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Rilonacept

Updated: April 20, 2020.

OVERVIEW

Introduction

Rilonacept is a recombinant interleukin-1 (IL-1) antagonist which is used in the therapy of cryopyrin-associated periodic syndromes (CAPS) and other autoinflammatory conditions. Rilonacept has had limited clinical use and has yet to be linked to cases of clinically apparent, acute liver injury.

Background

Rilonacept (ril on' a sept) is a recombinant fusion protein which includes the extracellular portion of the human IL-1 receptor and the IL-1 receptor accessory protein fused with the Fc portion of human IgG1. Rilonacept binds and inactivates IL-1, acting as an "IL-1 trap". IL-1 is a key proinflammatory cytokine that is a powerful inducer of fever and inflammation. Excessive production of IL-1 or lack of its inactivation is believed to play a major role in many autoinflammatory conditions and particularly in cold induced autoinflammatory conditions such as cryopyrin associated periodic syndromes (CAPS). IL-1 may also play an important role in inflammatory arthritides and familial Mediterranean fever. In controlled trials and open label studies, rilonacept has been shown to improve symptoms and laboratory abnormalities associated CAPS and, to a lesser extent, in patients with gouty arthritis, juvenile idiopathic arthritis, familial Mediterranean fever and in rare forms of autoinflammatory conditions such as Schnitzler syndrome. Rilonacept was approved for use in the United States in 2010 to treat CAPS. Rilonacept is given by subcutaneous injection in a loading dose of 320 mg and a maintenance dose of 160 mg weekly. Rilonacept is available in vials of 20 mL containing 222 mg of rilonacept under the brand name Arcalyst. The most frequent side effects are injection site reactions, upper respiratory symptoms, headache, nausea and hypertension. Potential serious adverse events include life-threatening infections and hypersensitivity reactions

Hepatotoxicity

In clinical trials, ALT elevations were rarely mentioned as an adverse event in patients receiving rilonacept, but minor overall increases in both ALT and AST levels were described (1-4%). The timing, severity and outcome of these elevations were not characterized, but there were no instances of jaundice or clinically apparent liver injury. Most ALT elevations were without symptoms or elevations in bilirubin or alkaline phosphatase and no long term hepatic effects were observed. Patients with autoinflammatory conditions such as CAPS frequently have mild-to-moderate elevations in serum enzymes and typically these improve with treatment using inhibitors of IL-1 signaling. Since its approval, there have been no published reports of hepatotoxicity due to rilonacept, although its use has been limited. In addition, rilonacept 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

Rilonacept is a recombinant protein and has little hepatic metabolism. Any liver injury due to rilonacept is more likely due to its effect on the immune system or on IL-1 pathways rather than a direct toxic effect on the liver.

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 serious hepatotoxicity. There is no reason to suspect that there may be cross sensitivity to hepatic injury between rilonacept and other immune modulating biologic agents or anti-IL1 blockers such as anakinra, canakinumab and tocilizumab.

Drug Class: Antirheumatic Agents

Other Drugs in the Subclass, Interleukin Receptor Antagonists: Anakinra, Canakinumab, Sarilumab, Tocilizumab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rilonacept – Arcalyst®

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
Rilonacept	501081-76-1	C9030-H13932-N2400-O2670-S74	No Structure

ANNOTATED BIBLIOGRAPHY

References updated: 20 April 2020

Abbreviations: IL-1, interleukin 1; CAPS, cryopyrin-associated periodic syndrome.

Abbreviations: IL1, interleukin 1; CAPS, cryopyrin-associated periodic syndrome; DMARD, disease modifying anti-rheumatic drug; TRAPS, tumor necrosis factor receptor associated periodic syndrome.

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 rilonacept and other recombinant proteins and anticytokines).

Krensky AM, Azzi JR, Hafler DA. Immunosuppressants and tolerogens. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 637-53.

(Textbook of pharmacology and therapeutics).

Goldbach-Mansky R, Shroff SD, Wilson M, Snyder C, Plehn S, Barham B, Pham TH, et al. A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. Arthritis Rheum. 2008;58:2432–42. PubMed PMID: 18668591.

(Among 5 patients with familial cold autoinflammatory syndrome treated with rilonacept [100-160 mg weekly], all had a clinical response to therapy and 3 had mild, transient elevations in ALT or AST).

Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A, Weinstein SP, et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum. 2008;58:2443–52. PubMed PMID: 18668535.

