Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions

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Summary

Objective: **To systematically review evidence on genetic risk factors for carbamazepine (CBZ)–induced hypersensitivity reactions (HSRs) and provide practice recommendations addressing the key questions: (1) Should genetic testing for HLA-B*15:02 and HLA-A*31:01 be performed in patients with an indication for CBZ therapy to reduce the occurrence of CBZ-induced HSRs? (2) Are there subgroups of patients who may benefit more from genetic testing for HLA-B*15:02 or HLA-A*31:01 compared to others? (3) How should patients with an indication for CBZ therapy be managed based on their genetic test results?**

Methods: **A systematic literature search was performed for HLA-B*15:02 and HLA-A*31:01 and their association with CBZ-induced HSRs. Evidence was critically appraised and clinical practice recommendations were developed based on expert group consensus.**

Results: **Patients carrying HLA-B*15:02 are at strongly increased risk for CBZ-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in populations where HLA-B*15:02 is common, but not CBZ-induced hypersensitivity syndrome (HSS) or maculopapular exanthema (MPE). HLA-B*15:02–positive patients with CBZ-SJS/TEN have been reported from Asian countries only, including China, Thailand, Malaysia, and India. HLA-B*15:02 is rare among Caucasians or Japanese; no HLA-B*15:02-positive patients with CBZ-SJS/TEN have been reported so far in these groups. HLA-A*31:01–positive patients are at increased risk for CBZ-induced HSS and MPE, and possibly SJS/TEN and acute generalized exanthematous pustulosis (AGEP). This association has been shown in Caucasian, Japanese, Korean, Chinese, and patients of mixed origin; however, HLA-A*31:01 is common in most ethnic groups. Not all patients carrying either risk variant develop an HSR, resulting in a relatively low positive predictive value of the genetic tests.**

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Significance: This review provides the latest update on genetic markers for CBZ HSRs, clinical practice recommendations as a basis for informed decision making regarding the use of HLA-B*15:02 and HLA-A*31:01 genetic testing in patients with an indication for CBZ therapy, and identifies knowledge gaps to guide future research.

KEY WORDS: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Maculopapular exanthema, Drug-induced hypersensitivity syndrome, Rash, Pharmacogenetic testing.

Carbamazepine

Carbamazepine (CBZ) belongs to the class of aromatic antiepileptic drugs (AEDs). It is approved for the treatment of epilepsy and trigeminal neuralgia,[1] and in some countries also for acute mania or prophylaxis in bipolar disorders.[2] Recently updated clinical practice guidelines for the treatment of epilepsy recommend CBZ as first-line treatment for focal seizures in adults, adolescents, and children, and also as drug for consideration in the treatment of general tonic–clonic seizures.[3,4]

Carbamazepine acts by blocking voltage-dependent sodium channels in neurons.[5,6] It preferably binds to the inactive conformation of these channels, slowing down their reactivation. Through this mechanism, CBZ reduces the frequency of repetitive firing of action potentials, and thus prevents abnormal activity of neurons in the brain.[5,6]

Carbamazepine-Induced Hypersensitivity Reactions

Carbamazepine-induced hypersensitivity reactions (HSRs) are dose-independent immune-mediated adverse reactions that most frequently involve the skin. They occur in approximately 5–10% of patients receiving CBZ.[7] Most of these reactions are relatively mild, such as erythematous maculopapular rash (maculopapular exanthema, MPE), and erythema multiforme (EM). Nevertheless, in addition to the discomfort caused to patients, these reactions frequently require the discontinuation of CBZ, thereby prolonging treatment of the underlying disorders. Rarely, CBZ-induced HSRs occur that are severe and life-threatening, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), the drug-induced hypersensitivity syndrome (HSS), and acute generalized exanthematous pustulosis (AGEP).[8]

SJS and TEN are characterized by extensive detachment of the epidermis and severe erosions of mucous membranes. Previously described as two different drug reactions, they are now considered variants of the same pathologic process, with TEN being the more severe form.[9] SJS and TEN are differentiated by the extent of skin detachment (SJS: <10%; SJS/TEN overlap: 10–30%; TEN: >30% of the body surface area).[8,10,11] HSS is characterized by a major organ manifestation (most frequently the skin), fever, and involvement of at least one other organ system (frequently the liver or kidney).[8,10,11] Hematologic abnormalities such as eosinophilia and atypical lymphocytosis, and lymph node enlargement are also common in patients with HSS. HSS is also known as drug reaction with eosinophilia and systemic symptoms (DRESS), drug-induced delayed multiorgan hypersensitivity, or drug-induced hypersensitivity syndrome (DIHS). AGEP involves an acute widespread pustular eruption, accompanied by neutrophilia and fever.[8]

Although rare, with an incidence of 1–10 per 10,000 patients taking CBZ,[12,13] SJS/TEN and HSS are among the most severe and life-threatening adverse drug reactions, associated with very high morbidity and mortality (up to 10% for SJS and HSS, and up to 50% for TEN).[9,14,15] All CBZ-induced HSRs addressed in this evidence review are considered delayed reactions because their onset is usually several days after the first dose of the drug was taken.[16] In contrast to milder HSRs (e.g., MPE), the time to onset of SJS/TEN and HSS is more delayed, with symptoms typically occurring after 1–3 weeks for SJS/TEN, and 4–8 weeks for HSS.[8] In cases where prior sensitization has occurred (secondary exposure or re-challenge), the time to onset of the reaction can be shorter.

