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Review

Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies

Giulio Cavalli[1,2] and Charles A. Dinarello[1,3]

Abstract

The inflammatory cytokines IL-1α and IL-1β orchestrate local and systemic inflammatory responses underlying a broad spectrum of diseases. Three agents for reducing IL-1 activities are currently available. Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist. Anakinra binds to the IL-1 receptor and prevents the activity of IL-1α and IL-1β. The soluble decoy receptor rilonacept and the neutralizing mAb canakinumab block IL-1β. A mAb directed against the IL-1 receptor and a neutralizing anti-human IL-1α are in clinical trials. The availability of therapies specifically targeting IL-1 unveiled the pathological role of IL-1-mediated inflammation in a broadening list of diseases. Conditions effectively treated with agents blocking IL-1 range from classic rheumatic diseases, such as RA and gout, to autoinflammatory syndromes, such as systemic JIA and FMF. However, IL-1 antagonism is also effective against highly prevalent inflammatory diseases, namely cardiovascular diseases and type 2 diabetes, conditions that are frequently encountered as co-morbidities in patients with rheumatic diseases. Thereby, IL-1 inhibition has the potential to lift the burden of disease for patients with rheumatic conditions, but also to provide clinical benefits beyond the efficacy on osteoarticular manifestations.

Key words: interleukin-1, IL-1α, IL-1β, rheumatoid arthritis, autoinflammatory syndromes, cardiovascular disease, diabetes, anakinra, canakinumab.

REVIEW

Rheumatology key messages

- IL-1 is a pro-inflammatory molecule playing a critical role in a broadening list of diseases.
- IL-1 neutralization is effective against rheumatological, autoinflammatory and inflammatory diseases, such as cardiovascular diseases and diabetes.
- In patients with rheumatological conditions, IL-1 inhibition may provide clinical benefits beyond the efficacy on osteoarticular manifestations.

Introduction

Unequivocal evidence on the role of IL-1 in orchestrating inflammation comes from deficiency of IL-1 antagonist, a genetic disease characterized by loss of function in IL-1 receptor antagonist (IL-1Ra). IL-1Ra is a naturally occurring endogenous member of the IL-1 family, which blocks the IL-1 receptor type 1. This receptor is expressed on all nucleated cells; therefore, IL-1Ra hinders systemic inflammation induced by IL-1. Newborns with deficiency of IL-1Ra rapidly succumb to rampant sterile inflammation, with neutrophil infiltration of skin, joints and bones and high levels of IL-17 [1, 2]. Daily treatment with the recombinant form of IL-1Ra, termed anakinra, promptly reverses inflammation and prevents a fatal outcome.

Two different genes code for IL-1 activity: IL-1α and IL-1β. Both bind to the same receptor, IL-1 receptor 1 (IL-1R1), and recruit the same co-receptor, IL-1 receptor 3, which initiates signal transduction. IL-1α is constitutively expressed as a precursor in most mesenchymal cells [3]. This cytokine is found in the intestine, liver, lung and kidney, in platelets and in epithelial cells of surface tissues throughout the body, such as skin keratinocytes, mucosal membranes and vascular endothelium [4]. During ischaemia followed by cell necrosis, IL-1α in endothelial cells is released in membrane fragments termed apoptotic bodies [5, 6], which induce neutrophil infiltration [4] and contribute to vascular inflammation in vasculitis [7]. In contrast, IL-1β

[1]Department of Medicine, University of Colorado Denver, Aurora, CO, USA, [2]Division of Internal Medicine and Clinical Immunology, IRCCS San Raffaele Scientific Institute, Milan, Italy and [3]Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands

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Correspondence to: Giulio Cavalli, Department of Medicine, University of Colorado Denver, 12700 East 19th Avenue, B168, Aurora, CO 80045, USA. E-mail: cavalli.giulio@gmail.com

is not expressed in mesenchymal tissues, instead being produced primarily by haematopoietic cells.

Synthesis and release of IL-1β

Mainly produced by blood monocytes, tissue macrophages and dendritic cells, IL-1β is not detected in healthy tissues with standard assays. Although the rate-limiting step in the production of IL-1β is transcription, synthesis from mRNA also requires an additional signal, which is provided by exogenous microbial products or exogenous cytokines, such as TNF-α, IL-18, IL-1α or IL-1β itself [8]. In fact, IL-1 induction of IL-1 is part of the mechanism of autoinflammation. IL-1β is synthesized as an inactive precursor and requires proteolytic cleavage by caspase-1 for activation. The activation of caspase-1, an intracellular cysteine protease, requires the oligomerization of a complex of intracellular proteins termed the inflammasome [9]. Activated caspase-1 cleaves the N-terminal amino acid of the inactive pro-IL-1β, thus allowing the release of the mature, active form of the cytokine.

The activation of the inflammasome represents an effective safety mechanism preventing deregulated release of IL-1β. For example, blood monocytes from persons with mutation in *NLRP3* (also known as cryopyrin), a component of the inflammasome, release significantly greater levels of mature IL-1β [10]. Unrestricted activation of caspase-1 and secretion of IL-1β characterize cryopyrin-associated periodic syndrome (CAPS), clinically manifesting as multi-organ sterile inflammation.

Autoinflammatory diseases are different from autoimmune diseases

Autoinflammatory syndromes differ from autoimmune diseases in that the pathogenesis does not revolve around recognition of self-antigens by dysfunctional T lymphocytes or autoantibodies. Rather, the hallmark of autoinflammatory syndromes is uncontrolled monocyte/macrophage-driven inflammation. Monocytes from patients with autoinflammatory diseases release more IL-1β, but not TNF-α, compared with healthy persons [11–13]. However, in many autoinflammatory diseases, a specific mutation to account for the increased secretion has not been determined. Fundamental differences in the pathogenesis of autoimmune and autoinflammatory conditions dictate the need for different treatment approaches. While autoimmune diseases are treated with a variety of cytokine-blocking agents, neutralizing antibodies and inhibitors of cell migration [14], autoinflammatory diseases are characteristically responsive to IL-1 blockade. Although the hereditary autoinflammatory diseases are rare, the clinical manifestations, biochemical and haematological manifestations are common to many inflammatory conditions, ranging from gout [15] to type 2 diabetes (T2D) [16]. These and several others are to some extent responsive to IL-1 blockade.

Treating a broad spectrum of inflammatory conditions with anakinra

The IL-1R1 is expressed in nearly all tissues and binds both IL-1α and IL-1β. Thus, the receptor-blocking agent anakinra antagonizes either IL-1α or IL-1β. Clinical efficacy of anakinra, rather than cytokine levels, confirms the role of IL-1 in a broad spectrum of inflammatory diseases. For example, in severe IL-1-mediated inflammatory conditions the amount of circulating IL-1β is in the picomolar range [17] and IL-1α is rarely found in the circulation, but resolution of clinical disease is effectively accomplished by anakinra.

