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프라바스타틴에서 SLCO1B1*15의 약동학적 영향: 체계적 고찰 및 메타분석

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Effect of SLCO1B1*15 on Pravastatin Pharmacokinetics: A Systematic Review and Meta-analysis

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Background and objective: Pravastatin has been shown to have favorable risk-benefit profile when it is administered to hypercholesterolemic subjects to prevent cardiovascular events. However, subjects with impaired OATP1B1 activity may be more susceptible to pravastatin-induced muscle toxicity than subjects with normal OATP1B1 activity. A systematic review was conducted to evaluate the effect of SLCO1B1 genetic polymorphism on pharmacokinetics of pravastatin. **Method:** Medline® and Embase® were searched for relevant studies until July 2013. The search terms used were pravastatin AND (SLCO1B1 OR OATP1B1 OR LST1 OR SLC21A6) AND (gene OR genetic* OR genomic* OR pharmacogenet* OR pharmacogenom* OR polymorph*). **Results:** A meta-analysis of the area under the concentration-time curve (AUC) of pravastatin in SLCO1B1*15 and SLCO1B1*1a/*1a was conducted. Five studies met all the inclusion criteria and methodological requirements. There was no statistically significant difference in the AUC value between SLCO1B1*15 and SLCO1B1*1a/*1a (p=0.728). However, SLCO1B1*15 participants exhibited significantly higher AUC values than SLCO1B1*1b/*1b carriers (p<0.001). In case of SLCO1B1*15*15 carriers, they had significantly higher AUC value than SLCO1B1*1a/*1a subjects (p=0.002). Lastly, compared with to the subjects of SLCO1B1*1a/*1a, the carriers of heterozygous SLCO1B1*15 increased the AUC value of pravastatin statistically significantly in Asian population (p=0.014). **Conclusion:** The present meta-analysis suggests that subjects with SLCO1B1*15 are associated with increased AUC of pravastatin.

□ Key words - OATP1B1, OATP2, OATP-C, SLCO1B1, pravastatin, pharmacokinetics

Membrane transporters play crucial roles in determining drug pharmacokinetics via drug absorption, distribution and excretion.[1)] There are lots of research about the effect of genetic polymorphisms in the transporters on interindividual differences in drug pharmacokinetics.[2)] Organic anion-transporting polypeptide 1B1 (OATP1B1, previously known as OATP2, OATP-C, and liver-specific transporter[1)] is one of the main influx transporters expressed on the basolateral membrane of human hepatocytes.[3)] Genes encoding organic anion transporting polypeptides (OATPs) form a large family of solute carrier organic anion transporter genes (SLCO).[4)] There is increasing evidence that some single nucleotide polymorphisms (SNPs) or haplotypes of the SLCO1B1 gene, which encodes OATP1B1 transporter, have functional

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significance for drug transporter activity.[5,6)]

Pravastatin, a semisynthetic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, is the most hydrophilic statin.[7)] It is mainly excreted by liver, attributing biliary excretion which is performed by primary active transport mechanism.[8)] Among several mechanisms related to hepatic clearance of pravastatin, uptake by OATP1B1 is considered as the rate limiting step in the overall elimination process.[9,10)] In accumulated clinical data, pravastatin has shown favorable tolerability in long-term use.[11)] However, many studies have demonstrated that subjects with impaired OATP1B1 activity are more susceptible to skeletal muscle-related adverse effects of statin therapy.[12)] A study conducted on ten healthy European volunteers reported that the AUC of pravastatin fluctuated about 12-fold,[13)] suggesting relevance for genetic variants. Morimoto *et al*. found that frequency of SLCO1B1*15 haplotype was significantly higher in Japanese subjects who experienced myopathy after use of pravastatin or atorvastatin than in the subjects without myopathy.[14)]

