Association of Oxcarbazepine-induced Cutaneous Adverse Drug Reactions with *HLA-B*15:02* Allele

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ABSTRACT

Objective: Oxcarbazepine (OXC) has similar structure and efficacy to carbamazepine (CBZ), but with fewer side effects. However, there have been only a few reports of serious cutaneous adverse reactions to OXC. *HLA-B*15:02*'s association with cutaneous adverse drug reactions (cADRs) induced by OXC is still inconsistent. This study investigated the incidence of cADRs that were induced by OXC and their association with the *HLA-B*15:02 allele* in Thais.

Methods: A retrospective cohort study of 494 patients receiving oxcarbazepine between January 2012 and January 2018 was undertaken. *HLA-B*15:02* testing had been carried out on 79 of the 494 patients.

Results: No incidents of serious cutaneous adverse reactions, Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) were found. A 2.4% (12/494) of OXC-related cADRs was determined. Four out of six patients with maculopapular eruptions (MPE) were *HLA-B*15:02* positive. Patients who had the allele potentially developed OXC-induced MPE, with an odds ratio of 6.58 (95% CI 1.11-39.15, p=0.040). Only a history of other antiepileptic drug (AED) allergies demonstrated a significant risk factor of OXC-induced MPE.

Conclusion: Our research demonstrated that the association between the *HLA-B*15:02 allele* and MPE induced by OXC was significant. Patients with a history of other AED allergies were also at risk of developing OXC-induced MPE.

Keywords: Antiepileptics; association; *HLA-B*15:02*; cutaneous adverse drug reactions; human leukocyte antigen; incidence; maculopapular eruption; oxcarbazepine; Stevens-Johnson syndrome (Siriraj Med J 2020; 72: 174-180)

INTRODUCTION

Carbamazepine (CBZ) and oxcarbazepine (OXC) are both aromatic antiepileptic drugs (AEDs). They are utilized extensively as treatments for epilepsy, bipolar disorder, some neuropathic pain conditions, particularly trigeminal neuralgia.[1] However, severe cutaneous adverse drug reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) occasionally occur with these AEDs. The reactions may lead to long-term sequelae and fatal outcomes. According to the US Food and Drug Administration (FDA), adverse events declared to the World Health Organization and CBZ producers reveal that the rate of SJS and TEN induced by CBZ can be ten-fold higher in some Asian countries (4.1-5.9 per 10,000 patient-years of exposure) than in Europe and the USA (0.2-0.9).[2]

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Although many studies have since identified a similar relationship between *HLA-B*15:02* and SJS/TEN induced by CBZ, the allele does not appear to be a universal marker for CBZ-induced SJS/TEN, but it seems to be ethnically specific, for example, Japanese and Caucasian populations did not have this relationship.[3,4] Also, an association between the allele and CBZ-induced maculopapular eruptions (MPE) has been inconclusive. To illustrate, Sukasem et al. calculated an Odds ratio of 7.27 (95% CI 2.04-25.97) in Thais[5] while Locharernkul et al. reported an Odds ratio of 1.21 (95% CI 0.21-6.99) in Thais[6] and Man et al. demonstrated an Odds ratio of 0.84 (95% CI 0.15-4.51) in Han Chinese.[7]

The strong correlation between the *HLA-B*15:02* allele in Han Chinese patients and SJS induced by CBZ was first reported by Chung et al. in 2004.[8] Subsequently, several case-control studies have since confirmed the finding in Han Chinese, Malaysians and Thais[5,6,9,10] and suggested that screening of patients for the allele should be conducted prior to prescribing CBZ.[4,11] If a positive result was obtained, they should not be treated with CBZ.[12]

Oxcarbazepine (OXC), a member of the aromatic AEDs, has a similar structure and efficacy to carbamazepine (CBZ) but fewer side effects. OXC is considered as an alternative AED, but allergic cross-reactions between CBZ and OXC occur in approximately 1 in 4 patients.[13] The incidence of OXC-induced cutaneous adverse drug reactions (cADRs) was 2.0-2.7%.[14,15] However, there have been only a few reports of serious adverse reactions to OXC, and the inter-relationship between the allele and cADRs induced by OXC in Thais is still controversial. Although a recent case-control study reported a significant association between the *HLA-B*15:02 allele* and OXC-induced SJS, the positive predictive value was only 0.73%.[16] In current practice, however, doctors usually avoid OXC in *HLA-B*15:02* positive patients who may benefit from the AED.

Our study aims were to ascertain the incidence of cADRs caused by OXC and their association with the *HLA-B*15:02 allele* in the Thai population.

