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Treating inflammation by blocking interleukin-1 in humans

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Abstract

IL-1 is a master cytokine of local and systemic inflammation. With the availability of specific IL-1 targeting therapies, a broadening list of diseases has revealed the pathologic role of IL-1-mediated inflammation. Although IL-1, either IL-1α or IL-1β, was administered to patients in order to improve bone marrow function or increase host immune responses to cancer, these patients experienced unacceptable toxicity with fever, anorexia, myalgias, arthralgias, fatigue, gastrointestinal upset and sleep disturbances; frank hypotension occurred. Thus it was not unexpected that specific pharmacological blockade of IL-1 activity in inflammatory diseases would be beneficial. Monotherapy blocking IL-1 activity in a broad spectrum of inflammatory syndromes results in a rapid and sustained reduction in disease severity. In common conditions such as heart failure and gout arthritis, IL-1 blockade can be effective therapy. Three IL-1blockers have been approved: the IL-1 receptor antagonist, anakinra, blocks the IL-1 receptor and therefore reduces the activity of IL-1α and IL-1β. A soluble decoy receptor, rilonacept, and a neutralizing monoclonal anti-interleukin-1β antibody, canakinumab, are also approved. A monoclonal antibody directed against the IL-1 receptor and a neutralizing anti-IL-1α are in clinical trials. By specifically blocking IL-1, we have learned a great deal about the role of this cytokine in inflammation but equally important, reducing IL-1 activity has lifted the burden of disease for many patients.

Keywords

Autoimmune; Autoinflammatory; Inflammation

1. Introduction

The importance of IL-1 as a master cytokine in inflammation comes from infants born with a loss of function mutation in the naturally occurring endogenous IL-1 receptor antagonist (IL-1Ra). IL-1Ra blocks the IL-1 receptor type 1 (IL-1R1), which is on all cells; therefore, systemic inflammation may come for either IL-1α or IL-1β. These infants succumb early in life with overwhelming sterile inflammation of the skin, joints and bone with large numbers of infiltrating neutrophils and high levels of interleukin-17 [1,2]. The condition is called deficiency of interleukin-1 antagonist (DIRA) and daily treatment with anakinra rapidly reverses the inflammation and prevents a fatal outcome. Mice deficient in IL-1Ra are similarly affected in that these mice develop spontaneous inflammation such as a rheumatoid arthritis-like disease and can succumb to lethal arteritis. The best evidence for a role for either IL-1α or IL-1β in disease comes from specific blockade, as correlations of

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circulating levels and disease severity are not informative and do not establish causality. Even in the most severe IL-1β-mediated autoinflammatory diseases, IL-1β levels in the circulation increase only by factor of five [3].

There are two IL-1's. IL-1α is expressed as a precursor and is constitutively present in most cells of healthy subjects. The cytokine is found in normal keratinocytes of the skin, the epithelial cells of mucosal membranes throughout the body and the cells of organs such as the liver, lung and kidney. Platelets also contain IL-1α. The entire endothelium of the vasculature contains the IL-1α precursor and in membrane fragments from the endothelium termed "apoptotic bodies" [4]. These membrane fragments are active in inducing neutrophil infiltration [4] in several inflammatory conditions of the blood vessels termed vasculitis [5]. During ischemia, however, cell death by necrosis takes place and the IL-1α precursor is released [6,7].

In contrast, IL-1β is not present in health or at levels not detected by standard assays. IL-1β is a product of blood monocytes, tissue macrophages and dendritic cells. The rate-limiting step in the production of IL-1β is transcription, but IL-1β mRNA requires an additional signal for synthesis. The stimulus can be a microbial product but cytokines, such as TNFα, IL-18, IL-1α or IL-1β itself induce IL-1β [8]. In fact, IL-1 induction of itself is part of the mechanism of "autoinflammation". IL-1β is first synthesized as an inactive precursor but the precursor requires cleavage by caspase-1, an intracellular cysteine protease. Caspase-1 itself requires activation in order to process IL-1β into an active cytokine. The activation of caspase-1 proceeds following the oligomerization of a complex of intracellular proteins termed the "inflammasome" by the late Tschopp [9,10]. With activation of caspase-1, the N-terminal amino acids are cut and mature IL-1β is readily secreted as an active cytokine. One of the components of the inflammasome termed "cryopyrin" (also termed NLRP3) plays a critical role in the secretion of IL-1β. A single amino acid mutation in cryopyrin [11] results in enhanced caspase-1 activity and greater secretion of IL-1β Increased production and secretion of IL-1β from blood monocytes is characteristic of a group of autoinflammatory diseases termed "cryopyrin associated periodic syndrome (CAPS)".

2. Autoinflammatory diseases are different from autoimmune diseases

Autoinflammatory diseases are chronic, debilitating syndromes [12]. As stated above, some autoinflammatory conditions are due to mutations in the intracellular proteins that control caspase-1, the enzyme that converts IL-1β to an active cytokine prior to release from the cell. Although these conditions are rare, the inflammatory manifestations are common to many diseases. Blood monocytes from patients with autoinflammatory diseases release more IL-1β compared to cells from healthy persons [13–17]. In autoimmune diseases, however, dysfunctional T-lymphocytes are fundamental to pathogenesis. Autoimmune diseases such as rheumatoid arthritis, Crohn's inflammatory bowel disease and plaque psoriasis are effectively treated with an expanding number of anti-cytokine-based therapies, depleting antibodies and inhibitors of cell migration [18]. Of these, agents to block tumor necrosis factor-alpha (TNFα) are used widely.

In contrast, classic autoinflammatory diseases are uniquely responsive to IL-1β blockade whereas neutralization of TNFα is not effective or can exacerbate the condition. Neutralization of TNFα in gout and in Type 2 diabetes, which are responsive to IL-1 blockade, is without effect. One explanation is that TNFα is not the dominant cytokine produced in the gouty joint [19] nor the insulin-producing pancreatic islet cells [20]. Whereas in autoinflammatory diseases, the release of IL-1β from the monocyte is elevated, but in the same cells the production of TNFα is not different from that of healthy controls.

