

The Presence of HLA-B75, DR13 Homozygosity, or DR14 Additionally Increases the Risk of Allopurinol-Induced Severe Cutaneous Adverse Reactions in HLA-B*58:01 Carriers



Ji-Su Shim, MD^{a,b}, James Yun, MD, PhD^{c,d}, Mi-Yeong Kim, MD^e, Soo Jie Chung, MD^{a,b}, Ji Hyun Oh, MD^{a,b}, Dong-Yoon Kang, MD^f, Jae-Woo Jung, MD, PhD^g, Sang-Heon Cho, MD, PhD^{a,b,f}, and Hye-Ryun Kang, MD, PhD^{a,b,f}
Seoul and Busan, Korea; and Sydney, Australia

What is already known about this topic? HLA-B*58:01 is a well-known genetic risk factor of allopurinol-induced severe cutaneous adverse reactions (SCARs). However, only some of the subjects with HLA-B*58:01 have allopurinol-induced SCARs.

What does this article add to our knowledge? This study revealed that HLA-B75, DR13 homozygosity, and DR14 increased the risk of allopurinol-induced SCARs when combined with HLA-B*58:01, especially in those with impaired kidney function (estimated glomerular filtration rate less than 30 mL/minute/1.73 m²).

How does this study impact current management guidelines? The results suggest that the secondary screening of the newly identified HLA risk factors for high-risk patients screened with the HLA-B*58:01 allele could increase the accuracy of the prediction.

BACKGROUND: Although HLA-B*58:01 is a well-known risk factor for the development of allopurinol-induced severe cutaneous adverse reactions (SCARs), most of the HLA-B*58:01 carriers do not suffer from SCARs despite a long-term use of allopurinol. This suggests that there are other risk factors that determine the fate of HLA-B*58:01 carriers.

OBJECTIVE: The aim of this study was to investigate the additional genetic factors that increase the risk of allopurinol-induced SCARs in HLA-B*58:01 carriers.

METHODS: The incidence of allopurinol-induced SCARs was investigated according to coexisting HLA alleles in all subjects with HLA-B*58:01 who took allopurinol between 2003 and 2017. The allopurinol tolerant group was defined as a group who took allopurinol for more than 60 days without developing hypersensitivity and was compared with the allopurinol-induced SCAR group.

RESULTS: Among the retrospective cohort consisting of 367 HLA-B*58:01 carriers treated with allopurinol, 11 (3.0%) were diagnosed with allopurinol-induced SCARs. When HLA-B75, DR13 homozygosity, or DR14 was present, the incidence of SCARs increased up to 22.2% (odds ratio [OR], 19.568; $P = .015$), 20.0% (OR, 38.458; $P = .001$), and 10.7% (OR, 19.355; $P = .004$), respectively. Among the 153 HLA-B*58:01 carriers with chronic renal insufficiency (CRI), the incidence of SCARs doubled to 6.5% and further increased to 40%, 30%, and 37.5% in the presence of HLA-B75, DR13 homozygosity, or DR14, respectively.

CONCLUSIONS: Secondary screening with HLA-B75, DR13 homozygosity, and DR14 in addition to primary screening with HLA-B*58:01 would enable a more accurate prediction of SCAR occurrence, especially in patients with CRI. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1261-70)

Key words: Allopurinol; Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug hypersensitivity syndrome; Human leukocyte antigen; Koreans

^aDivision of Allergy and Clinical Immunology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

^bInstitute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul National University College of Medicine, Seoul, Korea

^cDepartment of Immunology and Rheumatology, Nepean Hospital, Sydney, Australia

^dThe University of Sydney, Sydney, Australia

^eDepartment of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea

^fRegional Pharmacovigilance Center, Seoul National University Hospital, Seoul, Korea

^gDepartment of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

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Corresponding author: Hye-Ryun Kang, MD, PhD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. E-mail: helenmed@snu.ac.kr.

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Abbreviations used

AGEP- Acute generalized exanthematous pustulosis
 CI- Confidence interval
 CRI- Chronic renal insufficiency
 DRESS- Drug reaction with eosinophilia and systemic symptoms
 eGFR- Estimated glomerular filtration rate
 MPE- Maculopapular eruption
 OR- Odds ratio
 SCAR- Severe cutaneous adverse reactions
 SJS- Stevens-Johnson syndrome
 SSO- Sequence-specific oligonucleotide
 TEN- Toxic epidermal necrolysis
 TLS- Tumor lysis syndrome
 WHO- World Health Organization

Allopurinol is a urate-lowering agent that has been in use for the management of gout and asymptomatic hyperuricemia in chronic renal insufficiency (CRI)¹ and to prevent tumor lysis syndrome (TLS) in patients with hematologic malignancy.² There are other urate-lowering agents such as probenecid, benzbromarone, and sulfapyrazone, as well as the recently developed drug, febuxostat.³ However, allopurinol is still the most commonly prescribed urate-lowering agent because of its effectiveness, low price, and general safety other than severe hypersensitivity reactions.^{1,4} With these advantages, allopurinol currently belongs to the 20th World Health Organization's (WHO) list of essential medicines updated in 2017.

Severe cutaneous adverse reactions (SCARs) are life-threatening serious hypersensitivity reactions to drugs, which include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).⁵ Allopurinol is one of the major causes of SJS/TEN and DRESS, but it rarely causes AGEP.^{6,7} Allopurinol-induced SCARs are known to occur in 0.1% to 0.4% of newly prescribed patients, and its mortality was reported to be as high as 9% to 32%.^{1,8}

Since Hung et al⁹ first revealed the strong association between HLA-B*58:01 and allopurinol-induced SCARs in the Han Chinese population in 2005, HLA-B*58:01 has been regarded as a risk marker for allopurinol-induced SCARs in many different populations, mainly in Asians.¹⁰ However, the fact that only some of the subjects with HLA-B*58:01 had SCARs when they took allopurinol suggests that there should be other factors enhancing the risk of allopurinol-induced SCARs in conjunction with HLA-B*58:01.

The aim of this study was to identify additional genetic factors associated with allopurinol-induced SCARs by monitoring a retrospective cohort of all subjects with HLA-B*58:01 who took allopurinol.

METHODS**Study subjects**

We retrospectively reviewed the electronic medical records of all subjects with HLA-B*58:01 who took allopurinol from 2003 to 2017 at the Seoul National University Hospital. To select the study subjects, we screened all the patients who had HLA results and were medicated with allopurinol during the study period. According to

the chart review, the main indications for the HLA test were as follows: to be registered as a recipient or a donor for blood or bone marrow stem cell transplantation as well as kidney transplantation.

