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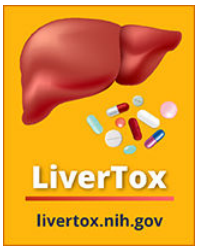

Anakinra

Updated: April 20, 2020.

OVERVIEW

Introduction

Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that has antiinflammatory and immunomodulatory actions and is used in the therapy of rheumatoid arthritis and other inflammatory arthritides. Anakinra is associated with a low rate of serum enzyme elevations during therapy and with rare instances of clinically apparent, acute liver injury.

Background

Anakinra (an a kin' ra) is used to treat serious inflammatory conditions such as rheumatoid arthritis and cryopyrin-associated periodic syndromes (CAPS). IL-1 like tumor necrosis factor alpha (TNF) is a proinflammatory cytokine that plays a major role in the immune responses underlying local and systemic inflammation. IL-1 also is the dominant cartilage destructive cytokine. Circulating IL-1 receptor antagonists (IL-1Ra) modulate the effects of IL-1 and are synthesized in response to inflammatory reactions, acting to prevent binding of circulating IL-1 to its receptor and thus helping to terminate the proinflammatory reaction. Anakinra is a recombinant version of IL-1Ra produced in E. coli, differing from the natural cytokine antagonist only in being nonglycosylated and having the addition of a single amino acid (methionine) on its amino terminus. Anakinra has been shown to be a disease modifying antirheumatologic drug (DMARD) and to improve signs and symptoms and decrease cartilage destruction in rheumatoid arthritis. Anakinra was approved for use in the United States in 2001 and its current formal indications are for severe rheumatoid arthritis and the autoinflammatory conditions known as cryopyrin-associated periodic syndromes (CAPS). It is used off label for idiopathic juvenile arthritis and other autoimmune forms of arthritis such as adult onset Still disease and macrophage activation syndrome. Anakinra must be given parenterally daily and is available under the brand name Kineret in prefilled syringes of 100 mg per 0.67 mL, which allow for doses between 20 and 100 mg. A typical regimen is 100 mg subcutaneously each day. Common side effects are local skin reactions, gastrointestinal upset, headache, arthralgias and possibly an increased incidence of bacterial infections. Less common but potentially severe adverse reactions include serious infections, reactivation of tuberculosis and hypersensitivity reactions.

Hepatotoxicity

In large registration trials, ALT elevations occurred in <1% of patients taking anakinra, a rate not different from that in placebo recipients, and no cases of clinically apparent liver injury with jaundice were reported. Since its approval and more wide scale use, however, anakinra has been linked to several instances of acute liver injury. The onset was within a few weeks to up to 6 months after starting subcutaneous injections of anakinra and the

typical clinical presentation resembled acute viral hepatitis, with a hepatocellular pattern of serum enzyme elevations, high levels of ALT and AST and mild to moderate jaundice. Immunoallergic features were not reported and autoantibodies were considered due to the underlying conditions being treated. Liver biopsies demonstrated an acute hepatocellular injury with prominence of eosinophils. Most patients recovered within 2 to 8 weeks of stopping anakinra without evidence of residual injury, but some cases have been severe, protracted and associated with transient features of hepatic failure. Not all published cases of anakinra-associated acute liver injury have been very convincing; virtually all have occurred in patients with Still's disease in which acute liver injury can be a manifestation of the underlying condition or a component of macrophage activation syndrome, a potentially life-threatening complication of adult onset Still's disease and other inflammatory arthritides. Furthermore, in many of the published instances, patients were taking other drugs capable of causing acute liver injury (such as high dose methylprednisolone). Anakinra has not been linked to reactivation of hepatitis B or exacerbation of chronic hepatitis C.

Likelihood score: C (probable cause of clinically apparent acute liver injury).

Mechanism of Injury

Anakinra binds to circulating IL-1 and is metabolized peripherally, probably largely in macrophages. It is a polypeptide and has minimal hepatic metabolism. The mechanism by which it causes liver injury is unknown, but may be the result of its effects on the immune system.

Outcome and Management

The hepatic injury caused by anakinra is usually self-limited and resolves within a few weeks of stopping the medication, although some cases have been severe and protracted. Cases of fatal, acute liver failure, chronic hepatitis and vanishing bile duct syndrome have not been reported with its use. There is no reason to suspect that there may be cross sensitivity to hepatic injury between anakinra and other immune modulating biologic agents including agents that modulate IL1 such as canakinumab and rilonacept.

