Polymorphisms of SLCO1B1 Gene in Sundanese Ethnic Population of Tuberculosis Patients in Indonesia

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ABSTRACT

Background: *The blood level of rifampicin, one of the tuberculosis (TB) drugs, depends on the organic anion transporting polypeptide 1B1 (OATP1B1) in hepatocytes. This protein is encoded by the solute carrier organic anion 1B1 (SLCO1B1) gene. Its genetic variation has been reported to have an impact on clinical outcomes and drug efficacy. However, the polymorphism in the SLCO1B1 gene has not been examined in Indonesia yet. We aimed to identify the frequency of polymorphism in SLCO1B1 gene among pulmonary TB patients in Bandung, Indonesia.* ***Methods:*** *Cross-sectional study was conducted in West Java. 145 pulmonary TB patients who were treated with first-line drugs treatment (including rifampicin 450 mg daily) were analyzed for polymorphism in SLCO1B1 gene. Patients aged between 18–64 years old and mainly came from Sundanese ethnic group (92.4%). Genetic variants were detected using Polymerase Chain Reaction (PCR) and Sanger sequencing.* ***Results:*** *Polymorphism of c.463C>A(rs11045819) was not identified, while heterozygous and homozygous polymorphism of c.85-7793C>T(rs4149032) were identified in 74 (51.0%) and 56 (38.6%) patients, respectively. The minor allele frequency (MAF) of T (mutant) allele of c.85-7793C>T(rs4149032) was 64.13% (186/209), higher than in the general population, which the MAF of rs4149032 is 53.6% based on 1000 genome database.* ***Conclusion:*** *This study highlights the presence of different allele frequencies of polymorphisms within the population, which might affect treatment outcomes.*

Keywords: *c.85-7793C>T (rs4149032), c.463C>A (rs11045819), drug transporter, gene polymorphism, West Java, Indonesia.*

INTRODUCTION

Lungs are the most commonly *M. tuberculosis (M.tb)*-infected organ. There are five standard first-line drugs for the treatment of pulmonary tuberculosis (TB), namely: rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin.[1,2] The administration of TB drugs is divided into two categories. The first category is given to new patients, who did not have a previous history of TB treatment, while the second one is given for relapsed cases or patients that were lost to follow-up during treatments, with additional injection regimens and longer duration.[2,3] Among those five drugs, rifampicin, derived from *Amycolatopsis rifamycinica* is the backbone for TB treatment, as it is one of the most effective bactericidal agents against *M. tuberculosis (M.tb)* by inhibiting mycobacterial RNA polymerase through suppression of chain formation in RNA synthesis.[4,5]

The activity of rifampicin against *M.tb* is determined by plasma concentrations of rifampicin.[6,7] Lower plasma concentrations of rifampicin can affect the results of the treatment, including a higher rate of relapse in the continuous phase.[8] Aside from the severity of the disease, low plasma concentration of rifampicin is also related to the course and absorption of drugs inside the patients' body or pharmacokinetics. Weiner et al. mentioned that the polymorphism of c.463C>A (rs11045819) Solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene significantly influenced the pharmacokinetics of rifampicin, resulting in lower plasma concentrations of rifampicin.[9] It was reported that patients with polymorphisms c.463C>A (rs11045819) in the *SLCO1B1* gene experienced lower peak concentrations of rifampicin by 42% compared to wild types.[9]

