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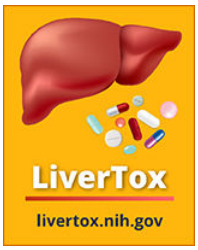

Sarilumab

Updated: May 11, 2021.

OVERVIEW

Introduction

Sarilumab is a human monoclonal IgG1 antibody to the interleukin-6 (IL-6) receptor which is used in the therapy of rheumatoid arthritis and other autoinflammatory conditions. Sarilumab commonly causes mild serum aminotransferase elevations which are usually short lived and asymptomatic and has also been linked to rare instances of clinically apparent liver injury with jaundice.

Background

Sarilumab (sar il' ue mab) is a human IgG1 monoclonal antibody to the IL-6 receptor that is used largely as therapy of refractory rheumatoid arthritis. Sarilumab binds to both soluble and membrane bound IL-6 receptors and blocks IL-6 signaling. IL-6 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 active rheumatoid arthritis. In controlled trials and open label studies, sarilumab therapy led to improvements in symptoms and laboratory abnormalities in patients with rheumatoid arthritis who had an inadequate response to other disease modifying antirheumatic drugs (DMARDs). Sarilumab was approved for use in the United States in 2017 for refractory rheumatoid arthritis. It is considered a DMARD, in that it improves signs and symptoms of disease and decreases cartilage and tissue destruction. Because IL-6 is found in high levels in patients with severe COVID-19 pneumonia, sarilumab was evaluated as therapy of the hyperinflammatory state in hospitalized patients with respiratory compromise. In prospective controlled trials, however, sarilumab therapy was associated with minimal or no improvement in clinical status or survival. Sarilumab is under evaluation in other inflammatory rheumatic diseases as well as other inflammatory autoimmune conditions, but has not been approved for these uses. For therapy of rheumatoid arthritis, sarilumab is given in doses of 200 mg by subcutaneous injection every 2 weeks either alone (monotherapy) or in combination with other conventional DMARDs. Sarilumab is available in single dose prefilled syringes of 150 and 200 mg in 1.14 mL under the brand name Kevzara. The most frequent side effects are neutropenia, upper respiratory symptoms, urinary tract infections headache, infusion reactions and hypertension. Rare, potentially serious adverse events include severe neutropenia, serious infections, reactivation of tuberculosis, gastrointestinal perforation and hypersensitivity reactions.

Hepatotoxicity

In registration trials, serum aminotransferase elevations occurred in a higher proportion of patients receiving sarilumab than placebo. Mean levels of ALT and AST increased within 2 weeks of starting the monoclonal

antibody and remained constant thereafter until stopping. At the same time, total bilirubin values increased slightly, while alkaline phosphatase values decreased. ALT elevations above 3 times the ULN occurred in 4% to 5% of patients receiving sarilumab (150 or 200 mg twice weekly) vs 1% of those receiving placebo. Despite the frequent elevations in liver tests, there were no instances of clinically apparent liver injury attributable to sarilumab therapy and most aminotransferase elevations were self-limited and without symptoms. Thus, sarilumab has not been linked to instances of clinically apparent liver injury.

Sarilumab is an immunosuppressive agent and is suspected to predispose to serious infections including reactivation of tuberculosis and hepatitis. Nevertheless, the frequency of serious infections in the controlled trials of sarilumab was similar to that with placebo therapy and there were no reports of tuberculosis or hepatitis B.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

Sarilumab is a monoclonal antibody and has minimal hepatic metabolism. The mechanism by which it might cause liver injury is unknown, but may be the result of its effects on the immune system or on the IL-6 pathway which is important in liver regeneration. A similar pattern of enzyme elevations occurs with tocilizumab, another monoclonal antibody to the IL-6 receptor used to treat rheumatoid arthritis.

Outcome and Management

The serum aminotransferase elevations associated with sarilumab therapy are generally mild and self-limited, improving spontaneously despite continuing therapy and resolving completely upon stopping. On the other hand, there is no reason to suspect that there may be cross sensitivity to hepatic injury between sarilumab and other immune modulating biologic agents or anti-IL1 blockers such as anakinra, canakinumab and rilonacept and the IL-6 antagonists siltuximab and tocilizumab.

Drug Class: Antirheumatic Agents, COVID-19 Drugs

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sarilumab – Kevzara®

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
Sarilumab	1189541-98-7	Monoclonal Antibody	No Structure

ANNOTATED BIBLIOGRAPHY

References updated: 23 March 2021

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, long before the availability of sarilumab and other monoclonal antibodies).

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).

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; sarilumab is not mentioned).

