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Extended Abstract

Euro Pharma Chemistry 2019: Association of Nat2 Gene Polymorphism with Antitubercular Drug-induced Hepatotoxicity in North Indian population- Sarvesh Singh- King George's Medical University

Sarvesh Singh

Abstract

Introduction: According to the Global Tuberculosis's Report 2017, the incidence of tuberculosis (TB) in India was approximately 28,00,000 that is one-fourth of the world's TB cases . The Government of India was started the Revised National Tuberculosis Control Programme (RNTCP) in the year 1992, headed by expert committee, for the entire country, in phased manner. This program helps to face the disease in a more managed and classified form by incorporating a new drug regimen – The Directly Observed Treatment Short Course (DON'T). DOTS make's the available to free and compulsory good-quality ant tubercular drugs under direct supervision and making the program more effective. According to the Union Ministry of Health and Family Welfare, 2.6 lakh TB cases were reported in Uttar Pradesh in 2016.

A combination of five ant tuberculosis drugs - isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin - was recommended for first-line treatment. But the success rate of these treatments were depends upon the pharmacokinetics of individual's. Hepatotoxicity is a serious adverse effect due to the use of ant tuberculosis drugs in great TB burden countries.

The occurrence of ATD-induced the hepatotoxicity affects' to management of TB, and leading to delay's or the failure of the treatment.

Materials and Methods:

In this prospective study, patients of age will more than 18 years were recruited from the outpatient department or the inpatient facility of the departments of pharmacology and Therapeutics, Clinical haematology, and Respiratory medicine, Gandhi Memorial and Associated Hospitals, King George's Medical University, Lucknow, Uttar Pradesh, India, between November 2017 to September 2018 after obtaining the ethical clearance from the institute's ethical committee.

A total no of 100 TB positive patients were recruited in this study. Further, the TB patients were divided into two groups on the basis of anti-TB drugs (ATDs)-induced toxicity. After the treatment with ATDs, 30 pulmonary TB patients developed to the clinical or laboratory-confirmed DIH, whereas 70 patients' with pulmonary TB did not develop DIH and constituted the controls.

Informed written consent was obtained from all the TB patients. Clinical data, such as the disease stage, liver function test, treatment details, and the history of comorbid conditions, were extracted from the patients' charts.

Results:

The demographic profiles of the TB patients of ATDIH group and the tolerant control group were shown in the Table 1.

Sarvesh Singh
King George's Medical University, India

There was a significant increase in AST and ALT in the ATDIH wasas compared to the tolerant control group after one month of treatment.

	ATDIH Group (n=30)	Tolerant Control Group (n = 70)	[1]p-value
Age (years) Mean±SD	32.20±7.41	33.38±9.75	0.669
Gender			
Female (%)	12 (40.0%)	34 (48.5%)	0.224
Male (%)	18 (60.0%)	36 (51.4%)	
Height (cm)	162.70±8.84	161.24±7.64	0.407
Weight (kg)	47.83±7.80	49.97±10.63	0.324
BMI (kg/m^2)	18.09±2.65	19.10±3.12	0.128
Baseline LFT			
AST	25.47±6.28	26.89±7.23	0.728
ALT	24.89±5.89	24.07±7.13	0.885
LFT at 1 month of treatment			
AST	139.60±72.70	27.61±16.46	<0.001*
ALT	101.47±52.55	33.43±23.49	<0.001*

TABLE 1: Demographic profile of patients in the ATDIH and tolerant control groups

Here the tolerant control group, localization was 78.57% pulmonary only, and 2.89% extra-pulmonary, and 18.57% both pulmonary as well as the extra-pulmonary. The distribution of TB patients were based on treatment type is shown in Table 2.

	ATDIH Group (n=30)	Tolerant Control Group (n = 70)	[1]p-value
Localization			
Pulmonary	23 (76.67%)	55 (78.57%)	
Extra pulmonary	1 (3.33%)	2 (2.89%)	0.976
Both	6 (20.0%)	13 (18.57%)	
Treatment type			
Category 1	21 (70.0%)	45 (64.29%)	0.65
Category 2	9 (30.0%)	25 (35.71%)	
Smokers (%)	9 (30.0%)	6 (8.57%)	0.571
Drug abusers (%)	5 (16.67%)	3 (4.29%)	0.71

TABLE 2: Distribution of TB patients on smokers, alcoholics, and drug abusers

In this ATDIH group and tolerant control group, the frequency was: fast acetylators (5.71%), intermediate acetylators (33.85%), and slow acetylators (61.40%). There was no significant difference between the ATDIH group and tolerant control group (Table 3)

Acetylator status	ATDIH group (n=30)	Tolerant control group (n=70)	OR (CI)	p-value
Fast acetylators	0 (0%)	4 (5.71%)	Reference	-
Intermediate acetylators	11 (36.66%)	23 (32.85%)	0.22 (0.01-4.59)	0.4432
Slow acetylators	19 (63.33%)	43 (61.40%)	0.24 (0.12-4.83)	0.4579

