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The risk of cutaneous adverse reactions among patients with the *HLA-A* 31:01* allele who are given carbamazepine, oxcarbazepine or eslicarbazepine: a perspective review

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Abstract: Carbamazepine is a drug that is widely used for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder. This drug is also known to cause cutaneous adverse drug reactions (cADRs) in up to 10% of patients. The recent progress in pharmacogenetics has revealed that human leukocyte antigen (HLA) genotypes are associated with a susceptibility to the cADRs caused by particular drugs. For carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis, very strong associations with *HLA-B*15:02* have been found mainly in patients of Southeastern Asian origin. In some countries, prescreening *HLA-B*15:02* allele has already been put to practical use as a biomarker to avoid the life-threatening adverse drug reactions. In this review, another risk factor for carbamazepine-induced cADRs is discussed, namely *HLA-A*31:01*. We compare the strength of the association between *HLA-A*31:01* and carbamazepine-induced cADRs based on reports for various ethnic populations; discuss the difference between the *HLA-A*31:01* and *HLA-B*15:02* biomarkers and the usefulness of prescreening *HLA-A*31:01* to detect patients at high risk for carbamazepine-induced cADRs; and refer to points that remain to be resolved.

Keywords: Biomarker, HLA genotype, hypersensitivity syndrome, Stevens–Johnson syndrome, toxic epidermal necrolysis

Introduction

Carbamazepine is one of most commonly prescribed drugs for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder. It is also known to be the most common inducer of cutaneous adverse drug reactions (cADRs). The clinical manifestations of cADRs caused by carbamazepine vary widely, ranging from a mild skin rash, such as maculopapular eruption (MPE) and erythema exsudativum multiforme (EEM) minor, to severe rashes such as EEM major, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS). SJS and TEN, with their characteristic mucosal and cutaneous disorders, including blisters, are considered to represent different severities of the same disease [Bastuji-Garin *et al.* 1993]. The most widely accepted classification for these two disorders is based on the degree of skin detachment expressed in terms of the percentage of body surface area affected. SJS is defined as an area of skin detachment that involves less than 10% of the body surface. SJS–TEN overlap is defined as an area of skin detachment that affects from 10% to less than 30% of the body surface. TEN is defined as a level of skin detachment of no less than 30%. DIHS and MPE are categorized as nonbullous cADRs [Naisbitt *et al.* 2003]. DIHS is a severe adverse reaction that leads to multiorgan failure and is hypothesized to be associated with the reactivation of herpesvirus 6 [Hashimoto, 2006]. DIHS has also been referred to as a drug reaction with eosinophilia and systemic symptoms (DRESS)

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or hypersensitivity syndrome (HSS). In this review, either DIHS or HSS is used according to the disease name used in the original article. Whereas MPE is a mild skin rash, SJS/TEN and DIHS are life-threatening adverse reactions. The incidences of SJS/TEN and DIHS are very low (two to three cases per million per year), but their mortality is very high (5–30%). SJS/TEN is currently understood to be reactions that involve cytotoxic CD8+ T cells, and DIHS and MPE are also believed to have immune etiologies [Naisbitt *et al.* 2003].

The occurrence of cADRs is a very significant problem, both for physicians and patients, because it is unpredictable and often leads to a discontinuation of treatment. However, recent studies have revealed that human leukocyte antigen (HLA) genotypes are linked to a predisposition to the cADRs induced by particular drugs, including carbamazepine, and these genotypes are thus thought to be promising biomarkers. In this review, the associations between *HLA-A*31:01* and cADRs induced by carbamazepine and its analogs are discussed.

HLA proteins

HLAs are a family of proteins that are involved in immune reactions by presenting antigens to T cells. HLA-A, -B and -C are categorized as class I molecules that are ubiquitously expressed on the surface of cells, including keratinocytes. HLA-DR, -DQ, and -DP are categorized as class II molecules that are expressed mainly on the surface of antigen-presenting cells, such as B cells, macrophages and dendritic cells. The genes for all the HLAs are on the short arm of chromosome 6 and are known to be highly polymorphic. For example, more than 1000 alleles of *HLA-A, -B* and *-C* have been identified to date [Robinson *et al.* 2011].

