Human leucocyte antigen association of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis with severe ocular complications in Han Chinese

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2020-317105).

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Received 4 June 2020
Revised 15 December 2020
Accepted 19 December 2020
Published Online First
13 January 2021

To cite: Ma KS-K, Chung WH, Hsueh Y-J, *et al*. *Br J Ophthalmol* 2022;**106**:610–615.

ABSTRACT

Background/aims Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) induced by cold medicine (CM) may result in severe ocular complications (SOCs). The purpose of this study was to investigate the human leucocyte antigen (HLA) polymorphism pattern in CM-induced patients with SJS/TEN developing SOCs.

Methods All participants, including patients with SJS/TEN (n=33) and control patients (n=98), were enrolled through visits to the clinic from 2016 to 2017. SOCs were diagnosed (n=26) via a chart review or eye examination. Patient saliva was collected with commercialised kits and genotyped with PCR assays followed by hybridisation with sequence-specific oligonucleotide (SSO) probes (PCR-SSO) using commercial bead-based typing kits.

Results In all patients with SJS/TEN with SOCs, the HLA-A*02:07 carrier frequency was significantly higher than that in controls (OR=3.24, 95% CI=1.09 to 9.60, p=0.049), as was the genotype frequency (OR=3.89, 95% CI=1.49 to 10.16, p=0.007). In patients with CM-SJS/TEN with SOCs, the HLA-A*02:07 carrier frequency was higher than that in controls (OR=5.56, 95% CI=1.52 to 20.00, p=0.016), as was the allele frequency (OR=6.67, 95% CI=2.33 to 20.00, p=0.001). In patients with CM-SJS/TEN with SOCs, the HLA-B*46:01 allele frequency was significantly higher than that in controls (OR=3.85, 95% CI=1.52 to 10.00, p=0.008).

Conclusions The HLA-A*02:07 and HLA-B*46:01 alleles were significantly associated with SOCs among Han Chinese patients with CM-SJS/TEN. These findings demonstrate the genetic diversity in SJS pathogenesis among different ethnic groups.

INTRODUCTION

Ocular complications are one of the most long-lasting and debilitating sequelae after acute Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[1–4] Patients may suffer from dry eye, trichiasis, symblepharon and lid margin keratinisation. Of note, recurrent corneal inflammation, which is manifested by progressive corneal neovascularisation, may result in limbal epithelial stem cell loss and conjunctival epithelial ingrowth. These phenotypes are also known as limbal stem cell deficiency, which is associated with poor wound healing and epithelial breakdown. If not treated properly and immediately, the epithelial defect may soon develop into corneal ulceration or even perforation, which is devastating to vision.

Cold medicine (CM)-induced ocular complications in the SJS/TEN context have been reported to be very severe[5 6]; CM refers to antipyretics or analgesics (including a variety of non-steroidal anti-inflammatory drugs; NSAIDs) that patients take if they catch a cold. CM does not include antibiotics that are usually taken during a cold. Regarding the association between NSAIDs and SJS/TEN, Ueta *et al* reported that 80% of severe ocular complications (SOCs) in patients with SJS/TEN were related to CM and NSAIDs.[7] Collaborative studies from Brazil[8] and Thailand[9] also demonstrated that more than half of patients with SJS/TEN with SOCs had taken CM. Strong associations were likewise confirmed for the risk of NSAID-induced severe cutaneous adverse reactions (SCARs) in the EuroSCAR Study.[10]

A number of studies have demonstrated that adverse drug reactions involve a strong genetic predisposition.[11–14] Among them, tremendous success in predicting the occurrence of carbamazepine (CBZ)-induced SJS/TEN with the biomarker human leucocyte antigen (HLA)-B*15:02 has inspired research on the correlation of specific HLA polymorphisms and drugs causing SJS/TEN.[15–17] For instance, the correlation of specific HLAs with CM-induced SJS/TEN (CM-SJS/TEN) has been reported in Japan,[5 18 19] Brazil,[8] India[20] and Thailand.[9] Within the Han Chinese population, a strong association of specific HLAs with CBZ,[5 15–17 21] allopurinol[22–24] or oxcarbazepine-induced SJS/TEN was investigated in Taiwan[25 26]; however, the specific HLA polymorphism in CM-SJS/TEN in the Han Chinese population remains unknown. The purpose of this study was therefore to identify HLA subtypes specifically associated with SOCs in patients with SJS/TEN, particularly patients with CM-SJS/TEN, to provide biomarkers for the prevention of these diseases.