Drug Class: Antirheumatic Agents

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

CASE REPORT

Case 1. Acute liver injury due to anakinra.(1)

A 22 year old woman with suspected adult onset Still disease was treated with anakinra, which resulted in a marked improvement in the inflammatory arthritis, but was followed by the development of jaundice 3 weeks after starting the daily injections. Before starting anakinra, the patient had presented with a systemic inflammatory condition marked by fever, skin rash and polyarthritis that was diagnosed as being adult onset Still disease, based upon the clinical presentation and laboratory findings of an elevated erythrocyte sedimentation rate and serum ferritin in the absence of autoantibodies or rheumatoid factor. She was treated with high doses of methylprednisolone followed by oral prednisone (1 mg/kg) with little change in symptoms, and persistent fever and arthralgias. Anakinra was started in a subcutaneous dose of 100 mg daily, which was followed by symptomatic improvement and fall of ESR to normal within a week. The dose of prednisone was decreased to 30 mg daily and anakinra was continued. Three weeks after starting the IL-1ra therapy she developed fatigue and jaundice. She had no previous history of liver disease, alcohol abuse or risk factors for viral hepatitis. When she initially presented with fever and polyarthritis, serum aminotransferase levels were mildly elevated. At the time of presentation with jaundice, the serum total bilirubin was 6.8 mg/dL (6.6 direct), ALT 3346 U/L, AST 2386 U/L, GGT 538 U/L and alkaline phosphatase 300 U/L. Tests for hepatitis A, B and C were negative and

abdominal ultrasound was normal, with no evidence of biliary obstruction. A liver biopsy showed an acute hepatitis with marked inflammation and necrosis without fibrosis or signs of hemophagocytosis. Stopping anakinra was followed by a rapid improvement in the liver injury, but two weeks later the reappearance of symptoms and signs of adult onset Still disease prompted treatment with intravenous immunoglobulin which led to a remission in disease.

Key Points

Medication:	Anakinra (100 mg daily)
Pattern:	Hepatocellular (R=32)
Severity:	3+ (jaundice, hospitalization)
Latency:	3 weeks
Recovery:	~2 weeks
Other medications:	Prednisone, folate

Comment

This patient developed acute hepatitis with jaundice 3 weeks after starting daily doses of anakinra for adult onset Still's disease. The pattern and course of the liver injury was quite typical of idiosyncratic drug induced liver injury and compatible with the type of injury that has been reported with anakinra with a 2 to 6 week latency and a hepatocellular or mixed pattern of liver enzyme elevations. The pathogenesis is unknown. Anakinra is a recombinant protein and is unlikely to be inherently hepatotoxic, but rather more likely to toe trigger the acute liver injury indirectly by its action against IL-1 or on the immune system. Patients with adult onset Still disease often have hepatic involvement and particularly with the complication of macrophage activation syndrome, marked by immune activation and proliferation of cytotoxic CD8 T cells and macrophages with hemophagocytosis. However, in this case there was no evidence of concurrent hemophagocytosis or macrophage activation.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Anakinra – Kineret®

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
Anakinra	143090-92-0	C759-H1186-N208-O232-S10	Protein

CITED REFERENCE

1. Diallo A, Mekinian A, Boukari L, Mouas H, Zamy M, Nahon P, Gérin M, et al. Rev Med Interne. 2013;34:168–70. [Severe hepatitis in a patient with adult-onset Still's disease treated with anakinra]. French. PubMed PMID: 23182291.

ANNOTATED BIBLIOGRAPHY

References updated: 20 April 2020

Abbreviations: IL-1ra, interleukin 1 receptor antagonist; CAPS, cryopyrin-associated periodic syndromes; TNF, tumor necrosis factor; IVIG, intravenous immunoglobulin.

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 anakinra).

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).

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).

Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, Nuki G, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum. 1998;41:2196–204. PubMed PMID: 9870876.

(Among 472 patients with rheumatoid arthritis enrolled in a controlled trial comparing anakinra [30, 75 or 150 mg] vs placebo, both given subcutaneously once daily for 24 weeks, the most frequent side effect was injection site reactions [50%-81% vs 25% with placebo]; "no other important adverse effects were detected in the laboratory analyses").

Nuki G, Bresnihan B, Bear MB, McCabe D; European Group Of Clinical Investigators. Long-term safety and maintenance of clinical improvement following treatment with anakinra(recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis; extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46:2838–46. PubMed PMID: 12428223.

