
ORIGINAL ARTICLE

*HLA-B*1502* Strongly Predicts Carbamazepine-Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis in Thai Patients with Neuropathic Pain

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■ Abstract:

Background: Carbamazepine (CBZ) is one of the standard pharmacological treatments for neuropathic pain. However, its serious adverse drug reactions include Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Recently, *HLA-B*1502* allele was implicated as a genetic marker of CBZ-induced SJS/TEN in some Asian epilepsy populations.

Methods: This is a case control study to describe the clinical characteristics of SJS/TEN in Thai patients with neuropathic pain who were treated with CBZ, and to determine the association of *HLA-B*1502* in these patients, comparing with those who exposed to CBZ for at least 6 months without any cutaneous reactions.

Results: Thirty-four SJS/TEN patients and 40 control patients were included in this study. Mean age of SJS/TEN

patients was 47 years. SJS/TEN was developed in 10.8 ± 1.4 days after initiation of CBZ. *HLA-B*1502* allele was found in 32 of 34 SJS/TEN patients (94.1%) but it was found only in 7 of 40 control patients (17.5%). The association was very strong with an odds ratio of 75.4. Sensitivity and specificity of this *HLA-B*1502* genotype test were 94.1% and 82.5%, respectively, while the positive predictive value and negative predictive value were 1.43% and 99.98%, respectively. Positive and negative likelihood ratios were 5.37 and 0.07, respectively.

Conclusions: *HLA-B*1502* is a strong genetic marker for CBZ-induced SJS/TEN in Thai patients with neuropathic pain. The screening for this marker should be performed prior to initiation of CBZ treatment to assess the risk of this serious side effect. ■

Key Words: neuralgia, Pain, carbamazepine, Stevens–Johnson syndrome, toxic epidermal necrolysis, *HLA-B*1502*, genetic markers

Abbreviations: HLA, Human leukocyte antigen; CBZ, carbamazepine; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; NeP, neuropathic pain; IVD, in vitro diagnostic; PCR, polymerase chain reaction; OR, odds ratio; CI, confidence intervals; AED, antiepileptic drugs; LR, likelihood ratio; OXC, oxcarbazepine; PHT, phenytoin; LTG, lamotrigine.

BACKGROUND

Carbamazepine (CBZ), a conventional antiepileptic drug, has been used for treatment of epilepsy, bipolar disorder and neuropathic pain for the past several decades. It is recommended in many clinical practice guidelines for trigeminal neuralgia and various neuropathic pain conditions.^{1,2} However, its common adverse drug reactions are dizziness, vertigo, nausea and skin rash. The rash varies from benign urticaria to life threatening reactions, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).^{3,4} The mortality of these two conditions is very high due to severe mucocutaneous and epidermal detachment involvement, which leads to infection and sepsis.^{3,5,6}

Recent reports in epilepsy patients indicating that many Asian ethnicities, including Han and central Chinese, Malay, Indian and Thai carry higher risk of SJS/TEN due to high frequency of *HLA-B*1502* in the population.^{7–13} Therefore, we performed a case control study to describe a large series of CBZ-induced SJS/TEN in Thai patients with neuropathic pain and assess the degree of association between *HLA-B*1502* allele in this specific population.

METHODS

Patients

Patients were recruited from seven hospitals in Thailand by retrospectively reviewed the medical records of patient who were diagnosed with CBZ-induced SJS/TEN and admitted in one of these hospitals from 2007 to 2010. The diagnoses of SJS and TEN were confirmed by either a dermatologist or an internist based on the clinical morphology of the patients' skin according to Roujeau et al.⁶ Stevens–Johnson syndrome is characterized by small blisters arising on purple macules. Lesions are widespread and usually predominate on the trunk. Confluence of blisters on limited areas leads to detachment below 10% of the body surface area. Toxic epidermal necrolysis is characterized by the same lesions than SJS but with confluence of blisters leading to positive Nikolski sign and to detachment of large epidermal sheets on more than 30% of the body surface area. Cases with detachment between 10% and 30% are labeled overlap SJS-TEN. CBZ was identified as the culprit drug if the symptoms occurred within the first 3 months of CBZ exposure and the symptoms resolved upon withdrawal of this drug.

