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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-. Erythropoiesis Stimulating Agents. [Updated 2017 Dec 5].
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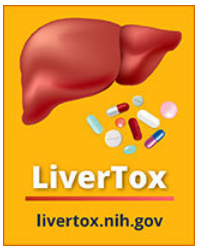

Erythropoiesis Stimulating Agents

Updated: December 5, 2017.

OVERVIEW

Introduction

Epoetin is a recombinant form of erythropoietin, a hematologic growth factor that induces proliferation and maturation of red blood cells and is used in the treatment of anemia caused by renal disease, myelodysplasia, cancer chemotherapy and hematopoietic cell transplantation. Epoetin and its various derivatives have not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Epoetin (e poe' e tin) is a recombinant form of erythropoietin, a 165 amino acid glycoprotein that induces red blood cell production from their progenitors in the bone marrow. Erythropoietin is normally made in the kidneys and acts on progenitor erythroblasts through the erythropoietin receptor to cause proliferation and maturation of red cells. The major stimulus to erythropoietin synthesis is tissue hypoxia, but other factors can modulate the response. Deficiency of erythropoietin synthesis is common in end stage renal disease and may also be present in premature infants and in patients with malignancies, chronic inflammation and cancer chemotherapy. Recombinant forms of erythropoietin became available in the 1980's and were shown to raise hemoglobin and hematocrit levels in patients with end stage renal disease on hemodialysis, as well as in patients receiving cancer chemotherapy and patients with AIDS on drugs that cause anemia. Epoetin alfa was approved for use to treat anemia in patients with renal disease and receiving cancer chemotherapy in 1989 and is now widely used. Indications have broadened to include reduction of allogeneic red cell transfusion in patients undergoing elective surgery and it is used off-label for other forms of anemia associated with relative erythropoietin deficiency. The target hemoglobin level is usually between 11 and 12 g/dL. Epoetin alfa is available as a liquid solution for subcutaneous administration in vials and prefilled syringes under the brands name Epogen and Procrit, the dose and regimen varying by indication and initial response, being given by subcutaneous or intravenous injection at intervals varying from daily, several times weekly, weekly or as needed to achieve a target hemoglobin. Longer acting formulations are also available including darbepoetin (Aranesp: 2001) and peginesatide (Omontys, 2012, now withdrawn). Darbepoetin alfa (dar" be poe' e tin) is a modified (hyperglycosylated) recombinant erythropoietin that has an extended half-life and can be administered every one to three weeks. Darbepoetin is available in single dose vials and prefilled syringes of varying concentrations and is administered intravenously or subcutaneously. Peginesatide (peg" in es' a tide) is a novel synthetic pegylated dipeptide that mimics the effects of erythropoietin on red cell progenitors, despite having no amino acid homology to the native growth factor. Peginesatide was typically given either subcutaneously or intravenously at 4 week intervals, but was withdrawn from the market in 2013 because of reports of severe hypersensitivity reactions. Epoetin, darbepoetin and peginesatide are collectively referred to as erythropoiesis-stimulating agents (ESA). Dosages and dose regimens (daily, three times weekly, weekly, and every two to four

weeks) vary by formulation, indications and initial response. Common side effects include hypertension (particularly in patients with renal disease), muscle and joint aches, fever, dizziness, headache, depression, cough and injection site reactions. Potentially serious, but rare side effects include hypersensitivity reactions, vascular occlusions, stroke and myocardial infarction.

Hepatotoxicity

Epoetin and the erythropoiesis-stimulating agents have not been linked to instances of significant serum enzyme elevations or clinically apparent liver injury. In multiple large prelicensure studies, acute liver injury was not mentioned as an adverse event and serum enzyme tests changed minimally, if at all. Since licensure and wide scale use, there have been no published reports of liver injury from epoetin or its long acting forms. Interestingly, instances of induction of attacks of acute porphyria have been reported after epoetin use, probably because of induction hemoglobin production which requires an increase in porphyrin synthesis.

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

Mechanism of Injury

A mechanism of injury that might lead to serum enzyme elevations during therapy with the ESAs is not known. Epoetin is a non-glycosylated form of erythropoietin and appears to be metabolized at multiple sites, probably by the cells on which they act.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) during ESA therapy should lead to dose reduction or temporary cessation. Epoetin and its derivatives have not been implicated in cases of severe hepatitis, acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no reason to suspect any degree of cross sensitivity in risk for hepatic injury among the various hematologic growth factors and other agents used to treat bone marrow insufficiency.

Drug Class: Hematologic Growth Factors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Epoetin – Epogen®, Procrit®

Darbepoetin – Aranesp®

Peginesatide – Omontys®

DRUG CLASS

Hematologic Growth Factors

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Epoetin	113427-24-0	Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 05 December 2017

Zimmerman HJ. Hormonal derivatives and related drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp 555-88.

