Original Article
Yonsei Med J 2016 Jan;57(1):118-126
http://dx.doi.org/10.3349/ymj.2016.57.1.118
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

HLA Allele Frequencies in 5802 Koreans: Varied Allele Types Associated with SJS/TEN According to Culprit Drugs

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Purpose: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are very serious forms of drug-induced cutaneous adverse reaction. SJS/TEN induced by certain drug is well known to be associated with some human leukocyte antigen (HLA) gene type. We aimed to explore HLA allele frequencies and their association with SJS/TEN according to culprit drugs in Korea.

Materials and Methods: We enrolled 5802 subjects who had results of HLA typing test from August 2005 to July 2014. Total 28 SJS/TEN patients were categorized based on culprit drugs (allopurinol, lamotrigine, carbamazepine) and identified the presence of HLA-B*58:01, HLA-B*44:03, HLA-B*15:02, and HLA-A*31:01.

Results: HLA-A*24:02 (20.5%), HLA-B*44:03 (10.0%), and HLA-Cw*01:02 (17.1%) were the most frequent type in HLA-A, -B, and -C genes, respectively. Allele frequencies of HLA-B*58:01, HLA-B*44:03, HLA-A*31:01, and HLA-B*15:02 were 7.0%, 10.0%, 5.0%, and 0.3%, respectively. In 958 allopurinol users, 9 subjects (0.9%) were diagnosed with SJS/TEN. Among them, 8 subjects possessed HLA-B*58:01 allele. SJS/TEN induced by allopurinol was more frequently developed in subjects with HLA-B*58:01 than in subjects without it [odds ratio: 57.4; confidence interval (CI) 7.12–463.50; $p<0.001$]. Allopurinol treatment, based on screening by HLA-B*58:01 genotyping, could be more cost-effective than that not based on screening. HLA-B*44:03 may be associated with lamotrigine-induced SJS/TEN (odds ratio: 12.75; CI 1.03–157.14; $p=0.053$). Among carbamazepine users, only two patients experienced SJS/TEN and possessed neither HLA-B*15:02 nor HLA-A*31:03.

Conclusion: HLA gene frequencies varied in Korea. Screening of HLA-B*58:01 before the use of allopurinol might be needed to anticipate probability of SJS/TEN.

Key Words: Allopurinol, human leukocyte antigen, HLA-B*58:01, Stevens-Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but very serious forms of drug-induced cutaneous adverse reaction. The incidence of SJS/TEN was estimated to be about 1–2 per one million inhabitants per year.[1] SJS and TEN are usually induced by specific drug and are characterized by erythematous skin lesion with extensive detachment of epidermis or mucous membrane.[2] They are differentiated according to the extent of skin detachment: less than 10% of body surface area (BSA) in SJS, 10–30% in overlap, more than 30% in TEN.[3] Although actual reason for death in SJS/TEN is not well defined, mortality rates of SJS/TEN are 5–49%.[2,4]

Not all medicines usually lead to SJS/TEN. There are some medicines with high risk to induce SJS/TEN, including allopurinol, carbamazepine, co-trimoxazole, lamotrigine, nevirapine, oxicam-nonsteroidal anti-inflammatory drugs (NSAIDs), phenobarbital and phenytoin.[5] Many studies revealed there are some association between development of SJS/TEN induced

Received: May 11, 2015 **Revised:** June 30, 2015
Accepted: July 2, 2015
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•The authors have no financial conflicts of interest.

by certain drug and specific human leukocyte antigen (HLA) allele. HLA molecules, which are located within major histocompatibility complex, are involved in improper activation of T-cells which finally causes SJS/TEN. Altered peptide repertoire theory, hapten/prohapten theory and direct interaction between HLA and drug are suggested to explain this mechanism.[6,7]

Allopurinol, drug used primarily to treat hyperuricemia, is known to frequently lead to SJS/TEN in subjects possessing HLA-B*58:01.[8-10] Carbamazepine, drug used primarily to treat seizures and neurologic pain, often causes SJS/TEN in subjects possessing HLA-B*15:02.[11] However, in Japan, carbamazepine-induced SJS/TEN is associated with HLA-A*31:01, not HLA-B*15:02.[12] Lamotrigine, new generation of anticonvulsants as carbamazepine, is considered relatively safe, but can lead to SJS/TEN in subjects possessing HLA-B*15:02 or HLA-B*44:03.[13,14] Therefore, researches on the relationship between varied allele types associated SJS/TEN which was induced by certain drug and ethnicity and geographical region might be needed to anticipate and prevent SJS/TEN in each area. However, there are few studies on the association between HLA-types and SJS/TEN induced by certain drugs in Korea.[15-17]

Although basic data about HLA gene frequency is needed to figure out distribution and characteristics of Korean genotype, there are few studies on HLA gene frequency.[18,19] HLA gene frequency varied according to ethnicity and country. HLA gene frequency data including medical and clinical records is needed nowadays when HLA genotyping has been highlighted as predisposition of SJS/TEN induced certain drugs.