A brief introduction of associations of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis with HLA-B*15:02 and HLA-B75

Very strong associations between *HLA-B*15:02* and carbamazepine-induced SJS/TEN have been found among the Han Chinese in Taiwan [Hung *et al.* 2006; Chung *et al.* 2004], which were confirmed by various case–control studies of Southeastern Asian patients [Kulkantrakorn *et al.* 2011; Wang *et al.* 2011; Zhang *et al.* 2011; Tassaneeyakul *et al.* 2010; Mehta *et al.* 2009; Locharernkul *et al.* 2008; Man *et al.* 2007; Lonjou *et al.* 2006]. *HLA-B*15:02* is a member of the serotype HLA-B75. In addition to *HLA-B*15:02*, carriers of some HLA-B75 members, including *HLA-B*15:08, HLA-B15:11* and *HLA-B*15:21*, with carbamazepine-induced SJS/TEN have also been detected in Asian countries, including India, Thailand, Korea and Japan [Kaniwa *et al.* 2010; Tassaneeyakul *et al.* 2010; Mehta *et al.* 2009]. The involvement of HLA-B75 members in the development of SJS/TEN was suggested by an *in vitro* study using a cell line transfected with cDNAs of these alleles, which underwent lysis by cytotoxic T cells activated by carbamazepine through recognition by the T-cell receptor (TCR) [Wei *et al.* 2012]. Thus, HLA-B75 can be said to be a risk factor for carbamazepine-induced SJS/TEN in Asian individuals. It is noteworthy that *HLA-B*15:02* is a risk factor only for SJS/TEN but not for other phenotypes of cADRs, and is also restricted to patients of Asian origin.

Associations of carbamazepine-induced cADRs with HLA-A*31:01

As shown in Table 1, *HLA-A*31:01* was reported for the first time to have associations with carbamazepine-induced MPE/HSS, but not with SJS/TEN, in Han Chinese patients in Taiwan [p = 0.0022, odds ratio (OR) = 17.5, 95% confidence interval (CI) = 4.6–66.5] [Hung *et al.* 2006]. The sensitivity of *HLA-A*31:01* in Han Chinese patients with carbamazepine-induced MPE/HSS was 0.25. This was followed by a report by Kashiwagi and colleagues that allelic frequency of *HLA-A*31:01* in Japanese patients with carbamazepine-induced severe cADRs (n = 22 including four SJS cases) was significantly higher than in a general Japanese population (p = 0.0004, OR = 4.33 and sensitivity = 0.50) [Kashiwagi *et al.* 2008]. The following five studies listed in Table 1, including our unpublished data, also revealed the tendency of a high allelic or carrier frequency of *HLA-A*31:01* in both SJS/TEN and various other types of cADRs, including DIHS/HSS, EEM or MPE, compared with that in tolerant control patients or in general populations. It should be noted, however, that the p values are dependent on the sample sizes of the studies, and sometimes no significant differences were detected because of a small sample size. In a study with Korean patients, three of seven patients with SJS/TEN and 10 of 17 patients with HSS carried *HLA-A*31:01*, and the carrier frequency in the latter was significantly higher than in tolerant

Table 1. Association of *HLA-A*31:01* or A31 with carbamazepine-induced cutaneous adverse reactions.

cADR phenotypes	Ethnic groups	Carrier frequency		*p* value	Odds ratio	95% Confidence interval	Reference
		Case group	Tolerant control group				
SJS/TEN	Han Chinese in Taiwan	1/60	4/144	NS			Hung *et al.* [2006]
MPE/HSS		8/31	4/144	0.0021	12.17	3.6–41.2	
HSS		2/13	4/144	NS			
MPE		6/18	4/144	2.2E-03	17.5	4.6–66.5	
Severe cADRs*	Japanese	11/22	53/371[$]	0.0004[‡]	4.33	2.07–9.06	Kashiwagi *et al.* [2008]
All phenotypes	Japanese	45/77	54/420	1.1E-19	9.5	5.6–16.3	Ozeki *et al.* [2011]
DIHS		21/36	54/420	2.1E-09	9.5	4.6–19.5	
SJS/TEN		5/6	54/420	2.4E-04	33.9	3.9–295.6	
Others		19/35	54/420	4.7E-08	8	3.9–16.6	
All phenotypes	Japanese	10/15	5/33	< 0.001	11.2	2.668–47.105	Niihara *et al.* [2012]
SJS/TEN		1/3	5/33				
DIHS		8/9	5/33				
EEM/MPE		1/3	5/33				
SJS/TEN	Japanese	9/21	484/2878[$]	0.0047	3.7	1.55–8.86	Our data (unpublished)
SJS	Korean	3/7	7/50	NS			Kim *et al.* [2011]
HSS		10/17	7/50	0.001 (p_c = 0.013)	7.3	2.3–22.5	
SJS	European	5/12	10/257	8.0E-05	25.93	4.93–116.18	McCormack *et al.* [2011]
HSS		10/27	10/257	3.5E-08	12.41	1.27–121.03	
MPE		23/106	10/257	1.1E-06	8.33	3.59–19.36	
SJS	Children originating from various ethnicities and living in Canada	0/9	3/91	NS			Amstutz *et al.* [2013]
HSS		3/6	3/91	0.0025	26.36	2.53–307.89	
MPE		6/26	3/91	0.0037	8.57	1.67–57.50	

