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Allopurinol Therapy and *HLA-B*58:01* Genotype

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Introduction

Allopurinol is a xanthine oxidase inhibitor that decreases the production of uric acid. It is most commonly used in the management of gout and hyperuricemia (high levels of uric acid).

The human leukocyte antigen B (HLA-B) plays an important role in how the immune system recognizes and responds to pathogens. The variant *HLA-B*58:01* allele is strongly associated with severe cutaneous adverse reactions (SCAR) during treatment with allopurinol. This allele is most commonly found in Asian subpopulations, notably in individuals of Korean, Han Chinese, or Thai descent (1-3).

At this time, the FDA-approved drug label does not discuss *HLA-B* genotype (4). However, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that allopurinol should not be prescribed to patients who have tested positive for *HLA-B*58:01*, and that an alternative medication should be considered to avoid the risk of developing SCAR (see Table 1) (1, 2).

Table 1. *HLA-B* phenotypes and the therapeutic recommendations for allopurinol therapy, adapted from CPIC

Genotype	Examples of diplotypes	Phenotype	Therapeutic recommendations
Noncarrier of *HLA-B*58:01*	**X/*X^b^*	Low or reduced risk of allopurinol-induced SCAR	Use allopurinol per standard dosing guidelines
Carrier of *HLA-B*58:01*	**5801/*X^b^ *5801/*5801*	Significantly increased risk of allopurinol-induced SCAR	Allopurinol is contraindicated

The strength of therapeutic recommendations is "strong" (1).
HLA-B, human leukocyte antigen B
SCAR, severe cutaneous adverse reaction
**X*, any *HLA-B* genotype other than *HLA-B*58:01*
**X^b^*, any *HLA-B* genotype other than *HLA-B*58:01*
Table is adapted from Hershfield M.S., Callaghan J.T., Tassaneeyakul W., Mushiroda T., Thorn C.F., Klein T.E., Lee M.T.Clinical pharmacogenetics implementation consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clinical pharmacology and therapeutics. 2013;93(2):153–8 (1, 2).

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Drug: Allopurinol

Allopurinol is a commonly prescribed drug for the management of gout and hyperuricemia. Uric acid is produced by the breakdown of purine nucleotides, and high concentrations of uric acid can lead to gout and uric acid kidney stones.

Allopurinol is an analogue of the purine hypoxanthine. Allopurinol decreases the production of uric acid by inhibiting xanthine oxidase, which catalyzes the conversion of hypoxanthine and xanthine to uric acid. In addition, allopurinol facilitates the incorporation of hypoxanthine and xanthine into DNA and RNA, and the resulting increase in nucleotide concentration leads to a feedback inhibition of *de novo* purine synthesis, which in turn leads to a decrease in uric acid levels (5).

Allopurinol is rapidly oxidized in the liver to the active metabolite oxypurinol, which also inhibits xanthine oxidase. Allopurinol has a short plasma half-life of ~1-2 hours, whereas oxypurinol has a half-life of ~15 hours. After the rapid oxidation of allopurinol, any remaining drug is promptly filtered and excreted by the kidneys. However, after oxypurinol is filtered by the kidneys, it is reabsorbed in a manner similar to how uric acid is reabsorbed. Therefore, it is thought that the effective inhibition of xanthine oxidase over a 24-hour period after a single dose of allopurinol is largely brought about by the effects of oxypurinol (4).

In general, allopurinol is well tolerated; however, allopurinol is one of the most common causes of severe cutaneous adverse reactions (SCAR), and the *HLA-B*58:01* allele is strongly associated with allopurinol-induced SCAR.

Allopurinol-induced Adverse Drug Reactions

In general, there are two categories of adverse drug reactions. Type A reactions account for up to 85-90% of all adverse drug reactions. They are predictable based on the known properties of the drug, and they can affect any individual, if their exposure to the drug is high enough. For allopurinol, one of the most common type A adverse effects is an acute attack of gout after starting allopurinol therapy (4).

Type B reactions account for the remaining 10-15% of adverse drug reactions. These include hypersensitivity reactions that occur in susceptible individuals. Such idiosyncratic hypersensitivity reactions can occur at any dose and develop through a mechanism that is unrelated to the mechanism of action of the drug. For this reason, it is difficult to predict in whom a drug-induced hypersensitivity reaction is likely to occur.