MATERIALS AND METHODS

Patients and controls

Patients with SJS/TEN visiting the outpatient clinic of the Department of Ophthalmology of Chang Gung Memorial Hospital, Linkou Branch were evaluated and recruited during July 2016 and June 2017. The purpose of this study and the

experimental protocols were explained to all participants, and informed consent was obtained before documentation as well as sample collection. The case report form (CRF) included information on ethnicity, sex, present age, age at onset, cold symptoms before onset, drug administration before onset, high fever at onset, stage at first consultation, ocular signs during the acute stage (including erosion of the ocular surface epithelium, pseudomembrane, lash loss and so on) and nail deformation.

In this study, we focused on the ocular manifestations mainly in the acute stage. Most of the patients recruited for this study were treated in our hospital from study initiation; therefore, we were able to evaluate the severity of ocular manifestations during the acute stage by electronic chart reviews. When patients presented in the acute stage of SJS/TEN, the Sotozono acute stage grading system was used,[27] while when patients presented in the chronic stage, the Sotozono chronic stage grading system was used.[28] The diagnosis of an SOC in the acute stage was made according to the classification of Sotozono *et al*: any appearance of conjunctival pseudomembrane formation and/or conjunctival or corneal epithelial defects was considered an SOC.[27] Digital images taken during both the acute and present stages were attached to the CRF for comparison. The culprit drug was determined by dermatologists not only by clinical judgement but also by objective tests, such as the lymphocyte transformation test, in some patients.

In the chronic stage, ocular involvement was assessed according to the classification system proposed by Sotozono *et al*.[28] Complications were broadly defined as corneal complications (including superficial punctate keratopathy, epithelial defects, loss of the palisades of Vogt, conjunctivalisation, neovascularisation, opacification and keratinisation); conjunctival complications (including hyperaemia and symblepharon) and eyelid complications (including trichiasis, mucocutaneous junction involvement, meibomian gland involvement and punctal damage). Patients with a severity classified above grade 3 or with a total score above 23 were considered to have developed an SOC, which applied to the patients who were not initially treated in our hospital. These patients also often presented with an SOC in the acute stage.

Three times the sample size of the study group was collected for the control group. These control patients visited the outpatient clinic and included those who were seen after cataract, corneal or refractive surgery, and those with blepharoconjunctivitis or mild dry eye. Given that HLA subtype polymorphisms do not change over time, we recruited sex-matched controls instead of age-matched controls, and the sex ratios in both groups were similar.

HLA genotyping

For each participant, 2 mL of saliva was collected with an Oragene DNA kit (OG-500, Kyodo International, Kanagawa Prefecture, Japan). The tubes were labelled and stored at room temperature. These samples were airmailed to Kyoto Prefecture University for HLA analysis under a collaboration agreement.

PCR assays followed by hybridisation with sequence-specific oligonucleotide (SSO) probes (PCR-SSO) was performed with commercial bead-based typing kits (Wakunaga, Hiroshima, Japan). Genotyping for the HLA-A, HLA-B and HLA-C subtypes was also achieved in control patients with PCR-SSO and commercial bead-based typing kits.

Table 1 Causative drugs/medications for SJS/TEN with SOC

Causative drugs	N=26
Cold medicine (NSAIDs)	N=13
Antibiotics (sulfa drugs and augmentin)	N=6
Anti-epileptics (CBZ and lamotrigine)	N=3
Proton pump inhibitors (omeprazole)	N=1
Allopurinol	N=1
Other causes (hair dye=1, mycoplasma=1)	N=2
Causative CM (NSAIDs)	N=13
Ibuprofen	N=2
Acetaminophen	N=1
Mefenamic acid	N=2
Pyrazolone derivatives	N=3
Diclofenac sodium	N=2
Unknown name	N=3

CBZ, carbamazepine; CM, cold medicine; NSAIDs, non-steroidal anti-inflammatory drugs; SJS, Stevens-Johnson syndrome; SOC, severe ocular complication; TEN, toxic epidermal necrolysis.

Statistical analysis

We compared the carrier frequency and allele frequency of individual HLA alleles between patients, including all patients with SJS/TEN with SOCs and patients with CM-SJS/TEN with SOCs, as well as controls, based on the dominant model using the χ^2 with Fisher's exact test. Moreover, because the multiple comparisons test, which is used in genetic studies, may inflate the alpha level, Bonferroni correction was applied to the p values. The relative risk measures, including the ORs and their corresponding CIs, were also calculated. All analyses were conducted with SAS V.9.4 software.