Patients from the same hospitals as the SJS/TEN patients who had used CBZ for at least 6 months without evidence of any cutaneous reactions were recruited as controls. The controls were recruited consecutively at their regular medical visit during the same study period (2007 to 2010) at participating study sites where SJS/TEN patients were recruited.

All case and control patients were interviewed by investigators about the history of their biologic parents and grandparents; they were classified as native Thai because both of their biologic parents and grandparents were born in Thailand. Subjects were informed both verbally and in writing about the procedures and the purpose of the study. The study protocol was approved by the institutional review boards of Khon Kaen University and Thammasat University, Thailand. Some patients in this study have been reported in part in our previous publication.¹⁰

Detection of *HLA-B*1502*

Genomic DNA of each patient was extracted from peripheral blood and used as template for *HLA-B*1502* detection. *HLA-B*1502* genotyping analysis was performed using a PG1502 DNA detection kit (Pharmigene Inc., Taipei, Taiwan) that was approved

by Taiwan's Department of Health as an in vitro diagnostic (IVD) test. The kits are real-time polymerase chain reaction (RT-PCR) based with sequencing specific primers directed toward *HLA-B*1502* and the internal control gene.

Statistical Analyses

Statistical analyses were performed using STATA version 9.1 (Stata Corporation, College Station, Texas, U.S.A.). For comparisons between descriptive sample characteristics in both groups, Student's *t*-test was used in case of continuous normally distributed or ordinal variables. Chi-square or Fisher's exact test were used for dichotomous variables and presented as odds ratio (OR). For all analyses, the level of statistical significance was defined as a *P* value of < 0.05. Sensitivity and specificity, including their 95% confidence intervals (CI) were calculated for the screening properties of the *HLA-B*1502* in CBZ-induced SJS/TEN. Likelihood ratios were calculated from sensitivity and specificity. Assuming the prevalence of CBZ-induced SJS/TEN in a Thai population as 0.27%, as previously reported,¹¹ the positive predictive value and negative predictive value of the *HLA-B*1502* genotyping test were calculated.

RESULTS

Characteristics of CBZ-Induced SJS/TEN and CBZ-Tolerant Patients

In this study, 34 SJS/TEN neuropathic pain patients were included as cases, and 40 CBZ-tolerant neuropathic pain patients were included as controls. Clinical characteristics of CBZ-induced SJS/TEN patients and CBZ-tolerant patients were summarized in Table 1. There was no significant difference in age, gender, etiology of neuropathic pain, regional ethnicity and presence of comorbidity. SJS/TEN patients were mostly middle age females with a mean age of 47.0 ± 14.7 years. SJS/TEN was developed at the mean of 10.8 ± 1.4 days after initiation of CBZ. The lesion almost always involved eye, oral mucosa, and some at genitalia. Although we cannot completely rule out the possibility of concurrent medication as a cause of SJS/TENS in some patients, there were no apparent difference of concomitant medications between the two groups. The common concomitant medications on both groups were amitriptyline, gabapentin, tramadol,

Table 1. Clinical Characteristics of CBZ-Induced SJS/TEN Neuropathic Pain Patients and CBZ-Tolerant Patients

	CBZ-Induced SJS/TEN Patients (n = 34)	CBZ-Tolerant Patients (n = 40)	<i>P</i> value
Age (years)	47.0 ± 14.7	52.6 ± 14.3	0.105
Gender (female)	70.6 (%)	62.5 (%)	0.622
Etiology of NeP			
Trigeminal neuralgia	11 (32.3%)	15 (37.5%)	0.807
Others	23 (67.7%)	25 (62.5%)	
Ethnicity			
Northeast Thailand	28 (82.4%)	21 (72.5%)	0.130
Central Thailand	4 (11.8%)	11 (27.5%)	
Others	2 (5.8%)	0 (0%)	
Comorbidity			
Present	22 (64.7%)	26 (65.0%)	0.979
Absent	12 (35.3%)	14 (35.0%)	
Duration of exposure (days)	10.8 ± 1.4	1290.8 ± 1236.0	< 0.001*
<i>HLA-B*1502</i> genotype	32 (94.1%)	7 (17.5%)	< 0.001*