Anakinra is currently approved for the treatment of RA refractory to DMARDs and for the treatment of neonatal-onset multisystem inflammatory disease, which is part of the CAPS spectrum. As shown in supplementary Table S1, available at *Rheumatology* Online, IL-1 blockade with anakinra is used off label in the management of several other rheumatological diseases, hereditary systemic inflammatory diseases and systemic and local inflammatory syndromes for which no genetic basis has been found. Even without a genetic basis, increased release of IL-1β from cultured monocytes has been demonstrated, for example, in subjects with systemic onset JIA [13]. The mAb canakinumab is approved for the treatment of CAPS and of systemic onset JIA, whereas the soluble decoy receptor rilonacept is approved only for the treatment of CAPS. However, various inflammatory conditions are also treated with mAbs targeting IL-1β (supplementary Table S2, available at *Rheumatology* Online) or with rilonacept (supplementary Table S3, available at *Rheumatology* Online).

For some diseases, such as RA, the data discussed in this review are derived from large randomized controlled trials; in other cases, the data come from smaller studies or case reports. Of note, clinical efficacy of anakinra is often described in patients refractory to standard therapy or common treatments, such as high-dose CSs, MTX and anti-TNF-α agents.

RA and associated co-morbidities

The efficacy of anakinra in patients with RA, alone or in association with MTX, was evaluated in several controlled studies [18], which consistently documented a significant reduction in disease severity, improvement in quality of life, reduction of joint space narrowing and significant slowing of radiographic joint damage and bone erosions [19]. No direct comparison is available between the efficacy of IL-1 blockade and other biologics, including TNF-α blockers, which dominate the field of biologic treatments for RA. Based upon indirect comparisons, anakinra seemed moderately efficacious in inducing ACR responses [20, 21]. Currently, anakinra is mostly administered to patients failing anti-TNF-α therapy or with contraindications to blocking TNF-α, such as malignancy or recurrent infections, particularly *Mycobacterium tuberculosis* infections. In patients refractory to anti-TNF-α therapy, anakinra was shown to be effective in controlling

disease activity [19, 22–25]. Similar to anakinra, the anti-IL-1β mAb canakinumab has reduced disease severity in RA patients, including those unresponsive to anti-TNF-α therapies [26]. Unfortunately, there are no new trials of canakinumab in RA, perhaps due to the overwhelming number of agents competing for the same market. Therefore, unlike anakinra, the long-term preservation of joint function with canakinumab remains unstudied.

Compared with the general population, RA patients are more prone to develop T2D as well as cardiovascular events [27]. Given the favourable effects on these co-morbidities [28], benefits of IL-1 blockade in RA may extend beyond the efficacy on articular inflammation. IL-1 is known to play a role in the progression of atherosclerosis, ischaemia–reperfusion injury and cardiac remodelling [29–32]. Anakinra was effective in two randomized trials in ST-segment elevation myocardial infarction [33, 34]. In particular, anakinra added to standard therapy for 14 days prevented left ventricular remodelling and the development of congestive heart failure. Eighteen months after ST-segment elevation myocardial infarction, 60% of patients in the placebo arm and no anakinra-treated patient had progressed to heart failure. A subsequent, expanded trial yielded similar results, with greater benefits observed in more severe cases [33]. The clinical improvement was correlated with reductions in serum CRP, a common marker of inflammation in patients with coronary artery disease.

Previous *ex vivo* studies with human atrial heart strips revealed that IL-1 suppresses contractile force [35]. Consistently, in patients with congestive heart failure, a 14-day course of anakinra was associated with improved exercise performance paralleled by dramatic drops in serum levels of IL-1β, CRP and IL-6, but not TNF-α [36]. Of note, RA patients receiving anakinra exhibited improved cardiac contractility, even within 3 h of a single administration [37, 38]. Anakinra was also evaluated in patients with diastolic heart failure, a condition characterized by normal systolic function but impaired ventricular diastolic filling, accounting for 50% of cases of congestive heart failure. In a double-blind, placebo-controlled trial of anakinra 100 mg for 14 days, anakinra-treated patients exhibited increased peak oxygen consumption and a 75% decrease in CRP [39]. Given the high prevalence of cardiac co-morbidities in RA patients, the benefits of IL-1 inhibition in this population are worth further exploration.

T2D and metabolic syndrome are major co-morbidities of RA [40]. Several observations point towards IL-1-mediated inflammation as pivotal in the progressive loss of β cells leading to insulin resistance and T2D [41]. High concentrations of glucose trigger IL-1β production from β cells [42], and IL-1β gene expression in β cells is dramatically elevated in T2D patients compared with β cells in unaffected subjects [16]. Moreover, IL-1β contributes to β-cell loss by promoting deposition of amyloid [43]. These observations contributed to the rationale for testing anakinra in T2D patients. In a randomized trial of anakinra for 13 weeks, insulin production and glycaemic control improved and were associated with decreased levels of CRP and IL-6 [44]. The reduction in IL-1-mediated islet inflammation was sustained, because in the following 39 weeks responders used 66% less insulin to maintain glycaemic control [45]. This pilot study led to trials of anti-IL-1β mAb in T2D; gevokizumab, canakinumab and LY2189102 afforded comparable clinical benefits [46–48]. These findings help to formulate a new concept of T2D as a chronic inflammatory disease, in which IL-1-driven inflammation results in progressive loss of β-cell function [16].

As IL-1β production has been demonstrated in macrophages infiltrating human fat tissue [49], anakinra was also tested in non-diabetic patients with metabolic syndrome and was found to induce a decrease in CRP and a significant increase in disposition index, thus reflecting improved β-cell function [41].

Infection and cardiovascular disease are leading causes of death in RA patients, diabetes being a burdensome contributory factor [40]. Thus, an ideal treatment for patients with RA should not only palliate pain and dampen articular damage, but also prevent or treat associated co-morbidities with minimal adverse effects. Given the association between cardiovascular disease and T2D, the potential of IL-1 blocking agents to improve cardiovascular health and glucose metabolism is currently being assessed in the large Canakinumab Anti-inflammatory Thrombosis Outcome Study trial (CANTOS, NCT01327846); the trial will test whether the dampening of IL-1-mediated inflammation using canakinumab can reduce the re-occurrence of ischaemic events in patients with prior cardiovascular accidents, while also assessing the potential clinical benefits of canakinumab administration in T2D.

Crystal arthritis

Monosodium urate crystals activate the inflammasome and induce the release of IL-1β, probably in concert with free fatty acids, thus accounting for nutrition-related flares of gout [50]. Given the robust neutrophil infiltration in gouty joints, extracellular processing by neutrophil enzymes may also have a role in the activation of IL-1β precursor [51]. Traditional options for managing acute flares include colchicine and NSAIDs. Gout patients in whom colchicine or NSAIDs are not tolerated, ineffective or contraindicated often require steroids to control disease flares. Treatment with anakinra, canakinumab or rilonacept prompts a dramatic reduction in articular inflammation [52–55]. The benefits of IL-1 blockade with anakinra are superior to those of steroids and result in more prolonged periods without flares; the shortest half-life among IL-1 blockers is a bonus in the treatment of acute gouty arthritis.

