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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-. Canakinumab. [Updated 2017 Jan 12].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Canakinumab

Updated: January 12, 2017.

OVERVIEW

Introduction

Canakinumab is a monoclonal antibody to interleukin-1 (IL-1) beta which is used in the therapy of juvenile idiopathic arthritis and other autoinflammatory conditions. Canakinumab is a relatively new biologic agent, has had limited clinical use, but has yet to be linked to cases of clinically apparent, acute liver injury.

Background

Canakinumab (kan" a kin' ue mab) is a human monoclonal antibody to IL-1 beta. The antibody reactivity is specific for IL-1 beta with no cross reactivity to other members of the IL-1 family or other cytokines. IL-1 is a key proinflammatory cytokine that medicates local and systemic inflammatory reactions and can induce fever, pain sensitization, bone and cartilage destruction and acute phase plasma protein reactions. In several controlled trials and open label studies, canakinumab has been shown to improve symptoms and laboratory abnormalities associated with juvenile idiopathic arthritis (formerly juvenile rheumatoid arthritis or Still disease) and several rare autoinflammatory conditions such as cryopyrin associated periodic syndrome (CAPS), Schnitzler syndrome and familial Mediterranean fever. Canakinumab was approved for use in periodic fever syndromes in the United States in 2009 and indications were expanded to include juvenile idiopathic arthritis in 2013. Canakinumab is considered a disease modifying antirheumatic drug (DMARD), and improves signs and symptoms of disease and decreases cartilage and tissue destruction. For juvenile idiopathic arthritis, canakinumab is given by subcutaneous injection every 8 weeks in a dose of 4 mg/kg (for patients weighing >7.5 kg) with a maximum dose of 300 mg. Lower doses are used in cryopyrin associated periodic syndromes. The most frequent side effects are local skin reactions, gastrointestinal upset, diarrhea, vertigo and possibly an increased incidence of bacterial infections.

Hepatotoxicity

In large registration trials, ALT elevations occurred in 1% to 4% of patients taking canakinumab, a rate similar to or minimally above that in placebo recipients. Serum aminotransferase levels are often raised in children with juvenile idiopathic arthritis and adult onset Still disease, and instances of improvement in serum enzyme elevations with initiation of canakinumab therapy have been reported. There have been no published reports of clinically apparent liver injury with jaundice attributed to canakinumab. This agent has had limited clinical use, but hepatic injury with jaundice due to canakinumab must be rare, if it occurs. In addition, canakinumab has not been linked to cases of reactivation of hepatitis B or exacerbation of chronic hepatitis C which can occur with other cytokines and anticytokines.

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

Mechanism of Injury

Canakinumab is a monoclonal antibody and has minimal hepatic metabolism. The mechanism by which it causes serum enzyme elevations during therapy is unknown, but may be the result of its effects on the immune system or on the IL-1 pathways which are important in inflammation and cell damage.

Outcome and Management

Agents that block the proinflammatory pathways of IL-1 and IL-6 share similar activity against autoinflammatory diseases and have little evidence for hepatotoxicity. However, there is no reason to suspect that there may be cross sensitivity to hepatic injury between canakinumab and other IL-1 antagonists such as anakinra and rilonacept or other immune modulating biologic agents such as tocilizumab or tumor necrosis factor antagonists.

Drug Class: Antirheumatic Agents

Other Drugs in the Subclass, Interleukin Receptor Antagonists: Anakinira, Rilonacept, Sarilumab, Tocilizumab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Canakinumab – Ilaris®

DRUG CLASS

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Canakinumab	914613-48-2	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 January 2017

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 canakinumab and the IL-1 blockers).

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).

Bywaters EG. Still's disease in the adult. Ann Rheum Dis 1971; 30: 121-33. PubMed PMID: 5315135.

(Clinical description of 14 patients with adult onset Still disease seen at a single referral center in the UK over a 25 year period; all woman, ages 17-35 years, presenting with urticarial, macular rash, high fevers, fatigue and arthritis, high ESR but no rheumatoid factor, the majority ultimately recovering completely without residual arthritis or problems).

Andrès E, Kurtz JE, Perrin AE, Pflumio F, Ruellan A, Goichot B, Dufour P, et al. Retrospective monocentric study of 17 patients with adult Still's disease, with special focus on liver abnormalities. Hepatogastroenterology 2003; 50: 192-5. PubMed PMID: 12630021.

(Among 17 patients with adult onset Still disease seen at a single French referral center, mean age was 27 years and 76% had "moderate liver dysfunction" with hepatomegaly in 47%, bilirubin 0.6-1.3 mg/dL and ALT 32-252 U/L, all eventually having a "complete recovery").

Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. Semin Arthritis Rheum 2006; 36: 144-52. PubMed PMID: 16949136.

(Adult onset Still disease is a rare, systemic inflammatory disorder of unknown cause characterized by fever, distinctive skin rash, arthritis and multiorgan involvement).

Zhu G, Liu G, Liu Y, Xie Q, Shi G. Liver abnormalities in adult onset Still's disease: a retrospective study of 77 Chinese patients. J Clin Rheumatol 2009; 15: 284-8. PubMed PMID: 19734733.

