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PHARMACOGENETICS

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

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Abstract
Purpose Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but fatal adverse mucocutaneous reactions to certain drugs. Recent studies suggest that ethnicity and genetic predisposition may play a crucial role in the manifestation of the reaction. In this study, we described the role of human leukocyte antigen (*HLA*)-*B* alleles in the development of clinical characteristics and treatment outcomes of SJS/TEN in a single Korean tertiary hospital.
Methods We retrospectively reviewed the medical records (from March 1, 2010 to February 28, 2014) of 30 patients diagnosed with SJS and/or TEN.
Results The main causative drugs were anticonvulsants (26.7 %) and allopurinol (26.7 %), followed by antibiotics (16.7 %), acetazolamide (10.0 %), acetaminophen (10.0 %), and herbal medication (6.7 %). The mean latencies of these drugs were variable. Liver damage was the most common symptom (observed in 63.3 % of the patients). Of the five patients with lamotrigine-induced SJS/TEN, three expressed the *HLA-B*4403* allele (60.0 %). Of the seven patients with allopurinol-induced SJS/TEN, five expressed the *HLA-B*5801* allele (71.4 %).
Conclusions The major SJS/TEN-inducing drugs were found to be allopurinol and anticonvulsants (such as lamotrigine). We speculated that Korean individuals expressing the *HLA-B*4403* allele may be highly susceptible to lamotrigine-induced SJS/TEN.

Keywords Stevens–Johnson syndrome · Toxic epidermal necrolysis · Lamotrigine · Human leukocyte antigens

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Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but fatal severe cutaneous adverse reactions (SCAR) associated with drug hypersensitivity [1–3]. Mortality rates of SJS are less than 5 %, but those of TEN are up to 30 % [4]. Almost all cases of SJS and TEN are triggered by the use of anticonvulsants (carbamazepine and phenytoin), allopurinol, painkillers, and anti-inflammatory drugs [5]. Although these drugs are widely prescribed, only a few patients develop SJS and/or TEN. The estimated incidence rate of SJS and TEN for a specific drug is less than 14 cases per 100,000 users [6–8]. Manifestation of SJS/TEN is usually dose-independent and unpredictable [9]. Therefore, it is important to evaluate predictable risk factors for predisposition to SJS and TEN. However, only a few markers are known to have an association with the development or treatment outcome of SJS/TEN.

Recent studies suggested that the human leukocyte antigen (*HLA*) genotype is associated with an increased risk for SJS and TEN. Furthermore, certain ethnicities are known to be

genetically predisposed *to specific* drug-induced SJS and TEN. For example, the *HLA-B*1502* allele is considered a marker of carbamazepine-induced SJS and TEN in Han Chinese [10]. Many studies have corroborated this association in Indian, Thai, and Chinese individuals [11–15]. Recently, it has been recommended that all patients of Oriental ethnicity be screened for the *HLA-B*1502* allele before being administered with carbamazepine [16]. However, some Japanese studies have shown that carbamazepine-induced SJS and TEN are associated with *HLA-B*3101* expression, and not with that of *HLA-B*1502* [17–19]. Although anticonvulsants are most the common drugs triggering SJS and TEN, one study so far has demonstrated an association between the *HLA* alleles and anticonvulsant-induced SJS and TEN in Korean patients [20]. Among the anticonvulsants, lamotrigine (LTG), a next generation anticonvulsant, has gained popularity in recent times. Although a couple of recent studies suggest that LTG can cause SJS/TEN, the role of the *HLA* alleles in LTG-induced SJS and TEN has not been analyzed [21, 22]. In this study, we elucidated the *HLA* genotype's role in SJS/TEN and described the etiologies, clinical characteristics, and treatment outcome of SJS and TEN in Korean patients. Our study also included five cases of LGT-induced SJS/TEN.

Methods

Patients

We retrospectively reviewed the medical records of 30 Korean patients diagnosed with SJS and/or TEN and who had been admitted to the Korean Severance Hospital from March 1, 2010 to February 28, 2014. All patients were diagnosed by allergy specialists. 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 body surface area) [23].

