Anakinra in the treatment of rheumatoid arthritis and other IL-1-driven conditions

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Fewer than 40% of newly diagnosed patients with rheumatoid arthritis (RA) reach remission with a combination of traditional DMARDs, and therefore new effective therapies are still needed. Proinflammatory cytokines, such as TNF-α and IL-1, are important pathogenetic mediators in RA and related conditions. Targeted therapies against these cytokines and downstream inflammatory mediators have greatly added to the therapeutic arsenal and brought new hope to patients in providing physicians with new effective treatment options. In this context, the current role for anakinra as a biological agent in treating RA or similar rheumatic conditions, based on data from clinical or observational studies, appears to be as a second-line drug or as an alternative to B-cell depletion after TNF-α blockade, especially for high-risk patients or patients who fail to respond to TNF-α blockade due to side-effects. On the other hand, the convincing findings seen in preferentially IL-1-driven diseases such as adult-onset Still's disease and systemic-onset juvenile idiopathic arthritis, and genetically inherited autoinflammatory syndromes such as neonatal-onset multisystem inflammatory disease, Muckle–Wells syndrome and familial cold autoinflammatory syndrome, have shown anakinra to have a strong role in targeting IL-1, the cytokine that appears to drive the inflammatory process in these conditions.

The inflammatory process

According to *in vitro* experiments and animal models, strong synergism exists between IL-1 and TNF-α with regard to many biologic functions [1]. IL-1 and TNF-α are mainly produced by monocytes/macrophages, which are activated by soluble factors and upon direct contact with stimulated T cells at the site of inflammation in rheumatoid arthritis (RA) [2]. TNF-α is predominantly observed during early phases of the disease at the systemic level. On the other hand, both IL-1α and IL-1β are detected in all phases of the disease and also at a local level. IL-1 and TNF-α play important roles in the communication between cells in the rheumatoid joint [3]. These cytokines upregulate the expression of cell-adhesion molecules on endothelial cells and stimulate production of chemokines, thereby, providing stimulatory signals for the inflammation process [4,5]. Furthermore, IL-1 and TNF-α stimulate synoviocytes and chondrocytes to release matrix metalloproteinases (MMPs) that degrade cartilage. These cytokines also upregulate the expression of proinflammatory genes such as cyclooxygenase-2 and nitric oxide synthase, leading to inflammation [6]. Furthermore, RANKL is produced by cytokine-stimulated T cells and triggers the differentiation of osteoclasts, leading to erosions [7].

The expanding IL-1 family consists of the proinflammatory molecules IL-1α and -1β, the naturally occurring IL-1 receptor antagonist (IL-1Ra) IL-18 [8], and an expanding range of new family members, perhaps including IL-33. They share common 3D structures, but are mostly produced by separate genes, and have specific amino acid sequences [8–10]. Of these, IL-1α is considered membrane–associated and has intracrine/intracellular modes of action. By contrast, IL-1β does not only exert its biological actions on other cells, it may also display autocrine activity [1–5]. Generation of the active form of IL-1β is controlled by the IL-1β-converting enzyme, also called caspase-1. IL-1β precursor colocalizes with procaspase-1 in specialized secretory lysosomes of involved cells. The conversion of the inactive procaspase-1 to active caspase-1 takes place by a complex of proteins named the IL-1β inflammasome, which also contains products of the *NALP3/CIAS1*/cryopyrin gene. When the IL-1β inflammasome, kept inactive by binding to a putative inhibitor, uncouples from procaspase-1 and creates active caspase-1, this results in the processing of IL-1β into the mature form. Toll-like receptor (TLR) agonists, such as endotoxins, are believed to be able to initiate this process [9,11].

Increased secretion of IL-1β in inherited chronic autoinflammatory syndromes such as neonatal-onset multisystem inflammatory disease (NOMID), Muckle–Wells syndrome and familial cold autoinflammatory syndrome (FCAS), is

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explained by a single amino acid mutation in the *NALP3* gene, which controls the activation of caspase-1 in the IL-1β inflammasome [12,13].

