Sys Rev Pharm 2021; 12(9): 642-646
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Research Article

NAT2 Genotype-Guided INH Dosage to Reduce Drug-Induced Liver Injury in Thai Patients

Sanchat Thanyanuch[1*], Chuchottaworn Charoen[1], Mahasirimongkol Surakameth[2], Wattanapokayakit Sukanya[2]

[1]Department of Medical Services, Central Chest Institute of Thailand, Ministry of Public Health, Nonthaburi, Thailand
[2]Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand

Article History: *Submitted: 09.09.2021* *Accepted: 23.09.2021* *Published: 30.09.2021*

ABSTRACT

Background: The Slow Acetylator (SA) was associated with a higher risk of Anti-Tuberculosis Drug-Induced Liver Injury (AT-DILI). This study aimed to evaluate whether a lower dose of Isoniazid than that allocated in the conventional treatment, can reduce the incidence of AT-DILI in Thai SA patients.

Methods: The Tuberculosis patients were screened for *NAT2* gene. The SA patients were recruited in an open-label, Randomized Control Trial and randomly assigned in a 1:1 ratio to receive an adjusted or the standard Isoniazid (INH) dose in the first-line regimen. The primary outcome was the AT-DILI incidence.

Results: Among 260 patients undergoing the *NAT2* gene screening, the frequencies of the *NAT2* acetylator were 37.30%, 49.62% and 13.08% for Slow, Intermediate and Rapid Acetylators respectively. 22 of 23 (95.65%) SA patients were included in the Intention-To-Treat analysis. No significant difference in the AT-DILI incidence between the two groups were found: 8.33% in the adjusted INH dose group *vs.* 18.18% in the standard dose INH group, P-value=0.5.

Conclusion: This study demonstrated that the lower dose of INH in Tuberculosis treatment in the SA patients did not reduce the risk of AT-DILI, the application of *NAT2* gene for a guided dosage of INH should be further investigate.

Keywords: *NAT2* gene, Isoniazid, Slow acetylator, Drug-Induced Liver Injury DILI

***Correspondence:** Sanchat Thanyanuch, Department of Medical Services, Central Chest Institute of Thailand, Ministry of Public Health, Nonthaburi, Thailand, E-mail: sthanyanuch@gmail.com

INTRODUCTION

TB is a major public health challenge worldwide. World Health Organization (WHO) reported that the treatment success rate in Thailand was only 82% in 2016 (World Health Organization, 2013) while WHO goal is set at 90%. The first-line treatment regimen for a new Drug-Sensitive Pulmonary Tuberculosis (DS-TB) is a standard six-month four-drug regimen that consists of Isoniazid (INH), Rifampicin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB) for two months, followed by Isoniazid and Rifampicin for four months (2HRZE/4HR). However, this regimen causes several Adverse Drug Reactions (ADRs) that contribute to poor adherences and discontinuation of the treatment 11% (Schaberg T, *et al.*, 1996), leading to treatment failure, and eventually emerging drug resistance (Huang YS, *et al.*, 2002). One of the common ADRs is Drug-Induced Liver Injury (DILI). The prevalence of Anti-Tuberculosis Drug-Induced Liver Injury (AT-DILI) in Thailand was 6.7% (Thongraung W, *et al.*, 2012). Although INH is one of the potential drugs in the first-line regimen, several DILI cases have been reported. The risk factors for INH-DILI include age, female gender, African descent, alcoholism, preexisting liver disease (hepatitis B or C), and concomitant medications such as Rifampicin and Pyrazinamide (LiverTox, 2012). INH is mainly metabolized by N-Acetyltransferase 2 coded by *NAT2* gene, The polymorphism of the *NAT2* gene results in a different rate of INH acetylation classified into three different phenotypes; Rapid (RA), Intermediate (IA), and Slow Acetylators (SA) (Khan S, *et al.*, 2019). Previous studies showed that the SA phenotype was strongly associated with a higher risk of AT-DILI consistently across different ethnic groups (Huang YS, *et al.*, 2002; Ohno M, *et al.*, 2000; Cho HJ, *et al.*, 2007; Khalili H, *et al.*, 2011; Lee SW, *et al.*, 2010; Rana SV, *et al.*, 2012; Wattanapokayakit S, *et al.*, 2016). In contrast, treatment failure was likely to occur in RA (Parkin DP, *et al.*, 1997; Donald PR, *et al.*, 2004). A meta-analysis study by Wang PY, *et al.* concluded that SA phenotype had a higher risk of AT-DILI. Odds Ratios (OR) of AT-DILI for SA compared with the other acetylators was 3.97 (95% Confidence Intervals; 95%CI 2.75-5.74) (Wang PY, *et al.*, 2012).