Definitions of clinical characteristics

Clinical data were retrieved from the electronic medical database and reviewed. We evaluated the acuteness of SJS/TEN by the severity of illness SCORe of Toxic Epidermal Necrolysis (SCORTEN). The score allots 1 point for each of the following variables: age over 40 years, tachycardia (>120 beats/min), comorbid malignancy, overlap syndrome or TEN, elevation of blood urea nitrogen (BUN) (>28 mg/dL), high glucose levels (>252 mg/dL), and acidosis (bicarbonate <20 mEq/L). These variables were evaluated within the first 24 h of admission to the hospital. A SCORTEN of >3 is associated with more than 32 % mortality [24–27]. In addition, we evaluated the involvement of multiple organs. Anemia was diagnosed by measuring hemoglobin levels (Hb <10 g/dL). Abnormalities in kidney and liver functions were determined using biochemical tests (kidney function abnormality, serum creatinine [Cr] >2.0 mg/L; liver function abnormality, serum AST or ALT >50 IU/L). Elevated C-reactive protein level was defined as >8 mg/L. Ocular complications such as corneal erosion, conjunctivitis, and decreased visual acuity were diagnosed by an ophthalmologist using the slit lamp examination.

HLA genotyping

A LIFECODES antibody detection system (Luminex® platform, San Diego, CA 92121, USA) with flow cytometric sensitivity was used to screen and identify the expression of *HLA* alleles. The LIFECODES DNA typing system utilizes SSO methodology in its HLA assays [28].

Statistical analyses

All statistical analyses were performed using SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). Fisher's exact test was used to compare the carrier frequencies of *HLA* alleles between specific drug-users and nonusers. The correlation between the variables in the two groups was assessed using Pearson's test. A P value of less than 0.05 was considered statistically significant.

Results

Demographics

Our study included a total of 30 patients with SJS, SJS/TEN overlap, and TEN. All patients were of Korean race and their mean age was 56.9±16.10 years. Women (70 % of the total patients) appeared to be more frequently affected than the men were. The mean duration of hospitalization was 18.0± 13.79 days. Nineteen (63.3 %), two (6.7 %), and nine patients (30 %) were diagnosed with SJS, SJS/TEN overlap, and TEN, respectively. Thirty (100 %) and 13 patients (43.3 %) received steroid therapy and intravenous immunoglobulin (IVIG), respectively. The mean SCORTEN was 1.7±1.04 for the group in which all patients survived, 3.0±0.00 for the mortality group, and 1.8±1.06 for the total number of patients. The difference in SCORTEN values was not statistically significant between the surviving and the mortality groups (P value 0.102; Table 1). The total mortality rate was 6.6 % (unpublished data).

Table 1 Demographics

Number	Sex	Age (year)	Hospital day	Phenotype	SCORTEN	Death
1	F	67	23	TEN	2	No
2	F	55	33	TEN	4	No
3	F	45	0	TEN	2	No
4	F	49	21	SJS	2	No
5	F	73	34	TEN	3	Yes
6	M	71	21	TEN	3	No
7	F	39	19	Overlap	1	No
8	F	77	4	SJS	1	No
9	F	52	16	SJS	3	No
10	M	74	24	Overlap	2	No
11	F	54	8	SJS	1	No
12	F	61	0	SJS		No
13	F	74	9	SJS	1	No
14	M	39	10	SJS	0	No
15	F	42	9	SJS	1	No
16	M	61	19	SJS	1	No
17	M	72	0	SJS		No
18	F	62	24	SJS	3	No
19	M	63	30	TEN	3	No
20	F	72	14	SJS	2	No
21	F	59	82	SJS	2	No
22	M	57	29	TEN	3	Yes
23	M	76	26	TEN	3	No
24	F	26	15	SJS	1	No
25	F	42	7	SJS	1	No
26	F	61	11	SJS	2	No
27	M	57	30	TEN	2	No
28	F	29	2	SJS	0	No
29	F	80	9	SJS	2	No
30	F	19	12	SJS	0	No

IVIG intravenous immunoglobulin, *F* female, *M* male, *TEN* toxic epidermal necrolysis, *Overlap* overlap syndrome, *SJS* Stevens–Johnson syndrome

Frequency and latency of the causative drugs and the mean age of patients with SJS and TEN

In almost all patients, SJS and TEN was drug-induced. The most common causative drugs were anticonvulsants (26.7 %) and allopurinol (26.7 %), followed by antibiotics (16.7 %), acetazolamide (10 %), acetaminophen (10 %), and herbal medication (6.7 %). We were unable to identify the causative drug in one case (3.3 %), mainly because the patient was administered with various SJS-inducing drugs, all of which were stopped immediately after the onset of SJS. Mean latency (the interval between exposure to the causative drug and the development of SJS/TEN) varied for the different causative drugs. The mean latencies for anticonvulsants, acetaminophen, and herbals were 36.00±27.934, 4.33±3.055, and 6.50±7.778 days, respectively. The mean age of patients who consumed anticonvulsants, allopurinol, antibiotics, and acetazolamide was 59–65 years. The mean age of patients who were treated with acetaminophen and herbals was 34.00 ±7.071 and 34.67±21.362 years, respectively (Table 2).

