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The Link between *HLA-B* Alleles and Causative Drugs in Vietnamese Patients with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Abstract

BACKGROUND: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions. Human leukocyte antigens (*HLA*) may play an important role in the pathogenesis of SJS/TEN.

AIMS: This study aims to identify *HLA-B* alleles in Vietnamese patients with SJS/TEN and to investigate the possible link between *HLA-B* alleles and causative drugs.

MATERIALS AND METHODS: Sixty patients including SJS (30 patients) and TEN (30 patients) were enrolled in a cross-sectional descriptive study at two hospitals in Hanoi, Vietnam, from July 2018 to July 2019. Clinical features and laboratory findings were noted, *HLA-B* alleles were analyzed by the polymerase chain reaction (PCR)-sequence-specific oligonucleotide assay and Luminex™ Multiplex Technology.

RESULTS: The most common *HLA-B* allele was *HLA-B*15:02* (41.7%) followed by *HLA-B*58:01* (25%) and *HLA-B*46:01* (15%). Of the 25 patients possessing *HLA-B*15:02* allele, culprit medicines were carbamazepine (13 patients; 52%), traditional medicine (two patients; 8%), and unknown drugs (seven patients; 28%). Of the 15 patients carrying *HLA-B*58:01* allele, there were 13 patients whose offending medicine was allopurinol. Of the eight patients whose culprit drug was traditional medicine, there were 6 patients (75%) carrying *HLA-B*51:02*. Patients who carry *HLA-B*15:02* were found to have 4 times higher risk of developing carbamazepine-induced SJS/TEN as compared with the tolerant control group (OR=4.17; 95% CI=2.07–8.37; $p < 0.001$).

CONCLUSION: *HLA-B*15:02* was the most common *HLA-B* allele in Vietnamese patients with SJS/TEN. In traditional medicine-induced SJS/TEN patients, *HLA-B*51:02* allele might play an important role. The link between the *HLA-B* genotypes and causative drugs may suggest physicians to avoid risk medications for certain patients.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions (SCARs) [1]. Although their incidence is of 2 per million per year, they are life threatening with a mortality rate of 5–30% [2], [3]. The common culprit drugs are allopurinol, carbamazepine, phenytoin, phenobarbital, lamotrigine, abacavir, and others [2], [3], [4], [5]. The time between the date of taking medicine and the onset of symptoms ranges from some days to 2 months [2], [4].

The main manifestations of SJS/TEN are apoptosis [6] and/or necroptosis [7] of epidermal keratinocytes that are initiated by cytotoxic T lymphocytes with the presence of culprit drugs [1], [6], [8]. Based on the percentage of necrotic skin area, SJS and TEN are classified by Bastuji-Garin as follows: (1) SJS is defined as epidermal detachment <10% body surface area (BSA) plus widespread purpuric macules or flat atypical targets; (2) overlap SJS/TEN is defined as detachment of 10–30% BSA plus widespread purpuric macules or flat atypical targets; (3) TEN with spots (detachment >30% BSA plus widespread purpuric macules or flat atypical targets); and (4) TEN without spots (detachment >30% BSA with loss of large epidermal sheets without purpuric macules or target lesions) [9].

Many studies have indicated associations between the human leukocyte antigens (*HLA*) and SCARs [1], [10], [11], [12], [13]. In Han Chinese population, there is a strong association between *HLA-B*15:02* allele with SJS/TEN due to some aromatic antiepileptic drugs such as carbamazepine, phenytoin, phenobarbital, and lamotrigine [14], and between *HLA-B*58:01* allele and allopurinol-induced

SJS/TEN [10], [15]. Some SJS/TEN drug associations have been also added, for example, *HLA-B*57:01* with abacavir in Caucasians [13], [15], [16] and *HLA-A*31:01* with carbamazepine in Japanese [17]. Studies in Vietnam have shown the association between *HLA-B* alleles and specific drug-induced SJS/TEN such as carbamazepine [18] and allopurinol [19]. In addition, common *HLA-B* alleles among general Kinh population (the major ethnicity in Vietnam) have been studied [20].