3. Treating a broad spectrum of inflammatory conditions with anakinra

The IL-1 receptor is expressed in nearly all tissues and thus anakinra provides an optimal therapy, as the antagonist prevents the binding of either IL-1α or IL-1β. However, how much of the efficacy of anakinra is due to blocking IL-1α and how much is due to blocking IL-1β? The amount of IL-1β that circulates in IL-1-mediated inflammatory conditions is in the low nanogram range [3]; IL-1α is rarely found in the circulation. Therefore, the use of anakinra has provided the data on the role of IL-1 in a broad spectrum of inflammatory diseases. Table 1 summarizes the joint, bone and muscle diseases, in which anakinra is effective. Some are large studies of randomized and placebo controlled trials such as rheumatoid arthritis whereas others are smaller studies and several are single case reports. Characteristically of the case reports are treatment benefits by anakinra in patients refractory to standards of therapy, such as often high doses of glucocorticoids, methotrexate and anti-TNFα based therapies.

4. IL-1 and acute onset diseases

IL-1-mediated inflammation contributes to catastrophic events such acute lung injury, myocardial infarction, acute kidney failure and stroke with end organ failure. There is no dearth of animal studies demonstrating an essential role for IL-1 following an ischemic injury of the heart [21], lung [22], liver [23], kidney [24] and brain [25] (Fig. 1). Inflammation following an ischemic event is characterized by infiltration of neutrophils and myeloid precursors into the surrounding ischemic area, often termed the penumbra (Fig. 2). For example, occlusion of a cerebral blood vessel results in necrotic brain tissue surrounded by a penumbra of healthy cells with infiltrating inflammatory cells. The area of gross necrosis is replaced by scar and loss of function; however, the cells in the penumbra of inflammation are salvageable by blocking IL-1. In fact, reducing IL-1 activity with anakinra has been tested in ischemic stroke patients and shown to be beneficial [26].

5. Blocking IL-1 in heart disease

5.1. Post-infarction cardiac remodeling

Based on a large number of animal studies, blocking IL-1 in humans with heart disease has entered clinical medicine [27]. Anakinra has been used successfully in patients with ST-elevation myocardial infarction (STEMI) [28] and repeated in a second trial [29]. Both trials were randomized and placebo controlled. STEMI has a high risk of death but patients who survive the acute event often progress to chronic heart failure due to loss of viable myocardium. In the first randomized, placebo-controlled trial of patients with STEMI, daily anakinra was added to standard of therapy the day after angioplasty and continued for 14 days. Serial imaging and echocardiographic studies were performed 90 days following the infarction. Left ventricular remodeling was significantly reduced with anakinra treatment compared to placebo-treated patients [28]. Moreover, the improvement with anakinra correlated with reductions in C-reactive protein (CRP). CRP is a large protein produced by the liver in response to any infectious or inflammatory condition. It is commonly measured in the circulation as a marker of the severity of inflammation, particularly in patients with coronary artery disease. After 18 months, 60% of placebo-treated patients had developed heart failure whereas none developed in the anakinra-treated patients. In the second, expanded trial, similar findings were observed, although the more severe the infarction, the greater the benefit of anakinra [29]. When the data were pooled with those from the first trial (n = 40), 5% of patients randomized to anakinra developed heart failure whereas 30% were affected in the placebo arm (p = 0.035) [29].

5.2. Heart failure

Despite several treatment regimens, heart failure continues to be a major medical problem with significant economic and social burdens. Poorly compensated patients with left ventricular ejection fraction less than 40% and elevated serum CRP greater than 2 mg/L were treated with anakinra and subjected to controlled exercise performance testing. Physiologically, after 14 days of anakinra, oxygen consumption increased significantly from baseline, carbon dioxide retention decreased and exercise performance improved [30]. Serum IL-1β levels fell by 89%, CRP by 88% and IL-6 by 90%, but there was no change in levels of TNFα [30]. Since IL-1β induces IL-6, a fall in IL-6 is indicative of a decrease in the biological activity of IL-1 itself, supporting the concept that heart failure is an autoinflammatory disease.

These data in humans with heart failure are similar to rheumatoid arthritis patients who were treated for 30 days with anakinra during which time left ventricular function improved [31]. In a related study, a single subcutaneous dose of anakinra resulted in increased blood flow 3 h later [31]. Overall, these improvements in heart function are also consistent with previous studies in human atrial heart strips ex vivo in that IL-1 suppresses contractile force [32] and that blocking IL-1 restores decreased function after ischemia-reperfusion [33]. Several animal models show that IL-1 suppresses the myocardium (reviewed in [30]). With only a 14-day course of anakinra in patients receiving current treatment standards, a greater duration of blockade may result in a greater return of function.

Although heart failure is often associated with decreased left ventricular ejection volume, some 50% of patients with hemo-dynamically defined heart failure have normal left ventricular systolic function but with impaired left ventricular diastolic filling. This type of heart failure is also called diastolic heart failure and patients with rheumatoid arthritis exhibit signs of this form of heart failure. Moreover, anakinra treatment of rheumatoid arthritis patients with heart failure restored left ventricular diastolic function [31]. In a double-blind, placebo-controlled, cross-over trial, patients received 14 days of anakinra 100 mg per day or placebo. Before and after the treatment schedules, exercise testing was performed. Anakinra resulted in improved in peak oxygen consumption ($p = 0.009$) and a 75% decrease in CRP [34]. For patients with rheumatoid arthritis and the co-morbidity of diastolic heart failure, anakinra treatment for the arthritis would provide an improved treatment option since no other anti-cytokine treatment for rheumatoid arthritis reduces heart failure, and in the case of TNF, blockers, there is a risk for patients with heart failure.

6. Diabetes

6.1. Type-1 diabetes

In 1986, the Danish scientists Mandrup-Poulsen and colleagues published their findings that picomolar concentrations of IL-1β were selectively toxic for the insulin-producing pancreatic beta-cell (reviewed in [35]). These studies resulted in a paradigm change for the pathogenesis of Type-1 diabetes in that a macrophage product rather than a cytotoxic T-cell became the target for salvaging the beta-cell. In the non-obese diabetic mouse strain, the *sine qua non* model for Type-1 diabetes, IL-1 blockade reduces spontaneous diabetes [35] but also in a rat model of spontaneous diabetes [36]. After 25 years of research on IL-1 in diabetes, trials of IL-1 blockade have begun.