Clinical characteristics

Of all the patients, 83.3 % were over 40 years old. Other SCORTEN variables such as tachycardia, comorbid malignancy, elevated BUN, high blood glucose levels, and acidosis showed low frequencies. Elevated levels of C-reactive protein were commonly observed (76.7 %). Ocular lesions and liver function abnormalities (63.3 %), anemia (30.0 %), and kidney function impairment (16.7 %) were also frequently observed (Table 3).

Influence of sex on disease manifestation

The sex of the patients seemed to have an influence on the disease manifestation. Among the female patients, 16 (76.2 %) were diagnosed with SJS, 1 (4.8 %) with SJS/TEN overlap, and four (19.0 %) with TEN. Among the male patients, 3 (33.3 %) were diagnosed with SJS, one (11.1 %) with SJS/TEN overlap, and five (55.6 %) with TEN (Table 4). It is likely that men are more prone to develop severe forms of adverse skin reactions ($P<0.05$).

The *HLA-B* alleles

Eighteen patients were screened for the expression of *HLA-B* alleles. Of the five patients with LTG-induced SJS and TEN, three patients expressed the *HLA-B*4403* allele. However, none of the patients expressed the *HLA-B*1502* or *HLA-B*3101* alleles, which are known markers of carbamazepine-induced SJS and TEN. Among the seven patients with allopurinol-induced SJS and TEN, five expressed *HLA-B*5801*, two expressed *HLA-B*4006*, and one expressed *HLA-B*1511*. Two

Table 2 Frequency, mean latency, and mean age according to culprit drug

	Frequency (%)	Mean latency (day)±SD	Mean age (year)±SD
Anticonvulsants	26.7	36.0±27.9	60.3±14.2
Allopurinol	26.7	19.5±13.1	59.0±15.8
Antibiotics	16.7	14.6±11.4	64.7±10.3
Acetazolamide	10	25.0±8.7	62.7±9.8
Acetaminophen	10	4.3±3.1	34.0±7.1
Herbs	6.7	6.5±7.8	34.7±21.4
Etc	3.3	2.0	54.0
Sum	100	20.1±19.0	56.9±16.1

SD standard deviation

Table 3 Clinical characteristics

	Frequency (%)
Older age than 40 years old	83.3
Tachycardia (HR >120 beats/min)	16.7
Comorbid malignancy	10.0
BUN >28 mg/dL	20.0
Glucose >252 mg/dL	3.3
Bicarbonate <20 mEq/L	10.0
CRP elevation (>8 mg/L)	76.7
Anemia (Hb <10 g/dL)	30.0
Kidney injury (creatinine >2 mg/dL)	16.7
Liver injury (AST or ALT >50 IU/L)	63.3
Ocular lesion	63.3

CRP C-reactive protein, *HR* heart rate, *BUN* blood urea nitrogen

patients who were administered with acetazolamide expressed *HLA-B*5901*. A patient who received herbal medication expressed the *HLA-B*4403* allele, which is associated with LTG-induced SJS and TEN. Another patient who was administered with acetaminophen expressed *HLA-B*5801*, which is associated with allopurinol-induced SJS and TEN. Lastly, one patient who was treated with various drugs simultaneously expressed *HLA-B*4403*. However, this patient was never administered with LTG (Table 5).

Differences between LTG users and nonusers

Among the five "LTG users," three patients expressed *HLA-B*4403*. Among the 13 "non-users" (diagnosed with SJS/TEN caused by drugs other than LTG), two patients expressed *HLA-B*4403*. There were no significant differences between anticonvulsant (LTG) users and nonusers (*P* value 0.099; Table 6).

Differences between allopurinol users and nonusers

Among the seven allopurinol users, five patients expressed *HLA-B*5801*. Among the "nonusers" (diagnosed with SJS/TEN caused by drugs other than allopurinol), only one patient expressed *HLA-B*5801*. There were no statistically significant differences between the disease manifestations of allopurinol users and nonusers (*P* value 0.013; Table 7).

