, Sun F, Zhan SY. Design of the anti-tuberculosis drugs induced adverse reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS). BMC Public Health. 2010; 21(10): 267.

26. Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, Stowasser S, Schlenker-Herceg R, Hansell DM. Effect of Nintedanib in Subgroups of Idiopathic Pulmonary Fibrosis by Diagnostic Criteria, Am J Respir Crit Care Med 2016 Jun 22.