(Among 47 adults with CAPS enrolled in a controlled trial of rilonacept vs placebo for 6 weeks followed by a 9 weeks of open therapy and then continuation or withdrawal, "small increases in mean ALT and AST levels" were reported with rilonacept, but these changes were not clinically significant).

Church LD, McDermott MF. Rilonacept in cryopyrin-associated periodic syndromes: the beginning of longer-acting interleukin-1 antagonism. Nat Clin Pract Rheumatol. 2009;5:14–5. PubMed PMID: 19015646.

(Commentary on studies of rilonacept in CAPS [Hoffman and Goldbach-Mansky, 2008]; no mention of hepatotoxicity or ALT elevations during treatment).

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% in anakinra treated patients vs 0.4% in controls; infections were primarily pneumonia and skin infections, none were fatal and few were opportunistic infections).

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; rilonacept has not been linked to reactivation of HBV, although the experience in treating patients with HBsAg has been limited).

Dubois EA, Rissmann R, Cohen AF. Rilonacept and canakinumab. Br J Clin Pharmacol. 2011;71:639–41. PubMed PMID: 21375570.

(Short review of mechanism of action, clinical efficacy and safety of rilonacept and canakinumab; no mention of ALT elevations or hepatotoxicity).

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

(Review of the clinical features and pathogenesis [mutation in NLRP3 gene] of cryopyrin associated periodic syndromes [CAPS] and currently available treatments including anakinra [recombinant IL-1Ra], rilonacept [recombinant IL-1 trap] and canakinumab [monoclonal antibody to IL-1 beta]; no mention of ALT elevations or hepatotoxicity).

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 rilonacept or canakinumab).

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]).

Hashkes PJ, Spalding SJ, Giannini EH, Huang B, Johnson A, Park G, Barron KS, et al. Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. Ann Intern Med. 2012;157:533–41. PubMed PMID: 23070486.

(Among 14 patients with familial Mediterranean fever treated with sequential 3 month courses of rilonacept or placebo, attacks were less frequent during rilonacept therapy; no mention of ALT elevations or hepatotoxicity).

Hoffman HM, Throne ML, Amar NJ, Cartwright RC, Kivitz AJ, Soo Y, Weinstein SP. Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic syndromes: results of a 72-week open-label extension study. Clin Ther. 2012;34:2091–103. PubMed PMID: 23031624.

(Analysis of long term efficacy and safety of rilonacept in 101 patients with CAPS treated in an open label study for up to 2 years; mean levels of ALT and AST rose in patients receiving rilonacept [2-4 U/L], and therapy was temporarily discontinued in 2 patients because of ALT elevations).

Krause K, Weller K, Stefaniak R, Wittkowski H, Altrichter S, Siebenhaar F, Zuberbier T, Maurer M. Efficacy and safety of the interleukin-1 antagonist rilonacept in Schnitzler syndrome: an open-label study. Allergy. 2012;67:943–50. PubMed PMID: 22583335.

(Among 8 patients with Schnitzler syndrome treated with rilonacept for up to 1 year, symptoms and inflammatory markers improved and there were "no significant changes in safety laboratory values").

Petryna O, Cush JJ, Efthimiou P. IL-1 Trap rilonacept in refractory adult onset Still's disease. Ann Rheum Dis. 2012;71:2056–7. PubMed PMID: 22679302.

(Among 3 patients with refractory adult-onset Still disease treated with weekly injections of rilonacept, all had a complete remission maintained for 16-28 months and were able to reduce or stop corticosteroids; no adverse events reported).

Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, Wallace CA, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis (sJIA). Arthritis Rheum. 2013;65:2486–96. PubMed PMID: 23754188.

(Among 24 children with juvenile idiopathic arthritis treated with rilonacept for up to 2 years, the most common adverse event was injection site reactions; no mention of ALT elevations or hepatotoxicity).

Mitha E, Schumacher HR, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, Wang J, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology (Oxford). 2013;52:1285–92. PubMed PMID: 23485476.

(Among 248 patients with acute gouty arthritis treated with 2 doses of rilonacept or placebo once weekly for 16 weeks, acute flares were reduced with rilonacept therapy, but adverse events were similar in the two groups except for injection site reactions; no mention of ALT elevations or hepatotoxicity).

Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, King-Davis S, Weinstein SP. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. Arthritis Res Ther. 2013;15:R25. PubMed PMID: 23375025.