IL-1 and also IL-18 have been characterized in the pathogenesis of adult-onset Still's disease (AOSD) [14,15]. IL-1 is a true hematopoietic cytokine, unlike TNF-α, which suppresses bone marrow precursors. Intravenous injections of IL-1α or -1β produce a rapid increase in levels of circulating neutrophils when administered to humans [1–4]. IL-18, a member of the IL-1 family, is thought to be a pivotal cytokine in AOSD as it is overproduced in the acute phase of the disease and is believed to be an upstream initiator of the inflammatory cascade that includes IL-6, TNF-α and IFN-γ [15].

This pattern of cytokine expression in the above disease conditions justifies the therapeutic use of both TNF-α and IL-1 blockade; and successful therapy results have underlined the important role of these cytokines in the pathogenesis of these diseases. The recombinant form of naturally occurring IL-1Ra – anakinra (Kineret®; r-metH-uIL-1ra) – is the only IL-1-modulating agent US FDA and EU approved for treating the signs, symptoms and joint-destructive components of RA and other similar rheumatic diseases naturally. IL-1Ra and the recombinant form of the molecule, anakinra, bind to the IL-1 receptor with high affinity, thereby preventing the binding of IL-1 to its receptor through classic competitive receptor antagonism mechanisms. However, anakinra is rapidly excreted by the kidneys and therefore blood levels of the compound are low after 24 h. Furthermore, IL-1Ra interactions take place on all cells except red blood cells and IL-1 receptors are generated daily, which means daily injections of anakinra are required [16]. *In vitro* studies have demonstrated that complete inhibition requires between a ten- and 100-fold molar excess of IL-1Ra over IL-1, which might pharmacokinetically explain why modest effects are seen in RA patients treated with anakinra compared with TNF-α blockade. However, when comparing the roles of TNF-α and IL-1 in rheumatic disease, studies have established the importance of IL-1 as a downstream mediator of TNF-induced disease. Therefore, one cannot exclude the possibility that, when treating rheumatic disease with TNF blockers, a reduction in IL-1 might also contribute to the treatment result. The paradigm of TNF-induced, IL-1-mediated disease has been established based on animal studies as well as clinical study results [17].

Diseases such as RA show a significant or at least intermediate response with the blocking of IL-1 with anakinra. However, in specifically IL-1-mediated states such as NOMID [18], Muckle–Wells syndrome [19], FCAS [20] and AOSD [21,22], IL-1 blockade with anakinra has demonstrated an effect and in part even superiority over TNF-α blockade. It also seems likely that treating these disease conditions with TNF-α blockade results in lower IL-1β production and, thus, disease activity. It has been known that infliximab infusions are associated with a fall in circulating IL-1β levels [23].

Monosodium urate crystals stimulate monocytes and macrophages to release IL-1β using the *NALP3* component of the inflammasome, mentioned previously. A pilot study that successfully used anakinra in gout patients failing anti-inflammatory therapies, might give IL-1 blockade a new role in treating difficult gout patients [24].

IL-1 blockade in various disease conditions
Anakinra in rheumatoid arthritis
A randomized, double-blind, multicenter monotherapy trial involving 472 patients with active and severe RA, showed that 43% of patients receiving 150 mg/day compared with placebo, achieved an ACR20 response. Patients were randomized to either placebo or anakinra at doses of 30, 75 or 150 mg/day for 24 weeks [25]. Clinical responses in the 150 mg/day group were superior with respect to the number of swollen and tender joints, Health Assessment Questionnaire, C-reactive protein and erythrocyte sedimentation rate, compared with the other treatment groups and placebo. Radiographic evaluation of the hands also showed efficacy, whereby a 41% reduction in the rate of radiologic progression using mean Larsen scores was seen at 24 weeks in the anakinra group compared with placebo (**Table 1**).

When using anakinra in combination with methotrexate (mean dose: MTX 16 mg weekly in both groups) ACR20 responses of 46, 38 and 19%, were seen at 12 weeks in the groups receiving anakinra 1.0 mg, 2.0 mg and placebo, respectively. This was also a 24 week, placebo-controlled, double-blind study, which involved 419 patients initially on MTX [26]. The corresponding results at 24 weeks showed similar results when 42 and 23% of the patients in the 1 mg/kg and placebo cohort, respectively, reached ACR20. ACR50 and ACR70 response was seen in 24 and 10% of patients, respectively,

Table 1. Responses with anakinra when targeting IL-1-driven diseases.