In the present study, we aimed to calculate HLA allele frequencies and evaluate their association with SJS/TEN according to culprit drugs such as allopurinol, lamotrigine and carbamazepine in Korea.

MATERIALS AND METHODS

Participants

We retrospectively reviewed electronic medical and clinical records and the test results of 5802 subjects admitted to Severance Hospital and the results of HLA typing test from August 2005 to July 2014. All subjects had already conducted HLA typing test to prepare organ or stem cell transplantation in patients with hepatic failure, renal failure and hematologic malignancy. Other reasons were to diagnosis specific diseases associated with HLA-typing, such as Behcet's disease, ankylosing spondylitis and SJS/TEN.

This study protocol was approved by the Institutional Review Board of the Yonsei University Health System (4-2014-1086), Seoul, Korea, and conducted in accordance with the Declaration of Helsinki.

The HLA typing test

The HLA typing test was performed with low resolution or high resolution DNA typing. A LIFECODES antibody detection system (Luminex® platform, San Diego, CA, USA) with flow cytometric sensitivity was used to screen and identify the expression of low resolution of DNA typing. The LIFECODES DNA typing system utilizes sequence specific oligonucleotide (SSO) methodology in its HLA assays.[20] AlleleSEQR® HLA PCR kits (Celera Co., Alameda, CA, USA) was used for high resolution DNA typing.

Definition of SJS/TEN

All patients with SJS/TEN were diagnosed by allergy specialists in Severance Hospital. SJS, SJS/TEN overlap, and TEN were diagnosed based on the percentage of skin area exhibiting epidermal detachment (SJS, <10%; SJS/TEN overlap, 10–30%; TEN, >30% of total BSA).[3] Total 28 SJS/TEN subjects were categorized based on culprit drug, including allopurinol, lamotrigine, and carbamazepine.

Identification of culprit drug

Culprit drugs were identified based on the recommended guideline, ALDEN (algorithm for assessment of drug causality in SJS/TEN), for identifying causal medications.[21] For example, in case of subjects taking medicine allopurinol, cephalosporins and beta-blockers, allopurinol was identified culprit drug based on the recommended guideline, because allopurinol is a high risk drug. In case of subjects taking more than two high risk drugs, allergy specialist identified culprit drug based on the duration of drug uses, changes of clinical manifestation after stopping or reusing of drugs. Duration of latency is defined from the date of drug start to the date of symptom start.

Statistical analysis

HLA gene frequency was calculated using a direct counting method. We defined samples containing one allele as a homozygous. In case of homozygous, we calculated twice in the analysis. All statistical analyses were performed using SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). Values are expressed as mean±standard deviation. Comparisons of variables were made with the chi-square, Fischer's exact, Student's t, and Mann-Whitney tests as appropriate. A p value of less than 0.05 was set as the level of statistical significance.

RESULTS

Demographic and clinical characteristics of study population

Of total 5802 subjects, male comprised 43.0%. The mean age of subjects was 44.5±13.7 years. Renal failure patients, including renal transplantation recipients, chronic renal failure and end-stage renal disease, made up 19.2%. Hematologic malig-

Table 1. Demographic and Clinical Characteristics of Study Population

Characteristics	Value
Age (mean±SD) (yrs)	44.5±13.7
Sex	
Male, n (%)	2541 (43.0)
Underlying disease, n (%)	3078 (53.0)
Diabetes mellitus	870 (15.0)
Renal transplantation recipients	689 (11.9)
Hematologic malignancy	512 (8.8)
Hypertension	469 (8.1)
Renal transplantation candidate	425 (7.3)
Other solid organ transplantation candidate	113 (2.0)
Drug history, n (%)	1017 (18.4)
Allopurinol	958 (16.5)
Carbamazepine	23 (0.4)
Lamotrigine	25 (0.4)
Abacavir	11 (0.2)
SCAR, n (%)	28 (0.5)
Toxic epidermal necrolysis	12 (0.2)
Overlap	2 (0.03)
Stevens Johnson syndrome	14 (0.2)
Total (%)	5802 (100)

SD, standard deviation; SCAR, severe cutaneous adverse reaction.

nancy patients, including peripheral stem cell transplantation recipients due to acute leukemia, and myelodysplastic syndrome, occupied 8.8%. Total number of SJS/TEN patients was 28 (0.5%). The number of SJS, overlap and TEN patients was 14, 2, and 12, respectively. Among certain drugs which are known to develop SJS/TEN and be associated with specific HLA-allele, allopurinol, was the most commonly described and used drug (16.5%), followed by carbamazepine (0.4%), lamotrigine (0.4%), and abacavir (0.2%) (Table 1). However, among abacavir users, no one developed SJS/TEN.

