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Association between HLA-B*5801 Allele and Other Risk Factors to Allopurinol - Induced Severe Cutaneous Adverse Reaction and Exfoliative Dermatitis in Thai Population

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ABSTRACT

To investigate the association of *HLA-B*5801* and *HLA-Cw*0302* alleles in Thai patients who had allopurinol induced SCAR including exfoliative dermatitis. Other risk factors besides genetic were also investigated. A case - control study was used. The study was performed during December 2009 – March 2010 at Siriraj Hospital, Bangkok. The totals of 82 patients were recruited into the study; 34 patients were recruited from patient with adverse drug reactions from allopurinol. Genotyping of *HLA-B*5801* and *HLA-Cw*0302* alleles were determined. Within 34 patients with ADR from allopurinol, there were 25 SCAR (SJS/TEN/HSS) cases *HLA-B*5801* and *HLA-Cw*0302* alleles were found in all 25 patients with SCAR. Odds ratio was 282.2. This study demonstrated that *HLA-B*5801* allele was also associated to allopurinol induced exfoliative dermatitis. Other significant risk factors for hypersensitivity to allopurinol besides genetics were female gender and the presence of diabetes mellitus along with chronic renal insufficiency.

***Key words*:** *HLA-B*5801* allele, SJS, TEN, Allopurinol, SCAR, risk factor.

INTRODUCTION

Allopurinol or 4-hydroxypirazolo pyrimidine is an analog of hypoxanthine and is widely used for gouty arthritis treatment because of its high efficacy to lower uric acid level and can be used in patient with renal insufficiency. Whereas drug allergy that related to allopurinol is frequently reported.,[1-5] non-serious allergic rash was found approximately 2%,[1,3,6] severe cutaneous adverse reactions (SCAR) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug hypersensitivity syndrome (HSS), also called DRESS (drug rash with eosinophillia and systemic symptoms), are frequently reported.[5] Multinational study (EuroSCAR) revealed that allopurinol is the most common drug associated with SJS and TEN in Europe and Israel.[2] Even though the incidence of these SCAR are rare but have significant impact on patient's well-being due to the high morbidity and mortality rate.[5] Mortality rate of SJS, TEN and HSS were found up to 5%, 30-50% and 10% respectively.[1,7] Retrospective study in Thai population revealed that allopurinol showed the highest mortality rate when compared to other high risk drugs.[8]

Strong association between *HLA-B*5801* allele and allopurinol-induced SCAR was reported from the case-control study by Hung et al. in Han Chinese ethnicity. *HLA-B*5801* allele was found in all 51 cases (100%) of SCAR. Risk of SCAR in patients with *HLA-B*5801* allele was 580 times higher. Likewise, *HLA-Cw*0302* allele was found in 48 of the 51 cases (94%) of SCAR.[9] Moreover, the study of Kang et al. showed obvious association of *HLA-B*5801* to the occurrence of SCAR in Korean patients. Risk of SCAR in patients with *HLA-*

*B*5801* allele was 97.8 times higher.[10] Another study which investigated in European patients who experienced SCAR, SJS or TEN from allopurinol, Lonjou et al. found only 61% of patients (19 from 31 cases) with SJS and TEN had *HLA-B*5801* allele.[5] Kaniwa et al. found that *HLA-B*5801* allele presented in only 40% of Japanese patients with SJS and TEN.[11] For Thai population, Wichittra et al. found that the presence of *HLA-B*5801* allele showed 348 times higher risk of SJS and TEN from allopurinol as compared to patients without this allele.[12] Somkrua et.al performed systematic review and meta-analysis about the association of *HLA-B*5801* allele in patients with allopurinol induced SJS and TEN, but limited the application of the result in HSS patient.[13] There is still no report about the association of *HLA-B*5801* and *HLA-Cw* 0302* alleles in allopurinol induced HSS patient including those with moderate to severe rash such as exfoliative dermatitis. Therefore, this study was performed to investigate the association of *HLA-B*5801* and *HLA-Cw*0302* alleles in Thai patient who had allopurinol induced SCAR including HSS and those with moderate to severe type, such as, exfoliative dermatitis. Besides, other risk factors, apart from genetic, which may contribute to higher chance of adverse drug reaction from allopurinol, would also be investigated.