RESULTS

A total of 33 patients with SJS/TEN, including 9 men and 24 women, were recruited, and the mean patient age was 46.1±8.5 (8–86) years. Twenty patients were recruited in the acute stage, while the rest in the chronic stage. Ninety-eight control patients, including 30 men and 68 women, were also enrolled, and the mean patient age was 53.0±17.9 (14–88) years. The mean age of clinical symptom onset among 7 patients without SOCs and 26 patients with SOCs was 32.7±21.4 (4–86) years. The causative drugs for SJS/TEN with SOCs included CM (NSAIDs; n=13), antibiotics (n=6), antiepileptics (n=3) and other medications. The causative NSAIDs are listed in table 1.

All HLA subtypes were analysed, with rare subtypes grouped as 'others'. Concerning the HLA allele distribution in all patients with SJS/TEN with SOCs, the HLA-A*02:07 carrier frequency was significantly higher than that in control patients (26.9% vs 10.2%; Fisher's p=0.049), with an OR=3.24 (95% CI=1.09 to 9.60). The HLA-A*02:07 allele frequency in all patients with SJS/TEN with SOCs was also significantly higher than that in control patients (17.3% vs 5.1%; Fisher's p=0.007), with an OR=3.89 (95% CI=1.49 to 10.16) (table 2, online supplemental table 1A). There was no significant difference in the HLA-B (online supplemental table 1B) or HLA-C (online supplemental table 1C) allele distribution between the study and control groups. Regarding the HLA allele distribution in patients with CM-SJS/TEN with SOCs, the HLA-A*02:07 carrier frequency was significantly higher than that in control patients (38.5% vs 10.2%; Fisher's p=0.016), with an OR=5.56 (95% CI=1.52 to 20.00). The HLA-A*02:07 allele frequency in patients with CM-SJS/TEN with SOCs was also significantly higher than that in control patients (26.7% vs 5.1%; Fisher's p=0.001), with an

Table 2 Comparison of carrier and allele frequencies of HLA subtypes between patients with SJS/TEN developing SOCs and normal controls

	Carrier frequency					Allele frequency				
			P value		OR			P value		OR
HLA subtype	Case	Control	Fisher	Bonferroni correction	(95% CI)	Case	Control	Fisher	Bonferroni correction	(95% CI)
A*02:06	7.7% (2/26)	5.1% (5/98)	0.636			3.9% (2/52)	3.1% (6/196)	0.675		
A*02:07	26.9% (6/26)	10.2% (10/98)	**0.049**	0.487	**3.24(1.09 to9.60)**	17.3% (9/52)	5.1% (10/196)	**0.007**	0.068	**3.89(1.49to 10.16)**
A*11:01	34.6% (9/26)	55.1% (54/98)	0.079			21.2% (11/52)	31.6% (62/196)	0.172		
B*46:01	30.8% (8/26)	19.4% (19/98)	0.284			19.2% (10/52)	10.2% (20/196)	0.093		

Bold type denotes p values with significance.
HLA, human leucocyte antigen; SJS, Stevens-Johnson syndrome; SOCs, severe ocular complications; TEN, toxic epidermal necrolysis.

OR=6.67 (95% CI=2.33 to 20.00, table 3, online supplemental table 2A). However, after Bonferroni correction, only in the CM-induced SOC group did the difference in the HLA-A*02:07 allele frequency remain statistically significant (p=0.012, table 3, online supplemental table 2A).

Concerning the HLA-B and HLA-C alleles, even though all patients with SJS/TEN with SOCs did not harbour significantly different HLA polymorphisms than control patients, in patients with CM-SJS/TEN with SOCs, the HLA-B*46:01 allele frequency was significantly higher than that in control patients (39.8% vs 10.2%; p=0.008 by Fisher's exact test; p=0.076 by Bonferroni correction), with an OR=3.85 (95% CI=1.52 to 10.00, table 3, online supplemental table 2B). There was no significant difference in the HLA-C allele distribution between the study and control groups (online supplemental table 2C).