(Among 309 patients with rheumatoid arthritis who entered an extension phase after a controlled trial of anakinra [Bresnihan 1998] and were treated for up to 76 weeks, the only common adverse event being injection site reactions; no mention of ALT elevations or clinically apparent liver injury).

Fleischmann RM, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, Modafferi D, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist(r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003;48:927–34. PubMed PMID: 12687534.

(Among 1414 patients with rheumatoid arthritis treated for 24 weeks with anakinra [100 mg] or placebo given subcutaneously once daily, serum biochemistry testing indicated "no evidence of hepatotoxicity").

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, ALT 32-252 U/L; all ultimately had "complete recovery").

Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. N Engl J Med. 2003;348:2583–4. PubMed PMID: 12815153.

(Two patients with Muckle-Wells syndrome, a hereditary autoinflammatory disease, had a dramatic and sustained response to therapy with anakinra).

Furst DE. Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004;26:1960–75. PubMed PMID: 15823761.

(Systematic review of literature on anakinra therapy of rheumatoid arthritis concluded that it was "mildly to moderately effective and well tolerated", the frequency of side effects other than injection site reactions being no different than that among placebo recipients).

Fleischmann RM, Tesser J, Schiff MH, Schechtman J, Burmester GR, Bennett R, Modafferi D, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006;65:1006–12. PubMed PMID: 16396977.

(Summary of an open label extension trial of anakinra in 1346 patients with rheumatoid arthritis who had participated in a randomized controlled trial [Fleischmann 2002], mentions that 5 patients [0.4%] had elevated serum enzymes, but no details of levels or outcomes given; among 15 deaths, there were none attributed to liver disease).

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).

Kötter I, Wacker A, Koch S, Henes J, Richter C, Engel A, Günaydin I, Kanz L. Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum. 2007;37:189–97. PubMed PMID: 17583775.

(Description of 4 patients with chronic or relapsing adult onset Still disease who had an immediate, dramatic response to anakinra therapy, having failed to respond to corticosteroids, methotrexate, TNF antagonists and leflunomide; ALT and AST values improved with treatment as well).

Mylona E, Golfinopoulou S, Samarkos M, Fanourgiakis P, Papadakos V, Skoutelis A. Acute hepatitis in adult Still's disease during corticosteroid treatment successfully treated with anakinra. Clin Rheumatol. 2008;27:659–61. PubMed PMID: 18095015.

(46 year old man with adult onset Still disease developed worsening liver tests during prednisone taper [bilirubin 1.5 mg/dL, ALT 3009 U/L, Alk P 185 U/L, INR normal] that improved when anakinra was added, with remission in disease and fall of all liver tests into the normal range).

Mertens M, Singh JA. Anakinra for rheumatoid arthritis: a systematic review. J Rheumatol. 2009;36:1118–25. PubMed PMID: 19447938.

(Systematic review of literature on efficacy and safety of anakinra in rheumatoid arthritis identified 5 clinical trials involving 2846 patients; the major adverse events were injection site reactions [71% vs 28% with placebo], nonsignificant increase in serious infections, but no mention of liver injury or ALT elevations).

Canna S, Frankovich J, Higgins G, Narkewicz MR, Nash SR, Hollister JR, Soep JB, et al. Acute hepatitis in three patients with systemic juvenile idiopathic arthritis taking interleukin-1 receptor antagonist. Pediatr Rheumatol Online J. 2009;7:21. PubMed PMID: 20028520.

(Description of 3 patients with systemic juvenile rheumatoid arthritis who developed symptomatic hepatitis 1-8 months after starting anakinra [bilirubin not given, AST ~1200 to 3000 U/L], resolving once anakinra was stopped).

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).

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 infection 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).

Hot A, Toh ML, Coppéré B, Perard L, Madoux MH, Mausservey C, Desmurs-Clavel H, et al. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore). 2010;89:37–46. PubMed PMID: 20075703.

(Among 8 patients with adult onset Still's disease and "reactive hemophagocytic syndrome [now referred to as macrophage activation syndrome], ages 22 to 75 years, 6 women, 2 men, with onset of syndrome at time of diagnosis of Still's disease in most, characterized by rash, fever, lymphopenia, lymphadenopathy, pharyngitis, arthralgia, abnormal liver tests [bilirubin elevated in 2, ALT in all, 46 to 388 U/L, high ferritin, low fibrinogen], achieving a remission ultimately on immunosuppression with corticosteroids, with or without IVIG, methotrexate, cyclophosphamide or cyclosporin).