MATERIALS AND METHODS

Study population: A case-control study design was used. The protocol was approved by Siriraj Institutional Review Board (SIRB), Siriraj Hospital, Mahidol University, Bangkok. The study was performed during December 2009 – March 2010. Patient with adverse drug reactions from allopurinol whose data had been recorded in the database of Adverse Drug Reaction Monitoring Center, Siriraj Hospital, and fulfilled the following inclusion criterias were included into the study as the case study group: both inpatients and outpatients who were diagnosed by dermatologists to be SJS, TEN, HSS, and other rash from allopurinol, willing to be included in the study and signed the informed consent form. At the same time, outpatients who had used allopurinol without adverse drug reactions were screened into the study as the control group. The inclusion criteria were as followed: use allopurinol for more than 6 months with no evidence of adverse drug reactions from allopurinol, willing to participate in the study and signed the informed consent form.

DNA isolation: Blood samples (5 milliliters) were obtained from each participant. Samples were collected in tubes containing EDTA which was used as an anticoagulant. Genomic DNA samples were isolated from lymphocytes and prepared by an improved salting-out methods**.**

Human leukocyte antigen genotyping: Genotyping of *HLA-B* and *HLA-C*0302* alleles were determined by polymerase chain reaction sequence specific primer method (PCR-SSP) and *HLA-B*5801* allele was confirmed by One Lambda test kit 57/58 subtype. (One Lambda, Inc., USA)

Statistical analysis: Data were analyzed using SPSS statistical package 17.0 for windows. The statistical analysis comparing the clinical characteristics between case and control were performed. The type of statistics could be descriptive, fisher exact test or non-parametric test, where appropriate. Dichotomous variables were presented as frequency and percentage while continuous variables were presented as mean and standard deviations. The strength of association was estimated by calculating the odds ratio and 95% confidence interval. Odds ratios were calculated with Haldane's modification, which 0.5 was added to all cells to accommodate possible zero count. All P values were two tailed and P values of less than 0.05 were considered to indicate possible statistical significance. Multivariate logistic regressions were used to create model for predicting the probability of allopurinol hypersensitivity**.**

RESULTS

There were 82 patients participated in the study. 34 out of the 82 patients were recruited from patients who had adverse drug reaction from allopurinol. Within these 34 patients, SCAR was found in 25 patients while other cutaneous reactions were found in 9 patients. The rest 48 patients were recruited from patients who were allopurinol tolerant. Comparisons the demographic data between case and control groups were shown in table 1. Female had 11.78 times higher risk compared with male in experiencing SCAR from allopurinol (95%CI = 2.87 to 48.29, P-value < 0.001). In the same direction, 94% of allopurinol tolerant patients were male. Patient with hyperuricemia and patients who did not have their dosage adjusted base on their creatinine clearances had 12.93 times (95% CI = 2.52 to 66.32, P-value < 0.001) and 8.66 times (95% CI = 2.84 to 26.45, P-value < 0.001) higher risk of SCAR, respectively. Patients with history of drug allergy had 2.35 times (95% CI = 0.85 to 6.57 P-value = 0.097) higher risk to SCAR. Moreover, we found that patients with underlying disease of diabetes mellitus and chronic renal insufficiency had 7.06 times (95% CI = 1.67 to 29.77, P-value = 0.006) and 4.2 times (95% CI = 1.41 to 12.46, P-value = 0.008) higher risk of SCAR, respectively.

Association between *HLA-B*5801* and *HLA-Cw*0302* alleles to SCAR:

Twenty five patients who had severe cutaneous adverse reaction (SCAR) and 9 patients who had other types of cutaneous adverse reactions were recruited into the study. Among the 25 patients who had SCAR, the SCAR was identified as SJS in 16 patients, HSS in 8 patients and TEN in 1 patient. *HLA-B*5801* and *HLA-Cw*0302* alleles were found in all these 25(100%) patients. When calculating odds ratio by Haldane's modification, which add 0.5 to all cells to accommodate possible zero count, we found that patients with *HLA-B*5801* and *HLA-Cw*0302* alleles had 282.2 times (P-value < 0.001) higher risk to have SCAR caused by allopurinol than patients who do not have these HLA alleles. The 9 patients who had other types of cutaneous adverse reaction, *HLA-B*5801* and *HLA-Cw*0302* alleles were found in 6 and 5 patients, respectively. The 5 patients who have both *HLA-B*5801* and *HLA-Cw*0302* alleles positive, all had exfoliative dermatitis; while the 1 patient who had maculopapular rash only *HLA-B*5801* allele was found. The association between HLA allele to different types of cutaneous reactions caused by allopurinol was shown in details in tables 2A, 2B, 2C.