Several studies evaluated associations between SLCO1B1*15 and the AUC of pravastatin. In the study by Ho *et al*., the AUC value of pravastatin was significantly higher in the SLCO1B1*15 carriers than in the non-carriers.[15)] Niemi *et al*. also found that the SLCO1B1*15B carriers significantly increased the AUC value of pravastatin compared to non-carriers.[16)] On the contrary, in the study by Maeda *et al*., the carriers of SLCO1B1*1b/*15 had lower AUC value than the subjects with SLCO1B1*1b/*1b.[17)] Similarly, in the study by Hedman *et al*., the cardiac transplant recipients with the SLCO1B1*15 had lower AUC of pravastatin than non-carriers.[18)]

To determine the effects of polymorphisms in SLCO1B1 gene on the pharmacokinetics of pravastatin, we conducted a systematic review and meta-analysis.

METHODS

Search Strategy

Medline® and Embase® were searched for relevant studies until July 2013. The search terms used were pravastatin AND (SLCO1B1 OR OATP1B1 OR LST1 OR SLC21A6) AND (gene OR genetic* OR genomic* OR pharmacogenet* OR pharmacogenom* OR polymorph*). Two investigators (JYK and PC) independently selected and reviewed the research articles. The reference lists of these reviews were also scrutinized.

Study Inclusion Criteria

The following inclusion criteria were applied: (1) Recruited patients were over age of 18; (2) Number and ethnicity of subjects were presented; (3) Genotyping of SLCO1B1 gene SNP was performed in all subjects; (4) Patients presented SLCO1B1*15 SNP; (5) Pharmacokinetic parameters of pravastatin in SLCO1B1*15 carriers were compared with SLCO1B1*15 non-carrier's references.

Exclusion Criteria

Studies were excluded if: (1) Duplicated in two databases; (2) Not primary articles, including review articles, case reports, conference abstracts, or conference papers; (3) *in vivo* or *in vitro* studies, other than clinical trials; (4) Drug interactions studies with pravastatin; (5) None of recruited patients were containing SLCO1B1*15 allele.

Data Extraction and Quality Assessment

Two investigators (JYK and PC) independently reviewed the full-text of the research articles and extracted the data on genotypes of SLCO1B1*15, number of total subjects, mean and standard deviation of AUC of pravastatin, pravastatin dosage, ethnicity of subjects, and nation of correspondence. Disagreements regarding inclusion of studies were compromised by sufficient discussion and consensus with a third investigator (KYR). To evaluate the reliability and validity of the risk of bias of the included studies, two investigators (JYK and PC) utilized the Newcastle-Ottawa Scale (NOS).[19)] Using the tool, each study was evaluated on eight items, categorized into three groups: selection of study groups, comparability of groups, and ascertainment of exposure and outcomes for cohort studies. The NOS assigns up to a maximum of nine points for the least risk

of bias.

Statistical Analyses

Heterogeneity of each research was tested by using an I^2 statistic. If the I^2 value is more than 50%, random effect model was used. If the I^2 value of ≤ 50% is presented, we assumed the absence of heterogeneity and used the fixed effects model. If published studies were more than three, publication bias was analyzed with funnel plot by using Begg's rank correlation method and Egger's regression method. The $p<0.05$ was considered statistically significant publication bias. All statistical analyses were performed with two-sided test by using Comprehensive Meta-analysis Software, Version 2 (Biostat, Englewood, USA).

RESULTS

Included Studies

A total of 189 records were searched through Medline® and Embase®. After removal of duplicates, titles and abstracts of 139 candidate articles were screened for eligibility criteria prior to full text review. Among these articles, 66 were excluded due to inappropriate form, which included 42 reviews, 17 conference abstracts, 3 conference papers, 1 article in press, 1 editorial, 1 letter, and 1 note. The full texts of the remaining 73 articles were reviewed for eligibility; of which 17 articles were excluded as they were *in vivo* or *in vitro* studies, 30 articles were excluded as they were not on pharmacokinetics, 5 articles were excluded as they were not on pravastatin, and 5 articles were excluded as they described drug interactions. Additionally, 2 articles were excluded: one was for pediatric subjects and the other was not on SLCO1B1. Among the remaining 14 articles, 5 articles were selected for analysis on SLCO1B1*15 and the selection process is shown on Fig. 1. The characteristics and result of quality assessment of each study was also presented on Table 1.