HLA allele frequencies

We analyzed the HLA gene results of 5802 subjects. There are 12 allele types in HLA-A gene in Korea. The most frequent allele type of HLA-A genes were HLA-A*02 (26.4%) followed by A*24 (20.4%) and A*33 (15.0%). Among 26 allele types in HLA-B gene, HLA-B*15 (13.4%), and B*44 (10.3%) was frequent allele types. HLA-Cw gene showed 16 allele types and HLA-Cw*03 (26.8%) was the most frequent allele type followed by Cw*01 (17.2%), Cw*14 (13.3%), and Cw*07 (12.1%). HLA-DRB1 and HLA-DQB1 had 13 and 7 allele types, respectively. HLA-DRB1*04 (19.9%), DRB1*15 (10.4%), DRB1*13 (10.3%), DRB1*09 (10.3%), and HLA-DQB1*03 (35.3%), DQB1*06

Table 2. HLA Allele Frequencies

HLA-A		HLA-B		HLA-Cw		HLA-DR		HLA-DQB1	
Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)
01	1.722	07	4.222	01	17.433	01	6.090	01	0.186
02	29.533	08	0.259	02	0.520	03	2.094	02	9.497
03	1.731	13	4.956	03	27.537	04	20.635	03	39.665
11	10.671	14	1.286	04	6.158	07	7.062	04	11.732
24	22.389	15	13.934	05	1.735	08	9.386	05	18.063
26	6.506	18	0.043	06	4.814	09	10.328	06	20.670
29	0.565	27	3.030	07	12.446	10	1.723	09	0.186
30	4.292	35	5.793	08	9.237	11	4.728		
31	5.768	37	1.425	12	3.166	12	7.863		
32	0.583	38	1.226	14	13.530	13	10.227		
33	16.083	39	1.278	15	3.296	14	8.474		
68	0.155	40	12.829	16	0.043	15	10.388		
		44	10.749			16	0.992		
		46	4.679						
		47	0.112						
		48	3.505						
		50	0.138						
		51	10.196						
		52	2.478						
		54	6.181						
		55	1.943						
		56	0.432						
		57	0.371						
		58	5.750						
		59	1.951						
		67	1.217						

HLA, human leukocyte antigen.

http://dx.doi.org/10.3349/ymj.2016.57.1.118

Table 3. High Resolution HLA Allele Frequencies

HLA-A		HLA-B		HLA-Cw		HLA-DR		HLA-DQB1	
Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)
A*01:01	1.639	B*07:02	3.086	Cw*01:02	17.125	DRB1*01:01	5.795	DQB1*01	0.186
A*02:01	15.970	B*07:05	0.448	Cw*01:03	0.786	DRB1*03:01	2.263	DQB1*02	9.497
A*02:03	0.687	B*08:01	0.398	Cw*02:02	0.505	DRB1*04:01	0.662	DQB1*03	39.665
A*02:06	10.259	B*13:01	1.941	Cw*03:02	7.299	DRB1*04:03	3.146	DQB1*04	11.732
A*02:07	4.125	B*13:02	2.588	Cw*03:03	10.893	DRB1*04:04	1.325	DQB1*05	18.063
A*02:10	0.159	B*14:01	1.244	Cw*03:04	9.096	DRB1*04:05	7.947	DQB1*06	20.670
A*03:01	1.639	B*14:02	0.050	Cw*03:43	0.056	DRB1*04:06	4.857	DQB1*09	0.186
A*03:02	0.264	B*15:01	9.209	Cw*04:01	6.176	DRB1*04:07	0.166		
A*11:01	10.048	B*15:02	0.299	Cw*05:01	1.909	DRB1*04:08	0.055		
A*11:02	0.053	B*15:07	0.896	Cw*06:02	4.604	DRB1*04:10	0.717		
A*11:07	0.053	B*15:08	0.050	Cw*06:12	0.056	DRB1*07:01	6.788		
A*24:02	20.465	B*15:11	2.489	Cw*07:01	3.257	DRB1*08:01	0.055		
A*24:07	0.053	B*15:18	1.244	Cw*07:02	7.861	DRB1*08:02	1.269		
A*24:08	0.159	B*15:25	0.050	Cw*07:04	1.123	DRB1*08:03	7.340		
A*24:10	0.106	B*15:27	0.398	Cw*08:01	7.580	DRB1*09:01	12.859		
A*24:20	0.159	B*15:38	0.199	Cw*08:02	1.348	DRB1*10:01	1.490		
A*26:01	4.072	B*15:85	0.050	Cw*08:03	0.561	DRB1*11:01	3.698		
A*26:02	1.957	B*18:02	0.100	Cw*12:02	2.358	DRB1*11:06	0.110		
A*26:03	0.740	B*27:04	0.149	Cw*12:03	0.561	DRB1*12:01	4.139		
A*29:01	0.423	B*27:05	2.140	Cw*14:02	7.243	DRB1*12:02	3.311		
A*30:01	2.697	B*35:01	4.679	Cw*14:03	6.345	DRB1*13:01	2.318		
A*30:04	1.428	B*35:03	0.199	Cw*15:02	2.639	DRB1*13:02	9.768		
A*31:01	5.024	B*35:05	0.050	Cw*15:04	0.112	DRB1*13:07	0.055		
A*31:11	0.053	B*35:31	0.050	Cw*15:05	0.449	DRB1*14:01	1.214		
A*32:01	0.635	B*35:57	0.050	Cw*16:02	0.056	DRB1*14:03	0.828		
A*33:03	16.816	B*37:01	1.543			DRB1*14:05	3.366		
A*68:01	0.264	B*38:01	0.249			DRB1*14:06	0.607		
		B*38:02	1.145			DRB1*14:07	0.166		
		B*39:01	0.796			DRB1*14:54	2.097		
		B*39:05	0.050			DRB1*15:01	7.561		
		B*40:01	3.733			DRB1*15:02	2.980		
		B*40:02	4.978			DRB1*15:04	0.058		
		B*40:03	0.249			DRB1*16:02	0.993		
		B*40:06	3.783						
		B*40:21	0.050						
		B*44:02	1.991						
		B*44:03	9.905						
		B*46:01	5.575						
		B*47:01	0.100						
		B*48:01	3.733						
		B*48:03	0.100						
		B*50:01	0.100						
		B*51:01	9.408						
		B*51:02	0.299						
		B*52:01	2.489						
		B*54:01	4.530						
		B*55:01	0.050						
		B*55:02	2.041						
		B*55:04	0.050						