Because HLA-B*58:01 is known as the only allele of the HLA-B58 serotype in the Korean population, the subjects with HLA-B58 were considered as HLA-B*58:01 allele positive.^{11,12}

The diagnosis of SCARs was made by allergy or dermatology specialists. The clinical features of SJS/TEN included skin blistering with epidermal detachment and mucosal involvement.⁵ SJS, overlap SJS/TEN, and TEN were defined when the affected skin was less than 10%, 10% to 30%, and more than 30% of the body surface area, respectively.¹³ The diagnosis of DRESS was made according to the RegiSCAR criteria, and those with 4 points ("probable") or higher were included.¹⁴ AGEP was excluded from the analysis because it is not known to be associated with HLA-B*58:01 and none of the patients with SCAR developed AGEP. Maculopapular eruption (MPE) that did not satisfy the SCAR diagnosis was excluded from the tolerant group and subsequent analyses.

Causality assessment of SCARs was performed by allergy specialists using the WHO-Uppsala Monitoring Center criteria, and the categories of certain and probable were considered causative.

The allopurinol-tolerant group was defined as patients who did not present any symptoms suggesting drug hypersensitivity after taking allopurinol for more than 60 consecutive days. Patients who took allopurinol less than 60 days were excluded from the tolerant group because the possibility of SCAR development with sufficient exposure could not be completely ruled out.

CRI was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/minute/1.73 m² at the onset of allopurinol administration. eGFR was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation. In children younger than 15 years, the creatinine-based "Bedside Schwartz" equation was used. We identified underlying cardiovascular diseases by ICD-10 (International Classification of Diseases, 10th revision)¹⁵ codes I20-I25 (ischemic heart disease).

This study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB number: 1805-060-945).

HLA typing

Before 2011, serologic typing of HLA-A, -B, and -C was performed with the microlymphocytotoxicity method with a Terasaki Oriental HLA-ABC well tray (One lambda, Canoga Park, Calif),² and from 2011, genotyping of HLA-A, -B, and -C was performed with the PCR-reverse sequence-specific oligonucleotide (SSO) method for low-resolution typing and the PCR-sequence-based typing method for high-resolution typing. In the case of HLA-DRB1, genotyping using the PCR-reverse SSO method was performed in all cases.

Statistical analysis

Statistical analysis for the basic characteristics of the subjects and the difference in SCAR incidence according to HLA status and/or eGFR was conducted with the χ^2 test, Fisher's exact test, and linear-by-linear association for the categorical variables and Student's *t* test for the continuous variables. Binary logistic regression (univariate and multivariate analysis) was performed to determine the risk of allopurinol-induced SCARs according to HLA status and other variables. The strength of the association was expressed as the odds ratio (OR) and 95% confidence intervals (CI), and a statistically significant difference was defined as a *P* value of <.05. All statistical

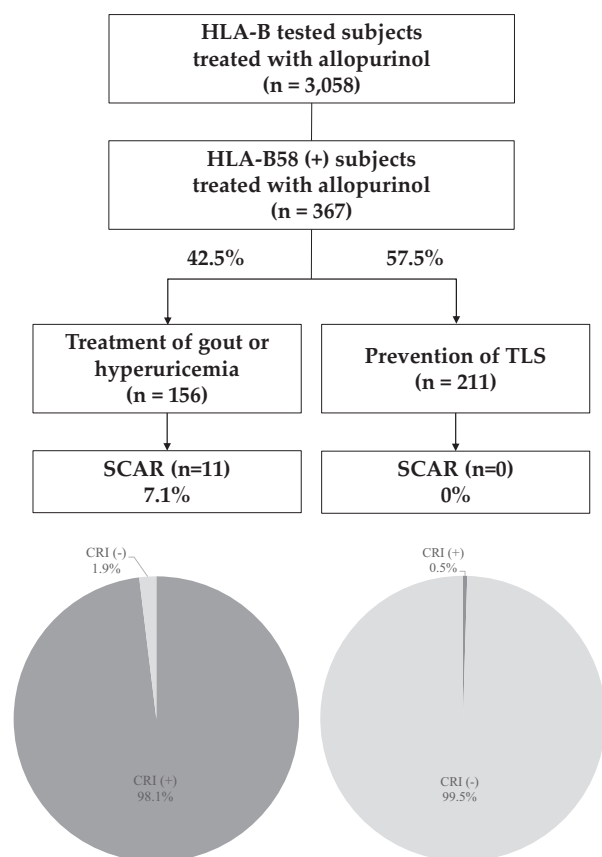


FIGURE 1. Study population and occurrence of hypersensitivity reactions. All 367 subjects had HLA-B58 and treated with allopurinol. HLA-B*58:01 is the only allele of HLA-B58 in the Korean population. The indication of allopurinol administration could be divided into 2 groups: hyperuricemia and tumor lysis syndrome. All SCARs occurred in the hyperuricemia group (11/156 = 7.1%). Chronic renal insufficiency (CRI) was defined as an eGFR less than 60 mL/minute/1.73 m². eGFR, Estimated glomerular filtration rate; SCAR, severe cutaneous adverse reaction; TLS, tumor lysis syndrome.

analyses were conducted with SPSS, version 22.0 (IBM Corporation, Armonk, NY).

RESULTS

Characteristics of the study subjects

A total of 367 patients were recruited as HLA-B*58:01 carriers treated with allopurinol. Of these patients, 41.7% (n = 153) had CRI. Indications for allopurinol were asymptomatic hyperuricemia (41.4%, n = 152), gouty arthritis (1.1%, n = 4), and prevention of TLS (57.5%, n = 211) (Figure 1). Allopurinol was administered for the prevention of TLS during induction chemotherapy before stem cell transplantation.

Among the B*58:01 carriers, MPE occurred in 4 cases (1.1%) and SCARs developed in 11 cases (3.0%) after allopurinol administration. SCARs consisted of 2 cases of SJS, 1 case of TEN, and 8 cases of DRESS. One patient died of TEN, and the mortality rate for SCARs was 9.1% (Table I). All cases of SCARs occurred only when allopurinol was administered for the management of

hyperuricemia, whereas no SCARs occurred when allopurinol was used for the prevention or treatment of TLS (Figure 1). Majority of patients who took allopurinol for the prevention of TLS were on allopurinol for 3 to 7 days (mean duration of 7.96 ± 10.16 days) and had unimpaired renal function (eGFR 104.60 ± 47.58 mL/minute/1.73 m²).

Of the 11 patients with SCAR, 10 had CRI with underlying renal diseases such as glomerulonephritis, diabetic nephropathy, IgA nephropathy, hypertensive nephropathy, autosomal dominant polycystic kidney disease, and Alport syndrome (Table II). The mean age of the SCAR group was 41.27 ± 19.77 years. Indication for taking allopurinol in the SCAR group was hyperuricemia: 10 cases for asymptomatic hyperuricemia and 1 for gouty arthritis (Table III). The mean eGFR of the SCAR group was 25.47 ± 33.05 mL/minute/1.73 m², belonging to stage 4 chronic kidney disease. The incidence of SCARs in the subjects with CRI was 6.54%, 2 times higher than that in the total patients.