A study conducted by Azuma J, *et al.* on Japanese patients found that in SA patients *NAT2* genotype-guided dosage of INH (approximately 2.5 mg/kg daily) results in a lower incidence of AT-DILI during the first eight weeks when compared with the conventional standard dose of INH, risk difference; 77.8 %, P=0.003 (Azuma J, *et al.*, 2013). This research study aimed to evaluate whether an adjusted dose of INH, a lower dose than conventional standard dose, can reduce the incidence of AT-DILI in SA patients in Thai population.

METHODS

Study design

An open-label, parallel, Randomized Control Trial was conducted at Central Chest Institute of Thailand (CCIT) from June 2017 to August 2019. The participants were randomly assigned in a 1:1 ratio to receive an adjusted dose or the standard dose of INH in the first-line regimen of Drug-Sensitive Pulmonary Tuberculosis by a computer-generated block of four randomizations. The study protocol was approved by the Ethics Committee of CCIT and has been registered on Thai Clinical Trials Registry: TCTR20210801005.

Study population and participants

The patients with 18 years of age or older who were newly diagnosed with active Pulmonary Tuberculosis for the first time in the TB clinic were recruited and underwent the *NAT2* gene screening, and also their blood samples were collected to identify *NAT2* genotype. During the first week of the screening phase, all patients were prescribed the four-drug standard treatments. After *NAT2* genotype results were reported, the patients with Slow Acetylator phenotype were identified and selected as eligible participant. Exclusion criteria were as follows 1) liver cirrhosis child-pugh C; 2) alcoholism or alcohol consumption within 14 days before re-

cruitment abnormal Liver Function Test at baseline; Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)>three times the Upper Limit of Normal (ULN); 3) the use of herbal medicine 4)HIV infection; 5) Chronic kidney disease with eGFR<30; 6) severe Tuberculosis with a high risk of poor outcome e.g., acute respiratory failure; 7) any condition that may contribute to unfavorable outcome; 8) life-threatening condition such as sepsis, respiratory failure, congestive heart failure; 9) Body Weight<35 Kg and >80 Kg; 10) pregnant and lactating woman. To ensure the efficacy of INH, after the allocation, the patients who had late exclusion criteria as follows 1) DST (Drug-Susceptibility Testing) found INH resistance; 2) Culture proven non-Tuberculosis *mycobacterium*; 3) severe ADRs leading to the disrupted or modified treatment regimen; 4) loss of follow-ups were excluded.

Identification of NAT2 phenotype

NAT2 genotypes were determined by the haplotype-speciic polymerase chain reaction-based method (Nuanjun W, *et al.*, 2020). SA phenotype is either homozygotes or heterozygotes of low activity enzymatic haplotypes (*NAT2**5B, *NAT2**6A, and *NAT2**7B). Homozygous or heterozygous genotypes of high-activity enzymatic haplotypes (*NAT2**4, *NAT2**12A, and *NAT2**13A) were interpreted as RA. Heterozygotes of high and low enzymatic activity haplotypes were determined as IA.

Study medication

In this study, all patients were treated according to the Thai National Tuberculosis Control Program (NTP) guidelines except for INH dosage. In the adjusted INH dose group, the dosage of INH was calculated based on Jung JA, *et al.* study (Jung JA, *et al.*, 2015) which found that the serum concentrations of INH were affected by *NAT2* genotype and Body Weight as in the equation below.

INH concentration (mg/L)=13.821-0.1(Body Weight, kg) × 2.273 (number of high-activity alleles of *NAT2* genotype; 0, 1, 2)

From this equation, to achieve a therapeutic INH concentration level at 3-5 mg/L in the Slow Acetylator participants, zero was substituted for the number of high activity alleles. The INH dosage was presented in *Table 1*.

Table 1: Dose of INH in the adjusted INH dose group

Body weight (Kg)	Dose of Isoniazid (mg/day)
>35-40	100
>40-50	150
>50-65	200
>65-80	250

In the control group, all patients received the standard-dose INH, 300 mg daily, regardless of their Body Weight.