There has been no study with regard to *HLA-B* genotypes of SJS/TEN generally. The aim of this study was to identify *HLA-B* alleles among Vietnamese patients with SJS/TEN and the possible link between *HLA-B* alleles and causative drugs.

Materials and Methods

Subjects

The study was conducted at National Hospital of Dermato-venereology and Bach Mai Hospital in Hanoi, Vietnam, from July 2018 to July 2019. In total, 60 patients including 30 SJS and 30 TEN were enrolled in our study. Clinical features and laboratory findings were recorded for each patient. We investigated all medicines, including the over the counter, that the patients took over a period of 2 months before the onset of the conditions. Other pieces of information were also obtained (reasons for using drugs, ethnicity, and allergy history). The patients were examined as regards their general condition, cutaneous, and mucous membrane lesions.

SJS and TEN were diagnosed and classified based on Bastuji-Garin criteria [9]. Calculation of necrotic skin and epithelial sloughing areas was based on burn area estimation (Lund-Browder formula) [21]. We determined the most culprit drugs using ALDEN algorithm [5].

DNA isolation and HLA-B typing

DNA extraction (MagNA Pure Compact nucleic acid purification kit, Roche Diagnostics Ltd., USA) was performed based on magnetic bead technology. DNA was aliquoted and stored at −20°C before *HLA* typing. Polymerase chain reaction (PCR)-sequence-specific oligonucleotide assay and Luminex™ Multiplex Technology were used to analyze *HLA-B* alleles. To summarize, PCR products were hybridized against a panel of oligonucleotide probes coated on polystyrene microspheres that have sequences which complement stretches of polymorphic sequence within the target *HLA-B* alleles. Using a colorimetric reaction and fluorescence detection technology, we were able to see the amplicon probe complex. Data analysis for the *HLA-B* assays was performed with *HLA* fusion TM2.0 software. This typing was conducted at National Institute of Hematology and Blood Transfusion in Hanoi, Vietnam.

Ethical clearance

The study was approved by the Ethical Review Committee on Research Involving Human Subjects, Hanoi Medical University, Hanoi, Vietnam (Number 04NCS17, dated February 8, 2018). Written consent was obtained from all participants.

Results

There were 30 patients with SJS and 30 patients with TEN, no patients with overlapping SJS/TEN. All patients were Kinh ethnicity. The patient's characteristics are shown in Table 1. The mean age was 52 years (range 19–77). The most common age group was over 50 years old (65%). The sex distribution was equal (male: 53.3%; female: 46.7%). Reasons for using causative drugs were gout disease (21.7%), arthralgia (18.3%), epilepsy (15%), headache (5%), other reasons (20%), and unknown (20%). The most frequent causative drugs used were allopurinol (13 patients; 21.7%), carbamazepine (13 patients; 21.7%), and traditional medicine (eight patients; 13.2%). Other medications were less common, such as nonsteroidal anti-inflammatory drugs (diclofenac, phenylbutazone, and piroxicam), lamotrigine, thalidomide, and antibiotics (zidocin). There were 33.2% of patients with unknown culprit drugs.

Table 1: Characteristics of patients with SJS/TEN (n=60)

Characteristics	SJS (n=30)	TEN (n=30)	SJS/TEN (n=60)
Age, year	51.2 ± 16.7	52.8 ± 15.5	52 ± 16
Range	19–77	19–77	19–77
Group of age, n (%)			
<30	3 (10)	3 (10)	6 (10)
30–39	5 (16.7)	3 (10)	8 (13.3)
40–50	4 (13.3)	3 (10)	7 (11.7)
>50	18 (60)	21 (70)	39 (65)
Sex, n (%)			
Male	16 (53.3)	16 (53.3)	32 (53.3)
Female	14 (46.7)	14 (46.7)	28 (46.7)
Indications of culprit drugs, n (%)			
Gout disease	9 (30)	4 (13.3)	13 (21.7)
Arthralgia	5 (16.7)	6 (20)	11 (18.3)
Epilepsy	4 (13.3)	5 (16.7)	9 (15)
Headache	2 (6.7)	1 (3.3)	3 (5)
Other reasons	4 (13.3)	8 (26.7)	12 (20)
Unknown cause	6 (20)	6 (20)	12 (20)
Causative drugs, n (%)			
Allopurinol	9 (30)	4 (13.3)	13 (21.7)
Carbamazepine	7 (23.4)	6 (20)	13 (21.7)
Traditional medicine	0 (0)	8 (26.7)	8 (13.2)
NSAIDs (diclofenac, phenylbutazone, and piroxicam)	1* (3.3)	2 (6.7)	3 (5.1)
Others (lamotrigine, thalidomide, and zidocin)	1** (3.3)	2 (6.7)	3 (5.1)
Unknown drugs	12 (40)	8 (26.6)	20 (33.2)

