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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-. Siltuximab. [Updated 2016 Apr 9].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Siltuximab

Updated: April 9, 2016.

OVERVIEW

Introduction

Siltuximab is a chimeric human-mouse monoclonal antibody to interleukin-6 which is used in the therapy of Castleman disease. Siltuximab commonly causes mild serum aminotransferase elevations which are usually short lived and asymptomatic, but it has not been linked to instances of clinically apparent liver injury with jaundice.

Background

Siltuximab (sil tux' i mab) is human-mouse chimeric IgG1 monoclonal antibody to IL-6 that is used largely as therapy of autoinflammatory diseases such as Castleman disease. Siltuximab binds to and blocks the action of IL-6, which is a key proinflammatory cytokine that mediates a wide spectrum of biologic activities including activation of T cells, differentiation of B cells, induction of acute phase reactants, proliferation of fibroblasts, and damage to cartilage and joints. IL-6 levels are elevated in patients with autoinflammatory conditions and in some forms of cancer. In controlled trials and open label studies, siltuximab therapy led to improvements in symptoms and laboratory abnormalities associated with Castleman disease. It has also been used in chemotherapy of prostate cancer and multiple myeloma, but with only limited effects. Siltuximab was approved for use in the United States in 2014 and current indications are limited to adults or children above the age of 12 with multicentric Castleman disease. Siltuximab is given by intravenous infusion every 3 weeks, in doses of 11 mg/kg. Siltuximab is available as lyophilized powder in single use vials of 100 and 400 mg under the brand name Sylvant. The most frequent side effects are itching, weight gain, rash, upper respiratory symptoms, headache, fatigue, diarrhea, infusion reactions and hyperuricemia. Rare, but potentially severe adverse reactions include worsening of severe infections, infusion reactions and gastrointestinal perforation.

Hepatotoxicity

In clinical trials of siltuximab combined with conventional chemotherapeutic agents in treatment of cancer, serum aminotransferase elevations occurred in a high proportion (10% to 30%) of patients. These trials included mention of some patients with elevations of ALT levels above 5 times the upper limit of normal and at least one example of reactivation of hepatitis B in a patient with multiple myeloma who also received dexamethasone. In studies of Castleman disease, however, rates of ALT elevations were usually not mentioned, although one instance of values above 5 times ULN were reported in one series. In these trials, no patient developed clinically apparent liver injury attributable to siltuximab. Since its licensure and general availability, there have been no published reports of hepatotoxicity due to siltuximab. Thus, siltuximab must be a rare cause of clinically apparent liver injury, if it occurs at all.

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

Mechanism of Injury

Siltuximab is a monoclonal antibody and is metabolized by many tissues into smaller polypeptides and amino acids. The mechanism by which it might cause liver injury is unknown, but it could possibly cause liver injury as a result of its effects on the immune system or on the IL-6 pathway which is important in liver regeneration. Siltuximab may be capable of causing reactivation chronic hepatitis B.

Outcome and Management

The serum enzyme elevations that have occurred during siltuximab therapy have been without symptoms or jaundice and short lived, resolving within a few weeks even without dose adjustment or discontinuation. There is no reason to suspect cross sensitivity to hepatic injury between siltuximab and other monoclonal antibodies known to cause liver injury such as infliximab and adalimumab.

Drug Class: Monoclonal Antibodies; Immunosuppressive Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Siltuximab – Sylvant®

DRUG CLASS

Immunosuppressive Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Siltuximab	541502-14-1	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 09 April 2016

Zimmerman HJ. 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. 517-53.

(Expert review of hepatotoxicity published in 1999 before the availability of siltuximab and other monoclonal antibodies and anticytokines).

Krensky AM, Bennett WM, Vincenti F. Immunosuppressants, tolerogens, and immunostimulants. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1005-29.

(Textbook of pharmacology and therapeutics).

Fizazi K, De Bono JS, Flechon A, Heidenreich A, Voog E, Davis NB, Qi M, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. Eur J Cancer 2012; 48: 85-93. PubMed PMID: 22129890.

(Among 97 patients with advanced prostate cancer treated with siltuximab or placebo with mitoxantrone and prednisone, survival rates were similar, but adverse events were greater in the siltuximab group; no mention of ALT elevations or hepatotoxicity).

Dorff TB, Goldman B, Pinski JK, Mack PC, Lara PN Jr, Van Veldhuizen PJ Jr, Quinn DI, et al. Clinical and correlative results of SWOG S0354: a phase II trial of CNTO328 (siltuximab), a monoclonal antibody against interleukin-6, in chemotherapy-pretreated patients with castration-resistant prostate cancer. Clin Cancer Res 2010; 16: 3028-34. PubMed PMID: 20484019.

(Among 53 patients with refractory prostate cancer treated with siltuximab, clinical responses were infrequent and 1 patient developed ALT elevations above 5 times ULN).

San-Miguel J, Bladé J, Shpilberg O, Grosicki S, Maloisel F, Min CK, Polo Zarzuela M, et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. Blood 2014; 123: 4136-42. PubMed PMID: 24833354.