In a 28-day long trial of anakinra in children within one week of the onset of diabetes, insulin use after one and four months from diagnosis were significantly lower compared to historical controls [37]. Repeated courses of IL-1 blockade will likely be needed to suppress ongoing IL-1-mediated islet inflammation. However, chronic use of anakinra or canakinumab appears safe in children with autoinflammatory diseases [38,39]. How does the

likelihood of repeated courses of an IL-1-blocking therapy compare to other therapies in Type-1 diabetes? Immunosuppressive agents such as cyclosporine arrest the progression of the autoimmune process in children with Type-1 diabetes [40], but at a cost of unacceptable risk [41] compared to daily insulin. More recently, anti-CD3 monoclonal antibodies that deplete T-cells [42] and an anti-CD20 B-cell depleting antibody [43] result in increases in serum C-peptide levels, a validated biomarker of improved beta-cell function. However, these depleting antibodies have limitations for continued treatments and carry the risk of progressive multifocal leukoencephalopathy, a fatal brain disease. Repeated courses of anakinra, on the other hand, could keep islet inflammation at bay, reduce episodes of dangerous low blood sugar and increase insulin sensitivity [44].

Two randomized, placebo controlled, double-masked trials of anakinra and canakinumab monotherapy in new-onset diabetes have been completed [45]. In the anakinra trial, subjects with newly diagnosed (within 3 months) Type-1 diabetes received 100 mg of daily subcutaneous anakinra or placebo for 9 months. The primary endpoint is beta-cell function assessed as C-peptide response to a standardized 2-h mixed-meal challenge. Secondary endpoints include insulin requirement, percent insulin-free remission, and 2-h glucose levels after an oral glucose load. In the canakinumab trial, treatment began within 3 months of diagnosis, subjects received either monthly subcutaneous injections of 2.0 mg/kg canakinumab or placebo for 12 months. All groups received standard intensive diabetes treatment with insulin and dietary management and followed for 1–3 years. The primary endpoint was levels of C-peptide following a mixed-meal test after one year of canakinumab or placebo treatment. There was no significant difference in C-peptide levels between either anakinra or canakinumab and the respective placebo arms [45]. However, in the anakinra trial, there was a statistically significant difference ($p = 0.006$) between anakinra and placebo when assessed by three categorized levels of C-peptide [45]. The authors of these studies suggested that a combination of IL-1 blockade plus targeting T-cells may be needed to arrest the loss of beta cells in Type 1 diabetes.

6.2. Type-2 diabetes

Studies of the role of IL-1β in the pathogenesis of Type-2 diabetes reported that high concentrations of glucose stimulated IL-1β production from the beta-cell itself [46], thus implicating a self-destructive role of IL-1β autoinflammation by the beta-cell (reviewed in [20]). Moreover, IL-1β increases the deposition of amyloid, which contributes further to beta-cell loss [47]. Indeed, gene expression for IL-1β is one hundred-fold higher in beta-cells from Type-2 patients [20] compared to non-diabetic patients. Thus, in Type-2 diabetes there is progressive loss of the beta-cell due to IL-1-mediated inflammation, which may also underlie the mechanism of insulin resistance [44].

Clinical proof of a role for IL-1 in the pathogenesis of Type-2 diabetes can be found in the randomized, placebo controlled study of anakinra for 13 weeks, in which there was improved insulin production and glycemic control associated with decreased CRP and IL-6 levels [48]. Unexpectedly, in the 39 weeks following the treatment, anakinra responders used 66% less insulin to obtain the same glycemic control compared to baseline requirements [49]. This observation suggests that blocking IL-1β, even for a short period restores the function of beta-cells or possibly allows for partial regeneration. These findings of anakinra treatment in Type-2 diabetic have been confirmed using anti-IL-1β monoclonal antibodies: Xoma gevokizumab [50], Novartis canakinumab[51] and Lilly LY2189102 [52]. Gevokizumab treatment also reduced the fatigue in Type-2 patients [53], as did anakinra in Sjoegren syndrome [54]. Anakinra has also been tested in obese non-diabetic patients with metabolic syndrome [44]. There was a decrease in CRP and circulating leukocytes; the

disposition index increased significantly after anakinra treatment, reflecting improved beta-cell function [44].

Thus, Type-2 diabetes emerges as a chronic inflammatory disease, in which IL-1 progressively destroys the insulin-producing beta-cells or renders the beta cell non-functional [20]. The IL-1β can come from the beta-cell itself, but also from blood monocytes that infiltrate the islet. Obesity is a high risk for Type-2 diabetes and caspase-1 dependent IL-1β production has been demonstrated in macrophages isolated from human fat [55]. IL-1α and IL-1β exert the same toxic effect on the insulin-producing beta cells and it is unclear to what extent IL-1α plays a role in humans with Type-2 diabetes. A neutralizing anti-human IL-1α will test a role for IL-1α in Type-2 diabetes.

6.3. Cardiovascular events in Type-2 diabetes

A large body of pre-clinical data reveals that IL-1 plays a role in the progression of atherosclerosis [56–58]. Because Type-2 diabetes increases the risk of cardiovascular events, blocking IL-1β activity in these patients may also reduce the incidence in myocardial infarction and stroke. The largest trial of an anti-cytokine is CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) testing whether canakinumab will reduce cardiovascular events in Type-2 diabetics with high CRP levels despite optimal statin therapy [59]. The rationale for CANTOS is based on the consistent decrease in CRP levels observed with anakinra [48], canakinumab [60] or gevokizumab [50].

7. Arthritis and joint diseases

7.1. Rheumatoid arthritis

Anakinra has been studied in several controlled studies in patients with rheumatoid arthritis with and without methotrexate (reviewed in [61]) (Table 1). Overall, each study revealed a statistically significant reduction in disease severity, improvement in quality of life and a decrease in radiographic evidence of joint space narrowing. Because of the half-life of 6 h, daily injections of anakinra are required. The subcutaneous injections can produce injection site reactions, although these usually resolve within 14 days. In patients failing TNFα blockers or for whom TNFα blockers are contraindicated, anakinra is effective in controlling disease activity. There is no controlled head to head comparison of the outcome of an IL-1 blocking therapeutic to one of the growing list of biologics presently used for rheumatoid arthritis. However, after one year of anakinra therapy alone or in combination with methotrexate, improvements seem to be similar to those of the other biologics [62–66].

Compared to anakinra, TNFα blockers dominate the field of biologics for rheumatoid arthritis. One explanation for the popularity of TNFα blockers is the often-described sense of well-being experienced by patients within hours of treatment. Using functional magnetic resonance imaging, antibodies to TNFα blunt pain receptors in the brain within minutes of an intravenous infusion [67]. This property likely contributes to the rapidity of efficacy in clinical outcome scores by reducing disease-associated pain, fatigue and depression. Similar to anakinra, canakinumab has reduced disease severity in new onset rheumatoid arthritis patients, including patients who fail anti-TNFα therapies [68]. However, canakinumab trials have been suspended in rheumatoid arthritis trials perhaps due to the increasing number of agents competing for the same market. Unlike anakinra, the long-term benefit of preservation of joint function with canakinumab remains unstudied.

