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

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Introduction

Allopurinol (brand names Zyloprim, Aloprim) is a xanthine oxidase inhibitor that decreases the production of uric acid. It is most commonly used to manage gout, tumor lysis syndrome, and symptomatic hyperuricemia (high levels of uric acid). It is not indicated for use in asymptomatic hyperuricemia (1).

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 common among Asian subpopulations, notably in individuals of Korean, Han-Chinese, or Thai descent.

At this time, the FDA-approved drug label for allopurinol does not discuss *HLA-B* genotype (Table 1) (1). However, the American College of Rheumatology (ACR) conditionally recommends testing *HLA–B*5801* before starting allopurinol for individuals of Southeast-Asian descent (for example, Han-Chinese, Korean, Thai) and African-Americans (Table 2) (2). For individuals who are positive for the *HLA-B*58:01* variant, an alternative drug is recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) (Table 3 and 4). While CPIC states allopurinol is contraindicated in carriers of *HLA-B*58:01*, both DPWG and ACR state that a possible option is allopurinol desensitization (3, 4, 5).

Table 1. The FDA Allopurinol Dosage and Administration (2019)

Drug	Dosage
Allopurinol	The minimal effective dosage is 100–200 mg daily and the maximal recommended dosage is 800 mg daily. To reduce the possibility of gout flares, it is recommended that the individual start with a low dose of allopurinol tablets (100 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dL or less is attained but without exceeding the maximal recommended dosage.

This FDA table is adapted from (1). Dosage information given is for individuals with normal renal function.

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Table 2. The ACR Recommendations for Individuals Taking Allopurinol (2020)

Genotype	Testing
*HLA–B*58:01*	We conditionally recommend testing *HLA–B*58:01* before starting allopurinol for individuals of Southeast-Asian descent (for example, Han-Chinese, Korean, Thai) and African-American individuals, who have a higher prevalence of *HLA–B*5801*. We conditionally recommend against *HLA–B*58:01* testing in all others. For individuals with a prior allergic response to allopurinol who cannot be treated with other oral urate-lowering therapies, we conditionally recommend using allopurinol desensitization.

Note: certainty of evidence is 'Very low'.
This ACR table is adapted from (2). ACR, American College of Rheumatology

Table 3. The DPWG Allopurinol Dosing based on *HLA-B*58:01* Genotype (2017)

Genotype	Dosing recommendations
Positive for *HLA-B*58:01*	Choose an alternative, such as febuxostat Another option is to induce allopurinol tolerance first: the allopurinol dose is increased every 3 days until a dose of 100 mg/day has been achieved on day 28. The consecutive daily doses in the induction protocol are 50 µg, 100 µg, 200 µg, 500 µg, 1 mg, 5 mg, 10 mg, 25 mg, 50 mg, and 100 mg.

This DPWG table is adapted from (5). DPWG, Dutch Pharmacogenetics Working Group

Table 4. CPIC Recommended Therapeutic Use of Allopurinol by *HLA-B* Genotype (2015)

Genotype test results	Example of diplotypes	Phenotype	Therapeutic recommendations
Negative for *HLA-B*58:01*	*(*X/*X)*[b]	Low or reduced risk of allopurinol-induced SCAR	Use allopurinol per standard dosing guidelines
Positive for *HLA-B*58:01*	**58:01/(*X)*[b] **58:01/*58:01*	Significantly increased risk of allopurinol-induced SCAR	Allopurinol is contraindicated

The strength of therapeutic recommendations is "strong" (3, 4).
SCAR, severe cutaneous adverse reaction, CPIC, Clinical Pharmacogenetics Implementation Consortium
[b] **X*, any *HLA-B* genotype other than *HLA-B*58:01*
This table adapted from (4) with standardized terminology (6).

Drug: Allopurinol

Allopurinol is a commonly prescribed drug for the management of gout, tumor lysis syndrome, or for individuals with recurrent calcium oxalate calculi with daily uric acid excretions above 800 mg/day for men and 750 mg/day for women (1, 7). It is not recommended for preventative treatment of asymptomatic and non-severe hyperuricemia (8). 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 (9).

Allopurinol is rapidly oxidized in the liver to the active metabolite oxypurinol, which is the primary inhibitor of xanthine oxidase. Allopurinol has a short plasma half-life of ~1–2 hours, whereas oxypurinol has a half-life of ~15 hours in individuals with normal renal function. After the rapid oxidation of allopurinol, any remaining drug is promptly filtered and excreted by the kidneys. Thus, oxypurinol clearance correlates with kidney function, and individuals with reduced renal function will have much longer plasma half-lives (10). 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 on by the effects of oxypurinol (1). It has been shown that oxypurinol can be removed by hemodialysis in individuals with end stage renal disease (11).

