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Pegloticase Therapy and *G6PD* Genotype

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Introduction

Pegloticase (brand name Krystexxa) is used to treat the high levels of uric acid associated with refractory gout. The use of pegloticase is reserved for individuals with symptomatic, chronic gout who have not responded to, or are unable to take, conventional gout treatments. Pegloticase is given once every 2 weeks as an intravenous infusion, and is given in a healthcare setting that is prepared to manage infusion reactions and anaphylaxis (1).

Pegloticase is a pegylated urate oxidase – a modified version of the enzyme that catalyzes the oxidation of uric acid to 5-hydroxyisourate and hydrogen peroxide in most mammalian species. However, urate oxidase is not active in humans due to an inactivating mutation in the gene (2). Subsequent hydrolysis and decarboxylation of 5-hydroxyisourate leads to the formation of a more soluble metabolite (allantoin), which is then excreted by the kidneys.

Red blood cells that lack the glucose-6-phosphate dehydrogenase (G6PD) enzyme are sensitive to oxidative damage caused by agents like hydrogen peroxide. Once exposed, the red blood cells become rigid, trapped, and are rapidly broken down (hemolysis). This can lead to a deficiency of mature red blood cells (hemolytic anemia) and the production of red blood cells with abnormally high levels of methemoglobin (methemoglobinemia).

Approximately 400 million people worldwide have G6PD deficiency. Most of these individuals are asymptomatic. However, they are at risk of life-threating hemolytic reactions and methemoglobinemia if given oxidizing drugs such as pegloticase.

Pegloticase is contraindicated in individuals with G6PD deficiency. The FDA-approved label states that individuals at higher risk for G6PD deficiency should be screened before starting pegloticase therapy, with specific examples including individuals of African, Mediterranean (including Southern European and Middle Eastern), and South Asian ancestry (Table 1) (1). Importantly, approximately 12% of African-Americans have G6PD deficiency.

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Table 1. The FDA Drug Label for Pegloticase. Glucose-6-phosphate dehydrogenase Deficiency Associated Hemolysis and Methemoglobinemia (2020)

Phenotype	Recommendations
G6PD deficiency	Screen individuals at risk for G6PD deficiency before starting pegloticase. For example, individuals of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency. Life threatening hemolytic reactions and methemoglobinemia have been reported with pegloticase in individuals with G6PD deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer pegloticase to individuals with G6PD deficiency.

This table is adapted from (1).

Drug: Pegloticase

Pegloticase is a urate-lowering drug for adults with severe, chronic refractory gout, which is administered intravenously every 2 weeks. Pegloticase is a member of the drug class of uricases (urate oxidases), which also includes rasburicase. While rasburicase (brand name Elitrek) is licensed for use in managing tumor lysis syndrome, pegloticase is used to treat adults with severe, refractory chronic gout who cannot tolerate or have failed to respond to adequate doses and combinations of available uricostatic or uricosuric urate-lowering drugs.

Gout is one of the most common types of inflammatory arthritis. It affects approximately 4% of adults in the USA and though its global incidence and prevalence are increasing, they have now stabilized in high income Western countries (3-6). Gout is caused by an inflammatory response to urate crystals. Prolonged asymptomatic elevation of serum urate levels (hyperuricemia) above a solubility saturation threshold of approximately 6.8 mg/dL always precedes the development of gout. However, most individuals with hyperuricemia do not develop clinical gouty arthritis, and urate-lowering drugs including pegloticase are not used to treat asymptomatic hyperuricemia.

Patients with gouty arthritis usually present for the first time with an extremely painful acute inflammatory monoarthritis (gout flare) in a lower limb joint such as the first metatarsophalangeal joint in the great toe (podagra), the ankle, or knee. Acute gout flares can occur in the elbows, wrists or small joints of the hands but flares in joints of the upper limbs and acute flares in multiple joints (polyarticular gout) are usually restricted to individuals with longstanding poorly controlled disease. Without treatment, acute gout attacks are self-limiting and will settle in 7–14 days. Following resolution, individuals have a pain-free period of variable length (intercritical gout) before experiencing a further flare. In a few individuals, persistent hyperuricemia is associated with palpable or visible, or both, sub-cutaneous granulomata containing masses of urate crystals known as tophi.