The mechanisms underlying CBZ-induced HSRs are largely unknown, and there are several hypotheses to explain the molecular events that lead from drug exposure to a hypersensitivity response.[16,17] Cellular death (apoptosis and necrosis) of keratinocytes in the skin is an important factor in the epidermal destruction and detachment of skin in SJS/TEN,[18] but is not seen in other CBZ-induced HSRs. The generation of reactive drug metabolites in the skin and oxidative stress may also contribute to the development of SJS/TEN.[18] All CBZ-induced HSRs appear to be immune-mediated through an interaction of the drug or a drug-related compound with immune receptors of the major histocompatibility complex (MHC), which results in stimulation of immune cells such as T cells (T lymphocytes) and eosinophils (eosinophil granulocytes).[16,19]

Genetic Risk Variants for Carbamazepine Hypersensitivity

Two genetic risk variants for CBZ-induced hypersensitivity reactions have been identified: HLA-B*15:02 (first reported in 2004) and HLA-A*31:01 (first reported in 2006).[7,20] The scientific evidence underlying the association of these genetic variants with CBZ hypersensitivity is reviewed and summarized below. HLA-A*31:01 and HLA-B*15:02 are specific variants (alleles) of the human leukocyte antigen (HLA) *HLA-A* and *HLA-B* genes, respectively, encoding for MHC proteins. The HLA genes are diverse and each have many different alleles. Therefore, each person has a unique combination of different MHC molecules on the surface of their cells, a MHC "fingerprint" that allows the immune system to differentiate between cells that are from a person's own body ("self") or foreign ("nonself").

The exact mechanism of how carrying HLA-B*15:02 or HLA-A*31:01 results in an increased risk of CBZ hypersensitivity is not clear. It is thought that the MHC molecules encoded by these particular HLA alleles interact with CBZ or a CBZ-derived molecule in a way that they are recognized by T cells as "nonself," which triggers an immune reaction.

Scope and Purpose

This review with clinical practice recommendations is intended to provide a basis for informed decision-making regarding genetic testing to identify patients at increased risk of developing CBZ-induced HSRs. The intentions were the following: (1) to present neurologists, primary care physicians, and other health care providers with the latest update on genetic markers that identify patients who are at increased risk of CBZ-induced HSRs; (2) to provide comprehensive evidence-based recommendations regarding genetic testing in patients with an indication for CBZ therapy; and (3) to identify gaps in knowledge and prioritize future research activities. Of importance, the recommendations provided should never be regarded as imperative. Instead, they should be interpreted individually in the context of the unique clinical circumstances for each patient.

The following key questions were addressed:

1. Should genetic testing for HLA-B*15:02 and HLA-A*31:01 be performed in patients with an indication for CBZ therapy prior to therapy initiation, in order to reduce the occurrence of CBZ-induced HSRs?
2. Are there subgroups of patients who may benefit more than others from genetic testing for HLA-B*15:02 or HLA-A*31:01 prior to initiation of CBZ therapy?
3. How should patients with an indication for CBZ therapy be managed based on their genetic test results for HLA-B*15:02 and HLA-A*31:01?

Supporting Evidence

HLA-B*15:02: SJS/TEN

A strong association of HLA-B*15:02 with CBZ-induced SJS/TEN has been shown in all retrospective case–control studies carried out in populations where HLA-B*15:02 is common with a carrier frequency of >1% (Chinese, Thai, Indian, Malaysian; Tables S1 and S2). These studies have consistently reported that 72–100% of patients with CBZ-induced SJS/TEN carried HLA-B*15:02, whereas this allele was observed in only 4–19% of patients who tolerated CBZ (Table S1). A majority of studies were carried out in Han Chinese patients (Taiwan Han Chinese,[21] Central China,[22,23] Hong Kong Han Chinese,[24,25] Southern China[26–29]) with a total of 144 investigated CBZ-induced SJS/TEN cases. Large case–control studies were also reported from Thailand (61 CBZ-SJS/TEN cases),[30–33] whereas studies in Indian[34–36] and Malaysian[34,37] patients included smaller numbers (29 and 20 CBZ-SJS/TEN cases, respectively). A recent meta-analysis synthesized association studies in Chinese, Thai, and Malaysian patients, reflecting this strong association with odds ratios of 236 (95% confidence interval 72–778), 55 (18–168), and 221 (4–12,695), respectively.[38]

In populations where HLA-B*15:02 is rare (carrier frequency <1%; Europeans, Japanese), retrospective case–control studies did not observe any carriers of this variant in 32 investigated patients with CBZ-SJS/TEN (Table S1). Similarly, in a study in Korean patients, where the carrier frequency is similar to the Japanese population, only one of seven patients with CBZ-SJS/TEN was positive for HLA-B*15:02.[39] However, as the variant was also not observed in >158 CBZ tolerant patients in these populations, these negative findings are most likely attributed to the absence of the risk allele in the overall population, and therefore do not add uncertainty to the overall evidence for an association of HLA-B*15:02 with CBZ-SJS/TEN. The overall evidence for an increased risk in carriers of this variant to develop CBZ-SJS/TEN is therefore classified as strong (++++ evidence; Table 1).