Of the remaining 356 patients without SCARs, 4 patients with MPE and 243 patients who were administered allopurinol less than 60 days were excluded from the allopurinol tolerant group. Finally, a total of 109 patients were selected as the allopurinol-tolerant group. When comparing the allopurinol-induced SCAR group and the tolerant group, there were no significant differences in age, sex, initial dose of allopurinol, indication for allopurinol administration, eGFR, uric acid level, and comorbid diseases (Table III). However, the duration of the exposure to allopurinol was significantly shorter in the SCAR group (47.73 ± 18.69 vs 792.18 ± 756.07 days; $P < .001$) because allopurinol was discontinued because of SCARs, but all patients with SCAR were continuously treated with allopurinol for at least 17 days.

The results of viral antigen detection test during the initial phase of SCAR were available in 6 patients with SCAR, which included herpes simplex virus 1/2 (n = 3), human herpes virus 6 (n = 2), cytomegalovirus (n = 5), and Epstein-Barr virus (n = 5), and there was no evidence of viral reactivation.

The risk for the development of allopurinol-induced SCARs according to HLA types

Figure 2 shows the allele frequencies of HLA-A, -B, -C, and -DR in the tolerant group and the SCAR group. It is known that HLA-A*33:03, -C*03:02, and -DR*13:02 have linkage disequilibrium with B*58:01 in Koreans.¹² Therefore, HLA-A33, -C3, and -DR13 were relatively frequent in our B*58:01 cohort compared with the Korean general population; however, there was no significant difference in these allele frequencies between the tolerant group and the SCAR group. HLA-B75 and -DR14 were more frequently found in the SCAR group than in the tolerant group (Figure 2).

The crude OR for SCARs according to the HLA serotype was obtained to compare the tolerant group and the SCAR group. In the 2 groups, the crude OR was significant in the presence of HLA-B75 (OR, 11.89; 95% CI, 1.49-94.66; $P = .019$), DR13 homozygosity (OR, 7.33; 95% CI, 1.74-30.87; $P = .007$), and DR14 (OR, 7.29; 95% CI, 1.50-35.49; $P = .014$) (Table IV).

We calculated the incidence of SCARs according to those HLA types in the total B*58:01 cohort after excluding the patients with MPE. For HLA-B75, the incidence of SCARs was 2.5% for B75-negative and 22.2% for B75-positive patients, respectively ($P = .027$). For the HLA-DR13 homozygotes, the

TABLE I. The incidence of allopurinol hypersensitivity reactions among the HLA-B58 (+) subjects

	Overall hypersensitivity*	Maculopapular eruption	SCAR	Type of SCAR		Mortality rate for SCAR
				SJS/TEN	DRESS	
Overall (N, %)	15/367, 4.1%	4/367, 1.1%	11/367, 3.0%	3/367, 0.8%	8/367, 2.2%	1/11, 9.1%
Chronic renal insufficiency [†] (N, %)	13/153, 8.5%	3/153, 2.0%	10/153, 6.5%	2/153, 1.3%	8/153, 5.2%	
Medication duration $\geq$ 2 wk (N, %)	15/169, 8.9%	4/169, 2.4%	11/169, 6.5%	3/169, 0.2%	8/169, 4.7%	
Prevention of TLS (N, %)	1/211, 0.5%	1/211, 0.5%	0/211, 0%			

CKD-EPI, the Chronic Kidney Disease Epidemiology Collaboration; DRESS, drug reaction with eosinophilia and systemic symptoms; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TLS, tumor lysis syndrome.

*Overall hypersensitivity includes simple maculopapular eruption and severe cutaneous adverse reaction.

[†]Chronic renal insufficiency was defined as the estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m². The eGFR was calculated by the CKD-EPI creatinine equation. In children younger than 15 years, creatinine-based "Bedside Schwartz" equation was used.

TABLE II. Clinical characteristics of the patients with allopurinol-induced SCARs

Age/sex	Type	Dose (mg/day)	Duration (days)	Indication	Underlying disease	eGFR	Mucosal involvement; sites	Systemic manifestation
13/M	SJS	200	17	HU	DCM, Becker muscular dystrophy	107.4	Oral, genital	Fever, azotemia, LFI
55/M	SJS	100	68	HU	MPGN	21.4	Oral	Fever, myalgia, skin detachment of back and both inguinal areas
58/M	TEN	100	61	HU	CKD due to previous chemotherapy, history of lymphoma	38.57	Oral, conjunctival	Fever, almost 100% of skin detachment, abdominal pain and diarrhea, LFI, leukocytosis, eosinophilia, died of TEN
23/F	DRESS	100	31	HU	Alport syndrome	20.0	(-)	Fever, MPE, cervical lymphadenopathy, LFI, worsening RF, leukocytosis, eosinophilia
18/F	DRESS	100	73	HU	Diabetic nephropathy	10.0	(-)	Fever, MPE, cervical lymphadenopathy, LFI, leukocytosis, eosinophilia
45/F	DRESS	100	28	HU	Hypertensive nephropathy	12.3	(-)	Fever, MPE, LFI, worsening RF, leukocytosis, eosinophilia
15/M	DRESS	150	66	HU	CKD due to reflux	13.0	(-)	Fever, MPE, LFI, leukocytosis, eosinophilia, atypical lymphocytes
56/F	DRESS	50	46	HU	IgA nephropathy	7.7	(-)	MPE, LFI, leukocytosis, eosinophilia
49/M	DRESS	100	34	Gout	CKD due to CGN	10.34	(-)	Fever, MPE, LFI, worsening RF, leukocytosis, eosinophilia
63/F	DRESS	100	43	HU	ADPKD	5.29	(-)	Fever, MPE, worsening RF, leukocytosis, eosinophilia
59/F	DRESS	100	58	HU	FSGS	15.63	(-)	Mild fever, MPE, worsening RF, leukocytosis, eosinophilia

ADPKD, Autosomal dominant polycystic kidney disease; CGN, chronic glomerulonephritis; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; DRESS, drug reaction with eosinophilia and systemic symptom; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HU, hyperuricemia, asymptomatic; LFI, liver function impairment; MPE, maculopapular eruption; MPGN, membranoproliferative glomerulonephritis; RF, renal function; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

incidence of SCARs was not different in the subjects with the HLA-DR13 heterozygosity at 1.6% compared with those without HLA-DR13 (2.1%); however, HLA-DR13 homozygotes had a conspicuously higher incidence of 20.0% ($P = .013$). HLA-DR14 also showed a 5-fold increase in SCAR incidence as well (2.1% vs 10.7%, $P = .036$). However, there were no gene dosage effect of B*58:01 on the development of allopurinol-induced SCARs (heterozygotes vs homozygotes, 2.8% vs 9.1%, $P = .291$) (Figure 3). Among patients with SCAR, there was no significant difference in cumulative dose ($P = .821$) or duration of allopurinol ($P = .459$) in those with risky HLA alleles.

