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The *SLCO1B1**15 haplotype associated with lower clinical outcome in Indonesian tuberculosis patients

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ABSTRACT

Rifampin is one of first-line drugs for the treatment of tuberculosis. In Indonesia nearly all tuberculosis patients show lower rifampin plasma concentration's possibly due to genetics. Rifampin is a substrate of the organic anion-transporting polypeptide 1B1 (OATP 1B1) encoded by the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*). This study aimed to identify haplotype polymorphisms of tuberculosis drug transporters with an impact on clinical outcome in tuberculosis patients. Thirty-six patients from I.A Moeis District Hospital, Samarinda, East Kalimantan were involved in the study. Buffy coat from patient blood samples were tested for *SLCO1B1* and *SLCO1B3* polymorphisms by RFLP and ARMS PCR, whereas the clinical outcome was examined based on the sputum conversion histopathology residuals. The frequency of patients with *SLCO1B1**15 haplotype was 63.9%. The *SLCO1B1**15 haplotype was associated with susceptibility to failure of clinical outcome ($p = 0.005$; RR = 4.52; 95% CI: 1.22-16.64). The OATP1B1*15 haplotype revealed that the failure of clinical outcome was markedly increased compared to the three other haplotypes. These results suggest that the SLCO1B1*15 haplotype is an important predisposing factor for lower clinical outcome. Our data indicate that individualized treatment should be considered for Indonesian tuberculosis patients based on genetics characteristics of patients.

ABSTRAK

Rifampin merupakan salah satu obat utama untuk pengobatan tuberkulosis. Di Indonesia hampir semua penderita tuberkulosis menunjukkan konsentrasi rifampisin yang rendah yang kemungkinan karena faktor genetik. Rifampin merupakan substrat dari Organic anion-transporting polypeptide 1B1 yang dikode oleh gen Solute carrier organic anion transporter family member 1B1 (*SLCO1B1*). Penelitian ini bertujuan mengidentifikasi polimorfisme haplotipe transporter obat tuberkulosis dan hubungannya dengan luaran klinis penderita tuberkulosis. Sebanyak 36 penderita tuberkulosis dari RSUD I.A. Moeis, Samarinda, Kalimantan Timur terlibat dalam penelitian. Buffy coat sampel darah pasien diperiksa polimorfisme *SLCO1B1* dan *SLCO1B3* menggunakan PCR RFLP dan ARMS, sedangkan luaran klinis ditentukan berdasarkan konversi sputum dan hasil histopatologi. Frekuensi penderita dengan *SLCO1B1**15 haplotipe sebanyak 63,9%. *SLCO1B1**15

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haplotipe berhubungan dengan risiko kegagalan pengobatan hasil klinis (p = 0,005; RR = 4,52; 95% CI: 1,22-16,64). OATP1B1*15 haplotipe mengungkapkan bahwa kegagalan hasil klinis lebih tinggi dibandingkan ketiga haplotipe lainnya. Hasil penelitian ini terbukti *SLCO1B1**15 haplotipe merupakan faktor predisposisi penting untuk memprediksi rendahnya luaran klinis. Disarankan agar pengobatan penderita tuberkulosis secara individu harus dipertimbangkan berdasarkan karakteristik genetik pasien.

Keyword: *SLCO1B1**15 haplotipe - tuberculosis - clinical outcome

INTRODUCTION

Tuberculosis (TB) is one of the major mortality risks in the world and is caused by *Mycobacterium tuberculosis,* which infects over 2 billion people, or almost one third of the world's 7 billion population.[1] Indonesia has the second ranked largest number of cases in the world. Rifampin (RIF) is a key component in the treatment regimen and due to its efficacy is used as a primary anti-TB drug.[1,2] The development of resistance to RIF is found to be related to RIF concentrations.[3] Despite this concern, there is limited RIF dosing information to ensure optimal outcome. A number of studies have shown interindividual RIF pharmacokinetic variability[4-6] and this genetic diversity may support the need to increase RIF dosage in Indonesian TB patients.[7] Recent research has explored a link between genetics and treatment efficacy[4,8] and the present study is the first to assess genetic diversity in Indonesian patients with confirmed diagnosis of pulmonary TB (PTB) and extrapulmonary TB (EPTB). In evaluating clinical outcomes, we examined major single-nucleotide polymorphisms (SNPs) of *SLCO1B1* and *SLCO1B3*. Considering genetic aspects potentially influential on the reduced levels of RIF concentration's.