Bannwarth B, Richez C. Clinical safety of tocilizumab in rheumatoid arthritis. Expert Opin Drug Saf. 2011;10:123–31. PubMed PMID: 21121872.

(Review of the adverse events reported in clinical trials of tocilizumab in rheumatoid arthritis; among 3689 patients with normal ALT levels before treatment, 10.3% had ALT elevations >3 times ULN and 2.4% above 5 times ULN, but there were no cases of clinical apparent liver injury).

Hiura M, Abe S, Tabaru A, Shimajiri S, Hanami K, Saito K, Tanaka Y, et al. Case of severe liver damage after the induction of tocilizumab therapy for rheumatoid vasculitis. Hepatol Res. 2011;41:492–6. PubMed PMID: 21435128.

(71 year old man with refractory rheumatoid arthritis and vasculitis developed mild serum enzyme elevations during 3 months of tocilizumab therapy [bilirubin 1.3 mg/dL, ALT 67 U/L, Alk P 380 U/L, platelets 93,000/μL], later developing ascites, and hepatic failure, autopsy showing hepatic atrophy and little fibrosis).

Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, Klearman M, et al; ADACTA Study Investigators. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381(9877):1541–50. [Erratum in: Lancet 2013; 381(9877): 1540.]. PubMed PMID: 23515142.

(Controlled trial comparing 24 week courses of 2 monoclonal antibody therapies in 326 patients with rheumatoid arthritis; ALT elevations above 2.5 times ULN occurred in 6% on tocilizumab vs 1.9% on adalimumab, but there were no serious adverse events attributed to liver injury).

Alfreijat M, Habibi M, Bhatia P, Bhatia A. Severe hepatitis associated with tocilizumab in a patient with rheumatoid arthritis. Rheumatology (Oxford). 2013;52:1340–1. PubMed PMID: 23315786.

(62 year old man with rheumatoid arthritis developed jaundice 1 week after a 3rd monthly injection of tocilizumab [bilirubin 10.5, ALT 2296, Alk P not given], resolving within 10 weeks on prednisone; accompanied by mild pancreatitis).

Drepper M, Rubbia-Brandt L, Spahr L. Tocilizumab-induced acute liver injury in adult onset Still's disease. Case Reports Hepatol. 2013;2013:964828. PubMed PMID: 25374723.

(18 year old woman with Still disease developed jaundice 6 months after starting tocilizumab [bilirubin 3.6 mg/dL, ALT 2628 U/L, Alk P 110 U/L, INR 1.21], with liver biopsy showing centrolobular necrosis, and resolving within 1 month of stopping).

Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, Huang X, et al. Sarilumab, a fully human monoclonal antibody against IL-6Rα in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. Ann Rheum Dis. 2014;73:1626–34. PubMed PMID: 24297381.

(Among 306 patients with rheumatoid arthritis and an inadequate response to methotrexate who were treated with 1 of 5 regimens of sarilumab or placebo for 12 weeks, highest response rates occurred with the highest doses and adverse events included infections [20-26% vs 14%], neutropenia [2-6% vs 0] and ALT elevations [4-6% vs 0], most of which resolved spontaneously and there were no hepatic severe adverse events).

Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, Rohane P, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. Arthritis Rheumatol. 2015;67:1424–37. PubMed PMID: 25733246.

(Among 1282 patients with rheumatoid arthritis and inadequate responses to methotrexate treated with intravenous sarilumab [150 or 200 mg] or placebo every 2 weeks for 52 weeks, clinical response rates were greater with sarilumab [58-66% vs 33%] as were rates of adverse events including neutropenia, infections, injection site reactions and ALT elevations above 3 times ULN [8.0-9.5% vs 2.1%], but there were no episodes of clinically apparent liver injury).

Sieper J, Braun J, Kay J, Badalamenti S, Radin AR, Jiao L, Fiore S, et al. Sarilumab for the treatment of ankylosing spondylitis: results of a Phase II, randomised, double-blind, placebo-controlled study (ALIGN). Ann Rheum Dis. 2015;74:1051–7. PubMed PMID: 24550171.

(Among 301 patients with ankylosing spondylitis treated with one of 5 dose regimens of sarilumab or placebo for 12 weeks, there were no differences in clinical response rates among treatment groups, and adverse events included neutropenia, infections and ALT elevations).

Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, van Hoogstraten H, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2017;76:840–7. PubMed PMID: 27856432.

(Among 363 patients with rheumatoid arthritis with an inadequate response to methotrexate treated with sarilumab vs adalimumab monotherapy, response rates were greater with sarilumab while adverse event rates were similar, overall rates being 64% vs 64%, neutropenia 13.6% vs 0.5% and ALT elevations 3.8% vs 3.8%).