Severe cutaneous adverse reactions are type B reactions, which include Stevens-Johnson syndrome (SJS), or the more severe toxic epidermal necrolysis (TEN); as well as drug reaction with eosinophilia and systemic symptoms (DRESS), and allopurinol hypersensitivity syndrome (AHS).

Allopurinol is the most common cause of SJS/TEN in Europe (6). SJS /TEN are life-threatening conditions that are primarily characterized by lesions of the skin (detachment of the epidermis) and mucus membranes (severe erosions). SJS/TEN is also associated with fever, raised white cell count, hepatitis, and acute renal failure.

The underlying mechanisms for allopurinol-induced SCARs remain unclear, but cytotoxic T cells (CD8+ T cells) are involved. In the case of allopurinol, although the presence of *HLA-B*58:01* substantially increases the risk of SCAR, it is not an absolute requirement, indicating that other variables also contribute to its etiology (1, 7).

One theory, known as the p-I concept, is that there is a direct pharmacological reaction of the drug (e.g., allopurinol) with the immune receptors (activated drug-specific T cells) and this provides an initial signal to induce T-cell activation and trigger a T cell–mediated hypersensitivity reaction. The signal may be strengthened by the additional interaction with HLA molecules (e.g., *HLA-B*58:01*) (7-11).

Although allopurinol induced-SCAR is rare (the risk is estimated to be 0.1–0.4%), allopurinol is one of the most serious causes of SCAR, which carries a mortality rate of up to 25% (1, 2).

The FDA-approved dose of allopurinol for the management of gout or hyperuricemia is to start with a daily dose of 100 mg, and titrate the dose upwards to a maximum daily dose of 800 mg, until the uric acid concentrations are less than 6.0 mg/dl. Allopurinol is often prescribed in doses that may be too low to achieve a therapeutic goal, an approach taken in part to reduce the risk of drug hypersensitivity (12). One study has found that a lower starting dose of allopurinol may reduce the risk of allopurinol hypersensitivity syndrome (13).

HLA Gene Family

The human leukocyte antigen (HLA) genes are members of the MHC gene family, which includes more than 200 genes. The MHC family has been subdivided in to 3 subgroups based on the structure and function of the encoded proteins: Class I, Class II, and Class III.

The class I region contains the genes encoding the HLA molecules HLA-A, HLA-B, and HLA-C. These molecules are expressed on the surfaces of almost all immune cells and play an important role in processing and presenting antigens. The class I gene region also contains a variety of other genes, many of which are not known to be involved in immune function.

An important role of HLA class I molecules is to present peptide fragments to immune cells (CD8+ T cells). Most of these peptides originate from the breakdown of normal cellular proteins ("self"). However, if foreign peptide fragments are presented (e.g., from a pathogen), CD8+T cells will recognize the peptides as "non-self" and will be activated to release inflammatory cytokines and launch an immune response to dispose of the pathogen or foreign body (14).

Because HLA molecules need to present such a wide variety of "self" and "non-self" peptides, the HLA genes are both numerous and highly polymorphic. More than 1,500 *HLA-B* alleles have been identified. Each HLA allele has a name that is prefixed by HLA, followed by the gene name, an asterisk and a two digit number that corresponds to antigen specificity, and the assigned allele number (15). For example, the *HLA-DRB1*13:01* allele is composed of:

- HLA: the HLA prefix (the HLA region on chromosome 6)
- DRB1: the DRB1 gene (a particular HLA gene in this region)
- 13: the allele group (historically determined by serotyping, i.e., a group of alleles that share the same serotype)
- 01: the specific HLA allele (a specific protein sequence; determined by genetic analysis).

Additional digits have recently been added to the nomenclature to discriminate alleles that do not differ in the protein amino acid sequence, but differ in their genetic sequence (i.e., due to synonymous and noncoding genetic variants).

Variation in the HLA genes plays an important role in the susceptibility to autoimmune disease and infections and they are also critical in the context of transplant surgery where better outcomes are observed if the donor and recipient are HLA-compatible (1, 2). More recently, specific HLA variants have been associated with susceptibility to adverse drug reactions, including allopurinol-induced hypersensitivity reactions.

Gene: *HLA-B*

The *HLA-B*58:01* allele is associated with an increased risk of severe hypersensitivity reactions to allopurinol, such as SJS/TEN. The allele is codominant, so an individual needs to carry only one copy of the *HLA-B*58:01* allele to be at increased risk.