Recent randomized clinical trials [53, 55] compared s.c. canakinumab with i.m. triamcinolone acetonide in the treatment of acute gout flares. Data from these trials indicate that, in comparison with triamcinolone, a single dose of 150 mg of canakinumab is associated with superior pain relief, resolution of joint swelling and overall treatment response, but probably also with an increased risk

of adverse events. No available studies have compared canakinumab with common first-line therapeutic options, such as NSAIDs or colchicine. In different trials, both canakinumab and rilonacept were shown to be effective in the prophylaxis of disease flares in patients initiating urate-lowering treatment [56, 57]. In a separate trial, the efficacy of a single s.c. injection of 320 mg of rilonacept was deemed not to provide greater pain relieve than high-dose indomethacin [58].

Similarly to gouty arthritis, pyrophosphate crystal arthritis is highly responsive to anakinra [59, 60]. The efficacy of anakinra was also demonstrated in another common crystal-induced inflammatory condition, that is, acute calcific periarthritis of the shoulder. In a pilot study on five patients, a 3-day course of anakinra afforded durable reduction of pain with normalization of inflammatory indexes, and almost restored normal shoulder mobility [61].

OA and related conditions

Given that IL-1 is involved in the pathogenesis of OA, various studies evaluated the efficacy of IA injections of anakinra in patients with knee OA [62, 63]. Nevertheless, benefits did not extend beyond 1 month, possibly due to a short persistence of anakinra in the joint space, because anakinra has a molecular weight of 20 000. Anakinra was found to dampen pain and swelling in erosive OA of the hand [64]. Systemic administration of antibodies to the IL-1 receptor has also been evaluated, but only modest improvement was observed [65].

Hereditary autoinflammatory diseases

Hereditary autoinflammatory diseases are a spectrum of conditions variably manifested with fever, neutrophilia, debilitating fatigue, myalgia, arthralgia, gastrointestinal involvement and skin rashes, with elevated inflammatory markers. Clinical and haematological abnormalities are characteristically reverted by IL-1 blockade. FMF is a classic autoinflammatory disease characterized by recurrent fevers, leucocytosis and serositis. Episodes are typically self-limited in 3–5 days. The majority of patients bear a mutation in the *MEFV* gene, coding for pyrin, a protein involved in the activation of caspase-1 and release of active IL-1β [66]. Colchicine is the mainstay of treatment for FMF, but is ineffective in a fraction of patients. Colchicine-resistant patients are successfully treated with anakinra [67–70]. Given different pharmacokinetics that result in a prolonged duration of action, canakinumab may represent a suitable alternative in FMF patients enduring frequent relapses.

IL-1 induces serum amyloid A, which is commonly elevated in several chronic inflammatory diseases. Left untreated, IL-1-mediated diseases such as FMF and CAPS lead to amyloidosis, a disease in which deposition of amyloid fibrils in tissues results in severe organ dysfunction, including lethal kidney or heart failure. Treatment with IL-1 blockers in FMF effectively controls chronic inflammation and prevents progression to amyloidosis and organ failure [67, 69, 71–73]. Intriguingly, amyloid deposition in insulin-producing islets and brain is associated with T2D and Alzheimer's disease, respectively [43, 74]. In both diseases, IL-1 blockade has been proposed as a possible therapeutic strategy to hinder disease progression.

Hyper-IgD syndrome

Hyper-IgD syndrome (HIDS) is an autosomal recessive autoinflammatory disorder also known as mevalonate kinase deficiency. The clinical picture features recurrent fever, myalgia, skin rash, aphthous ulcers and lymphadenopathy lasting 4–6 days. Several intracellular pathways link mevalonate kinase deficiency with activation of caspase-1 and IL-1 production [75]. IL-1-blocking agents in HIDS effectively reduced the frequency and severity of the attacks [76].

CAPS and neurological complications

CAPS is the collective designation of three clinical entities: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome and neonatal onset multiinflammatory disease (NOMID). In CAPS, mutations in the NLRP3 inflammasome result in deregulated activation of caspase-1, which leads to increased release of IL-1β [11, 12, 77, 78]. FCAS, Muckle–Wells syndrome and NOMID are characterized by clinical phenotypes of escalating severity, ranging from self-limited episodes of fever, myalgia and skin rash (FCAS) to chronic systemic inflammation with major neurological complications and growth retardation (NOMID). Anakinra, rilonacept and canakinumab are highly effective in the treatment of CAPS [79–81]. A 2-year follow-up of canakinumab in 166 CAPS patients, including cases with neurological involvement, confirmed sustained efficacy and few side effects [82].

Neurological complications in CAPS reflect IL-1-mediated inflammation in the brain. In one survey, 92% of patients had headache with features of migraine, 54% had sensorineural hearing loss and 46% had papilloedema due to elevated intracranial pressure, often associated with mental impairment [83]. Treatment with anakinra or canakinumab leads to complete resolution of neurological symptoms [82–84]. In particular, mental and hearing impairment reverse upon IL-1 blockade [12, 80, 82, 85, 86].

Sensorineural hearing loss also occurs in vasculitis and autoimmune inner ear disease. Patients experience rapidly progressive, often irreversible hearing loss. Treatment relies on high-dose glucocorticoids, but many patients are refractory or become unresponsive over time. In refractory cases, elevated IL-1β was demonstrated in the circulation and in monocyte cultures [87]. In a phase I/II open-label, single-arm clinical trial in CS-resistant autoimmune inner ear disease, 10 patients received anakinra for 84 days; of these, 7 demonstrated audiometric improvement, paralleled by reduced IL-1β plasma levels [88].

TNF receptor-associated periodic syndrome

TNF receptor-associated periodic syndrome is an autosomal dominant disease caused by mutations in TNF

receptor type 1 [89, 90], clinically manifesting as recurrent bouts of fever. Lack of soluble TNF-α receptors, which bind and neutralize circulating TNF-α, was postulated. Nevertheless, clinical response to the soluble TNF-α receptor etanercept is partial or absent in some patients [91, 92]. Anakinra is effective in these refractory cases, thus suggesting that IL-1 plays a role in this disease, as in other autoinflammatory conditions [93–95].

Adult-onset Still's disease

Adult-onset Still's disease is a rare, systemic inflammatory syndrome characterized by fever, a highly characteristic rash, arthritis, neutrophilia and unusually elevated inflammatory indexes, particularly serum ferritin. Treatment with CS and DMARDs controls the disease in 60% of cases [96]; refractory cases are treated with biologic agents. Monotherapy with anakinra represents the mainstay of biologic treatment [97–99]. Canakinumab and rilonacept are also effective.