(Review of hepatotoxicity published in 1999; the hematologic growth factors are not specifically mentioned).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Textbook on hepatotoxicity; hematologic growth factors are not discussed).

Kaushansky K, Kipps TJ. Hematopoietic agents: growth factors, minerals and vitamins. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1067-99.

(Textbook of pharmacology and therapeutics).

Lim VS, DeGowin RL, Zavala D, Kirchner PT, Abels R, Perry P, Fangman J. Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. Ann Intern Med 1989; 110: 108-14. PubMed PMID: 2909202.

(Controlled trial of 3 doses of epoetin vs placebo given intravenously 3 times weekly for 8 weeks in 14 patients with renal disease and anemia showed dose related increases in hematocrit and no adverse events: "liver function tests …were normal and did not change").

Sundal E, Kaeser U. Correction of anaemia of chronic renal failure with recombinant human erythropoietin: safety and efficacy of one year's treatment in a European multicentre study of 150 haemodialysis-dependent patients. Nephrol Dial Transplant 1989; 4: 979-87. PubMed PMID: 2516891.

(Among 150 patients with anemia and ESRD on hemodialysis treated with epoetin for one year, almost all achieved an increase in hemoglobin to target levels; side effects included increase in blood pressure, hypertensive episodes, myocardial infarction, seizures [n=4] and thrombosis; no mention of ALT elevations or hepatotoxicity).

Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, Evans RW, et al. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. Ann Intern Med 1989; 111: 992-1000. PubMed PMID: 2688507.

(Among 333 anemic patients with ESRD on hemodialysis who were treated with epoetin 3 times weekly, hematocrit levels rose and side effects included hypertension [35%], seizures [5.4%], flu-like symptoms, decrease in ferritin and increase in platelet counts; no mention of ALT elevations or hepatotoxicity).

Erythropoietin for anemia. Med Lett Drugs Ther 1989; 31 (801): 85-6. PubMed PMID: 2671624.

(Concise review of the efficacy and safety of epoetin shortly after its US approval for the anemia of chronic renal disease mentions adverse events of hypertension, seizure and clotting of arteriovenous fistulas and shunts; no mention of ALT elevations or hepatotoxicity).

Nissenson AR. National cooperative rHu erythropoietin study in patients with chronic renal failure: a phase IV multicenter study. Report of National Cooperative rHu Erythropoietin Study Group. Am J Kidney Dis 1991; 18 (4 Suppl 1): 24-33. PubMed PMID: 1928075.

(In a postmarketing prospective study of 447 patients with chronic renal failure treated with epoetin and followed at 68 centers, average hematocrit levels increased from 25.1% to 30.6% at 3 months and there were "no increases in the incidence of adverse events").

Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. The safety of epoetin-alpha: results of clinical trials in the United States. Contrib Nephrol 1991; 88: 72-80. PubMed PMID: 2040198.

(Analysis of safety in 493 anemic hemodialysis patients treated with epoetin in 5 clinical trials found the most common side effects were myalgias, fever, local injection reactions; other adverse events were iron deficiency [43%], increase in blood pressure [31%], seizures [4%], and access thromboses; there were "no consistent changes in liver function tests").

Obladen M, Maier R, Segerer H, Grauel EL, Holland BM, Stewart G, Jorch G, et al. Efficacy and safety of recombinant human erythropoietin to prevent the anaemias of prematurity. European Randomized Multicenter Trial. Contrib Nephrol 1991; 88: 314-26. PubMed PMID: 2040194.

(Among 93 preterm newborns treated with recombinant epoetin or placebo subcutaneously every 3 days, there was no difference in need for or amount of red cell transfusion and no differences in adverse events; no mention of ALT or bilirubin elevations).

Samtleben W, Ehmer B, Lutz-Knochenhauer I, Hagmann C, Scigalla P, Gurland HJ. Side effects during recombinant human erythropoietin therapy in 2,000 ESRD patients. Contrib Nephrol 1991; 88: 107-16. PubMed PMID: 2040172.

(Among 2138 patients on hemodialysis treated with epoetin, severe complications included convulsions in 28 patients and 14 malignancies, but survival was better than predicted from historical controls; no mention of liver injury, but two patients developed hepatitis B and 2 non-A, non-B hepatitis).

Henry DH, Beall GN, Benson CA, Carey J, Cone LA, Eron LJ, Fiala M, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med 1992; 117: 739-48. PubMed PMID: 1416576.

(Combined results of 4 controlled trials of epoetin in 297 patients with AIDS found overall increase in hematocrit by 4.6% [vs 0.5% with placebo] and no difference in incidence of adverse events).