As a substrate of organic anion transporting polypeptides OATP1B1 (coded by *SLCO1B1*) and OATP1B3 (coded by *SLCO1B3*),[9,10] SNP research has associated the *SLCO1B1* SNP C463A[4] and rs4149032[8] with reduced RIF exposure. Other recent studies showed that it did not influence the exposure and involves genetic variability[11,12] while presently there are no studies of the major SNPs in Indonesian patients. This study aimed to determine the major SNPs which may influence efficacy of treatment among Indonesian PTB and EPTB patients and the second objective of the study was to evaluate their potential impact on the clinical outcome. Applying our assessment of genetic variability to clinical outcomes, the data may assist in therapeutic-drug treatment schedules and monitoring in PTB and EPTB patients in Indonesia.

MATERIALS AND METHODS

Participants

This study used a cohort study, where we analyzed 36 patients with PTB and EPTB who had received an oral anti-TB regimen at I.A. Moeis District Hospital, Samarinda, Indonesia in 2014. The study participants had sputum smear-positive pulmonary TB or extrapulmonary TB from tissue biopsy which was definite if histopathology results showed the typical necrotizing granuloma containing macrophages, lymphocytes and Langhans giant cells. Caseous necrosis can be sometimes found in the central part of the granuloma, including: lymph node TB, gastrointestinal TB, skin and soft tissue TB. Directly observed daily administration of treatment involved

fixed-dose combination tablets (4FDC) with 150 mg rifampin, 75 mg isoniazid, 400 mg pyrazinamide and 275 mg ethambutol. Following Indonesian standard tuberculosis treatment guidelines, patients < 38 kg received 2 tablets daily, those weighing 38 to 54 kg received 3 tablets, 55 to 70 kg received 4 tablets daily and patients > 71 kg received 5 tablets once daily.[13] All patients received TB drugs from the same manufacturer. The following variables were available: sex, age, BMI, ethnic and clinical outcome, including sputum smear and post-treatment biopsy. The study has been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta.

Genotyping

We extracted blood sample DNA from the buffy coat by using the GeneJET Genomic DNA Purification Kit #K0722 (Thermo Fisher Scientific). We used the restriction fragment length polymorphism (RFLP) PCR for allelic discrimination in genotyping [*SLCO1B1* rs2306283 (c.388 A>G), *SLCO1B1* rs11045818 (c.411 G>A), *SLCO1B3* rs4149117 (c.334 T>G) and rs7311358 (c.699 G>A)] and the amplification refractory mutation system (ARMS) PCR [*SLCO1B1* rs4149056 (c.521T>C)]. Primers were sourced from Integrated DNA Technologies (Coralville, Iowa, USA). Two samples of each genotype were directly sequenced to confirm and validate our genotyping results with Applied Biosystems 3730 DNA Analyzer. The protocol to prepare the PCR involved an initial denaturation step at 94°C for 5 to 7 min, followed by 35 to 40 cycles of denaturation at 94°C for 30 to 60 s and then annealing temperature for 30 to 60 s and extension at 72°C for 30 to 60 s (TABLE 1). All PCR amplifications were conducted in a PCR-engine apparatus T100™ Thermal Cycler (Bio-Rad Life Science, USA). Restriction enzymes were sourced from Thermo Fisher Scientific. TABLE 1 below identifies the following SNPs based on allele frequencies previously shown to be involved in drug transport from the blood to the liver.

TABLE 1. Primers and PCR conditions used for genotyping of gene polymorphisms

Polymorphism	Primer sequence (5' ➡3')[a]	Fragment size (bp)	Annealing temperature (°C)	Amplification cycles	Restriction enzyme
SLCO1B1 rs2306283 and rs11045818	F: GCAAATAAAGGGGAATATTTCTC R: AGAGATGTAATTAAATGTATAC	274	46	37	TaqI
SLCO1B1 rs4149056	F:AAGTAGTTAAATTTGTAATAGAAATGC WT: GGGTCATACATGTGGATATAAGT MT: AAGCATATTACCCATGAACG R: GTAGACAAAGGGAAAGTGATCATA	260	48	35	-
SLCO1B3 rs4149117	F: GAAGGTACAATGTCTTGGGC R: CTCTCAAAAGGTAACTGCCC	339	58	35	AluI
SLCO1B3 rs7311358	F: ATGATTACATTCCCTGGATC R: ACTATCATGGTACCTTGTTC	303	56.3	40	RsaI

[a]F: Forward primer; R: reverse primer; WT: wild-type; MT: mutant-type

For *SLCO1B1* rs2306283 and rs11045818, the PCR product was digested using 5U of restriction enzyme at 65°C overnight. The products of restriction were placed in 3% agarose gel for electrophoresis and visualized by ethidium bromide staining. The restriction pattern consist of four distinct zones (154, 142, 132 and 119 bp), each representative for 388A>G and 411G>A wild-type and mutant alleles. This pattern in descending order stands for the two polymorphisms as follows: 154 bp for 411A, 142 bp for 388A, 132 bp for 411G and 119 bp for 388G.[14]