While acute gout flares are treated with anti-inflammatory medications, definitive treatment of gout requires continuous medication with urate-lowering drugs at doses that maintain the serum urate level below that required to prevent urate crystal formation and dissolve existing urate deposits.

There are 3 main types of urate-lowering drugs:

- Uricostatic xanthine oxidase inhibitors that decrease the production of uric acid (for example, allopurinol, febuxostat)
- Uricosuric drugs that inhibit the reabsorption of uric acid in the kidneys (for example, benzbromarone, probenecid, and lesinurad)
- Uricase drugs that convert uric acid to a more soluble metabolite (for example, pegloticase, rasburicase)

Xanthine oxidase inhibitors are the mainstay treatment for gout, with the addition of uricosuric drugs being reserved for individuals who do not have an adequate response.

Despite conventional urate-lowering therapy for gout with uricostatic or uricosuric, or both drugs, a few individuals may continue to have symptomatic, chronic gouty arthritis, with tophi, and high serum uric acid levels. Intravenous infusions of pegloticase can lead to rapid and persistent lowering of urate levels and significant clinical improvement of symptoms in approximately 45% of these individuals (7-9).

Pegloticase is a pegylated urate oxidase –– a modified version of the enzyme that catalyzes the oxidation of uric acid to 5-hydroxyisourate and hydrogen peroxide in most mammalian species, but which is not active in humans. Subsequent hydrolysis and decarboxylation lead to the formation of a more soluble metabolite (allantoin), which is then excreted by the kidneys. Pegloticase is a predominantly porcine-like recombinant uricase, which is modified ("pegylated") to increase its half-life and to reduce the development of anti-drug protein antibodies. However, clinically significant anti-pegloticase antibodies are detected in approximately 40% of individuals treated with pegloticase, and a high level of antibodies is associated with a higher incidence of infusion reactions (10). However, most of the anti-pegloticase antibodies are directed at the polyethylene glycol component of the drug, rather than the uricase, leading to reduced efficacy as a result of increased drug clearance, and reduction in drug concentration associated with a secondary rise in serum urate levels.

The safety of pegloticase in pregnant women has not been studied, but animal studies showed no evidence of fetal harm. In pregnant rats and rabbits, no fetal structural abnormalities were seen after sub-cutaneous injections of pegloticase during the organogenesis stages of pregnancy.

Gout flares are the most common adverse reactions associated with pegloticase therapy despite flare prophylaxis with colchicine, nonsteroidal anti-inflammatory drugs, or corticosteroids. Infusion reactions and—very rarely—reactions fulfilling criteria for anaphylaxis can occur despite pre-treatment with antihistamines and corticosteroids. Approximately a quarter of individuals experience a mild to moderate infusion reaction with a pruritic urticarial rash, dyspnea, or chest discomfort. More severe anaphylactoid reactions with wheezing, swelling around the mouth and lips, and reduced blood pressure occur in less than 1% of individuals, usually within 2 hours of the infusion. Because of the risk of infusion reactions and anaphylaxis, pegloticase should only be administered in a healthcare setting with monitoring of the individual during the infusion and reducing or stopping treatment if necessary, and subsequently monitoring the individual after the infusion for any signs of anaphylaxis (7, 8, 11). The severity and frequency of these infusion reactions remains an area of debate within the field. The current FDA drug label includes a boxed warning regarding the possibility of anaphylaxis and infusion reactions that could occur during or after pegloticase administration, including the first infusion; thus pegloticase is recommended only for administration in a healthcare setting by providers prepared to manage anaphylaxis and infusion reactions (1, 12).