Table 3. High Resolution HLA Allele Frequencies (Continued)

HLA-A		HLA-B		HLA-Cw		HLA-DR		HLA-DQB1	
Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)	Genotype	Frequency (%)
		B*55:07	0.050						
		B*56:01	0.199						
		B*57:01	0.398						
		B*58:01	7.018						
		B*59:01	2.190						
		B*67:01	1.145						

HLA, human leukocyte antigen.

Table 4. Clinical Characteristics of SJS/TEN Patients According to Culprit Drugs

Culprits	Case (n)	Frequency (%)	Mean latency±SD (day)	Mean age±SD (yr)
Anticonvulsants*	9	32.1	34.3±15.3	52.9±17.4
Allopurinol	9	32.1	28.9±16.0†	67.7±10.9
Antibiotics	2	7.1	20.5±5.0	66.0±2.9
Acetazolamide	2	7.1	20.5±5.0	66.0±11.3
NSAIDs	2	7.1	21†	42.0±18.4
Herbs	1	3.6	†	37.0±0.0
Etc.	3	10.7	†	43.0±24.0
Total	28	100		57.9±16.2

SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs.
*Anticonvulsants contain carbamazepine, lamotrigine, zonisamide (excegran), †Some data was excluded because mean latency was uncertain due to lack of records.

(20.1%), DQB1*05 (15.8%), and DQB1*04 (11.1%) were frequent allele types (Table 2).

High resolution HLA allele frequencies

Not all 5802 subjects underwent high resolution study. The number of subjects was 1891, 2009, 1768, 1788, and 500 in HLA-A, HLA-B, HLA-Cw, HLA-DRB1, and HLA-DRQ1, respectively. Among HLA-A genes, the most frequent allele was HLA-A*24:02 (20.5%) followed by HLA-A*33:03 (16.8%) and HLA-A*02:01 (16.0%). Among HLA-B genes, HLA-B*44:03 (10.0%), HLA-B*51:01 (9.4%), and HLA-B*15:01 (9.2%) were frequent allele. Among HLA-C genes, HLA-Cw*01:02 (17.125%), and HLA-CW*03:03 (10.9%) were frequent allele. HLA-DRB1*09:01 (12.9%) and HLA-DRQ1*03 (39.7%) were the most frequent allele in each HLA-DR types. Allele frequencies of HLA-B*58:01, HLA-B*44:03, HLA-A*31:01, and HLA-B*15:02 were 7.0%, 10.0%, 5.0%, and 0.3%, respectively. All of 332 subjects with HLA-B*58 have HLA-B*58:01 (100%). Among 808 subjects with HLA-B*15, only 6 subjects have HLA-B*15:02 (Table 3).