Individual cases of CBZ-SJS/TEN patients positive for HLA-B*15:02 have been reported with origins from Vietnam, Cambodia, Reunion Island, and Sri Lanka, suggesting the presence of the risk allele in these populations. In Vietnam, the carrier frequency for HLA-B*15:02 is estimated to be 23% (Table S2), suggesting a high relevance of the risk allele in this population.

No studies were retrieved assessing HLA-B*15:02 in patients of other ethnic origins, except for one study in Canadian children of mixed origin, which included two patients with CBZ-SJS/TEN from the Caribbean (Table S1). Both children did not carry HLA-B*15:02, which is in agreement with very low carrier frequencies suggested for African and African American populations (Table S2). Of importance, population frequency data for HLA-B*15:02

Table 1. Grading scheme used for critical appraisal of evidence

Grade	Results	Description
++++	Consistent, generalizable, based on high quality studies	Strong general conclusions can be drawn that are unlikely to change based on further research
+++	Consistent, but limited quantity or quality of studies, limiting generalizability	Evidence allows general conclusions, but with reduced confidence; further research is likely to have an important impact on confidence in conclusions
++	Inconsistent or insufficient quantity/quality, encouraging	No general conclusions can be drawn or conclusions are likely to change based on further research, but current evidence is encouraging
+	Inconsistent or insufficient quantity/quality, discouraging	No conclusions can be drawn or conclusions are likely to change based on future studies, and current evidence is discouraging

suggest high HLA-B*15:02 carrier frequencies and thus a high relevance of this risk variant for the Filipino (34%) and Indonesian (15–21%) populations (Table S2). In agreement with the frequency differences of HLA-B*15:02 in different populations, the incidence of CBZ-SJS/TEN has been reported to be higher in populations where HLA-B*15:02 is common.[40]

One study in Taiwan Han Chinese patients so far has applied prospective genotyping before initiation of CBZ therapy.[41] In this study, 4,855 patients were screened for HLA-B*15:02, of whom 372 were HLA-B*15:02 positive, and 367 subsequently did not take CBZ. No cases of SJS/TEN were observed. Compared to the historical incidence of SJS/TEN in the same population, it was estimated that 10 CBZ-SJS/TEN cases were prevented with the genetic test.

HLA-B*15:02: MPE, HSS

Four studies in Han Chinese[21,23,26,42] and one study in Thai patients[30] consistently did not show an association of HLA-B*15:02 with milder CBZ-induced cutaneous reactions, broadly classified as MPE (see Glossary in the Supporting Information, Data S1). In all studies, the frequency of HLA-B*15:02 was found to be similar to the frequency observed in CBZ-tolerant patients.

Four studies investigated HLA-B*15:02 in patients with CBZ-HSS. No carriers of HLA-B*15:02 were observed in 13 Han Chinese HSS cases,[21] in 17 Korean HSS patients,[39] and in 29 Japanese HSS patients.[43] Furthermore, a similar frequency of HLA-B*15:02 compared to CBZ tolerant controls was observed in a combined sample of 21 MPE and HSS cases in another Han Chinese study.[42] Whereas the absence of HLA-B*15:02 carriers in Korean and Japanese patients can be attributed to the low carrier frequency of the allele in the general population, the absence of carriers among Chinese patients with CBZ-HSS provides evidence that HLA-B*15:02 is not associated with an increased risk for CBZ-HSS.

Current findings therefore consistently suggest that HLA-B*15:02 is a risk variant specific to SJS/TEN and does not increase the risk for other CBZ-induced HSRs. The strength of the evidence for a lack of association of HLA-B*15:02 with CBZ-MPE or CBZ-HSS is classified as consistent, but with reduced confidence due to the limited number of studies available (+++ evidence).

HLA-A*31:01: HSS, MPE

A consistent association has been shown for HLA-A*31:01 with CBZ-induced HSS and MPE. Retrospective case–control studies were conducted in European, Japanese (three studies), Taiwan Han Chinese, Korean, and patients of mixed ancestry. In the Korean study, no patients with CBZ-MPE were included, and one Japanese study included only patients with MPE. All but one study reported a significantly increased frequency of HLA-A*31:01 in patients with CBZ-MPE or HSS compared to CBZ-tolerant patients (Table S3). The sole negative study investigated 10 Japanese patients with CBZ-MPE and observed HLA-A*31:01 in only 2 of these cases. Most studies observed a significant association of HLA-A*31:01 with CBZ-HSS and MPE, both when analyzing HSS and MPE separately and in combination, and reported a stronger association of HLA-A*31:01 with HSS compared to MPE (Table S3), except for one study in Taiwan Han Chinese, where the association of HLA-A*31:01 with CBZ-HSS alone was not statistically significant. The proportion of HLA-A*31:01–positive patients among CBZ-HSS cases ranged from 37% to 67%, whereas 22–54% of patients with CBZ-MPE carried the risk allele. The frequency of HLA-A*31:01 in CBZ-tolerant patients ranged from 3% to 14%. Higher carrier frequencies of HLA-A*31:01 were observed in Japanese and Korean patients, both with and without CBZ-HSRs compared to European and Chinese patients, which is in agreement with reported population frequencies (Table S5).