(Among 106 patients with refractory multiple myeloma treated with bortezomib, melphalan and prednisone, overall and progression-free survival was not different with the addition of siltuximab and side effects of neutropenia and thrombocytopenia were more common; no mention of ALT elevations or hepatotoxicity).

Angevin E, Tabernero J, Elez E, Cohen SJ, Bahleda R, van Laethem JL, Ottensmeier C, et al. A phase I/II, multiple-dose, dose-escalation study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with advanced solid tumors. Clin Cancer Res 2014; 20: 2192-204. PubMed PMID: 24563479.

(Among 84 patients with advanced solid tumors treated with escalating doses of siltuximab, hepatic function abnormalities were reported in 15% of patients, but details were not given).

Voorhees PM, Manges RF, Sonneveld P, Jagannath S, Somlo G, Krishnan A, Lentzsch S, et al. A phase 2 multicentre study of siltuximab, an anti-interleukin-6 monoclonal antibody, in patients with relapsed or refractory multiple myeloma. Br J Haematol 2013; 161: 357-66. PubMed PMID: 23432640.

(Among 53 patients with refractory multiple myeloma treated with siltuximab with or without dexamethasone, frequent side effects included hepatic dysfunction [31%], enzyme elevations [16%] and one case of HBV reactivation [2%]; but no details provided).

Garcia-Manero G, Gartenberg G, Steensma DP, Schipperus MR, Breems DA, de Paz R, Valcárcel D, et al. A phase 2, randomized, double-blind, multicenter study comparing siltuximab plus best supportive care (BSC) with placebo plus BSC in anemic patients with International Prognostic Scoring System low- or intermediate-1-risk myelodysplastic syndrome. Am J Hematol 2014; 89: E156-62. PubMed PMID: 24888488.

(Among 76 patients with anemia due to myelodysplastic syndromes treated with siltuximab or placebo for 12 weeks, reduced red cell transfusion requirements occurred in 12% vs 4% and adverse events were frequent including "abnormal hepatic function" in 10% vs 12%; no details given).

van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fosså A, Simpson D, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2014; 15: 966-74. PubMed PMID: 25042199.

(Among 89 patients with Castleman disease treated with siltuximab or placebo [11 mg/kg every 3 weeks], durable tumor and symptomatic responses occurred in 34% vs 0% while side effects included pruritus [42% vs 12%], fatigue [34% vs 38%], edema [32% vs 23%], weight gain [21% vs 0%], abdominal pain, thrombocytopenia; no mention of ALT or hepatotoxicity).

Orlowski RZ, Gercheva L, Williams C, Sutherland H, Robak T, Masszi T, Goranova-Marinova V, et al. A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. Am J Hematol 2015; 90: 42-9. PubMed PMID: 25294016.

(Among 281 patients with refractory multiple myeloma treated with siltuximab or placebo combined with bortezomib, addition of siltuximab was not associated with improved progression free survival, but was associated with increased rates of neutropenia and thrombocytopenia, and slight increases in ALT and AST were observed on day 1 of cycle 2 in both groups, "but mean values remained in the normal range throughout the randomized treatment phase").

Deisseroth A, Ko CW, Nie L, Zirkelbach JF, Zhao L, Bullock J, Mehrotra N, et al. FDA approval: siltuximab for the treatment of patients with multicentric Castleman disease. Clin Cancer Res 2015; 21: 950-4. PubMed PMID: 25601959.

(Review of the clinical trial results that were the basis for approval of siltuximab as therapy of Castleman disease; no mention of ALT elevations or hepatotoxicity).

Siltuximab (Sylvant) for treatment of multicentric Castleman's disease. Med Lett Drugs Ther 2015; 57 (1459): e8 PubMed PMID: 25555075.

(Concise review of the mechanism of action, clinical efficacy, adverse effects and costs of siltuximab shortly after its approval in the US for Castleman disease mentions adverse events of rash, pruritus, weight gain, hyperuricemia and nasopharyngitis, but does not mention ALT elevations or hepatotoxicity).

van Rhee F, Casper C, Voorhees PM, Fayad LE, van de Velde H, Vermeulen J, Qin X, et al. A phase 2, open-label, multicenter study of the long-term safety of siltuximab (an anti-interleukin-6 monoclonal antibody) in patients with multicentric Castleman disease. Oncotarget 2015; 6: 30408-19. PubMed PMID: 26327301.

(Among 19 patients with Castleman disease who responded to siltuximab in a controlled trial and were continued on therapy long term [11 mg/kg every 3 to 6 weeks for an average of 5 years], side effects decreased with prolonged therapy, but included "hepatobiliary disorders" in 42% during the first year, but none thereafter and no patient stopped therapy because of liver test abnormalities).

Koff JL, Lonial S. Emerging treatments in Castleman disease - a critical appraisal of siltuximab. Biologics 2016; 10: 9-15. PubMed PMID: 26869762.

(Review of Castleman disease and its therapy including use of siltuximab; no mention of ALT elevations or hepatotoxicity).