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NLM Citation: Dean L. Lesinurad Therapy and *CYP2C9* Genotype. 2019 Feb 11. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Lesinurad Therapy and *CYP2C9* Genotype

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Created: February 11, 2019.

Introduction

Lesinurad (brand name Zurampic) is a urate transport inhibitor used in the treatment of gout. Gout is one of the most common types of inflammatory arthritis, affecting approximately 3% of adults worldwide. It is caused by the accumulation of urate crystals in joints. The long-term management of gout includes reducing risk factors (e.g., obesity, alcohol use, diuretic use, poor renal function), and medication to lower uric acid levels.

Lesinurad reduces the high level of uric acid (hyperuricemia) associated with gout. Lesinurad should only be used in combination with a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat) –– the risk of acute renal failure is increased if lesinurad is used alone.

The addition of lesinurad to gout treatment is reserved for patients who have failed to achieve their target uric acid level despite being treated with a xanthine oxidase inhibitor. Xanthine oxidase inhibitors reduce uric acid by inhibiting its production, whereas lesinurad reduces uric acid by blocking its reabsorption in the kidney.

Lesinurad is primarily metabolized by CYP2C9 to several inactive metabolites. Individuals who lack CYP2C9 activity ("CYP2C9 poor metabolizers") have an increased exposure to lesinurad, and an increased risk of side effects. Adverse reactions of lesinurad therapy include kidney stones and other kidney problems. Lesinurad is also associated with an increased risk of cardiovascular events.

The FDA-approved drug label for lesinurad states that lesinurad should be used with caution in CYP2C9 poor metabolizers, but does not provide specific dose adjustments in this group (Table 1). The standard dose of lesinurad is 200 mg daily (1). Lesinurad is contraindicated in patients with severe impairment of kidney function (e.g., kidney transplant and hemodialysis patients) as well as individuals with tumor lysis syndrome or Lesch-Nyhan syndrome.

Table 1. The FDA (2018) Drug Label for Lesinurad. CYP2C9 Inhibitors, CYP2C9 Poor Metabolizers, and CYP2C9 Inducers.

Phenotype	Recommendations
CYP2C9 Poor metabolizer	Lesinurad exposure is increased when lesinurad is co-administered with inhibitors of CYP2C9 and in CYP2C9 poor metabolizers. Lesinurad should be used with caution in patients taking moderate inhibitors of CYP2C9 (e.g., fluconazole, amiodarone), and in CYP2C9 poor metabolizers.

This table is adapted from (1).

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Drug: Lesinurad

Lesinurad is a urate transporter inhibitor used to treat the increased level of uric acid in patients with gout. Lesinurad should only be used for patients with gout who have high levels of uric acid despite being treated with a xanthine oxidase inhibitor, and lesinurad should only be used in combination with a xanthine oxidase inhibitor (1).

Gout is one of the most common types of inflammatory arthritis. It affects approximately 3% of adults worldwide, and the prevalence is increasing (2-5). Gout is caused by the body's inflammatory response to an accumulation of urate crystals. A high level of uric acid in the blood (above 6.8 mg/dl indicates hyperuricemia) always precedes gout. However, the majority of individuals with hyperuricemia do not develop urate crystal deposits and gout, and lesinurad should not be used to treat asymptomatic hyperuricemia.

Patients with gout usually have an extremely painful, swollen joint –– this is known as acute gouty arthritis. A single joint in the lower limb is most commonly affected (e.g., the base of the big toe, knee), and the joint will remain painful for at least several days. In a minority, persistent hyperuricemia leads to chronic gout, which is associated with deposits of urate crystals known as tophi.

Medications for gout focus on lowering uric acid levels. There are 3 main types of drugs:

- xanthine oxidase inhibitors that decrease the production of uric acid (e.g., allopurinol, febuxostat)
- uricosuric drugs that inhibit the reabsorption of uric acid in the kidneys (e.g., benzbromarone, probenecid, and lesinurad)
- uricase drugs that convert uric acid to a more soluble metabolite (e.g., pegloticase, rasburicase)

Lesinurad is the newest uricosuric drug to be approved for gout. However, since the introduction of allopurinol in the 1960s, uricosuric drugs have not been commonly used. This is because they are associated with numerous drug interactions and side effects (6-8).

Like other uricosuric drugs, lesinurad inhibits the urate transporter 1 (URAT1), which mediates reabsorption of uric acid in the kidney, and the organic anion transporter 4 (OAT4), which is implicated with hyperuricemia associated with diuretic use. But unlike probenecid, lesinurad does not appear to inhibit OAT1 or OAT3, and this may result in fewer drug interactions and adverse events (9). However, like all uricosuric agents, lesinurad is associated with the development of kidney stones (10-12).