CBZ, carbamazepine; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; NeP, neuropathic pain. * denotes statistically significant.

paracetamol, metformin, and glibenclamide. Out of 34 cases, the complications were conjunctivitis (22), gastrointestinal bleeding (11), sepsis (4), urinary tract infection (1), renal failure (1) and hepatitis (1).

*HLA-B*1502* Genotype

The characteristics and *HLA-B* genotypes of SJS/TEN patients were summarized in Table 2. *HLA-B*1502* allele was found in 32 from 34 cases (94.1%) while it was found only in 7 of 40 controls (17.5%). In these seven cases, there was no other baseline characteristic, noncompliance or concomitant medications, which may explain the absence of cutaneous reaction. The risk of CBZ-induced SJS/TENS was significantly higher in patients with *HLA-B*1502* with an OR of 75.4 (95% CI, 13.0 to 718.9, *P* < 0.001). Sensitivity and specificity of this *HLA-B*1502* genotype test were 94.1% (95% CI, 80.3% to 99.3%) and 82.5% (95% CI, 67.2% to 92.7%), respectively. Positive and negative likelihood ratios (LR) were 5.37 and 0.07, respectively. Thus, by assuming the prevalence of CBZ-induced SJS/TEN in a Thai population as 0.27% as previously reported,¹¹ positive and negative predictive value were 1.43% and 99.98%, respectively.

DISCUSSION

This case control study demonstrates a strong association between *HLA-B*1502* and CBZ-induced SJS/TEN

Table 2. Clinical Characteristics and HLA-B Genotypes of CBZ-Induced SJS/TEN Patients

	Age/Sex	Type of SCAR	CBZ Indication	Comorbidity	Latency (days)	Mucosal Involvement, Sites of Lesions	Comedication	HLA-B*1502
1	30/M	SJS	TGN	No	5	(+) Eye, oral	Orphenadrine, paracetamol	Positive
2	40/F	SJS	TGN	SLE	1	(+) Oral, genitalia	Chloroquine, haloperidol, prednisolone	Positive
3	27/F	TEN	TGN	No	7	(+) Eye, oral, genitalia	Piroxicam	Positive
4	51/F	SJS	TGN	No	14	(+) Oral	No	Positive
5	50/F	SJS	NeP	DM, HT, OA	7	(+) Eye, oral, genitalia	Atenolol, glipizide, metformin, mefenamic acid	Positive
6	50/F	SJS	NeP	No	14	(+) Eye, oral	Paracetamol, tolperisone	Positive
7	61/F	SJS	NeP	No	NA	(+) Eye, oral	Amoxycillin	Positive
8	56/M	SJS	NeP	No	5	(+) Eye, oral	No	Positive
9	33/F	SJS	NeP	No	13	(+) Eye, oral	Codeine, dimenhydrinate, paracetamol	Positive
10	78/F	SJS	TGN	DM, HT	3	(+) Eye, oral	Enalapril, metformin, insulin	Positive
11	53/F	SJS	NeP	No	3	(+) Oral	No	Positive
12	59/M	SJS	TGN	No	10	(+) Eye, oral, genitalia	Amitriptyline, gabapentin	Positive
13	67/M	SJS	TGN	No	12	(+) Eye, oral	No	Positive
14	53/F	SJS	NeP	DM	3	(+) Eye, oral	Glibenclamide, metformin	Positive
15	35/F	SJS	NeP	No	7	(+) Eye, oral	No	Positive
16	62/M	SJS	NeP	PD	14	(+) Eye, oral	Trihexyphenidyl, levodopa	Positive
17	63/F	SJS	TGN	DM, HT	4	(+) Eye, oral, genitalia	Amitriptyline, hydrochlorothiazide	Negative
18	65/F	SJS	NeP	No	11	(+) Eye, oral, genitalia	Cephalexin	Positive
19	59/F	SJS	NeP	DM	14	(+) Eye, oral	Cyproheptadine, dimenhydrinate, glibenclamide	Positive
20	20/F	SJS	TGN	No	30	(+) Oral	No	Positive
21	44/M	TEN	NeP	DM	10	(+) Eye, oral, genitalia	Diclofenac, glipizide	Positive
22	22/F	TEN	NeP	No	7	(+) Eye, oral, genitalia	No	Negative
23	59/F	SJS	TGN	DM	NA	(+) Eye, oral	NA	Positive
24	33/M	TEN	NeP	No	14	(+) Eye, oral	No	Positive
25	50/F	TEN	NeP	No	11	(+) Eye, oral	No	Positive
26	37/F	TEN	TGN	No	7	(+) Eye, oral	Cetirizine, bromhexine, roxithromycin, ibuprofen	Positive
27	55/F	SJS	NeP	No	30	(+) Eye, oral	NA	Positive
28	39/F	TEN	NeP	Zoster	10	(+) Eye, oral, genitalia	Mecobalamin, tramadol, acyclovir	Positive
29	32/M	SJS	NeP	No	21	(+) Oral	Doxycycline,	Positive
30	63/F	SJS	NeP	DM,HT	30	(+) Eye, oral	Cimetidine, diltiazem, glibenclamide, piroxicam, paracetamol, atenolol	Positive
31	28/M	TEN	NeP	No	1	(+) Eye, oral	No	Positive
32	54/F	SJS	NeP	HT	5	(+) Eye, oral, genitalia	Amoxycillin	Positive
33	40/F	SJS	NeP	No	9	(+) Eye, oral	No	Positive
34	30/M	SJS	NeP	No	15	(+) Eye, oral	Amitriptyline, ibuprofen, vitamin B1-6-12	Positive