7.2. Crystal arthritis: gout and calcium pyrophosphate crystal arthritis

Patients with recurrent attacks of gouty arthritis unable to use colchicine and other standards of therapy often require steroids to control disease flares. When treated with anakinra (Table

4), canakinumab (Table 5) or rilonacept (Table 6), a rapid, sustained and remarkable reduction in pain as well as objective signs of reduced inflammation have been observed [69–79]. The effect of IL-1 blockade appears to be superior to that of steroids and result in prolonged periods without flares. The likely mechanism for urate crystal-induced IL-1 is in combination with free fatty acids, which accounts for nutrition-related flares of gout [80]. Given the characteristic neutrophilic infiltration in gouty joints, it is also likely that the IL-1β precursor is processed extracellularly by neutrophilic enzymes [81]. Pyrophosphate crystal arthritis is highly responsive to anakinra [71,77].

7.3. Osteoarthritis

In humans, subcutaneous anakinra improved pain and swelling in an aggressive form of erosive osteoarthritis [82]. Anakinra has also been injected intraarticularly in patients with knee osteoarthritis [83,84], but the benefit did not extend beyond one month [84], which may be due the brief duration in the joint space. Systemic treatment of osteoarthritis with an antibody to the IL-1 receptor was carried-out and a modest improvement was reported, particularly in those patients with high pain levels at enrollment [85].

8. Hereditary autoinflammatory diseases

8.1. Diseases of Mendelian inheritance

A group of rare genetic disorders, which have a common phenotype of recurrent fevers, debilitating fatigue, myalgia, arthralgia, gastrointestinal symptoms and skin rashes, are treated with IL-1 blocking therapies. These include FMF, CAPS, TRAPS, HIDS, MKD and PAPA. Neutrophilia, elevated hepatic acute phase proteins and increased erythrocyte sedimentation rates are characteristic during the episodes. A common feature to nearly all hereditary autoinflammatory syndromes is the rapid and sustained arrest of both clinical and hematologic abnormalities to IL-1 blocking monotherapy, regardless whether the agent is anakinra, canakinumab or rilonacept (Tables 2, 5 and 6). However, in about 50% of the cases of FMF and CAPS, similar if not identical clinical and laboratory manifestations are present without the mutations. Elevated secretion of IL-1β from blood monocytes in vitro can often be demonstrated.

8.2. Familial Mediterranean fever

Familial Mediterranean fever (FMF), known by episodes which last about three-four days and are characterized by fever, leukocytosis and severe serositis (mostly peritonitis, but pleuritis, pericarditis and synovitis occur). FMF is caused by mutations in the *MEFV* gene, encoding pyrin, a protein involved in the activation of caspase-1 and the processing and release of active IL-1β [86]. Although colchicine is the mainstay of treatment, in a minority of patients colchicine is not sufficient to prevent the attacks. In several case reports, treatment with anakinra or canakinumab in colchicine-resistant patients is highly effective [87–94]. Not all patients with FMF have the classic mutation, despite classic signs and symptoms of the disease [95]. Whole exome sequencing revealed a novel missense sequence in FMF. The study concluded that heterozygous mutations at amino acid position 577 of pyrin can induce an autosomal dominant autoinflammatory syndrome [95].

8.3. Hyper-IgD syndrome

Hyper-IgD syndrome (HIDS) is an autosomal recessive autoinflammatory disorder caused by mutations in the mevalonate kinase gene; thus, HIDS is also known as mevalonate kinase deficiency (MKD). Several intracellular pathways of protein modification have linked mevalonate kinase deficiency to control of IL-1 production, as reviewed in [96], including activation of caspase-1 [97]. HIDS episodes last 4–6 days with fever, myalgia, skin rash,

aphthous ulcers and lymphadenopathy. Several case reports have demonstrated success of IL-1 blockade in reducing the frequency and severity of the attacks [96,98–103].

8.4. Cryopyrin associated periodic syndrome

Cryopyrin associated periodic syndrome (CAPS) is the term for three syndromes that were previously known under separate names: familial cold autoinflammatory syndrome, Muckle–Wells syndrome and neonatal onset multi inflammatory diseases. Each is linked to mutations in the NLRP3 inflammasome, which activates caspase-1 and results in increased release of IL-1β [9,13–15,104–107]. The CAPS phenotype can vary from discrete inflammatory episodes of fever, myalgia and skin rash, lasting a few days, to almost continuous systemic inflammation with neurological involvement, including aseptic meningitis, raised intracranial pressure, deafness and growth retardation. Anakinra is highly efficacious in the treatment of CAPS (Table 2) and has been approved. Rilonacept [108] as well as canakinumab [109–112] are approved for the treatment of this rare genetic disorder (Tables 5 and 6). A report of a 2-year follow-up of canakinumab treatment in 166 patients with CAPS revealed long-term efficacy with few side effects [113], even in previously severely affected patients with neurologic involvement. Sensorineural deafness is a common manifestation of CAPS as are other neurologic abnormalities but is reversible with IL-1 blockade [110,114,115].

8.5. TNF-receptor associated periodic syndrome

TNF-receptor associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by mutations in the TNF-receptor type 1 [116]. Patients experience recurrent bouts of fever with local and systemic inflammation, initially thought to be due to a lack of circulating soluble TNFα receptors, which bind TNFα and prevent TNFα binding to cells [117]. However, treatment with IL-1 blockers is significantly more effective than with TNF inhibitors [118–120].

9. Chronic inflammatory diseases

A growing number of chronic inflammatory disorders without a known genetic basis respond to reducing IL-1 activity. For example, treating idiopathic recurrent pericarditis with immunosuppressive agents, anti-TNFα antibodies, non-steroidal anti-inflammatory agents, intravenous gamma globulin or high dose glucocorticoids often results partial remissions whereas anakinra (Table 3) provides complete remission in all cases reported [121–124]. Although most chronic inflammatory conditions without a known basis can be controlled with glucocorticoids, monotherapy with IL-1 blockade provides improved control without the metabolic and gastrointestinal side effects. In children, glucocorticoids retard growth and development and treating systemic onset juvenile idiopathic arthritis with anakinra or canakinumab allows for reduced glucocorticoid dosing and catchup growth [16,38,125,126] (Table 4).