For *SLCO1B1* rs4149056, the tetra primer used in ARMS-PCR with slight modifications.[15] Because the restriction endonuclease was unnecessary, the PCR products were detected by means of 2% agarose gel with electrophoresis and by ethidium bromide staining. This pattern stands for the polymorphisms as follows: wild-type (260 and 179 bp); heterozygote (260, 123 and 179 bp) and mutant (260 and 123 bp). For *SLCO1B3* rs4149117, the PCR product was digested using 5U of restriction enzyme at 37°C overnight. The products of restriction were placed in 2% agarose gel for electrophoresis and visualized by ethidium bromide staining. The restriction pattern consists of two distinct zones (253 and 213 bp). This pattern stands for the polymorphisms as follows: wild-type (253 bp); heterozygote (253 and 213 bp) and mutant (213 bp).[16]

For *SLCO1B3* rs7311358, the PCR product was digested using 5U of restriction enzyme. The restriction pattern consists of two distinct zones (242 and 275 bp). This pattern stands for the polymorphisms as follows: wild-type (242 bp); heterozygote (242 and 275 bp) and mutant (275 bp).[16] In follow-up we assessed the clinical outcome with sputum conversion (PTB) or tissues through fine needle aspiration biopsy (EPTB). We compared the pre and post-treatment results. We categorized success if sputum conversion or lesions typically disappeared and improved histopathologically after the initiation of treatment. The failure of treatment outcome meant sputum conversion or lesions did not disappear and did not improve histopathologically.

Statistical analysis

Data were presented as median or percentage. The association between genetics polymorphisms of *SLCO* and clinical outcome was analysed using Fisher's exact test. A p-value <0.05 was considered as significant.

RESULTS

Thirty-six tuberculosis patients including 24 (66.7%) PTB and 12 (33.3%) EPTB were involved in this study. The demographics and genetics of the patients are presented in TABLE 2.

TABLE 2. Demographics and genotype description of cohort

Demographics		**Median (range) or *n* (%)**	
		Male 22 (61.11%)	**Female 14 (38.89%)**
Age (years)		42 (23-60)	39 (16-65)
Body weight (kg)		48 (37-65)	46.5 (35-98)
Height (m)		1.56 (1.42-1.72)	1.51 (1.4-1.63)
BMI (kg/m^2)		20.1 (16-27.7)	21.4 (15.4-38.3)
Genetics	**Homozygous wild type, *n* (%)**	**Heterozygous mutant type, *n* (%)**	**Homozygous mutant type, *n* (%)**
SLCO1B1 rs11045818	31 (86.11)	5 (13.89)	0 (0)
SLCO1B1 rs2306283	0 (0)	10 (27.78)	26 (72.22)
SLCO1B1 rs4149056	3 (8.33)	32 (88.89)	1 (2.78)
SLCO1B3 rs4149117	2 (5.55)	14 (38.89)	20 (55.56)
SLCO1B3 rs7311358	2 (5.55)	14 (38.89)	20 (55.56)
Haplotype	***n* (%)**	**Male, *n* (%)**	**Female, *n* (%)**
SLCO1B1 *1a	9 (25)	3 (13.6)	6 (42.8)
SLCO1B1 *1b	35 (97.2)	22 (100)	13 (92.3)
SLCO1B1 *5	8 (22.2)	3 (13.6)	5 (35.7)
SLCO1B1 *15	23 (63.9)	11 (50)	12 (85.7)

BMI: body mass index

The two most common *SLCO1B1* SNPs (c.521T>C and c.388A>G) form four functionally distinct haplotypes: *SLCO1B1**1a (c.388A-c.521T, as reference haplotype), *1b (c.388G-c.521T), *5 (c.388A-c.521C), and *15 (c.388G-c.521C).[17-19] All polymorphisms were in Hardy-Weinberg equilibrium. The patients carrying at least one *15 haplotype had a significantly increased risk for failure of treatment (p=0.005), and subjects carrying the *15 haplotype had a 4.52-fold significantly elevated risk (95% CI: 1.22-16.64) for failure of treatment. The *SLCO1B1* rs11045818 was not analyzed due to its insignificance. The *SLCO1B3* rs4149117 and rs7311358 polymorphisms did not have a statistically significant association with clinical outcome. We evaluated the differences in the haplotype-associated effects on clinical outcome, which also were associated with differences in overall drug exposures (TABLE 3).