(Among 225 patients with acute gouty arthritis treated with rilonacept versus indomethacin vs the combination, there were no differences in pain scores with addition of rilonacept; no mention of ALT elevations or hepatotoxicity).

Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, Verbsky JW, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2014;66:2570–9. PubMed PMID: 24839206.

(Among 50 children with juvenile idiopathic arthritis treated with rilonacept or placebo for 4 weeks and then with open label rilonacept for up to 24 weeks, response rates were higher with rilonacept, and 4 patients receiving rilonacept developed elevated ALT levels that were above 5 times ULN in 2 [4%]).

Sundy JS, Schumacher HR, Kivitz A, Weinstein SP, Wu R, King-Davis S, Evans RR. Rilonacept for gout flare prevention in patients receiving uric acid-lowering therapy: results of RESURGE, a phase III, international safety study. J Rheumatol. 2014;41:1703–11. PubMed PMID: 25028379.

(Among 1315 adults with gout treated with rilonacept or placebo for 16 weeks, rilonacept was associated with fewer gout flares but higher rates of ALT elevations [1.1% vs 0.6%]).

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 rilonacept or other IL-1 antagonists).

Winthrop KL, Mariette X, Silva JT, Benamu E, Calabrese LH, Dumusc A, Smolen JS, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH). Consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect. 2018;24 Suppl 2:S21–S40. PubMed PMID: 29447987.

(Review of the risk of infections in patients receiving biologic therapies targeting interleukins and immunoglobulins concludes that patients taking IL-1 targeted agents have a moderate increased risk for infections, should be prescreened for tuberculosis and monitored for infections during therapy).

Garg M, de Jesus AA, Chapelle D, Dancey P, Herzog R, Rivas-Chacon R, Muskardin TLW, et al. Rilonacept maintains long-term inflammatory remission in patients with deficiency of the IL-1 receptor antagonist. JCI Insight. 2017;2:94838. pii. PubMed PMID: 28814674.

(6 children with IL-1r antagonist deficiency receiving daily injections of anakinra for 3 to 6 years were switched to once-weekly rilonacept and all had complete remissions with improved quality of life; adverse events included upper respiratory infections and gastrointestinal symptoms but no patient discontinued therapy; no mention of ALT elevations or hepatotoxicity).

Mantero JC, Kishore N, Ziemek J, Stifano G, Zammitti C, Khanna D, Gordon JK, et al. Randomised, double-blind, placebo-controlled trial of IL1-trap, rilonacept, in systemic sclerosis. A phase I/II biomarker trial. Clin Exp Rheumatol. 2018;36 Suppl 113:146–9. PubMed PMID: 30277862.

(Among 19 patients with systemic sclerosis treated with 6 weekly injections or rilonacept or placebo, symptoms and markers of disease activity did not change with therapy while adverse events included injection site reactions).

Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun. 2018;93:24–36. PubMed PMID: 30077425.

(Review of the pathogenesis, clinical features, complications and therapy of adult onset Still's disease mentions that liver test abnormalities have been reported in 37-74% of subjects and that anakinra has been studied in at least

13 small open label trials with response rates of 46-100%, and both canakinumab or rilonacept have been found to be helpful in cases with intolerance or an inadequate response to anakinra).

Crayne CB, Albeituni S, Nichols KE, Cron RQ. The Immunology of macrophage activation syndrome. Front Immunol. 2019;10:119. PubMed PMID: 30774631.

(Review of the immunopathogenesis of the macrophage activation syndrome, a complication of several systemic inflammatory disorders including juvenile idiopathic arthritis, systemic lupus erythematosus and adult onset Still's disease, characterized by high circulating levels of proinflammatory cytokines which has led to the experimental use of cytokine inhibitors such as anakinra, canakinumab and rilonacept).

Sfriso P, Bindoli S, Doria A, Feist E, Galozzi P. Canakinumab for the treatment of adult-onset Still's disease. Expert Rev Clin Immunol. 2020;16:129–38. PubMed PMID: 31957508.

(Review of the clinical efficacy and safety of canakinumab for adult-onset Still's disease for which it is not approved in the US, despite evidence for its efficacy in small case series and clinical trials; mentions that small studies of rilonacept in patients with adult-onset Still disease found it to be highly effective in alleviating symptoms and has the advantage of a longer half-life that allows weekly or every other week administration).