9.1. Adult onset Still's disease

Adult onset Still's disease (AOSD) is a systemic inflammatory syndrome that is characterized by recurrent fevers, prominent neutrophilia, rash, systemic inflammation and arthritis with unusually high CPR and ferritin levels. Some patients develop a resistance to steroid therapy and anti-TNFα and methotrexate have been ineffective. In these patients monotherapy with anakinra is highly effective (Table 3) and has become the standard of therapy [127–131]. Canakinumab and rilonacept are also effective in AOSD (Tables 5 and 6).

9.2. Systemic onset juvenile idiopathic arthritis

The juvenile form of Still's disease is called systemic onset juvenile idiopathic arthritis (SJIA) and is the severe form of juvenile idiopathic arthritis. As in the adult form, IL-1 contributes significantly to the inflammation in SJIA and several reports describe a remarkable efficacy with anakinra (see Table 3) in patients who are refractory to steroids, methotrexate and TNF blockers [16,126,132]. Neutralization of IL-1β with canakinumab has been approved [38,133] (Table 5).

9.3. Schnitzler's syndrome

Schnitzler's syndrome is a debilitating systemic inflammatory disease characterized by repeated bouts of fever, chronic urticaria and a gammopathy. Patients with Schnitzler's syndrome can progress to hematopoietic malignancies. There is increased risk of developing Waldenström macroglobulinemia. Patients with Schnitzler syndrome are treated with anakinra, which results in rapid improvement, often within hours, and complete remission within days [134–138]. This effect has been observed in many cases, and the Schnitzler syndrome international registry, which collects data on Schnitzler's syndrome patients, reports nearly 100% efficacy with anakinra. Canakinumab [139] is also highly effective whereas depletion of B-cells with rituximab has failed to reduce the systemic symptoms.

9.4. Behçet's disease

The inflammation in Behçet's disease affects nearly all organs and tissues, as there is systemic vasculitis with oral, gastrointestinal and genital ulcers and a hypercoagulation state. Patients resistant to steroids respond to anakinra [140]. Uveitis and retinal vasculitis result in loss of sight and the use of glucocorticoids and immunosuppressive drugs are associated with significant adverse effects. Panuveitis was treated with a single dose of anti-IL-1β (gevokizumab) and complete resolution of intraocular inflammation and return of vision was achieved in 4–21 days [141]. Treatment resulted in a rapid onset, marked and sustained reduction in intraocular inflammation in these refractory patients.

9.5. Dry eye disease

Anakinra was applied topically to patients with dry eye disease in a prospective, double-blinded, randomized trial involving 75 patients. Treatment was randomized to topical 2.5%, 5% anakinra or vehicle 3 times daily for 12 weeks. Subjects receiving 2.5% anakinra achieved a 46% reduction in their mean severity score ($P < 0.001$ compared with baseline) [142]. By week 12, treatment with 2.5% or 5% anakinra led to significant reductions in symptoms of 30% and 35%, respectively ($P = 0.02$ and $P = 0.01$, respectively, compared with vehicle).

9.6. Giant cell arteritis

Steroids are the treatment of choice in giant cell arteritis in order to save vision; however, alternate therapies for refractory cases are limited. IL-1β expression is elevated in this disease as are other cytokines and chemokines. Three cases of refractory giant cell arteritis were successfully treated with anakinra [143]. Anakinra treatment was associated with reductions in inflammatory biomarkers as well as disappearance of arterial inflammation by PET/CT for two of the three patients treated [143].

9.7. Hydradenitis suppurativa

It is estimated that between 1 and 4% of the western world's population is affected by hydradenitis suppurativa. Inflammatory lesions derived from hair follicles in the groin, axilla and rectal areas and resulting in scarring characterize the disease. The disease is debilitating

both physiologically as well as socially due to the odorous nature of the inflammation. Although antibiotics are used, recurrences are common and presently, there is no treatment that reduces the fundamental nature of the follicular inflammation. Cytokine-mediated inflammation has been considered as immunosuppressive agents have been used. Blocking TNFα is effective in some patients but TNFα failures have been reported [144]. Elevated levels of TNFα as well as IL-1β are released from 24 h cultures of skin from these patients; the elevated levels are not only in lesional skin biopsies but also in the unaffected peripheral skin of the lesions [145]. Blocking IL-1 with anakinra in hydradenitis suppurativa patients at the approved dose for rheumatoid arthritis (100 mg/day) is effective [146–149]. Canakinumab has also been reported as effective [150].

10. Other indications for treating IL-1-mediated inflammation

10.1. Mental impairment and hearing loss

CAPS patients exhibit various neurologic abnormalities such as aseptic lepo-meningitis and thus reflecting IL-1-mediated inflammation in the brain. In a study of CAPS patients, 92% had headache with features of migraine, 54% had sensorineural deafness and 46% had papilledema [110]. Treatment with either anakinra or canakinumab leads to complete resolution of symptoms [110,113,151]. Children with severe CAPS show manifestations of elevated intracranial pressure and are believed to be mentally slow or even retarded. However, both mental and hearing impairment are reversed upon treatment with anakinra [15,115,151–154] but also with specific neutralization of IL-1β with canakinumab [109,111–113,155].

In autoimmune inner ear disease, there is either sudden onset or progressive loss in hearing. Patients are usually treated with glucocorticoids; however, those not responding to glucocorticoid therapy have elevated IL-1β in the circulation and peripheral blood monocytes release more IL-1β than monocytes from unaffected subjects [156]. Meniere Disease can also be characterized by progressive sensorineural hearing loss and is also associated with dysregulation of IL-1β [156–158]. A randomized, placebo controlled trial of anakinra in Meniere disease has been initiated.

10.2. Amyloidosis

Amyloidosis is a destructive process for several organs due to the deposition of amyloid fibrils. IL-1 is an inducer of serum amyloid A (SAA), which is commonly elevated in several chronic inflammatory diseases, including atherosclerosis. Left untreated, IL-1-mediated diseases such as FMF and CAPS result in kidney failure due to amyloid deposits, which is fatal. However, treatment with anakinra, canakinumab or rilonacept markedly reduces SAA, kidney function improves and a fatal outcome can be avoided [89,91,159–162]. Amyloid deposits have also been observed in the insulin-producing islets where they may contribute to Type-2 diabetes [47]. Amyloid deposits in the brain are associated with Alzheimer disease and whether this pathogenic process can be arrested by IL-1-blocking therapies in this disease has been proposed [163].

10.3. Recurrent pericarditis

Although patients with AOSD and also other autoinflammatory diseases will have manifestation of pericarditis that is resolved with anakinra, canakinumab or rilonacept, idiopathic recurrent pericarditis is also responsive to anakinra [121–123,164–167].

