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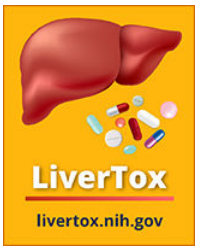

Colony Stimulating Factors

Updated: October 30, 2017.

OVERVIEW

Introduction

Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are glycosylated polypeptides that induce an increase in the proliferation and maturation of white blood cells including neutrophils and monocytes-macrophages. Recombinant forms of these colony stimulating factors are used to treat severe neutropenia in patients receiving cancer chemotherapy or undergoing hematopoietic cell transplantation. Recombinant forms include filgrastim (G-CSF) and sargramostim (GM-CSF), both of which are commercially available for therapy of severe neutropenia and bone marrow failure. Neither filgrastim nor sargramostim have been linked to serum enzyme elevations during therapy or to clinically apparent liver injury.

Background

Filgrastim (fil gra' stim) is a recombinant, non-glycosylated form of the 175 amino acid protein, granulocyte colony stimulating factor (G-CSF) that induces the proliferation and maturation of neutrophils. G-CSF is normally produced by multiple cell types including monocytes, fibroblasts, macrophages and stromal cells. It acts on specific receptors found on granulocyte progenitors and causes an increase in circulating neutrophils. Recombinant filgrastim has been shown to increase total neutrophil counts and to protect, in part, against severe infections in patients with neutropenia for various causes.

Filgrastim was approved for use in the United States in 1991, and current indications are for chemotherapy induced neutropenia, in hematopoietic cell transplantation after myeloablation and in congenital and cyclic neutropenias. Filgrastim is also used in patients undergoing autologous peripheral blood progenitor (stem) cell collection. Filgrastim is available as a solution in single use vials or prefilled syringes (300 and 600 mcg each) for subcutaneous or intravenous administration under the brand name Neupogen. Dose regimens vary by indication (5 or 10 mcg/kg per day) and route of administration (intravenous or subcutaneous).

A pegylated, long acting form of G-CSF (pegfilgrastim) became available in 2002 under the brand name Neulasta which can be given once weekly and has similar efficacy and safety as filgrastim. The current formal indications for pegfilgrastim are limited to prevention of febrile neutropenia during myelosuppressive cancer chemotherapy for non-myeloid malignancies. Pegfilgrastim is available in solution of 6 mg/0.6 mL in prefilled syringes. The typical dose is 6 mg subcutaneously once per chemotherapy cycle. Common side effects of filgrastim and pegfilgrastim include fever, musculoskeletal pain, rash, cough and shortness of breath. Rare side effects include acute allergic reactions, splenic rupture and acute respiratory distress syndrome.

Sargramostim (sar gra' moe stim) is a recombinant form of granulocyte-macrophage stimulating factor (GM-CSF) that stimulates the proliferation and maturation of neutrophils and macrophages. Sargramostim is

prepared in yeast (S. cerevisae) and is a 127 amino acid glycoprotein that is 98% identical to native, human GM-CSF. Sargramostim increases the number and activity of circulating neutrophils and monocytes. Sargramostim was approved in the United States in 1991 for use in patients with acute myelogenous leukemia after chemotherapy induced neutropenia. Current indications also include support of patients undergoing hematopoietic cell transplantation as well as for patients undergoing autologous peripheral blood progenitor (stem) cell collection. Sargramostim is available in liquid and lyophilized forms under the brand names Leukine and Prokine. Sargramostim is given either intravenously or subcutaneously daily or three times weekly, the dose and regimen varying by indication. Common side effects include fever, headache, fatigue, bone pain, nausea and weakness, but similar rates of these symptoms are reported with placebo or comparator therapies.

Hepatotoxicity

Filgrastim and sargramostim have not been linked to instances of significant serum enzyme elevations during therapy and have not been implicated in cases of clinically apparent liver injury. In multiple large prelicensure studies, acute liver injury was not mentioned as an adverse event and serum aminotransferase elevations were elevated in a similar or lower proportion of patients receiving these growth factors than in placebo or comparator arms. G-CSF and GM-CSF are often given to critically ill patients receiving high doses of chemotherapy in whom serum enzyme elevations are common, but which usually can be attributed to the chemotherapy itself or the underlying malignancy. In addition, serum alkaline phosphatase elevations during filgrastim and sargramostim therapy may be from a bone source rather than the liver, in that both agents stimulate the bone marrow and not infrequently cause bone pain. In children, colony stimulating factors can cause hepatomegaly due to extramedullary hematopoiesis. However, since licensure and wide scale use, there have been no published reports of idiosyncratic acute liver injury attributed to filgrastim, pegfilgrastim or sargramostim.

