Antiviral Drug Allergy

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KEYWORDS

- Altered peptide repertoire • Abacavir • Nevirapine • Antiretroviral
- Telaprevir pharmacogenomics • Human leukocyte antigen
- Major histocompatibility complex

KEY POINTS

- Antiviral drugs successful in suppressing replication of human immunodeficiency virus (HIV) and hepatitis C (HCV) are common causes of delayed drug hypersensitivities for which an increasing number have more recently been shown to be human leukocyte antigen alleles (HLA) class I and/or II–restricted and T-cell-mediated.
- HLA-B*57:01 screening before abacavir prescription to prevent abacavir hypersensitivity is an example of a translational success story whereby a marker with 100% negative predictive value has now been implemented into guideline-based routine HIV clinical practice.
- Ancillary in vivo and ex vivo laboratory tests have been useful to define the true immunologically mediated phenotype of antiviral drug hypersensitivity (eg, patch testing for abacavir); however, the lower sensitivity of these tests for severe drug hypersensitivity syndromes means that clinical diagnosis remains the gold standard to guide management.
- Most allergic syndromes associated with antiviral medications consist of mild-to-moderate delayed rash without other serious manifestations (eg, fever, mucosal involvement, blistering rash, organ impairment). In these cases, treatment can be continued with careful observation and symptomatic management, and the discontinuation rate is low.

INTRODUCTION

Pharmacologically predictable adverse drug reactions and drug interactions have been commonly associated with anti-infective drugs and, particularly, antiretroviral agents. Immunologically mediated adverse drug reactions have also been commonly

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described in patients receiving drugs used to treat viral infections, including those used to treat human immunodeficiency virus (HIV) and hepatitis C infection.[1–3] These hypersensitivity reactions associated with antiviral drugs can be classified by their immunologic mechanisms as well as their specific clinical manifestation or phenotype. Gell-Coombs types I–III (immediate drug allergy, antibody mediated, and immune complex mechanisms) are not commonly associated with antiviral drugs. Gell-Coombs type IV (T-cell-mediated) reactions, however, have been commonly associated with drugs used to treat viral infection.[2–4] For instance, the antiretroviral drug, abacavir (ABC), causes a hypersensitivity syndrome, which has a distinct phenotype not shared by other drugs and is characterized by fever, malaise, and gastrointestinal symptoms. Mild-to-moderate skin rash is a late manifestation of ABC hypersensitivity, which occurs in 70% of cases.[4] The antiretroviral drug, nevirapine, has been commonly associated with a delayed rash as well as more severe hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms [DRESS], also known as drug-induced hypersensitivity syndromes [DIHS], Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN], and drug-induced liver disease [DILI]).[5] Many drugs, such as the nonnucleoside reverse transcriptase inhibitor (NNRTI), efavirenz, and the anti-hepatitis C virus (HCV) NS3.4A serine protease inhibitor, telaprevir, are commonly associated with a nonspecific exanthem without systemic symptoms, which is not treatment limiting, and continued treatment is usually possible with symptom control.[5–9] More severe reactions with fever and/or mucosal and/or severe cutaneous involvement and/or internal organ (eg, liver) involvement warrant immediate discontinuation and careful clinical monitoring. A major advance in pharmacogenomics has been the discovery that many immunologically mediated drug reactions are mediated through interactions with class I and/or class II human leukocyte antigen alleles (HLA) (**Table 1**). In the case of ABC, a strong association between HLA-B*57:01 was discovered by 2 independent groups in 2002 and HLA-B*57:01 is now used as a routine screening test with a proven 100% negative predictive value, before ABC prescription to exclude those at risk.[10,11] Abacavir patch testing was also a useful research tool in this context that was used in clinical trials to identify those with true immunologically mediated ABC hypersensitivity reaction (HSR).[21–23] ABC patch testing has a diagnostic sensitivity of 87% but there is currently no in vivo or ex vivo diagnostic test for antiviral drug hypersensitivity that has a 100% sensitivity or negative predictive value, and clinical diagnosis is used as the gold standard on which future recommendations are based. Drug hypersensitivity reactions associated with nevirapine have also been associated with class I and II HLA alleles, which seem to be ethnicity-dependent and phenotype-dependent, with associations that seem currently too complex to apply as a screening strategy in routine clinical practice (see **Table 1**).[24–26] A major recent advance has been the elucidation of the science of ABC hypersensitivity, which has defined the specific mechanism by which ABC specifically interacts with HLA-B*57:01 and alters the repertoire of self-peptide ligands.[22,27,28] Based on this work, the crystal structure of ABC-bound peptide-HLA-B*57:01 has been resolved and a new mechanistic paradigm for how drugs affect T-cell-mediated reactions was defined.[29] Future applications of this work could include preclinical strategies to determine drugs at high risk to cause immunologically mediated adverse drug reactions and hence inform drug design and development.

IMMUNOPATHOGENESIS AND PHARMACOGENOMICS OF ANTIVIRAL DRUG ALLERGY

Models that have been proposed to define the immunopathogenesis of drug allergy and hypersensitivity syndromes include the prehapten/hapten hypothesis, the