There are many risk factors that may contribute to triggering a gout attack. These include dietary factors, dehydration, and alcohol use. In addition, medications that alter serum concentrations of uric acid, such as diuretics and gout medications, can trigger gout. Therefore, when starting medical therapy for gout, it is recommended that urate levels are reduced slowly (e.g., 1–2 mg/dl per month). To prevent flare-ups, an additional drug such as colchicine may be used to reduce swelling and pain until target serum levels have been achieved and maintained (13).

Allopurinol is the mainstay treatment for gout –– it is effective in lowering uric acid levels, reduces the frequency of gout attacks, and contributes to resolving tophi. However, in individuals who are carriers of the genetic variant *HLA-B*58:01*, allopurinol is associated with severe cutaneous adverse reactions (SCAR) (14, 15). For these individuals, febuxostat may be the safer choice –– it is a structurally different xanthine oxidase inhibitor that is not associated with SCAR (13).

In general, when allopurinol is used at an adequate dose, levels of uric acid can reach the target range of below 6 mg/dl (16, 17). If uric acid levels stay in this range, subsequent attacks of gout are unlikely. However, allopurinol therapy is needed long term; compliance is often poor; therefore, patient education is important (11, 18).

Several trials have shown that the addition of lesinurad to allopurinol therapy leads to a greater reduction in uric acid levels, and at the recommended dose of 200 mg daily, lesinurad is generally well tolerated (19-21).

Adverse effects associated with lesinurad therapy include rising creatinine levels, which are often reversible, nephrolithiasis (kidney stones), urolithiasis (stones in the bladder or urinary tract), and acute renal failure – which is associated more with lesinurad monotherapy (not recommended by the FDA) at the higher drug dose of 400 mg (twice the FDA-approved dose). Lesinurad is also associated with an increased risk of cardiovascular events (22).

Patients with moderate renal impairment experience a 150% increase in exposure to lesinurad, which should be used with caution in these patients (23). Lesinurad is contraindicated in individuals with severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis as well as individuals with tumor lysis syndrome or Lesch-Nyhan syndrome.

Lesinurad is primarily metabolized by CYP2C9 to several inactive metabolites. The co-administration of lesinurad with moderate inducers of CYP2C9 (e.g., rifampin, carbamazepine), may decrease the therapeutic effect of lesinurad by reducing its exposure.

In contrast, the co-administration of lesinurad with drugs that are CYP2C9 inhibitors (e.g., fluconazole, amiodarone), or the administration of lesinurad to patients who lack CYP2C9 activity ("CYP2C9 poor metabolizers"), will increase exposure to lesinurad. This may increase the risk of adverse reactions.

Therefore, lesinurad should be used with caution in patients with moderate kidney disease, patients taking CYP2C9 inhibitors, and patients who are CYP2C9 poor metabolizers (1, 24).

Gene: CYP2C9

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The CYP450 genes are very polymorphic and can result in reduced, absent, or increased enzyme activity (25).

The *CYP2C9* gene is highly polymorphic, with approximately 60 known alleles. *CYP2C9*1* is considered the wild-type allele when no variants are detected and is categorized as normal enzyme activity (26). Individuals who have 2 normal-function alleles (e.g., *CYP2C9 *1/*1*) are classified as "normal metabolizers" (Table 2).

Table 2. Assignment of likely *CYP2C9* Phenotype based on Genotype (CPIC, 2014)

Likely phenotype[a]	Genotype	Examples of diplotypes
Ultrarapid metabolizer (increased activity) (frequency unknown)	Unknown – currently there are no known increased activity alleles	Unknown
Normal metabolizer (normal activity) (approximately 91% of individuals)	An individual with 2 normal-function alleles	*1/*1
Intermediate metabolizer (heterozygote or intermediate activity) (approximately 8% of individuals)[b]	An individual with one normal-function allele plus one decreased-function allele	*1/*3, *1/*2

Table 2. continued from previous page.

Likely phenotype[a]	Genotype	Examples of diplotypes
Poor metabolizer (homozygous variant, low or deficient activity) (approximately 1% of individuals)	An individual with 2 decreased-function alleles	*2/*2, *3/*3, *2/*3

Note: There are no known cases of CYP2C9 ultrarapid metabolizers.
a Global frequencies are approximate. Because haplotype frequencies vary considerably among popualations, please see (26) for individual population frequencies.
[b] The enzyme activity in this grouping varies widely. Please see (26) for activity ranges.
This table is adapted from (26). Note: The nomenclature used in this table reflects the standardized pharmacogenetic terms proposed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) (27).

Two allelic variants associated with reduced enzyme activity are *CYP2C9*2* and **3*. The **2* allele is more common in Caucasian (10-20%) than Asian (1-3%) or African (0-6%) populations. The **3* allele is less common (<10% in most populations) and is extremely rare in African populations. In African-Americans, the *CYP2C9*5*, **6*, **8* and **11* alleles are more common (28-30).

Linking Gene Variation with Treatment Response

Currently, data are limited on the relationship between an individual's *CYP2C9* status and their response to lesinurad therapy.