MATERIALS AND METHODS

After protocol approval was obtained from the Institutional Review Board of Siriraj Hospital (Si 400/2017), a retrospective cohort study was conducted. We included 494 patients who had received OXC at Siriraj Hospital between January 2012 and January 2018. The research team reviewed the patients' demographic data and the histories of drug and substance allergies documented in their electronic medical records.

Diagnosis of oxcarbazepine-induced cutaneous adverse drug reactions

The diagnoses of OXC-induced cADRs were obtained from the Adverse Drug Reaction and Counselling Unit at the hospital and a manual search of the medical records. This was based on the patients' histories and the clinical morphology of their skin reported by the attending physicians and dermatologists. Diagnoses of SCARs were reached by consensus by the physicians and dermatologists; they were based on the presence of life-threatening skin reactions, as evidenced by full-thickness epidermal necrosis, extensive erythema, and bullous epidermal detachment accompanied by mucosal involvement. SJS was defined as involving a body surface area detachment of ≤ 10%, while SJS/TEN overlap involved 10-30% of body surface area and TEN involved ≥ 30%.[17] Diagnoses of a drug reaction with eosinophilia and systemic symptoms (DRESS) were established using the criteria and scoring system of the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group; the reactions included acute rash, fever, enlarged lymph nodes, systemic involvement of at least 1 internal organ, blood count abnormalities, eosinophilia, and lymphadenopathy.[18] MPE were defined as self-limited, diffuse, erythematous macules and papules without blistering or pustulation.[14] As the cADRs usually develop within 3 months after exposure to OXC, the OXC-induced cADRs were diagnosed when skin lesions were identified within 3 months after the first prescription of OXC.

HLA-B genotyping

With the cooperation of the Division of Medical Genetics, Siriraj Hospital, 79 patients who had had a genomic test for *HLA-B*15:02* and received OXC were identified. Genomic DNA was extracted by QIAGEN quick DNA prep according to the manufacturer's protocol. DNA quality was measured by spectrophotometry. A modified PCR-SSCP was performed using sequence specific primers to amplify *HLA-B*15:02* locus using Real-time PCR (PCRmax Eco48, UK) followed by melting curve analysis.[19] Both negative and positive controls were run in parallel. A positive melting curve peak at 91.4 degree Celsius was interpreted as the presence of *HLA-B*15:02*. A positive melting curve peak at 77 degree Celsius is used as an internal control of PCR reaction. This PCR-SSCP cannot distinguish *HLA-B*15:02* from *HLA-B*15:13* and *HLA-B*15:25*, both of which are rarely present in Thai population.

Statistical analysis

Based on a prescription-event monitoring study,

the sample size of at least 252 patients used in this study was calculated from a 95% confidence interval (CI) of the OXC-induced cADRs incidence of 2.7% with an allowable error of 2%.[15] Statistical analyses were conducted on SPSS for Windows, version 18 (SPSS Inc., Chicago, IL, USA). Patients' clinical and demographic data were presented as number (%) or mean ± SD. The *HLA-B*15:02 allele* test results were reported as positive or negative. The risk factors related to cADRs induced by OXC were analyzed with Fisher's exact test of independence and the unpaired t-test. The association strength was determined by employing the odds ratio and its 95% confidence intervals (95% CI). A two-sided *p*-value of < 0.05 was defined as being statistically significant.

RESULTS

A total of 494 patients (194 males; 300 females; mean age = 59.0 ± 18.7 years) who received OXC between January 2012 and January 2018 were reviewed. Only 79 had a genomic DNA test for *HLA-B*15:02*.

Table 1 summarizes the 494 patients' demographic data (age and gender) and clinical characteristics (body mass index, indication for OXC usage). Only a history of other AED allergies (including gabapentin, pregabalin, carbamazepine, phenytoin and sodium valproate) demonstrated a significant association with OXC-induced MPE (Table 2). One out of nine patients with CBZ allergy also developed OXC-induced cADRs.

We found that 12 out of the 494 patients had had OXC-induced cADRs; six patients had had a genomic test for *HLA-B*15:02*, while the other 6 had not. There were no reports of SCARs. As a result, the incidence of OXC-induced cADRs in this study was 2.4% (12/494).

Of the 79 patients who underwent genomic testing, 21 (26.6%) were positive for *HLA-B*15:02*. Four out of the six patients with OXC-induced cADRs were *HLA-B*15:02* positive, with a positive predictive value of 19% and a negative predictive value of 96.6%. Patients who had the allele potentially developed OXC-induced cADRs, having an odds ratio of 6.58 (95% CI 1.11-39.15, p = 0.040; Table 3). The sensitivity and specificity of the allele predicting OXC-induced cADRs were 66.6% and 76.7%, respectively.