10.4. Multiple sclerosis and neuromyelitis optica

Patients being treated with TNFα blockers may have clinical and magnetic resonance imaging (MRI) evidence of brain demyelinization or exacerbations of existing multiple

sclerosis (MS) [168]. The FDA requires labels for all TNFα blockers state the risk. Is anakinra treatment also a risk for MS or demyelinization? In a cohort of 104,000 patients with rheumatoid arthritis (87% females), those patients without a history of MS or optic neuritis who were treated with anti-TNFα agents revealed an adjusted rate ratio of 1.31 whereas those treated with anakinra had a rate of 0.80 [169]. Levels above 1.0 indicate more disease whereas levels below 1.0 indicate less disease. The lower disease level of anakinra is consistent with preclinical reports of a protective effect of IL-1 blockade in mice exposed to allergic autoimmune encephalitis, the model for MS. Also, interferon-β (IFNβ), widely used to treat MS, induces IL-1Ra in microglia and IL-1Ra levels are increased in the serum of progressive MS patients during IFNβ therapy. Thus, there is a clear rationale for a trial of anakinra in MS, optic neuritis and neuromyelitis optica, which is a severe form of optic neuritis.

10.5. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive loss of motor neurons resulting in death within a few years following diagnosis. The pathogenesis of ALS is associated with mutations in superoxide dismutase-1 (SOD1), in which a malfolding of this protein results in increased neuroinflammation. In a mouse model of mutant SOD1 as well as in ALS patients, IL-1β levels are elevated [170]. Deficiency in caspase-1 or IL-1β or treatment with anakinra extended the lifespan of the SOD1 transgenic mice and attenuated inflammatory pathology [170]. There is a case report of a patient being treated with anakinra for acquired cold urticaria in which improvement in the early manifestations of ALS was observed [171]. Therefore, there is a rationale for treating ALS with IL-1β blockade [172]. A trial is underway using anakinra to treat ALS patients early in the course of their disease.

10.6. Inflammation in the demise of hemodialysis

A role for IL-1 in the systemic and local inflammation of hemodialysis has been a topic of many studies [173]. Patients with endstage renal disease on maintenance hemodialysis have increased risk of all cause mortality as serum albumin levels fall. In a randomized, placebo controlled trial of 4 weeks of anakinra in these patients, there was a 23% increase in mean albumin compared with 6% in the placebo arm [174]. In addition, markers of systemic inflammation such as CRP and IL-6 fell significantly [174]. Extending the duration of IL-1 blockade would assess whether treatment improves survival.

11. Anti-IL-1α

The monoclonal antibody against IL-1α is being tested in Type 2 diabetes, cancer, cancer cachexia, leukemia, psoriasis, vascular disease and scarring acne vulgaris. Indeed, inflammation resulting from ischemic damage starts with the release of the IL-1α precursor from dying cells. The IL-1α is active (Fig. 2) but as the inflammation progresses, IL-1β becomes the dominant cytokine the process becomes an IL-1β-mediated process. Due to its specificity and long half-life, neutralization of IL-1β is emerging an optimal agent for some diseases such as in the CANTOS trial; nevertheless, there are specific disease conditions in which anakinra, particularly given intravenously, provides an optimal therapy for some diseases. In fact, intravenous anakinra is the preferred IL-1 blocking therapy in acute conditions such as MAS due to its ability to prevent either IL-1α or IL-1β activity, its long history of safety even at doses 100–1000-fold higher that the subcutaneous dose, and upon stoppage, blood levels fall within hours, providing another aspect for safety.

12. Smoldering/indolent myeloma

In the microenvironment of the bone marrow, IL-1β produced by myeloma precursor plasma cells stimulates the stromal cells to release large amounts of IL-6, which in turn promotes

the survival and expansion of the pre-myeloma cells [175]. It was reasoned that in the indolent stages of multiple myeloma, blocking IL-1β would reduce IL-6 activity [176]. Patients with smoldering or indolent myeloma at high risk for progression to multiple myeloma were selected with the clinical objective of slowing or preventing progression to active disease. During 6 months of treatment with anakinra, there were decreases in CRP in most but not all patients, which paralleled a decrease in myeloma cell proliferation. After 6 months of anakinra, a low dose of dexamethasone was added. Of the 47 patients that received anakinra with dexamethasone, progression-free disease was over three years and in 8 patients over 4 years [176]. Compared to historical experience, the findings indicate a significant failure to progress to active disease. Given the increasing incidence of multiple myeloma in the aging population, an option of anti-IL-1β as an early intervention treatment in the indolent stages of multiple myeloma might have a significant impact on this fatal cancer.

13. Safety issues with IL-1 blockade

13.1. IL-1 and host defense against infection

Since its introduction in 2002, anakinra has had a remarkable record of safety [61,177]. It is estimated that over 150,000 patients have received anakinra, some treated daily for over 10 years. Anakinra has been administered to patients with active infections [178,179]. Following the introduction of anti-TNFα blocking therapies, a wide-spectrum of opportunistic infections were reported, similar to those observed in immunosuppressed persons. Host defense against opportunistic organisms as well as routine bacterial infections have since become a major concern for all anti-cytokine agents because of the indolent and dangerous nature of these infections. Reactivation of latent *Mycobacterium tuberculosis* in patients receiving anti-TNFα therapies can be 25-times higher than in untreated persons [180] and is often the disseminated form, similar to that observed in HIV-1 infected patients. *M. tuberculosis* also occurs in patients treated with TNFβ blockers without evidence of prior exposure to the organism. In contrast, opportunistic infections in patients treated with anakinra are rare [181], including populations at high risk for reactivation of *M. tuberculosis* infections [182]. There is a single case report of a 77 year old man with severe rheumatoid arthritis and a history of pulmonary tuberculosis who developed reactivation 23 months after starting anakinra [183]. Despite tuberculin testing each patient before beginning any anti-cytokine for previous exposure to *M. tuberculosis*, reactivation continues to occur in patients and can be as high as 9.3% with the notable exception of anakinra [184].