Study procedures

The baseline clinical assessment included demographic data, medical history, symptom profile score, Chest Radiographs, Liver Function Test (LFT), three consecutive sputum AFB (Acid-Fast Bacillus) examinations and culture. All patients were given follow-up treatment in week 2, 4, and 8 during the intensive phase. The symptom profile score, LFT, sputum sample, ADR assessment were collected at each visit. Chest Radiographs were taken in week 8, and week 26 or at the end of the treatment.

Study outcome

The primary outcome was the proportion of patients who had a DILI defined by ALT or AST level ≥ 3 times ULN in the presence of hepatitis symptoms or ALT or AST ≥ 5 times ULN with the absence of symptoms. The secondary outcomes were the proportion of sputum smear conversion in week 2, 4 and 8, culture conversion in week 8, clinical symptoms score, and adverse drug reactions.

Statistical analysis

The data from Azuma J, *et al.* study showed that the incidence of DILI in Slow Acetylators was 77.8% in the conventional standard regimen (Azuma J, *et al.*, 2013). Thongraung W, *et al.* study found that the prevalence of Anti-Tuberculosis drug-induced hepatotoxicity in Thailand was 6.7% (Thongraung W, *et al.*, 2012). The sample size was identified to achieve a power of 0.9 with an alpha of 0.05 and an estimated 15% drop-out rate. The calculated number of subjects in each group was 10.

The primary outcome was analyzed based on the Intention-To-Treat (ITT) approach. The secondary outcomes were analyzed with a Per-Protocol (PP) approach in patients who completed treatment in an intensive phase of the first-line drug regimen. Categorical variables were compared between the two groups with Fisher's exact test and presented as number and percentage. Depending on the distribution of data, continuous variables were presented as the mean and Standard Deviation or median and IQR, and compared using an independent t-test or a Wilcoxon signed-rank test. Univariate analysis was performed to determine the possible risk ratio of DILI between the two groups. Mixed model analysis was used for repeated outcomes.

A two-sided test with a P-value ≤ of 0.05 was considered statistically significant. The precision of the estimates was reported using 95% Confidence Intervals (95% CI). The analysis was carried out using STATA version 15.

RESULTS

Study participants

Between June 2017 and August 2019, the total of 260 TB patients were screened with a blood test for *NAT2* gene, the frequency of *NAT2* genotype and acetylator phenotype are summarized in *Table 2*. The total of 23 Slow Acetylator TB patients were recruited and randomly assigned to a treatment group. According to the late exclusion criteria, two patients were excluded due to severe ADR and loss of follow-ups in the adjusted group, and one patient due to loss of follow-ups in the standard group *(Figure 1)*. The demographic and clinical characteristics of the participants in the two groups were similar except for the cavity lesions in the Chest Radiograph (CXR) and the total bilirubin level *(Table 3)*.

Table 2: Frequency distribution of *NAT2* genotype and acetylator phenotype in screening participants

Diplotype	No. (%)	Acetylator phenotype, No. (%)
*NAT2**5B/*5B	4 (1.54)	Slow 97 (37.30%)
*NAT2**5B/*6A	17 (6.54)	
*NAT2**5B/*7B	11(4.23)	
*NAT2**6A/*6A	23(8.85)	
*NAT2**6A/*7B	31 (11.92)	
*NAT2**7B/*7B	11 (4.23)	
*NAT2**4/*6A	67 (25.77)	Intermediate 129 (49.62%)
*NAT2**4/*5B	19 (7.31)	
*NAT2**4/*7B	33 (12.69)	
*NAT2**5B/*13A	1 (0.38)	
*NAT2**6A/*12A	5 (1.92)	
*NAT2**6A/*13A	1 (0.38)	
*NAT2**7B/*12A	2 (0.77)	
*NAT2**7B/*13A	1 (0.38)	
*NAT2**4/*4	30 (11.54)	Rapid 34(13.08%)
*NAT2**4/*12A	2(0.77)	
*NAT2**4/*13A	2(0.77)	
Note: *indicates Polymorphism		

