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Carbamazepine, *HLA-B*1502* and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations

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Abstract

Recently, the USA FDA has made a labeling change to the drug information contained in carbamazepine. Owing to recent data implicating the *HLA* allele *B*1502* as a marker for carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese, the FDA recommends genotyping all Asians for the allele. This allele is seen in high frequency in many Asian populations other than Han Chinese, but there are few data on whether the allele is a marker for this severe outcome in anyone other than Han Chinese. In fact, the association has not been found in Caucasian patients. We review the data that prompted this recommendation, list data for other ethnic groups, both Asian and non-Asian, and briefly discuss the implication of this recommendation for clinical practice.

Keywords

carbamazepine; genotype; human leukocyte antigen; pharmacogenetics; Stevens–Johnson syndrome; toxic epidermal necrolysis

The US FDA has been conducting systematic evaluations of pharmacogenetic predictors for previously approved medications. The past 4 years have seen pharmacogenetic information included into the prescribing information (so-called ‘package insert’) for 6-mercaptopurine, azathioprine, irinotecan and warfarin. The FDA Committee on Clinical Pharmacology has recommended similar changes for tamoxifen. On 12 December 2007, the FDA released a warning to health professionals and patients that serious and potentially fatal skin reactions may occur with the administration of carbamazepine in patients positive for the *HLA-B*1502* allele [101]. In addition, the FDA recommended genetic screening for patients of Asian ancestry before initiation of carbamazepine therapy. We review the data upon which this decision was made and offer insight into some of the factors limiting these data.

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Background

Carbamazepine is an important treatment for seizure disorders, bipolar disorder, trigeminal neuralgia and chronic pain. However, carbamazepine is also associated with hypersensitivity reactions that range from benign urticaria to life-threatening cutaneous disorders, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1–3]. The latter two disorders carry a mortality that can be as high as 30% and require early diagnosis, with prompt withdrawal of all suspected potential causative drugs. While SJS and TEN occupy the ends of a continuous clinical spectrum, SJS, overlap SJS/TEN, and TEN are three distinct diagnoses. Each presents with erythematous or purpuric macules or flat atypical targets with less than 10% (SJS), 10−30% (overlap SJS/TEN) and greater than 30% (TEN) detachment of body surface area (BSA). A similar condition, TEN without spots, presents with epidermal detachment greater than 10% BSA, but no macular lesions [4]. Gastrointestinal and tracheobronchial epithelial involvement may lead to increased mortality, while immunologic and epidermal disruption often lead to infection and sepsis [5]. Treatment of these conditions requires admission to an intensive care unit or burn center, but no single treatment modality has been shown to be clearly most effective [6]. Pharmacologic therapies aimed at altering the immune response, such as corticosteroids, ciclosporin and intravenous immunoglobulin, are most often employed [7].

Increased risk with *HLA-B*1502* allele

Chung *et al.* were the first to identify an association between carbamazepine-induced SJS/TEN and *HLA-B*1502* [8]. This case–control analysis included 44 (out of 73 reported) cases of carbamazepine-induced SJS/TEN (carbamazepine-SJS/TEN) in Taiwan between 1996 and 2003 and compared genotyping data for 157 SNPs in CYP genes as well alleles of the *HLA-A, -B, -C* and *DRB1* genes. The patients were all Han Chinese living in Taiwan during this time, while 101 carbamazepine-tolerant (at least 3 months of use with no adverse reactions) and 93 samples of randomly selected, biobanked DNA from normal, healthy individuals served as study controls. The authors reported that all 44 (100%) were positive for the *HLA-B*1502* allele, while only three (3%) carbamazepine-tolerant and eight (8.6%) normal controls had the allele. The odds ratio for developing carbamazepine-induced SJS/TEN if positive for *HLA-B*1502* was 2504 (95% CI: 126−49,522) and a corrected p-value (p_c) of 3.13×10^{-21}.

In 2006, these authors added 16 new cases, all Chinese descent, with carbamazepine-SJS/TEN and reported that 59 out of 60 were positive for the *HLA-B*1502* allele, while the one subject without *HLA-B*1502* was positive for another B15 allele, *HLA-B*1558* [9]. Reported odds ratio and p_c were 1357 (95% CI: 193.4−8838.3) and 1.6×10^{-21}, respectively. In addition, a report has been published by Man *et al.* that highlights, among others, four Han Chinese patients who had SJS/TEN when exposed to carbamazepine. All four were positive for *HLA-B*1502* [10].

HLA-B*1502 *as a screening test in Han Chinese*

These data suggest that Han Chinese who have the *HLA-B*1502* allele are at a much increased risk of developing SJS/TEN when exposed to carbamazepine. Assuming a 0.25% incidence of carbamazepine-SJS/TEN in newly prescribed carbamazepine patients in Taiwan [9] and a 3% false-positive rate for *HLA-B*1502*, the estimated performance would be 98.3% sensitivity, 97% specificity, 7.7% positive predictive value and 100% negative predictive value. Given the fact that one would detect 98.3% of the one case in every 400 people, the number needed to

[101] Websites
US FDA: 2007 Safety Alerts for Drugs, Biologics, Medical Devices, and Dietary Supplements (2008) www.fda.gov/medwatch/safety/2007/safety07.htm#carbamazepine

screen is 407 people, with subsequent carbamazepine avoidance, to prevent one case of SJS/TEN. As they were obtained from a case–control study, all of these data are estimated values, not actual ones, although it is probably not practical to expect observational data for such a rare outcome as SJS/TEN.