Overall, studies regarding an association of HLA-A*31:01 with CBZ-HSS and MPE have shown consistent results across different ethnicities, although with a smaller magnitude of effect compared to HLA-B*15:02 and with somewhat limited generalizability because of the smaller number of available studies (+++ evidence). There is some variability in the observed effect size, which can in part be attributed to differences in the frequency of HLA-A*31:01 between different populations (Table S5). HLA-A*31:01 is

common with carrier frequencies ≥3% in many ethnic groups, suggesting a worldwide relevance of this risk variant. In particular, this risk variant is common in various indigenous American populations (Table S5).

HLA-A*31:01: SJS/TEN, AGEP

There is some uncertainty about the association of HLA-A*31:01 with CBZ-induced SJS/TEN (Table S4). Two studies reported a high frequency of this allele among patients with CBZ-SJS/TEN (5 of 6 Japanese patients;[43] 5 of 12 European patients[7]), suggesting a stronger association of HLA-A*31:01 with CBZ-SJS/TEN compared to HSS or MPE. In a Korean study, three of seven patients with CBZ-SJS/TEN carried HLA-A*31:01, showing a similar but nonsignificant trend.[39] On the other hand, another Japanese study reported only one carrier of HLA-A*31:01 among five patients with CBZ-SJS/TEN.[44] Similarly, no HLA-A*31:01–positive patients were observed among nine children with CBZ-SJS/TEN with mixed ancestries, with at least six of the nine cases originating from populations where HLA-A*31:01 is common.[45] All negative studies reported HLA-A*31:01 carrier frequencies in CBZ-tolerant patients that were similar to the frequencies reported by positive studies, suggesting that differences in overall study population carrier frequencies alone did not account for these discrepancies (Table S4).

The overall strength of evidence for an association of CBZ-HLA-A*31:01 with CBZ-SJS/TEN is graded as low but encouraging (++ evidence), due to significant inconsistency in findings and the small number of cases in individual studies, making it likely that conclusions drawn from current evidence will change based on future research.

HLA-A*31:01 has been studied in only two patients with CBZ-AGEP so far.[7,45] Only one of the two patients carried HLA-A*31:01, making it difficult to draw any conclusions regarding an association of this risk allele with CBZ-induced AGEP (++ evidence).

Sensitivity/specificity/positive predictive value (PPV)

Because of the rarity of these reactions, but also because of a paucity of studies, there are limited data about the frequency of CBZ-SJS/TEN and HSS. Also for CBZ-MPE, only few data on the frequency of these reactions exist. Combined with the variable estimates of population frequencies of HLA-B*15:02 and HLA-A*31:01, this results in uncertainties in the estimation of the PPVs, sensitivity, and specificity of the genetic tests (see Glossary in the Supporting Information for a definition of sensitivity, specificity, and PPV).

The sensitivity of the genetic test for HLA-B*15:02 is estimated to be high (80–97%; Table 3) in populations where the risk allele is common. However, the PPV of the test is low (1–5%) because the frequency of SJS/TEN is much lower than the frequency of the risk allele in these populations. This PPV is much lower than the PPV of HLA-B*57:01 genotyping for abacavir hypersensitivity (47.9%),[46] a test that is recommended as standard of care in HIV patients prior to therapy.[46–48] Therefore, although carrying HLA-B*15:02 increases the risk of CBZ-SJS/TEN by up to >700-fold compared to noncarriers (Table 3), a majority of patients carrying HLA-B*15:02 (95–99%) do not develop SJS/TEN from CBZ (Table 3).

Due to the variability in the effect size reported between different studies, there is some uncertainty about the sensitivity of the genetic test for HLA-A*31:01, with estimates ranging from 26% to 61%. Compared to HLA-B*15:02, the sensitivity of HLA-A*31:01 to identify patients at risk for CBZ-HSS or MPE is lower, as a larger proportion of patients with CBZ-HSS or MPE do not carry this risk variant. Accordingly, there is also uncertainty about the PPV of this test (12–42%; Table 3). Even though the PPV is higher compared to HLA-B*15:02 because of the higher incidence of CBZ-MPE compared to CBZ-SJS/TEN and the upper range of the estimate (42%) similar to the PPV for HLA-B*57:01 and abacavir hypersensitivity,[46] also for this risk variant a majority of carriers (58–88%) are expected to tolerate CBZ (Table 3).

Clinical Practice Recommendations

Question 1: Should genetic testing for HLA-B*15:02 and HLA-A*31:01 be performed in patients with an indication for CBZ therapy prior to therapy initiation, in order to reduce the occurrence of CBZ-induced HSRs?

Recommendation 1.1: Genetic testing for HLA-B*15:02 is recommended for all CBZ-naive patients before initiation of CBZ therapy (Level A – strong in patients originating from populations where HLA-B*15:02 is common, its frequency unknown or whose origin is unknown; Level C – optional in patients originating from populations where HLA-B*15:02 is rare). Genetic testing for HLA-A*31:01 is recommended for all CBZ-naive patients before initiation of CBZ therapy (Level B – moderate in all patients; Table 2).