Model for prediction of cutaneous adverse reaction from allopurinol: Logistic regression was performed. Among the 82 patients participated in this study, only 79 patient's data were complete and therefore were selected for the creation of the model. Univarate logistic regressions were performed. *HLA-B*5801* and *HLA-Cw*0302* alleles showed high significant and high odds ratio. The significant factors from univariate regression were further included into the multivariate logistic regression model. Multivariate logistic regression was used to create the model for prediction of cutaneous adverse reaction from allopurinol. Significant risk factors that related to incidence of cutaneous adverse reaction were shown in table 3. These factors were analyzed by forward stepwise method and 3 factors was found to be significantly related to adverse drug reaction from allopurinol which included *HLA-B*5801* allele, gender and diabetes.

The model was created as below:

Logit (Y) = - 4.793 + 5.242 (*HLA-B*5801*) + 3.238 (diabetes) + 3.197(gender)….. (1)

$P(Y) = e^{\text{logit}(Y)} / 1 + e^{\text{logit}(Y)}$…….. (2)

Nagelkerke's R^2 (Pseudo R^2) = 0.7

DISCUSSION

The 25 patients who experienced SCAR participated in this study; the cutaneous reactions could be categorized into 3 groups including SJS, TEN and HSS. HLA genotyping revealed that *HLA-B*5801* and *HLA-Cw*0302* alleles were found in all patients (100%). This finding is consistent with the studies of Hung et al.[9]., Kang et al.[10] and Wichittra et al.[12] who studied in Han Chinese, Korean and Thai patients with SCAR, respectively. Besides SJS and TEN, our study also included 8 patients who had HSS while Wichittra et al. recruited only patients with SJS and TEN. Inconsistency result was noted in European and Japanese population. Lonjou et al. who studied in European population with SJS and TEN revealed that *HLA-B*5801* allele was found in only 61% of these patients. Kaniwa et al. who studied in Japanese patients and report that *HLA-B*5801* allele was found in only 40% of their patients. In contrary, *HLA-B*5801* allele was found up to 14.58% (7 from 48 patients) in allopurinol tolerant control group. This finding is consistent with the study of Hung et al. (14.81%) Kang et al. (10.51%) and Wichittra et al. (12.96%) Unlike in European and Japanese study, they found *HLA-B*5801* allele in allopurinol tolerant patients only 1.5% and 0.6%, respectively. However, our results demonstrated that there was a strong association between SCAR induced by allopurinol and *HLA-B*5801* and *HLA-Cw*0302* alleles. The odds ratio was 282.2.

Even though not as strong as SCAR, This study demonstrated that *HLA-B*5801* allele was also associated to allopurinol induced exfoliative dermatitis which has been classified to be moderate to severe dermatitis (the patient had no internal inflammation and/or diagnostic criteria of HSS or DRESS have not been completely fulfilled). The odds ratio in this group of patients was 11.71.

The results from Hung et al. Kang et al., Wichittra et al. and this study indicated that *HLA-B58* found in patients was all *HLA-B*5801* allele. Therefore, if the laboratory or testing kit is not available to test specific *HLA-B*5801* allele genotyping, or to save the cost, low to intermediate resolution method which can identify *HLA-B58* might be sufficient for screening patients with high risk to allopurinol induced SCAR and exfoliative dermatitis. *HLA-B*5801* and *HLA-Cw*0302* alleles were both found in all patients with SCAR. This demonstrated that *HLA-B*5801* allele is usually transmitted together with *HLA-Cw*0302* allele as known as linkage disequilibrium. In clinical practice, either *HLA-B*5801* or *HLA-Cw*0302* alleles testing can be used to identify patient with high risk of allopurinol induced SCAR. However, *HLA-B*5801* allele had been reported to be more specific.

Pathogenesis of allopurinol hypersensitivity syndrome is unclear; its etiology is related to many factors including immunology, genetics, and accumulation of oxypurinol and reactivate of latent virus. Among allopurinol tolerant patients, *HLA-*

*B*5801* allele was found in 7 patients of 48 patients recruited. It was noticed that *HLA-B*5801* allele was found only in male and only 1 diabetes mellitus patient was found in this group, dosage of allopurinol was adjusted according to renal function in 6 of 7 patients (85.71%). All patients with *HLA-B*5801* allele were using allopurinol for treating gouty arthritis.