Clinical characteristics of SJS/TEN patients according to culprit drugs

The most common culprit drug inducing SJS/TEN was allopurinol (n=9, 32.1%) and anticonvulsants (n=9, 32.1%), followed by antibiotics, acetazolamide, NSAIDs and herbals. In two cases (etc. cases), patients could not remember the names of medication taken. Mean latency of SJS/TEN varied according to culprit drugs and ranged between 20.5–34.3 days. Mean age of subjects ranged between 37.0–67.7 years (Table 4).

Association between allopurinol induced SJS/TEN and HLA-B*58:01 allele

In 958 allopurinol users, 9 subjects (0.9%) were diagnosed with SJS/TEN. Among them, 8 subjects (88.9%) had HLA-B*58:01 allele. Among 949 allopurinol tolerant subjects, only 116 subjects (12.2%) had HLA-B*58:01 allele. SJS/TEN induced by allopurinol more frequently developed in subjects with HLA-B*58:01 than in subjects without it [odds ratio: 57.4; confidence interval (CI) 7.12–463.50; $p<0.001$] (Table 5).

Cost-effectiveness of allopurinol treatment based on screening by HLA-B*58:01 genotyping

The cost of HLA-B*58:01 genotyping, a service that is commercially available in Korea, is 70000 Korean won (KRW) (approximately $62). The average total medical cost for SJS/TEN including admission fee, charges for the test, and treatment was 10394667 KRW ($9227), which was estimated by reviewing the medical records of 9 patients who experienced allopurinol-induced SJS/TEN in this study. Additional costs incurred when allopurinol was used without screening by HLA-B*58:01 genotyping totaled to 93552003 KRW ($83395). If we screened the patients by HLA-B*58:01 genotyping before administering allopurinol and prohibited HLA-B*58:01 (+) patients from using allopurinol, we could save 83157336 KRW ($74129), which can then be used for SJS/TEN management. However, in this case, the genotyping fee, totaling to 67060000 KRW ($59779) for the

http://dx.doi.org/10.3349/ymj.2016.57.1.118

screening of 958 allopurinol users, will be added. Thus, the total expected medical costs with and without screening by HLA-B*58:01 genotyping prior to allopurinol use were 77454667 KRW ($69034) and 93552003 KRW ($83395), respectively.

Association between lamotrigine induced SJS/TEN and HLA-B*44:03 allele

In 25 lamotrigine users, 7 subjects (28.0%) developed SJS/TEN. Among them, 3 patients (42.9%) had HLA-B*44:03. Among 18 lamotrigine tolerant subjects, only one subject (5.6%) showed HLA-B*44:03. HLA-B*44:03 may be associated with lamotrigine-induced SJS/TEN (odds ratio: 12.75; CI 1.03–157.14; p=0.053) (Table 6).

Association between carbamazepine-induced SJS/TEN and HLA-B*15:02 allele

Although data is not shown, only two patients who had taken carbamazepine experienced SJS/TEN and possessed neither HLA-B*15:02 nor HLA-A*31:03.

DISCUSSION

HLA system is the locus of genes that encode for proteins on the surface of cells that are responsible for regulation of the immune system. This group of genes resides on chromosome 6, and encodes cell-surface antigen-presenting proteins and has many other functions. HLA gene affects the development of various diseases associated with immunity, including autoimmune disease, infection and cancer.[22,23] Many genetic association studies have shown strong linkage between specific HLA alleles and drug hypersensitivity reaction, especially T-cell mediated reaction, including SJS/TEN.[24,25] Because distribution and characteristics of HLA type are different according to ethnicity, these associations also vary, depending on different ethnic populations.[26]

SJS/TEN are very serious form of adverse cutaneous reactions induced by drug and can cause systemic symptoms including conjunctivitis, gastrointestinal inflammation, and bronchiolitis obliterans.[27] Specific HLA-alleles according to several SJS/TEN-causing culprit drugs have been adequately studied. Allopurinol, a well-known xanthine oxidase inhibitor, reduces the production of uric acid and is widely used to treat hyperuricemia, gout and kidney stones. Because the incidence of hyperuricemia and gout is 15–20% and <1%, respectively, the number of patients using allopurinol is assumed to be very large.[28] Allopurinol hypersensitivity develops in 0.4% of subjects during allopurinol use.[29] Therefore, potential number of patients experiencing SJS/TEN is nothing to sneeze at. The most frequently identified culprit drug of SJS/TEN is allopurinol, accounting for 17.4% of all cases of drug-induced SJS/TEN.[30] Fortunately, many studies revealed that SJS/TEN induced by allopurinol is associated with HLA-B*58:01 allele. Allopurinol users with HLA-B*58:01 develop SJS/TEN much more frequently than those without it. Some countries realizing the seriousness of this risk factor for SJS/TEN in allopurinol users recommend that the HLA-B*58:01 should be determined before the use of allopurinol.[31] In addition, many other studies have tried to demonstrate the association between HLA-B*58:01 and allopurinol induced SJS/TEN in their countries.[8]