TABLE 3: Distribution of patients on the basis of N-acetyltransferase-2 (NAT2) genotypes in the ATDIH and tolerant control groups

The frequencies of intermediate acetylators NAT2*5/4, NAT2*6/4, and NAT2*7/4 were comparable between the TDIH and tolerant control groups (p>0.05) (Table 4)

	ATDIH Group (n=30)	Tolerant Control Group (n=70)	OR (CI)	p-value
Fast acetylators	n=0	n=4		
NAT2*4/4	0 (0%)	4 (100%)	Reference	-
Intermediate acetylators	n=11	n=23		
NAT2*5/4	2 (18.18%)	1 (4.34%)	0.06 (0.00-2.33)	0.2771
NAT2*6/4	4 (36.36%)	15 (65.21%)	0.38 (0.01-8.54)	0.7764
NAT2*7/4	5 (45.45%)	7 (30.43%)	0.18 (0.00-3.44)	0.3052
Slow acetylators	n=19	n=43		
NAT2*6/7	3 (15.78%)	4 (9.30%)	0.14 (0.00-3.64)	0.4056
NAT2*5/7	14 (73.68%)	31 (72.09%)	0.24 (0.01-4.79)	0.4578
NAT2*5/6	2 (10.52%)	8 (18.66%)	0.37 (0.01-9.69)	0.9039

TABLE 4: Genotypes frequencies of N-acetyltransferase-2 (NAT2) in the ATDIH and tolerant control groups

The allele frequencies of NAT2*4, NAT2*5, NAT2*6, and NAT2*7 in the ATDIH group were 18.33%, 30.0%, 15.0%, and 36.66%, and in the tolerant control group, they were 22.14%, 28.57%, 19.28%, and 30%, respectively. Allele frequencies of NAT2*4, NAT2*5, NAT2*6, and NAT2*7 were not significantly different in ATDIH and tolerant control groups (Table 5)

	ATDIH Group (n=60)	Tolerant Control Group (n=140)	OR (CI)	p-value
NAT2*4	11 (18.33%)	31 (22.14%)	Reference	------
NAT2*5	18 (30.0%)	40 (28.57%)	0.78 (0.31-1.91)	0.7614
NAT2*6	9 (15.0%)	27 (19.28%)	1.06 (0.38-2.95)	0.9045
NAT2*7	22 (36.66%)	42 (30%)	0.67 (0.28-1.60)	0.4992

TABLE 5: Allele frequencies of N-acetyltransferase-2 (NAT2) in the hepatotoxicity and non-hepatotoxicity groups

Discussion

The Tuberculosis (TB) remains an important cause of mortality and morbidity worldwide. In the present study, we observed that gender did not a significant difference between the hepatotoxicity (ATDIH) and the tolerant control groups in eastern Uttar Pradesh patients. The findings of Bose et al. (2011), Rana et al. (2014), and Teixeira et al. (2011) support our study, who observed that the age and gender were not significant risk factors for hepatotoxicity in TB patients. Contrary to our findings, the previous study was done by An et al. (2012) in the Chinese population reported that men formed a significantly higher proportion in the non-hepatotoxicity group were compared with the hepatotoxicity group. The difference in these results may be due to different ethnicity. Another study was also suggests that the female

gender with SA status is an important predictor factor for the anti-TB DIH.

In our study, the mean age of hepatotoxicity is 32.20±7.41 years, which favours the argument that the disease is common in the economically productive age group as compared to other age groups. However, findings by other studies done by Gupta et al. (2013) in the Western India population in terms of the age "median years. Another study on the North Indian population done by Rana et al. (2014) who reported that the mean age of hepatotoxicity was 43.6±18.7 years. Some other studies' by Bose et al. (2010) and Signal et al. (2014) reported that the mean age of hepatotoxicity was 48.17±17 years and 38±6.62 years, respectively. Our study showed that the incidence of hepatotoxicity in Eastern Uttar Pradesh population is more in the earlier age group. This may be due to the poor nutritional condition of a lower socio-economic state population, which may result in more compromised state of liver and more prone to free radical injury.

Limitations

We had to less than one year to be complete our study with a small sample size. The incidence of antitubercular drug was induced hepatotoxicity is very low. Our study is single-centered, not multicentered. Our study is a tertiary level, hospital-based study and not a community based or endogenous study. Due to a lack of funding, we were unable to include the measurement of the plasma concentration of drugs and its metabolites. For a better outcome, we have to study the other genes and oxidizing radicals.

Conclusion

We conclude that NAT2 gene polymorphism was not associated with drug-induced hepatotoxicity in tubercular patients. Gender, age, smoking, and category of treatment were also not risk factors for the development of hepatotoxicity during tuberculosis treatment. Further studies with large sample sizes will be necessary to confirm our findings

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Sarvesh Singh
King George's Medical University, India