Considerations: Although the PPVs of the genetic tests are relatively low, the severity of SJS/TEN and HSS justifies a recommendation for genetic testing because equally effective alternative treatments are available. For HLA-B*15:02, the strength of the reported associations combined with the severity of SJS/TEN and the availability of equally effective alternative medications warrants a strong recommendation for testing despite the lower PPV compared to the abacavir HLA-B*57:01 test.[46] For HLA-A*31:01 the level of strength of the recommendation is reduced due to the smaller number of studies available compared to HLA-B*15:02, the uncertainties related to sensitivity and PPV, and the current lack of a prospective evaluation of the potential of the genetic test to reduce HSRs. See Recommendations 2.1 and 2.1 below

Table 2. Grading scheme used for clinical practice recommendations

Level	Strength	Evidence basis
A	Strong	Based on strong scientific evidence; benefits clearly outweigh risks
B	Moderate	Based on reduced confidence scientific evidence and expert opinion; benefits likely to outweigh risks
C	Optional	Based mainly on expert opinion, for use with evidence development in a research context

for additional considerations regarding testing in patients with different ancestries.

Recommendation 1.2: In patients who have previously taken CBZ for > 3 months without any adverse effects, and in whom reinitiation of CBZ is considered, genetic testing is NOT recommended (B). In patients who have previously taken CBZ for a shorter period, genetic testing should be considered (B).

Considerations: The onset of symptoms for CBZ-induced HSRs is usually within the first 3 months of therapy. In patients who have previously taken CBZ for a duration of >3 months without experiencing any adverse reaction, a HSR is therefore unlikely to occur upon reinitiation of CBZ. In patients who have previously taken CBZ for a duration of ≤3 months, there is the possibility of a HSR occurring even if no symptoms were observed during the previous administration, due to their delayed onset. Depending on the duration of CBZ therapy during the previous administration, genetic testing should be considered in such patients.

Recommendation 1.3: In patients who have previously experienced a HSR potentially related to CBZ, genetic testing is recommended as part of the differential diagnosis and for the direction of future therapy (B).

Considerations: In patients with a history of a HSR, for which CBZ is a possible culprit drug, a positive test results for HLA-B*15:02 or HLA-A*31:01 increases the likelihood of the previous HSR being related to CBZ. Genetic testing is therefore recommended as part of the differential diagnosis to assist in the causality assessment of the HSR, in the context of other possible culprit drugs or other etiologies (e.g., infections). Furthermore, the risk of a severe HSR upon readministration of CBZ is likely to be strongly increased in patients who previously experienced a HSR while taking CBZ and test positive for HLA-B*15:02 or HLA-A*31:01. Therefore, genetic testing is particularly recommended in such patients if reinitiation of CBZ is considered.

Recommendation 1.4: In patients for whom no alternative treatment options are available, genetic testing is recommended to ensure increased alertness to hypersensitivity symptoms in positive patients (B).

Considerations: Early discontinuation of the culprit drug has been shown to reduce the risk of mortality associated with severe drug HSRs.[49] Knowledge of a patient's increased risk of hypersensitivity is therefore valuable even if no alternative treatment options are available to ensure increased alertness and monitoring for symptoms of HSRs, allowing for rapid discontinuations of CBZ if a HSR occurs. See section *Recommendations for the choice of alternative medications* below for additional recommendations regarding CBZ treatment in patients carrying a risk variant.

Question 2: Are there subgroups of patients who will benefit more than others from genetic testing for HLA-B*15:02 or HLA-A*31:01 prior to initiation of CBZ therapy?

Recommendation 2.1: Genetic testing for HLA-B*15:02 is most beneficial in patients originating from a population where HLA-B*15:02 is common (e.g., Chinese, Thai, Indian, Malay, Filipino, Indonesian; A). Nevertheless, genotyping for HLA-B*15:02 should be considered in ALL patients, irrespective of their ancestry, as the safest option (C).

Considerations: Caucasians, Japanese, and Korean patients will benefit less from genetic testing for HLA-B*15:02 because HLA-B*15:02 is rare in these populations (carrier frequency of <1%). However, even in populations where HLA-B*15:02 is rare, it is still possible that carriers of HLA-B*15:02 can occur.[39] Moreover, the frequency of HLA-B*15:02 is not known for many populations and patients may be unaware of their genetic ancestry.[50] Therefore, in agreement with a recently published clinical practice guideline,[50] testing for HLA-B*15:02 in all patients is recommended as the safest approach, particularly in ethnically diverse populations where many patients are of mixed or unknown ancestry, or if a combined test for both HLA risk variants is available at no or only a small extra cost.

Recommendation 2.2: HLA-A*31:01 is common in most populations studied so far. Therefore, genetic testing for this variant is recommended in patients of all ancestries (B).

Considerations: Based on the population frequency data available for HLA-A*31:01, genetic testing for HLA-A*31:01 is beneficial in patients of all ancestries (B). Because HLA-A*31:01 and HLA-B*15:02 are usually not inherited together, genetic testing for HLA-A*31:01 may be less beneficial in patients who are already known to be positive for HLA-B*15:02 (C).