The clinical characteristics of the 12 individuals with OXC-induced MPE are presented at Table 4. The OXC-induced cADRs patients aged from 21 to 84 years and maximal tolerable dose of OXC ranged from 150-1200 mg/day. The cADRs could occur as early as 2 days or up to 34 days after the first dose.

TABLE 1. Demographic and clinical characteristics of patients receiving oxcarbazepine (OXC).

Characteristics	N = 494
Gender	
Male	194 (39.3)
Female	300 (60.7)
Age (yr)	59.0 ± 18.7
Body mass index (kg/m^2)	25.1 ± 5.7
OXC indication	
Neuropathic pain	407 (82.4)
Epilepsy	30 (6.1)
Mood disorder	57 (11.5)
History of drug allergy	
Other drugs	123 (24.9)
Other AEDs	20 (4.0)

The data are presented as mean ± standard deviation or n (%).
Abbreviations: AEDs = antiepileptic drugs; OXC = oxcarbazepine

TABLE 2. Potential risk factors associated with OXC-induced cADRs.

Risk factors	Number of patients		Odds ratio	95% CI	*p*-value
	OXC-induced cADRs (N = 12)	OXC-tolerant (N = 482)			
Male	4 (33.3)	190 (39.4)	1.30	0.39-4.38	0.772
BMI	23.2 ± 4.9	25.1 ± 5.7	-	-	0.255
History of other drug allergies	4 (33.3)	119 (24.7)	1.53	0.45-5.16	0.504
History of other AED allergies	2 (16.7)	18 (3.73)	5.16	1.05-25.27	0.043*

The data are presented as mean ± standard deviation or n (%). *$p < 0.05$ was statistically significant

Abbreviations: AED = antiepileptic drug; BMI = body mass index; cADRs = cutaneous adverse drug reactions; CI = confidence interval; OXC = oxcarbazepine

TABLE 3. Association of the *HLA-B*15:02 allele* with OXC-induced cADRs.

HLA-B 15:02 allele*	Number of patients		Odds ratio	95% CI	Positive likelihood ratio	Negative likelihood ratio	*p*-value
	OXC-induced cADRs (N = 6)	OXC-tolerant (N = 73)					
Positive	4	17	6.58	1.11-39.15	2.86	0.43	0.040*
Negative	2	56					

The data are presented as n (%). *$p < 0.05$ was statistically significant

Sensitivity 66.6%; Specificity 76.7%; Positive predictive value 19%; Negative predictive value 96.6%

Abbreviations: cADRs = cutaneous adverse drug reactions; CI = confidence interval; OXC = oxcarbazepine

TABLE 4. Clinical characteristics of patients with OXC-induced MPE.

No.	Sex	Age	Indication	Maximum dose (mg)	*HLA-B*15:02*	Latency (days)	History of other drug allergies
1	F	84	Pain	900	Negative	30	No
2	F	54	Pain	1,200	Positive	28	No
3	M	44	Pain	300	Positive	4	No
4	M	32	Pain	450	Positive	14	No
5	F	52	Pain	900	Positive	14	Carbamazepine
6	M	21	Pain	150	Negative	3	No
7	F	35	Pain	1,200	NA	2	No
8	F	74	Pain	600	NA	NA	Actifed®
9	F	35	Pain	600	NA	9	No
10	F	39	Pain	300	NA	10	Phenytoin
11	F	43	Pain	600	NA	NA	No
12	M	64	Pain	900	NA	34	Ceftriaxone

Abbreviations: F = Female; M = Male; NA = not available

DISCUSSION

Oxcarbazepine is considered as an alternative AED, and there is evidence to suggest that it has a safer profile, and a better tolerance than CBZ. On the other hand, OXC and CBZ have an allergic cross-reaction of about 25%-30%.[13,20]

Incidence of OXC-induced cADRs in Thais

The present study found the overall incidence of OXC-induced cADRs was 2.4% (12/494), while that of SJS/TEN induced by OXC was 0% (0/494). The latter figure was comparable to that published in the 2016-version of the Thai-FDA's annual report on ADRs (the incidence of OXC-induced SJS/TEN was 0.02%). Moreover, this study's overall figure of 2.4% for OXC-induced cADRs was similar to the 2% incidence found in Han Chinese;[14] and the present study's figure of 0% for OXC-induced SJS/TEN was lower than corresponding figure reported in Taiwanese, which was 0.08% (8.26/10,000 new users).[16] The findings of the current study therefore confirm previous reports that the incidence of SCARs is lower with OXC than CBZ.

