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Current Indications for IL-1 Inhibition in Rheumatology

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Abstract

Interleukin-1 pro-inflammatory cytokines orchestrate local and systemic inflammatory responses in several diseases. Three therapeutic agents for reducing the activities of IL-1 are currently available. Conditions effectively treated with IL-1 blocking agents range from classical rheumatic diseases to autoinflammatory syndromes. In addition, IL-1 antagonism is also effective against other very common diseases, namely cardiovascular disease and type 2 diabetes, which are also co-morbidities, frequently found in patients with rheumatic diseases. Therefore, inhibition of IL-1 may provide clinical benefits beyond the efficacy of osteoarticular manifestations. The purpose of this article is to review the indications for anti-interleukins 1 in rheumatology.

Keywords

Interleukin 1, Anti-Interleukin 1, Auto-Inflammatory Disease, Anakinra, Canakinumab, Rilonacept

1. Introduction

Interleukin-1 (IL-1) is a key pro-inflammatory cytokine involved in innate immunity. It plays a central role in the pathophysiology of numerous diseases. The neutralization of IL-1 has proven effective in several rheumatologic and autoinflammatory conditions. In patients with rheumatic diseases, IL-1 inhibition may offer clinical benefits beyond the control of osteoarticular manifestations. The aim of this article is to review the current indications for IL-1 inhibitors in the field of rheumatology.

2. Overview

The IL-1 family includes 11 members: seven pro-inflammatory cytokines (IL-1α, IL-1β, IL-18, IL-36α, IL-36β, IL-36γ, and IL-33), and three with anti-inflamma-

tory properties (IL-1Ra, which blocks IL-1α and IL-1β; IL-36Ra, which blocks IL-36α, β, and γ; and IL-37). The function of IL-38 remains unclear. The three best-known members of the IL-1 family are IL-1α and IL-1β, which bind to the same receptor, and the IL-1 receptor antagonist (IL-1Ra). These molecules are produced by macrophages, monocytes, dendritic cells, fibroblasts, and epithelial cells in response to infection, trauma, or immune stimulation [1].

Various forms of cellular stress can lead to mitochondrial production of reactive oxygen species (ROS). These ROS may serve as a priming signal that activates the NLRP3 inflammasome. The precursors of IL-18 and IL-1β require cleavage by intracellular caspase-1 or extracellular neutrophil-derived proteases to become active and bind their receptor. These cytokines induce cell damage and sustain the inflammatory process [2].

Three IL-1 inhibitors are currently available: anakinra, a recombinant form of the IL-1 receptor antagonist (IL-1Ra); rilonacept, a dimeric fusion protein that traps IL-1; and canakinumab, a humanized monoclonal antibody that prevents IL-1β binding to its receptor [3].

3. Adverse Events and Safety Profile

IL-1 inhibitors are generally well tolerated, but clinicians should be aware of common adverse events. The most frequently reported are injection-site reactions, upper respiratory tract infections, neutropenia, and increased risk of serious infections, particularly in immunocompromised patients. Long-term data suggest that most adverse events are manageable, though careful monitoring is warranted when treating chronic diseases [4] [5].

4. Autoinflammatory Diseases

4.1. Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (sJIA)

Recent studies suggest that the pathogenesis of sJIA may follow a biphasic pattern. The early phase is primarily driven by innate immunity, with IL-1β identified as a key cytokine. In contrast, the later phase appears to be dominated by adaptive immunity and IL-17A, with chronic arthritis becoming the predominant clinical feature. Based on these observations, IL-1 blockade represents a rational therapeutic strategy in the initial phase of sJIA, while in persistent disease with chronic arthritis, other biologic agents may offer better efficacy [6].