(Retrospective analysis of clinical features of 77 patients with adult onset Still disease presenting at a single referral center in China reported hepatomegaly in 12%, ALT or AST elevations in 62%, values >5 times ULN in 16% [some on therapy], hepatitis with jaundice in 8%; 2 patients developed acute liver failure and one died, the rest recovered without residual injury).

Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitton X, et al; Canakinumab in CAPS Study Group. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009; 360: 2416-25. PubMed PMID: 19494217.

(Among 35 patients with CAPS from 11 centers in 5 countries treated with either canakinumab or placebo in various regimens, 34 of 35 receiving canakinumab had a clinical remission which was maintained in those who continued drug; ALT elevations [>5 times ULN] occurred in 1 treated patient [3%]).

Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum 2010; 39: 327-46. PubMed PMID: 19117595.

(Review of the excess risk of infections during biologic therapy of rheumatoid arthritis mentions that the rate of infections was 2.1% vs 0.4% in controls; infections were primarily pneumonia and skin infections, none were fatal and few were opportunistic infections).

So A, De Meulemeester M, Pikhlak A, Yücel AE, Richard D, Murphy V, Arulmani U, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, phase II, dose-ranging study. Arthritis Rheum 2010; 62: 3064-76. PubMed PMID: 20533546.

(Among 200 patients with an attack of acute gouty arthritis, ALT elevations occurred in 2 of 143 patients [1.4%] given a single dose of canakinumab, but in 0 of 57 [0%] given a single dose of triamcinolone).

Carroll MB. The impact of biologic response modifiers on hepatitis B virus infection. Expert Opin Biol Ther 2011; 11: 533-44. PubMed PMID: 21269234.

(Review of reactivation of hepatitis B by biologic response modifiers; canakinumab has not been linked to reactivation of HBV, but experience with its use has been limited).

Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, Hachulla E, Leslie KS, Mouy R, Ferreira A, et al.; Canakinumab in CAPS Study Group. Sustained remission of symptoms and improved health-related quality

of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther 2011; 13: R202. PubMed PMID: 22152723.

(Further follow up on 31 patients with CAPS treated with canakinumab [Lachmann 2009] focusing upon quality of life; no mention of ALT elevations or hepatotoxicity).

Kuemmerle-Deschner JB, Hachulla E, Cartwright R, Hawkins PN, Tran TA, Bader-Meunier B, Hoyer J, et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis 2011; 70: 2095-102. PubMed PMID: 21859692.

(Open label study of canakinumab [every 8 weeks for up to 2 years] in 166 patients with CAPS; predominant adverse effects were infections [66%]; "biochemistry evaluations at the end of the study showed no clinically significant changes from baseline").

Rubbert-Roth A. Assessing the safety of biologic agents in patients with rheumatoid arthritis. Rheumatology (Oxford) 2012; 51 Suppl 5: v38-47. PubMed PMID: 22718926.

(Overview of safety of biologic agents in rheumatoid arthritis discusses anakinra, but not canakinumab).

Drugs for rheumatoid arthritis. Treat Guidel Med Lett 2012; 10 (117): 37-44. PubMed PMID: 22538522.

(Concise summary on current therapies of rheumatoid arthritis discusses anakinra and tocilizumab, but not canakinumab).

Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, Brik R, et al.; PRINTO; PRCSG. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012; 367: 2396-406. PubMed PMID: 23252526.

(Among 177 patents with systemic juvenile arthritis treated with canakinumab [4 mg/kg] every 8 weeks for 12 to 32 weeks, the major adverse effects were infections [55%]; although median values for ALT and AST did not change during therapy, values ranged from 5-82 U/L before therapy and were 7-828 at the end of 29 days and 0-282 U/L at the end of an open label phase [12-32 weeks]).

Sandborg C, Mellins ED. A new era in the treatment of systemic juvenile idiopathic arthritis. N Engl J Med 2012; 367: 2439-40. PubMed PMID: 23252530.

(Editorial in response to Ruperto [2012] and De Benedetti [2012] on IL-1 antagonists as therapy of juvenile idiopathic arthritis; "the therapeutic benefits of these biologic agents will need to be weighed against the apparent risks of infection, neutropenia and liver dysfunction").

Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov 2012; 11: 633-52. PubMed PMID: 22850787.

(Review of the biologic actions of IL-1 and the clinical efficacy and safety of agents that block its activity including anakinra [IL-1Ra], canakinumab [monoclonal antibody to IL-1 beta] and rilonacept [recombinant soluble IL-1 receptor]).

Brizi MG, Galeazzi M, Lucherini OM, Cantarini L, Cimaz R. Successful treatment of tumor necrosis factor receptor-associated periodic syndrome with canakinumab. Ann Intern Med 2012; 156: 907-8. PubMed PMID: 22711098.

(35 year old woman with TRAPS had a beneficial response to course of canakinumab; no mention of hepatotoxicity).

Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, Krammer G, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre,

active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012; 71: 1839-48. PubMed PMID: 22586173.