Question 3: How should patients with an indication for CBZ therapy be managed based on their genetic test results for HLA-B*15:02 and HLA-A*31:01?

Recommendation 3.1: In patients who are positive for HLA-B*15:02 or HLA-A*31:01, alternative medications should be used as first-line therapy (A). Consideration in the choice of alternative medications should be given to the possibility of cross-reactivity with structurally simi-

lar AEDs (oxcarbazepine, lamotrigine, phenytoin, phenobarbital, primidone).

Considerations: Besides CBZ, several other drugs are recommended as alternative treatments for epilepsy, bipolar disorder, and trigeminal neuralgia. Clinical practice guidelines on the treatment of these respective disorders should be consulted for recommended alternative therapies. However, several of these alternative medications also belong to the class of aromatic AEDs, and thus have structural similarity to CBZ: oxcarbazepine (OXC), lamotrigine, phenytoin, phenobarbital, and primidone. Because of their structural similarity to CBZ, patients who are at increased risk of CBZ hypersensitivity may also have an increased risk for developing HSRs to these other aromatic AEDs. In particular, OXC is a derivative of CBZ with a similar mechanism of action, but is metabolized differently from CBZ.

Genetic risk variants and structurally similar AEDs. So far, only few studies of CBZ-HLA risk variants exist in the context of structurally similar AEDs. Of four Chinese patients with OXC-induced SJS/TEN tested for HLA-B*15:02, three were positive for the risk allele (75%).[51,52] Even though the number of patients studied is very small, there is thus suggestive evidence for a similar association of HLA-B*15:02 with SJS/TEN for OXC as for CBZ (++ evidence). On the other hand, the incidence of OXC-induced SJS/TEN has been estimated to be 30–40 fold lower compared to CBZ in Taiwan Han Chinese patients,[53] suggesting a difference in the risk of SJS/TEN between the two drugs. Therefore, there is currently insufficient evidence to provide a strong recommendation regarding the administration of OXC to patients carrying CBZ hypersensitivity risk variants. However, given the observation of several cases of OXC-SJS/TEN in HLA-B*15:02–positive patients, avoiding OXC as a first-line therapy in such patients may be the safest approach until further evidence is available (C).

Associations of HLA-B*15:02 with SJS/TEN have also been reported for phenytoin and lamotrigine. However, the strength of the reported associations was moderate, with only 8 (31%) of 26 patients with phenytoin-induced SJS/TEN,[51] and 5 (26%) of 19 patients with lamotrigine-induced SJS/TEN[51,54,55] carrying HLA-B*15:02. Current evidence therefore suggests an increased risk for SJS/TEN for patients who are positive for HLA-B*15:02 also when taking phenytoin or lamotrigine; however, the associated risk appears to be lower compared to CBZ (++ evidence).

Only one study so far has investigated HLA-A*31:01 in the context of phenytoin-induced (42 MPE, 3 HSS, one SJS) and lamotrigine-induced (40 MPE, 4 HSS) HSRs.[56] The frequency of HLA-A*31:01 compared to tolerant controls was not increased, suggesting that there is no association of this risk variant with phenytoin or lamotrigine HSRs of the same magnitude as observed for CBZ.

Recommendations for the choice of alternative medications. The first choice should be given to alternative medications that are structurally different from CBZ (A). If structurally different medications are not effective or not tolerated, aromatic AEDs other than CBZ or OXC should be used. Despite a risk of cross-reactivity for these medications, the risk of a severe HSR appears to be lower than for CBZ or OXC (B). CBZ and OXC should be used only as a last resort, if all alternative medications prove ineffective or are not tolerated by the patient, or if no alternative medications are available (C). Because the majority of carriers of HLA-B*15:02 and HLA-A*31:01 will not develop a severe HSR, there is a possibility that a patient who is positive for a risk variant will tolerate CBZ. In particular, only 1–5% patients positive for HLA-B*15:02 are expected to develop CBZ-induced SJS/TEN (Table 3). For HLA-A*31:01, even though up to 40% of carriers may develop a mild cutaneous reaction, the proportion that is expected to develop a serious HSR (HSS, SJS/TEN) is much lower (<2% of all positive patients; Table 3). However, if CBZ or OXC is administered to a patient who is positive for HLA-B*15:02 or HLA-A*31:01, strongly increased alertness to the first symptoms of a HSR is warranted. Patients should therefore be asked to immediately discontinue CBZ and consult their treating physician upon the occurrence of a rash or fever.

Recommendation 3.2: In patients who are negative for HLA-B*15:02 and HLA-A*31:01, CBZ can be used as first-line therapy (A). However, the occurrence of a HSR cannot be excluded based on a negative genetic test result.

Considerations: As not all patients experiencing CBZ-induced HSRs carry HLA-B*15:02 or HLA-A*31:01, the occurrence of such a reaction cannot be excluded based on a negative test result. Similarly, consideration should be given to the differences in the sensitivity of the genetic tests in different populations, depending on the frequencies of the risk variants. For example, a negative test result for HLA-B*15:02 in a patient originating from a population with a low frequency of HLA-B*15:02 (e.g., European or Japanese) only marginally reduces the risk of SJS/TEN compared to the general population. Even with negative test results, patients should be made aware of the symptoms of severe CBZ HSRs, in order to enable rapid discontinuation of the drug if a HSR occurs.