In a study by Vastert *et al*., anakinra was administered at a dose of 2 mg/kg in 20 patients with new-onset sJIA. Fever resolved within three days in 90% of patients, and inflammatory markers (CRP and ferritin) normalized in 80% of those receiving anakinra monotherapy within 30 days of treatment initiation [7]. In another trial, canakinumab was assessed in three age groups—children, adolescents, and adults—with comparable efficacy outcomes across all groups. By day 15, ≥70% improvement in ACR criteria was observed in at least 50% of patients in each group [8]. A recent phase-III study (NCT02296424, 2021) further confirmed the

sustained efficacy of canakinumab in Still's disease, strengthening its role as a first-line biologic [9].

Rilonacept was evaluated in three patients with Still's disease refractory to DMARDs and anakinra; all achieved complete remission, with partial improvement observed as early as the first month [10].

Several studies also highlight the efficacy of anakinra in AOSD. A de novo mutation in the inflammasome component NLRC4 has been identified as causing constitutive caspase-1 activation and deregulated release of IL-1β and IL-18, leading to recurrent macrophage activation syndrome. In such cases, treatment with anakinra has shown favorable outcomes [11].

4.2. Familial Mediterranean Fever (FMF)

IL-1 plays a central role in the inflammatory response observed in FMF, making IL-1 inhibitors a promising therapeutic option. These agents effectively control chronic inflammation and prevent disease progression to amyloidosis and organ failure. In a case series from a referral centre involving adult patients with FMF complicated by amyloidosis, four patients were treated with anakinra. The treatment showed a marked effect on both inflammatory manifestations and overall clinical condition, potentially altering the prognosis of these patients [12].

4.3. Hyper-IgD Syndrome (Mevalonate Kinase Deficiency)

This autosomal recessive autoinflammatory disorder, also known as mevalonate kinase deficiency, is clinically characterized by recurrent fever, myalgia, rash, aphthous ulcers, and lymphadenopathy. Several intracellular pathways link mevalonate kinase deficiency to the activation of caspase-1 and subsequent IL-1 production. IL-1 blocking agents have proven effective in reducing both the frequency and severity of inflammatory flares.

4.4. Cryopyrin-Associated Periodic Syndromes (CAPS)

CAPS refers to a spectrum of three clinical entities: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). These conditions are caused by mutations in the NLRP3 inflammasome, leading to dysregulated activation of caspase-1 and excessive release of IL-1β. CAPS is characterized by a continuum of increasing severity—from episodic fever, myalgia, and skin rash to chronic systemic inflammation, with serious neurologic complications and growth retardation. Anakinra, rilonacept, and canakinumab have all demonstrated high efficacy in the treatment of CAPS.

4.5. Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

TRAPS is an autosomal dominant autoinflammatory disorder caused by mutations in the type 1 TNF receptor. Clinically, it presents with recurrent episodes of

fever. The condition is also characterized by a deficiency of soluble TNF-α receptors, which normally bind and neutralize circulating TNF-α. Anakinra has shown effectiveness in refractory TRAPS cases, suggesting that IL-1 plays a significant role in its pathophysiology, as in other autoinflammatory diseases [13].

5. Behçet's Disease

The role of IL-1 as a key cytokine in the pathogenesis of Behçet's disease (BD) supports its classification among polygenic autoinflammatory diseases. Notably, IL-1 levels have been shown to be significantly elevated in both active and inactive forms of BD compared to healthy controls. Additionally, increased serum levels of IL-33 have also been observed in patients with BD [14].

Crystal-Induced Arthropathies

Monosodium urate crystals activate the inflammasome, triggering the release of IL-1β. Treatment with anakinra, canakinumab, or rilonacept results in a marked reduction of joint inflammation. IL-1 blockade with anakinra has shown greater efficacy than corticosteroids, leading to longer flare-free periods. Its short half-life among IL-1 inhibitors offers an additional advantage in the management of acute gouty arthritis [15].

Giant Cell Arteritis (GCA)

Histopathological analysis of temporal arteries has shown local expression of IL-1 in inflamed vessels. Three cases of refractory giant cell arteritis were successfully treated with anakinra. The treatment was effective in all patients [16].