The lesinurad drug label discusses an analysis of a small group of patients –– 2 patients were CYP2C9 poor metabolizers, and 41 were normal CYP2C9 metabolizers. At the 400 mg dose of lesinurad (which is twice the recommended dose of 200 mg daily), exposure to lesinurad was approximately 1.8 times higher in poor metabolizers compared to normal metabolizers. Therefore, the label states that lesinurad should be used with caution in CYP2C9 poor metabolizers.

The drug label also states that lesinurad should be used with caution in patients taking drugs that are CYP2C9 inhibitors (because of increased exposure and risk of side effects) and in patients taking drugs that are CYP2C9 inducers (because of decreased exposure and risk of reduced therapeutic effect). Drugs that inhibit CYP2C9 include fluconazole (antifungal agent) and amiodarone (antiarrhythmic); and drugs that induce CYP2C9 include rifampin (antibiotic) and carbamazepine (anti-seizure drug) (1).

Genetic Testing

Clinical genotyping tests are available for several *CYP2C9* alleles. The NIH Genetic Testing Registry (GTR) displays genetic tests that are currently available for lesinurad response and for the *CYP2C9* gene.

The *CYP2C9* variants that are routinely tested for include *CYP2C9*2* and **3*. Usually the results are reported as a diplotype, such as *CYP2C9 *1/*1*, and may also include an interpretation of the patient's predicted metabolizer phenotype (normal, intermediate, or poor). Table 2 summarizes common CYP2C9 phenotypes.

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.

[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 labelled all formulations containing the generic drug.

2018 Statement from the US Food and Drug Administration (FDA)

Lesinurad exposure is increased when lesinurad is co-administered with inhibitors of CYP2C9, and in CYP2C9 poor metabolizers. Lesinurad should be used with caution in patients taking moderate inhibitors of CYP2C9 (e.g., fluconazole, amiodarone), and in CYP2C9 poor metabolizers.

Lesinurad exposure is decreased when lesinurad is co-administered with moderate inducers of CYP2C9 (e.g., rifampin, carbamazepine), which may decrease the therapeutic effect of lesinurad.

[…]

Patients who are CYP2C9 poor metabolizers are deficient in CYP2C9 enzyme activity. A cross-study pharmacogenomic analysis assessed the association between CYP2C9 polymorphism and lesinurad exposure in patients receiving single or multiple doses of lesinurad at 200 mg, 400 mg or 600 mg. At the 400 mg dose, lesinurad exposure was approximately 1.8-fold higher in CYP2C9 poor metabolizers (i.e., subjects with *CYP2C9 *2/*2* [N=1], and **3/*3* [N=1] genotype) compared to CYP2C9 extensive metabolizers (i.e., *CYP2C9 *1/*1* [N=41] genotype). Use with caution in CYP2C9 poor metabolizers, and in patients taking moderate inhibitors of CYP2C9.

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

Nomenclature for selected *CYP2C9* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C9*2*	430C>T Arg144Cys	NM_000771.3:c.430C>T	NP_000762.2:p.Arg144Cys	rs1799853
*CYP2C9*3*	1075A>C Ile359Leu	NM_000771.3:c.1075A>C	NP_000762.2:p.Ile359Leu	rs1057910
*CYP2C9*5*	1080C>G Asp360Glu	NM_000771.3:c.1080C>G	NP_000762.2:p.Asp360Glu	rs28371686
*CYP2C9*6*	818delA Lys273Argfs	NM_000771.3:c.817delA	NP_000762.2:p.Lys273Argfs	rs9332131
*CYP2C9*8*	449G>A Arg150His	NM_000771.3:c.449G>A	NP_000762.2:p.Arg150His	rs7900194
*CYP2C9*11*	1003C>T Arg335Trp	NM_000771.3:c.1003C>T	NP_000762.2:p.Arg335Trp	rs28371685

Note: the normal "wild-type" allele is *CYP2C9*1* and is reported when no variant is detected.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (31).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

Acknowledgments

The author would like to thank Andy R. Eugene, MD, PhD, Assistant Professor of Pharmacogenomics, Bernard J. Dunn School of Pharmacy, Shenandoah University - Fairfax Inova Center for Personalized Health, Fairfax, VA, USA; Houda Hachad, PharmD, MRes, Chief Science Officer, Translational Software, Seattle, WA, USA; Neil William McGill, Clinical Associate Professor, University of Sydney, and Rheumatologist, Royal Prince Alfred Hospital, Syndey, NSW, Australia; Mohamed Nagy, Clinical Pharmacist, Head of the Personalised Medication Management Unit, Department of Pharmaceutical Services, Children's Cancer Hospital, Cairo, Egypt; and

Chakradhara Rao S. Uppugunduri, Maître-Assistant at the CANSEARCH Laboratory, University of Geneva, Geneva, Switzerland, for reviewing this summary.

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