Table 4 Disease phenotype according to sex

	SJS	Overlap	TEN
Female	16 (76.2 %)	1 (4.8 %)	4 (19.0 %)
Male	3 (33.3 %)	1 (11.1 %)	5 (55.6 %)

SJS Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

Table 5 HLA-B genotype according to culprit drug

Number	Culprit drug	HLA-B genotype
1	Lamotrigine	B*44:03, B*52:01
2	Lamotrigine	B*44:02, B*44:03
3	Lamotrigine	B*44:03, B*51:01
4	Lamotrigine	B*15:07, B*39:01
5	Lamotrigine	B*15:01, B*35:03
6	Allopurinol	B*35, B*58
7	Allopurinol	B*44:02, B*58:01
8	Allopurinol	B*07:02, B*58:01
9	Allopurinol	B*15:01, B*40:06
10	Allopurinol	B*40:06, B*5801
11	Allopurinol	B*15:11, B*58:01
12	Allopurinol	B*08:01, B*58:01
13	Acetazolamide	B*07:02, B*59:01
14	Acetazolamide	B*40:06, B*59:01
15	Herbal	B*15:01, B*44:03
16	Acetaminophen	B*40:01, B*58:01
17	Amoxicillin	B*08:01, B*51:01
18	Unknown	B*07:02, B*44:03

Discussion

Knowledge of the risk factors involved in the development of SJS and TEN will help in disease prevention. Although a few studies describe the causes and risk factors associated with these diseases, their analyses were restricted to specific drugs or clinical outcomes. In this study, we described the etiology, clinical characteristics, and the expression of the *HLA-B* alleles in 30 patients diagnosed with SJS or TEN.

The most common causative drugs of SJS and TEN were anticonvulsants and allopurinol, followed by antibiotics. The proportion of nonsteroidal anti-inflammatory drugs (NSAIDs) was lower than the previous study [1]. However, this tendency is in concordance with that described in other Korean studies [29, 30]. Therefore, caution should be exercised when administering such drugs. Alternative drugs with less dangerous side effects may be considered for the first line of treatment. Mean latency and mean patient age varied for different drugs. Mean latencies of anticonvulsants, allopurinol, antibiotics, and acetazolamide were longer than those were of acetaminophen and herbals. These results are in agreement with those of previous reports [31]. In cases where a number of drugs have been

Table 6 Differences between lamotrigine users and nonusers

	Lamotrigine users	Nonusers	Sum
HLA B*4403 (+)	3 (60 %)	2 (15.4 %)	6
HLA B*4403 (−)	2 (40 %)	11 (84.6 %)	12
Sum	5 (100 %)	13 (100 %)	

Table 7 Differences between allopurinol users and nonusers

	Allopurinol users	Nonusers	Sum
HLA-B*5801 (+)	5 (71.4 %)	1 (9.1 %)	5
HLA-B*5801 (−)	2 (28.6 %)	10 (90.9 %)	11
Sum	7 (100 %)	11 (100 %)	

administered simultaneously, latency may be used to identify the causative drug. The mean patient age was higher for the use of anticonvulsants, allopurinol, antibiotics, and acetazolamide. These drugs showed shorter latencies in younger patients. However, no statistically significant tendency could be observed (Pearson's r=0.188, P value 0.328).

We used the SCORTEN scale to evaluate the severity of illness. Of the patients whose SCORTEN was 3 points, two died (28.57 % mortality rate). These results are in agreement with the results of an earlier study [24]. In patients with SCORTEN values of more than 5 points, the mortality rates were over 85 % [24]. As reported in other Korean studies [29], liver and optical impairments were observed in 63.3 % of the patients in this study. Therefore, it is essential to conduct a follow-up study for assessing multiple-organ damage (especially of the eyes and liver) in patients with SJS/TEN.

The overall mortality rate of SJS/TEN was only 6.6 %. The first fatality was that of a 57-year-old man diagnosed with acetazolamide-induced TEN involving more than 90 % of the surface area of the body. The patient showed liver and kidney damage, with death occurring due to septic shock caused by a wound infection. The second fatality was that of a 73-year-old woman, who was admitted to the neurosurgery division, with left thalamic intracranial hemorrhage. The patient was in rehabilitation when LTG-induced TEN developed. She presented symptoms of pneumonia and liver and kidney damage. The cause of death was aspiration pneumonia associated with refractory confused mental status. An analysis of the risk factors of mortality was difficult owing to the low mortality rate observed in our study.