Organic anion transporting polypeptide 1B1 (OATP1B1), encoded by the *SLCO1B1* gene, plays a role in mediating drugs and their absorption in hepatocytes.[10-13] A study conducted by Kwara in 2014, reported that polymorphism c.463C>A (rs11045819) *SLCO1B1* gene resulted in lower plasma concentrations of rifampicin, especially in men.[14] Other than c.463C>A (rs11045819) polymorphism, Chigutsa et al., identified that c.85-7793C>T (rs4149032) polymorphism in *SLCO1B1* decreased rifampicin concentration in pulmonary TB patients.[8] Moreover, the study detected an allele frequency for this polymorphism of around 70%.[8] In Asia, it is found that the allele frequency for polymorphisms of c.85-7793C>T (rs4149032) *SLCO1B1* is around 56%. While the allele frequency for polymorphism of c.463C>A (rs11045819) *SLCO1B1* is approximately 3%.[8,9,15,16] Minor allele frequencies of these polymorphisms in TB patients have not been reported yet. We aimed to determine the frequency of polymorphisms of the *SLCO1B1* gene in TB patients. Knowing the frequencies of the polymorphisms is important to determine the association between these variables and the effect of TB drugs on clinical outcomes.

METHODS

This is a cross-sectional descriptive study to evaluate the frequency of c.463C>A (rs11045819) and c.85-7793C>T (rs4149032) polymorphisms in the *SLCO1B1* gene in pulmonary TB patients receiving anti-TB drug. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran, (15/UN6. C1.3.2/KEPK/PN/2016, 22). Written informed consent was obtained from all the subjects before the commencement of the study.

Population

A total of 145 TB patients receiving first-line anti-TB drugs and residing in Bandung were enrolled in this study. Patients included were patients aged between 18 and 65 years old, undergoing an intensive phase at the time of the study, and with normal liver function. Normal liver function was defined as an SGPT level below 2.5 x the upper normal limit. The ethnicity of study participants was determined by interview, which is the ethnicity of the subjects' previous two generations (parents and grandparents).

Data Collection

Two phases of data collection were done; initial screening was performed to collect and sort out pulmonary TB patients who met the inclusion and exclusion criteria. When the inclusion criteria are met, whole blood samples were taken. DNA extraction followed by PCR of

the *SLCO1B1* gene was performed. Furthermore, the PCR products were sequenced to obtain the sequence of nucleotide bases which is further analyzed for c.463C>A (rs11045819) and c.85-7793C>T (rs4049302) polymorphisms. An in-depth analysis of each with polymorphism in each patient was done.

DNA Extraction

Genomic DNA was extracted from patients' whole blood using the Salting Out method. The cleaned and washed DNA pellet was re-suspended with TE buffer to complete the process of DNA extraction.[17]

PCR Reaction

The primer mixtures were used to produce amplicons. Forward primer was GGGGAAGATAATGGTGCAAA, and reverse primer was CATCCAGTTCAGATGGACAAAA.

The amplification was done in the following condition: 10 min of initial denaturation PCR activation at 94^{O}C; 35 cycles of denaturation at 94^{O}C for 5 min; annealing at 58^{O}C for 30 seconds, elongation at 72^{O}C for 1 min; and final elongation at 72^{O}C for 7 min. The PCR products were then visualized by mixing 10 ul amplicons with SyberSafe and loading it to 2% gel agarose then electrophoresis with 1% TAE buffer was performed at 100 V for 40 min.[17]

Sanger Sequencing

The PCR product was purified by adding 2 µL of ExoSAP-IT reagent (USB Corporation, Cleveland, OH, USA) to 5 µL of PCR product and incubated for 15 minutes at 37^{O}C and 15 minutes at 80^{O}C for denaturation.[17] Furthermore, DNA concentration was measured using an ND-1000 spectrophotometer (NanoDrop Tech., Rockland, DE, USA) and dissolved up to 100 mg.[17] After adding 0.1 µM of the sequencing primer sequence, the solution was reacted with the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) when the cycle sequencing is performed in a thermal cycler.[17] The result was analyzed using Bioedit software to detect SNPs.

RESULTS

Patient characteristics data related to subsequent data analysis, including age, ethnicity, sex, drugs other than anti TB drugs, body weight, body mass index, HIV status, diabetes mellitus status, and the dose of rifampicin/kg body weight were collected. The basic characteristics of the patients involved are presented in **Table 1**.

Table 1. Patient characteristics.