Likelihood scores (recombinant colony stimulating factors): E (unlikely causes of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which the colony stimulating factors might cause liver injury is not known. Both filgrastim and sargramostim are polypeptides and are usually metabolized by the cells on which they act.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) during colony stimulating factor therapy should lead to dose reduction or temporary cessation. Neither filgrastim nor sargramostim have 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

Filgrastim – Neupogen®

Pegfilgrastim – Neulasta®

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Sargramostim – Leukine, Prokine®

DRUG CLASS

Hematologic Growth Factors

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Filgrastim	121181-53-1	Protein	Not Available
Pegfilgrastim	208265-92-3	Protein	Not Available
Sargramostim	123774-72-1	Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 30 October 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).

Nemunaitis J, Rabinowe SN, Singer JW, Bierman PJ, Vose JM, Freedman AS, Onetto N, et al. Recombinant granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med 1991; 324: 1773-8. PubMed PMID: 1903847.

(Among 128 patients with lymphoma receiving chemotherapy and hematopoietic cell transplantation who were given prophylaxis with sargramostim [GM-CSF] or placebo, the duration of neutropenia and hospitalization were shorter with GM-CSF, but infection rates and survival were not different and there were no differences in frequency of side effects; no mention of ALT elevations or hepatotoxicity).

Granulocyte colony-stimulating factors. Med Lett Drugs Ther 1991; 33 (847): 61-3. PubMed PMID: 1710761.

(Concise review of the efficacy and safety of recombinant granulocyte colony stimulating factors, including filgrastim and sargramostim, shortly after their approval in the US for prophylaxis against infections during cancer chemotherapy, mentions that transient elevations in serum aminotransferase and alkaline phosphatase levels can occur with either agent).

Gorin NC, Coiffier B, Hayat M, Fouillard L, Kuentz M, Flesch M, Colombat P, et al. Recombinant human granulocyte-macrophage colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation with unpurged and purged marrow in non-Hodgkin's lymphoma: a double-blind placebo-controlled trial. Blood 1992; 80: 1149-57. PubMed PMID: 1515637.

(Among 91 patients with lymphoma undergoing chemotherapy and hematopoietic cell transplantation who were treated with sargramostim or placebo found shorter periods of neutropenia with the GM-CSF, but no difference in rates of infection or survival; adverse events attributed to GM-CSF included bone pain, fever and capillary leak syndrome).

Kellihan MJ. Drug formulary review process for sargramostim and filgrastim: focus on analysis of adverse drug reactions. Clin Ther 1993; 15: 927-37. PubMed PMID: 7505717.

(Comparison of published and unpublished reports on sargramostim and filgrastim showed similar rates of adverse events including "liver damage", but no details given).

Dale DC, Bonilla MA, Davis MW, Nakanishi AM, Hammond WP, Kurtzberg J, Wang W, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. Blood 1993; 81: 2496-502. PubMed PMID: 8490166.

(Among 120 patients with chronic neutropenia treated with filgrastim, most patients had a clinically important increase in neutrophil counts within a few days of starting therapy and subsequent decreased rate of infections; side effects were generally mild, but included bone pain, headache, fever and splenic enlargement [averaging 34%]; no mention of ALT elevations or hepatotoxicity).

Stahel RA, Jost LM, Cerny T, Pichert G, Honegger H, Tobler A, Jacky E, Fey M, Platzer E. Randomized study of recombinant human granulocyte colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation for high-risk lymphoid malignancies. J Clin Oncol 1994; 12: 1931-8. PubMed PMID: 7521907.

(Among 43 patients with lymphomas undergoing chemotherapy and hematopoietic cell transplantation [HCT] given filgrastim in two different doses, efficacy and tolerance were similar and the only adverse events attributed to the GCSF were bone pain and skin reactions).

Stahel RA, Jost LM, Honegger H, Betts E, Goebel ME, Nagler A. Randomized trial showing equivalent efficacy of filgrastim 5 micrograms/kg/d and 10 micrograms/kg/d following high-dose chemotherapy and autologous bone marrow transplantation in high-risk lymphomas. J Clin Oncol 1997; 15: 1730-5. PubMed PMID: 9164179.

(Among 86 patients with lymphomas undergoing chemotherapy and hematopoietic cell transplantation [HCT] given filgrastim in two different doses, efficacy and tolerance were similar and were largely attributed to HCT).

Skowron G, Stein D, Drusano G, Melbourne K, Bilello J, Mikolich D, Rana K, et al. The safety and efficacy of granulocyte-macrophage colony-stimulating factor (Sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. J Infect Dis 1999; 180: 1064-71. PubMed PMID: 10479132.