Klinkmann H, Wieczorek L, Scigalla P. Adverse events of subcutaneous recombinant human erythropoietin therapy: results of a controlled multicenter European study. Artif Organs 1993; 17: 219-25. PubMed PMID: 8498900.

(Among 362 anemic hemodialysis patients in Europe treated with epoetin for 1-2 years, "the observed biochemistry profile shows no significant changes that could be attributed to" epoetin therapy).

Tanaka H, Kan E, Takegaki Y, Inariba H, Yoshimoto M, Ohno Y, Maekawa M et al. Multicenter study with recombinant human erythropoietin. Artificial Organs 1993; 17: 213-8. PubMed PMID: 8498899.

(Among 172 Japanese patients with ESRD treated with epoetin for 24 weeks, side effects included increases in blood pressure and heart rate, but not seizures; no mention of ALT elevations or hepatotoxicity).

Sowade B, Sowade O, Möcks J, Franke W, Warnke H. The safety of treatment with recombinant human erythropoietin in clinical use: a review of controlled studies. Int J Mol Med 1998; 1: 303-14. PubMed PMID: 9852232.

(Systematic review of published studies of epoetin for rates of adverse events identified side effects that were more frequent with epoetin than placebo in renal anemia, as hypertension [23%], menstrual disorders [9.1% vs 4.1%], injection site reactions [5.7% vs 0], and headache [4.9% vs 2%], among others; liver enzyme increases were no more frequent with epoetin than placebo [5.3% vs 6.5%]).

Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. An open-label, randomized study to compare the safety and efficacy of perioperative epoetin alfa with preoperative autologous blood donation in total joint arthroplasty. Orthopedics 1999; 22 (1 Suppl): s105-12. PubMed PMID: 9927110.

(Among 450 patients undergoing joint replacement treated with 4 weekly injections of epoetin or placebo to aid in preoperative blood donation before surgery, side effects were similar between the two groups, although two epoetin treated patients had a stroke and one a myocardial infarction, no mention of ALT elevations or hepatotoxicity).

Darbepoetin (Aranesp) – a long-acting erythropoietin. Med Lett Drugs Ther 2001; 43 (W2210A): 109-110. PubMed PMID: 11740411.

(Concise review of the efficacy and safety of darbepoetin a recombinant erythropoietin with 2 additional N-glycosylation sites, which prolongs its half-life allowing once weekly or every other week administration; side effects are similar to those of epoetin; no mention of ALT elevations or hepatotoxicity).

Erythropoietin (Procrit; Epogen) revisited. Med Lett Drugs Ther 2001; 43 (1104): 40-1. PubMed PMID: 11353925.

(Concise review of the formal indications for epoetin in response to direct patient advertising about its effects on fatigue and ability to work; no mention of adverse events on the liver).

Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, Siena S, et al.; Aranesp 980297 Study Group. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002; 94: 1211-20. PubMed PMID: 12189224.

(Among 320 patients with anemia due to cancer chemotherapy who were treated with weekly injections of darbepoetin or placebo for 12 weeks, adverse events and "changes in laboratory test variables" were similar between the 2 groups; no mention of ALT elevations or hepatotoxicity).

Hedenus M, Adriansson M, San Miguel J, Kramer MH, Schipperus MR, Juvonen E, Taylor K, et al.; Darbepoetin Alfa 20000161 Study Group. Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: a randomized, double-blind, placebo-controlled study. Br J Haematol 2003; 122: 394-403. PubMed PMID: 12877666.

(Among 344 patients with lymphoma or myeloma receiving cancer chemotherapy and treated with either darbepoetin or placebo for 12 weeks, adverse events occurred equally in the 2 groups and were considered due to the underlying disease or chemotherapy rather than the interventions; no mention of ALT elevations or hepatotoxicity).

Farrell F, Lee A. The erythropoietin receptor and its expression in tumor cells and other tissues. Oncologist 2004; 9 Suppl 5: 18-30. PubMed PMID: 15591419.

(Epoetin and its receptor are found on red cell progenitors, but also in the central nervous system, liver, tumors and the uterus where their function is unknown, but may be involved in cytoprotection and angiogenesis which may be beneficial for some tissue, but may promote cancer cell growth).

Glaspy J, Vadhan-Raj S, Patel R, Bosserman L, Hu E, Lloyd RE, Boccia RV, et al. Randomized comparison of every-2-week darbepoetin alfa and weekly epoetin alfa for the treatment of chemotherapy-induced anemia: the 20030125 Study Group Trial. J Clin Oncol 2006; 24: 2290-7. PubMed PMID: 16710026.

(Among 1220 patients with chemotherapy induced anemia treated with darbepoetin weekly or every 2 weeks, adverse events "were consistent with existing clinical experience for adverse events in anemic cancer patients"; no mention of ALT elevations or hepatotoxicity).