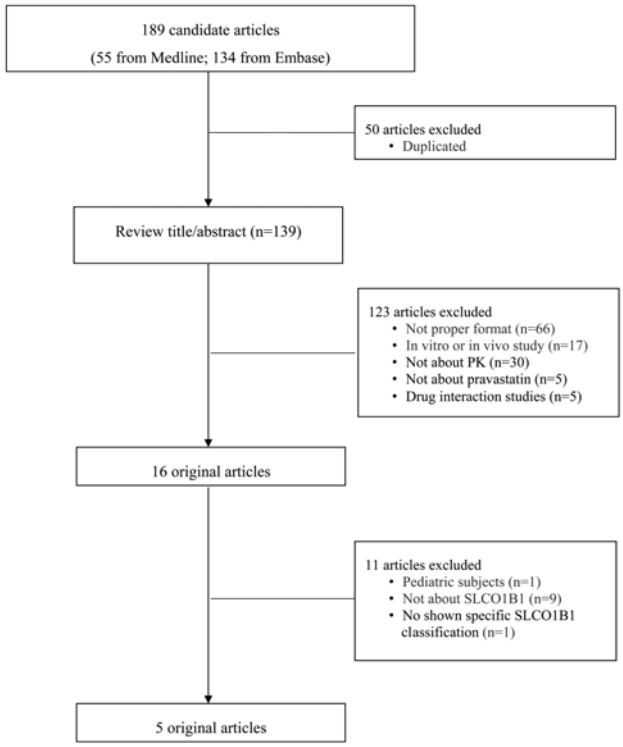


Fig. 1. Flow diagram of assessment of studies identified in the systematic review.

Meta-analysis

Analysis of the pravastatin AUC values of heterozygous SLCO1B1*15 and SLCO1B1*1a/*1a was based on the three clinical studies: Ho *et al*. (2007),[15] Maeda *et al*. (2006),[17] and Nishizato *et al*. (2003).[37] Not all three studies showed statistically significant difference of pravastatin AUC and the results from the studies were not consistent with the subjects' genotypes. In the study by Ho *et al*., the subjects with SLCO1B1*15 exhibited significantly higher AUC than the participants with SLCO1B1*1a/*1a. In the study by Nishizato *et al*., the carriers of SLCO1B1*1b/*15 showed higher pravastatin AUC than the subjects with SLCO1B1*1a/*1a. But it was not statistically significant. On the other hand, Maeda *et al.* observed significantly lower AUC value in the group of SLCO1B1*1b/*15 than in the group of SLCO1B1*1a/*1a. Based on the pharmacokinetics of SNP-related pravastatin observed in the three studies, effect size (standard differences in means) of pravastatin AUC increase was 0.090 (95% CI. -0.417, 0.597), which was not statistically significant (p=0.728) (Fig. 2(A)).

Analysis of the pravastatin AUC values of heterozygous SLCO1B1*15 and SLCO1B1*1b/*1b was based on

Table 1. Characteristics of the included studies.

Study Name	Nation of correspondence	No. of total subjects	Ethnicity of participants	Types of SLCO1b1 genotype	No. of SLCO1b1 genotype subjects	Types of control genotype	No. of control genotype subjects	Pravastatin dose	NOS Quality assessment
Ho *et al.* (2007)[15]	Canada	107	69 European-Americans/ 38 African-Americans	*1a/*15	8	*1a/*1a	29	40 mg	8
				*1b/*15	7	*1b/*1b	25		
				*15/*15	2	*1a/*1a	29		
Maeda *et al.* (2006)[17]	Japan	23	23 Asian (Japanese)	*1a/*15	6	*1a/*1a	5	10 mg	7
				*1b/*15	5	*1a/*1a	5		
				*1a/*15, *1b/*15	11	*1b/*1b	7		
Nishizato *et al* (2003)[37]	Japan	23	23 Asian (Japanese)	*1b/*15	9	*1a/*1a	2	10 mg	6
				*1b/*15	9	*1b/*1b	4		
Wen *et al.* (2008)[38]	China	18	18 Asian (Chinese)	*1a/*15, *1b/*15	8	*1b/*1b	9	40 mg	6
Deng *et al.* (2008)[39]	South Korea	11	11 Asian (Korean)	*15/*15	6	*1a/*1a	5	40 mg	6