During controlled trials of anakinra, canakinumab and rilonacept, there were more viral-type upper airway infections compared to placebo-treated patients but these type infections are also reported for all biologics. Although these upper airway infections are not life-threatening, bacterial infection with organisms such as *Streptococcus pneumoniae* and *Staphylococcus aureus* are of concern in any patient receiving a biologic. However, in hidradenitis suppurativa with skin flora of *S. aureus*-infected apocrine glands, anakinra treatment resolves the inflammatory nature of the disease without increasing the infection [146,185–187]. Also in patients with chronic granulomatous disease, a inherited condition with multiple bouts of infections with Gram-positive and Gram-negative bacteria as well as fungi, treatment with anakinra reduces the severity of inflammatory bowel disease and granulomas associated with the disease without increased infection [178]. Although use of anti-IL-1β monoclonal antibodies and the soluble IL-1 receptor rilonacept are relatively recent compared to the experience with anakinra, there has been no unexpected increase in infections.

13.2. Effects of IL-1 on hematopoiesis

One of the more salient properties of IL-1 is its ability to increase circulating neutrophil numbers (reviewed in [188]). Only 3 ng/kg of IL-1β injected into humans results in a neutrophilia [189]. To shorten the nadir in neutrophils following chemotherapy for bone marrow transplantation, low doses of either IL-1α or IL-1β were administered as hematopoietic factors; increased neutrophilic responses were consistently reported (reviewed in [188]). Neutrophilia is perhaps the most characteristic findings in many IL-1-mediated inflammatory diseases, particularly in autoinflammatory diseases. Thus, a response to IL-1 blockade is usually heralded by a mild to modest reduction in circulating neutrophils, rarely falls below the normal range, is an indication of efficacy, not bone-marrow suppression. In healthy subjects, intravenous infusions of anakinra at 10 mg/kg did not affect peripheral neutrophil counts [190]. Sustained neutropenia is not observed and neutrophils rapidly rise upon cessation of treatment [85].

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Abbreviations

FMF	familial Mediterranean fever
FCAS	familial cold autoinflammatory syndrome
NOMID	neonatal onset multi-inflammatory diseases
CAPS	cryopyrin autoinflammatory periodic syndromes
TRAPS	TNF receptor associated periodic syndrome
HIDS	hyper IgD syndrome
PAPA	pyogenic arthritis, pyoderma gangrenosum, and acne
DIRA	deficiency of IL-1Ra
SAPHO	synovitis, acne, pustulosis, hyperostosis and osteitis
PASH	pyoderma-gangrenosum, acne, and suppurativa hidradenitis
PFAPA	periodic fever, aphthous stomatitis, pharyngitis, and adenitis
SJIA	systemic-onset juvenile idiopathic arthritis
NLRP3	nucleotide-binding domain and leucine-rich repeat pyrin containing 3
NLRP12	nucleotide-binding domain and leucine-rich repeat pyrin containing 12
AOSD	adult onset Still’s disease
CRP	C-reactive protein

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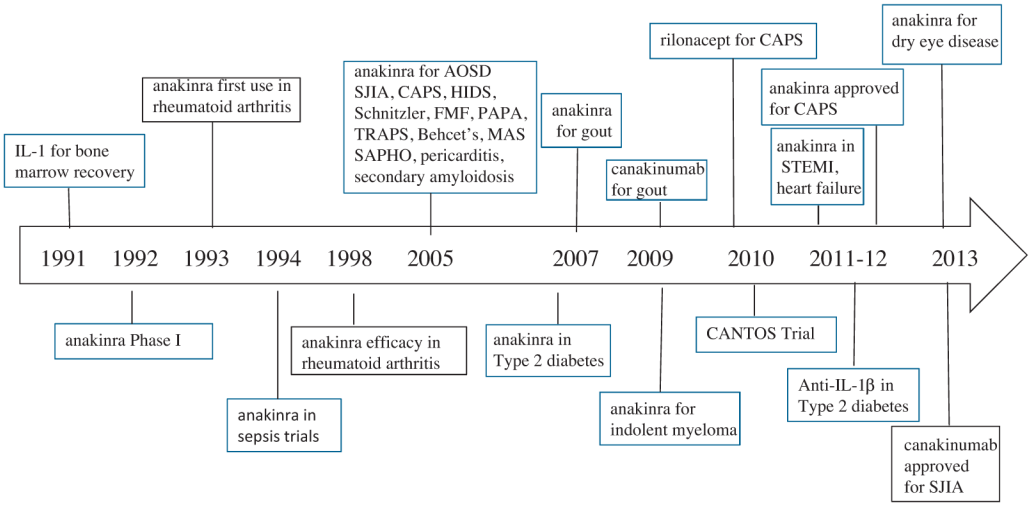

Fig. 1.

Time line for milestones in clinical applications with IL-1 blocking therapeutics. HIDS, hyper IgD syndrome; CAPS, cryopyrin associated periodic syndromes; FMF, familial Mediterranean fever; TRAPS, TNF receptor associated periodic syndrome; MWS, Muckle–Wells syndrome; AOSD, adult onset Still disease; SJIA, systemic juvenile idiopathic arthritis; STEMI, ST segment elevated my myocardial infarction.