Osteoarthritis (OA)

IL-1 plays a role in the pathogenesis of osteoarthritis. The benefits of intra-articular anakinra injections in patients with knee OA have been shown to be short-lived, lasting less than one month. Systemic administration of IL-1 inhibitors has also been evaluated, but only modest improvement has been observed.

Rheumatoid Arthritis (RA)

Although IL-1 is found in plasma and synovial fluid of RA patients, IL-1 inhibition has shown limited success in established RA. This may be explained by redundancy in cytokine pathways, with TNF and IL-6 playing dominant roles. However, IL-1 inhibitors may provide added value in RA patients with comorbid metabolic or cardiovascular conditions, where anti-inflammatory and vascular effects are clinically relevant.

IL-1 Blockade in RA and Comorbidities

Compared to the general population, patients with RA are at higher risk for developing type 2 diabetes (T2D) and cardiovascular events. Due to their favorable effects on these comorbidities, IL-1 inhibitors in RA may offer benefits that extend beyond joint inflammation. IL-1 is known to contribute to atherosclerosis progression, ischemia-reperfusion injury, and cardiac remodeling. Positive outcomes have been reported in two RA patients with comorbid T2D treated with IL-1 inhibitors. These findings suggest that targeting IL-1 could represent a valuable therapeutic option for managing RA associated with type 2 diabetes [17] [18].

The indications of IL-1 inhibitors across rheumatologic diseases are summarized in Table 1, which compiles efficacy data and levels of evidence. This table highlights the strong efficacy in autoinflammatory syndromes, moderate benefits in gout and vasculitis, and limited or transient effects in RA and OA.

Dose Adjustments and Long-Term Outcomes

Anakinra is typically administered at 100 mg/day subcutaneously, though dose escalation to 200 mg/day has been reported in refractory cases with acceptable tolerability. Canakinumab, given every 4 - 8 weeks, allows sustained suppression of IL-1β, while rilonacept provides weekly dosing. Dose adjustments are sometimes necessary in renal impairment or in cases of incomplete clinical response. Long-term extension studies in Still's disease, CAPS, and gout have shown that sustained efficacy can be achieved over 3 - 5 years, with no new safety signals. Nevertheless, more data from real-world registries are needed to confirm persistence of benefit and to evaluate risks of prolonged immunosuppression [19] [20].

Table 1. Indications for Interleukin-1 Inhibitors in Rheumatology.

Disease Category	Conditions	IL-1 Inhibitors Evaluated	Reported Efficacy/Level of Evidence
Autoinflammatory Diseases	Adult-onset Still's disease (AOSD)-Systemic juvenile idiopathic arthritis (sJIA)	Anakinra, Canakinumab, Rilonacept	Strong efficacy in systemic and early-onset disease
	Familial Mediterranean Fever (FMF)	Anakinra	Effective for flare control and amyloidosis prevention
	Hyper-IgD syndrome (Mevalonate kinase deficiency)	Anakinra, Canakinumab	Reduces frequency and severity of inflammatory attacks
	Cryopyrin-Associated Periodic Syndromes (CAPS)	Anakinra, Canakinumab, Rilonacept	High efficacy across the CAPS spectrum (FCAS, MWS, NOMID)
	TNF Receptor-Associated Periodic Syndrome (TRAPS)	Anakinra	Effective in refractory cases
Mixed Autoimmune Conditions	Behçet's disease	Anakinra, Canakinumab	Effective in refractory cases; elevated IL-1 and IL-33 levels observed
Crystal-Induced Arthropathies	Gout (acute and chronic)	Anakinra, Canakinumab, Rilonacept	Greater efficacy than corticosteroids; prolongs flare-free periods
Vasculitis	Giant Cell Arteritis (GCA)	Anakinra	Clinical response in refractory cases
Degenerative Joint Diseases	Knee Osteoarthritis	Anakinra	Modest and short-lived benefit (<1 month)
Rheumatoid Arthritis (RA) and Comorbidities	RA with Type 2 Diabetes-RA with high cardiovascular risk	Anakinra, Canakinumab	Limited efficacy on joint inflammation, but metabolic and vascular benefit

