Drug hypersensitivity: Pharmacogenetics and clinical syndromes

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Severe cutaneous adverse reactions include syndromes such as drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). An important advance has been the discovery of associations between HLA alleles and many of these syndromes, including abacavir-associated hypersensitivity reaction, allopurinol-associated DRESS/DIHS and SJS/TEN, and SJS/TEN associated with aromatic amine anticonvulsants. These HLA associations have created the promise for prevention through screening and have additionally shed further light on the immunopathogenesis of severe cutaneous adverse reactions. The rollout of HLA-B*5701 into routine clinical practice as a genetic screening test to prevent abacavir hypersensitivity provides a translational roadmap for other drugs. Numerous hurdles exist in the widespread translation of several other drugs, such as carbamazepine, in which the positive predictive value of HLA-B*1502 is low and the negative predictive value of HLA-B*1502 for SJS/TEN might not be 100% in all ethnic groups. International collaborative consortia have been formed with the goal of developing phenotypic standardization and undertaking HLA and genome-wide analyses in diverse populations with these syndromes. (J Allergy Clin Immunol 2011;127:S60-6.)

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Drug hypersensitivity remains an important clinical issue. It consists of a variety of phenotypes, mainly the cutaneous adverse reactions that range from milder skin reactions (eg, exanthem, urticaria, and angioedema) to severe cutaneous adverse reactions (SCARs). SCARs are life-threatening, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS). An updated description of the clinical syndromes and pharmacogenetics of these entities as discussed during the recent 4th Drug Hypersensitivity Meeting 2010 in Rome, Italy, is provided below.

PHARMACOGENETICS OF DRUG HYPERSENSITIVITY

Associations between HLA alleles and specific drug hypersensitivity syndromes, such as abacavir hypersensitivity, have been paradigm shifting in heralding the widespread use of a pharmacogenetic test in clinical practice to prevent the development of a specific life-threatening drug toxicity. More recently, HLA associations between DRESS/DIHS and SJS/TEN have been described (Table I).[1-20] Identifying the true phenotypic drug hypersensitivity entity with specificity has proved to be key to identifying the pharmacogenetic markers associated with these syndromes. In the case of abacavir, this was achieved by using the skin patch test, which identifies patients with true immunologically mediated abacavir hypersensitivity.[21-23] More recent work with nevirapine suggests that the specific phenotypic components of the drug hypersensitivity reaction are important for identifying specific HLA associations.[20] The association between the class I major histocompatibility allele HLA-B*5701 and abacavir hypersensitivity has also furthered our understanding of the immunopathogenesis of this and other drug reactions and has provided a roadmap from discovery to widespread implementation of a pharmacogenetic association.[24] Most work currently has focused on the pharmacogenetics of drug hypersensitivity syndromes and SJS/TEN of drugs such as abacavir, nevirapine, anticonvulsants, and allopurinol. Further work and international collaborations will be needed to determine the pharmacogenetic basis of other

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Abbreviations used
CBZ: Carbamazepine
CTL: Cytotoxic T lymphocyte
DIHS: Drug-induced hypersensitivity syndrome
DRESS: Drug reaction with eosinophilia and systemic symptoms
SCAR: Severe cutaneous adverse reaction
SJS: Stevens-Johnson syndrome
TEN: Toxic epidermal necrolysis

drugs and reactions, such as IgE-mediated reactions, and other syndromes, such as acute generalized exanthematous pustulosis.

Abacavir

The pathway from discovery of a pharmacogenetic association to widespread clinical implementation is not without significant hurdles, as illustrated by the "abacavir example." Abacavir, an antiretroviral drug approved by the US Food and Drug Administration for use since 1998, was known to be associated with a drug hypersensitivity syndrome in approximately 8% of those starting the drug. In 2002, 2 groups independently published a strong association between HLA-B*5701 and abacavir hypersensitivity.[12,13] Early doubts as to the widespread applicability of HLA-B*5701 as a potential routine screening test to prevent abacavir hypersensitivity were raised based on an apparent low sensitivity in black and Hispanic populations, in which there is a much lower carriage rate of HLA-B*5701.[25] This apparent low sensitivity was actually the result of a high rate of clinical false-positive diagnosis in these populations with a low prevalence of HLA-B*5701, and this is highlighted in abacavir double-blind, randomized clinical trials in which up to 7% of patients not receiving abacavir had a clinical diagnosis of abacavir hypersensitivity.[24]

