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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Pegloticase. [Updated 2018 May 21].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Pegloticase

Updated: May 21, 2018.

OVERVIEW

Introduction

Pegloticase is a pegylated, recombinant urate oxidase enzyme that is used to treat patients with chronic refractory and symptomatic gout. Pegloticase has not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Pegloticase (peg loe' ti kase) is a recombinant DNA-produced form of the porcine enzyme uricase that metabolizes urate to allantoin, an inert and water soluble purine metabolite that, unlike uric acid, is rapidly cleared by the kidney. Infusions of pegloticase decrease serum uric acid concentrations and can alleviate the symptoms and complications of gout. Pegloticase was approved in the United States in 2010 for use in patients with chronic symptomatic gout who are refractory to conventional therapy with uricourics and xanthine oxidase inhibitors, which should be discontinued before pegloticase is started. It is available as a sterile concentrate of 8 mg in a single use vial under the brand name Kystexxa. The recommended dose 8 mg given intravenously every two weeks. Common side effects of pegloticase include local and systemic infusion reactions, nausea, vomiting, constipation, chest pain and nasopharyngitis. Pegloticase infusions are associated with paradoxical flares of clinical gout during the first 3 months of therapy in up to 80% of patients. Severe adverse reactions may include anaphylaxis (in up to 7% of patients), severe infusion reactions, hemolysis and methemoglobinemia (in patients with G6PD deficiency) and congestive heart failure. Because resistance to pegloticase is associated with antibodies to the molecule and with rise of uric acid levels and initial control, it is recommended that patients be monitored for uric acid levels and that pegloticase be stopped if uric acid levels rise above 6 mg/dL.

Hepatotoxicity

In large clinical trials, serum enzyme elevations were rare (<1%) during pegloticase therapy and no more common than with placebo. Since licensure and its more wide scale, there have been no published case reports of hepatotoxicity due to pegloticase and the product label does not list liver injury as an adverse event. Thus, liver injury due to pegloticase must be rare, if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Pegloticase is a polypeptide and is metabolized to amino acids by serum and tissue proteases, and is unlikely to have any direct hepatotoxic potential.

Drug Class: Antigout Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pegloticase – Krystexxa®

DRUG CLASS

Antigout Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Pegloticase	885051-90-1	Protein	Complex Polypeptide

ANNOTATED BIBLIOGRAPHY

References updated: 21 May 2018

Zimmerman HJ. Drugs used to treat gout. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 543-4.

(Textbook of hepatotoxicity published in 1999 and before the availability of pegloticase).

Grosser T, Smyth E, FitzGerald GA. Pharmacotherapy of gout. Anti-inflammatory, antipyretic and analgesic agents; pharmacotherapy of gout. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 994-1000.

(Textbook of pharmacology and therapeutics).

Sundy JS, Becker MA, Baraf HS, Barkhuizen A, Moreland LW, Huang W, Waltrip RW 2nd, et al.; Pegloticase Phase 2 Study Investigators. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. Arthritis Rheum 2008; 58: 2882-91. PubMed PMID: 18759308.

(Among 41 patients with severe, refractory gout treated with pegloticase in four dose regimens, adverse reactions included flares of gout and infusion reactions).

Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, Vázquez-Mellado J, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA 2011; 306: 711-20. PubMed PMID: 21846852.

(Among 225 patients with severe gout treated with pegloticase [8 mg every 2 or 4 weeks] or placebo for 6 months, a decrease in plasma uric acid levels to less than 6 mg/dL was achieved in 35-42% on pegloticase compared to 0% on placebo, and common adverse events were gout flares, infusion reactions, nausea, headache, pruritus and confusion; no mention of ALT elevations or hepatotoxicity).

Pegloticase (krystexxa) for treatment of refractory gout. Med Lett Drugs Ther 2011; 53 (1357): 9-10. PubMed PMID: 21304442.

(Concise summary of the mechanism of action, pharmacology, clinical efficacy, safety and costs of pegloticase shortly after its approval for use in gout in the US mentions anaphylaxis, infusion reactions and gout flares, but not ALT elevations or hepatotoxicity).