The use of pegloticase is contraindicated in individuals with G6PD deficiency because of the risk of acute hemolytic anemia and methemoglobinemia (1, 13, 14). This is because a byproduct of the conversion of uric acid to 5-hydroxyisourate is hydrogen peroxide, an oxidizing agent.

Individuals who have G6PD deficiency have red blood cells that are susceptible to oxidative damage. If exposed to agents such as hydrogen peroxide, the red blood cells become rigid, get trapped, and are subsequently destroyed by macrophages in the spleen, bone marrow, and liver. The rapid destruction of red blood cells is called hemolysis, and it may result in hemolytic anemia (a deficiency of red blood cells or hemoglobin, caused by hemolysis).

In addition, hemoglobin may be oxidized to methemoglobin. Hemoglobin binds oxygen and delivers oxygen to the body's tissues, while methemoglobin does not. Normally, approximately 1% of red blood cells contain methemoglobin. When the levels of methemoglobin increase, red blood cells are less able to delivery oxygen to tissues, resulting in cyanosis (bluish skin color), and potentially life-threatening arrhythmias and seizures (15).

Gene: *G6PD*

The G6PD enzyme is encoded by the *G6PD* gene, which is located on chromosome Xq28. As such, males are hemizygous for one *G6PD* allele, making them more susceptible to this X-linked disorder. Females randomly inactivate one X chromosome during development, resulting in a mosaic expression of either one X chromosome or the other in their somatic cells. This mosaicism can occur in the hematopoietic progenitor cells that give rise to red blood cells, resulting in mixed expression of *G6PD* alleles. Females with Turner syndrome (45, X) have only one X chromosome and thus are also hemizygous for the *G6PD* gene.

Glucose-6-phosphate dehydrogenase deficiency is the most common enzyme deficit in humans, affecting 400 million people worldwide (16), with a worldwide prevalence of approximately 5%. Glucose-6-phosphate dehydrogenase deficiency appears to be protective against malaria infection leading to a higher prevalence (more than 25%) in countries where malaria is, or once was, endemic (for example, tropical Africa, tropical and subtropical Asia, the Middle East, and some parts of the Mediterranean) (17-19). In the US, G6PD deficiency is more common among African-Americans, affecting approximately 12% (20).

The G6PD enzyme catalyzes the first step in the hexose monophosphate shunt (HMP) pathway, which converts glucose to pentose sugars for nucleic acid synthesis. In this step nicotinamide adenine dinucleotide phosphate (NADP+) is reduced to NADPH, which protects cells from oxidative stress. In mature red blood cells, the HMP pathway is the only source of NADPH. This promotes the generation of reduced glutathione that protects the sulfhydryl groups of hemoglobin, which are susceptible to oxidation by hydrogen peroxide and oxygen radicals. Red blood cells that lack G6PD also have a deficiency of NADPH.(21)

Red blood cells that are G6PD and NADPH deficient are more susceptible to oxidative stress by oxygen free radicals and hydrogen peroxide. Oxidative stress occurs naturally, but is increased during illnesses, such as infections and diabetic ketoacidosis. Oxidative stress can also follow the ingestion of fresh fava beans (favism) and is an adverse effect of several drugs (for example, the uric acid lowering drugs pegloticase and rasburicase, the antimalarial drugs primaquine and tafenoquine, the skin cancer drug dabrafenib, and the antibacterials, dapsone and sulfamethoxazole).

Most individuals with G6PD deficiency are asymptomatic –– they have a normal lifespan and may not know they have G6PD deficiency. However, at birth, they are predisposed to neonatal jaundice, and throughout life, they are sensitive to oxidizing agents. All individuals with G6PD deficiency should avoid oxidizing agents when possible, including drugs such as pegloticase.

Symptomatic individuals with G6PD deficiency may suffer from episodes of acute hemolytic anemia, jaundice, and hemoglobinuria or chronic, non-spherocytic, hemolytic anemia. The management of hemolytic episodes depends on the severity of hemolysis, with more severe cases requiring blood transfusions. Folic acid may be given to prevent the worsening of anemia in individuals with folate deficiency and to induce formation of new red blood cells.