Many studies suggest that screening by HLA-B*58:01 genotyping prior to allopurinol use could be cost-effective. We also found that the cost incurred with screening by HLA-B*58:01 genotyping prior to allopurinol use, which prevents SJS/TEN in patients with HLA-B*58:01 (+), is lower than the total treatment fees of 9 patients with allopurinol-induced SJS/TEN. In contrast to others studies, we did not calculate the cost of allopurinol and febuxostat (considered a substitute for allopurinol for the treatment of patients with gout who are contraindicated to allopurinol) because not all allopurinol users, in this study, were using another urate-lowering agent, febuxostat, to treat gout. Although this calculation is limited to the present study alone, we would like to conclude by saying that the findings in this study are in accordance with previous studies that demonstrated that allopurinol treatment based on screening by HLA-B*58:01 genotyping could be more cost-effective than that not based on screening.

The frequency of subjects with HLA-B*58:01 vary consider-

Table 5. The Risk of Allopurinol Induced SJS/TEN Occurrence According to Existence of HLA-B*58:01

	HLA-B*58:01 (+)	HLA-B*58:01 (-)	Total	OR (95% CI)	*p* value
SJS/TEN (+)	8	1	9	57.4 (7.12–463.50)	<0.001
SJS/TEN (-)	116	833	949		
Total	124	834	958		

OR, odds ratio; CI, confidence interval; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; HLA, human leukocyte antigen.

Table 6. The Risk of Lamotrigine-Induced SJS/TEN Occurrence According to Existence of HLA-B*44:03

	HLA-B*44:03 (+)	HLA-B*44:03 (-)	Total	OR (95% CI)	*p* value
SJS/TEN (+)	3	4	7	12.75 (1.03–157.14)	0.053
SJS/TEN (-)	1	17	18		
Total	4	21	25		

OR, odds ratio; CI, confidence interval; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; HLA, human leukocyte antigen.

ably according to ethnicity. The frequency is reported to be 2–4% in Africans, 1–6% in Europeans, 3–15% in Asian Indians, and 8–11% in Chinese.[32] In Korea, frequency of HLA-B*58:01 is known to be about 6% in general population.[18,19] In the countries with higher frequency of HLA-B*58:01, including Han Chinese and Southeast Asian, the association between HLA-B*58:01 and allopurinol inducing SJS/TEN is noted to be more strong.[10,33] Because HLA-B*58:01 is common allele type in Korea, considerable fraction of allopurinol users in Korea may possess HLA-B*58:01. These patients in danger of SJS/TEN are recommended to stop using allopurinol or get to know the risk. Although there are two studies on the risk of HLA-B*58:01 in allopurinol users who has oriental ethnicity, the screening for HLA-B*58:01 before use of allopurinol is not yet recommended in Korea.[15,17] In this study, we also demonstrated the risk of HLA-B*58:01 in developing SJS/TEN (odds ratio: 57.4; CI 7.12–463.50; p<0.001).

Carbamazepine is widely used to control certain types of seizures or neuralgia. This medicine may cause side effects including drowsiness, dizziness, nausea, vomiting, and drug hypersensitivity. HLA-B*15:02 and HLA-A*31:01 alleles have been suggested to be a risk factors for development of SJS/TEN induced by carbamazepine. In Japan and Korea, only HLA-A*31:01, but not HLA-B*15:02, was found to be associated with carbamazepine-induced SJS/TEN.[16,34] In this study, we included only two patients with SJS/TEN induced by carbamazepine. They had neither HLA-A*31:01 or HLA-B*15:02. These differences are most likely due to gene frequency of HLA-B*15:02. In Malay, Han Chinese showed strong association between HLA-B*15:02 and SJS/TEN induced by carbamazepine; frequency was 0.12–0.16% and 0.06–0.15%, respectively. However, frequency of HLA-B*15:02 is lower in Japanese (0.002%) and Korean (0.004%).[35] Although frequency of HLA-B*15:02 (0.299%) in this study is relatively higher than those of previous studies, facts that no one possessed HLA-B*15:02 in carbamazepine-induced SJS/TEN in this study may indicate that HLA-B*15:02 is not associated with carbamazepine-inducing SJS/TEN in Korea. However, too small number of carbamazepine users in the study limit the strength. Further study including many more carbamazepine users is needed to assure the irrelevance between them.