TABLE 3. Response treatment based on genotype of TB patients (n = 36)

Genetics	Success 18 (50%)	Failure 18 (50%)	p^a	RR (CI)[b]
SLCO1B1 rs11045818				
GG	15 (41.7)	16 (44.4)	1	0.775 (0.25-2.39)
GA	3 (8.3)	2 (5.6)		
AA	0 (0)	0 (0)		
SLCO1B1 rs2306283				
AA	0 (0)	0 (0)	0.711	-
AG	6 (16.7)	4 (11.1)		
GG	12 (33.3)	14 (38.9)		
SLCO1B1 rs4149056				
TT	2 (5.5)	1 (2.8)	0.603	1.54 (0.30-7.92)
TC	15 (41.7)	17 (47.2)		
CC	1 (2.8)	0 (0)		
SLCO1B3 rs4149117				
TT	1 (2.8)	1 (2.8)	0.389	1 (0.24-4.16)
TG	9 (25)	5 (13.9)		
GG	8 (22.2)	12 (33.3)		
SLCO1B3 rs7311358				
GG	1 (2.8)	1 (2.8)	0.389	1 (0.24-4.16)
GA	9 (25)	5 (13.9)		
AA	8 (22.2)	12 (33.3)		
Haplotype				
[c]*1a (388A521T)	5	4	1	0.85 (0.38-1.93)
Other *1a	13	14		
[d]*1b (388G521T)	17	18	1	-
Other *1b	1	0		
[e]*5 (388A521C)	5	3	0.691	0.7 (0.27-1.82)
Other *5	13	15		
Haplotype groups				
-/-[f]	11	2	0.005	4.52 (1.22-16.64)
*15/-[g]	7	16		

[a]Data are calculated using Fisher's exact test, [b]Risk ratio (Confidence Interval), [c]*1a including (*1a/*1a, *1a/*1b, *1a/*15), [d]*1b including (*1b/*1b, *1a/*1b, *1b/*5, *1b/*15), [e]*5 including (*1b/*5, *1a/*5, *5/*5, *5/*15), [f]-/- including (*1a/*1a, *1a/*1b, *1b/*1b), [g]*15/- indicates at least one *15 allele (*1b/*15, *1a/*15, *5/*15, *15/*15).

DISCUSSION

Our study is the first in an Indonesian population to demonstrate that the *SLCO1B1**15 haplotype can be associated with clinical outcome in patients with PTB and EPTB. Among the TB patients with lower RIF concentrations,[20] we found this haplotype in 63.9%, which is consistent with other studies of Indonesian patients.[7] The lower RIF concentrations observed for Indonesians could be partially accounted for by the *SLCO1B1**15 haplotype. The high frequency of the *SLCO1B1**15 haplotype suggests that the haplotype can help to predict the clinical outcome for certain Indonesian populations. We investigated the effect of major haplotypes

of drug transporters and related demographics on clinical outcome. We analyzed factors that could influence outcome of treatment in Indonesian PTB and EPTB patients. The variable - *SLCO1B1**15 haplotype -was found to significantly affect the clinical outcome. We identified a significant link between *SLCO1B1**15 haplotype and treatment,[21-23] which could be explained by decreased hepatocellular uptake due to reduced drug transporter activity mediated by OATP1B1.[24]

Some studies examining both peak plasma concentration (C_{max}) and area under the curve (AUC) of RIF exposure have demonstrated definite correlation with clinical outcomes.[25,26] Related to genetic diversity, advances in genotyping of *SLCO1B1* rs11045818 have identified a synonymous variant (411G>A) (https://www.ncbi.nlm.nih.gov/clinvar/variation/307936/). For *SLCO1B3*, we did not observe any significant pharmacogenetic effects due to its limited impact. Our findings confirmed there is some effect of the *SLCO1B1**15 haplotype on RIF exposure and treatment outcome, but presently it is not well understood. Although c.521T>C and c.388A>G SNPs appear to be insignificant, the *SLCO1B1**15 haplotype (which includes both SNPs) has been consistently associated with reduced OATP1B1 transport activity.[21]

There were also some limitations in our study. For example, all of our investigated patients were coadministered isoniazid, ethambutol and pyrazinamide with RIF, and thus any confounding effects of medicines could not be fully eliminated in this study. Nonetheless, the present results indicate that OATP1B1 variants may be involved in the failure of clinical outcome and provide a new potential failure risk for patients with this disease.

CONCLUSION

Our final results show the *SLCO1B1**15 haplotype exists in the Indonesian population and is associated with the effect of reducing the clinical outcome. This link was examined in an Indonesian population with PTB and EPTB. Because of high frequency of the *SLCO1B1**15 haplotype compared to non-*15 haplotype, our data suggests that this genotype may provide some prediction for clinical outcome and therefore, specialized diagnosis and treatment should be considered for select Indonesian patients discriminatively based on individual genetic assessment. Actual clinical studies are needed to evaluate and confirm the variability of genotypes for the general population.

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