Next, a binary logistic regression analysis was performed to determine the OR for the SCARs of HLA-B75, DR13

homozygosity, and DR14 in the total HLA-B*58:01 cohort after excluding MPE. In addition, the uric acid level along with previously known risk factors such as female, age >60 years, eGFR, initial dose of allopurinol, and cardiovascular disease was also analyzed. The results are shown in Table V. HLA-B75, DR13 homozygosity, DR14, eGFR, uric acid, and initial dose of allopurinol all had significant OR values in the univariate analysis. As a next step, we conducted multivariate analysis with significant parameters, and the adjusted OR values of HLA-B75 (OR, 19.568; 95% CI, 1.776-215.612; $P = .015$), DR13 homozygosity (OR, 38.458; 95% CI, 4.443-332.870; $P = .001$), and DR14 (OR, 19.355; 95% CI, 2.564-146.123; $P = .004$) were still significant. The adjusted OR of eGFR <30 mL/minute/1.73 m² was also

TABLE III. Demographic characteristics of the study subjects with HLA-B58

	Allopurinol-induced SCAR n = 11 (3.00%)	Allopurinol-tolerant group* n = 109 (29.7%)	P value
Sex (male, %)	5 (45.5%)	74 (67.9%)	.135
Age (median, y)	41.27 ± 19.77	39.39 ± 19.31	.759
Duration of allopurinol exposure (days)	47.73 ± 18.69	792.18 ± 756.07	<.001
Initial dosage of allopurinol (mg/day)	109.09 ± 37.54	104.4 ± 56.44	.788
Indication of allopurinol (%)			
Hyperuricemia	11 (100%)	107 (98.2%)	.651
Treatment or prevention of TLS	0 (0%)	2 (1.8%)	
Blood urea nitrogen (mg/dL)	56.09 ± 34.69	48.08 ± 26.63	.357
Creatinine (mg/dL)	3.97 ± 2.37	4.23 ± 3.11	.783
eGFR (mL/min/1.73 m ²)	25.47 ± 33.05	20.77 ± 15.30	.651
Uric acid (mg/dL)	8.33 ± 1.41	8.13 ± 2.20	.776
Comorbidities (%)			
Hypertension	6 (54.5%)	61 (56%)	.928
Diabetes mellitus	1 (9.1%)	29 (26.6%)	.201
Cardiovascular disease	1 (9.1%)	7 (6.4%)	.735
Gout	1 (9.1%)	8 (7.3%)	.834

eGFR, Estimated glomerular filtration rate; SCAR, severe cutaneous adverse reaction; TLS, tumor lysis syndrome.

*Patients tolerated allopurinol at least 60 consecutive days.

significant (OR, 14.203; 95% CI, 1.064-189.520; $P = .045$). However, the uric acid level and initial dose of allopurinol were no longer significant (Table V).

Allopurinol-induced SCARs according to renal function

Among the 11 patients with SCAR, 10 patients had CRI (Table I). The incidence of SCARs in the HLA-B*58:01 carriers showed a remarkable difference according to the eGFR; it was only 0.5% for >60 mL/minute/1.73 m² but increased to 2.4% for 30 to 60 mL/minute/1.73 m² and 7.1% for an eGFR <30 mL/minute/1.73 m² ($P = .001$) (Figure 4). The adjusted OR for an eGFR <30 mL/minute/1.73 m² was 14.203, and this was significant ($P = .045$).

Then, the incidence of SCARs according to HLA status combined with eGFR was examined. Interestingly, the incidence of allopurinol-induced SCARs in the HLA-B*58:01 carriers with an eGFR less than 30 mL/minute/1.73 m² sharply increased up to 40.0% ($P = .055$), 30.0% ($P = .044$), and 37.5% ($P = .024$) in the presence of HLA-B*57:01, DR13 homozygosity, or DR 14, respectively (Figure 4).

DISCUSSION

A recent pharmacogenomic study revealed an apparent genetic predisposition associated with the occurrence of SCARs due to specific culprit drugs by HLA analysis such as HLA-B*57:01 for abacavir (Caucasians),^{16,17} HLA-B*15:02 for carbamazepine (Han Chinese),^{18,19} and HLA-B*58:01 for allopurinol (Asians).^{9,20} Despite this marked progress, recent advancements in the pharmacogenomics of SCARs are insufficient to open a new chapter of precision medicine.

The association of HLA-B*58:01 with allopurinol-induced SCARs is well known since the first study reported HLA-B*58:01 as a strong genetic marker for allopurinol-induced SCARs in 2005 (OR, 580.3; $P = 4.7 \times 10^{-24}$).⁹ This association was proven in Thais, Caucasians, Japanese, Portuguese, and Koreans.²⁰⁻²⁴ Meta-analysis including 10 studies of Thailand,

Korea, Japan, China, Hong Kong, Europe, Portugal, and Australia showed a pooled OR of 57.33 ($P < 1.0 \times 10^{-5}$) for allopurinol-induced SJS/TEN and 54.16 ($P < 1.0 \times 10^{-5}$) for allopurinol-induced DRESS²⁵ in the presence of B*58:01.

However, HLA-B*58:01 cannot completely explain the development of allopurinol-induced SCARs; in other words, only some of the patients with HLA-B*58:01 experience SCARs with the administration of allopurinol, and there are a small number of allopurinol-induced SCAR cases in the absence of HLA-B*58:01.^{1,25} This suggests that there are other important factors that finely tune the inception of allopurinol-induced SCARs in addition to B*58:01.

The American College of Rheumatology guidelines for the management of gout recommended the screening test of HLA-B*58:01 for Koreans with stage 3 to 5 chronic kidney disease and for the total Han Chinese and Thai populations.²⁶ This recommendation has a limitation in its clinical application because of the low positive predictive value of HLA-B*58:01.^{4,25} The overall incidence of allopurinol-induced SCARs was only 3.0% among HLA-B*58:01 carriers in this study. When confined to those treated for a relatively longer time for the treatment of hyperuricemia considering the possibility of being underestimated due to the short duration of medication, the incidence of SCARs was up to 7.1% (Figure 1), much higher than that of the general population at 0.1% to 0.4% in the literature.^{1,8} However, most of the patients with HLA-B*58:01 still can use allopurinol without any serious hypersensitivity reaction.