Therefore, we concluded that female had higher risk to allopurinol induced cutaneous adverse reaction than male. About 75% (6 from 8 patients) of diabetes mellitus patients in the case group had poor renal function; and no dosage adjustment based on his/her creatinine clearance was done to decrease the accumulation of oxypurinol (allopurinol metabolite); this might put the patient at higher risk of adverse drug reaction. Renal insufficiency might be the factor underneath diabetes mellitus. Patient with chronic renal disease whose drug dosage was adjusted according to his/her renal function, then, oxypurinol might not be accumulated. Therefore, main factors included in the model equation for predicting cutaneous adverse drug reaction cause by allopurinol were *HLA-B*5801* allele, female gender and underlying disease of diabetes mellitus. However, the model should be validated before use.

CONCLUSION

Strong association between *HLA-B*5801* and *HLA-Cw*0302* alleles and SCAR including exfoiative dermatitis was found. With the study results, the following factors may affect safely use of allopurinol, 1) reasonably drug use 2) appropriate dosage regimen based on patient's renal function 3) screening test of *HLA-B*5801* allele before administration of allopurinol.

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Table 1 Demographic data of the study population.

(Comparisons between allopurinol tolerant and allopurinol induced skin reactions)

	Allopurinol tolerant control (C) (n=48)	Allopurinol induced skin reactions			P-value		
		SCAR (A) (n=25)	Other skin (B) (n=9)	Total (A+B) (n=34)	(C) VS (A)	(C) VS (B)	(C) VS (A+B)
Characteristic							
Age (years, mean ±SD	60.25 ± 12.52	63.96 ± 14.89	75.77±3.52*	67.08±13.86*	0.141	< 0.001	0.007
(min-max, median)	(32-82, 58.50)	(22-85,67)	(70-80, 77)	(22-85, 70)			
Age < 60	25 (52.08)	8 (32.0)	0 (0)*	8 (23.53)*	0.102	0.003	0.009
≥ 60	23 (47.92)	17 (68.0)	9 (100.0)	26 (76.47)			
Native Thai n (%)	19 (39.58)	15(60.0)	7 (77.78)	22 (64.70)	0.217	0.106	0.068
Thai-Chinese n (%)	28 (58.33)	10 (40.0)	2 (22.22)	12 (35.29)			
Other n (%)	1 (2.08)	0 (0)	0 (0)	0 (0)			
Male n (%)	45 (93.75)	14 (56.0)	6 (66.67)	20 (58.82)	< 0.001	0.044	< 0.001
Female n (%)	3 (6.25)	11 (44.0)*	3(33.33)*	14 (41.18)*			
Duration of drug exposure (days)							
(mean ±SD, min-max)	4.09 ± 2.50 years (0.8-9.52 years)	23.83±13.30* (1-72)	23.86±29.45* (1-85)	23.84±17.58* (1-85)	< 0.001	< 0.001	< 0.001
Serum creatinine (mg/dl)							
(mean ±SD, min-max)	1.22 ± 0.366 (0.8-3.0)	1.51 ± 0.81 (0.8 – 4.5)	1.58 ± 0.31* (1.2-2.1)	1.52 ± 0.70* (0.8-4.5)	0.087	0.001	0.008
Indication for allopurinol							
Gouty arthritis n (%)	46 (95.83)	16 (64.0)	8 (88.89)	24 (70.59)	0.003	0.409	0.001
Hyperuricemia n (%)	2 (4.17)	9 (36.0)*	1 (11.11)	10 (29.41)*			

Table 1 Demographic data of the study population. (cont.)