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, NSAIDs: Nonsteroidal anti-inflammatory drugs, *phenylbutazone; **zidocin.

A total of 60 patients were underwent *HLA-B* typing. The results (as shown in Table 2) demonstrated

that the most common *HLA-B* allele was *HLA-B*15:02* (25/60 patients; 41.7%) followed by *HLA-B*58:01* (15/60 patients; 25%) and *HLA-B*46:01* (9/60 patients; 15%). Other less common alleles were *HLA-B*51:01* (eight patients; 13.2%); *HLA-B*13:01* (eight patients; 13.2%); and *HLA-B*07:05* (four patients; 6.6%).

Table 2: *HLA-B* genotypes in Vietnamese patients with SJS/TEN (n=60)

Patient No.	Diagnosis	Causative medicine	Allele 1	Allele 2
1	SJS	Carbamazepine	15:02	15:25
2	SJS	Carbamazepine	15:02	40:01
3	SJS	Carbamazepine	15:02	51:01
4	SJS	Carbamazepine	15:02	56:04
5	SJS	Carbamazepine	15:02	15:02
6	SJS	Carbamazepine	15:02	46:01
7	SJS	Carbamazepine	15:02	46:01
8	TEN	Carbamazepine	15:02	44:03
9	TEN	Carbamazepine	15:02	40:01
10	TEN	Carbamazepine	15:02	55:02
11	TEN	Carbamazepine	15:02	54:01
12	TEN	Carbamazepine	15:02	13:01
13	TEN	Carbamazepine	15:02	13:01
14	SJS	Unknown	15:02	51:02
15	SJS	Unknown	15:02	13:01
16	SJS	Unknown	15:02	73:01
17	SJS	Unknown	15:02	57:01
18	SJS	Unknown	15:02	40:01
19	TEN	Unknown	15:02	35:05
20	TEN	Unknown	15:02	15:02
21	TEN	Traditional medicine	15:02	51:02
22	TEN	Traditional medicine	15:02	54:01
23	SJS	Allopurinol	15:02	58:01
24	SJS	Zidocin	15:02	15:02
25	TEN	Piroxicam	15:02	15:02
26	SJS	Allopurinol	58:01	13:02
27	SJS	Allopurinol	58:01	57:01
28	SJS	Allopurinol	58:01	40:06
29	SJS	Allopurinol	58:01	13:01
30	SJS	Allopurinol	58:01	46:01
31	SJS	Allopurinol	58:01	51:01
32	SJS	Allopurinol	58:01	38:02
33	SJS	Allopurinol	58:01	40:01
34	TEN	Allopurinol	58:01	40:01
35	TEN	Allopurinol	58:01	46:01
36	TEN	Allopurinol	58:01	56:04
37	TEN	Allopurinol	58:01	40:01
38	TEN	Unknown	58:01	07:02
39	SJS	Unknown	58:01	35:05
40	SJS	Unknown	07:05	46:01
41	SJS	Unknown	38:02	46:01
42	TEN	Unknown	15:25	46:01
43	TEN	Unknown	13:01	51:02
44	TEN	Unknown	56:04	51:02
45	SJS	Unknown	13:01	38:02
46	SJS	Unknown	13:01	07:02
47	SJS	Unknown	07:05	51:01
48	TEN	Unknown	07:05	51:01
49	SJS	Unknown	56:02	38:02
50	TEN	Unknown	07:05	73:01
51	TEN	Traditional medicine	51:02	46:01
52	TEN	Traditional medicine	15:01	51:02
53	TEN	Traditional medicine	15:21	51:02
54	TEN	Traditional medicine	37:01	51:02
55	TEN	Traditional medicine	15:25	51:02
56	TEN	Traditional medicine	54:01	54:01
57	TEN	Diclofenac	13:01	51:01
58	SJS	Phenylbutazone	35:05	38:02
59	TEN	Thalidomide	15:21	57:01
60	TEN	Lamotrigine	15:21	46:01

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, *HLA-B*: Human leukocyte antigen-B.