Systemic onset JIA

Systemic onset JIA (SOJIA) and adult-onset Still's disease probably represent manifestations of the same disease in infancy and adulthood, respectively. Thus, the efficacy of anakinra in SOJIA is not unexpected, even in patients refractory to steroids, MTX and TNF-α blockers [13, 100]. Interestingly, two distinct clinical phenotypes of SOJIA can be identified according to the patient's response to anakinra. In particular, neutrophilia and a lower number of active joints predict the efficacy of IL-1 blockade [101]. Neutralization of IL-1β with canakinumab in patients with SOJIA has shown remarkable benefits, with many patients achieving an ACR score of 100. Canakinumab has received approval for use in the treatment of SOJIA [102, 103].

As the safety of immunosuppressive-based therapies in children is controversial, SOJIA poses challenges beyond the mere achievement of disease control. In this scenario, IL-1 blockade may be more advantageous than other available therapeutic options. For instance, steroid treatment is associated with growth retardation. Treating SOJIA with anakinra or canakinumab allows for reduced glucocorticoid dosing and catch-up growth [13, 100, 102]. Given the adverse effects of conventional treatments, a prospective study explored a therapeutic strategy with anakinra (2 mg/kg) used as a first-line drug in 20 children with new-onset SOJIA. A dramatic and durable clinical response was observed within 3 months from the initiation of the treatment and was preserved at 32 months of follow-up. Although maintenance therapy was required in some cases, the majority of patients were ultimately able to discontinue the treatment [104].

Schnitzler syndrome

Schnitzler syndrome is characterized by recurrent fevers, chronic urticaria and development of haematopoietic malignancies, particularly Waldenström macroglobulinaemia. Treatment with anakinra yields improvement within hours and remission within days [105]. The Schnitzler syndrome International Registry reports nearly 100% efficacy with anakinra. A nationwide French survey confirms prompt and durable remission rates, with disease flares occurring at discontinuation [106]. Data on the efficacy of anakinra in Schnitzler syndrome are so consistent that diagnosis should be reconsidered in the event of anakinra failure. Canakinumab is also highly effective in Schnitzler syndrome [107].

Behçet's disease

Behçet's disease is characterized by ocular and cutaneous inflammation, oral and genital ulcers, gastrointestinal or brain vasculitis and hypercoagulable state. Ocular involvement may cause organ-threatening uveitis and retinal vasculitis. Patients with severe steroid-resistant disease respond to anakinra, and anti-IL-1β mAb treatment is associated with dramatic and sustained reversal of intraocular inflammation [108, 109]. In a report, a single dose of anti-IL-1β antibodies (gevokizumab) prompted complete resolution of panuveitis and return of vision within 4–21 days [110].

Dry eye disease

Topical administration of low-dose anakinra proved effective in a randomized controlled trial on 75 dry eye disease patients. Subjects receiving 2.5% anakinra achieved a significant reduction in mean severity score and symptoms [111]. It is tempting to envisage similarly favourable results in patients with SS and sicca syndrome.

Vasculitides: GCA, urticarial vasculitis and Kawasaki disease

Therapies for steroid- and DMARD-refractory GCA are limited. Analysis of temporal artery specimens revealed that IL-1 is locally expressed in inflamed vessels [112]. Anakinra dampened systemic and arterial inflammation (as evaluated by PET/CT) in two patients refractory to conventional treatment [113].

Urticarial vasculitis features chronic urticarial lesions with histological findings of leucocytoclastic vasculitis. In a patient with refractory urticarial vasculitis, anakinra completely abrogated clinical manifestations [114]. Canakinumab administration to 10 urticarial vasculitis patients significantly improved cutaneous and systemic manifestations, paralleled by reductions in inflammation markers and cytokine levels [115].

Typically affecting coronary arteries, Kawasaki disease is one of the most common systemic vasculitides and a leading cause of acquired heart disease in children. Residual coronary artery abnormalities often cause complications later in life, including myocardial infarctions. Classic treatment options include IVIG and aspirin. However, recent evidence from murine models [116], as well as reports on the efficacy of anakinra treatment [117], suggest that IL-1 plays a pivotal role in the development of vascular damage in Kawasaki disease. Also, these novel findings cast new light on the hypothesis that a reduction in IL-1 production with an increase in IL-1Ra account for the beneficial anti-inflammatory and therapeutic effects of IVIG in several immune-mediated disorders [118].

A prospective trial on anakinra in Kawasaki disease is underway (NCT02179853).

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a life-threatening condition characterized by uncontrolled macrophage activation and haemophagocytosis, clinically manifesting as fever, pancytopenia and elevated serum triglyceride and ferritin levels. MAS is a feared complication of SLE, adult-onset Still's disease and SOJIA. Several studies report on the efficacy of anakinra in MAS [119–122]. Recently, a *de novo* missense mutation in the inflammasome component NLRC4 causing constitutive activation of caspase-1 and deregulated release of IL-1β and IL-18 was identified to cause recurrent fever and MAS [123]. Taken collectively, these findings strongly advocate the inclusion of MAS in the spectrum of autoinflammatory conditions.

Idiopathic recurrent pericarditis

This difficult disease, often refractory to immunosuppressive agents, anti-TNF-α medications, non-steroidal anti-inflammatory agents or high-dose glucocorticoids, was nevertheless responsive to anakinra in all reported cases [124–126].

Histiocytic disorders and cellular senescence

Erdheim–Chester disease (ECD) is a rare, systemic histiocytosis characterized by the infiltration of different tissues by lipid-laden macrophages. An activating mutation in the oncogene *BRAF* ($BRAF^{V600E}$) is frequently identified in ECD lesions [127, 128]. Clinical manifestations include bone pain, neurological symptoms, retroperitoneal fibrosis and congestive heart failure [129]. Anakinra is effective in ameliorating skeletal, cardiac, retroperitoneal and systemic manifestations [130–133], thus substantiating the central role of macrophages in diseases responsive to IL-1 blockade. Interestingly, ECD management traditionally relies on the administration of IFN-α, although the mechanisms underlying clinical efficacy are unclear [127]. IFN-α induces IL-1Ra [134] and inhibits inflammasome activation [135]. Modulation of the IL-1 pathway may indeed explain the efficacy of IFN-α in the management of ECD, as well as in a spectrum of clinical conditions similarly characterized by the $BRAF^{V600E}$ mutation and activation of the IL-1 pathway, including hairy cell leukaemia and melanoma.

The $BRAF^{V600E}$ mutation in ECD activates oncogene-induced senescence, a protective mechanism against cancer transformation characterized by cell cycle arrest and induction of a network of pro-inflammatory mediators, including IL-1β [128, 136]. Cellular senescence is a highly conserved response to stress and ageing, and chronic inflammation is indeed a hallmark of ageing tissues [137]. Thus, experience with ECD could translate into a broader use of anakinra in different age-related conditions.