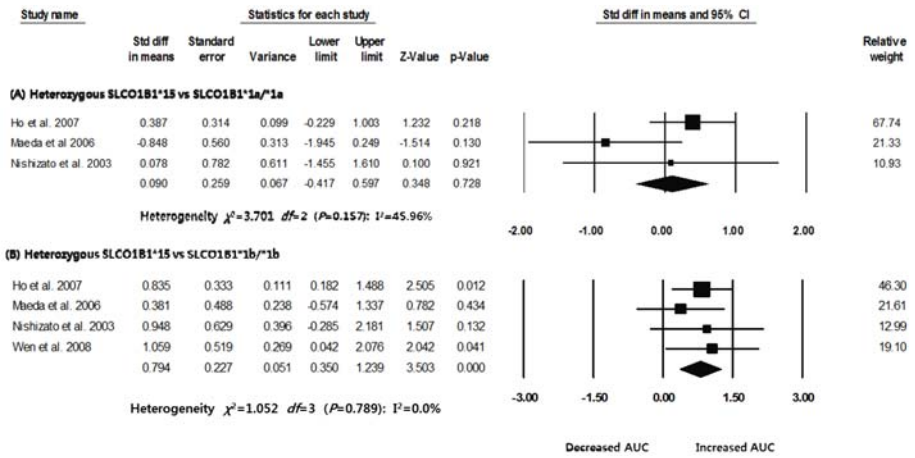
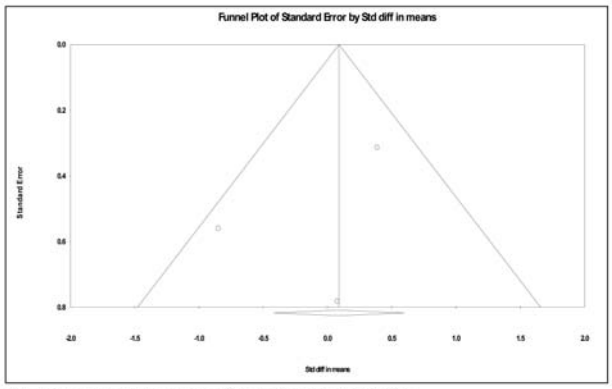


Fig. 2. Forest plot for pravastatin AUC of SLCO1B1*15 heterozygous carriers compared to SLCO1B1*1a/*1a subjects (A) and SLCO1B1*1b/*1b subjects (B).

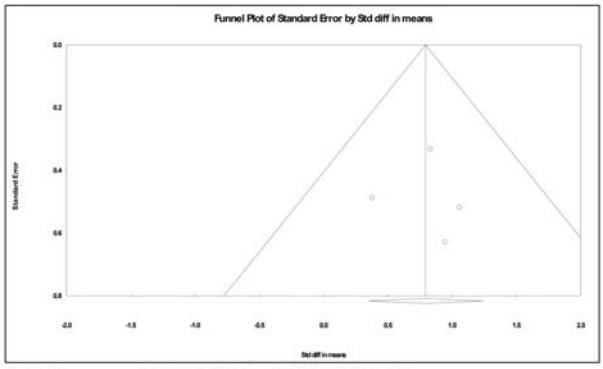
four studies: Ho *et al*. (2007), [15] Maeda *et al.* (2006),[17] Nishizato *et al*. (2003),[37] and Wen *et al*. (2008).[38] The only one study[17] showed statistically significant increase in AUC of SLCO1B1*15 while the other three studies had not statistically significant increase. A meta-analysis of the four studies has shown a statistically significant increase of effect size of 0.794 (95% CI. 0.350, 1.239) in heterozygous SLCO1B1*15 ($p<0.001$) (Fig. 2(B)).