Mahamid M, Paz K, Reuven M, Safadi R. Hepatotoxicity due to tocilizumab and anakinra in rheumatoid arthritis: two case reports. Int J Gen Med. 2011;4:657–60. PubMed PMID: 21941451.

(49 year old woman with rheumatoid arthritis and nonalcoholic fatty liver disease developed fatigue and mild serum enzyme elevations 2 months after starting anakinra [bilirubin normal, ALT 50 U/L, Alk P 161 U/L], resolving rapidly upon stopping).

Mahamid M, Mader R, Safadi R. Hepatotoxicity of tocilizumab and anakinra in rheumatoid arthritis: management decisions. Clin Pharmacol 2011; 3:3 9-43.

(Description of same two patients as in Mahamid [Int J Gen Med 2011]).

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; anakinra has not been linked to reactivation of HBV, either in the published literature or in reports to the sponsor).

Lim KB, Schiano TD. Still disease and the liver-an underappreciated association. Gastroenterol Hepatol (N Y). 2011;7:844–6. PubMed PMID: 22347828.

(Concise review of liver dysfunction in adult-onset Still's disease which can vary from asymptomatic ALT elevations to acute liver failure and diagnosis of superimposed drug induced liver injury [from anakinra, methotrexate, penicillamine, leflunomide or cyclophosphamide among others] is often difficult).

Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA, Cortis E, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011;63:545–55. PubMed PMID: 21280009.

(Retrospective analysis of 46 patients with juvenile idiopathic arthritis treated with anakinra at 11 referral centers in 4 countries; clinical responses occurred in more than 95% of patients, often within the first month; one 8 year old child developed acute hepatitis [described in Canna 2009] and two other patients had elevations in serum enzymes on treatment, but no details given).

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 mentions that anakinra has not been associated with reactivation of tuberculosis, and the incidence of malignancies is not increased with its use; no mention of ALT elevations or hepatotoxicity).

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]).

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

(Concise summary on current therapies of rheumatoid arthritis states that anakinra is considered the least effective biologic DMARD and is not recommended).

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).

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 in 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).

Diallo A, Mekinian A, Boukari L, Mouas H, Zamy M, Nahon P, Gérin M, et al. Rev Med Interne. 2013;34:168–70. [Severe hepatitis in a patient with adult-onset Still's disease treated with anakinra]. French. PubMed PMID: 23182291.

(22 year old woman with adult onset Still disease developed jaundice 3 weeks after starting anakinra which had induced a remission in disease [bilirubin 6.8 mg/dL, ALT 3346 U/L, Alk P 300 U/L], improving promptly when anakinra was stopped: Case 1).

Aly L, Iking-Konert C, Quaas A, Benten D. Subacute liver failure following anakinra treatment for adult-onset Still disease. J Rheumatol. 2013;40(10):1775–7. PubMed PMID: 24085761.

(20 year old man with adult onset Still disease developed fever and jaundice 3 months after starting anakinra and prednisone [bilirubin ~10 mg/dL, ALT ~4000 U/L, INR 2.7], with splenomegaly and ascites, improving upon stopping anakinra and increasing prednisone with eventual resolution 5 months after onset).

Néel A, Henry B, Barbarot S, Masseau A, Perrin F, Bernier C, Kyndt X, et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: a French multicenter study. Autoimmun Rev. 2014;13:1035–41. PubMed PMID: 25220180.

(Among 42 patients with Schnitzler's syndrome followed in 16 centers in France, 29 were treated with anakinra, all of whom had marked improvements on therapy which were maintained during an average follow up of 3 years; side effects included injection site reactions [17%], neutropenia [10%], infections [21: mostly pneumonia, 2 being fatal] and colon cancer [1 case]; no mention of hepatotoxicity or ALT elevations and no discontinuations for liver related complications),

Ahmed O, Brahmania M, Alsahafi M, Alkhowaiter S, Erb S. Anakinra hepatotoxicity in a patient with adult-onset Still's disease. ACG Case Rep J. 2015;2(3):173–4. PubMed PMID: 26157954.

(46 year old woman with adult-onset Still's disease developed ALT elevations 2 weeks after starting anakinra [bilirubin 1.2 mg/dL, ALT 1202 U/L, Alk P not given], with worsening of liver injury one week after restarting anakinra [bilirubin 6.7 mg/dL, ALT 1945 U/L, GGT 696 U/L] which gradually resolved on stopping and did not recur on subsequent therapy with etanercept).

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;148:1340–1352.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to anakinra or other interleukin 1 receptor antagonists).