Demyelination

Anti-TNF-α-based therapies may cause or worsen demyelination and are contraindicated in multiple sclerosis [138]. Conversely, anakinra is not a risk for demyelination. In a cohort of 104 000 RA patients, treatment with TNF-α-blocking agents had an adjusted rate ratio for demyelination of 1.31, whereas anakinra treatment had a rate ratio of 0.80 [139]. IFN-β and glatiramer acetate, common treatments for multiple sclerosis, induce IL-1Ra [135, 140], consistent with preclinical reports of protective IL-1 blockade in autoimmune encephalitis, the murine model for multiple sclerosis. A trial of anakinra in optic neuritis is underway.

Safety issues with IL-1 blockade

Impaired host defence against pathogens is a concern for cytokine-blocking agents. For instance, TNF-α-blocking agents are associated with a wide spectrum of opportunistic infections. Insidious, potentially life-threatening reactivation of latent *M. tuberculosis* is 25 times more frequent in patients receiving anti-TNF-α therapies [141], often in the form of disseminated infection, similar to that observed in HIV patients. Primary *M. tuberculosis* infection is also more likely in individuals treated with TNF-α blockers.

It is estimated that over 150 000 patients have received anakinra since its introduction in 2002. Anakinra has a remarkable record of safety [18, 142], also afforded by a short half-life of 6 h, allowing prompt discontinuation. Anakinra treatment is a risk for virus-type, non-life-threatening upper airway infections, whereas opportunistic infections are rare, even in populations at high risk of reactivation of *M. tuberculosis* infection [143, 144]. A single case of *M. tuberculosis* reactivation is reported [145]. In the trials of anakinra in patients with sepsis [146], no increase in overall mortality was observed in spite of doses administered exceeding 30–40 times the conventional 100 mg daily dose. Anakinra treatment has been administered in other cases of active infection [147] and in chronic granulomatous disease, a genetic condition characterized by vulnerability to bacterial and fungal infections [148]. No unexpected increase in infections has been observed with anti-IL-1β mAb, the use of which is relatively recent compared with anakinra.

Daily s.c. administrations of anakinra often cause injection site reactions. For most patients, these usually resolve within 14 days. Intravenously administered anti-IL-1 antibodies help to circumvent this issue. IL-1 injected into humans at doses as low as 3 ng/kg induces neutrophil mobilization from the bone marrow and neutrophilia [149, 150]. Most patients receiving anakinra or canakinumab have neutrophilia as a haematological manifestation of their disease, and a reduction in circulating neutrophils often heralds a response to IL-1 blockade. Although neutrophils fall below the normal range in some patients, sustained neutropenia is not observed, and neutrophils rise rapidly upon cessation of treatment [65].

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Reddy S, Jia S, Geoffrey R *et al*. An autoinflammatory disease due to homozygous deletion of the *IL1RN* locus. New Engl J Med 2009;360:2438–44.

2 Aksentijevich I, Masters SL, Ferguson PJ *et al*. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. New Engl J Med 2009;360:2426–37.

3 Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117:3720–32.

4 Berda-Haddad Y, Robert S, Salers P *et al*. Sterile inflammation of endothelial cell-derived apoptotic bodies is mediated by interleukin-1α. Proc Natl Acad Sci USA 2011;108:20684–9.

5 Rider P, Carmi Y, Guttman O *et al*. IL-1α and IL-1β recruit different myeloid cells and promote different stages of sterile inflammation. J Immunol 2011;187:4835–43.

6 Cohen I, Rider P, Carmi Y *et al*. Differential release of chromatin-bound IL-1α discriminates between necrotic and apoptotic cell death by the ability to induce sterile inflammation. Proc Natl Acad Sci USA 2010;107:2574–9.

7 Beyer C, Pisetsky DS. The role of microparticles in the pathogenesis of rheumatic diseases. Nat Rev Rheumatol 2011;6:21–9.

8 Dinarello CA, Ikejima T, Warner SJ *et al*. Interleukin 1 induces interleukin 1. I. Induction of circulating interleukin 1 in rabbits in vivo and in human mononuclear cells in vitro. J Immunol 1987;139:1902–10.

9 Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. Annu Rev Immunol 2009;27:229–65.

10 Hoffman HM, Wanderer AA. Inflammasome and IL-1beta-mediated disorders. Curr Allergy Asthma Rep 2011;10:229–35.

11 Gattorno M, Tassi S, Carta S *et al*. Pattern of interleukin-1β secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with *CIAS1* mutations. Arthritis Rheum 2007;56:3138–48.

12 Goldbach-Mansky R, Dailey NJ, Canna SW *et al*. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1β inhibition. New Engl J Med 2006;355:581–92.

13 Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 2005;201:1479–86.

14 Dinarello CA. Anti-inflammatory agents: present and future. Cell 2010;140:935–50.

15 Dinarello CA. How interleukin-1β induces gouty arthritis. Arthritis Rheum 2010;62:3140–4.

16 Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 2011;11:98–107.

17 Lachmann HJ, Lowe P, Felix SD *et al*. In vivo regulation of interleukin 1β in patients with cryopyrin-associated periodic syndromes. J Exp Med 2009;206:1029–36.

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

19 Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol 2004;31:1103–11.

20 Thaler K, Chandiramani DV, Hansen RA, Gartlehner G. Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project. Biologics 2009;3:485–98.

21 Singh JA, Christensen R, Wells GA *et al*. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Sao Paulo Med J 2010;128:309–10.

22 Botsios C, Sfriso P, Furlan A *et al*. Anakinra, a recombinant human IL-1 receptor antagonist, in clinical practice. Outcome in 60 patients with severe rheumatoid arthritis. Reumatismo 2007;59:32–7.

23 Jiang Y, Genant HK, Watt I *et al*. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 2000;43:1001–9.

24 Genant HK, Bresnihan B, Ng E *et al*. Treatment with anakinra reduces the rate of joint destruction and shows accelerated benefit in the second 6 months of treatment for patients with rheumatoid arthritis. Ann Rheumat Dis 2001;40 (Suppl 1):169 (abstract).

25 Miller DM, Ng E, Schiff MH, Cohen SB, Bresnihan B. Durability and rapidity of response for rheumatoid arthritis patients receiving therapy with anakinra. Ann Rheumat Dis 2001;60(Suppl 1):171 (abstract).

26 Alten R, Gomez-Reino J, Durez P *et al*. Efficacy and safety of the human anti-IL-1β monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study. BMC Musculoskelet Disord 2011;12:153.

27 Primdahl J, Clausen J, Horslev-Petersen K. Results from systematic screening for cardiovascular risk in outpatients with rheumatoid arthritis in accordance with the EULAR recommendations. Ann Rheum Dis 2013;72:1771–6.

28 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.

29 Duewell P, Kono H, Rayner KJ *et al*. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature 2010;464:1357–61.

30 Kamari Y, Werman-Venkert R, Shaish A *et al*. Differential role and tissue specificity of interleukin-1α gene expression in atherogenesis and lipid metabolism. Atherosclerosis 2007;195:31–8.