Two studies reported the AUC values of pravastatin in both SLCO1B1*15/*15 carriers and SLCO1B1*1a/*1a carriers. In the study by Deng *et al*.,[39] homozygous SLCO1B1*15 carriers exhibited statistically significantly higher AUC value than SLCO1B1*1a/*1a participants. Contrarily, in the study by Ho *et al*., the homozygous SLCO1B1*15 group failed to show a statistically significant increase in the AUC value compared to SLCO1B1*1a/*1a group.[15] The result of our meta-analysis shows a statistically significant difference in the pravastatin AUC between SLCO1B1*1a/*1a and SLCO1B1*15/*15 with the effect size of 1.633 (95% CI. 0.597, 2.670) (Fig. 4).

There are three studies that have reported differences of pravastatin levels between heterozygous SLCO1B1*15 and SLCO1B1*1b/*1b in Asian population: Maeda *et al.*



(A) Heterozygous SLCO1B1*15 vs SLCO1B1*1a/*1a
Begg's rank correlation method; Tau=0.0000, p-value (2 tailed) =1.0
Egger's regression method; Intercept = -1.90762, Standard error =2.41747, p=0.5747



(B) Heterozygous SLCO1B1*15 vs SLCO1B1*1b/*1b
Begg's rank correlation method; Tau=0.16667, p-value (2 tailed)=0.73410
Egger's regression method; Intercept=0.12976, Standard error =1.52386, p=0.9399

Fig. 3. Funnel plot for pravastatin AUC of SLCO1B1*15 heterozygous carriers compared to SLCO1B1*1a/*1a subjects (A); SLCO1B1*1b/*1b subjects (B).

(2006),[17] Nishizato *et al*. (2003) [37], and Wen *et al*. (2008). [39] In the studies by Nishizato *et al.* and Wen *et al.,* higher AUC values of pravastatin was observed in the heterozygous SLCO1B1*15 group than in the SLCO1B1*1b/*1b group. But the differences were not statistically significant. On the contrary, in the study by Maeda *et al.,* heterozygous SLCO1B1*15 carriers had statistically significant high AUC value compared to SLCO1B1*1b/*1b participants. Our meta-analysis has concluded that among Asian, heterozygous SLCO1B1*15 significantly increases pravastatin AUC compared to SLCO1B1*1b/*1b with the effect size of 0.759 (95% CI. 0.153, 1.366, p=0.014) (Fig. 5(A)).

Sensitivity Analysis and Publication Bias

A sensitivity analysis presented there is no considerable differences. The publication bias was conducted for available meta-analyses. The shape of the funnel plots were symmetry. Both Begg's test and Egger's test assessments suggested also no publication bias existed (Fig. 3, Fig. 5(B)).

DISCUSSION

The impact of the SLCO1B1 polymorphism on pravastatin in humans was previously suggested by several reviews.[20,21] The findings from our systematic review are consistent with the previous suggestion. The results of our meta-analysis conclude that heterozygous SLCO1B1*15 seems to be an important determinant of pravastatin pharmacokinetics.

In the study of pravastatin pharmacokinetics which included 69 European-Americans (EA) and 38 African-Americans (AA), significantly higher pravastatin AUC was demonstrated in EA compare to AA.[15] However, as only 1% of the AA participants were genotyped as SLCO1B1 521TC (SLCO1B1*5, SLCO1B1*15), it cannot be certain that ethnicity is the factor of exclusion of genotype. To determine whether the AUC values of pravastatin is affected by ethnicity, this study also examined the AUC values in SLCO1B1*15 carriers and

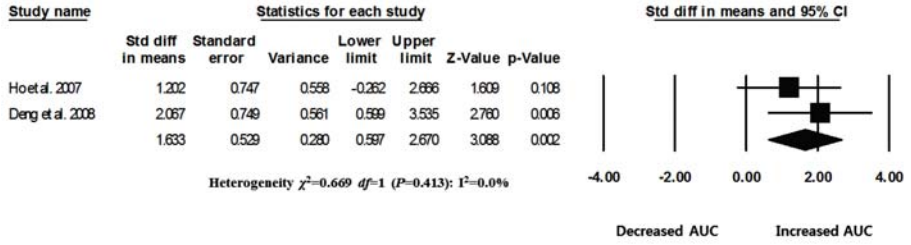


Fig. 4. Forest plot for pravastatin AUC of SLCO1B1*15 homozygous carriers compared to SLCO1B1*1a/*1a subjects.