6. Conclusion

IL-1 inhibitors have revolutionized the management of autoinflammatory diseases such as Still's disease, CAPS, FMF, and TRAPS, where their efficacy is robust and sustained. They are also emerging as valuable therapeutic options in gout and

Behçet's disease. In RA, their role remains limited due to cytokine redundancy, though metabolic and cardiovascular benefits may support their use in select patients. Overall, IL-1 blockade is a valuable addition to the rheumatologist's therapeutic armamentarium. Future research should focus on long-term safety, optimization of dosing strategies, and better stratification of patients who will benefit most.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Palomo, J., Dietrich, D., Martin, P., Palmer, G. and Gabay, C. (2015) The Interleukin (IL)-1 Cytokine Family—Balance between Agonists and Antagonists in Inflammatory Diseases. *Cytokine*, **76**, 25-37. https://doi.org/10.1016/j.cyto.2015.06.017

[2] Harijith, A., Ebenezer, D.L. and Natarajan, V. (2014) Reactive Oxygen Species at the Crossroads of Inflammasome and Inflammation. *Frontiers in Physiology*, **5**, Article 352. https://doi.org/10.3389/fphys.2014.00352

[3] Fabreguet, I. and So, A. (2012) Canakinumab: Un traitement prometteur. *Revue Médicale Suisse*, **8**, 57-60. https://doi.org/10.53738/revmed.2012.8.323.0057

[4] Yu, L., Luo, R., Qin, G., Zhang, Q. and Liang, W. (2023) Efficacy and Safety of Anti-Interleukin-1 Therapeutics in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Orthopaedic Surgery and Research*, **18**, Article No. 100. https://doi.org/10.1186/s13018-023-03590-2

[5] Sota, J., Vitale, A., Insalaco, A., Sfriso, P., Lopalco, G., Emmi, G., *et al.* (2018) Safety Profile of the Interleukin-1 Inhibitors Anakinra and Canakinumab in Real-Life Clinical Practice: A Nationwide Multicenter Retrospective Observational Study. *Clinical Rheumatology*, **37**, 2233-2240. https://doi.org/10.1007/s10067-018-4119-x

[6] Gerfaud-Valentin, M., Seve, P., Hot, A., Broussolle, C. and Jamilloux, Y. (2014) Données actualisées sur la physiopathologie, les phénotypes et les traitements de la maladie de Still de l'adulte. *La Revue de médecine interne*, **36**, 319-327.

[7] Vastert, S.J., de Jager, W., Noordman, B.J., Holzinger, D., Kuis, W., Prakken, B.J., *et al.* (2014) Effectiveness of First-Line Treatment with Recombinant Interleukin-1 Receptor Antagonist in Steroid-Naive Patients with New-Onset Systemic Juvenile Idiopathic Arthritis: Results of a Prospective Cohort Study. *Arthritis & Rheumatology*, **66**, 1034-1043. https://doi.org/10.1002/art.38296

[8] Feist, E., *et al.* (2018) Efficacy and Safety of Canakinumab in Patients with Still's Disease: Exposure-Response Analysis of Pooled Systemic Juvenile Idiopathic Arthritis Data by Age Groups. *Clinical and Experimental Rheumatology*, **36**, 668-675.