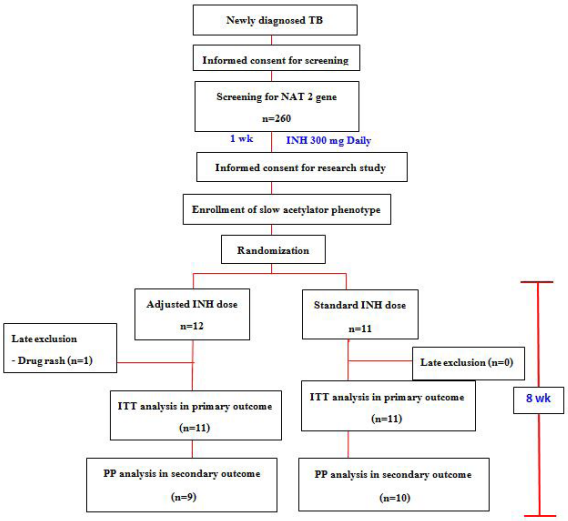

Figure 1: Study flow

Table 3: The demographic and clinical characteristics

Characteristic	Adjusted dose (n=12)	Standard dose (n=11)	P-value
Age (SD)	39.64 (15.13)	50.75 (12.59)	0.07
Male gender-No (%)	9	8	0.64
Female gender-No (%)	2	4	
BW, kg (SD)	59 (8.67)	54.17 (8.07)	0.18
BMI (SD)	20.76 (2.86)	19.78 (2.56)	0.39
Previous TB treatment(n)	0	1(8.33%)	0.87
Smear positive- No. (%)	8 (72.73%)	9 (75%)	0.9
Cavity lesions in CXR (n,%)	8 (72.73%)	2 (16.67%)	0.01
LFT			
AST (IU/ml) (Median,IQR)	20 (17,21)	30 (21,36.5)	0.24
ALT	22 (13,29)	21.5 (13.5,30.5)	0.93
ALP	91 (60,129)	88 (77,125)	0.6
Total bilirubin	0.4 (0.3,0.6)	0.6 (0.45,0.85)	0.05
Direct bilirubin	0.19 (0.16,0.3)	0.3 (0.23,0.39)	0.06
Serum albumin	4.1 (3.9,4.3)	3.9 (3.5,4.25)	0.18
History of smoking (n, %)	4 (36.36%)	1(8.33%)	0.1
Alcohol consumption (n,%)			
Never	6 (54.55%)	8 (66.67%)	0.69
>50 gm/day	3 (27.27%)	2 (16.67%)	
<50 gm/day	2 (18.18%)	2 (16.67%)	
Herb	1 (9.09%)	1 (8.33%)	0.95
NAT2 genotype			
*5B/*5B	2 (16.67%)	0 (0%	0.19
*5B/*6A	0 (0%)	2 (18.18%)	
*5B/*7B	2 (16.67%)	3 (27.27%)	
*6A/*6A	1 (8.33%)	3 (27.27%)	
*6A/*7B	4 (33.33%)	3 (27.27%)	
*7B/*7B	3 (25%)	0 (0%	
Dose of anti-TB drugs, mg/kg/day			
Isoniazid	3.77 ± 0.57	5.01 ± 0.87	<0.01
Rifampicin	11.05 ± 1.75	9.80 ± 1.06	0.05
Pyrazinamide	23.35 ± 8.26	24.27 ± 4.82	0.75
Ethambutol	18.14 ± 2.66	14.52 ± 5.11	0.04

Note: Values are presented as mean ± SD (Standard Deviation), number (%), or median (IQR). BW: Body Weight; BMI: Body Mass Index; LFT: Liver Function Test; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; *NAT2* : N-Acetyltransferase 2; TB: Tuberculosis; * indicates polymorphism

Primary outcome

In total, 22 of 23 (95.65%) patients were included in the ITT analysis. Between the two groups, no significant differences were found in AT-DILI within the first eight weeks of Tuberculosis treatment: 1 out of 11 (8.33%) in the adjusted INH dose group *vs.* 1 out of 11 (18.18%) in the standard dose INH group, P-value=0.51 *(Table 4)*. The risk ratio of AT-DILI in the adjusted INH dose group compared to the other was 0.46 (95% CI 0.05-4.38, P=0.48). Also, there were no significant differences in AST and ALT levels between the two groups during the first eight weeks of treatment *(Figures 2 and 3)*.