	Allopurinol tolerant control (C) (n=48)	Allopurinol induced skin reactions SCAR (A) (n=25)	Other skin (B) (n=9)	Total (A+B)(n=34)	P-value (C) VS (A)	(C) VS (B)	(C) VS (A+B)
Thiazide used							
Thiazide use	12 (25.0)	6 (24.0)	2 (22.22)	8 (23.53)	0.925	1.000	0.879
No thiazide use	36 (75.0)	19 (76.0)	7 (77.77)	26 (76.47)			
Adjust dose base on CrCl							
Recommended dose	39 (81.25)	8 (32.0)	4 (44.44)	12 (35.29)	< 0.001	0.074	< 0.001
Overdose	9 (18.75)	16 (64.0)*	4 (44.44)	20 (58.82)*			
Other drug allergy							
No drug allergy n (%)	36 (75.0)	14 (56.0)	4 (44.40)	18 (52.94)	0.097	0.109	0.038
Drug allergy n (%)	12 (25.0)	11 (44.0)*	5 (55.56)	16 (47.06)*			
Underlying disease n (%)							
Benign prostatic hypertrophy	5 (10.42)	0 (0)	1 (11.11)	1 (2.94)	0.158	1.000	0.393
Cardiovascular disease	9 (18.75)	4 (16.0)	5 (55.56)*	9 (26.47)	1.000	0.032	0.405
Chronic renal insufficiency[#]	20 (41.67)	18 (72.0)*	9 (100.0)*	27 (79.41)*	0.008	0.002	< 0.001
Diabetes mellitus	3 (6.25)	8 (32.0)*	6 (66.67)*	14 (41.18)*	0.006	< 0.001	< 0.001
Dyslipidemia	19 (39.58)	12 (48.0)	7 (77.78)	19 (55.88)	0.490	0.065	0.145
Fatty liver	6 (12.50)	1 (4.0)	0 (0)	1 (2.94)	0.410	0.575	0.230
Hypertension	34 (70.83)	19 (76.0)	9 (100)	28 (82.35)	0.639	0.095	0.231
Hyperthyroid	1 (2.08)	3 (12.0)	1 (11.11)	4 (11.76)	0.113	0.293	0.155
Osteoarthritis	4 (8.33)	3 (12.0)	0 (0)	3 (8.82)	0.685	1.000	1.000

Table 2A Association between *HLA* allele to allopurinol induced SCAR

HLA-allele	Allopurinol tolerant (Total N=48) n (%)	Allopurinol induced SCAR (Total N = 25) n (%)	P-value	Odds ratio
*HLA-B*5801*	7 (14.58)	25 (100.0)	< 0.001	282.2
*HLA-Cw*0302*	7 (14.58)	25 (100.0)	< 0.001	282.2
*HLA-B*15*	15 (31.25)	4 (16.0)	0.260	0.42
*HLA-B*27*	7 (14.58)	1 (4.0)	0.250	0.24
*HLA-B*38*	1 (2.08)	1 (4.0)	1.000	1.96
*HLA-B*39*	3 (6.25)	3 (12.0)	0.406	2.04
*HLA-B*40*	16 (33.33)	8 (32.0)	0.908	0.94
*HLA-B*46*	11 (22.92)	4 (16.0)	0.557	0.64

Table 2B Association between *HLA* allele to allopurinol induced other type of skin reactions.

HLA-allele	Allopurinol Tolerant (Total N=48) n (%)	Allopurinol induced other skin reactions (Total N = 9) n (%)	P-value	Odds ratio
*HLA-B*5801*	7 (14.58)	6 (66.67)	0.003	11.71
*HLA-Cw*0302*	7 (14.58)	5 (55.56)	0.015	7.32
*HLA-B*15*	15 (31.25)	0 (0)	0.094	0.11
*HLA-B*27*	7 (14.58)	0 (0)	0.582	0.29
*HLA-B*38*	1 (2.08)	0 (0)	1.000	1.67
*HLA-B*39*	3 (6.25)	0 (0)	1.000	0.68
*HLA-B*40*	16 (33.33)	3 (33.33)	1.000	1.0
*HLA-B*46*	11 (22.92)	2 (22.22)	1.000	0.96

Table 2C Association between *HLA* allele to allopurinol induced all types of skin reaction.

HLA-allele	Allopurinol Tolerant (Total N=48) n (%)	Allopurinol induced skin reactions (Total N = 34) n (%)	P-value	Odds ratio
*HLA-B*5801*	7 (14.58)	31 (91.18)	< 0.001	60.52
*HLA-Cw*0302*	7 (14.58)	30 (88.24)	< 0.001	43.92
*HLA-B*15*	15 (31.25)	4 (11.76)	0.062	0.29
*HLA-B*27*	7 (14.58)	1 (2.94)	0.131	0.18
*HLA-B*38*	1 (2.08)	1 (2.94)	1.000	1.42
*HLA-B*39*	3 (6.25)	3 (8.82)	0.688	1.45
*HLA-B*40*	16 (33.33)	11 (32.35)	0.926	0.96
*HLA-B*46*	11 (22.92)	6 (17.65)	0.562	0.72

Table 3 Significant risk factors for allopurinol induced skin reactions according to multivariate logistic regression.

Factor	B	P-value	Odds ratio	95.% C.I. for odds ratio
*HLA-B*5801*	5.242	< 0.001	189.06	13.40 – 2667.36
Diabetes	3.238	0.019	25.48	1.719 – 377.70
Gender	3.197	0.022	24.46	1.584 – 377.60
Constant	-4.793	< 0.001	0.008	

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