Failure to use allopurinol in HLA-B*58:01-positive patients may result in the loss of a clinically effective and inexpensive drug; therefore, it is necessary to enhance the predicting power of the B*58:01 screening test by combining it with other risk factors. In this study, we newly found meaningful genetic risk factors of allopurinol-induced SCARs other than HLA-B*58:01 for the first time by analyzing the accompanying HLA alleles in subjects with HLA-B*58:01. The risk of allopurinol-induced SCARs in B*58:01 carriers significantly increased in the

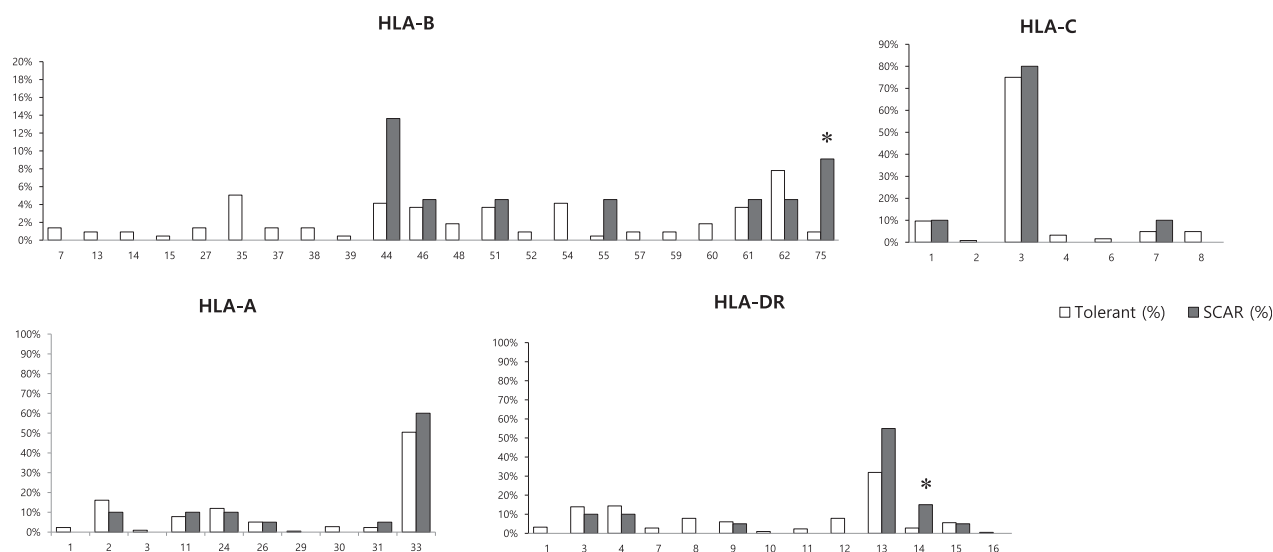


FIGURE 2. The frequency of the HLA-A, -B, -C, and -DR alleles in the subjects with HLA-B58. HLA allele frequency of the tolerant ($n = 109$) and SCAR groups ($n = 11$) was compared, and only HLA-B75 and -DR14 showed significant differences (marked with an asterisk). The tolerant group contained the patients who were administered allopurinol for at least 60 consecutive days without any hypersensitivity reactions such as SCAR and MPE. *MPE*, Maculopapular eruption; *SCAR*, severe cutaneous adverse reaction.

presence of HLA-B75, HLA-DR13 homozygosity, and HLA-DR14 (Table V). Because HLA-DR13 had linkage disequilibrium with HLA-B58 in the Korean population, the DR13 allele frequency was significantly higher compared with the general population (32% vs 9.6%). However, only the HLA-DR13 homozygosity, not HLA-DR13 heterozygosity, increases the risk of allopurinol-induced SCARs. There is no linkage disequilibrium across HLA-B58 and -DR14.¹² In our study population, no one inherited HLA-B75, -DR13 homozygosity, and DR 14 simultaneously.

The HLA-B75 serotype is one of the subgroups of HLA-B15. In the Korean general population, HLA-B75 consists of HLA-B*15:02 and -B*15:11.²⁷ As for its prevalence, HLA-B*15:02 is very rare (0.41%), and HLA-B*15:11 is relatively more prevalent at 3.92%.¹² Therefore, most of the HLA-B75 in this study are likely to be HLA-B*15:11. Both HLA-B*15:02 and -B*15:11 were already reported as a risk factor of carbamazepine-induced SCARs.²⁸ The fact that HLA-B75 is a risk factor for both carbamazepine and allopurinol hypersensitivity is intriguing considering that these 2 drugs are not structurally related. Similarly with this finding, HLA-B*57:01 is a risk factor for both abacavir and flucloxacillin hypersensitivity. For this HLA association with structurally unrelated drugs, we hypothesized the possibility that (1) a specific HLA type such as HLA-B75 may influence the T-cell repertoire in thymic selection,²⁹ (2) viral specific T cells that bind to the viral peptide-HLA-B75 complexes may have peculiar features that make these more all-or-none,³⁰ or (3) there may be a linkage disequilibrium with another unknown gene that could make an individual more susceptible to drug hypersensitivity. Chung et al^{31,32} showed preferential TCR (T-cell receptor) usage in allopurinol-induced SCAR, but unlike HLA-B*15:02 and carbamazepine-induced SJS/TEN, identical TCR clonotypes were not observed. These findings raise the possibilities of complex interactions between HLA-B*58:01, HLA-B75, and TCR selection in addition to the

TABLE IV. Crude odds ratio for the development of SCAR in the allopurinol-tolerant group and allopurinol-induced SCAR group

HLA	Odds ratio* (95% CI)	P value
A11	1.35 (0.26-6.93)	.717
A31	2.31 (0.24-21.98)	.466
B7	1.32 (0.06-27.25)	.856
B44	4.17 (0.94-18.52)	.061
B55	10.80 (0.63-186.07)	.101
B58, homozygosity	2.63 (0.27-25.80)	.408
B61	1.26 (0.14-11.15)	.834
B75	11.89 (1.49-94.66)	.019
C7	2.33 (0.22-24.41)	.479
DR13	1.87 (0.46-7.61)	.384
DR14	7.29 (1.50-35.49)	.014
DR13, homozygosity	7.33 (1.74-30.87)	.007

CI, Confidence interval; SCAR, severe cutaneous adverse reaction.

*Odds ratio for SCARs was calculated based on the HLA phenotype frequency.

drug binding on peptide-MHC complexes, but these possibilities will need to be further investigated.³³

On the other hand, there are some reports that insist on the protective effect of certain HLA alleles. Chan and Tan³⁴ suggested that the HLA-A2 allele may have a protective role in the development of allopurinol-induced SCARs, and a previous study on a Korean population also showed A*02:01 as a protective marker of allopurinol-induced SCARs.²² However, no protective allele was found in our study, and the subtype information of HLA-A2 was not available. In addition, the gene dosage effect of HLA-B*58:01 has been reported previously.²⁵ In the current study, the incidence was higher in B*58:01 homozygotes than in heterozygotes; however, this difference was not statistically significant (Figure 3), and the crude OR for the HLA-B*58:01 homozygote showed no significance due to