Strength of evidence	Disease	Evidence from studies	Ref.
Category A evidence	RA	Several clinical trials, anakinra alone or in combination with methotrexate, ACR20 40%, reduction of radiologic progression	[25,26]
Category C evidence	SoJIA	A few clinical studies, rapid improvement of clinical symptoms	[21,22,47,49]
Category C evidence	NOMID Muckle–Wells syndrome FCAS	A few clinical studies, rapid response in syndrome clinical symptoms	[18–20]
Category C evidence	Gout	A pilot study, rapid response in clinical symptoms	[24]

AOSD: Adult-onset Still's disease; FCAS: Familial cold autoinflammatory syndrome; NOMID: Neonatal-onset multisystem inflammatory disease; RA: Rheumatoid Arthritis; SoJIA: Systemic-onset juvenile idiopathic arthritis.

compared with 4 and 0%, with placebo. Anakinra was considered safe and well tolerated with injection-site reaction being the most frequently noted adverse event leading to study withdrawal in 7% of patients receiving anakinra 1 mg/kg/day.

Safety aspects of anakinra

Anakinra has been evaluated to have a favorable safety profile, which is an advantage when deciding which biological agent to choose, especially in patients prone to infections or with coexisting comorbidities. Large, placebo-controlled studies have demonstrated that anakinra is safe and well tolerated in diverse populations with RA [25–28]. A study by Schiff *et al.* examined the safety profile of anakinra in a high-risk patient cohort with a wide range of comorbidities in order to reflect the true target population in RA [29]. The matched patient population consisted of 1116 anakinra patients and 284 with placebo who were considered to be at high risk of adverse events if they had a history of one of the following: cardiovascular event, pulmonary event, CNS-related event, infection, diabetes, malignancy or renal impairment. Within the treatment groups using anakinra or placebo, incidence of serious adverse events, infectious events and serious infectious events were compared between high-risk patients and those with no comorbidities. The 6-month study revealed that in the high-risk population the incidence of serious adverse events or infectious events was similar to the placebo population. The incidence of serious infectious events in anakinra patients at high-risk was also similar (2.5 vs 2.1%) to that of the entire anakinra population.

TNF blockade versus IL-1 blockade or both

There is still ongoing debate regarding whether cytokine blockade with anakinra leads to a sufficient response in RA, especially in patients refractory to TNF-α blockade or in patients with adverse events to TNF-α blockers. Poor responses to anakinra after failure of TNF-α-blocker treatment has been well demonstrated [30–32]. However, it has been reported that a slightly better response is observed if TNF inhibition treatment is stopped due to drug side-effects. Buch *et al.* reported that only 8% of patients reached ACR20 after 3 months of treatment and only 33% of patients reached a moderate EULAR response [30]. The small observational study by Saxne and colleagues, however, reported that 57% of patients who discontinued TNF-α blockade due to side-effects reached ACR20, but only 22% reached ACR20, belonging to the group that had discontinued TNF-blockade due to lack of efficacy [31]. Thus, these findings suggest the hypothesis that both TNF-α inhibition and IL-1 inhibition pathways are similar in RA and, therefore, it does not seem effective to pursue IL-1 inhibition if TNF-α inhibition fails.

On the other hand, the German clinical practice study by Langer and Missler-Karger shows more favorable results for anakinra in patients also pretreated with TNF-α inhibition [33]. In biological-naive patients, 28 and 39% reached good and moderate EULAR responses, respectively, at 6 months, compared with 10 and 59%, respectively, in biological-pretreated patients. These findings might argue for a TNF-α-independent activation path for IL-1.

The observational study by den Broeder *et al.* report similar efficacy data but mentioned poor drug-survival due to a lack of efficacy [34]. The patients in this series were not separated into biological-naive or TNF-α blocker pretreated patients.