Of the 30 patients, 21 were women and nine were men. The frequency of TEN, which is more severe than SJS is, was significantly higher in men (P<0.05) than in the women. Previously, drug-induced skin reactions were reported to be more frequent in women, while the severity of drug-induced skin reactions was higher in men [32, 33]. Our study showed a similar trend.

Drug hypersensitivity, including exfoliative skin reactions such as SJS and TEN, develops in response to the improper activation of T-cells. HLA molecules, which are located within the major histocompatibility complex (MHC), are primarily involved in these responses. A number of theories have been proposed to explain the association between SJS/TEN and the HLA molecules. According to the altered peptide repertoire theory, drugs are inserted into the peptide-binding groove of the MHC proteins. This insertion leads to an altered peptide repertoire. This alteration induces the immune system to recognize self as nonself, thereby negatively affecting the T-cell immunity and inducing drug hypersensitivity. Many studies suggest that this theory best explains the pathogenesis of hypersensitivity reactions induced by drugs such as carbamazepine [34–36].

A number of studies have described the association between specific *HLA* genotypes and carbamazepine-induced SJS and TEN. Different *HLA* genotypes are associated with sensitivity to different drugs. In studies on Han Chinese, Thai, and Indian individuals, *HLA-B*1502* expression was associated with SJS/TEN caused by anticonvulsants, especially carbamazepine [37, 12, 13]. However, in a Japanese study, *HLA-B*1502* was not detected in patients with carbamazepine-induced SJS/TEN. Instead, *HLA-B*1511* expression was found to be associated with carbamazepine-induced SJS/TEN in Japanese and Korean individuals [18, 20]. Another marker, *HLA-A*3101*, was also detected in Japanese and White individuals with carbamazepine-induced SJS/TEN [19, 38]. Therefore, the *HLA* genotype associated with carbamazepine-induced SJS and TEN can vary according to ethnicity and geography. Recently, a number of studies have reported the association between the *HLA* genotype and drug hypersensitivity.

*HLA-B*4403* allele frequencies are 8.5 % in Korea, as similar levels of *HLA-B*5801* (6.5 %) and higher levels than that of *HLA-B*1502* (0.2 %) [39]. Several studies have examined the structure and interactions of the *HLA-B*4403* allele. However, only one report published the association between *HLA-B*4403* and clinical diseases. In the Japanese study, *HLA-B*4403* expression was significantly associated with post-herpetic neuralgia (PNH) [40]. Recently, LTG, which is a newly developed anticonvulsant drug, has seen increased use as an alternative to carbamazepine. To our knowledge, this is the first time that an association between *HLA-B*4403* expression and LTG-induced SJS/TEN has been shown. We proposed that the *HLA-B*4403* allele may be a novel marker for LTG-induced SJS and TEN.

There are some limitations of our study. The causative drugs were identified based on patient history and not by immunological or provocation tests. We selected the causative drug that was used 3 months prior to hospitalization. In cases that involved the use of multiple drugs, the most probable SJS/TEN-inducing drug was selected. However, in LTG-induced SJS and TEN cases, LTG was the only causative drug. Moreover, we evaluated only the *HLA-B* alleles and did not include those of *HLA-A*, *HLA-C*, *HLA-DP*, *HLA-DQ*, and *HLA-DR*. These alleles may also play a role in the development of drug-induced SJS/TEN. Therefore, it is necessary to evaluate these alleles as well. Other limitations of this study include its small sample size (number of patients, n=30) and the data being collected from a single center. Therefore, a study or multiple

studies featuring a larger sample size and multiple study centers need to be conducted to demonstrate the association between *HLA-B*4403* expression and LTG-induced SJS and TEN. In addition, the odds ratio can be calculated if the expression frequency of *HLA-B*4403* in LTG-tolerant patients were analyzed.

In the present study, the most common causative drugs causing SJS and TEN were found to be anticonvulsants and allopurinol. LTG was frequently used as a substitute for carbamazepine. Of the five LTG users in our study, three patients expressed the *HLA-B*4403* allele. We speculate that the *HLA-B*4403* allele might be a potential marker of LTG-induced SJS and TEN in Korean individuals.

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