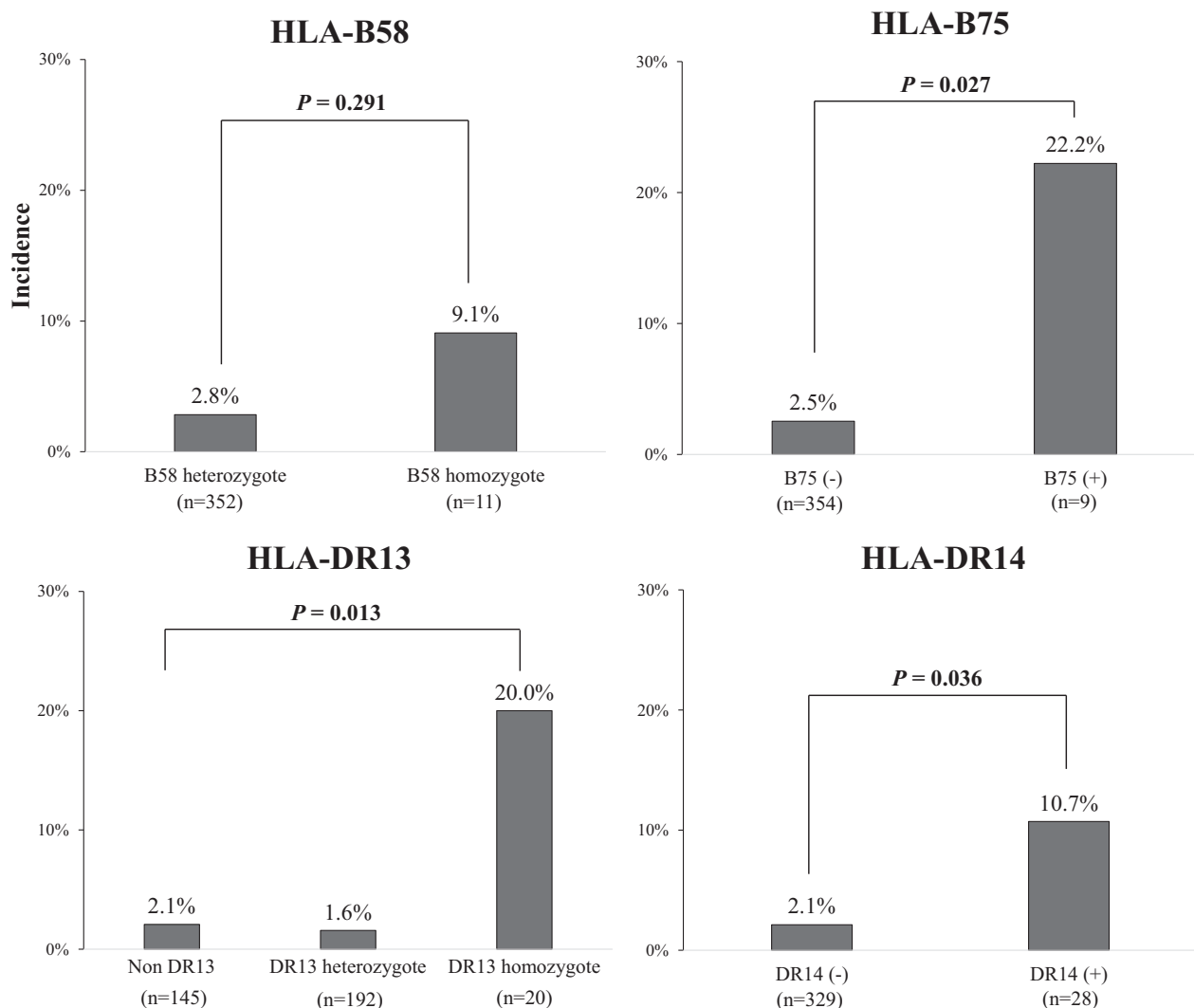


FIGURE 3. The incidence of SCARs according to the HLA status in subjects with HLA-B58. P values for HLA-B58, -B75, and -DR14 were obtained by Fisher's exact test. In the case of HLA-DR13, a linear-by-linear association was used. The patients with MPE were excluded from analysis. *MPE*, Maculopapular eruption; *SCAR*, severe cutaneous adverse reaction.

limited numbers (Table IV). When the eGFR was lower than 30 mL/minute/1.73 m², the incidence of allopurinol-induced SCARs was 3 times higher in HLA-B*58:01 homozygotes (20.0%) compared with HLA-B*58:01 heterozygotes (6.9%), but this difference was also not statistically significant.

Class II HLA molecules such as HLA-DP, -DQ, and -DR have been shown to be associated with CD4⁺ T-cell-mediated MPE. However, its association with SCARs has been infrequently reported.^{1,2} There was a report of the association between HLA-DRB1*01:01 and nevirapine-induced DRESS in Hispanics and Africans.^{35,36} In our study, the association of DR13 homozygosity or DR14 and the risk of SCARs was found. In the Korean population, the HLA-DR13 and HLA-DR14 serologic groups consist of 2 alleles (DRB1*13:01 [allele frequency of 0.93%] and DRB1*13:02 [8.66%]) and 7 alleles (DRB1*14:01 [2.99%], DRB1*14:03 [0.93%], DRB1*14:05 [3.51%], DRB1*14:06 [0.82%], DRB1*14:07 [0.41%], DRB1*14:10 [0.41%], and DRB1*14:12 [0.41%]), respectively.^{12,37} Although the exact

subtype information of each serotype was not available because HLA-DR was identified only by serologic typing in this study, most of the DR13 subjects were probably DRB1*13:02 considering its proportion in the Korean general population.¹² There were some studies that have shown that single-amino-acid residues of the β -chain of the MHC class II molecules such as HLA-DR13 and -DP2 were involved in beryllium presentation to CD4⁺ T cells in chronic beryllium disease.^{38,39} In case of HLA-DR14, it was found to have a positive association with benzylpenicilloyl-hypersensitivity and allopurinol-induced MPE.² The result of our study may suggest that not only CD8⁺ T cells but also CD4⁺ T cells may be involved in the pathomechanism of SCAR development. To verify the precise genetic risk factor, detailed HLA subtype information is needed.

In this study, HLA-B75 and -DR13 homozygosity were identified in both SJS/TEN and DRESS, and DR14 was only found in DRESS. Because of a limited number of SCAR cases in our study, we were unable to establish clear associations between these HLA alleles and specific phenotypes of SCAR. In addition,

TABLE V. Factors associated with allopurinol-induced SCARs using binary logistic regression (univariate and multivariable analysis)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
HLA-B*58:01				
No B*58:01	1.00		1.00	
B*58:01 (+)	10.952 (1.991-60.261)	.006	19.568 (1.776-215.612)	.015
HLA-DR*14				
No DR*14	1.00		1.00	
DR*14 (+)	5.520 (1.344-22.664)	.018	19.355 (2.564-146.123)	.004
HLA-DR*13				
No DR*13	1.00		1.00	
DR*13 heterozygosity	0.751 (0.149-3.778)	.729	0.908 (0.135-6.083)	.920
DR*13 homozygosity	11.833 (2.428-57.661)	.002	38.458 (4.443-332.870)	.001
Sex				
Male	1.00			
Female	2.074 (0.621-6.932)	.236		
Age (y)				
<60	1.00			
≥60	0.803 (0.100-6.440)	.836		
eGFR (mL/min/1.73 m ²)				
>60	1.00		1.00	
30-60	4.707 (0.288-76.811)	.277	<0.001 (0.000)	.998
<30	14.720 (1.842-117.668)	.011	14.203 (1.064-189.520)	.045
Uric acid	1.181 (1.008-1.384)	.040	1.197 (0.877-1.633)	.257
Initial dose of allopurinol (mg/day)				
≤100	1.00		1.00	
>100	0.148 (0.032-0.698)	.016	1.428 (0.176-11.603)	.739
Cardiovascular disease				
No	1.00			
Yes	3.420 (0.399-29.350)	.262		

