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Oprelvekin

Updated: June 8, 2016.

OVERVIEW Oprelvekin [Interleukin-11]

Introduction

Oprelvekin is a recombinant form of human interleukin 11, a cytokine that stimulates proliferation and maturation of bone marrow stem cells and megakaryocytes and is used to treat severe thrombocytopenia caused by chemotherapy. Interleukin 11 therapy has not been linked to serum enzyme elevations or with instances of jaundice or clinically significant acute liver injury.

Background

Oprelvekin (oh prel' veh kin") is a recombinant DNA form of interleukin 11, a human cytokine produced by bone marrow stromal cells that induces the proliferation and maturation of hematopoietic stem cells and megakaryocytes. While it stimulates several bone marrow lineages in rodents, IL-11 effects in humans are largely upon megakaryocytes, stimulating a robust increase in platelet counts. Recombinant forms of interleukin 11 have been developed and shown to have potent thrombopoietic activity. Oprelvekin was approved for use in the United States in 1997 and current indications are as prevention of severe thrombocytopenia and need for platelet transfusions in adults receiving myelosuppressive chemotherapy of non-myeloid malignancies. Oprelvekin is available as lyophilized powder in single use vials of 5 mg under the brand name Neumega. The typical dose is 50 µg/kg subcutaneously once daily for 10 to 21 days, usually starting within 6 to 24 hours of completing chemotherapy. Common side effects include the complications of sodium retention such as peripheral edema, dyspnea, pleural effusions, dilutional anemia, tachycardia and atrial arrhythmias. Other side effects include headache, fever, dizziness and syncope. Less common but potentially severe adverse reactions include severe arrhythmias, allergic reactions and anaphylaxis, capillary leak syndrome, optic neuropathy, papilledema, visual disturbances and renal failure.

Hepatotoxicity

In multiple controlled trials, interleukin 11 was not found to cause elevations in serum enzymes or episodes of clinically apparent liver injury. Furthermore, no specific instances of hepatitis or jaundice have been reported in the literature and liver injury is not listed as an adverse event in the product label. Thus, liver injury during interleukin-11 therapy must be rare, if it occurs at all.

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

Mechanism of Liver Injury

The mechanism by which interleukin-11 infusions might cause liver injury is unclear as it is a recombinant human protein and thus is unlikely to have direct hepatotoxicity. Interleukin 11 does induce acute phase reactions in the liver and serum levels of fibrinogen and other proteins made in the liver may increase while expansion of the plasma volume may decrease serum albumin and hemoglobin levels.

Outcome and Management

Serum enzyme elevations during oprelvekin therapy have not been reported or characterized. In situations in which ALT or AST levels rise and remain above 5 times ULN, dose modification or temporary discontinuation of the intravenous infusions is prudent.

Other cytokines used in cancer chemotherapy include interferon alfa, interferon beta and interferon gamma. Other agents used to treat thrombocytopenia include eltrombopag and romiplostim both of are thrombopoietin receptor agonists.

Drug Class: Thrombopoietin Receptor Agonists and Thrombopoiesis Stimulators, Cytokines

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Oprelvekin – Neumega®

DRUG CLASS

Thrombopoietin Receptor Agonists and Thrombopoiesis Stimulators

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Oprelvekin	145941-26-0	Cytokine	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 08 June 2016

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of recombinant interleukin-11).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, Longo DL, Mitsiades C, Richardson P. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Tepler I, Elias L, Smith JW 2nd, Hussein M, Rosen G, Chang AY, Moore JO, et al. A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. Blood 1996; 87: 3607-14. PubMed PMID: 8611684.

(Among 93 patients with severe thrombocytopenia due to cancer chemotherapy who were treated with IL-11 [25 or 50 µg/kg] or placebo subcutaneously once daily for 14-21 days, need for platelet transfusions were less with IL-11 therapy and "no evidence of direct liver or kidney toxicity was identified").

Gordon MS. Thrombopoietic activity of recombinant human interleukin 11 in cancer patients receiving chemotherapy. Cancer Chemother Pharmacol 1996; 38 Suppl: S96-8. PubMed PMID: 8765426.

(Review of the mechanism of action and clinically efficacy of oprelvekin).

Isaacs C, Robert NJ, Bailey FA, Schuster MW, Overmoyer B, Graham M, Cai B, Beach KJ, Loewy JW, Kaye JA. Randomized placebo-controlled study of recombinant human interleukin-11 to prevent chemotherapy-induced thrombocytopenia in patients with breast cancer receiving dose-intensive cyclophosphamide and doxorubicin. J Clin Oncol 1997; 15: 3368-77. PubMed PMID: 9363868.

(Among 77 patients with breast cancer receiving intensive chemotherapy who were treated with IL-11 [50 µg/kg] or placebo injections daily for 10 or 17 days, IL-11 decreased the need for platelet transfusion and was "well tolerated", side effects being edema [63% vs 14%], dyspnea [48% vs 19%], pleural effusions [18% vs 0%], conjunctival injection [25% vs 0%]; no mention of ALT elevations or hepatotoxicity).

Recombinant interleukin-11 for chemotherapy-induced thrombocytopenia. Med Lett Drugs Ther 1998; 40 (1032): 77-8. PubMed PMID: 9706284.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of oprelvekin shortly after its approval for use in the US; mentions side effects of sodium retention, edema, anemia, dyspnea, tachycardia and atrial arrhythmias, but does not mention ALT elevations or hepatotoxicity).

Kaye JA. FDA licensure of NEUMEGA to prevent severe chemotherapy-induced thrombocytopenia. Stem Cells 1998; 16 Suppl 2: 207-23. PubMed PMID: 11012193.

(Summary of medical evidence for safety and efficacy of oprelvekin supporting its FDA approval; mentions that changes in laboratory parameters during IL-11 therapy were limited to plasma proteins and red blood cells due to dilutional effects of sodium retention and stimulation of acute phase protein synthesis by the liver with increases in fibrinogen, ferritin, haptoglobin and C-reactive protein).

Moreland L, Gugliotti R, King K, Chase W, Weisman M, Greco T, Fife R, et al. Results of a phase-I/II randomized, masked, placebo-controlled trial of recombinant human interleukin-11 (rhIL-11) in the treatment of subjects with active rheumatoid arthritis. Arthritis Res 2001; 3: 247-52. PubMed PMID: 11438043.

(Among 91 patients with rheumatoid arthritis treated with 1 of 4 doses of IL-11 or placebo [once or twice weekly] for 12 weeks, disease activity was minimally improved but IL-11 was "well-tolerated"; adverse events included injection site reactions [61% vs 0%] and infections [8% vs 0%]; no mention of ALT elevations or hepatotoxicity).