F, Female; M, Male; SCAR, severe adverse cutaneous reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TGN, trigeminal neuralgia; NeP, neuropathic pain; DM, diabetes mellitus; HT, hypertension; SLE, systemic lupus erythematosus; OA, osteoarthritis; PD, Parkinson's disease; NA, data not available.

in Thai patients with neuropathic pain. *HLA-B*1502* allele were found in almost all of CBZ-induced SJS/TEN patients (32 of 34 patients, 94.1%), in contrast with control neuropathic pain patients (7 of 40 controls, 17.5%). The frequency of *HLA-B*1502* carrier in the control group, was in the same range as general Thai population.^{14,15} Despite the limited number of control subjects, the association and risk were still robust with very high OR of 75.4. The high positive LR of 5.37 and very low negative LR of 0.07 also confirms the usefulness of this test for risk assessment. This risk was in line with previous reports in epilepsy population.^{10,11,13,16} The morbidity and mortality data

in our patients were limited because we enrolled only survivors after the events.

Many SJS/TEN cases are still related to “old drugs” such as CBZ and allopurinol. Most CBZ-induced SJS/TEN cases occurred within the first few weeks after initiation of treatment.¹⁷ This association of *HLA-B*1502* and skin rash is phenotype specific, ie it is associated with SJS/TENS but not maculopapular rash.^{11,13} The increased use of CBZ, especially for control of pain, may be the reason for the increased incidence of SJS/TEN due to the same drug. The combination of CBZ and acetaminophen may further increase the risk for the occurrence of EM, SJS, or

TEN.¹⁸ Awareness about the drugs implicated in life threatening drug reactions will help physicians in preventing them by judicious use of the drugs.¹⁹

Reports across Asia has shown that the prevalence of *HLA-B*1502* is high among Han Chinese (5% to 15%), Malays (12% to 15%), and Thais (8% to 27%), but low among Japanese, Korean, Sri Lankans, and most ethnic groups in India.¹⁵ In northeastern part of Thailand, the prevalence of *HLA-B*1502* carrier was even higher at 16.4%²⁰ and in the same range with Burmese (17.3%).²¹ This may explain why most SJS/TENS patients were from this region of the world. The example of population pharmacogenetics study in *HLA-B*15* subtypes distribution in Han population in Beijing also confirmed the genetic anthropology and migration among different Chinese ethnicity.²² This information and future study across many Asian populations will be helpful in future study about the epidemiologic and burden of this condition.

