A TECHNICAL REVIEW

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HLA-B*57:01 Genotyping
Association With Abacavir Hypersensitivity

Abacavir sulfate (or Ziagen®) is a nucleoside reverse-transcriptase inhibitor (NRTI) with potent antiviral activity against human immunodeficiency virus (HIV).[1,2] Approximately 5% of individuals being treated with abacavir develop a potentially life-threatening hypersensitivity reaction.[1,3] Abacavir hypersensitivity incidence varies among different racial groups, with higher prevalence in the Australian Caucasian population and lower prevalence in the African American population.[4,5]

Symptoms of hypersensitivity usually appear within the first six weeks of starting abacavir and include any two or more of the following: fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), respiratory symptoms (dyspnea, cough, or pharyngitis), malaise, fatigue, or achiness.[1,3] Since these symptoms often overlap with other clinical conditions in HIV patients, it can be challenging to confirm a hypersensitivity reaction. When hypersensitivity is suspected, abacavir or abacavir-containing drugs should be discontinued immediately, and rechallenge should be strictly avoided because more severe life-threatening systemic manifestations, including hypotension and death, can occur.[1]

HLA-B*57:01 and Abacavir Hypersensitivity

Several studies have demonstrated an increased risk of abacavir hypersensitivity with the human leukocyte antigen (HLA) B*57:01 allele of the major histocompatibility complex (MHC).[4-6] The MHC family of genes codes for a highly variable set of cell surface glycoproteins (HLAs) that play a critical role in presenting antigens to T-cell receptors to elicit an immune response. Susceptibility to abacavir hypersensitivity appears to be mapped specifically to the HLA-B*57:01 allele.[7] High resolution HLA testing is needed to identify the HLA-B*57:01 allele and to differentiate it from closely related alleles, such as HLA-B*57:02, HLA-B*57:03, and HLA-B*58:01/58:02, which do not appear to be associated with abacavir hypersensitivity.[7,8]

Carriage of the HLA-B*57:01 allele is not uniform across racial groups,[4,6,8] which contributes to the variable incidence of abacavir-mediated hypersensitivity reactions in different populations. Although increased risk of abacavir hypersensitivity with carriage of the HLA-B*57:01 allele was observed in most studies, the strength of the association varied depending on the study and the population tested.[4-6] Further clarification from more recent data suggests that the variability in the strength of association may have, at least in part, been due to the variability in the clinical diagnosis of abacavir hypersensitivity. When skin patch testing was used to confirm suspected abacavir hypersensitivity reactions, the association between HLA-B*57:01 allele carriage and confirmed abacavir hypersensitivity was significantly strengthened across all racial populations tested.[9,11,12]

Clinical Utility

The HLA-B*57:01 test for increased risk of abacavir hypersensitivity may be clinically useful in identifying HIV patients at risk of developing a hypersensitivity reaction to abacavir. The test can be used for genetic risk stratification prior to initiating abacavir therapy. Abacavir and abacavir-containing regimens should be avoided in patients found to be carriers of the HLA-B*57:01 allele. Several prospective trials have now demonstrated the efficacy of the HLA-B*57:01 test in significantly reducing and/or eliminating the incidence of hypersensitivity reactions when the test was used prior to administration of abacavir therapy.[7,9,11] Genetic risk stratification based on HLA-B*57:01 testing led to a decrease in incidence of hypersensitivity from 8%–9% down to 0%–1% in various prospective studies.[7,9,11] Furthermore, for patients who do not carry the HLA-B*57:01 allele, the use of the test led to many fewer discontinuations of abacavir therapy for suspected hypersensitivity reactions.[7,9] A cost-effectiveness study that demonstrates the test is cost-effective for a screening application prior to administering abacavir has also been conducted.[10]

A negative result for HLA-B*57:01 cannot completely preclude the development of an allergic response to abacavir; therefore, individuals suspected of having a hypersensitivity reaction to abacavir (even if HLA-B*57:01-negative) should not have abacavir reintroduced. HLA-B*57:01 testing cannot substitute for appropriate clinical vigilance and patient management

for persons receiving abacavir therapy. Restarting abacavir or an abacavir-containing formulation (such as Epzicom™ [abacavir plus lamivudine] or Trizivir® [abacavir, lamivudine, and zidovudine]) in a hypersensitive individual can be life-threatening.[1]

Ziagen®, Epzicom™, and Trizivir® are all products of GlaxoSmithKline, Research Triangle Park, NC.

Leadership in HLA Typing

LabCorp has provided comprehensive HLA typing services to the medical and transplant communities for more than 25 years. Molecular HLA typing methods have been developed by LabCorp scientists in order to provide the most reliable results possible. LabCorp is accredited for HLA typing by the College of American Pathologists (CAP), the American Society for Histocompatibility and Immunogenetics (ASHI), and the New York State Department of Health.

Test Name	HLA-B*57:01
Test Number	006926
Test Includes	HLA-B*57:01 Test; QC
Special Instructions	If necessary, telephone 800-533-1037 (HLA customer service) for assistance in ordering this HLA B*57:01 test for the patient. Ship specimen so it will arrive in the laboratory Monday through Friday.
Specimen	Whole blood or buccal swabs
Volume	7 mL whole blood or four buccal swabs
Minimum Volume	3 mL whole blood or four buccal swabs
Container	Lavender-top (EDTA whole blood) tube or four buccal swabs in a sealed envelope (buccal swab kit). When submitting buccal swabs, please use a buccal swab kit provided by LabCorp. To obtain the buccal swab kit, telephone 800-533-1037.
Collection	Ship specimen so it will arrive in the laboratory Monday through Friday.
Storage Instructions	Maintain blood specimen at room temperature. Keep buccal swabs dry and at room temperature.
Causes for Rejection	Hemolysis; clotted specimen; insufficient volume of DNA on buccal swabs
Reference Interval	The genetic sequences coding for the HLA-B*57:01 are probed and reported as either P (positive) if it is present or N (negative) if it is absent.
Use	Determine the presence of the HLA-B*57:01 allele
Limitations	Even with appropriate precautions, an occasional specimen may not be satisfactory for testing. In such cases, an additional specimen should be collected for testing.
Methodology	Polymerase chain reaction (PCR)/sequence-specific oligonucleotide probes (SSOP)

For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.

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