Becker MA, Baraf HS, Yood RA, Dillon A, Vázquez-Mellado J, Ottery FD, Khanna D, et al. Long-term safety of pegloticase in chronic gout refractory to conventional treatment. Ann Rheum Dis 2013; 72: 1469-74. PubMed PMID: 23144450.

(Among 149 patients with gout treated with pegloticase infusions every 2 weeks for an average of 25 months, adverse events included gout flares [71%], infusion reactions [44%], arthralgia [20%] and nausea [11%], but clinical chemistry results did not change from baseline).

Gentry WM, Dotson MP, Williams BS, Hartley M, Stafford KR, Bottorff MB, Gandhi PK. Investigation of pegloticase-associated adverse events from a nationwide reporting system database. Am J Health Syst Pharm 2014; 71: 722-7. PubMed PMID: 24733135.

(Among 118 adverse events attributed to pegloticase therapy reported to the FDA over a 2 year period, 11 were cases of anaphylaxis and 35 were infusion related reactions; miscellaneous reactions included 2 cases of hepatic failure, 2 hepatocellular injury, 3 hepatotoxicity, 1 liver function test abnormal and 1 transaminase increased; but no specific details given).

Pegloticase. An excessively dangerous and inadequately evaluated hypouricaemic drug. Prescrire Int 2014; 23: 173-6. PubMed PMID: 25162087.

(Commentary on the limited efficacy and potential toxicity of pegloticase infusions).

Geraldino-Pardilla L, Sung D, Xu JZ, Shirazi M, Hod EA, Francis RO. Methaemoglobinaemia and haemolysis following pegloticase infusion for refractory gout in a patient with a falsely negative glucose-6-phosphate dehydrogenase deficiency result. Rheumatology (Oxford) 2014; 53: 2310-1. PubMed PMID: 25224415.

(38 year old Hispanic man developed severe hemolytic anemia and methemoglobinemia within 48 hours of an infusion of pegloticase for refractory gout, testing demonstrating G6PD deficiency despite reports of a negative assay done before therapy).

Baraf HS, Yood RA, Ottery FD, Sundy JS, Becker MA. Infusion-related reactions with pegloticase, a recombinant uricase for the treatment of chronic gout refractory to conventional therapy. J Clin Rheumatol 2014; 20: 427-32. PubMed PMID: 25417679.

(Among 208 patients who received 6389 infusions of pegloticase in 3 studies, 94 [45%] had an infusion reaction with symptoms usually arising during the infusion [chest discomfort, flushing, dyspnea, back pain, sweating, nausea, erythema, urticarial rash, pruritus, muscle spasms and headache], all resolving with stopping the infusion but leading to discontinuation in 31 [15%] patients, but no patient died or required intubation and ventilation).

Baldo BA. Enzymes approved for human therapy: indications, mechanisms and adverse effects. BioDrugs 2015; 29: 31-55. PubMed PMID: 25648140.

(Review of the safety and efficacy of enzyme therapy including pegloticase and rasburicase; no mention of ALT elevations or hepatotoxicity).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the 96 was attributed to pegloticase or other therapies for gout).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury in the US collected between 2004 and 2012, 8 cases were attributed to drugs used for gout [allopurinol in 7 and febuxostat in 1], but no cases were attributed to pegloticase or rasburicase).

Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Adv Chronic Kidney Dis 2014; 21: 18-26. PubMed PMID: 24359983.

(Review of the clinical features and epidemiology of tumor lysis syndrome which is most common during chemotherapy of hematologic malignancies, but can occur during therapy of solid tumors as well as spontaneously without chemotherapy).

Guttmann A, Krasnokutsky S, Pillinger MH, Berhanu A. Pegloticase in gout treatment - safety issues, latest evidence and clinical considerations. Ther Adv Drug Saf 2017; 8: 379-88. PubMed PMID: 29204266.

(Careful review of the clinical features and epidemiology of gout and efficacy and safety of pegloticase, common side effects being a flare of gout [71-85%], infusion reactions [26-42%], headache [9-11%], nausea [7-12%] and cardiovascular events [2-7%]; no mention of ALT elevations or hepatotoxicity).