*Association between HLA-B*15:02 and OXC-induced cADRs*

The present research determined that there is a correlation between the *HLA-B*15:02 allele* in the Thai population and MPE induced by OXC, the odds ratio being 6.58 (95% CI 1.11-39.15; p = 0.040). A similar result, but not statistically significant, was found in a case-control association study by Hu et al.[21] (odds ratio 6.4; 95% CI 0.55-74.89; p = 0.294). We therefore suggest that if a Thai patient carries the allele, the attending physician should take the risk of OXC-induced MPE into consideration. The prescribing of alternative non-aromatic AEDs would be prudent; however, if OXC is prescribed, it should be done with caution, with the patient being informed about the risk of drug allergies and requested to closely observe for any symptoms to ensure the earliest detection of potential problems.

Nevertheless, two studies in Han Chinese population determined that the inter-relationship between the *HLA-B*15:02* allele and OXC-induced cADRs is not significant; rather, they identified two other genotypes (*HLA-B*1302*[14] and H*LA-B*3802*[22]) as risk factors. Similarly, a study by Moon et al.[23] demonstrated that two different genotypes, *HLA-B*40:02* and *HLA-DRBI*04:03*, are risk factors among Koreans. The results of those three studies show that different genomic types might be specifically associated with particular ethnic populations.

*Recommendation of HLA-B*15:02 testing prior to OXC prescription*

Many studies have found no correlation between *HLA-B*15:02* and SJS/TEN induced by OXC.[14,22,23] However, a recent prospective study reported that, in Han Chinese and Thais, the allele is significantly related to OXC-induced SJS/TEN (odds ratio 27.90; 95% CI 7.84-99.23, positive predictive value 0.73%).[16] This supports a concern of avoiding OXC for patients with *HLA-B*15:02* allele, although OXC-induced SJS/TEN is less severe and has a lower incidence than CBZ-induced SJS/TEN.[16] This advice may not be applicable for some populations as *HLA-B*15:02* is very commonly found in certain populations in Asia[3] (5.7%-14.5% in Han Chinese, 12%-15.7% in Malays and 15.9% in Thais[24]).

In addition, there have also been reports of an allergic cross-reaction between CBZ and OXC. In the present study, we found 1/9 case who had an allergy to CBZ and OXC, and who was *HLA-B*15:02* positive.

Regarding other predicting factors, a study by He et al.[14] found that a history of AED or non-AED allergies were strong predicting factors for OXC-induced cADRs, but especially an allergy to other AEDs (OR 121.23, 95% CI 3.99-3686.59, p = 0.005). However, our study found a significant association with only a history of other AED allergies (OR 5.16, 95% CI 1.05-25.27, p = 0.043), but not with a history of non-AED allergies (OR 1.53, 95% CI 0.45-5.16, p = 0.504).

Taking all this into consideration, OXC-induced cADRs have a minor impact on allergic patients, who can simply discontinue use of the drug. Given that the positive predictive value of the allele is only 19% for MPE and 0.73% for SJS/TEN[16], *HLA-B*15:02* test before prescribing OXC is still recommended in order to surveil SCARs. There may be patients who test positive to genomic testing but may still benefit from sodium channel blocking antiepileptics to treat their pain, such as those with trigeminal neuralgia and painful tonic spasm.[25] *HLA-B*15:02* has a high prevalence in Thai populations, so it is reasonable to prescribe OXC rather than CBZ with good patient-education, close monitoring of MPE and discontinue the drug immediately if a rash occurs.

Limitations

The incidence of OXC-induced cADRs may be higher than reported due to undocumented histories of rash or unclear medical records (which were excluded). Moreover, some individuals were lost to follow-up after receiving the drug, while others did not register at the

ADR center, resulting in their cases not being recorded in the hospital's electronic record system.

In addition, there has been no standard recommendation to test for *HLA-B*15:02* prior to prescribe OXC. The genomic testing is also costly and time-consuming, with the results taking 1-2 weeks to be reported. Therefore, only 79/494 patients had been tested for *HLA-B*15:02*.

This study also had too small a sample size to detect the incidence of SCARs induced by OXC. Thus, we support the conduct of a further study to establish the inter-relationship between the allele and OXC-induced cADRs/SJS/TEN/DRESS by using a larger sample size and a multicenter design in Thailand.

Our study demonstrated that the association between the *HLA-B*15:02 allele* and MPE induced by OXC is significant. Patients with a history of other AED allergies also had an increased risk of developing OXC-induced MPE. However, a larger sample size and multicenter study should be conducted.

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