CI, Confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; SCAR, severe cutaneous adverse reaction.

our study targeted only subjects with HLA-B*58:01, and the additive effect of the above alleles was investigated. Most of patients with allopurinol SCAR are HLA-B*58:01 positive in Korea, and all patients with SCAR had HLA-B*58:01 in this study.^{2,11} In fact, HLA-B*58:01 was not found in 3 patients without HLA-B*58:01 in our previous study.²² There were no available HLA-DR data in those patients with HLA-B*58:01-negative SCAR. Therefore, it is difficult to assess the independent risk of these alleles on the development of allopurinol SCARs. Even if these risk alleles are independent risk factors, it is extremely difficult to prove given OR is increased by 7- to 12-folds (Table IV) compared with OR of 580 for HLA-B*58:01.⁹ Therefore, in the absence of HLA-B*58:01, these HLA alleles are unlikely to be significant independent risk factors.

There already have been attempts to increase the predictive power by combining eGFR and HLA-B*58:01. Allopurinol is rapidly oxidized in the liver and converted to its functional metabolite, oxypurinol.^{33,40} Although allopurinol has a short plasma half-life of 1 to 2 hours, the half-life of oxypurinol is longer up to 15 hours,⁸ and it can be increased to 1 week in patients with impaired kidney function because oxypurinol is excreted through the kidneys.^{41,42} The plasma oxypurinol concentration was significantly higher in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m²).⁴³ A previous study suggested that allopurinol administration should be

carefully considered in HLA-B*58:01-positive patients if their kidney function was decreased especially under an eGFR of 30 mL/minute/1.73 m².²⁵ In our study, we reconfirmed the contribution of renal impairment to the development of allopurinol-induced SCARs. Among the subjects with HLA-B*58:01, the SCAR incidence was significantly increased with a severe renal impairment of <30 mL/minute/1.73 m² (Figure 4), and this may be explained by the fact that as the renal function worsens, the plasma concentration of oxypurinol becomes higher.⁴³ Jung et al¹¹ reported the risk of allopurinol-induced SCARs in CRI up to 18%, much higher than the result of this study at 6.5%. This difference may be partly attributed to the different criteria of DRESS syndrome because the previous study adopted the less strict criteria by Singer and Wallace,⁴⁴ whereas the current study adopted the RegiSCAR criteria.

When allopurinol was administered to treat or prevent TLS, no SCARs occurred. It seems to be related to the short duration of administration and unimpaired renal function. This is compatible with the results of a previous retrospective cohort study that reported that none of the patients with hematologic malignancy who took allopurinol for prevention of TLS developed SCARs.² Therefore, we suggest that allopurinol for the prevention of TLS can be used without major concern for a risk of SCARs, and there is no need for the HLA screening test in these cases.

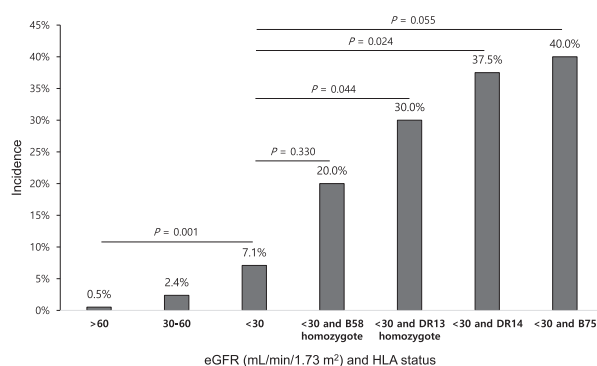


FIGURE 4. The incidence of SCARs in subjects with HLA-B*58 according to the eGFR or the combination of the eGFR and HLA status. *P* value for the eGFR was obtained by a linear-by-linear association. In the combination of the eGFR and HLA status, Fisher's exact test was used for each *P* value and the incidence of each case was compared with the incidence of eGFR less than 30 mL/minute/1.73 m² and HLA-B*58-positive (7.1%). *eGFR*, Estimated glomerular filtration rate; *SCAR*, severe cutaneous adverse reaction.

TABLE VI. Sensitivity, specificity, positive predictive value, and negative predictive value of each HLA type for predicting allopurinol-induced SCARs in subjects with HLA-B*58

HLA status	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
B58 homozygosity	9.1	97.2	9.1	97.2
B75	18.2	98.0	22.2	97.5
DR13 homozygosity	40.0	95.4	20.0	98.2
DR14	30.0	92.8	10.7	97.9

NPV, Negative predictive value; PPV, positive predictive value; SCAR, severe cutaneous adverse reaction.

To date, some nongenetic risk factors of allopurinol-induced SCARs such as female, age ≥ 60 years, initial allopurinol dosage >100 mg/day, chronic renal diseases, and cardiovascular diseases^{1,4} have been revealed; however, no genetic risk factors other than HLA-B*58:01 have been found. To our knowledge, this is the first study reporting additional genetic factors complementing the low positive predictive power of HLA-B*58:01 on the development of allopurinol-induced SCARs. If HLA-B*58:01-positive patients do not have HLA-B*75, DR13 homozygosity, and DR14, the negative predictive value of allopurinol-induced SCARs increased to 99.3%. This is clinically important because it may be able to increase the diagnostic predictability by secondary screening of these additional genetic risk factors after the primary screening of HLA-B*58:01 (Table VI). Particularly, when the screening of these genetic markers is combined with an eGFR less than 30 mL/minute/1.73 m², its clinical usefulness will become even more powerful.

However, this study has some limitations. First, it was limited by its retrospective design in which the incidence of SCARs could have been underestimated. In addition, there is a possibility of selection bias because we confined study subjects to those who underwent HLA typing. As a result, most of our cohort had either CRI or hematological malignancy and

allopurinol was used to treat gout in only 4 patients. According to Jung et al, HLA distribution in Korean patients with CRI¹¹ or hematologic malignancy² was not significantly different from those of Korean general population. Most patients with CRI were treated with allopurinol for a long period before they underwent renal transplant or received immunosuppressive agents. Although the indications are different, the treatment regimen for asymptomatic hyperuricemia in CRI is similar to the treatment used for gout. Therefore, even with the selection bias, we expect that the results of this study are applicable to Korean general population. HLA-B*58:01 has been consistently identified as a risk factor for allopurinol-induced SCAR across different ethnic populations. However, to determine whether HLA-B*75, DR13 homozygosity, and DR14 also increase the risk of allopurinol-induced SCAR in other ethnic groups, replication studies in other population are needed.