More than 180 genetic variants of the *G6PD* gene have been identified, with approximately 400 biochemical and enzyme variants (22). Most known *G6PD* variants are missense, which can also be inherited as haplotypes that are comprised of more than one variant allele (23). Large deletions are rare, and a complete lack of G6PD activity is thought to be fatal in utero.

The normal (wild-type) copy of the *G6PD* gene is known as *G6PD B*, and is found in most individuals with European, Asian, or African ancestry. Common *G6PD* variants include:

- *G6PD* A+ (p.Asn126Asp) has normal enzyme activity and is not associated with hemolysis, and is found in up to 30% of blacks from Africa (24).

- *G6PD* A- (p.Asn126Asp and p.Val68Met) is associated with mild to moderate hemolysis, and is found in up to 15% of African-Americans (25). Additional *A*-haplotypes have also been identified, both with the A+ variant with a second single nucleotide polymorphisms (p.Asn126Asp with p.Arg227Leu; and p.Asn126Asp with p.Leu323Pro. See Nomenclature table below for additional information) (26).
- *G6PD* Mediterranean (p.Ser218Phe) can cause severe hemolysis, and is the most common abnormal variant in Caucasians (27).
- *G6PD* Canton (p.Arg489Leu) can cause severe hemolysis, and is found in Asians (28).

The World Health Organization categorized *G6PD* variants into 5 classes according to the level of enzyme activity and severity of hemolysis. Class 1 variants are the most severe, but rare in the general population. These variants have less than 10% of normal GP6D enzyme activity and are associated with chronic hemolytic anemia.

Most individuals with G6PD deficiency have Class II (enzyme activity less than 10% but no chronic hemolytic anemia) or Class III (enzyme activity between 10–60%) variants. Class II and III variants are associated with intermittent hemolysis, usually triggered by infection or drugs, but for most of the time, affected individuals have no symptoms. Class IV and V variants are not considered to be clinically significant, as they are associated with normal (class IV) or increased (class V) enzyme activity (29).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has assigned *G6PD* phenotypes based on *G6PD* genotypes (Table 2) (29).

Table 2. Assignment of likely *G6PD* Phenotype based on Genotype/Diplotype (CPIC 2014)

Likely phenotype	Definition	Genotype	Who class for *G6PD* variants[a]	Example of diplotype[b]
Normal	Very mild or no enzyme deficiency (less than 60% of normal enzyme levels)	A male who has a non-deficient (class IV) allele	IV	B, Sao Boria
		A female who has 2 non-deficient (class IV) alleles	IV/IV	B/B, B/Sao Boria
Deficient	Less than 10–60% of normal enzyme activity	A male who has a deficient (class II–III) allele	II, III	A–, Orissa, Kalyan-Kerala, Mediterranean, Canton, Chatham
		A female who has 2 deficient (class II–III variants) alleles	II/II, II/III, III/III	A–/A–, A–/Orissa, Orissa/Kalyan-Kerala, Mediterranean/Mediterranean, Chatham/Mediterranean, Canton/Viangchan
Deficient with CNSHA	Severe enzyme deficiency (<10% activity) and associated with CNHSA	A male who has a class I allele	I	Bangkok, Villeurbanne
		A female who has 2 deficient (class I variants) alleles	I/I	Bangkok/Bangkok, Bangkok/Villeurbanne

Table 2. continued from previous page.