31 Pomerantz BJ, Reznikov LL, Harken AH, Dinarello CA. Inhibition of caspase 1 reduces human myocardial ischemic dysfunction via inhibition of IL-18 and IL-1β. Proc Natl Acad Sci USA 2001;98:2871–6.

32 Abbate A, Van Tassell BW, Biondi-Zoccai GG. Blocking interleukin-1 as a novel therapeutic strategy for secondary prevention of cardiovascular events. BioDrugs 2012;26:217–33.

33 Abbate A, Van Tassell BW, Biondi-Zoccai G *et al*. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2) pilot study]. Am J Cardiol 2013;111:1394–400.

34 Abbate A, Van Tassell BW, Seropian IM *et al*. Interleukin-1β modulation using a genetically engineered antibody prevents adverse cardiac remodelling following acute myocardial infarction in the mouse. Eur J Heart Fail 2010;12:319–22.

35 Cain BS, Meldrum DR, Dinarello CA *et al*. Tumor necrosis factor-α and interleukin-1β synergistically depress human myocardial function. Crit Care Med 1999;27:1309–18.

36 Van Tassell BW, Arena RA, Toldo S *et al*. Enhanced interleukin-1 activity contributes to exercise intolerance in patients with systolic heart failure. PLoS One 2012;7:e33438.

37 Ikonomidis I, Tzortzis S, Lekakis J *et al*. Lowering interleukin-1 activity with anakinra improves myocardial deformation in rheumatoid arthritis. Heart 2009;95:1502–7.

38 Ikonomidis I, Lekakis JP, Nikolaou M *et al*. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation 2008;117:2662–9.

39 Van Tassell BW, Arena R, Biondi-Zoccai G *et al*. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART Pilot Study). Am J Cardiol 2014;113:321–7.

40 Kelly C, Hamilton J. What kills patients with rheumatoid arthritis? Rheumatology 2007;46:183–4

41 van Asseldonk EJ, Stienstra R, Koenen TB *et al*. Treatment with anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2011;96:2119–26.

42 Maedler K, Sergeev P, Ris F *et al*. Glucose-induced β cell production of IL-1β contributes to glucotoxicity in human pancreatic islets. J Clin Invest 2002;110:851–60.

43 Masters SL, Dunne A, Subramanian SL *et al*. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1β in type 2 diabetes. Nat Immunol 2010;11:897–904.

44 Larsen CM, Faulenbach M, Vaag A *et al*. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. New Engl J Med 2007;356:1517–26.

45 Larsen CM, Faulenbach M, Vaag A *et al*. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. Diabetes Care 2009;32:1663–8.

46 Cavelti-Weder C, Babians-Brunner A, Keller C *et al*. Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. Diabetes Care 2012;35:1654–62.

47 Rissanen A, Howard CP, Botha J, Thuren T. Effect of anti-IL-1β antibody (canakinumab) on insulin secretion rates in impaired glucose tolerance or type 2 diabetes: results of a randomized, pacebo-controlled trial. Diabetes Obes Metab 2012;14:1088–96.

48 Sloan-Lancaster J, Abu-Raddad E, Polzer J *et al*. Double-blind, randomized study evaluating the glycemic and anti-inflammatory effects of subcutaneous LY2189102, a neutralizing IL-1β antibody, in patients with type 2 diabetes. Diabetes Care 2013;36:2239–46.

49 Stienstra R, Joosten LA, Koenen T *et al*. The inflammasome-mediated caspase-1 activation controls adipocyte differentiation and insulin sensitivity. Cell Metab 2011;12:593–605.

50 Joosten LA, Netea MG, Mylona E *et al*. Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1β production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis. Arthritis Rheum 2010;62:3237–48.

51 Joosten LA, Netea MG, Fantuzzi G *et al*. Inflammatory arthritis in caspase 1 gene-deficient mice: contribution of proteinase 3 to caspase 1-independent production of bioactive interleukin-1β. Arthritis Rheum 2009;60:3651–62.

52 McGonagle D, Tan AL, Shankaranarayana S *et al*. Management of treatment resistant inflammation of acute on chronic tophaceous gout with anakinra. Ann Rheum Dis 2007;66:1683–4.

53 So A, De Meulemeester M, Pikhlak A *et al*. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. Arthritis Rheum 2010;62:3064–76.

54 Terkeltaub R, Sundy JS, Schumacher HR *et al*. The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. Ann Rheum Dis 2009;68:1613–7.

55 Schlesinger N, De Meulemeester M, Pikhlak A *et al*. Canakinumab relieves symptoms of acute flares and improves health-related quality of life in patients with difficult-to-treat Gouty Arthritis by suppressing inflammation: results of a randomized, dose-ranging study. Arthritis Res Ther 2012;13:R53.

56 Schlesinger N, Mysler E, Lin HY *et al*. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis 2011;70:1264–71.

57 Schumacher HR Jr, Evans RR, Saag KG *et al*. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res 2012;64:1462–70.

58 Terkeltaub RA, Schumacher HR, Carter JD *et al*. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. Arthritis Res Ther 2013;15:R25.

59 Announ N, Palmer G, Guerne PA, Gabay C. Anakinra is a possible alternative in the treatment and prevention of

acute attacks of pseudogout in end-stage renal failure. Joint Bone Spine 2009;76:424–6.

60 McGonagle D, Tan AL, Madden J, Emery P, McDermott MF. Successful treatment of resistant pseudogout with anakinra. Arthritis Rheum 2008;58:631–3.

61 Zufferey P, So A. A pilot study of IL-1 inhibition in acute calcific periarthritis of the shoulder. Ann Rheum Dis 2013;72:465–7.

62 Chevalier X, Giraudeau B, Conrozier T *et al*. Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. J Rheumatol 2005;32:1317–23.

63 Chevalier X, Goupille P, Beaulieu AD *et al*. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 2009;61: 344–52.

64 Bacconnier L, Jorgensen C, Fabre S. Erosive osteoarthritis of the hand: clinical experience with anakinra. Ann Rheum Dis 2009;68:1078–9.

65 Cohen SB, Proudman S, Kivitz AJ *et al*. A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL 1R1) in patients with osteoarthritis of the knee. Arthritis Res Ther 2011;13:R125.

66 Chae JJ, Wood G, Masters SL *et al*. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1β production. Proc Natl Acad Sci USA 2006;103:9982–7.

67 Stankovic Stojanovic K, Delmas Y, Torres PU *et al*. Dramatic beneficial effect of interleukin-1 inhibitor treatment in patients with familial Mediterranean fever complicated with amyloidosis and renal failure. Nephrol Dial Transplant 2012;27:1898–901.

68 Ozen S, Bilginer Y, Ayaz NA, Calguneri M. Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine. J Rheumatol 2011;38:516–8.

69 Moser C, Pohl G, Haslinger I *et al*. Successful treatment of familial Mediterranean fever with anakinra and outcome after renal transplantation. Nephrol Dial Transplant 2009;24:676–8.