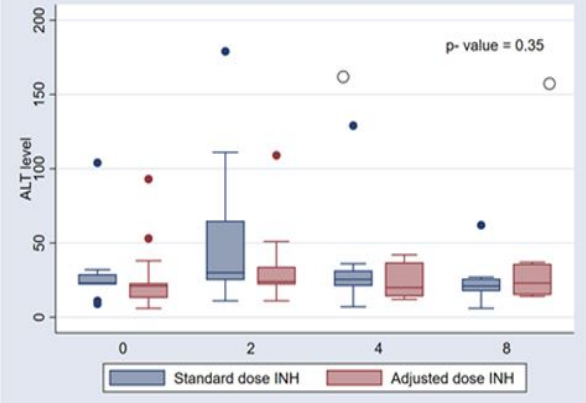

Figure 2: Aspartate Transaminase (AST) between 2 group

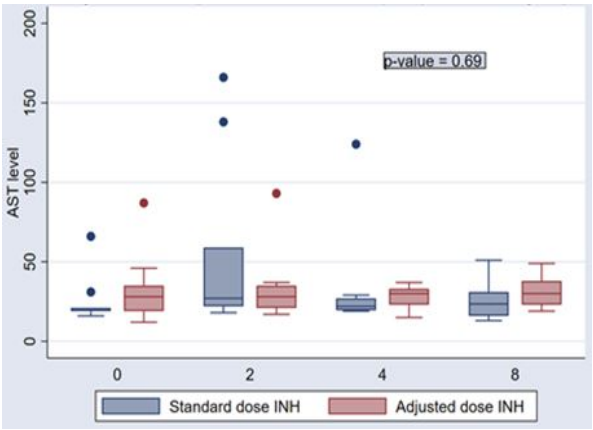

Figure 3: Alanine Transaminase (ALT) between 2 group

Table 4: Primary outcome and secondary outcome

Outcome	Adjusted dose	Standard dose	P-value
AT-DILI (n,%)	1 (8.33%)	2 (18.18%)	0.51
Sputum conversion at 2 week	6 (50%)	4 (36.36%)	0.53
Sputum conversion at 4 week	6 (50%)	5 (45.45%)	0.68
Sputum conversion at 8 week	6 (50%)	7 (63.64%)	0.68
Culture conversion at 8 week	3 (25%)	7 (63.64%)	0.14
Adverse Drug Reaction (ADR)	3 (25%)	3 (27.27%)	0.91
Serious Adverse Effect (SAE)	1 (8.33%)	0 (0%)	0.35

Secondary outcome

The total of 19 of 23 (82.60%) patients were included in the PP analysis to assess the efficacy in terms of sputum conversion in week 2, 4 and 8 and sputum culture conversion in week 8. In addition, the safety profile was evaluated in the secondary outcomes. There were no significant differences in secondary outcomes between the two groups, as shown in *Table 2*.

DISCUSSION

In the present study, the frequencies of *NAT2* acetylator were respectively 37.30% 49.62%, and 13.08% for Slow, Intermediate, and Rapid Acetylators. The distribution of SA phenotype in the Thai population in our study was concordance with previously reported from the northeastern region of the country which showed that the frequency of SA phenotype was 36.2% (Kukongviriyapan V, *et al.*, 2003). However, another study from the southern region demonstrated a higher prevalence of SA phenotype, 52.7%, among new TB patients (Ungcharoen U, *et al.*, 2020). The different distribution of *NAT2* acetylator in different regions in Thailand has to be confirmed.

This study concluded that in Tuberculosis patients with SA phenotype, the potential risk factor for AT-DILI, no significant differences in the incidence of AT-DILI between the adjusted INH dose and the standard dose group were established. This finding corresponded to that of Ungcharoen U, *et al.* study which showed that the median INH plasma concentration two hours after drug administration was 4.25 (IQR 3.56-5.51) µg/mL in SA patients who received treatment with the standard first-line anti-TB drug containing Isoniazid 5.3 ± 0.7 mg/kg daily (Ungcharoen U, *et al.*, 2020); as a result, this plasma concentration remained within the therapeutic range (3-5 µg/ml). In contrast, according to a previous study by Azuma J, *et al.* TB patients with SA phenotype who received the standard dose treatment (INH 5 mg/kg) had a higher incidence of DILI compared to those given the *NAT2* genotype-guided dose treatment (2.5 mg/kg); 77.8% *vs.* 0% P=0.003) (Azuma J, *et al.*, 2013).