Canon JL, Vansteenkiste J, Bodoky G, Mateos MV, Bastit L, Ferreira I, Rossi G, et al. Randomized, double-blind, active-controlled trial of every-3-week darbepoetin alfa for the treatment of chemotherapy-induced anemia. J Natl Cancer Inst 2006; 98: 273-84. PubMed PMID: 16478746.

(Among 705 patients with anemia due to cancer chemotherapy treated with darbepoetin given either every week or every 3 weeks, both efficacy and safety were similar with both schedules; hepatic failure was reported in 3 patients, but was considered due to the chemotherapy rather than darbepoetin).

Shin DH, Kwon YI, Choi SI, Park US, Lee J, Shin JH, Lee JU, et al. Accidental ten times overdose administration of recombinant human erythropoietin (rh-EPO) up to 318,000 units a day in acute myocardial infarction: report of two cases. Basic Clin Pharmacol Toxicol 2006; 98: 222-4. PubMed PMID: 16445599.

(Two patients with acute myocardial infarction received an incorrect dose of epoetin [318,000 U: 10 times intended] in a clinical trial of cardiac protection and both had an immediate increase in ALT [peak 386 and 98 U/L] that fell to baseline several weeks after; no mention of bilirubin, Alk P or symptoms).

Arcasoy MO. The non-haematopoietic biological effects of erythropoietin. Br J Haematol 2008; 141: 14-31. PubMed PMID: 18324962.

(Review of the non-hematologic functions and potential therapeutic uses of epoetin in development, the central nervous system, kidneys, and during inflammation and wound healing; no discussion of liver disease).

Peginesatide (Omontys) for anemia in chronic kidney failure. Med Lett Drugs Ther 2012; 54 (1392): 45-6. PubMed PMID: 22683926.

(Concise review of the efficacy and safety of a pegylated synthetic peptide analogue of erythropoietin shortly after its approval for the anemia of chronic renal disease, mentions that its adverse events are similar to those of epoetin; no mention of ALT elevations or hepatotoxicity).

Macdougall IC. New anemia therapies: translating novel strategies from bench to bedside. Am J Kidney Dis 2012; 59: 444-51. PubMed PMID: 22192713.

(Overview of erythropoiesis stimulating agents focusing on the long acting forms, including darbepoetin and pegylated epoetin beta and the unique erythropoietin-mimetic dipeptide, peginesatide).

Schmid H. Peginesatide for the treatment of renal disease-induced anemia. Expert Opin Pharmacother 2013; 14: 937-48. PubMed PMID: 23506424.

(Review of the structure, mechanism of action, pharmacokinetics, clinical efficacy and safety of peginesatide does not mention ALT elevations or hepatotoxicity).

Macdougall IC, Provenzano R, Sharma A, Spinowitz BS, Schmidt RJ, Pergola PE, Zabaneh RI, et al.; PEARL Study Groups. Peginesatide for anemia in patients with chronic kidney disease not receiving dialysis. N Engl J Med 2013; 368: 320-32. PubMed PMID: 23343062.

(Among 983 patients with renal disease and anemia, not on dialysis, who were treated in 2 clinical trials of peginesatide versus darbepoetin for at least 52 weeks, severe adverse events [including sudden death] were more frequent with peginesatide, but an extensive discussion of adverse events included no mention of ALT elevations or hepatotoxicity).

Fishbane S, Schiller B, Locatelli F, Covic AC, Provenzano R, Wiecek A, Levin NW, et al.; EMERALD Study Groups. Peginesatide in patients with anemia undergoing hemodialysis. N Engl J Med 2013; 368: 307-19. PubMed PMID: 23343061.

(Among 1418 patients on hemodialysis who were treated in two clinical trials comparing standard regimens of epoetin with peginesatide, rates of severe adverse events were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to epotein, darbepoetin or other erythropoiesis stimulating agents).

Park S, Fenaux P, Greenberg P, Mehta B, Callaghan F, Kim C, Tomita D, et al. Efficacy and safety of darbepoetin alpha in patients with myelodysplastic syndromes: a systematic review and meta-analysis. Br J Haematol 2016; 174: 730-47. PubMed PMID: 27214305.

(Systematic review of the literature on safety of darbepoetin in myelodysplasia, no mention of hepatotoxicity or ALT elevations and no instances of hepatic failure in listings of causes of death).

Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, Slama B, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. Leukemia 2017; 31: 1944-50. PubMed PMID: 28626220.

(Among 147 patients with myelodysplastic syndromes treated with darbepoetin or placebo once weekly for 48 weeks, there were no hepatic severe adverse events and no mention of ALT elevations or hepatotoxicity).