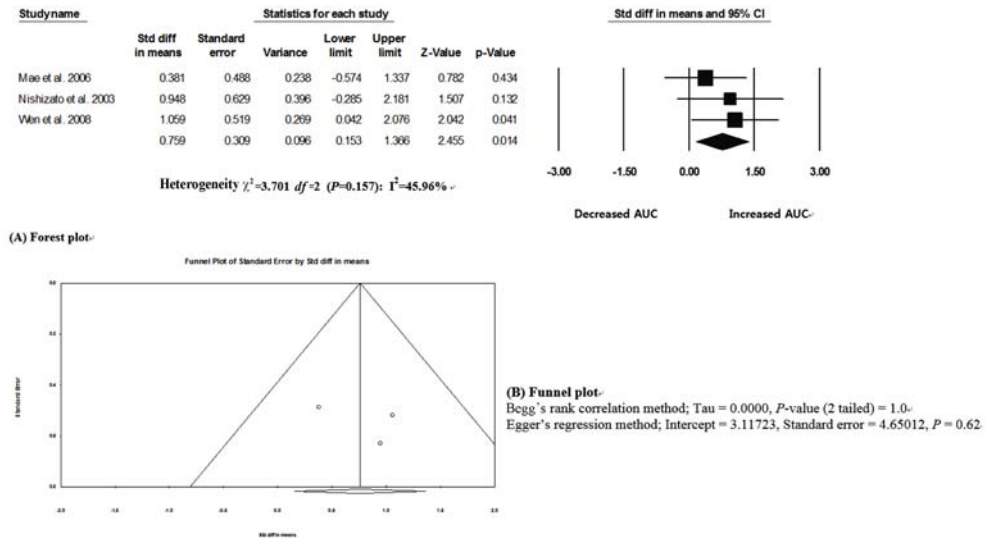


Fig. 5. Forest plot (A) and funnel plot (B) for pravastatin AUC of SLCO1B1*15 heterozygous carriers compared to SLCO1B1*1b/*1b subjects in Asian population.

non-carriers according to the races. As a result, there was no statistically significant difference in the AUC values between Asian-only population and all ethnicity population in two studies (95% CI, -0.524, 1.337, p=0.434; 95% CI, -0.285,2.181, p=0.132). However, the thing that most of them were Asian (64% of the subjects included in this SLCO1B1*15 heterozygous carriers) cannot be ignored. If a variety of ethnic groups were included in the study, the result could be different.

As shown on Fig. 2(A), the heterozygous SLCO1B1*15 groups doesn't significantly increased the AUC values of pravastatin compared to SLCO1B1 *1a/*1a groups. Pravastatin is actively transported from portal vein into hepatocytes via uptake by OATP1B1.[23] Considering the fact that OATP1B1 is expressed on the basolateral membrane of hepatocytes and SLCO1B1 polymorphism affects the transport activity of OATP1B1,[24,25] impaired activity of OATP1B1 might result in reduced hepatic uptake of pravastatin. In fact, one research performed in a pediatric group showed the elevated level of pravastatin in blood when cyclosporine, a potent inhibitor of SLCO1B1, was given simultaneously with pravastatin.[26] This finding suggests a potential impact of SLCO1B1 on pharmacokinetics of pravastatin. Even though the fact that other transporters including P-glycoprotein can affect the blood level of pravastatin cannot be overlooked, the data from numerous clinical trials have reported that several haplotypes of SLCO1B1, such as *5, *15, *17, are related to the elevation of pravastatin blood level.[27]

It is well known that lipid-lowering ability of statins is affected by genetic factors.[23] Also, genetic differences in hepatic transporters are considered to play a significant role in exposure of statins to their active site, thus affecting cholesterol lowering efficacy.[28] Many research on OATP1B1 transporters and efficacy of pravastatin are being actively conducted as these transporters are known to have effects on pharmacokinetics of statins.