Lamotrigine, phenyltriazine derivative, is also well-known new generation antiepileptic drug. Until now, no single HLA-allele has been definitely identified for lamotrigine-induced SJS/TEN. HLA-B*58:01, HLA-A*68:01, HLA-A*31:01, and HLA-B*15:02 were reported to be weakly associated with lamotrigine-induced SJS/TEN.[36-39] In Korea, the only one study concerning HLA-allele associated with lamotrigine-induced SJS/TEN revealed that HLA-B*44:03 may be associated with lamotrigine-induced SJS/TEN. In this study, no one had HLA-A*68:01, HLA-A*31:01, or HLA-B*15:02, which have been suggested as a risk factor for lamotrigine-induced SJS/TEN. The only two patients possessed HLA-B*58:01. However, HLA-B*58:01 showed no statistically significant meanings in development of lamotrigine-induced SJS/TEN. Recently, lamotrigine usage is increasing. Further study for lamotirigine-induced SJS/TEN to determine the real association with HLA-B*44:03 allele in Korea is in need.

This study includes basic data with gene frequency of Korean. These results will be helpful to research various immune-associated diseases, especially drug hypersensitivity associated with specific HLA-allele type. Furthermore, this is the largest study containing largest number of allopurinol users and allopurinol-induced SJS/TEN in Korea. This study showed strong association between allopurinol-induced SJS/TEN and HLA-B*58:01. Because this study covers various drug-induced SJS/TEN, this study will be useful to doctors and patients who prescribed or use these medicines, including allopurinol, lamotrigine and carbamazepine.

The limitation of this study is selection bias which occurred while selecting subjects; limited to patients who undergone HLA-typing test to prepare organ or stem cell transplantation or to diagnose specific disease associated with HLA typing. Therefore, subjects in this study are neither general populations nor certain disease populations. Nevertheless, this study enrolled 5802 patients, therefore, this selection bias may be corrected and improved. Another limitation is that HLA typing was done by two methods: low resolution and high resolution. We thought that HLA-B*58 is identical with HLA-B*58:01 because a previous study showed a 100% coincidence of HLA-B*58:01 in serologic-type HLA-B*58 in Korean population.[40]

In this study, HLA-B*58:01 gene frequencies was 7.0%, in concordance with previous studies on general population.[18,19] However, HLA-B*58:01 gene frequencies in 949 allopurinol users was 12.9%. This result is also concordant with previous studies targeted at renal failure subjects.[15] Although the fact that HLA-B*58:01 is a risk factor for development of renal failure is not yet known, we suggest that there may be significant correlation between HLA-B*58:01 and renal failure. Further study on the effects of HLA-B*58:01 on renal function will be needed.

We defined drug-users as subjects who ever took certain drugs. Because this is a retrospective study based on medical records, we cannot assure if these subjects really take this medicine. Because we fully rely on the medical records, but not direct interview and medical examination, we cannot fully confirm the culprit drug. In the same vein, we cannot conclude that three drugs, such as allopurinol, carbamazepine and lamotrigine, are the major causative drugs for SJS/TEN. Furthermore, we included all subjects who ever prescribed certain drug. We defined drug-users regardless of duration of certain drug uses. Usually, almost all the doctors in this institute, tertiary teaching hospital, prescribe medicines for more than 1 week. Furthermore, some medicines sometimes can cause SJS/TEN despite of short duration usage of certain drug, even less than 7 days. Therefore, we didn't exclude the subject who took certain drug for short term period.

http://dx.doi.org/10.3349/ymj.2016.57.1.118

This study showed the variety of gene frequencies in Korean. Furthermore, we demonstrated the risk of possessing specific HLA-allele in certain drug users. We suggest that screening of HLA-B*58:01 before the use of allopurinol might be needed to anticipate the probability of SJS/TEN. Further study on HLA gene associated lamotrigine or carbamazepine-induced SJS/TEN should be conducted.

ACKNOWLEDGEMENTS

This research was supported by a grant from Ministry of Food and Drug Safety to the regional pharmacovigilance center in 2015.