70 Meinzer U, Quartier P, Alexandra JF *et al*. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum 2011;41:265–71.

71 Ait-Abdesselam T, Lequerre T, Legallicier B *et al*. Anakinra efficacy in a Caucasian patient with renal AA amyloidosis secondary to cryopyrin-associated periodic syndrome. Joint Bone Spine 2011;77:616–7.

72 Bilginer Y, Ayaz NA, Ozen S. Anti-IL-1 treatment for secondary amyloidosis in an adolescent with FMF and Behcet's disease. Clin Rheumatol 2010;29:209–10.

73 Thornton BD, Hoffman HM, Bhat A, Don BR. Successful treatment of renal amyloidosis due to familial cold autoinflammatory syndrome using an interleukin 1 receptor antagonist. Am J Kidney Dis 2007;49:477–81.

74 Tan ZS, Beiser AS, Vasan RS *et al*. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. Neurology 2007;68:1902–8.

75 Stoffels M, Simon A. Hyper-IgD syndrome or mevalonate kinase deficiency. Curr Opin Rheumatol 2011;23:419–23.

76 Bodar EJ, Kuijk LM, Drenth JP *et al*. On-demand anakinra treatment is effective in mevalonate kinase deficiency. Ann Rheum Dis 2011;70:2155–8.

77 Rosengren S, Mueller JL, Anderson JP *et al*. Monocytes from familial cold autoinflammatory syndrome patients are activated by mild hypothermia. J Allergy Clin Immunol 2007;119:991–6.

78 Agostini L, Martinon F, Burns K *et al*. NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle-Wells auto-inflammatory disorder. Immunity 2004;20:319–25.

79 Hoffman HM, Throne ML, Amar NJ *et al*. Efficacy and safety of rilonacept (interleukin-1 trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum 2008;58:2443–52.

80 Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB *et al*. Use of canakinumab in the cryopyrin-associated periodic syndrome. New Engl J Med 2009;360:2416–25.

81 Kone-Paut I, Lachmann HJ, Kuemmerle-Deschner JB *et al*. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther 2011;13:R202.

82 Kuemmerle-Deschner JB, Hachulla E, Cartwright R *et al*. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis 2011;70:2095–102.

83 Kitley JL, Lachmann HJ, Pinto A, Ginsberg L. Neurologic manifestations of the cryopyrin-associated periodic syndrome. Neurology 2010;74:1267–70.

84 Goldbach-Mansky R. Current status of understanding the pathogenesis and management of patients with NOMID/CINCA. Curr Rheumatol Rep 2011;13:123–31.

85 Lepore L, Paloni G, Caorsi R *et al*. Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with Anakinra. J Pediatr 2011;157:310–5.e1.

86 Neven B, Marvillet I, Terrada C *et al*. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheum 2011;62:258–67.

87 Pathak S, Goldofsky E, Vivas EX, Bonagura VR, Vambutas A. IL-1β is overexpressed and aberrantly regulated in corticosteroid nonresponders with autoimmune inner ear disease. J Immunol 2011;186:1870–9.

88 Vambutas A, Lesser M, Mullooly V *et al*. Early efficacy trial of anakinra in corticosteroid-resistant autoimmune inner ear disease. J Clin Invest 2014;124:4115–22.

89 McDermott MF, Aksentijevich I, Galon J *et al*. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999;97:133–44.

90 Galon J, Aksentijevich I, McDermott MF, O'Shea JJ, Kastner DL. TNFRSF1A mutations and autoinflammatory syndromes. Curr Opin Immunol 2000;12:479–86.

91 Hull KM, Drewe E, Aksentijevich I *et al*. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. Medicine 2002;81:349–68.

92 Bulua AC, Mogul DB, Aksentijevich I *et al*. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study. Arthritis Rheum 2012;64:908–13.

93 Gattorno M, Pelagatti MA, Meini A *et al*. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008;58:1516–20.

94 Simon A, Bodar EJ, van der Hilst JCH *et al*. Beneficial response to interleukin-1 receptor antagonist in TRAPS. Am J Med 2004;117:208–10.

95 Sacre K, Brihaye B, Lidove O *et al*. Dramatic improvement following interleukin 1β blockade in tumor necrosis factor receptor-1-associated syndrome (TRAPS) resistant to anti-TNF-α therapy. J Rheumatol 2008;35:357–8.

96 Franchini S, Dagna L, Salvo F *et al*. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum 2010;62:2530–5.

97 Naumann L, Feist E, Natusch A *et al*. IL1-receptor antagonist anakinra provides long-lasting efficacy in the treatment of refractory adult-onset Still's disease. Ann Rheum Dis 2010;69:466–7.

98 Fitzgerald AA, Leclercq SA, Yan A, Homik JE, Dinarello CA. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum 2005;52:1794–803.

99 Cavalli G, Franchini S, Aiello P *et al*. Efficacy and safety of biological agents in adult-onset Still's disease. Scand J Rheumatol 2015 Feb 6 [Epub ahead of print].

100 Quartier P, Allantaz F, Cimaz R *et al*. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis 2011;70:747–54.

101 Gattorno M, Piccini A, Lasiglie D *et al*. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2008;58:1505–15.

102 Ruperto N, Quartier P, Wulffraat N *et al*. Evaluation of safety and preliminary efficacy of canakinumab in children with systemic onset juvenile idiopathic artritis. Arthritis Rheum 2009;60(Suppl 10):2055.

103 Ruperto N, Quartier P, Wulffraat N *et al*. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum 2012;64:557–67.

104 Vastert SJ, de Jager W, Noordman BJ *et al*. 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 Rheumatol 2014;66:1034–43.

105 Ryan JG, de Koning HD, Beck LA *et al*. IL-1 blockade in Schnitzler syndrome: *ex vivo* findings correlate with clinical remission. J Allergy Clin Immunol 2008;121:260–2.

106 Neel A, Henry B, Barbarot S *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.

107 de Koning HD, Schalkwijk J, van der Ven-Jongekrijg J *et al*. Sustained efficacy of the monoclonal anti-interleukin-1β antibody canakinumab in a 9-month trial in Schnitzler's syndrome. Ann Rheum Dis 2013;72:1634–8.

108 Cantarini L, Vitale A, Scalini P *et al*. Anakinra treatment in drug-resistant Behcet's disease: a case series. Clin Rheumatol 2015;34:1293–301.

109 Cantarini L, Lopalco G, Caso F *et al*. Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behçet's disease. Autoimmun Rev 2015;14:1–9.

110 Gül A, Tugal-Tutkun I, Dinarello CA *et al*. Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behcet's disease: an open-label pilot study. Ann Rheum Dis 2012;71:563–6.

111 Amparo F, Dastjerdi MH, Okanobo A *et al*. Topical interleukin 1 receptor antagonist for treatment of dry eye disease: a randomized clinical trial. JAMA Ophthalmol 2013;131:715–23.