Recently, we reported an observational finding from the Register on Biological Therapy of Rheumatic Diseases in Finland (ROB-FIN) [35]. A total of 47 out of 1135 registered patients on anakinra were identified. Of the patients with complete data at 3 months, 46% reached ACR20 and 27% reached ACR50. Subgroup analysis indicated that anakinra performed best in patients not previously treated with anti-TNF-α therapy, the response rate at 3 months being 60% for ACR20 and 20% for ACR50. The corresponding response rates for those having switched to anakinra due to poor response to TNF-α blockade were 44 and 31%. Thus, approximately one third of the patients with poor response to anti-TNF-α treatment benefited from switching to anakinra. The most significant changes in both groups were seen in the number of swollen and tender joints. Of the patients with sufficient data allowing ACR response calculations at 6 months, 69% reached ACR20 and 23% reached ACR50. The corresponding ACR20 and ACR50 at 12 months were 56 and 22%, respectively. All patients were on various combination therapies (DMARDs and anakinra) during follow-up. The corresponding results from the ROB-FIN database for ACR20 and ACR50 response for patients on infliximab without previous biological treatment at 3 and 12 months were 64/41% and 68/51%, respectively [36].

The concept of simultaneously inhibiting both TNF-α and IL-1 seemed promising according to existing cytokine cascades of pathogenesis. However, the double-blind study by Genove *et al.* involving 244 patients demonstrated no added benefit from using both etanercept and anakinra, but was instead associated with an increased safety risk as the incidence of serious infections was increased (3.7–7.4 vs 0%), as was the incidence of neutropenia and injection-site reactions [37]. This study has led to the current recommendations stating that combination therapy with other biologicals/targeted therapies is not recommended and that a full dose of the drug should not be administered when both etanercept and anakinra are used together [38].

Anakinra when targeting IL-1-driven diseases

In the treatment of RA a somewhat modest or intermediate response is seen with anakinra. However, there are a few IL-1 mediated diseases that tend to respond remarkably well with anakinra (**Table 1**). These diseases include AOSD [21,22], systemic-onset juvenile idiopathic arthritis (SoJIA) [39], and genetically inherited NOMID [18], Muckle–Wells syndrome [19] and FCAS [20]. In AOSD, the improvement seen with TNF-α-blockade is likely to be a result of subsequent lower IL-1 production as infusions of infliximab are associated with a fall of circulating IL-1β levels within 24 h [23].

The distinct clinical entity of AOSD predominantly affects young adults aged 16–35 years. It is a rare, cytokine-driven disorder, presenting with high circadian rhythm, recurrent spiking fever, transient maculopapular rash, myalgias, polyarthralgias or arthritis, lymphadenopathy, hepatosplenomegaly and sore throat, and is associated with leucocytosis and neutrophilia. It is linked with negative blood cultures whereby rheumatic and antinuclear factors are mostly negative. Very high ferritin levels are frequently observed and could be a marker of the disease. Early diagnosis is difficult because clinical features are nonspecific. AOSD may affect multiple organs and may have a fatal course [38], but liver failure has rarely been described. Endogenous pyrogens include a number of well known cytokines, such as IL-1, -6, -18 and TNF-α [14,15]. The *in vivo* effects of IL-1, -6 and TNF-α have been well characterized and many of these correspond to the distinctive features of AOSD. Both IL-1 and -6, but not TNF-α, have been demonstrated to be produced in a circadian fashion. It therefore seems likely that IL-1, -6 or -18 may act as effector molecules that give rise to many of the features that characterize AOSD.

Clinical studies in adult-onset Still's disease

The clinical response to NSAIDs is often unsatisfactory in adult patients. Chronic use of steroids, sometimes in very high doses, is frequently required, but may result in severe side effects [40]. Recently, DMARDs and immunosuppressive agents including cyclosporine A [41] and MTX have been shown to be effective for alleviating refractory cases of AOSD. Immunoglobulins have also been used in AOSD [42]. A report of the results of an uncontrolled, unblinded trial of intravenous immunoglobulin (IVIG) in seven

patients with AOSD has been published [43]. Anti-TNF-α therapy may be helpful for patients with refractory AOSD, but many patients achieve only partial remission [44,45]. However, there are cases of successful treatment with infliximab and etanercept in AOSD refractory to conventional drugs [46].