Fleischmann R, van Adelsberg J, Lin Y, Castelar-Pinheiro GD, Brzezicki J, Hrycaj P, Graham NM, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients 2ith active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. Arthritis Rheumatol. 2017;69:277–90. PubMed PMID: 27860410.

(Among 546 patients with rheumatoid arthritis and an inadequate response to conventional therapy who were treated with sarilumab [150 or 200 mg every 2 weeks] or placebo for an average of 34 weeks, clinical responses were greater with sarilumab [56-61% vs 34%] as were adverse events including neutropenia [13% vs 1%] and ALT elevations above 3 times ULN [2.2-4.3% vs 1.1%], but all resolved, only one requiring discontinuation).

Scott LJ. Sarilumab: First global approval. Drugs. 2017;77:705–12. PubMed PMID: 28290137.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of sarilumab shortly after its approval in the US for rheumatoid arthritis; no mention of ALT elevations or hepatotoxicity).

FDA safety review of elevations in liver associated enzymes during sarilumab therapy. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761037Orig1s000MedR.pdf

(Accessed July 31, 2017).

Sarilumab (Kevzara) for rheumatoid arthritis. Med Lett Drugs Ther. 2017;59(1527):134–6. PubMed PMID: 28787744.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of sarilumab shortly after its approval for use in rheumatoid arthritis in the US mentions side effects of infections, neutropenia, ALT elevations [5%], and injection site reactions).

Drugs for rheumatoid arthritis. Med Lett Drugs Ther. 2018;60(1552):123–8. PubMed PMID: 30044766.

(Concise review of the drugs approved for use in rheumatoid arthritis mentions two monoclonal antibodies to IL-6).

Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, Mangan EK, Spindler A, et al; EXTEND study investigators. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. Rheumatology (Oxford). 2018;57:1423–31. PubMed PMID: 29746672.

(Among 901 patients with rheumatoid arthritis who were enrolled in an extension trial of sarilumab beneficial effects were sustained for the duration of treatment, and ALT elevations continued to arise but were generally short lived and none were associated with jaundice and symptoms; elevations above 3 times ULN arose in 12%, were above 5 times ULN in 3.8% and were the reason for dose reductions in 3.6% of patients).

Fleischmann R, Genovese MC, Lin Y, St John G, van der Heijde D, Wang S, Gomez-Reino JJ, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. Rheumatology (Oxford). 2020;59:292–302. PubMed PMID: 31312844.

(Analysis of pooled results from trials of sarilumab in rheumatoid arthritis with up to 7 years of exposure found ALT elevations above 3 times ULN in 6% on sarilumab monotherapy and 10% on combination therapy with another DMARD [usually methotrexate], abnormalities usually arising within the first 6 months of therapy, but none were associated with clinically apparent hepatitis).

Della-Torre E, Campochiaro C, Cavalli G, De Luca G, Napolitano A, La Marca S, Boffini N, et al; SARI-RAF Study Group. SARI-RAF Study Group members. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study. Ann Rheum Dis. 2020;79:1277–85. PubMed PMID: 32620597.

(28 patients with severe COVID-19 pneumonia and elevated inflammatory markers in serum were treated with intravenous sarilumab [400 mg] and were followed for 28 days, at which point comparison to a matched concurrently follow group found no difference in clinical improvement [61% vs 64%] or death [7% vs 18%], but higher rates of liver enzyme elevations [14% vs none]).

Gremese E, Cingolani A, Bosello SL, Alivernini S, Tolusso B, Perniola S, Landi F, et al; GEMELLI AGAINST COVID-19 Group. Sarilumab use in severe SARS-CoV-2 pneumonia. EClinicalMedicine. 2020;27:100553. PubMed PMID: 33043284.

(Among 53 patients with severe COVID-19 pneumonia treated with sarilumab [400 mg iv] in an uncontrolled open-label trial, the mortality rate was 5.7% and there were no serious adverse events).

REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021: NEJMoa2100433.

(Among 366 patients receiving tocilizumab, 48 sarilumab and 412 standard of care therapy for severe COVID-19 pneumonia enrolled in a prospective, multinational adaptive clinical trial, organ-support free days were greater and mortality less in those receiving anti-IL6 therapy; there were no serious adverse events associated with sarilumab but other specific results were not provided).

Lescure FX, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, Patel N, et al.; Sarilumab COVID-19 Global Study Group. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2021: S2213-2600(21)00099-0.

(Among 420 patients with severe COVID-19 pneumonia treated with sarilumab [200 or 400 mg iv] or placebo, there were no differences in the median time to improvement or 29 day survival and ALT elevations arose in 19% of placebo vs 30-32% of sarilumab treated subjects; no mention of clinically apparent liver injury).