The association between *HLA-B*58:01* and allopurinol-induced adverse effects was first discovered in the Han Chinese population, where a study found that all patients who had allopurinol-induced SJS/TEN (51/51, 100%) carried *HLA-B*58:01*, compared with only 15% of the allopurinol-tolerant patients (20/135, 15%) (16).

Further studies also found an association with *HLA-B*58:01* and severe allopurinol-induced adverse effects in other populations, including Thai, Korean, European, and Japanese populations (17-19). The association is stronger in the Han Chinese than in European and Japanese populations, which is most likely due to differences in *HLA-B*58:01* allele frequencies between racial and ethnic populations (20).

The *HLA-B*58:01* allele is most common in individuals of Asian descent, with a frequency of ~10-15% in the Han Chinese, ~12% in Koreans, and ~6-8% in individuals of Thai descent (3, 21-25). The risk allele is less common among Europeans and Japanese with a frequency of only ~1-2% (26, 27).

Although the risk of SCAR due to allopurinol is generally low (0.1–0.4%) and certain populations have a low frequency of the *HLA-B*58:01* risk allele (e.g., Europeans), the risk of allopurinol-induced SCAR is substantially elevated in *HLA-B*58:01* carriers. The odds ratio for allopurinol-induced SCAR among *HLA-B*58:01* carriers in a meta-analysis was 73 using healthy controls and 165 using allopurinol-tolerant controls (5).

Genetic Testing

Genetic testing is available for several *HLA-B* alleles, including *HLA-B*58:01*. The genotype results are either "positive" (*HLA-B*58:01* being present in one or both copies of the *HLA-B* gene) or "negative" (no copies of *HLA-B*58:01* are present). There are no intermediate phenotypes because *HLA-B* is expressed in a codominant manner (1, 2).

Several studies have looked in to the cost-effectiveness of *HLA-B*58:01* testing to guide urate-lowering therapy (ULT). A 2012 American College of Rheumatology guideline recommended that prior to treatment with allopurinol, the *HLA-B*58:01* genotype of gout patients at high risk for SCARs, including Korean patients with chronic renal insufficiency, should be determined (3). One study reported that in Korean patients with kidney disease, ULT guided by *HLA-B58:01* genotyping was less costly and more effective than treatment without genotyping, and that *HLA-B*58:01* genotyping could considerably reduce the occurrence of allopurinol-induced SCARs and related deaths (28). Cost-effectiveness analysis of treating patients with chronic gout (without additional risk factors) in Singapore and in Portugal found that *HLA-B*58:01*-guided ULT was not cost-effective at this time.

A potential alternative to costly HLA genotyping, may be to test for single nucleotide variants that are tightly associated with *HLA-B*58:01*. A number of variants have been found to be in linkage disequilibrium (LD) with *HLA-B*58:01*, for example, the rs9263726 variant in the *PSORS1C1* gene is strongly associated with *HLA-B*58:01* in the Japanese population (20).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): Given the high specificity for allopurinol-induced SCAR, allopurinol should not be prescribed to patients who have tested positive for *HLA-B*58:01*. Alternative medication should be considered for these patients to avoid the risk of developing SCAR. For patients who have tested negative, allopurinol may be prescribed as usual (see Table 1).

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

However, testing negative for *HLA-B*58:01* does not totally eliminate the possibility of developing SCAR, especially in the European population.

Please review the complete therapeutic recommendations that are located here (1, 2).

2012 Statement from the American College of Rheumatology (ACR): Prior to initiation of allopurinol, rapid polymerase chain reaction-based *HLA-B*5801* screening should be considered as a risk management component in subpopulations where both the *HLA-B*5801* allele frequency is elevated and the *HLA-B*5801*-positive subjects have a very high hazard ratio ("high risk") for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse chronic kidney disease and all those of Han Chinese and Thai descent).

Please review the complete therapeutic recommendations that are located here (3).

Nomenclature

Allele name	Other name(s)	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*HLA-B*58:01*		Not applicable*	Not applicable*	Not applicable*

* For the MHC region, variations in genes such as *HLA-B* occur across the whole sequence of the gene, not a single locus. Therefore, the *HLA-B*58:01* allele is defined by its sequence (GenBank: EU499350.1) rather than single coding or protein variants.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Guidelines on nomenclature of the HLA system are available from HLA Nomenclature: http://hla.alleles.org/

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Version history

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