Anakinra in adult-onset Still's disease & systemic-onset juvenile idiopathic arthritis

Recently, Fitzgerald *et al.* reported four cases of AOSD treated with anakinra, two of which had been exposed to anti-TNF-α therapy with a less than satisfactory response [22]. In the discussion, the authors hypothesize that anti-TNF-α strategies may play a role in AOSD, especially by decreasing the level of IL-1, thus gaining benefit indirectly. Positive results with anakinra in patients with AOSD have also been reported by others [47]. In most of the reports the efficacy has been substantial, even in cases with extended disease duration and severity [21,48]. Adverse events are reported with a similar rate and severity to those usually found in clinical trials with RA patients. As IL-1 is a pivotal cytokine in RA, and its involvement in AOSD has been shown, it is therefore logical that open studies are performed in AOSD patients to test the effect of anakinra in treating the often severe clinical symptoms associated with this disease. Our own experiences in AOSD have shown rapid and sustained responses with anakinra in several patients with DMARD-resistant AOSD and have led to the initiation of a Nordic, randomized, multicenter study of 60 patients treated with either anakinra or traditional DMARDs [49]. This study is designed to identify eventual genetic alterations in patients, as observed in cryopyrinopathies or pyrinopathies, conditions which share symptomatic phenotypes with AOSD.

SoJIA, which encompasses 10% of childhood arthritis cases, is an important cause of long-term disability. SoJIA children present with systemic symptoms, fever and/or rash, which may precede the development of arthritis by months or years. As with AOSD; fever, anemia, leukocytosis and elevated erythrocyte sedimentation rate are the main features of the condition [39]. The pathogenesis of SoJIA is unclear but the novel study by Pascual *et al.* has highlighted the role of IL-1 in the pathogenesis of this disease on the basis of convincing results with IL-1 inhibition with anakinra in nine patients having failed other treatments [50]. The study showed that three sets of findings led to the conclusion that dysregulated production of

IL-1 plays a critical role in the pathogenesis of SoJIA. First, the study showed that the serum of SoJIA patients upregulates the expression of IL-1α, -1β and other innate immunity genes by healthy peripheral blood mononuclear cells (PBMCs); second, the patients' PBMCs seem to produce an excess of IL-1β upon activation; and third, treatment with anakinra efficiently ameliorated disease symptoms. Even though SoJIA serum induced IL-1β secretion by healthy PBMCs, IL-1β serum levels in patients were as low as in healthy individuals. All patients resistant to other forms of treatment responded to IL-1Ra treatment and seven of nine patients cleared symptoms and laboratory abnormalities within days to weeks of initiation. The study suggested that IL-1 production is dysregulated in SoJIA and that *de novo* mutations and/or subtle polymorphisms of genes within the IL-1 pathway may contribute to the pathogenesis of SoJIA.

Chronic autoinflammatory conditions

IL-1β is involved in the pathogenesis of familial autoinflammatory syndromes and blocking IL-1 with anakinra alters the clinical symptoms seen in conditions associated with mutations in the *NALP3/CIAS1*/cryopyrin gene. NALP3 encodes cryopyrin, which belongs to a group of interacting proteins that form the macromolecular inflammasome complex mentioned above. Activation of the inflammasome leads to the activation of caspase-1, which cleaves into the IL-1β precursor bioactive form. NOMID is characterized by fever, urticarial rash, aseptic meningitis, deforming arthropathy, hearing loss and mental retardation. Mutations in the *NALP3/CIAS1* gene encoding cryopyrin have been shown in these patients. A study by Goldbach-Mansky *et al.* [51], demonstrated a rapid response with anakinra in 18 patients identified as having *CIAS1* mutations and NOMID, and withdrawal of anakinra at 3 months uniformly led to relapse of symptoms within days. Significant decreases in levels of serum amyloid A, C-reactive protein and erythrocyte sedimentation rate were also noted in all patients. The findings suggested that peripheral, as well as CNS manifestations of the disease, are driven by IL-1β, and that clinical and molecular phenotype of NOMID is induced by IL-1β excess. The favorable reports concerning administration of anakinra in other members of the autoinflammatory syndromes, Muckle–Wells syndrome and FCAS clearly suggest that IL-1β has a fundamental role in the pathogenesis of inflammation associated with *CIAS1* mutations in these conditions [19,20].