Likely phenotype	Definition	Genotype	Who class for *G6PD* variants[a]	Example of diplotype[b]
Variable[c]	Normal or deficient enzyme activity[c]	A female who has one non-deficient (class IV) and one deficient (class I–III variants) allele	IV/I, IV/II, IV/III	B/A–, B/Mediterranean, B/Bangkok

CNSHA, chronic nonspherocytic hemolytic anemia
WHO, World Health Organization
[a] WHO classifications (Ref. 14 and Ref. 17, from (29)). Class I variants are extremely rare; the distinction between class II and III variants is not clear, and the "class V" very high activity variant has been reported in only a single case. Therefore, almost all individuals will have class II, III, or IV alleles. It should be noted that the class of a variant may have been assigned only by the clinical manifestations of an individual in which the variant was subsequently identified.
[b] Due to the large number of *G6PD* variants, many other diplotypes may be possible besides those given as examples here; see Supplementary Table S1 online for a more comprehensive list of variant alleles with their assigned WHO class (29). For HGVS terms, please see the Nomenclature table below.
[c] Due to X-linked mosaicism, females heterozygous for one non-deficient (class IV) and one deficient (class I–III variants) allele may display a normal or a deficient phenotype. It is therefore difficult to predict the phenotype of these individuals (Supplementary Material online (*G6PD* heterozygotes)) (29).
This table is adapted from (29).

Linking Gene Variation with Treatment Response

Although evidence that directly links G6PD status with an increased risk of hemolytic anemia is limited to case reports of individuals taking pegloticase, it is well established that hydrogen peroxide, which is produced during pegloticase therapy, can cause acute hemolysis in individuals with G6PD deficiency.

The first case of severe hemolysis and methemoglobinemia associated pegloticase therapy was reported in 2014, and a later case of hemolytic anemia was reported in 2016. In both cases, the individuals were later diagnosed to have G6PD deficiency (13-15).

Genetic Testing

The NIH Genetic Testing Registry, GTR, displays genetic tests that are available for pegloticase response and the *G6PD* gene. Molecular genetic testing can be used to confirm the diagnosis of G6PD and may also be used to screen females with a family history of G6PD to see if they are carriers.

Glucose-6-phosphate dehydrogenase deficiency is an X-linked recessive trait and most individuals are asymptomatic throughout life.

X-linked disorders affect males at a much higher rate than females because males only have one copy of the X chromosome (hemizygous, XY). Since females have 2 copies of the X chromosome (XX) they tend to be less affected. However, female carriers can present with a range of phenotypes from no symptoms through a severe deficiency due to the high frequency of *G6PD* variants. Females randomly inactivate one X chromosome in somatic cells during development, resulting in a mixed population of somatic cells expressing one *G6PD* allele or the other.

Glucose-6-phosphate dehydrogenase deficiency occurs in homozygous and compound heterozygous females (who have inherited 2 copies of *G6PD* deficiency alleles) and in heterozygous females (one normal *G6PD* allele and one deficiency *G6PD* allele) with skewed X-chromosome inactivation of the functional allele (18). Genetic testing alone is insufficient for heterozygous females with one normal function *G6PD* allele, as the expression of the 2 alleles will vary between blood cells and over time (29).

A heterozygous mother has a 50% chance of passing G6PD deficiency to a son and a 50% chance of passing the carrier trait to a daughter. Affected fathers pass the variant *G6PD* to their daughters, but not to their sons (21, 30).

The FDA recommends that individuals at risk of G6PD deficiency be screened for G6PD deficiency before starting pegloticase therapy. However, individuals of all ancestries may be G6PD deficient (worldwide prevalence of 5%). Therefore, caution must be taken in all individuals when initiating pegloticase therapy.

In routine clinical practice, G6PD deficiency is diagnosed by measuring the level of G6PD activity in red blood cells. Two different types of enzyme activity tests are used: qualitative and quantitative. Often, qualitative tests do not accurately detect individuals with intermediate G6PD activity. False results may be obtained immediately after a blood transfusion, because transfused cells are likely to have normal G6PD levels, and immediately after an episode of hemolysis, because young red blood cells have higher levels of G6PD. Therefore, screening for G6PD should be performed 2–3 months after a blood transfusion or hemolytic episode. Of note, G6PD activity false negatives have been reported (14, 21, 29, 31).