Characteristics	n=145
Age, years	
Median (Range)	36 (18–64)
Age categories, years (%)	
18–60	134 (92.4)
>60	11 (7.6)
Gender (%)	
Male	80 (55.2)
Female	65 (44.8)
Ethnicity (%)	
Ambonese/ South Moluccans	1 (0.7)
Bataknese	1 (0.7)
Buginese	1 (0.7)
Javanese	7 (4.8)
Minangnese	1 (0.7)
Sundanese	134 (92.4)
Body weight, kilograms	
Mean (SD)	46 (5)
Range	34–58
Body Mass Index/BMI, kg/m^2	
Mean (SD)	17.4 (1.9)
Range	13.8–23.1
BMI categories, kg/m^2 (%)	
<18.5	107 (73.8)
18.5–23.0	38 (26.2)
HIV (+) (%)	3 (2.1)
Diabetes Mellitus (%)	3 (2.1)

A total of 145 patients were enrolled in this study. Most patients were under 60 years old. The proportion of gender in this study (male vs. female) was similar. Since this study was conducted in Bandung, nine out of ten subjects' ethnicity were Sundanese. The mean weight of the patients in this study was 46 kg and about three-quarters were underweight (BMI <18.5 kg/m^2). There were three patients with HIV co-infection (2.1%) and three patients with diabetes mellitus comorbidity (2.1%).

Table 2. The number of polymorphism c.463C>A (rs11045819) and c.85-7793C>T (rs4149032) of SLCO1B1 gene

Characteristics	n=145
c.463C>A (rs11045819) *SLCO1B1* (%)	
CC	145 (100)
CA	0 (0.0)
AA	0 (0.0)
c.85-7793C>T (rs4149032) *SLCO1B1* (%)	
CC	15 (10.3)
CT	74 (51.1)
TT	56 (38.6)

There were no polymorphism c.463C>A (rs11045819) identified as presented in **Table 2**. However, 130 (89.6%) patients were identified carrying c.85-7793C>T (rs4149032) polymorphism of the *SLCO1B1* gene from the analysis of sequencing results. Half of the patients were heterozygous c.85-7793C>T (rs4149032), around 40% were homozygous (c.85-7793T>T (rs4149032) and the remaining 10% of the patients were wild type c.85-7793C>C (rs4149032). Furthermore, the minor allele frequency of c.85-7793C>T (rs4149032) in this group of patients was 64.13% (186/290). The distribution of these polymorphisms based on gender, ethnicity, body weight, and rifampicin dose are presented in **Table 3**.

DISCUSSION

Tuberculosis (TB) is one of the top global problems in the world requiring special attention. It is also the second leading cause of death from a single infectious agent, after the Human Immunodeficiency Virus (HIV).[18] The success of pulmonary TB treatment is influenced by many factors, such as the dose of the drug, the method of administration of the drug, patient compliance, and TB germs. What is important and often overlooked is the achievement of therapeutic concentrations of rifampicin in plasma.

From a previous study, it has been proved that genetic variation in the *SLCO1B1* gene affects rifampicin OATP1B1 transporter and has a negative effect on plasma rifampicin concentration, which might contribute to TB treatment outcome.[8,9,14] Several studies in Indonesia, especially in Bandung, showed low concentrations of plasma rifampicin which varied between individuals. This variation can be caused by the polymorphism of the OATP1B1 transporter encoding gene in the pharmacokinetics process of rifampicin, the *SLCO1B1* gene. Most of the patients were under 60 years and 92.4% were Sundanese.[19,20] Further study needs to be done, including other Indonesian ethnicities to generalize the result of the Indonesian population.