Conclusions & future perspective

On the basis of efficacy and effectiveness data from clinical or observational studies, the role for anakinra as a biological agent in treating RA or similar rheumatic conditions appears to be as a second-line drug after TNF-α blockade as an alternative to B-cell depletion, especially in the case of patients failing TNF-α blockade due to side-effects (**Table 1**). Currently, anakinra competes against the use of rituximab, a chimeric anti-CR20 monoclonal antibody, also showing category A evidence when treating signs, symptoms and also retardation of radiographic progression in RA [38,52,53].

However, randomized, as well as observational clinical studies, suggest that anakinra might be valuable as first choice biological treatment in RA on the basis of its good safety profile, in certain groups of high-risk patients with comorbidities in those prone to infections. Whether these patients present with a different cytokine activation profile emphasizing IL-1 requires further investigation. Pharmacokinetically, the short half-life of anakinra gives more flexible control of eventual side-effects, but at the same time this might account for lower efficacy compared with TNF-α blockade.

The convincing findings seen in preferentially IL-1-driven diseases such as AOSD and SoJIA and genetically inherited autoinflammatory syndromes such as NOMID, Muckle–Wells syndrome and FCAS have demonstrated anakinra's strong role in targeting IL-1 blockade. The robust clinical results with anakinra show IL-1 to have a fundamental role in inflammation, including manifestations such as fever, neutrophilia, thrombocytosis, elevated C-reactive protein, erythrocyte sedimentation rate, serum amyloid A, skin rash and anemia. It remains to be seen whether other therapeutic agents, such as IL-1 Trap, IL-1β-specific monoclonal antibodies or even caspase-1 inhibitors that prevent IL-1β mediated conditions, will be effective in RA, AOSD, SoJIA or other autoinflammatory disease conditions.

Author disclosure

Executive summary

Mechanism of action

- Anakinra (Kineret®, r-metHuIL-1ra) is a recombinant form of the endogenous IL-1 receptor antagonist (IL-1Ra). It is the first, and presently only, approved IL-1Ra that selectively and competitively blocks the IL-1 from its receptor, diminishing its impact on the release of other harmful mediators and processes, and consequently improving signs and symptoms of rheumatoid arthritis (RA).

Clinical efficacy in rheumatoid arthritis

- Anakinra has shown efficiacy in clinical trials, involving large numbers of patients with RA, both as monotherapy or in combination therapy. ACR20, -50 and -70 responses are in the region of 45, 20 and 10%, respectively, but somewhat less impressive compared with responses seen with TNF-α blockers.
- Anakinra slows radiographic progression of joint destruction, reduces patient disability and improves productivity.

Safety in rheumatoid arthritis

- Safety and tolerability of anakinra have been established in several studies. The safety profile is more favorable, compared with the one for TNF-α blockers.

Anakinra in other IL-1-driven diseases

- Promising clinical responses are seen in IL-1-linked diseases, such as adult-onset Still's disease (AOSD) and systemic onset juvenile idiopathic arthritis (SoJIA), and genetically inherited autoinflammatory syndromes such as neonatal-onset multisystem inflammatory disease, Muckle–Wells syndrome and familial cold autoinflammatory syndrome. Results have shown anakinra to have a strong role in targeting IL-1 blockade.

Future usage of anakinra

- Anakinra's role as a biological agent in treating RA or similar rheumatic conditions might be as a second-line drug or an alternative to B-cell-depletion therapy following TNF-α blockade, especially for patients failing TNF-α blockade due to side-effects.
- On the basis of its good safety profile, anakinra might be valuable as a first-choice biological treatment in RA in certain groups of high-risk patients with comorbidities or in those prone to infections.
- A new role for anakinra is emerging, in the treatment of IL-1-linked conditions, such as AOSD and SoJIA and the inherited autoinflammatory syndromes and similar diseases. Preliminary findings when treating acute gout are also interesting.

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359

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