(Controlled trial of single dose of canakinumab in patients with an attack of acute gouty arthritis; ALT elevations [>3 times ULN] occurred in 4 of 225 [2%] treated with canakinumab vs 7 of 229 [3%] given triamcinolone).

Kontzias A, Efthimiou P. The use of Canakinumab, a novel IL-1β long-acting inhibitor, in refractory adult-onset Still's disease. Semin Arthritis Rheum 2012; 42: 201-5. PubMed PMID: 22512815.

(38 year old man and 36 year old woman with adult onset Still disease who were resistant to treatment with prednisone, methotrexate and anakinra had a complete and maintained response to canakinumab; no mention of side effects or ALT levels on treatment).

Miyamae T. Cryopyrin-associated periodic syndromes: diagnosis and management. Paediatr Drugs 2012; 14: 109-17. PubMed PMID: 22335455.

(Review of the clinical features, pathogenesis and therapy of CAPS with specific discussion of anakinra, rilonacept and canakinumab; no mention of hepatotoxicity).

Ruperto N, Quartier P, Wulffraat N, Woo P, Ravelli A, Mouy R, Bader-Meunier B, et al.; Paediatric Rheumatology International Clinical Trials Organisation. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum 2012; 64: 557-67. PubMed PMID: 21953497.

(Open label, dose escalation study of canakinumab in 23 children with juvenile idiopathic arthritis treated for up to 6 months; "There were no clinically relevant changes in the laboratory findings").

Vanderschueren S, Knockaert D. Canakinumab in Schnitzler syndrome. Semin Arthritis Rheum 2013; 42: 413-6. PubMed PMID: 22901459.

(37 year old man with Schnitzler syndrome resistant to other therapies [including anakinra] had an immediate and sustained response to canakinumab; "chemistry laboratory values were monitored and no abnormalities were observed").

Moran A, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Greenbaum CJ, et al.; Type 1 Diabetes TrialNet Canakinumab Study Group; AIDA Study Group. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet 2013; 381 (9881): 1905-15. PubMed PMID: 23562090.

(Two parallel trials comparing anakinra or canakinumab to placebo is 69 patients with recent onset of type 1 diabetes found no evidence of benefit and similar side effects of both drugs; no mention of ALT elevations or hepatotoxicity).

Akgul O, Kilic E, Kilic G, Ozgocmen S. Efficacy and safety of biologic treatments in familial mediterranean Fever. Am J Med Sci 2013; 346: 137-41. PubMed PMID: 23276893.

(Systematic review of reports on biologic response modifiers in familial Mediterranean fever identified no controlled trial, but 24 single reports and 7 case series describing 59 patients, 35 on anti-TNF agents, 29 anakinra, 4 canakinumab; 2 had adverse events that required stopping, but the rest seemed to have a beneficial effect; no discussion of hepatotoxicity).

Canakinumab (Ilaris) for systemic juvenile idiopathic arthritis. Med Lett Drugs Ther 2013; 55 (1416): 65-6. PubMed PMID: 23959387.

(Concise review of the pharmacology, mechanism of action, efficacy and safety of canakinumab shortly after its approval for juvenile idiopathic arthritis in the United States; mentions that neutropenia, thrombocytopenia and elevated aminotransferases have been reported with its use).

Banse C, Vittecoq O, Benhamou Y, Gauthier-Prieur M, Lequerré T, Lévesque H. Reactive macrophage activation syndrome possibly triggered by canakinumab in a patient with adult-onset Still's disease. Joint Bone Spine 2013; 80: 653-5. PubMed PMID: 23751410.

(49 year old woman with Still disease developed suspected macrophage activation syndrome after a second infusion of canakinumab with high fever, abdominal pain and hepatomegaly [bilirubin not given, ALT 20 times ULN], resolving with high dose glucocorticoid therapy).

Wulffraat NM. A safety evaluation of canakinumab for the treatment of systemic onset juvenile idiopathic arthritis. Expert Opin Drug Saf 2015; 14: 1961-7. PubMed PMID: 26568054.

(Systematic review of the adverse events associated with canakinumab therapy focuses on common events such as abdomninal pain, injection site reactions and infections and the more serious events such as septicemia and macrophase activtion syndrome; no mention of ALT elevations or hepatotoxicity).

Krause K, Tsianakas A, Wagner N, Fischer J, Weller K, Metz M, Church MK, et al. Efficacy and safety of canakinumab in Schnitzler syndrome: A multicenter randomized placebo-controlled study. J Allergy Clin Immunol 2016 Sep 19. [Epub ahead of print] PubMed PMID: 27658762.

(Among 20 patients with Schnitzler syndrome treated with canakinumab or placebo for 7 days followed by open label therapy, canakinumab was associated with marked clinical improvements in most patients and "no significant changes in safety laboratory parameters were observed").

Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JM, Cohen N, Pope TD, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatology (Oxford) 2016; 55: 669-79. PubMed PMID: 26628580.

(Systematic review of the literature of the safety of biologic agents for JIA mentions that serious adverse events including infections were no more frequent with canakinumab than placebo therapy; no mention of ALT elevations or hepatotoxicity).