Abacavir Hypersensitivity Reaction

Abacavir (ABC) hypersensitivity reaction is a multi-organ systemic reaction that can occur in up to 8% of HIV-infected patients initiated on this therapy. The reaction resembles a delayed hypersensitivity reaction, which can cause life-threatening complications with continued use during initial therapy, or immediate and potentially fatal reactions in people who are re-challenged following a prior hypersensitivity reaction.

The presentation of a Hypersensitivity Reaction

The incidence of ABC hypersensitivity, which occurs in 4-8% of users, predominantly affects Caucasians and Asians while the risk among people of African descent is unknown and is approximately 2% in African Americans. Typically almost all abacavir hypersensitivity reactions occur within the first 4-6 weeks of therapy and are reversible with discontinuation of use, however failure to recognize the reaction has been associated with fatalities when therapy was continued despite progressive symptoms.

Clinical Presentation

ABC hypersensitivity involves a host of general non-specific signs and symptoms including fever, nausea, vomiting, diarrhoea, rash, sore throat, malaise and non productive cough, as observed in our case study. In contrast to the more prominent rash that can develop with sulfonamides or non-nucleoside reverse transcriptase inhibitors (NNRTIs), the rash associated with ABC is often mild and not the predominant symptom. Typically the constellation of symptoms associated with ABC hypersensitivity frequently mimic those of viral illnesses, such as influenza. A key component of ABC hypersensitivity is the accentuation of symptoms within hours of taking each dose of the drug and the escalation of symptoms with each subsequent dose.

Although much emphasis is placed on the importance of recognizing ABC hypersensitivity, it is also important not to overdiagnose and to obtain supporting empirical evidence. Of note, once ABC has been discontinued, because of presumed hypersensitivity, the patient cannot be treated with ABC again. Thus, when abacavir is discontinued prematurely or without adequate assessment of symptoms, therapeutic options may be lost. Therefore it is important that patients are assessed carefully for risk of developing ABC hypersensitivity prior to starting the regimen.

If hypersensitivity to ABC occurs, drug should be discontinued and supportive care provided. After withdrawal, symptoms usually resolve within a few days.

HLA-B*57:01 as a genetic risk marker

Since 2000, studies have been conducted of ABC hypersensitivity using various genetic markers and found that individuals (mostly of Caucasian decent) who possess the Human Leukocyte Antigen
(HLA)-B*57:01 is highly predictive of whether they will develop ABC hypersensitivity syndrome. It is thus recommended that patients who are to be provided with ABC, that an HLA-B*57:01 screen is done. We will discuss below why hypersensitivity occurs with the specific HLA type and not others.

Understanding Abacavir activity

Since 2000, studies have been conducted of ABC hypersensitivity using various genetic markers and found that individuals (mostly of Caucasian decent) who possess the Human Leukocyte Antigen (HLA)-B*57:01 is highly predictive of whether they will develop ABC hypersensitivity syndrome. It is thus recommended that patients who are to be provided with ABC, that an HLA-B*57:01 screen is done. We will discuss below why hypersensitivity occurs with the specific HLA type and not others.

Understanding Abacavir activity

First, let's understand the mode of action of ABC as an antiretroviral drug. ABC is a prodrug formulated nucleoside reverse transcriptase inhibitor (NRTI), which once inside a cell is converted to the active drug, carbovir triphosphate, by cytosolic enzymes. During reverse transcription mediated by viral reverse transcriptase, carbovir triphosphate competes with deoxy-guanosine triphosphate (dGTP) for incorporation into viral DNA and once incorporated inhibits HIV replication by terminating the DNA chain.

Metabolism of ABC to the active drug is achieved through a series of cellular biochemical processes. Firstly adenosine phosphotransferase adds a phosphate group to ABC to produce abacavir.
monophosphate. A cytosolic deaminase then removes an amine group to produce carbovir monophosphate. The process continues and cellular kinases add a second phosphate to produce carbovir diphosphate followed by addition of a third phosphate group to produce the active metabolite, carbovir triphosphate. In this form ABC competes with dGTP to inhibit the reverse transcription of HIV RNA.

What role does HLA-B*57:01 play?