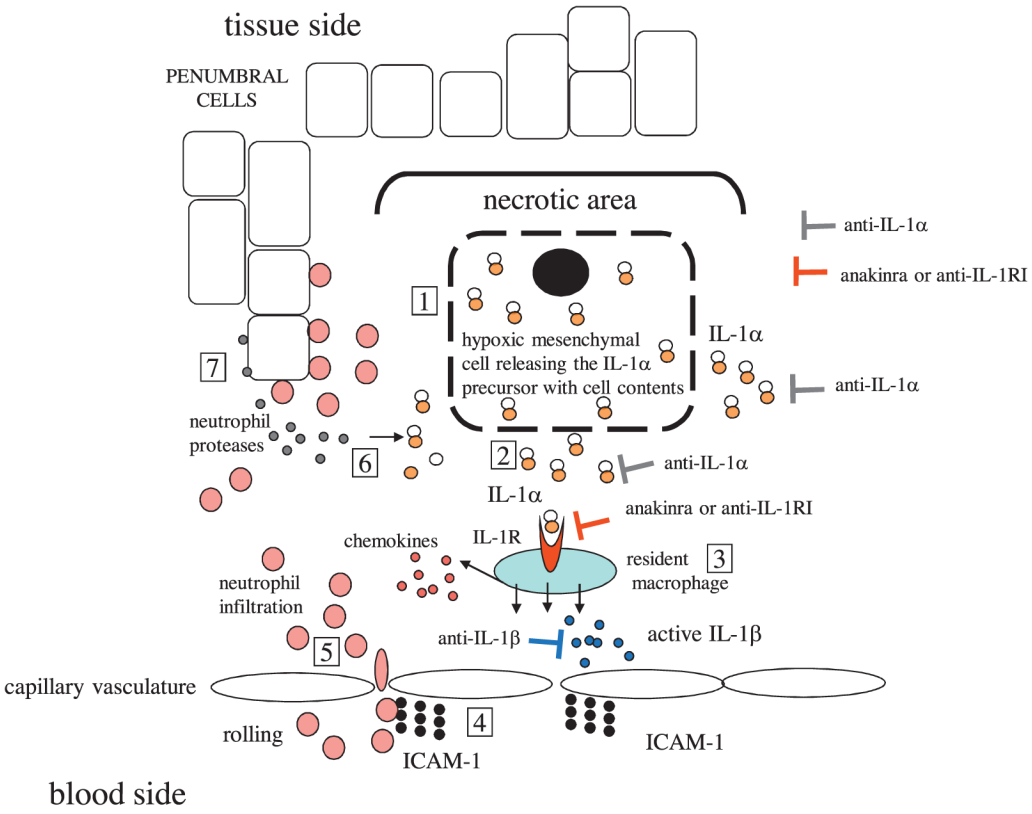

Fig. 2.

Role of IL-1α and IL-1β in sterile inflammation. Event **1**. With hypoxic damage in the necrotic area, dying cells loose membrane integrity. Event **2**. With cellular necrosis, cell contents are released including the active IL-1α precursor [354]. Anti-IL-1α antibodies neutralize IL-1α at this step. Event **3**. The IL-1α precursor binds to IL-1R1 on nearby resident macrophages; anakinra and anti-IL-1R1 antibodies prevent this event. With binding of the IL-1α precursor to the IL-1R1, synthesis of IL-1β precursor takes place, caspase-1 cleaves the precursor releasing active IL-1β. Anti-IL-1β blocks at this step. Triggered by IL-1α binding to the IL-1R1 on resident macrophages, chemokines are also released. Event **4**. IL-1β activates capillaries in the ischemic tissues to express the intracellular adhesion molecule-1 (ICAM-1). Circulating blood neutrophils roll on the endothelium, adhere to ICAM-1 and enter the ischemic tissue via diapedesis [6]. Anakinra or anti-IL-1R1 prevents this event. Event **5**. With resident macrophages releasing chemokines, a chemokine gradient forms, which facilitates the passage to blood neutrophils into the ischemic area. Event **6**. The number of neutrophils increases into the area of the ischemic event and local IL-1 prolongs the survival of neutrophils at this step. Event **7**. Neutrophils scavenge dying cells and release proteases that contribute the destruction of penumbral cells.

Table 1

Anakinra treatment for joint, bone and muscle diseases.

Rheumatoid arthritis	[62–65,181,182,191–205]
Psoriatic arthritis	[206,207]
Osteoarthritis	[83,84]
Erosive osteoarthritis of the hand	[82]
Arthrofibrosis/traumatic knee injury	[208,209]
Anterior cruciate knee ligament tear	[210]
Relapsing polychondritis	[211–213]
chronic recurrent multifocal osteomyelitis	[214,215]
Ankylosing spondylitis	[216–218]
Gout and pseudogout	[69–72,74,77,219–221]
Calcium pyrophosphate arthritis	[222–224]
Gout of the lumbar spine	[225]
Antisynthetase syndrome	[140]
Idiopathic inflammatory myopathies	[226]
Hemochromatosis-related arthritis of the hands	[227]

Table 2

Hereditary systemic inflammatory diseases treated with anakinra.

Familial Mediterranean fever (FMF)	[87–93,160,228–232]
FCAS	[107,233] [234]
Muckle–Wells syndrome	[14,115,124,235–241]
NLRP12 autoinflammatory syndrome	[242]
NOMID	[14,15,39,151–153,243–245]
TRAPS	[118–121,246–248]
HIDS	[96,98–100,102,249]
PAPA	[147,185,250–254]
PASH	[185,255]
DIRA	[1,2,256]
Blau syndrome/granulomatous arthritis	[257,258]
Mevalonate kinase deficiency	[259]
Majeed syndrome	[260,261]

Table 3

Systemic and local inflammatory diseases.

Schnitzler syndrome	[134,135,138,262–273]
Behçet disease	[140,160,274]
secondary amyloidosis	[89,91,124,138,154,159–162,275]
Henoch–Schonlein purpura	[276]
Idiopathic recurrent pericarditis	[121–124,164,165,167]
Systemic-onset juvenile idiopathic arthritis	[13,16,126,151,153,154,277–279]
Adult onset Still disease	[127–131,280–297]
Macrophage activation syndrome	[298–307]
Sweet's syndrome/neutrophilic dermatoses	[147,308–310]
Neutrophilic panniculitis	[299,301,311]
Erdheim–Chester/histiocytoses	[312–314]
SAPHO	[17,215,315]
PFAPA	[316,317]
Multicentric Castleman disease	[318]
Jessner–Kanof disease	[319]
Primary Sjoegren syndrome fatigue	[54]
Kawasaki disease	[320]
Colitis in chronic granulomatous disease	[178]

Table 4

Common diseases (non-arthritic) responsive to anakinra.

Post-myocardial infarction cardiac remodeling	[28,29]
Systolic heart failure	[30]
Diastolic heart failure	[34]
Smoldering myeloma	[176]
Cerebrovascular accident	[26]
Hidradenitis suppurativa	[146,185–187]
Type 2 diabetes	[48,49]
Type 1 diabetes	[37]
Metabolic syndrome	[44]
Giant cell arteritis	[143]
Dry eye disease	[142]

Table 5

Treatment of inflammatory diseases with anti-IL-1β monoclonal antibodies.

	References
Canakinumab	
Rheumatoid arthritis	[68,321]
Type 2 diabetes	[60,322,323]
SJIA	[133,324]
Refractory gout	[73,78,79,325]
FMF	[231,326,327]
TRAPS	[328]
Behcet's	[329,330]
CAPS	[111–113,155,331–333]
Schnitzler's syndrome	[334,335]
AOSD	[336]
MKD	[337]
PAPA	[338]
Majeed syndrome	[260]
Blau syndrome	[339]
HIDS	[340]
Gevokizumab	
Type 2 diabetes	[50]
Behcet's disease	[141]
Fatigue in Type 2 diabetes	[53]
LY2189102	[52]

Table 6

Rilonacept therapies for inflammatory diseases.

Condition	References
CAPS	[341–343]
FMF	[108,344–347]
Schnitzler's syndrome	[348]
SJIA	[349]
Gout	[75,350–352]
AOSD	[353]