Rifampicin is a substrate with OATP1B1 as its transporter. This transporter is expressed on the sinusoidal membrane of hepatocytes.[13] In the liver, it has a role in metabolic processes. The OATP1B1 transporter is encoded by the *SLCO1B1* gene.[16] Solute Carrier Organic Anion Transporter family member 1B1 (SLCO1B1) is a gene that encodes the organic anion protein transporter for membrane binding (OATP1B1). This protein transporter facilitates the absorption of rifampicin in the hepatocellular level. The *SLCO1B1* gene is known to have many possibilities for polymorphisms.[10,12,14-16] SNP or single nucleotide polymorphism is the change of a single nitrogenous base in a gene that has > 1% frequency of occurrence. This genetic variation can cause molecular changes both at the level of metabolic enzymes, drug targets or receptors, and

Table 3. The distribution of polymorphism c.85-7793C>T (rs4149032) of SLCO1B1 gene based on gender, ethnicity, body weight, and rifampicin dose.

Variables	Polymorphism c.85-7793C>T (rs4149032) *SLCO1B*1			P value
	CC (reference) n=15	CT n=72	TT n=56	
Gender (%)				
- Male	8 (53.3)	32 (44.4)	39 (69.6)	0.017*
- Female	7 (46.7)	40 (55.6)	17 (30.4)	
Ethnicity (%)				
- Ambonese	0 (0.0)	1 (1.4)	0 (0.0)	0.188
- Bataknese	0 (0.0)	1 (1.4)	0 (0.0)	
- Buginese	1 (6.7)	0 (0.0)	0 (0.0)	
- Javanese	0 (0.0)	5 (6.9)	2 (3.6)	
- Minangnese	0 (0.0)	0 (0.0)	1 (1.8)	
- Sundanese	14 (93.3)	65 (90.3)	53 (94.6)	
Body weight, kg				
Mean ± SD	47.0 ± 5.3	45.5 ± 5.0	47.6 ± 5.5	0.073
Dose per kg BW				
Mean ± SD	9.7 ± 1.3	10.0 ± 1.1	9.6 ± 1.1	0.095

*: statistically significant

protein transporters.[21] Pharmacokinetic changes, caused by genetic polymorphisms, might affect drug efficacy.[22-24]

The polymorphisms of *SLCOB1* gene, c.463C>A (rs11045819) and c.85-7793C>T (rs4149032) have been reported to be associated with lower plasma rifampicin concentrations compared to wild type.[8,9,14] Genetic variations between individuals can cause differences in the concentration of rifampicin through the role of the transporter. For example, polymorphism c.85-7793C>T (rs414903232) *SLCO1B1* gene is associated with C-max, AUC, and confounding factors such as gender, ethnicity, weight, rifampicin dose per kgs of body weight.[14,16]

Pharmacogenetic polymorphism is an important factor in the high variation of plasma rifampicin concentration. Genetic polymorphisms in enzyme metabolism and drug transporters might explain the occurrence of 30% pharmacokinetics variations of the drug.[25]

In this study, two types of polymorphisms were examined, which are c.463C>A (rs11045819) and c.85-7793C>T (rs4149032) of *SLCO1B1* gene. At the end of the examination, not a single polymorphism of c.463C>A (rs11045819) *SLCO1B1* gene was identified in the group of TB patients in Bandung, Indonesia. Based on data from dbSNP150 database at NCBI (National Center for Biotechnology Information), the minor allele frequency (MAF) of rs11045819 (c.463C>A) was 0,0649/325, meaning that a minor (mutant) allele (A allele), was identified in 6,5% within the population (these data were generated from sequencing of 325 individuals/650 chromosome).[8,26,27] If the sample size is 100 (200 chromosomes), it means that the probability of allele A will be found in 6 samples with heterozygous genotype or 3 samples with homozygous genotype (minor/ mutant) or a mix between heterozygous and homozygous type. The obtained information after tracing the data on dbSNP150, MAF data of rs11045819 showed that this polymorphism only occured populations/ ethnicity of African Americans, Mexicans, and Caucasians. On the contrary, Asian ethnicities, including Japanese and Chinese (Han Chinese) do not have this polymorphism. In this study, the majority of patients came from a relatively homogeneous ethnic group which is Sundanese. The Sundanese is part of the Deutro-Melayu ethnic group which gnomically is similar to the Chinese. This might explain why this polymorphism was also not identified in this study.