Kullenberg T, Löfqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology (Oxford). 2016;55(8):1499–506. PubMed PMID: 27143789.

(Among 43 patients with severe cryopyrin-associated periodic syndromes [84% <18 years of age] treated with anakinra for up to 5 years, adverse events were common but mostly due to the underlying condition; 14 patients [33%] had a serious adverse event, but none were liver related and there was no mention of ALT elevations or hepatotoxicity).

Taylor SA, Vittorio JM, Martinez M, Fester KA, Lagana SM, Lobritto SJ, Ovchinsky N. Anakinra-induced acute liver failure in an adolescent patient with Still's disease. Pharmacotherapy. 2016;36:e1–4. PubMed PMID: 26749403.

(19 year old man with Still's disease developed serum ALT and AST elevations 16 days after starting high dose methylprednisone and 5 days after starting anakinra [direct bilirubin 1.7 mg/dL, ALT rising from 19 to 2002 U/L, Alk P not given, INR 1.7], biopsy showing acute hepatitis and liver test abnormalities, resolving within 30 days of stopping anakinra and switching iv methylprednisolone to oral prednisone).

Lenert A, Yao Q. Macrophage activation syndrome complicating adult onset Still's disease: A single center case series and comparison with literature. Semin Arthritis Rheum. 2016;45:711–6. PubMed PMID: 26672682.

(Description of 7 patients with adult onset Still's disease who developed macrophage activation syndrome soon after initial presentation manifested by fever, rash, arthralgias, lymphopenia, leukocytosis and liver test abnormalities [mean bilirubin 4.2 mg/dL, ALT 290 U/L, LDH 2167 U/L, INR 1.58], and variable degrees of renal and pulmonary failure and hemophagocytosis present in 3 of 7 bone marrow biopsies, with excellent response to anakinra).

Colafrancesco S, Priori R, Valesini G, Argolini L, Baldissera E, Bartoloni E, Cammelli D, et al. Response to interleukin-1 inhibitors in 140 Italian patients with adult-onset Still's disease: a multicentre retrospective observational study. Front Pharmacol. 2017;8:369. PubMed PMID: 28659802.

(Among 140 patients with adult onset Still's disease followed at 18 Italian referral centers treated with anakinra, clinical responses were common and the most frequent adverse events were local injection reactions, rash and infections [15%] while hepatomegaly and liver test abnormalities decreased on treatment (from 47% to 5%]; therapy was switched to canakinumab in 4 patients with an unsatisfactory response to anakinra and 3 responded and "no adverse events were registered").

Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat NM, Horneff G, Kasapcopur O, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. Ann Rheum Dis. 2018;77:1710–9. PubMed PMID: 30269054.

(Among 144 children with juvenile idiopathic arthritis enrolled in controlled trials [Ruperto 2012] who were continued on therapy in extension studies, 102 discontinued treatment because of lack of efficacy while clinical efficacy was maintained in the rest, adverse events included macrophage activation syndrome [6%], hepatitis [1%] and hepatic enzyme elevations [2%]).

Sota J, Vitale A, Insalaco A, Sfriso P, Lopalco G, Emmi G, Cattalini M, et al. "Working Group" of Systemic Autoinflammatory Diseases of SIR (Italian Society of Rheumatology). Safety profile of the interleukin-1 inhibitors anakinra and canakinumab in real-life clinical practice: a nationwide multicenter retrospective observational study. Clin Rheumatol. 2018;37:2233–40. PubMed PMID: 29770930.

(Among 475 patients treated with anakinra or canakinumab for various inflammatory conditions for an average of 24 months, the most frequently reported adverse events were rash, injection site reactions, infections, cytopenias, and anaphylaxis; one patient developed serum enzyme elevations and one macrophage activation syndrome).

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 21-61% of subjects and that anakinra has been studied in at least 13 small open label trials with response rates of 46-100% and tocilizumab in 8 trials with response rates of 65-100%).

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).

Vastert SJ, Jamilloux Y, Quartier P, Ohlman S, Osterling Koskinen L, Kullenberg T, et al. Anakinra in children and adults with Still's disease. Rheumatology (Oxford). 2019;58 Suppl 6:vi9–vi22. PubMed PMID: 31769856.

(Review of the mechanism of action, clinical efficacy and safety of anakinra in pediatric and adult-onset Still's disease with summary of 27 publications reporting response rates of 23-81% usually with complete remission and ability to stop or decrease corticosteroid use; mentions that liver injury attributed to anakinra has been reported).