Due to lower frequency of this gene in European and Japanese populations, this association was not found in these populations.^{23–25} This discrepancy between Japanese and other Asian countries also suggest different population genetic background. In Japanese population, *HLA-B*1511* was recently implicated as a risk factor for CBZ-induced SJS/TEN,²⁶ while genome-wide association studies identified an association between *HLA-A*3101* and CBZ-induced cutaneous adverse drug reactions or hypersensitivity syndrome in Japanese and European population.^{27,28} Therefore, other mechanisms involving in CBZ hypersensitivity must be involved. Other genetic polymorphisms such as TNF-308 may play roles and warrant further study.²⁴ Moreover, drug-specific T cells in CBZ-hypersensitive patients are phenotypically different from T cells involved in other serious cutaneous adverse drug reactions.²⁹

Cross-sensitivity rates between certain antiepileptic drugs (AEDs) are high, especially when involving CBZ and phenytoin. Specific cross-sensitivity rates provided here may be useful for AED selection and counseling in individual patients.³⁰ Other anticonvulsants which have been used for neuropathic pain, such as oxcarbazepine (OXC), phenytoin (PHT), and lamotrigine (LTG), are also associated with SJS/TENS. OXC, PHT, and LTG, which possess an aromatic ring as CBZ does, when causing SJS/TEN, may share a common risk allele. Aromatic antiepileptic drugs causing SJS/TEN in *HLA-B*1502* carriers may act on a similar pathogenetic mechanism, although other genetic/non-

genetic factor(s) may also contribute to the pathomechanism of the disease. Therefore, the aromatic antiepileptic drugs, including CBZ, OXC, and PHT, should be avoided in the *HLA-B*1502* carrier.³¹

The strong association between *HLA-B*1502* and CBZ-induced SJS/TEN in this study is in line with previous report in mixed population of neuropathic pain and epilepsy patients.¹⁰ Thus, by assuming the prevalence of CBZ-induced SJS/TEN in a Thai population as 0.27% as previously reported,¹¹ positive and negative predictive value were 1.43% and 99.98%, respectively. Owing to the above screening properties of this *HLA-B*1502* genotype test, it is very suitable to use as a screening tool for risk management.³² It should be performed prior initiation of CBZ and withholding CBZ from *HLA-B*1502*-positive patients. A recent report from Taiwan confirmed the benefit of this screening test in reducing the incidence of CBZ-induced SJS/TEN in their population.³³ Therefore, this test should be used in patients with Asian ancestry, especially Han Chinese, Malays, Burmese, South Asian Indians, and Thai. This recommendation is in line with recent U.S.-FDA black box warning for this medication.¹⁶

A recent retrospective study in Thailand has demonstrated that the screening costs would be less than SJS treatment costs if tests specific to the *HLA-B*1502* allele are used instead of testing the whole *HLA* or *HLA-B* genomes.³⁴ The PCR assay kit in this study is based on the detection of presence of PG1502 DNA without actual allelic information. As PCR technique is widely used and is available in several laboratories worldwide, this test is simple and less time-consuming (turnaround time of less than 3 hours) when compared with other HLA typing methods. In addition, it has been successfully used for detection in almost 5,000 patients before prescribing CBZ to prevent SJS/TEN in Taiwan.³³

In conclusion, *HLA-B*1502* is a strong genetic marker for CBZ-induced SJS/TEN in Thai patients with neuropathic pain. The screening for this marker should be performed prior to initiation of CBZ treatment. It will help clinician to assess the risk of this serious side effect in this population and patients with ancestry from with high frequency of *HLA-B*1502*, but not for Caucasian or Japanese.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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