To overcome this problem of false-positive clinical diagnosis, abacavir patch testing was used as a specific test to identify true immunologically mediated abacavir hypersensitivity.[21-23] Two clinical trials, the Prospective, Randomized Evaluation of DNA Screening in a Clinical Trial (PREDICT-1) and Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation (SHAPE) studies, incorporated skin patch testing into their study design as a way of identifying the true phenotype of abacavir hypersensitivity.[14,15] The PREDICT-1 study was the first randomized, double-blind controlled study to prospectively test the clinical utility of a pharmacogenetic test to prevent a specific toxicity. This study, which enrolled 84% white subjects, was compelling in showing a 100% negative predictive value of HLA-B*5701 as a screening test for the prevention of abacavir hypersensitivity.[14] The SHAPE study was a case-control study enrolling both black and white American patients that suggested a 100% negative predictive value of HLA-B*5701 for abacavir hypersensitivity generalizable across black and white race.[15] Additional evidence from observational studies from different centers suggested HLA-B*5701 screening to be cost-effective in real clinical practice not only by eliminating true immunologically mediated abacavir hypersensitivity but also by reducing false-positive clinical diagnosis.[24]

The abacavir story provides a translational roadmap from the discovery of a genetic association through to implementation of a pharmacogenetic test in routine clinical care (Fig 1). In addition, important lessons were gleaned from abacavir clinical trials that can be applied to other drugs and pharmacogenetic markers. The PREDICT-1 study illustrated that using coprimary end points, where one was sensitive and not specific (clinical diagnosis) and the other was specific and not 100% sensitive (patch testing), was a powerful tool. The validation of a simple, inexpensive, allele-specific molecular test against the gold standard of high-resolution full allelic HLA typing in the PREDICT-1 study was also crucial to the widespread implementation of cost-effective and feasible methods for HLA-B*5701 screening.

The abacavir story also clearly illustrated that any randomized controlled trial aiming to study the clinical utility of a pharmacogenetic marker to prevent a specific toxicity must look at the dominant ethnic group. Case-control studies, such as the SHAPE study, on the other hand are most ideally used to generalize the results from the dominant ethnic group to other groups with low prevalence of the allele in question.

Finally, observational and open screening studies are useful to define the role, practical issues surrounding implementation, and benefits of genetic testing in real clinical practice and can sometimes pick out different effects, such as the decrease in false-positive clinical diagnosis in addition to decreasing the rates of true hypersensitivity in the case of abacavir. Much of the success of the implementation of HLA-B*5701 testing in clinical practice relates to the 100% negative predictive value of this pharmacogenetic marker, as well as the high (55%) positive predictive value.[14] Taking into account the high rates of false-positive diagnosis, this means that only 13 subjects would need to be screened to prevent 1 case of hypersensitivity.[24] Although many other HLA alleles associated with specific drug-induced diseases share a 100% or close to 100% negative predictive value, the positive predictive value and the prevalence of these diseases is much lower, creating challenges from the large number that would be needed to test to prevent 1 case (Fig 2).

Nevirapine

Nevirapine is a nonnucleoside reverse transcriptase inhibitor used in the combination treatment of patients with HIV-1 infection and is associated with a drug hypersensitivity syndrome in approximately 5% of those starting the drug and SJS/TEN in 0.3% or less of those starting the drug.[24] Nevirapine differs from abacavir in that distinct class I and II associations have been described in association with nevirapine-associated rash and hypersensitivity across different populations. A population-based study from Western Australia associated the MHC class II allele HLA-DRB1*0101 with rash-associated hepatitis in those with a CD4 percentage of 25% or greater.[16] This clinical work has been supported by *ex vivo* studies suggesting that nevirapine hypersensitivity is a CD4 cell–dependent process.[24]

Another case-control study in a Thai population associated nevirapine rash and hypersensitivity with HLA-B*3505, which was present in 17.5% of patients with HIV with nevirapine-associated rash or hypersensitivity versus 1.1% of nevirapine-tolerant control subjects and less than 1% of the general Thai population.[19] This same group is attempting to validate findings through a prospective, blinded randomized screening study in which subjects randomized to the HLA-B*3505 testing arm will be excluded from nevirapine treatment, if positive.[26]

Additional studies have associated MHC class I alleles with nevirapine hypersensitivity, such as HLA-B*1402 and HLA-Cw8,