A preferential association of HLA-B*44:03 in patients with CM-SJS/TEN with SOCs was previously reported in Japan,[18] Thailand,[9] India[20] and Brazil.[8] An association with HLA-C*07:01 was also reported in Thailand[9] and India.[20] However, neither HLA-B*44:03 nor HLA-C*07:01 was found in the patients with SJS/TEN or control patients in the present cohort study. HLA-A*02:06 is recognised uniquely in Japanese patients with SJS/TEN with SOCs.[18 29] The HLA-A*02:06 subtype associations in our recruited patients with SJS/TEN and control patients were similar, with 7.6% vs 5.1% in terms of carrier frequency (p=0.535) and 3.8% vs 3.1% in terms of allele frequency (p=0.587) (table 3, online supplemental table 2A). Finally, it has been reported that HLA-A*11:01 might be a marker of resistance for Japanese and Brazilian patients with CM-SJS/TEN[8 18]; however, there was no difference in the HLA-A*11:01 subtype among our patients with SJS/TEN with SOCs and control patients (30.8% vs 55.1% in carrier frequency, p=0.140; and 23.1% vs 31.6% in allele frequency, p=0.498) (table 3, online supplemental table 2A).

DISCUSSION

According to the nationwide cohort data from the Taiwan SCAR Consortium in 2018, among the 47 newly diagnosed cases of SJS/TEN attributable to a specific drug, 18 were induced by antibiotics (notably sulfa drugs, n=5), followed by antiepileptics (n=13), NSAIDs (n=3), antigout agents (n=3), proton pump inhibitors (n=2) and miscellaneous drugs (n=9) (Chung *et al*, unpublished data, 2018). Although NSAIDs or CM comprised a small proportion of causative agents among all patients with SJS/TEN in previous studies, our cohort data based on 26 patients with SOCs suggest that half of SOCs were attributable to CM, while none of the 7 patients without SOCs had disease caused by CM. This finding is echoed by previous studies reporting that CM is likely to induce SOCs in patients with SJS/TEN in Japan (80%),[5 19] Brazil (53%)[8] and Thailand (69%).[9]

The risk of SJS/TEN caused by NSAIDs is very low. A study on the incidence of NSAID-induced SJS/TEN in the USA estimated that it is less than 2 per 1 million users per week for oxicam derivatives, less than 1 per 1 million users per week for other NSAIDs and 6 cases per 1 million person-years for celecoxib.[30] Ward *et al* reported that older patients, women and patients within the first month of treatment initiation endure a high risk

Table 3 Comparison of carrier and allele frequencies of HLA subtypes between CM-induced patients with SJS/TEN developing SOCs and normal controls

	Carrier frequency					Allele frequency				
			P value					P value		
HLA-A	Case	Control	Fisher	Bonferroni correction	OR (95% CI)	Case	Control	Fisher	Bonferroni correction	OR (95% CI)
A*02:06	7.7% (1/13)	5.1% (5/98)	0.535			3.8% (1/26)	3.1% (6/196)	0.587		
A*02:07	38.5% (5/13)	10.2% (10/98)	**0.016**	0.155	**5.56 (1.52 to 20.00)**	26.9% (7/26)	5.1% (10/196)	**0.001**	**0.012**	**6.67 (2.33 to 20.00)**
A*11:01	30.8% (4/13)	55.1% (54/98)	0.140			23.1% (6/26)	31.6% (62/196)	0.498		
B*46:01	30.77% (6/13)	19.4% (19/98)	0.070			30.8% (8/26)	10.2% (20/196)	**0.008**	0.076	**3.85 (1.52 to 10.00)**

Bold type denotes p values with significance.
CM, cold medicine; HLA, human leucocyte antigen; SJS, Stevens-Johnson syndrome; SOCs, severe ocular complications; TEN, toxic epidermal necrolysis.

of NSAID-induced SJS/TEN.[30] Several epidemiological studies, case reports and case series involving SJS/TEN associated with NSAIDs have revealed that of the available NSAIDs, oxicam derivatives appeared to have the greatest association with SJS and TEN. The relative risks reported with other NSAIDs are much lower.[10 21 31 32]

Since ocular complications caused by SJS/TEN are serious and difficult to treat, it is worthwhile to develop diagnostic tools to screen susceptible patients. Previous studies have identified a strong association between HLA-B*15:02 and phenytoin-induced SJS/TEN in Han Chinese[26]; HLA-B*58:01 and allopurinol-induced SCARs in Chinese,[24 33–35] Japanese,[36 37] Korean,[36] Thai[36 38] and European Caucasians[33]; HLA-A*31:01 and CBZ-induced SCARs in European Caucasians,[39] Japanese[37] and Koreans[40]; HLA-B*13:01 and dapsone-induced SJS/TEN in Thai[41]; HLA-B*B*59:01 and HLA-CW*01:02 in methazolamide-induced SJS/TEN in Koreans and Japanese[42]; and HLA-B*57:01 and abacavir hypersensitivity in Caucasians.[41 42]