Testing in non-Chinese Asians

Although no published data have yet confirmed such a strong correlation of *HLA-B*1502* and carbamazepine-SJS/TEN in non-Chinese Asians, the relatively high incidence of *HLA-B*1502* in many Asian populations has resulted in the FDA's decision to recommend testing for all Asians. In India, several reports have implicated carbamazepine as among the most common causes for SJS/TEN [3,11,12]. Similarly, studies in Singapore and Malaysia have reported carbamazepine as the most common cause of SJS/TEN, accounting for 27.7 and 35.7% of cases, respectively [13,14]. However, Thailand has reported much lower proportions of SJS/TEN being caused by carbamazepine [15]. Prevalence of the *HLA-B*1502* allele in Asian populations is also much higher than in Caucasian and African populations (Table 1).

Non-Asian concerns

In Caucasians, at least two studies have failed to show a correlation between *HLA-B*1502* status and carbamazepine-SJS/TEN [16,17]. In the first study, the authors report that none of the 56 patients with carbamazepine-associated cutaneous reactions had *HLA-B*1502* [16]. However, there were only two cases of SJS/TEN (one SJS, one TEN), with the remaining patients having other classifications of cutaneous reaction. This is important, as the Taiwanese study only found a strong genetic correlation in carbamazepine-SJS/TEN and no other carbamazepine-induced severe cutaneous reactions [9]. Therefore, this study may only highlight the relative rarity of both the allele and outcome in question. The second study investigated 12 cases of carbamazepine-SJS/TEN taken from a larger European study on SJS/TEN, the European Registry of Severe Cutaneous Reactions (RegisSCAR) [17]. Only four of these were positive for the *HLA-B*1502* allele, but all four of them had Asian ancestry. These authors concluded that perhaps ethnicity has an important effect on the penetrance of the allele in question. Based on the lack of evidence and relative infrequency of *HLA-B*1502* in those with non-Asian ancestry, genotypic screening for *HLA-B*1502* in non-Asian patients is of little apparent value.

Class effect or drug specific?

Oxacarbazepine has a highly similar chemical structure to carbamazepine and is used to treat many of the same clinical indications. However, whether there is a similar genetic predisposition to SJS/TEN is unclear. Although cross-reactivity for skin reactions from the two drugs has been reported to occur in one in four patients, a small case series (n = 3) demonstrated the need to proceed cautiously when using oxacarbazepine for already carbamazepine-intolerant patients [18]. In three consecutive patients, all had skin reactions with exposure to a low dose of oxacarbazepine. For this reason, oxacarbazepine is not likely to be a good choice when prescribing for patients who are *HLA-B*1502* positive. Geno-typing before primary oxacarbazepine treatment has neither been recommended nor studied.

Conclusion

Current recommendations for genotyping all Asian patients are based on a strong correlation between *HLA-B*1502* and carbamazepine-SJS/TEN in Han Chinese. Importantly, there is a wide access to high-resolution HLA typing within the USA and other developed countries. The relative lack of information regarding the correlation in both Asian population groups who have a high frequency of *HLA-B*1502* should prompt further investigation. Given the

availability of other effective medications for similar indications, it is likely prudent to avoid carbamazepine when patients have tested positive, despite the low estimated positive predictive value of the test.

Future perspective

Further study in this field should take a three-pronged approach. First, robust clinical studies that include large cohorts of carbamazepine-exposed patients are needed, particularly in non-Asian patient populations. This will be possible through the creation of patient drug registries. Second, immunological investigation, which is currently underdeveloped, detailing the molecular mechanisms responsible for precipitating severe skin reactions would pave the way for novel treatments or preventive measures for these serious, debilitating clinical disorders. There has been little more than theoretical explanation in this field as yet. Moreover, these are complex problems with multifactorial causes; therefore, our investigation should be wide-ranging and thorough. Third, genetic risk factors for hypersensitivity reactions and other life-threatening conditions related to a variety of drugs should be investigated. Other drugs and alleles have already been implicated, including abacavir and allopurinol, and more should be assessed [19,20].

Executive summary

- Carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis is an uncommon, but severe, occurrence.
- Recent recommendations by the US FDA include genotyping for all Asian carbamazepine patients before therapy.
- The *HLA-B*1502* allele is highly associated with the outcome of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis.
- This association has been found mostly in the Han Chinese, but not in Caucasian patients.
- The recommendation for testing other Asians groups is the relatively high incidence of *HLA-B*1502*.
- Future directions in this field include prospective screening studies and more genotyping of patients who have already experienced the outcome.

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Table 1

*HLA-B*1502* frequencies in major populations.

Continent	Population/ethnicity	Allele frequency (%)	n
North America	Asian	5.1	396
	African	0.2	251
	European	0	287
	Hispanic	0	240
	Native American	0	235
Asia	Korean	0.5	200
	Han Chinese	10.2	572
	Singapore	11.6	86
	Malay	8.4	101
	Thai	6.1	99
	Filipino	5.3	94
	India Mumbai Marathas	1	72
	India North Hindi	2	91
	India Khandesh Pawra	6	50

Data obtained from [102,103].

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[103]International Histocompatibility Working Group www.ihwg.org