Of the 25 patients possessing *HLA-B*15:02* allele, the culprit drugs were carbamazepine among 13 patients (52%), traditional medicine 2 patients (8%), allopurinol 1 patient (4%) (who had *HLA-B* phenotype that was *15:02* and *58:01*), piroxicam 1 patient (4%), zidocin (metronidazole and spiramycin) 1 patient (4%), and unknown drugs 7 patients (28%). Of the 15 patients with *HLA-B*58:01*, there were 13 patients with allopurinol-induced SJS/TEN and two patients with unknown causative drugs. Among eight patients with traditional medicine-induced SJS/TEN, there were six *HLA-B*51:02* allele carriers (75%).

We compared the risk of carbamazepine-induced SJS/TEN between the 13 carbamazepine-induced SJS/TEN patients carrying *HLA-B*15:02* with the control group (epilepsy tolerating carbamazepine) from a previous study in Vietnam [18]. A significant association between carbamazepine-induced SJS/TEN and *HLA-B*15:02* was found when compared with the tolerant control group (OR=4.17; 95% CI=2.07–8.37; $p < 0.001$). However, there was no significant association between carbamazepine-induced SJS/TEN and *HLA-B*46:01* (OR=0.32; 95% CI=0.06–1.8; $p = 0.184$), as shown in Table 3.

Table 3: Correlation between *HLA-B*15:02, HLA-B*46:01,* and phenotypes (carbamazepine-induced SJS/TEN)

Allele positive	SJS/TEN (n=13)	Control** (n=25)	OR (95% CI)	p-value
*HLA-B*15:02*	13	6	4.17 (2.07–8.37)	<0.001
*HLA-B*46:01*	2	9	0.32 (0.06–1.8)	0.184

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, *HLA-B*: Human leukocyte antigen-B; OR: Odds ratio, CI: Confidence interval, **following the study of Nguyen *et al*. [18].

Discussion

Among 60 SJS/TEN patients, *HLA-B*15:02* was the most common allele which is higher than that in general Kinh population [20]. This finding might be due to the fact that all participants in our study were SJS/TEN patients, whose the most frequent culprit drug was carbamazepine. Of the 25 *HLA-B*15:02* carriers in this study, there were 13 carbamazepine-induced SJS/TEN patients (52%). Studies in Asian countries have demonstrated the strong association between carbamazepine-induced SJS/TEN and *HLA-B*15:02* [14], [15], [22]. A previous study in Vietnam shows the most common *HLA-B* allele among general population is *HLA-B*15:02* [20]. While, a study in Korean population shows that *HLA-B*44:03* is the most frequent type in *HLA-B* genes; allele frequency of *HLA-B*15:02* is 0.3% [23]. Among Thai population, the most common *HLA-B* alleles observed is *HLA-B*46:01* (11.5%), while the *HLA-B*15:02* allele frequency is 8.2% [24]. These results show the diversity of *HLA-B* polymorphisms in different ethnicities. The high frequency of *HLA-B* pharmacogenomic markers in population emphasizes the importance of such screening to predict and avoid SCARs [13], [24], [25].

In the present study, there were 15 out of 60 patients carry *HLA-B*58:01* allele (25%). Among them, there were 13 patients with allopurinol-induced SJS/TEN and two patients with unknown drug-induced SJS/TEN. The strong association between *HLA-B*58:01* and allopurinol-induced SJS/TEN has been shown in Asian [10] as well as in Caucasians [15], [25], while the association between *HLA-B*15:02* and carbamazepine has been only observed in Asian ancestries [14], [15], [18], [23], [26]. We found 15% of SJS/TEN patients (nine patients) having *HLA-B*46:01* allele, which is similar to the findings from the previous

studies among Vietnamese [20], Korean [23], and Thai [24]. A study in Vietnam shows that the prevalence of *HLA-B*46:01* in the carbamazepine-induced SCARs group was significantly lower than that in the carbamazepine-tolerant epilepsy patient group [18]. This allele may be considered as a protective factor against the development of carbamazepine-induced SCARs in Vietnamese [18]. However, in our study, *HLA-B*46:01* allele did not reveal the association with carbamazepine-induced SJS/TEN. Therefore, the role of *HLA-B*46:01* in SCARs needs to be investigated further.