The finding of a strong association between specific HLA subtypes and drug-induced SCARs has enabled screening strategies to prevent SCARs, including HLA-B*15:02 screening for CBZ-induced SJS/TEN,[15 21 41 42] HLA-B*57:01 screening for abacavir hypersensitivity[41 42] and HLA-B*58:01 screening for allopurinol-induced SCARs.[43 44]

Previously, Ueta *et al* reported that the HLA-A*02:06 polymorphism presented a strong association with the incidence of SOCs in patients with SJS/TEN[18 19 29] and that HLA-A*02:06 together with TLR3 polymorphisms exerted an additive effect.[45–47] Moreover, interactive effects between HLA-A*02:06 and prostaglandin E receptor 3 (also known as subtype EP3, PTGER3 SNPs) were discerned not only in the Japanese but also in the Korean population, indicating aggravation of the manifestation.[13 48–51]

Single amino acid substitutions in major histocompatibility complex class I molecules play a role in distinct peptide repertoires. For instance, three HLA-A2 subtypes, namely, HLA-A*02:04, HLA-A*02:06 and HLA-A*02:07, differ only by a single amino acid residue substitution, and each possesses the HLA-A*02:01 molecule at the floor of their binding grooves. Allele-specific peptide motifs for each HLA-A2 subtype substantially differ from that of HLA-A*02:01 in the dominant anchor residues.[52] Even though the carrier and allele frequencies of HLA-A*02:06 in Japanese patients with CM-SJS/TEN with SOCs were significantly higher than those in control patients, the frequency of HLA-A*02:07 was similar in both groups.[18] In contrast, we found that the HLA-A*02:07 allele, instead of the HLA-A*02:06 allele, was associated with patients with CM-SJS/TEN with SOCs. A high frequency of the HLA-A*02:07 allele has been documented in Taiwanese patients with Graves' disease,[53] whereas the HLA-B*46:01 allele appears to be associated with the severity of SARS infection in the Taiwanese population.[54] The finding that HLA-B*46:01 is also significantly associated with CM-SJS/TEN with SOCs is not surprising because HLA-A*02:07 and HLA-B*46:01 are among the three most common HLA-A and HLA-B haplotypes within Taiwanese cord blood (CB) units (6.61%); on the other hand, HLA-A*02:07, HLA-B*46:01 and HLA-DRB1*09:01 belong to one of the most common three-locus haplotypes discovered in the general Taiwanese CB units (3.47%)[55] as well as bone marrow donor registers (4.430%).[56] Previously, HLA-B*44:03 was reported to be associated with patients with CM-SJS/TEN in Japan,[6 18 19] Thailand,[9] India[20] and Brazil[8] developing SOCs. In this study, we found no HLA-B*44:03 association in either patients with SJS/TEN or control patients. This finding is compatible with the findings of previous studies in which HLA-B*44:03 was only sparsely distinguished in the Han Chinese population in Taiwan (0.41%–0.63%).[21 55]

The major drawback of the current study is the limited sample size compared with those in previous studies. Consequently, after Bonferroni correction, only in the CM-induced SOC group did the difference in the HLA-A*02:07 allele frequency remain statistically significant. The reasons for this infeasibility involve the following: first, the population of Taiwan is much smaller than that of other countries where similar studies were conducted; second, although Chang Gung Memorial Hospital treats most patients with SJS/TEN in Taiwan, the sample size was still confined by the nature of this single-centre study. To illustrate the impact caused by the small sample size, we calculated that by doubling the sample size, the p value for the carrier frequency of A*02:07 and the allele frequency of B*46:01 in CM-induced SOC and the allele frequency of A*02:07 in the total population with SJS/TEN with SOCs would be significant even after Bonferroni correction. In the case of a carrier frequency of A*02:07 in the total population with SJS/TEN with SOCs, tripling the sample size would be needed. Further long-term and nationwide surveillance could be conducted to confirm these findings.