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

Allopurinol-induced Adverse Drug Reactions

In general, there are 2 categories of adverse drug reactions. Type A reactions account for up to 85–90% of all adverse drug reactions (12). 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 a gout flare after starting allopurinol therapy.

Type B reactions account for the remaining 10–15% of all adverse drug reactions (12). 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.

Allopurinol-induced SCARs are examples of 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). Both SJS and TEN are disorders on the same spectrum, differentiated by the extent of skin detachment. Detachment on less than 10% of the total body surface area is classified as SJS, and on over 30% is classified as TEN; 10–30% detachment is SJS-TEN overlap. In contrast, DRESS has significantly less (or no) skin detachment or mucocutaneous involvement, maculopapular exanthema is the most common presentation. As the name implies, DRESS is also characterized by common multisystemic involvement that may include hematologic, renal, hepatic, cardiac, pulmonary, neurologic, gastrointestinal, and endocrine abnormalities. (13)

Allopurinol is one of the most common causes of SJS/TEN in Europe and Israel with similar reports from Singapore, Korea, and China (14, 15, 16, 17). Both are life-threatening conditions that are primarily characterized by lesions of the skin (detachment of the epidermis) and mucus membranes (severe erosions). Both conditions are 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 (3, 18). 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 has a mortality rate of up to 25% (3, 4).

One theory, known as the p-I concept, is that there is a direct pharmacological reaction of the drug (for example, 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 (for example, *HLA-B*58:01*) (18, 19, 20, 21, 22).

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 to a maximum daily dose of 800 mg, until the uric acid concentrations are less than 6.0 mg/dl. It has been suggested that titrating the starting dose based on kidney function can reduce the risk of adverse drug reactions (ADR). One proposed dosage model is starting allopurinol at a dose of 1.5 mg per unit of estimated glomerular filtration rate (23). 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 (24). One study has found that a lower starting dose of allopurinol may reduce the risk of allopurinol hypersensitivity syndrome (23). An additional retrospective database study similarly found that older individuals prescribed higher

allopurinol starting doses (≥300 mg/day versus <200 mg/day) had a higher hazard ratio of an adverse drug reaction (25). The DPWG guidelines recommend a gradual titration regimen to support allopurinol tolerance in individuals with ADR-associated genotypes (5). There is emerging evidence supporting a gradual dose escalation approach to achieve target serum urate levels in most individuals, including those with chronic kidney disease. This approach depends upon appropriate monitoring and should be limited to individuals who do not experience adverse effects to allopurinol therapy (26, 27).

The HLA Gene Family

The HLA genes are members of the major histocompatibility complex (MHC) gene family, which includes more than 200 genes. The MHC family has been subdivided into 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 (for example, 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 (28).

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 2 digit number that corresponds to antigen specificity, and the assigned allele number (29). 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, namely, 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 (namely, 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 (3, 4). 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 have 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 individuals who had allopurinol-induced SJS/TEN (51/51, 100%) carried *HLA-B*58:01*, compared with only 15% of the allopurinol-tolerant individuals (20/135, 15%) (30).

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 (31, 32, 33). 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 (34).

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% among individuals of Thai descent (35, 36, 37, 38, 39, 40). The risk allele is less common among Europeans and Japanese with a frequency of only ~1–2% (41, 42).

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 (for example, Europeans), the risk of allopurinol-induced SCAR is substantially elevated in *HLA-B*58:01* carriers.

Linking *HLA-B* Genetic Variation with the Risk of Side Effects and Treatment Response

The relationship between *HLA-B*58:01* and allopurinol-induced SJS/TEN continues to be reported in many ethnicities, including in Taiwanese, Japanese, Korean, Thai, and Malaysian individuals (2, 43, 44, 45, 46, 47, 48, 49).

While *HLA-B*58:01* is the most well-known risk factor, other genetic risk factors may include *HLA-B75*, *DR13* homozygosity, and *DR14*, especially in individuals with chronic kidney disease (50). Non-genetic risk factors include kidney impairment, allopurinol starting dose, and concomitant diuretic use (10). Experts caution against reliance of the *HLA-B*58:01* as a sole predictor for development of allopurinol-induced adverse drug reactions (51). Both genetic and non-genetic risk factors contribute to adverse effect risks, and tolerance induction protocols now exist for individuals at higher risk (regardless of genotype) (10).

Genetic Testing

Genetic testing is available for several *HLA-B* alleles, including *HLA-B*58:01*, and for allopurinol response. 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 (3, 4).