We also observed an allopurinol-induced SJS patient possessing *HLA-B*15:02.* In fact, this patient's *HLA-B* genotype was *15:02* and *58:01.* He was at high risk of being allergic to both carbamazepine and allopurinol. In addition, there were two traditional-induced SJS/TEN patients and seven unknown drug-induced SJS/TEN patients all carrying *HLA-B*15:02*; two patients with unknown causative drugs carrying *HLA-B*58:01*. Typing of *HLA-B* alleles in these patients could be significant to avoid the high risk of drug-induced SCARs.

In our study, traditional medicine was the third most common culprit drug of SJS/TEN (13.3%), which is similar to the finding from a previous study in Hanoi [27]. Interestingly, among these patients, there were six patients with *HLA-B*51:02* allele (75%). *HLA-B*51:02* allele belongs to *B5101* serotype. There has been no study indicating its role in SJS/TEN so far.

In Vietnam, the use of medications without prescriptions is rather common, even mixing of western medicines in some traditional medicines intentionally done by traditional healers, is not rare. Consequently, it is more difficult to identify the offending drugs. Therefore, the possible association between *HLA-B*51:02* allele and traditional medicine-induced SJS/TEN needs to be investigated further, and, studies about *HLA-B* genotypes in SCARS are crucial and may provide evidences for advising certain patients to avoid using certain medications.

We found a significant association between carbamazepine-induced SJS/TEN and *HLA-B*15:02* allele. This is consistent with those of other studies in Asia [14], [18]. Hence, screening this allele is very essential before indicating carbamazepine as well as other aromatic anticonvulsant agents because among these drugs, cross-reactivity exists frequently [28], [29], [30], [31]. In our study, there was one patient with lamotrigine-induced TEN who took lamotrigine to treat her depressed condition. This patient possessed *HLA-B*15:21* and *HLA-B*46:01* genotype. In a study among Thai population, the prevalence of *HLA-B*15:02* and *HLA-A*02:07* alleles has been shown higher in the lamotrigine-induced SCARs than in the lamotrigine-tolerant control group [32]. *HLA-B*15:21* allele is an *HLA-B75* serotype marker similar to *HLA-B*15:02*, *-B*15:11,* and *-B*15:08*, they have the same carbamazepine binding sites *in silico* analysis [11]. There was a case report of a Filipino carbamazepine-induced SJS/TEN overlap patient without *HLA-B*15:02* allele but with positive *HLA-B75* serotype [33]. A study in Korean population reveals that three out of five lamotrigine-induced SJS/TEN patients carry *HLA-B*44:03* allele [23]. Out of 60 patients, we observed one patient with carbamazepine-induced TEN caring this allele. This may be due to the fact that there is a difference in *HLA-B*44:03* allele frequencies between Korean [23] and Vietnamese population [20].

There were some limitations in our study. First, the sample size was of 60 SJS/TEN patients but the causative drugs varied. Accordingly, we could not focus on analyzing a big sample of SJS/TEN patients due to a special drug. Second, using the control group of the previous study [18] might not be ideal for comparison. Third, we typed only *HLA-B* alleles, but not other *HLA* genes associated with SJS/TEN and SCARs, such as *HLA-A*, *HLA-C,* or some metabolic genes beyond *HLA* genes.

Conclusion

*HLA-B*15:02* was the most common *HLA-B* allele in Vietnamese patients with SJS/TEN. *HLA-B*51:02* allele may play an important role in the pathogenesis of the traditional medicine-induced SJS/TEN. There may be a link between *HLA-B* alleles and causative drugs of SJS/TEN. The *HLA-B* genotypes may be useful for suggesting the causative drugs in some cases and preventing SCARs.

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