In conclusion, our findings suggest that the HLA-A, HLA-B and HLA-C subtypes are associated with CM-SJS/TEN with SOCs among the Han Chinese population in Taiwan; these findings are distinct from those of previous reports. Instead of HLA-A*02:06 or HLA-B*44:03, associations of HLA-A*02:07 and HLA-B*46:01 were notable. This demonstrates that genetic diversity exists in SJS/TEN pathogenesis among different ethnic groups, which may regulate the outcome of the disease and be a potential predictive diagnostic tool for prognosis.

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Acknowledgements We thank Dr Yu-Tung Anton Huang, Center for Big Data Analytics and Statistics, Chang Gung Memorial Hospital, Linkou, for assistance with statistical analysis.

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Funding This work was supported by Chang Gung Memorial Hospital grants (CMRPG3G0021-3, CMRPG1H0091) and the Japan Society for the Promotion of Science (JSPS) Core-to-Core Program grants-in-aid Type A Advanced Research Networks.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study procedure used to collect SJS/TEN and control patient genomes for HLA analysis was approved by the Institutional Review Boards of Chang Gung Medical Foundation (IRB approval number: 104-0927B) and of Kyoto Prefectural University of Medicine. All experimental procedures were conducted in accordance with the principles set forth in the Helsinki Declaration.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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Supplementary Table 1. Comparison of carrier and allele frequencies of HLA subtypes between SJS/TEN patients developing SOCs and normal controls

A. HLA-A association with SJS/TEN with SOCs

HLA-A	Carrier frequency					Allele frequency				
	Case	Control	*p*-value		Odds ratio (95% CI)	Case	Control	*p*-value		Odds ratio (95% Cl)
			Fisher	Bonferroni correction				Fisher	Bonferroni correction	
A*02:01	7.7% (2/26)	23.5% (23/98)	0.100			3.9% (2/52)	11.8% (23/196)	0.121		
A*02:03	26.9% (7/26)	15.3% (15/98)	0.245			15.4% (8/52)	8.2% (16/196)	0.121		
A*02:06	7.7% (2/26)	5.1% (5/98)	0.636			3.9% (2/52)	3.1% (6/196)	0.675		
A*02:07	26.9% (6/26)	10.2% (10/98)	**0.049**	0.487	**3.24 (1.09-9.60)**	17.3% (9/52)	5.1% (10/196)	**0.007**	0.068	**3.89 (1.49- 10.16)**
A*11:01	34.6% (9/26)	55.1% (54/98)	0.079			21.2% (11/52)	31.6% (62/196)	0.172		
A*11:02	0.0% (0/26)	12.2% (12/98)	0.069			0.0% (0/52)	6.1% (12/196)	0.077		
A*24:02	23.1% (6/26)	27.6% (27/98)	0.804			13.5% (7/52)	14.8% (29/196)	1.000		
A*30:01	3.9% (1/26)	6.1% (6/98)	1.000			1.9% (1/52)	3.1% (6/196)	1.000		
A*33:03	34.6% (9/26)	24.5% (24/98)	0.324			21.2% (11/52)	12.8% (25/196)	0.182		
Others	3.9% (1/26)	7.1% (7/98)	1.000			1.9% (1/52)	3.6% (7/196)	1.000		

B. HLA-B association with SJS/TEN with SOCs

HLA-B	Carrier frequency					Allele frequency				
	Case	Control	*p*-value		Odds ratio	Case	Control	*p*-value		Odds ratio
			Fisher	Bonferroni correction	(95% CI)			Fisher	Bonferroni correction	(95% Cl)
B*13:01	3.9% (1/26)	15.3% (15/98)	0.189			1.9% (1/52)	7.7% (15/196)	0.205		
B*13:02	3.9% (1/26)	6.1% (6/98)	1.000			1.9% (1/52)	3.1% (6/196)	1.000		
B*15:01	7.7% (2/26)	11.2% (11/98)	1.000			5.77% (3/52)	6.1% (12/196)	1.000		
B*15:02	15.4% (4/26)	9.2% (9/98)	0.469			7.7% (4/52)	4.6% (9/196)	0.481		
B*38:02	11.5% (3/26)	11.2% (11/98)	1.000			5.77% (3/52)	5.6% (11/196)	1.000		
B*39:01	0.0% (0/26)	7.1% (7/98)	0.343			0.0% (0/52)	3.6% (7/196)	0.351		
B*40:01	34.6% (9/26)	33.7% (33/98)	1.000			19.2% (10/52)	18.9% (37/196)	1.000		
B*46:01	30.8% (8/26)	19.4% (19/98)	0.284			19.2% (10/52)	10.2% (20/196)	0.093		
B*51:01	0.0% (0/26)	8.2% (8/98)	0.202			0.0% (0/52)	4.6% (9/196)	0.211		
B*52:01	3.9% (1/26)	6.1% (6/98)	1.000			1.9% (1/52)	3.1% (6/196)	1.000		
B*55:02	3.9% (1/26)	7.1% (7/98)	1.000			1.9% (1/52)	3.6% (7/196)	1.000		
B*58:01	38.5% (10/26)	29.6% (29/98)	0.477			21.2% (11/52)	15.3% (30/196)	0.302		
Others	26.9% (7/26)	26.5% (26/98)	1.000			13.5% (7/52)	13.8% (27/196)	1.000		