REFERENCES

1. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Chem Immunol Allergy 2012;97:1-17.
2. Struck MF, Hilbert P, Mockenhaupt M, Reichelt B, Steen M. Severe cutaneous adverse reactions: emergency approach to non-burn epidermolytic syndromes. Intensive Care Med 2010;36:22-32.
3. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 1993;129:92-6.
4. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, et al. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013;133:1197-204.
5. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol 2008;128:35-44.
6. Wei CY, Chung WH, Huang HW, Chen YT, Hung SI. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. J Allergy Clin Immunol 2012;129:1562-9.
7. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, et al. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. Nature 2012;486:554-8.
8. Cao ZH, Wei ZY, Zhu QY, Zhang JY, Yang L, Qin SY, et al. HLA-B*58:01 allele is associated with augmented risk for both mild and severe cutaneous adverse reactions induced by allopurinol in Han Chinese. Pharmacogenomics 2012;13:1193-201.
9. Chiu ML, Hu M, Ng MH, Yeung CK, Chan JC, Chang MM, et al. Association between HLA-B*58:01 allele and severe cutaneous adverse reactions with allopurinol in Han Chinese in Hong Kong. Br J Dermatol 2012;167:44-9.
10. 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.
11. Ganesan S, Hussain N. Question 2 Should phenytoin and carbamazepine be avoided in Asian populations with the HLA-B*1502 positive genetic variant? Arch Dis Child 2011;96:104-6.
12. Genin E, Chen DP, Hung SI, Sekula P, Schumacher M, Chang PY, et al. HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. Pharmacogenomics J 2014;14:281-8.
13. Park HJ, Kim SR, Leem DW, Moon IJ, Koh BS, Park KH, et al. Clinical features of and genetic predisposition to drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a single Korean tertiary institution patients-investigating the relation between the HLA -B*4403 allele and lamotrigine. Eur J Clin Pharmacol 2015;71:35-41.
14. Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, Hui RC, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 2010;11:349-56.
15. Jung JW, Song WJ, Kim YS, Joo KW, Lee KW, Kim SH, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. Nephrol Dial Transplant 2011;26:3567-72.
16. 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.
17. 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.
18. Huh JY, Yi DY, Eo SH, Cho H, Park MH, Kang MS. HLA-A, -B and -DRB1 polymorphism in Koreans defined by sequence-based typing of 4128 cord blood units. Int J Immunogenet 2013;40:515-23.
19. Chung HY, Yoon JA, Han BY, Song EY, Park MH. [Allelic and haplotypic diversity of HLA-A, -B, -C, and -DRB1 genes in Koreans defined by high-resolution DNA typing]. Korean J Lab Med 2010;30:685-96.
20. Trajanoski D, Fidler SJ. HLA typing using bead-based methods. Methods Mol Biol 2012;882:47-65.
21. Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis: clinical patterns, diagnostic considerations, etiology, and therapeutic management. Semin Cutan Med Surg 2014;33:10-6.
22. Balnyte R, Rastenyte D, Vaitkus A, Mickeviciene D, Skrodeniene E, Vitkauskiene A, et al. The importance of HLA DRB1 gene allele to clinical features and disability in patients with multiple sclerosis in Lithuania. BMC Neurol 2013;13:77.
23. Dong DD, Yie SM, Li K, Li F, Xu Y, Xu G, et al. Importance of HLA-G expression and tumor infiltrating lymphocytes in molecular subtypes of breast cancer. Hum Immunol 2012;73:998-1004.
24. Phillips EJ, Mallal SA. HLA and drug-induced toxicity. Curr Opin Mol Ther 2009;11:231-42.
25. Phillips EJ, Mallal SA. Pharmacogenetics of drug hypersensitivity. Pharmacogenomics 2010;11:973-87.
26. Aihara M. Pharmacogenetics of cutaneous adverse drug reactions. J Dermatol 2011;38:246-54.
27. Park H, Ko YB, Kwon HS, Lim CM. Bronchiolitis obliterans associated with Stevens-Johnson syndrome: a case report. Yonsei Med J 2015;56:578-81.
28. Mikuls TR, Saag KG. New insights into gout epidemiology. Curr Opin Rheumatol 2006;18:199-203.
29. Pluim HJ, van Deuren M, Wetzels JF. The allopurinol hypersensitivity syndrome. Neth J Med 1998;52:107-10.
30. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25-32.
31. 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.
32. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug

hypersensitivity. Curr Opin Allergy Clin Immunol 2007;7:317-23.
33. 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.
34. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Hum Mol Genet 2011;20:1034-41.
35. Yip VL, Marson AG, Jorgensen AL, Pirmohamed M, Alfirevic A. HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. Clin Pharmacol Ther 2012;92:757-65.
36. Kazeem GR, Cox C, Aponte J, Messenheimer J, Brazell C, Nelsen AC, et al. High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients. Pharmacogenet Genomics 2009;19:661-5.
37. McCormack M, Urban TJ, Shianna KV, Walley N, Pandolfo M, Depondt C, et al. Genome-wide mapping for clinically relevant predictors of lamotrigine- and phenytoin-induced hypersensitivity reactions. Pharmacogenomics 2012;13:399-405.
38. Shi YW, Min FL, Liu XR, Zan LX, Gao MM, Yu MJ, et al. Hla-B alleles and lamotrigine-induced cutaneous adverse drug reactions in the Han Chinese population. Basic Clin Pharmacol Toxicol 2011;109:42-6.
39. An DM, Wu XT, Hu FY, Yan B, Stefan H, Zhou D. Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. Epilepsy Res 2010;92:226-30.
40. 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.

http://dx.doi.org/10.3349/ymj.2016.57.1.118