(Among 20 patients with HIV infection given sargramostim or placebo 3 times weekly for 8 weeks, side effects included fever, nausea, injection site reactions and neutrophilia; no mention of ALT elevations or hepatotoxicity).

Milkovich G, Moleski RJ, Reitan JF, Dunning DM, Gibson GA, Paivanas TA, Wyant S, et al. Comparative safety of filgrastim versus sargramostim in patients receiving myelosuppressive chemotherapy. Pharmacotherapy 2000; 20: 1432-40. PubMed PMID: 11130215.

(Retrospective analysis of 490 patients treated with filgrastim or sargramostim for prophylaxis against infection during cancer chemotherapy found that adverse reactions including bone pain, fatigue and unexplained fever were slightly more frequent with sargramostim than filgrastim; no mention of ALT elevations or hepatotoxicity).

Bennett JM, Young MS, Liesveld JL, Paietta E, Miller KB, Lazarus HM, Marsh RD, et al. Phase II study of combination human recombinant GM-CSF with intermediate-dose cytarabine and mitoxantrone chemotherapy in patients with high-risk myelodysplastic syndromes (RAEB, RAEBT, and CMML): an Eastern Cooperative Oncology Group Study. Am J Hematol 2001; 66: 23-7. PubMed PMID: 11426487.

(Among 10 patients with severe myelodysplastic syndromes treated with cytarabine, mitoxantrone and sargramostim prophylaxis, hepatic toxicity occurred in 7, marked by high serum bilirubin [2.2 to 22.4 mg/dL] despite normal AST in all except one, leading to an early discontinuation of the trial, but attributed to the anticancer drugs rather than GM-CSF).

Pegfilgrastim(Neulasta) for prevention of febrile neutropenia. Med Lett Drugs Ther 2002; 44 (1130): 44-5. PubMed PMID: 12011756.

(Review of the efficacy and safety of pegfilgrastim for prophylaxis against infections in neutropenic patients shortly after its US approval for use, mentions that side effects are similar to those with filgrastim and can include bone pain [26%] and reversible elevations of serum Alk P).

Vose JM, Crump M, Lazarus H, Emmanouilides C, Schenkein D, Moore J, Frankel S, et al. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. J Clin Oncol 2003; 21: 514-9. PubMed PMID: 12560443.

(Among 66 patients receiving chemotherapy for lymphoma given filgrastim or pegfilgrastim as prophylaxis against infection, side effects were similar with the two CSFs, but bone pain was more frequent with the pegylated product; no mention of ALT elevations or hepatotoxicity).

Spitler LE, Weber RW, Allen RE, Meyer J, Cruickshank S, Garbe E, Lin HY, et al. Recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) administered for 3 years as adjuvant therapy of stages II (T4), III, and IV melanoma. J Immunother 2009; 32: 632-7. PubMed PMID: 19483646.

(Among 98 patients with melanoma given cyclic therapy with sargramostim for up to 3 years, side effects were mostly injection site reactions and flu-like symptoms, and there were no serious adverse events clearly linked to therapy and no mention of ALT elevations or hepatotoxicity).

Takazoe M, Matsui T, Motoya S, Matsumoto T, Hibi T, Watanabe M. Sargramostim in patients with Crohn's disease: results of a phase 1-2 study. J Gastroenterol 2009; 44: 535-43. PubMed PMID: 19352588.

(Among 11 patients with Crohn disease treated with sargramostim once daily for 4 or 8 weeks, side effects included injection site reactions, fever, back and bone pain, but there were no "clinically significant laboratory abnormalities" or mention of hepatotoxicity).

Kilic SC, Alaygut D, Unal E, Koç E, Patiroglu T. Acute colchicine intoxication complicated with extramedullary hematopoiesis due to filgrastim in a child. J Pediatr Hematol Oncol 2014; 36: e460-2. PubMed PMID: 24309614.

(3 year old boy took an overdose of his mother's colchicine and developed nausea, vomiting and diarrhea followed by rhabdomyolysis, acidosis, neutropenia and sepsis, which was treated with recombinant G-CSF and was followed by leukocytosis and hepatomegaly which the authors attributed to extramedullary hematopoiesis).

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 seen over a ten year period at 8 US medical centers, none were attributed to the recombinant colony stimulating factors).

Engelmann C, Splith K, Berg T, Schmelzle M. Effects of granulocyte-colony stimulating factor (G-CSF) on stem cell mobilization in patients with liver failure. Eur J Intern Med 2016; 36: e37-e39. PubMed PMID: 27745994.

(Among 13 patients with various forms of acute liver failure treated with filgrastim [12 doses over 26 days], 9 survived; adverse events were not mentioned).