C. HLA-C association with SJS/TEN with SOCs

HLA-C	Carrier frequency					Allele frequency				
	Case	Control	*p*-value		Odds ratio	Case	Control	*p*-value		Odds ratio
			Fisher	Bonferroni correction	(95% CI)			Fisher	Bonferroni correction	(95% Cl)
C*01:02	26.9% (7/26)	26.5% (26/98)	1.000			17.3% (8/52)	14.8% (27/196)	0.661		
C*03:02	38.5% (10/26)	29.6% (29/98)	0.477			23.1% (12/52)	15.3% (30/196)	0.212		
C*03:03	3.6% (1/26)	8.2% (8/98)	0.683			1.9% (1/52)	4.1% (8/196)	0.689		
C*03:04	15.4% (4/26)	27.6% (27/98)	0.308			9.62% (5/52)	15.3% (30/196)	0.374		
C*04:01	15.4% (4/26)	13.3% (13/98)	0.754			9.62% (5/52)	7.7% (15/196)	0.579		
C*06:02	3.9% (1/26)	7.1% (7/98)	1.000			1.9% (1/52)	3.6% (7/196)	1.000		
C*07:02	26.9% (7/26)	27.6% (27/98)	1.000			17.3% (8/52)	14.8% (28/196)	0.667		
C*08:01	19.2% (5/26)	14.3% (14/98)	0.546			9.62% (5/52)	7.1% (14/196)	0.560		
C*12:02	7.7% (2/26)	10.2% (10/98)	1.000			3.9% (2/52)	5.1% (10/196)	1.000		
C*14:02	0.0% (0/26)	7.1% (7/98)	0.343			0.0% (0/52)	3.6% (6/196)	0.351		
C*15:02	11.5% (3/26)	8.2% (8/98)	0.698			5.77% (3/52)	4.1% (8/196)	0.704		
Others	0.0% (0/26)	9.2% (9/98)	0.202			0.0% (0/52)	5.1% (10/196)	0.127		

Supplementary Table 2. Comparison of carrier and allele frequencies of HLA subtypes between CM-induced SJS/TEN patients developing SOCs and normal controls

A. HLA-A association with CM-SJS/TEN with SOCs

HLA-A	Carrier frequency					Allele frequency				
	Case	Control	*p*-value		Odds ratio (95% CI)	Case	Control	*p*-value		Odds ratio (95% Cl)
			Fisher	Bonferroni correction				Fisher	Bonferroni correction	
A*02:01	7.7% (1/13)	23.5% (23/98)	0.292			3.8% (1/26)	11.8% (23/196)	0.324		
A*02:03	15.4% (2/13)	15.3% (15/98)	1.000			7.7% (2/26)	8.2% (16/196)	1.000		
A*02:06	7.7% (1/13)	5.1% (5/98)	0.535			3.8% (1/26)	3.1% (6/196)	0.587		
A*02:07	38.5% (5/13)	10.2% (10/98)	**0.016**	0.155	**5.56 (1.52-20.00)**	26.9% (7/26)	5.1% (10/196)	**0.001**	**0.012**	**6.67 (2.33- 20.00)**
A*11:01	30.8% (4/13)	55.1% (54/98)	0.140			23.1% (6/26)	31.6% (62/196)	0.498		
A*11:02	0.0% (0/13)	12.2% (12/98)	0.354			0.0% (0/26)	6.1% (12/196)	0.369		
A*24:02	15.4% (2/13)	27.6% (27/98)	0.508			11.5% (3/26)	14.8% (29/196)	1.000		
A*30:01	7.7% (1/13)	6.1% (6/98)	0.593			3.8% (1/26)	3.1% (6/196)	0.587		
A*33:03	38.5% (5/13)	24.5% (24/98)	0.319			19.2% (5/26)	12.8% (25/196)	0.363		
Others	0.0% (0/13)	7.1% (7/98)	1.000			0.0% (0/26)	3.6% (7/196)	1.000		