112 Hernández-Rodríguez J, Segarra M, Vilardell C *et al*. Tissue production of pro-inflammatory cytokines (IL-1β, TNFα and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology 2004;43:294–301.

113 Ly KH, Stirnemann J, Liozon E, Michel M, Fain O, Fauchais AL. Interleukin-1 blockade in refractory giant cell arteritis. Joint Bone Spine 2014;81:76–8.

114 Botsios C, Sfriso P, Punzi L, Todesco S. Non-complementaemic urticarial vasculitis: successful treatment with the IL-1 receptor antagonist, anakinra. Scand J Rheumatol 2007;36:236–7.

115 Krause K, Mahamed A, Weller K *et al*. Efficacy and safety of canakinumab in urticarial vasculitis: an open-label study. J Allergy Clin Immunol 2013;132:751–4.e5.

116 Lee Y, Schulte DJ, Shimada K *et al*. Interleukin-1β is crucial for the induction of coronary artery inflammation in a mouse model of Kawasaki disease. Circulation 2012;125:1542–50.

117 Cohen S, Tacke CE, Straver B *et al*. A child with severe relapsing Kawasaki disease rescued by IL-1 receptor blockade and extracorporeal membrane oxygenation. Ann Rheum Dis 2012;71:2059–61.

118 Aukrust P, Frøland SS, Liabakk NB *et al*. Release of cytokines, soluble cytokine receptors, and interleukin-1 receptor antagonist after intravenous immunoglobulin administration in vivo. Blood 1994;84:2136–43.

119 Rajasekaran S, Kruse K, Kovey K *et al*. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children*. Pediatric Crit Care Med 2014;15:401–8.

120 Kelly A, Ramanan AV. A case of macrophage activation syndrome successfully treated with anakinra. Nat Clin Pract Rheumatol 2008;4:615–20.

121 Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology 2012;50:417–9.

122 Verbsky JW, White AJ. Effective use of the recombinant interleukin 1 receptor antagonist anakinra in therapy resistant systemic onset juvenile rheumatoid arthritis. J Rheumatol 2004;31:2071–5.

123 Canna SW, de Jesus AA, Gouni S *et al*. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. Nat Genet 2014;46:1140–6.

124 Cantarini L, Lucherini OM, Cimaz R, Galeazzi M. Recurrent pericarditis caused by a rare mutation in the TNFRSF1A gene and with excellent response to anakinra treatment. Clin Exp Rheumatol 2010;28:802.

125 Picco P, Brisca G, Traverso F *et al*. Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1β receptor antagonist (anakinra): an unrecognized autoinflammatory disease? Arthritis Rheum 2009;60:264–8

126 Scott IC, Vijay Hajela V, Hawkins PN, Lachmann HJ. A case series and systematic literature review of anakinra and immunosuppression in idiopathic recurrent pericarditis. J Cardiol Cases 2011;4:e93–7.

127 Diamond EL, Dagna L, Hyman DM *et al*. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood 2014;124:483–92.

128 Cangi MG, Biavasco R, Cavalli G *et al*. $BRAF_{V600E}$-mutation is invariably present and associated to oncogene-induced senescence in Erdheim-Chester disease. Ann Rheum Dis 2015;74:1596–602.

129 Cavalli G, Guglielmi B, Berti A *et al*. The multifaceted clinical presentations and manifestations of Erdheim-Chester disease: comprehensive review of the literature and of 10 new cases. Ann Rheum Dis 2013;72:1691–5.

130 Killu AM, Liang JJ, Jaffe AS. Erdheim-Chester disease with cardiac involvement successfully treated with anakinra. Int J Cardiol 2013;167:e115–7.

131 Courcoul A, Vignot E, Chapurlat R. Successful treatment of Erdheim-Chester disease by interleukin-1 receptor antagonist protein. Joint Bone Spine 2014;81:175–7.

132 Tran TA, Pariente D, Lecron JC *et al*. Treatment of pediatric Erdheim-Chester disease with interleukin-1-targeting drugs. Arthritis Rheum 2011;63:4031–2.

133 Aouba A, Georgin-Lavialle S, Pagnoux C *et al*. Rationale and efficacy of interleukin-1 targeting in Erdheim-Chester disease. Blood 2010;116:4070–6.

134 Tilg H, Mier JW, Vogel W *et al*. Induction of circulating IL-1 receptor antagonist by IFN treatment. J Immunol 1993;150:4687–92.

135 Guarda G, Braun M, Staehli F *et al*. Type I interferon inhibits interleukin-1 production and inflammasome activation. Immunity 2011;34:213–23.

136 Cavalli G, Biavasco R, Borgiani B, Dagna L. Oncogene-induced senescence as a new mechanism of disease: the paradigm of Erdheim-Chester disease. Front Immunol 2014;5:281.

137 Chung HY, Cesari M, Anton S *et al*. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev 2009;8:18–30.

138 Mohan VP, Scanga CA, Yu K *et al*. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. Infect Immun 2001;69:1847–55.

139 Bernatsky S, Renoux C, Suissa S. Demyelinating events in rheumatoid arthritis after drug exposures. Ann Rheum Dis 2010;69:1691–3.

140 Burger D, Molnarfi N, Weber MS *et al*. Glatiramer acetate increases IL-1 receptor antagonist but decreases T cell-induced IL-1β in human monocytes and multiple sclerosis. Proc Natl Acad Sci USA 2009;106:4355–9.

141 Solovic I, Sester M, Gomez-Reino JJ *et al*. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J 2011;36:1185–206.

142 Fleischmann RM, Tesser J, Schiff MH *et al*. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1006–12.

143 Fleischmann RM, Schechtman J, Bennett R *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.

144 Bresnihan B, Alvaro-Gracia JM, Cobby M *et al*. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41:2196–204.

145 Settas LD, Tsimirikas G, Vosvotekas G, Triantafyllidou E, Nicolaides P. Reactivation of pulmonary tuberculosis in a patient with rheumatoid arthritis during treatment with IL-1 receptor antagonists (anakinra). J Clin Rheumatol 2007;13:219–20.

146 Opal SM, Fisher CJJ, Dhainaut JF *et al*. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. Crit Care Med 1997;25:1115–24.

147 Hennig S, Bayegan K, Uffmann M, Thalhammer F, Winkler S. Pneumonia in a patient with familial Mediterranean fever successfully treated with anakinra—case report and review. Rheumatol Int 2012;32:1801–4.

148 van de Veerdonk FL, Netea MG, Dinarello CA, van der Meer JW. Anakinra for the inflammatory complications of chronic granulomatous disease. Neth J Med 2011;69:95.

149 Dinarello CA. Biological basis for interleukin-1 in disease. Blood 1996;87:2095–147.

150 Ogilvie AC, Hack CE, Wagstaff J *et al*. IL-1 beta does not cause neutrophil degranulation but does lead to IL-6, IL-8, and nitrite/nitrate release when used in patients with cancer. J Immunol 1996;156:389–94.