A meta-analysis study of Suvichapanich S. *et al.* reported that the *NAT2* ultra-Slow Acetylators (*NAT2* genotypes of *6A/*6A, *6A/*7B, and *7B/*7B) contributed to a higher risk of AT-DILI (OR 3.60; 95% CI: 2.30-5.63; p<0.001) than all *NAT2* Slow Acetylators (OR 2.80; 95% CI: 2.20-3.57; p<0.001) (Suvichapanich S, *et al.*, 2018). Mushiroda T, *et al.* study also demonstrated that among the SA patients, the variant diplotype, *NAT2* *6A/*6A, had the highest risk of DILI (OR 6.47, 95% CI 1.78-23.6, P=0.006) (Mushiroda T, *et al.*, 2016). This finding was supported by the data from Ungcharoen U, *et al.* study, which showed that only *6A/*6A diplotype had INH plasma concentration higher than the therapeutic range (the median INH plasma concentration two hours after administration 6.54 (Interquartile Range (IQR) 6.45-6.62) µg/mL) (Ungcharoen U, *et al.*, 2020). Therefore, some specific *NAT2* genotypes such as *6A/*6A may pose a much greater risk of AT-DILI than the others.

In this study, there were only three cases of 6A/*6A diplotype out of 23 (13.04%), which may result in a lower incidence of AT-DILI than in the previous studies. Moreover, some patients who experienced AT-DILI during the screening phase in the first week after receiving the Anti-Tuberculosis drug were not enrolled in this study. This brought about a lower incidence of AT-DILI than that in the general population, causing no detected statistical differences. In opposition to the previous Randomized Control Trial (RCT) study (Jung JA, *et al.*, 2015), this study found that a lower dose of INH in Tuberculosis treatment for reducing the risk of AT-DILI was inconclusive outcomes and further study with more subjects is required.

There were several limitations to this study. Firstly, INH plasma concentrations were not measured; it is therefore not conclusive that the AT-DILI was directly associated with INH toxicity. Secondly, even though the

sample size was statistically calculated based on the incidence of DILI in SA patient population, the total number of participants was minimal. This perhaps underestimated the outcome of the treatment, and was the reason why statistical difference could not be detected. Lastly, the study was designed to follow up on the patients for only eight weeks of their intensive treatment; consequently, the efficacy outcome in terms of relapse/recurrent of Pulmonary Tuberculosis (PTB) was not evaluated.

CONCLUSION

In conclusion, this study demonstrated that the lower dose of INH in the first-line drug treatment for drug-susceptible Tuberculosis in the SA patients did not reduce the risk of AT-DILI. The finding counters that in the previous RCT study. Therefore, to treat TB patients with a lower dose of INH to prevent AT-DILI is still controversial. The application of *NAT2* gene for a guided dosage of INH should be further investigated.