*Erythroderma maculopapular and nutiform, *n* = 6; erythroderma, *n* = 3; DIHS, *n* = 4; SJS, *n* = 2 and other drug eruptions, *n* = 7.
[$]General population
[‡]Allelic frequencies were compared.
cADR, cutaneous adverse drug reaction; DIHS, drug-induced hypersensitivity syndrome; EEM, erythema exsudativum multiforme; HSS, hypersensitivity syndrome; MPE, maculopapular eruption; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

controls or a general population [Kim *et al.* 2011]. The sensitivity of *HLA-A*31:01* in Korean patients with carbamazepine-induced SJS or HSS was 0.54 (13/24). In a study of Japanese patients conducted by Ozeki and colleagues, *HLA-A*31:01* was significantly associated with carbamazepine-induced DIHS, SJS/TEN and other types of skin rashes (sensitivity for all phenotypes = 0.58) [Ozeki *et al.* 2011]. In their study, an especially strong association was detected between SJS/TEN and *HLA-B*31:01*. In another Japanese study by Niihara and colleagues, eight of nine patients with carbamazepine-induced DIHS carried *HLA-A*31:01*, an association that was statistically significant (sensitivity for all phenotypes = 0.67) [Niihara *et al.* 2012]. We previously reported the involvement of *HLA-B*15:11* in the development of carbamazepine-induced SJS/TEN in Japanese patients [Kaniwa *et al.* 2010]. In our sample, 9 of 21 patients with carbamazepine-induced SJS/TEN carried *HLA-A*31:01*, and the association was statistically significant ($p = 0.0047$, OR = 3.7, 95% CI = 1.55–8.86; sensitivity = 0.43) (unpublished data). *HLA-A*31:01* was also reported to be a biomarker for various carbamazepine-induced cADRs in Europeans, ranging from a mild skin rash, such as MPE, to severe cADRs, including SJS/TEN, and the sensitivity of *HLA-A*31:01* for all phenotypes was 0.26 (38/145) [McCormack *et al.* 2011]. The situation that *HLA-A*31:01* is involved in various phenotypes of skin rash caused by carbamazepine in white patients was similar to those observed in Asian patients. A recently conducted case–control study including children living in Canada also detected significant correlations of *HLA-A*31:01* with carbamazepine-induced HSS and MPE, but there were no correlations with SJS [Amstutz *et al.* 2013]. In this study, three patients with SJS who were of Asian origin carried the *HLA-B*15:02* allele.

As mentioned above, the sensitivities of *HLA-A*31:01* observed in studies with Korean and Japanese patients ranged from 43% to 67%, and they were higher than those observed among Han Chinese in Taiwan and among Europeans (26% for both ethnic groups). However, the observed variation in association strengths of *HLA-A*31:01* with carbamazepine-induced cADRs among various ethnic groups was smaller than that in associations of *HLA-B*15:02* with carbamazepine-induced SJS/TEN. Yip and colleagues estimated a pooled OR of 9.5 (95% CI = 6.4–13.9) for the association of *HLA-A*31:01* with carbamazepine-induced cADRs among the studies with Korean, Japanese, Chinese and European patients [Yip *et al.* 2012].

Population allelic frequency of HLA-A*31:01 in various ethnic groups

The *HLA-A*31:01* allele in general populations varies among different ethnic groups [Kurose *et al.* 2012]. *HLA-A*31:01* is a common allele among Japanese individuals (allelic frequency 0.071–0.093). Its frequency is comparable among Korean individuals and white individuals (0.050, and 0.018–0.042 respectively) and is lower among Chinese in both mainland China and Taiwan (0.022 and 0.018 respectively). HLA-A*31:01 is a rare allele among African individuals, in whom its frequency is on average 0.01. There have been no reports on whether *HLA-A*31:01* is linked to carbamazepine-induced cADRs in African patients.