Case examples to illustrate the use of genetic testing

Case 1

A 50-year-old Caucasian man was admitted to hospital with generalized tonic–clonic seizures. He developed ataxia and diplopia on phenytoin and continued to have seizures. The attending internist instructed the house staff to prescribe CBZ. The residents told the attending that they had been taught that a genetic test must be done first

Table 3. Proportions of patients expected to develop HSRs without test, with and without risk variants

Risk variant	HLA-A*31:01		HLA-A*31:01		HLA-B*15:02	
Associated hypersensitivity reactions (HSRs)	HSS		HSS, MPE, SJS/TEN, AGEP		SJS/TEN	
Population with approximate carrier frequencies	Caucasian	Japanese/Korean	Caucasian	Japanese	Thai, Indian, Malay	Chinese
Frequency of HSR in patients taking CBZ (f_{HSR}; risk of CBZ-HSR without genetic test), %	0.02–0.05[a]	0.02–0.05[a]	3–10[b]	3–10[b]	0.23[c]	0.23[c]
Risk variant frequency in patients with HSR (f_{cases}; Sensitivity), %[d]	**37**	**58–59**	**26**	**58**	**80–93**	**97**
Risk variant frequency in patients without HSR ($f_{tolerant}$; 1-Specificity), %[d]	4	13–14	4	13	10–19	4–15
Frequency of HSR in patients who are positive for the risk variant (PPV; risk of HSR with positive test), %	**0.2–0.4**	**0.1–0.2**	**17–42**	**12–33**	**1–2**	**1–5**
Proportion of patients carrying risk variant NOT developing HSR (1-PPV), %	99	99	58–83	67–88	98–99	95–99
Frequency of HSR in patients who are negative for the risk variant (risk of HSR with negative test), %[e]	0.01–0.03	0.01–0.02	2–8	1–5	0.02–0.05	0.007
Maximum fold risk increase (positive vs. negative)	14	10	7	8	117	735

[a]Incidence estimate from Caucasian population.[12]
[b]Incidence estimates for Caucasian patients: 10%[60]; incidence reported for Japanese: 3%.[43]
[c]Historical incidence in Taiwan Han Chinese patients.[41]
[d]Estimation based on results from case–control studies (Tables S1 and S3).
[e]Calculated using: $(f_{HSR} * (1 - f_{cases}))/(f_{HSR} * (1 - f_{cases}) + (1 - f_{HSR}) * (1 - f_{tolerant}))$.
Sensitivity and PPV are indicated in bold.

due to an association between skin reactions from this drug and HLA variants. The attending physician wanted to know if this testing recommendation is correct and how the test should be done, and contacted clinical pharmacology, which confirmed this recommendation and that the test was to be ordered from the hospital immunogenetics laboratory, requesting high resolution typing for HLA-A and -B. The reason for the test was to prevent hypersensitivity reactions (e.g., rash, hypersensitivity syndrome, SJS/TEN). The attending physician agreed with the plan and the test was ordered. Two days later, the attending physician was notified that the patient was positive for the HLA-A*31:01 allele. Use of CBZ was avoided and topiramate was started, which is structurally dissimilar to carbamazepine.

Case 2

A 6-year-old girl of Asian descent was seen in the neurology clinic for routine follow-up. She experienced several focal seizures and was prescribed a variety of antiseizure medications, including CBZ, which was started 6 weeks before the clinic visit. Her seizures were controlled, but she developed maculopapular exanthema on her trunk and extremities. During this period, she experienced an infection that was treated with antibiotics. It was unclear whether the rash was due to CBZ or infection. The decision to discontinue CBZ was made in case the rash was an initial sign of SJS/TEN. Divalproex therapy was initiated. Unfortunately, after 2 weeks of therapy with divalproex there was a recurrence of seizures. Reinstituting CBZ is now being considered. To help determine if the rash this patient experienced is likely to be due to CBZ and may develop into a more severe HSR, a test for HLA-B *15:02 and HLA-A *31:01 was ordered. The result was negative, so CBZ was reintroduced with a plan of close monitoring of skin, oral mucosa, and fever for the next month.

Future Directions

Additional studies on HLA-B*15:02 and HLA-A*31:01

Only one prospective study so far has investigated the potential of the HLA-B*15:02 genetic test to reduce CBZ-induced SJS/TEN. Further prospective studies should be conducted, particularly in other ethnic groups. Similarly, studies on prospective testing for HLA-A*31:01 should be performed.

Further studies are also needed to clarify the association of HLA-A*31:01 with CBZ-SJS/TEN. Differences in the classification of HSRs as SJS/TEN is one possible explanation for the discrepancies between studies. Standardized criteria for the classification of CBZ-HSRs should therefore be used.[8] In particular, studies should include detailed clinical characterization of HSRs, in order to optimally apply these criteria.