In men, if genetic testing determined that an individual was positive for G6PD deficiency, the use of pegloticase would be contraindicated. However, a negative result cannot be entirely relied upon because only a small subset of *G6PD* variants are routinely tested (21, 29, 30). In addition, *G6PD* phenotypes may be unpredictable in heterozygous females due to random X-chromosome inactivation.

Universal neonatal screening programs for G6PD deficiency are employed in some countries with a high incidence of G6PD deficiency (more than 3–5% of males) (32). These populations are primarily in Asia, Africa, along the Mediterranean and in the Middle East. Screening either uses quantitative enzyme activity assays, or the fluorescent spot test that visually identifies NADPH, which is produced by G6PD (if the blood spot does not fluoresce, the test is positive for G6PD deficiency) (29).

Relatively inexpensive rapid point of care qualitative tests are used in countries where G6PD deficiency is frequent and can identify individuals with severe G6PD deficiency who would be at risk of severe hemolysis with commencement of antimalarial drug therapy. Unfortunately, however, they are insufficiently sensitive for the detection of individuals with less severe G6PD deficiency in whom pegloticase is also contraindicated. (31)

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.

2020 Statement from the US Food and Drug Administration (FDA):

Contraindications: Glucose-6-phosphate dehydrogenase (G6PD) deficiency

[...]

Life threatening hemolytic reactions and methemoglobinemia have been reported with pegloticase in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer pegloticase to patients with G6PD deficiency. Screen patients at risk for G6PD deficiency prior to starting pegloticase. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

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

Nomenclature for Selected *G6PD* Variants

Common allele name / condition	Alternative names / condition	HGVS reference sequence		WHO Classification*	dbSNP reference identifier for allele location
		Coding	Protein		
G6PD B	WT	NM_001042351.3	NP_001035810.1	IV/ Normal	--
G6PD A+	p.Asn126Asp	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	IV/ Normal	rs1050828
G6PD Sao Boria	p.Asp113Asn	NM_001042351.3:c.337G>A	NP_001035810.1:p.Asp113Asn	IV/ Normal	rs5030870
G6PD A-	A-$^{202A/376G}$	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs1050829
		NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met		
G6PD A-	A-$^{680T/376G}$	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs137852328
		NM_001042351.3: c.680G>T	NP_001035810.1:p.Arg227Leu		
G6PD A-	A-$^{968C/376G}$	NM_001042351.3 :c.376A>G	NP_001035810.1:p.Asn126Asp	III/ Deficient	rs1050828 rs76723693
		NM_001042351.3:c.968T>C	NP_001035810.1:p.Leu323Pro		
G6PD Bangkok	p.Lys275Asn	NM_001042351.3:c.202G>A	NP_001035810.1:p.Val68Met	III/ Deficient	
G6PD Kalyan-Kerala	p.Glu317Lys	NM_001042351.3:c.949G>A	NP_001035810.1:p.Glu317Lys	III/ Deficient	rs137852339
G6PD Orissa	p.Ala44Gly	NM_001042351.3:c.131C>G	NP_001035810.1:p.Ala44Gly	III/ Deficient	rs78478128
GP6D Canton	p.Arg459Leu	NM_001042351.3: c.1376G>T	NP_001035810.1:p.Arg459Leu	II/ Deficient	rs72554665
G6PD Chatham	p.Ala335Thr	NM_001042351.3:c.1003G>A	NP_001035810.1:p.Ala335Thr	II/ Deficient	rs5030869
G6PD Mediterranean	p.Ser188Phe	NM_001042351.3:c.563C>T	NP_001035810.1:pSer188Phe	II/ Deficient	rs5030868
G6PD Viangchan	p.Val291Met	NM_001042351.3:c.871G>A	NP_001035810.1:p.Val291Met	II/ Deficient	rs137852327
G6PD Villeurbanne	p.Thr334del	NM_001042351.3:c.1000_1002delACC	NP_001035810.1:pThr334del	I/Deficient with CNSHA	

Additional allele information available from PharmGKB and CPIC's G6PD Allele Definition Table (revised 2018).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
* WHO classifications based on (33)

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