In the case of pharmacodynamics of pravastatin, in the two studies on small sample size, SLCO1B1*15 carriers showed greater reduction in LDL level than non-carriers.[29,30] On the contrary, one study on large sample size showed opposite results.[31] Therefore, definite dosage control of pravastatin based on genetic factors cannot be established for now, and it is expected that clinically useful genetic tests may be developed from large-scale studies in the future.[32]

The study by Morimoto *et al*. reported pravastatin-induced myopathy from SLCO1B1*15.[14] In addition, severe toxicity after specific drug such as irinotecan-based chemotherapy was observed in a patient with

homozygous SLCO1B1*15.[33] Recently, the guideline of the Clinical Pharmacogenetics Implementation Consortium (CPIC) stressed muscle toxicity associated with simvastatin use in SLCO1B1 carriers.[34] Although association between pravastatin-induced toxicity and SLCO1B1*15 is not well known, the finding that higher level of pravastatin in SLCO1B1*15 carriers is noteworthy because of the potential for increased risk of pravastatin-mediated toxicity in those populations.

Nozawa *et al*. revealed that countries in Asia including Japan have higher frequency of SLCO1B1*1b/*1b than SLCO1B1*1a/*1a.[35] Thus it is appropriate to consider SLCO1B1*1b/*1b genotype as reference genotype in Asians. In addition, two independent studies reported that the subjects carrying SLCO1B1*1b (*1a/*1b or *1b/*1b genotype) lowered AUC (after receiving pravastatin 40 mg, 10mg, respectively) by 35% compared to the subjects carrying *1a/*1a.[18,36]

As shown in Fig. 2(A), analysis of pravastatin AUC in heterozygous SLCO1B1*15 and SLCO1B1*1a/*1a failed to show a significant impact of SNP on pravastatin AUC. However, when comparing with SLCO1B1*1b/*1b, heterozygous SLCO1B1*15 carriers had significantly higher pravastatin AUC (Fig. 2(B)).

In Fig. 5, the population of the two studies were limited to Asian. The heterozygous SLCO1B1*15 carriers significantly increased the AUC value of pravastatin compared to SLCO1B1*1b/*1b subjects.

The present study has several limitations on flaws and quality of the underlying studies. The results were built exclusively on data reports, which may not be necessarily complete or accurate. Also, population included in the research was limited and biased to Asian. Accordingly, it is important to note that although SLCO1B1 allele may have effect on AUC value of pravastatin, this results cannot be said for changing its clinical outcomes. Moreover, there remains potential heterogeneity among studies because the used doses of pravastatin and the follow-up point of AUC were various. Then, when assessing increase of AUC, AUC of reference allele should be assessed under the same condition as variant allele group in each study. Lastly, possible effects of other gene polymorphisms were not considered in the research that may influence AUC of pravastatin with or without interactions with SLCO1B1.

Despite of these limitations, the present study provides reliable finding that SLCO1B1*15 has significant association with higher AUC level of pravastatin, for the first time. The finding supports a rationale in terms of clinical SLCO1B1 transporter gene test, especially for patients with high doses of pravastatin to predict potential toxicities. Further studies are required to assess efficacy and toxicity of pravastatin for SLCO1B1 polymorphisms including SLCO1B1*15 genotypes.

CONCLUSION

The result from our meta-analysis suggests that SLCO1B1*15 is associated with higher AUC of pravastatin. The findings from this study may be clinically applied for the subjects on high-dose pravastatin therapy. Further studies of large trials with unbiased selection methods and with more detailed individual data are required to confirm these findings.

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