Comparison between HLA-B*15:02 and HLA-A*31:01 as risk factors for carbamazepine-induced cutaneous adverse drug reactions

Although, as mentioned above, the association between *HLA-B*15:02*/HLA-B75 and carbamazepine-induced SJS/TEN appears to be restricted to Asian patients, associations between *HLA-A*31:01* and carbamazepine-induced cADRs have been detected both in Asian and European patients. However, its associations with cADRs were rather weak compared with the associations between *HLA-B*15:02* and carbamazepine-induced SJS/TEN observed in Southeast Asian countries, for which the sensitivities were nearly 100%.

At first, the association of *HLA-A*31:01* was thought to be limited to carbamazepine-induced HSS or MPE, but not with SJS/TEN in Han Chinese populations. However, various case–control studies that were conducted independently in other Asian countries and in Europe showed significant correlations between *HLA-A*31:01* and the SJS/TEN caused by carbamazepine. Therefore, it can be concluded that *HLA-A*31:01* is involved in the onset of both SJS/TEN and nonbullous cADRs, such as HSS and MPE.

The mechanism by which small molecules such as drugs (<1000 Da) become antigenic and recognized by T cells has not been elucidated. Two major concepts have been proposed [Adam *et al.* 2011]. One is the hapten/prohapten concept, and

the other is the p-i concept (pharmacological interactions of drugs with immune receptors). β-Lactam antibiotics have been shown to bind covalently to lysine residues of serum albumin as a hapten, and peptides modified with a hapten, which are generated by intracellular processing, embedded in HLA molecules are considered to be presented by antigen-presenting cells to TCRs (hapten concept) [Monshi *et al.* 2013; Jenkins *et al.* 2009]. Using a cell line transfected with *HLA-B*15*, Wei and colleagues showed that HLA-B75 members, including *HLA-B*15:02* and *HLA-B*15:11* proteins, promoted cell lysis by cytotoxic T cells that had been activated by carbamazepine [Wei *et al.* 2012]. In contrast, members of other serotypes of *HLA-B*15*, such as HLA-B62 and HLA-B72, cannot promote cell lysis by cytotoxic T cells activated by carbamazepine. The 63rd amino acid (the next amino acid of putative carbamazepine binding site) of members of serotype HLA-B75 is asparagine, whereas that of serotypes HLA-B62 or HLA-B72 is glutamic acid. Thus, carbamazepine is bound noncovalently to the HLA-B75 molecules, and the TCR recognizes its complex for T-cell activation (p-i concept). In addition to the specific HLA allele, *HLA-B*15:02*, a skewed usage of specific repertoires of the third complementarity-determining region of the TCR, such as VB-11-ISGSY, is reported to be required to develop carbamazepine-induced SJS/TEN [Ko *et al.* 2011].

To date, no information has been available on the pathogenic mechanisms of *HLA-A*31:01* molecules inducing hypersensitive reactions to carbamazepine (or its metabolites), including mechanisms of antigen presentation and TCR recognition. The pathogenesis for the HLA-A*31:01 molecule may be different from that for HLA-B*15:02 molecules, because *HLA-A*31:01* is linked not only to SJS/TEN but also to various phenotypes of cADRs. The diverging points for such clinical manifestations should be clarified.

The alleles *HLA-A*31:01* and *HLA-B*15:11* were found exclusively in each case of our Japanese patients (our unpublished data) and of Korean patients [Kim *et al.* 2011]. Unlike other ethnic groups, either *HLA-A*31:01* or *HLA-B*15:11* can be said to be a risk factor for carbamazepine-induced SJS/TEN in Korean and Japanese individuals because more than half of the patients with carbamazepine-induced SJS/TEN in these countries carry either of the alleles (6/7 in Korean patients and 14/21 in Japanese patients) [Kim *et al.* 2011] (our unpublished data). Therefore, the combined biomarkers may be of use to detect patients at high risk of carbamazepine-induced SJS/TEN in Korean and Japanese individuals.