In addition, further research is needed to investigate the risk of HSRs in HLA-B*15:02 and HLA-A*31:01

carriers in the context of structurally similar drugs, in order to improve the recommendations that can be made regarding the choice of alternative medications. In particular, more studies are needed to investigate a possible association of HLA-A*31:01 with HSRs to other aromatic AEDs.

HLA-B*15:11

Two recent studies in Japanese and Korean patients, respectively, reported an association of HLA-B*15:11 with CBZ-SJS/TEN. In the Japanese study, 4 (14%) of 28 CBZ-SJS/TEN cases carried the allele,[57] and in the Korean study, 3(43%) of 7 CBZ-SJS/TEN cases carried the risk variant.[39] In both studies, this frequency was significantly higher than the frequencies observed in the control populations (1% and 4%, respectively). On the other hand, no carriers of any HLA-B*15 allele were observed in eight European CBZ-SJS/TEN cases.[58] Similarly, only one carrier of HLA-B*15:11 was observed among 42 CBZ-SJS/TEN cases in Thailand.[31] Population frequency data indicate that HLA-B*15:11 is very rare or absent in Europeans, but is present at a low frequency in the Japanese, Korean, and Thai populations, which is in agreement with the published findings. However, further research is needed to strengthen the evidence for an association of this allele with CBZ-SJS/TEN.

Additional risk factors, cost-effectiveness

Of great importance, further research is needed to investigate additional risk factors for CBZ hypersensitivity to improve the predictive accuracy of genetic testing. Not all patients experiencing a CBZ-induced HSR carry one of the currently known risk variants. Identification of additional genetic risk factors could therefore increase the sensitivity of genetic testing. Furthermore, a substantial number of patients who are positive for HLA-A*31:01 or HLA-B*15:02 tolerate CBZ without any adverse reaction, indicating that carrying one of these risk variants is not sufficient to trigger a HSR. Given the rarity, in particular of severe HSRs, it is possible that only the presence of a combination of several risk factors can trigger these reactions. Identifying such factors could therefore substantially improve the positive predictive power of genetic testing, in order to avoid unnecessary withholding of CBZ from patients in whom it could be administered safely. In the context of HLA-A*31:01, investigation of additional risk factors could also provide important information to specifically identify patients at risk for the more severe and life-threatening HSS, as opposed to milder CBZ-induced MPE. Finally, as genetic testing for CBZ HSRs is used more frequently, an evaluation of the cost-effectiveness of genetic testing will become increasingly important and should be performed.

Methods

A standard clinical practice recommendation development process was followed, based on the quality criteria suggested by the Appraisal of Guidelines Research and Evaluation Enterprise (AGREE), an international endeavor aimed at improving the quality of practice guidelines.[59] This process involved a systematic literature search (details provided in the Supporting Information), followed by critical appraisal of the retrieved evidence (Table 1), taking into consideration the consistency of results, magnitude of the effect, as well as the number and quality of studies conducted. Clinical practice recommendations were developed during a workshop meeting of clinical recommendation group members and were assigned one of three levels of strength, based on the strength of available evidence on which the recommendation was formulated, the balance between benefits and risks of genetic testing and genotype-guided treatment, as well as the likelihood of variability in the individual values and preferences of patients (Table 2). Draft guidance documents were submitted to a tiered review process, which included internal review by the recommendation development group members, followed by external review both by content experts and by members of the intended target audience. Additional details on the evidence review, critical appraisal, and recommendation development are provided in the Supporting Information (Data S2).

An evaluation of the cost-effectiveness of genetic testing was not performed due to the rapidly changing and locally varying costs of genetic testing. Similarly, the laboratory standards (analytical sensitivity/specificity) of available diagnostic genetic tests were not systematically assessed. A brief discussion of test availability is provided in the Supporting Information (Data S3). Possible implications of genetic test results in the context of diseases or the response to medications other than those included in the clinical practice recommendations were also not systematically addressed. Other therapies should therefore not be changed based on genetic test results and recommendations provided.

The provided case examples are for illustration purposes and do not represent actual patient cases. Thus, no consent or ethical approval was needed.

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Disclosure or Conflicts of Interest

M.J.R. holds the Canadian Institute of Health Research–GlaxoSmith-Kline chair in Pediatric Clinical Pharmacology at the University of Western Ontario. N.H.S. has been a paid consultant for Novartis in legal cases relevant to carbamazepine-induced hypersensitivity. The other authors declared no conflict of interest. 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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Glossary: Definitions and abbreviations used throughout the document.

Table S1. Summary table of evidence regarding the association of HLA-B*15:02 with CBZ-induced SJS/TEN.

Table S2. Population frequencies of HLA-B*15:02.

Table S3. Summary table of evidence regarding the association of HLA-A*31:01 with CBZ-induced HSS and MPE.

Table S4. Summary table of evidence regarding the association of HLA-A*31:01 with CBZ-induced SJS/TEN.

Table S5. Population frequencies of HLA-A*31:01.

Data S2. Supplementary methods: Additional details on the evidence review and clinical practice recommendation development, including the systematic literature search strategy.

Data S3. Test availability: A brief discussion of test availability for HLA-B*15:02 and HLA-A*31:01.

Data S4. Quick reference document: Summary of key messages and recommendations in bullet point format.