In conclusion, there are hidden genetic markers that increase the potential risk of allopurinol-induced SCARs in HLA-B*58:01 carriers, and combinatorial screening of these risk markers after the primary screening with HLA-B*58:01 may enable the precise prevention of SCARs when targeting high-risk patients.

REFERENCES

- Wang CW, Dao RL, Chung WH. Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. *Curr Opin Allergy Clin Immunol* 2016;16:339-45.
- Jung JW, Kim JY, Yoon SS, Cho SH, Park SY, Kang HR. HLA-DR9 and DR14 are associated with the allopurinol-induced hypersensitivity in hematologic malignancy. *Tohoku J Exp Med* 2014;233:95-102.
- Frampton JE. Febuxostat: a review of its use in the treatment of hyperuricaemia in patients with gout. *Drugs* 2015;75:427-38.
- Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, et al. Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med* 2015;175:1550-7.
- Sukasem C, Puangpet A, Medhasi S, Tassaneeyakul W. Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation. *Asian Pac J Allergy Immunol* 2014;32:111-23.
- Teo WL, Pang SM, Koh HY. Allopurinol hypersensitivity syndrome with acute generalized exanthematous pustulosis manifestations. *Cutan Ocul Toxicol* 2011; 30:243-4.
- Jung JW, Kim DK, Park HW, Oh KH, Joo KW, Kim YS, et al. An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing. *Genet Med* 2015;17:807-14.
- Dean L. Allopurinol therapy and HLA-B*58:01 genotype. In: Pratt V, McLeod H, Dean L, Malheiro A, Rubinstein W, editors. *Medical Genetics Summaries*. Bethesda, Md: National Center for Biotechnology Information (US); 2012.
- Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005;102:4134-9.
- Wu R, Cheng YJ, Zhu LL, Yu L, Zhao XK, Jia M, et al. Impact of HLA-B*58:01 allele and allopurinol-induced cutaneous adverse drug reactions: evidence from 21 pharmacogenetic studies. *Oncotarget* 2016;7:81870-9.
- Jung JW, Song WJ, Kim YS, Joo KW, Lee KW, Kim SH, et al. HLA-B*58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant* 2011;26:3567-72.
- Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue Antigens* 2005;65:437-47.
- Balakirski G, Merk HF. Cutaneous allergic drug reactions: update on pathophysiology, diagnostic procedures and differential diagnosis. *Cutan Ocul Toxicol* 2017;36:307-16.
- Choudhary S, McLeod M, Torchia D, Romanelli P. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *J Clin Aesthet Dermatol* 2013;6:31-7.
- World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision. 2nd ed. Geneva, Switzerland: World Health Organization; 2004:3-13.

16. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002;359:727-32.
17. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358:568-79.
18. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;16:297-306.
19. Chung WH, Hung SI, Hong HS, Hsieh MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004;428:486.
20. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics* 2009;19:704-9.
21. Goncalo M, Coutinho I, Teixeira V, Gameiro AR, Brites MM, Nunes R, et al. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. *Br J Dermatol* 2013;169:660-5.
22. Kang HR, Jee YK, Kim YS, Lee CH, Jung JW, Kim SH, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenet Genomics* 2011;21:303-7.
23. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 2008;9:1617-22.
24. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008;18:99-107.
25. Ng CY, Yeh YT, Wang CW, Hung SI, Yang CH, Chang YC, et al. Impact of the HLA-B(*)58:01 allele and renal impairment on allopurinol-induced cutaneous adverse reactions. *J Invest Dermatol* 2016;136:1373-81.
26. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)* 2012;64:1431-46.
27. Lee KW, Jeon H, Park JY. HLA-B*15 diversity in the Korean population. *Tissue Antigens* 2000;56:428-35.
28. Kim SH, Lee KW, Song WJ, Kim SH, Jee YK, Lee SM, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res* 2011;97:190-7.
29. Wang B, Primeau TM, Myers N, Rohrs HW, Gross ML, Lybarger L, et al. A single peptide-MHC complex positively selects a diverse and specific CD8 T cell repertoire. *Science* 2009;326:871-4.
30. Kosmrlj A, Read EL, Qi Y, Allen TM, Altfield M, Deeks SG, et al. Effects of thymic selection of the T-cell repertoire on HLA class I-associated control of HIV infection. *Nature* 2010;465:350-4.
31. Chung WH, Pan RY, Chu MT, Chin SW, Huang YL, Wang WC, et al. Oxypurinol-specific T cells possess preferential TCR clonotypes and express granulysin in allopurinol-induced severe cutaneous adverse reactions. *J Invest Dermatol* 2015;135:2237-48.
32. Chung WH, Wang CW, Dao RL. Severe cutaneous adverse drug reactions. *J Dermatol* 2016;43:758-66.
33. Yun J, Marcaida MJ, Eriksson KK, Jamin H, Fontana S, Pichler WJ, et al. Oxypurinol directly and immediately activates the drug-specific T cells via the preferential use of HLA-B*58:01. *J Immunol* 2014;192:2984-93.
34. Chan SH, Tan T. HLA and allopurinol drug eruption. *Dermatologica* 1989;179:32-3.
35. Martin AM, Nolan D, James I, Cameron P, Keller J, Moore C, et al. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*0101 and abrogated by low CD4 T-cell counts. *AIDS* 2005;19:97-9.
36. Su SC, Hung SI, Fan WL, Dao RL, Chung WH. Severe cutaneous adverse reactions: the pharmacogenomics from research to clinical implementation. *Int J Mol Sci* 2016;17:E1890.
37. Park MH, Kim HS, Kang SJ. HLA-A, -B, -DRB1 allele and haplotype frequencies in 510 Koreans. *Tissue Antigens* 1999;53:386-90.
38. Bill JR, Mack DG, Falta MT, Maier LA, Sullivan AK, Joslin FG, et al. Beryllium presentation to CD4+ T cells is dependent on a single amino acid residue of the MHC class II beta-chain. *J Immunol* 2005;175:7029-37.
39. Rossman MD, Stubbs J, Lee CW, Argyris E, Magira E, Monos D. Human leukocyte antigen Class II amino acid epitopes: susceptibility and progression markers for beryllium hypersensitivity. *Am J Respir Crit Care Med* 2002;165:788-94.
40. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. *Nat Rev Rheumatol* 2016;12:235-42.
41. Murrell GA, Rapeport WG. Clinical pharmacokinetics of allopurinol. *Clin Pharmacokinet* 1986;11:343-53.
42. Stamp LK, Chapman PT, Palmer SC. Allopurinol and kidney function: an update. *Joint Bone Spine* 2016;83:19-24.
43. Chung WH, Chang WC, Stocker SL, Juo CG, Graham GG, Lee MH, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. *Ann Rheum Dis* 2015;74:2157-64.
44. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986;29:82-7.