Cutaneous adverse drug reactions caused by oxcarbazepine and eslicarbazepine

Oxcarbazepine and eslicarbazepine, which are metabolized differently from carbamazepine, have been developed to avoid the severe adverse reactions caused by carbamazepine. Oxcarbazepine was approved in 2007 in the USA and eslicarbazepine was approved in 2009 in Europe. Although SJS/TEN cases caused by oxcarbazepine were fewer than those caused by carbamazepine [Buggy *et al.* 2010; Dogan *et al.* 2008; Le Louët *et al.* 2008], there have been many reports of oxcarbazepine-caused severe cADRs. To date, two studies with Chinese patients have pointed out the involvement of *HLA-B*15:02* in oxcarbazepine-induced SJS/TEN [Hu *et al.* 2011; Hung *et al.* 2010]; however, another study with Chinese patients detected no significant correlation between the disease and this allele [He *et al.* 2012]. There have been no reports concerning the involvement of *HLA-A*31:01* in oxcarbazepine-induced SJS/TEN. Since eslicarbazepine, which is the active metabolite of oxcarbazepine, was approved only quite recently, reports on severe cADRs have not been accumulating.

Usefulness of prescreening HLA-A*31:01

On the basis of the knowledge obtained from various retrospective case–control studies with Southeastern patients [Kulkantrakorn *et al.* 2011; Wang *et al.* 2011; Zhang *et al.* 2011; Tassaneeyakul *et al.* 2010; Mehta *et al.* 2009; Locharernkul *et al.* 2008; Man *et al.* 2007; Hung *et al.* 2006; Lonjou *et al.* 2006; Chung *et al.* 2004] and a positive result obtained from a prospective case–control study performed in Taiwan to examine the usefulness of prescreening the risk factor [Chen *et al.* 2011], the screening for *HLA-B*15:02* prior to the initiation of carbamazepine treatment is currently mandatory in Taiwan and Singapore, and for patients in the USA who have ancestry at high risk for carbamazepine-induced SJS/TEN.

For *HLA-A*31:01*, Yip and colleagues [Yip *et al.* 2012] examined the usefulness of prescreening by a meta-analysis, using data obtained from three studies [McCormack *et al.* 2011; Ozeki *et al.*

2011; Hung *et al.* 2006]. The performance characteristics of *HLA-A*31:01* for Han Chinese, Japanese and European patients estimated by Yip and colleagues are as follows: sensitivity 0.262–0.584; specificity 0.871–0.972; positive predictive value 0.119–0.427; and negative predictive value 0.921–0.986. In every ethnic group, the number of patients needing to be tested in order to prevent one case (NNT) was estimated at less than 100, which was much smaller than the NNT (461) for screening *HLA-B*15:02* for Taiwanese individuals [Yip *et al.* 2012]. This difference may be caused by the fact that *HLA-B*15:02* is linked only with the rarer, but more severe cADRs, SJS/TEN, whereas *HLA-A*31:01* is linked even with frequently occurring mild skin rashes, such as MPE, as well as with SJS/TEN. The usefulness of *HLA-A*31:01* prescreening should be further discussed taking several points into consideration: the clinical impact of avoiding mild skin reactions, alternative drugs for *HLA-A*31:01*-positive patients and cost-effectiveness of the prescreening test. The results of an ongoing prospective study on the effects of a *HLA-A*31:01* prescreening test for prevention of carbamazepine-induced cADRs conducted in Japan by a Riken group (M. Kubo, http://www.biobankjp.org/pgx/outline/cbz.html) would have much impact on this issue.

Because HLA genotyping methods currently being used in clinical laboratory testing are laborious, time consuming and expensive, a more inexpensive, simple and rapid genotyping method is required for prescreening *HLA-A*31:01*. A new, simple and rapid pharmacogenetic test for detecting *HLA-A*31:01* was developed, which uses the InvaderPlus (Hologic, Inc., Bedford, MA, USA) assay and surrogate single-nucleotide polymorphisms that were found by a genome-wide association study to be highly linked with *HLA-A*31:01* [Aoki *et al.* 2012]. Uchiyama and colleagues developed another simple and inexpensive method for the detection of *HLA-A*31:01*, using a nested *HLA-A* allele-specific primer polymerase chain reaction combined with restriction fragment length polymorphism analysis [Uchiyama *et al.* 2013].

Conclusion

Unlike the case of HLA-B**15:02, HLA-A*31:01* is a risk factor for various types of carbamazepine-induced cADRs, ranging from mild ones such as MPE to severe ones, including SJS/TEN and DIHS, in both Asian and white patients. The pathogenesis of *HLA-A*31:01* involvement in the development of cADRs remains to be elucidated, which could help discriminate rashes that are likely to progress from those that are likely to resolve.

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Conflict of interest statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflict of interest to disclose.

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