[9] Kedor, C., Listing, J., Zernicke, J., Weiß, A., Behrens, F., Blank, N., *et al.* (2020) Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): Phase II, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Investigator-Initiated Trial. *Annals of the Rheumatic Diseases*, **79**, 1090-1097. https://doi.org/10.1136/annrheumdis-2020-217155

[10] Petryna, O., Cush, J.J. and Efthimiou, P. (2012) IL-1 Trap Rilonacept in Refractory Adult Onset Still's Disease. *Annals of the Rheumatic Diseases*, **71**, 2056-2057. https://doi.org/10.1136/annrheumdis-2012-201409

[11] Canna, S.W., de Jesus, A.A., Gouni, S., Brooks, S.R., Marrero, B., Liu, Y., *et al.* (2014) An Activating NLRC4 Inflammasome Mutation Causes Autoinflammation with Recurrent Macrophage Activation Syndrome. *Nature Genetics*, **46**, 1140-1146. https://doi.org/10.1038/ng.3089

[12] Stankovic Stojanovic, K., Delmas, Y., Urena Torres, P., Peltier, J., Pelle, G., Jeru, I., *et al.* (2011) Dramatic Beneficial Effect of Interleukin-1 Inhibitor Treatment in Patients with Familial Mediterranean Fever Complicated with Amyloidosis and Renal Failure. *Nephrology Dialysis Transplantation*, **27**, 1898-1901. https://doi.org/10.1093/ndt/gfr528

[13] Gentileschi, S., Rigante, D., Vitale, A., Sota, J., Frediani, B., Galeazzi, M., *et al.* (2017) Efficacy and Safety of Anakinra in Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) Complicated by Severe Renal Failure: A Report after Long-Term Follow-Up and Review of the Literature. *Clinical Rheumatology*, **36**, 1687-1690. https://doi.org/10.1007/s10067-017-3688-4

[14] Vitale, A., Rigante, D., Lopalco, G., Selmi, C., Galeazzi, M., *et al.* (2016) Interleukin-1 Inhibition in Behçet's Disease. *The Israel Medical Association Journal*, **18**, 171-176.

[15] Rkain, H. (2019) Recommandations de la Société Marocaine de Rhumatologie (SMR) sur la goutte. *Revue Marocaine de Rhumatologie*, **48**, 3-18.

[16] Ly, K., Stirnemann, J., Liozon, E., Michel, M., Fain, O. and Fauchais, A. (2014) Interleukin-1 Blockade in Refractory Giant Cell Arteritis. *Joint Bone Spine*, **81**, 76-78. https://doi.org/10.1016/j.jbspin.2013.06.004

[17] Ruscitti, P., Cipriani, P., Cantarini, L., Liakouli, V., Vitale, A., Carubbi, F., *et al.* (2015) Efficacy of Inhibition of IL-1 in Patients with Rheumatoid Arthritis and Type 2 Diabetes Mellitus: Two Case Reports and Review of the Literature. *Journal of Medical Case Reports*, **9**, Article No. 123. https://doi.org/10.1186/s13256-015-0603-y

[18] Ikonomidis, I., Tzortzis, S., Andreadou, I., Paraskevaidis, I., Katseli, C., Katsimbri, P., *et al.* (2014) Increased Benefit of Interleukin-1 Inhibition on Vascular Function, Myocardial Deformation, and Twisting in Patients with Coronary Artery Disease and Coexisting Rheumatoid Arthritis. *Circulation*: *Cardiovascular Imaging*, **7**, 619-628. https://doi.org/10.1161/circimaging.113.001193

[19] Ajeganova, S., De Becker, A. and Schots, R. (2020) Efficacy of High-Dose Anakinra in Refractory Macrophage Activation Syndrome in Adult-Onset Still's Disease: When Dosage Matters in Overcoming Secondary Therapy Resistance. *Therapeutic Advances in Musculoskeletal Disease*, **12**, 1-9. https://doi.org/10.1177/1759720x20974858

[20] Cavalli, G. and Dinarello, C.A. (2018) Anakinra Therapy for Non-Cancer Inflammatory Diseases. *Frontiers in Pharmacology*, **9**, Article 1157. https://doi.org/10.3389/fphar.2018.01157