ACKNOWLEDGEMENTS

This project was financially supported by the Government of Thailand through the Department of Medical Services, Ministry of Public Health (MOPH). *NAT2* genotype analysis was also supported by the Medical Genetics Center, Department of Medical Sciences, MOPH. The authors would like to thank all medical staff at TB clinic, Central Chest Institute of Thailand for their facilities and to care for participants.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2013. World Health Organization. 2013.
2. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of Isoniazid, Rifampicin and Pyrazinamide in patients hospitalized for pulmonary tuberculosis. Eur Respir J. 1996; 9(10): 2026-2030.
3. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, *et al.* Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for anti-tuberculosis drug-induced hepatitis. Hepatology. 2002; 35(4): 883-889.
4. Thongraung W, Sittidach M, Khwansuwan P, Sariyasuntorn K, Wongsampan S. Evaluation of the physicians' approach to the diagnosis and treatment of patients with anti-tuberculosis drug-induced hepatotoxicity. J Eval Clin Pract. 2012; 18(6): 1119-1125.
5. LiverTox. Clinical and research information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. 2012.
6. Khan S, Mandal RK, Elasbali AM, Dar SA, Jawed A, Wahid M, *et al.* Pharmacogenetic association between *NAT2* gene polymorphisms and Isoniazid induced hepatotoxicity: Trial sequence meta-analysis as evidence. Biosci Rep. 2019; 39(1): BSR20180845.
7. Ohno M, Yamaguchi I, Yamamoto I, Fukuda T, Yokota S, Maekura R, *et al.* Slow N-Acetyltransferase 2 (*NAT2*) genotype affects the incidence of Isoniazid and Rifampicin-induced hepatotoxicity. Int J Tuberc Lung Dis. 2000; 4(3): 256-261.
8. Cho HJ, Koh WJ, Ryu YJ, Ki CS, Nam MH, Kim JW, *et al.* Genetic polymorphisms of *NAT2* and CYP2E1 associated with anti-tuberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis. Tuberculosis. 2007; 87(6): 551-556.
9. Khalili H, Fouladdel S, Sistanizad M, Hajiabdolbaghi M, Azizi E. Association of N- acetyltransferase-2 genotypes and anti-tuberculosis drug induced liver injury: First case-controlled study from Iran. Curr Drug Saf. 2011; 6(1): 17-22.
10. Lee SW, Chung L, Huang HH, Chuang TY, Liou YH, Wu L. *NAT2* and CYP2E1 polymorphisms and susceptibility to first-line anti- tuberculosis drug-induced hepatitis. Int J Tuberc Lung Dis. 2010; 14(5): 622-666.
11. Rana SV, Ola RP, Sharma SK, Arora SK, Sinha SK, Pandhi P, *et al.* Comparison between acetylator phenotype and genotype polymorphism of N-Acetyltransferase-2 in tuberculosis patients. Hepatol Int. 2012; 6(1): 397-402.
12. Wattanapokayakit S, Mushiroda T, Yanai H, Wichukchinda N, Chuchottawon C, Nedsuwan S, *et al. NAT2* Slow Acetylator associated with anti-tuberculosis drug-induced liver injury in Thai patients. Int J Tuberc Lung Dis. 2016; 20(10): 1364-1369.
13. Parkin DP, Vandenplas S, Botha FJ, Vandenplas ML, Seifart HI, van Helden PD, *et al.* Trimodality of Isoniazid elimination: Phenotype and genotype in patients with tuberculosis. Am J Respir Crit Care Med. 1997; 155(5): 1717-1722.
14. Donald PR, Sirgel FA, Venter A, Parkin DP, Seifart HI, van de Wal BW, *et al.* The influence of human N-Acetyltransferase genotype on the early bactericidal activity of Isoniazid. Clin Infect Dis. 2004; 39(10): 1425-1430.
15. Wang PY, Xie SY, Hao Q, Zhang C, Jiang BF. NAT2 polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: A meta-analysis. Int J Tuberc Lung Dis. 2012; 16(5): 589-595.
16. Azuma J, Ohno M, Kubota R, Yokota S, Nagai T, Tsuyuguchi K, *et al. NAT2* genotype guided regimen reduces Isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: A Randomized Controlled Trial for pharmacogenetics-based therapy. Eur J Clin Pharmacol. 2013; 69(5): 1091-1101.
17. Nuanjun W, Jirapa P, Punna K, Wimala I, Licht TO, Katsushi T, *et al.* Haplotype-specific PCR for *NAT2* diplotyping. Hum Genome Var. 2020; 7(1).
18. Jung JA, Kim TE, Lee H, Jeong BH, Park HY, Jeon K, *et al.* A proposal for an individualized pharmacogenetic-guided Isoniazid dosage regimen for patients with tuberculosis. Drug Des Devel Ther. 2015; 9: 5433.
19. Kukongviriyapan V, Prawan A, Tassaneyakul W, Aiemsa-ard J, Warasiha B. Arylamine N-Acetyltransferase-2 genotypes in the Thai population. Br J Clin Pharmacol. 2003; 55(3): 278-281.
20. Ungcharoen U, Sriplung H, Mahasirimongkol S, Chusri S, Wichukchinda N, Mokmued P, *et al.* The influence of *NAT2* genotypes on Isoniazid plasma concentration of pulmonary tuberculosis patients in Southern Thailand. Tuberc Respir Dis. 2020; 83(1): S55.
21. Suvichapanich S, Fukunaga K, Zahroh H, Mushiroda T, Mahasirimongkol S, Toyo-Oka L, *et al. NAT2* ultra-slow acetylator and risk of anti-tuberculosis drug-induced liver injury: A genotype-based meta-analysis. Pharmacogenet Genomics. 2018; 28(7): 167-176.
22. Mushiroda T, Yanai H, Yoshiyama T, Sasaki Y, Okumura M, Ogata H, *et al.* Development of a prediction system for anti-tuberculosis drug-induced liver injury in Japanese patients. Hum Genome Var. 2016; 3(1): 1-4.