Medical Genetics Summaries

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

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Allopurinol is a xanthine oxidase inhibitor that decreases the production of uric acid. It is most commonly used in the management of gout and high levels of uric acid (hyperuricemia). It is also used to prevent or treat uric acid kidney stones and tumor lysis syndrome that can occur during chemotherapy resulting in acute uric acid nephropathy.

The human leukocyte antigen B (HLA-B) plays an important role in how the immune system recognizes and responds to pathogens. The variant allele, *HLA-B*58:01* 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, 2]).

At this time, the FDA-approved drug label does not discuss *HLA-B* genotype ([3]). 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 alternative medication should be considered to avoid the risk of developing SCAR (see Table 1) ([1, 3]).

Table 1.

HLA-B phenotypes and the therapeutic recommendations for allopurinol therapy

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]).

Drug: Allopurinol

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 a commonly prescribed drug for the management of gout and hyperuricemia. It 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 ([4]).

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 ([3]).

In general, allopurinol is well tolerated. However, allopurinol is one of the most common causes of SCAR. SCAR may manifest as Stevens-Johnson syndrome (erythema multiforme exudativum), or as toxic epidermal necrolysis. It is also associated with fever, raised white cell count, hepatitis, and acute renal failure. Although allopurinol induced-SCAR is rare (the risk is estimated to be 0.1–0.4%), it is one of the most serious causes of SCAR, with a mortality rate of up to 25% ([1]).

The FDA-approved dose of allopurinol for the management of gout or hyperuricemia is to start with a daily dose of 100mg, and titrate the dose upwards to a maximum daily dose of 800mg, until the uric acid concentrations are less than 6.0mg/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 ([5]). One study has found that a lower starting dose of allopurinol may reduce the risk of allopurinol hypersensitivity syndrome ([6]).

The *HLA-B*58:01* allele has been strongly associated with allopurinol-induced SCAR. The ability to identify individuals with the at-risk allele may lead to safer prescribing practices for allopurinol.

Gene: *HLA-B*

The human leukocyte antigen B (*HLA-B*) gene is a member of the major histocompatibility complex (MHC) gene family, which consists of HLA class I, II, and III subgroups. HLA-B is a class I HLA molecule and it presents peptide fragments to immune cells (CD8+ T cells). Most of these peptides are the breakdown products from normal cell proteins (“self”). However, if foreign peptide fragments are presented, e.g., from a pathogen, the CD8+T cells will recognize the peptides as “non-self” and be activated to release inflammatory cytokines and launch an immune response ([7]).

Because the HLA genes 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. Variations in the HLA genes play an important role in determining susceptibility to autoimmune disease and infections; they are also critical in the field of transplant surgery where the donor and recipient must be HLA-compatible ([1]).

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

The frequency of the *HLA-B*58:01* allele varies significantly by population. The allele is most common in individuals of Asian descent, with a frequency of ~12% in Koreans, and ~6-8% in the Han Chinese and individuals of Thai extraction ([2, 8-11]). In Europeans, the allele is less common, with a frequency of ~1% ([12, 13]).

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 in *HLA-B*58:01* carriers was 73 (using healthy controls) and 165 (using allopurinol-tolerant controls) in a meta-analysis ([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]).

Therapeutic Recommendations based on Genotype

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

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). 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]).

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 ([2]).

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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Tests in GTR by Gene

HLA gene