B. HLA-B association with CM-SJS/TEN with SOCs

HLA-B	Carrier frequency					Allele frequency				
	Case	Control	*p*-value		Odds ratio	Case	Control	*p*-value		Odds ratio
			Fisher	Bonferroni correction	(95% CI)			Fisher	Bonferroni correction	(95% CI)
B*13:01	0.0% (0/13)	15.3% (15/98)	0.209			0.0% (0/26)	7.7% (15/196)	0.227		
B*13:02	3.9% (1/13)	6.1% (6/98)	0.593			3.8% (1/26)	3.1% (6/196)	0.587		
B*15:01	7.7% (2/13)	11.2% (11/98)	0.648			11.5% (3/26)	6.1% (12/196)	0.394		
B*15:02	15.4% (0/13)	9.2% (9/98)	0.595			0.0% (0/26)	4.6% (9/196)	0.603		
B*38:02	11.54% (1/13)	11.2% (11/98)	1.000			3.8% (1/26)	5.6% (11/196)	1.000		
B*39:01	0.00% (0/13)	7.1% (7/98)	1.000			0.0% (0/26)	3.6% (7/196)	1.000		
B*40:01	34.62% (2/13)	33.7% (33/98)	0.222			7.7% (2/26)	18.9% (37/196)	0.269		
B*46:01	30.77% (6/13)	19.4% (19/98)	0.070			30.8% (8/26)	10.2% (20/196)	**0.008**	0.076	**3.85 (1.52-10.00)**
B*51:01	0.00% (0/13)	8.2% (8/98)	0.593			0.0% (0/26)	4.6% (9/196)	0.603		
B*52:01	3.9% (1/13)	6.1% (6/98)	0.593			3.8% (1/26)	3.1% (6/196)	0.587		
B*55:02	3.9% (0/13)	7.1% (7/98)	1.000			0.0% (0/26)	3.6% (7/196)	1.000		
B*58:01	38.5% (6/13)	29.6% (29/98)	0.340			23.1% (6/26)	15.3% (30/196)	0.393		
Others	26.9% (4/13)	26.5% (26/98)	0.746			15.4% (4/26)	13.8% (27/196)	0.767		

C. HLA-C association with CM-SJS/TEN with SOCs

HLA-C	Carrier frequency					Allele frequency				
	Case	Control	*p*-value		Odds ratio	Case	Control	*p*-value		Odds ratio
			Fisher	Bonferroni correction	(95% CI)			Fisher	Bonferroni correction	(95% CI)
C*01:02	26.9% (5/13)	26.5% (26/98)	0.511			26.9% (7/26)	14.8% (27/196)	0.146		
C*03:02	38.5% (6/13)	29.6% (29/98)	0.340			23.1% (6/26)	15.3% (30/196)	0.393		
C*03:03	3.58% (1/13)	8.2% (8/98)	1.000			3.8% (1/26)	4.1% (8/196)	1.000		
C*03:04	15.4% (1/13)	27.6% (27/98)	0.178			3.8% (1/26)	15.3% (30/196)	0.140		
C*04:01	15.4% (3/13)	13.27% (13/98)	0.397			15.4% (4/26)	7.7% (15/196)	0.251		
C*06:02	3.9% (1/13)	7.1% (7/98)	1.000			3.8% (1/26)	3.6% (7/196)	1.000		
C*07:02	26.9% (2/13)	27.6% (27/98)	0.508			11.5% (3/26)	14.8% (28/196)	1.000		
C*08:01	19.23% (1/13)	14.29% (14/98)	1.000			3.8% (1/26)	7.1% (14/196)	1.000		
C*12:02	7.7% (1/13)	10.2% (10/98)	1.000			3.8% (1/26)	5.1% (10/196)	1.000		
C*14:02	0.00% (0/13)	7.1% (7/98)	1.000			0.0% (0/26)	3.6% (6/196)	1.000		
C*15:02	11.54% (1/13)	8.2% (8/98)	1.000			3.8% (1/26)	4.1% (8/196)	1.000		
Others	0.00% (0/13)	9.2% (9/98)	0.595			0.0% (0/26)	5.1% (10/196)	0.611		