The ACR and CPIC recommend *HLA-B*58:01* screening for select populations before initiation of allopurinol therapy. However, *HLA-B*58:01* testing has not been approved by the FDA for this indication, and screening in select populations is underutilized (52, 53, 54). The ACR 2020 guidelines recommend *HLA-B*58:01* testing for Southeast-Asian and African-American descent individuals, but discourage use of this test in other ethnic groups unless the individual and their medical provider agree to proceed with testing (2) (see Therapeutic Recommendations based on Genotype). The rationale likely stems from the rarity of this allele outside of those specific populations and lack of cost-effectiveness of the testing.

Both *HLA-B*58:01* screening and avoidance of allopurinol when testing positive has shown to be, or estimated to be, cost-effective in several ethnic groups (for example, Chinese, Taiwanese, Korean, and in the US-Asians and African-Americans). Screening may not be cost-effective in other groups for example, Malaysians (43, 48, 55, 56, 57); however, routine testing for *HLA-B*58:01* is expected to become cost-effective with reductions in genotyping cost and the costs of alternative treatments for gout (for example, cheaper, generic febuxostat) (58, 59).

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 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 (34); however, the sensitivity and specificity of these linked variants may not be adequate in different ancestral populations.

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.

2019 Statement from the US Food and Drug Administration (FDA)

The dosage of allopurinol tablets to accomplish full control of gout and to lower serum uric acid to normal or near-normal levels varies with the severity of the disease. The average is 200 to 300 mg/day for individuals with mild gout and 400 to 600 mg/day for those with moderately severe tophaceous gout. The appropriate dosage may be administered in divided doses or as a single equivalent dose with the 300-mg tablet. Dosage requirements in excess of 300 mg should be administered in divided doses. The minimal effective dosage is 100 to 200 mg daily and the maximal recommended dosage is 800 mg daily. To reduce the possibility of flare-up of acute gouty attacks, it is recommended that the individual start with a low dose of allopurinol tablets (100 mg daily) and increase at weekly intervals by 100 mg until a serum uric acid level of 6 mg/dL or less is attained but without exceeding the maximal recommended dosage.

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

2020 Statement from the American College of Rheumatology (ACR)

Testing for the *HLA–B*58:01* allele prior to starting allopurinol is conditionally recommended for individuals of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American individuals, over not testing for the *HLA–B*58:01* allele.

Universal testing for the *HLA–B*5801* allele prior to starting allopurinol is conditionally recommended *against* in individuals of other ethnic or racial background over testing for the *HLA–B*5801* allele. [Conditional recommendations are those "which would warrant provider-individual shared medical decision-making discussion."]

As noted above, starting allopurinol in daily doses of ≤100 mg (and lower doses in individuals with CKD [chronic kidney disease]) is strongly recommended over starting at a higher dose.

The *HLA–B*58:01* allele is associated with a markedly elevated risk for AHS. The prevalence of *HLA–B*58:01* is highest among persons of Han Chinese, Korean, and Thai descent (7.4%), lower among African Americans (3.8%), and even lower among whites and Hispanics (0.7% each). Testing for this allele among Asians and African American individuals was reported to be cost-effective (incremental cost-effectiveness ratios <$109,000 per quality-adjusted life years). Asian and African American individuals taking allopurinol both have a 3-fold increased risk of AHS compared with white individuals taking allopurinol (for recommendations for ULT medications, see Table 4 and Supplementary Figure 3, available [online]).

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

[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.

2017 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

Individuals with the *HLA-B*58:01* genetic variation have a strongly increased risk of developing the life-threatening cutaneous side effects Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and DRESS. The risk of an allopurinol-induced life-threatening cutaneous side effect in these individuals is 1.6-13% in the case of a normal or slightly reduced renal function and 12-100% in the case of a severely reduced renal function.

Recommendation:

- Choose an alternative, such as febuxostat.

Another option is to induce allopurinol tolerance first:

To induce allopurinol tolerance, the allopurinol dose is increased every 3 days until a dose of 100 mg/day has been achieved on Day 28. The consecutive daily doses in the induction protocol are 50 µg, 100µg, 200µg, 50 µg, 1mg, 5mg, 10mg, 25 mg, 50mg and 100mg.

Please review the complete therapeutic recommendations that are located here (5).

2015 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Given the high specificity for allopurinol-induced SCAR, allopurinol should not be prescribed to individuals who have tested positive for *HLA-B*58:01*. Alternative medication should be considered for these individuals to avoid the risk of developing SCAR. For individuals who have tested negative, allopurinol may be prescribed as usual. 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 (3, 4).

Allele 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/
MHC, major histocompatibility complex

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