In a previous study, Pasanen (2008) investigated the diversity of *SLCO1B1* gene at a global level. This study involved 941 patients within 52 populations. The study was carried out by dividing populations into 8 regions, namely: Sub-Saharan Africa, North Africa, Middle East, Europe, South/ Central Asia, East Asia, Oceania, and America. The allele frequency of polymorphism c.463C>A was found to be 0.4% in the East Asian region. This number was considered very small compared to Europe (17%) and the United States (7.2%).[27,28] The presence of *SLCO1B1* polymorphisms correlated with geography.[29] This is consistent with a study conducted by Niemi et al (2011) which stated that polymorphism in c.463C>A associated with decreased rifampicin concentration in plasma, only be around 0–3% of the population in East Asia.[16]

Polymorphism heterozygous and homozygous mutant of c.85-7793C>T (rs4149032) of the *SLCO1B1* gene was found in 74 and 56 patients, respectively (51.0% and 38.6%). Hence the MAF of this polymorphism in this group of TB patients is 64.13% (186/290). A previous study by Chigutsa et al. in Africa found at least 70% of allele frequency of polymorphism c.85-7793C>T (rs4149032) of *SLCO1B1* gene.[8] In other reports, allele frequency of polymorphism c.85-7793C>T (rs4149032) was 75% in Nigerians, 29% in Caucasians, and 56% in Asian.[8,26,27]

This study found a higher minor allele frequency of polymorphism c.85-7793C>T (rs4149032) *SLCO1B1* gene than that in Caucasians, and other Asian but lower than that in the African population. Preliminary studies conducted by OD Sampurno in Jakarta, included 30 healthy people, 60% of men aged between 25–58 years received the results of the *SLCO1B1* gene with the SNP in c.463C>A, with the proportion of genotype CC 46.7%, CA 46.7%, and AA 6.6% whereas in rs4149032 there was no polymorphism detected.[30] This is

likely due to differences in study location setting, patients, and ethnicity. The relative difference in the contribution of transporter polymorphisms that affect the pharmacokinetics depends on the patient's ethnic background.[31]

Presence of polymorphism found in this study highlights the possibility of suboptimal plasma rifampicin concentration in TB patients treated with first-line drugs in Bandung. It is necessary to determine the optimal dose in different populations to ensure that each patient is given ideal treatment. Since examination of SLCO1B1 polymorphisms before starting therapy is rather difficult to implement, increasing the dose of rifampicin may be considered. Previous study showed that increasing the dose of rifampicin by 150 mg daily in subjects with homozygous polymorphism c.85-7793TT (rs4149032) and heterozygous polymorphism c.85-7793CT (rs4149032) will give the same plasma rifampicin concentration value as the wild type c.85-7793CC (rs4149032).[8] Higher dose of rifampicin will increase the peak concentration (C_{max}) in the polymorphism group.[8] The possibility of suboptimal treatment also accentuates the need of drug monitoring during TB treatments.

This study's limitation is that it focused on the Sundanese population, therefore it is essential to characterize the frequency of polymorphisms and their functional consequences in other ethnic groups, as different genetic variations may be observed in different ethnic groups. There is also a need for further study regarding rifampicin pharmacokinetics and *SLCO1B1* polymorphisms. The relationship between the polymorphisms and treatment outcomes also still needs to be identified. It is recommended to discover all the polymorphisms that might occur in pulmonary TB patients by examining samples with whole-genome sequencing.

CONCLUSION

This study reported the high presence of polymorphism c.85-7793C>T (rs4149032) of the *SLCO1B1* gene in TB patients in Bandung, especially in the Sundanese population. There were no polymorphisms c.463C>A. (rs11045819) of the *SLCO1B1* gene identified in this study. This study highlights the presence of polymorphism allele frequency in TB patients, which may affect treatment outcomes.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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