The role of HLA class I molecules is important in cell-mediated immunity since they function as antigen presenting molecules to CD8+ cytotoxic T cells. The source of the antigen is short peptide fragments of around 9-11 amino acids long derived from cytosolic proteins or in the case of dendritic cells they can be cross-presented on both HLA class I and II molecules via phagocytosed proteins. HLA class I genes occur at three genetic loci on chromosome 6 in humans (HLA-A, B and C) and a large number of allelic variants have been identified worldwide. HLA class I molecules encoded by different alleles primarily differ in their peptide binding specificity. It is known that HLA-B*57:01 molecules preferentially bind peptides with alanine, threonine or serine at position 2 while tryptophan, tyrosine or phenylalanine is preferred at the C-terminal position 9. Peptide antigens with these residues are generated by cleavage of cytosolic proteins by the proteosome in the cytoplasm and imported into the endoplasmic reticulum where they bind to newly synthesised HLA-B*57:01 molecules that are exported via the Golgi body to the cell surface for presentation to CD8+ cytotoxic T cells. In most cases these peptides will be derived from “self” proteins and will therefore not be recognised by the T cell receptor (TCR) of CD8+ cytotoxic T cells due to negative selection in the thymus. In HIV-infected individuals who carry the HLA-B*57:01 gene and who are treated with abacavir, an autoimmune hypersensitivity reaction involving CD8+ cytotoxic T cells can develop.

How is abacavir involved?

It is known that HLA-B*57:01 molecules preferentially bind peptides with alanine, threonine or serine at position 2 while tryptophan, tyrosine or phenylalanine is preferred at the C-terminal position 9. Peptide antigens with these residues are generated by cleavage of cytosolic proteins by the proteosome in the cytoplasm and imported into the endoplasmic reticulum where they bind to newly synthesised HLA-B*57:01 molecules that are exported via the Golgi body to the cell surface for presentation to CD8+ cytotoxic T cells. In most cases these peptides will be derived from “self” proteins and will therefore not be recognised by the T cell receptor (TCR) of CD8+ cytotoxic T cells due to negative selection in the thymus. In HIV-infected individuals who carry the HLA-B*57:01 gene and who are treated with abacavir, an autoimmune hypersensitivity reaction involving CD8+ cytotoxic T cells can develop.
It has been shown that unmetabolised abacavir prodrug is able to bind to a site in the peptide binding cleft of the HLA-B*57:01 molecule and interacts directly with aspartate at position 114 and serine at position 116. The presence of abacavir does not prevent peptide antigens from binding to the HLA molecule, however, the peptide specificity is altered. A preference of other amino acids, particularly leucine and isoleucine, at position 9 instead of tryptophan, tyrosine or phenylalanine is evident. The amino acid preference at position 2 remains unchanged. Abacavir bound to HLA-B*57:01 molecules alters the peptide repertoire that is presented to CD8+ cytotoxic T cells. Many of the abnormal peptides that now bind HLA-B*57:01 are derived from “self” proteins. Recognition of “self” peptides by circulating CD8+ cytotoxic T cells precipitates an autoimmune reaction resulting in attack of healthy cells and overproduction of pro-inflammatory cytokines, such as IFN-gamma and TNF-alpha.

**Does abacavir bind to other HLA-B*57 molecules?**

Abacavir has a specificity for HLA-B*57:01 molecules and does not bind to other members of the B*57 family, such as HLA-B*57:02 and HLA-B*57:03. This is due to a requirement of aspartate at position 114 and serine at position 116 which is present in the HLA-B*57:01 protein structure. These two amino acids map to the peptide binding cleft and interact directly with the abacavir molecule. HLA-B*57:02 and HLA-B*57:03 molecules have asparagine at position 114 and tyrosine at position 116 which do not interact with the abacavir molecule.

**What do the CD8+ cytotoxic T cells do that results in hypersensitivity?**

The activated CD8+ T cells that are specific to drug-modified peptides derived from the protein-ABC conjugate have been shown to secrete gamma-interferon (IFN-g) and tumour necrosis factor-alpha (TNF-a), which are pro-inflammatory cytokines that contribute to the symptoms and severity of the immune hypersensitivity reaction. Gamma-interferon enhances antigen-presentation by upregulating the numbers of HLA molecules on antigen-presenting cells that could promote further activation of CD8+ T cells. It is noted that severe skin rashes develop in most hypersensitivity reactions and may relate to the large numbers of Langerhans’ cells present on the skin that may be participating in the activation of large numbers of CD8+ T cells responding to “self” skin antigens now presented by HLA-
B*57:01 molecules. Large doses of TNF-alpha promotes fever and vascular permeability that can lead to sepsis and organ failure. Notably, it is thought that abacavir-specific CD8+ T cells are activated independently of CD4+ T cells, which is why patients who are severely immunocompromised with low CD4 counts can develop these reactions.

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