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Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases

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Abstract

Interleukin-1 (IL-1) is a highly active pro-inflammatory cytokine that lowers pain thresholds and damages tissues. Monotherapy blocking IL-1 activity in autoinflammatory syndromes results in a rapid and sustained reduction in disease severity, including reversal of inflammation-mediated loss of sight, hearing and organ function. This approach can therefore be effective in treating common conditions such as post-infarction heart failure, and trials targeting a broad spectrum of new indications are underway. So far, three IL-1-targeted agents have been approved: the IL-1 receptor antagonist anakinra, the soluble decoy receptor rilonacept and the neutralizing monoclonal anti-IL-1β antibody canakinumab. In addition, a monoclonal antibody directed against the IL-1 receptor and a neutralizing anti-IL-1α antibody are in clinical trials.

Most human disease is due to chronic inflammation resulting in loss of function of a joint, a blood vessel or an entire organ. In some organs, such as the heart and brain, acute inflammation can be fatal. Interleukin-1 (IL-1) is a master cytokine of local and systemic inflammation, and the availability of specific IL-1-targeting agents has revealed a pathological role of IL-1-mediated inflammation in a growing list of diseases.

There are two related but distinct IL-1 genes, *IL1A* and *IL1B*, encoding IL-1α and IL-1β, respectively. Each IL-1 binds to the same cell surface receptor, termed IL-1 receptor type 1 (IL-1RI), which is present on nearly all cells. Once bound to its receptor, IL-1 triggers a cascade of inflammatory mediators, chemokines and other cytokines. We have learned much about IL-1-mediated inflammation from studies of individuals who were injected with low nanogram doses of either IL-1α or IL-1β[1]. Although IL-1 was administered to patients to improve bone marrow function, these patients experienced unacceptable toxicity with fever, loss of appetite, generalized muscle and joint aches, fatigue, as well as gastrointestinal and sleep disturbances; hypotension also occurred[1]. Thus it was not unexpected that specific pharmacological blockade of IL-1 activity in inflammatory diseases would be beneficial.

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Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION
ClinicalTrials.gov website: http://clinicaltrials.gov
SUPPLEMENTARY INFORMATION
See online article: S1 (table)
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Targeting IL-1 began in 1993 with the introduction of anakinra (Kineret; Amgen) (TIMELINE), a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra), which blocks the activity of both IL-1α and IL-1β; this therapeutic has since been used to demonstrate a role for IL-1 in numerous diseases (BOX 1; Supplementary information S1 (table)). Anakinra currently dominates the field of IL-1 therapeutics owing to its excellent safety record, short half-life and multiple routes of administration. Neutralizing IL-1 with antibodies or soluble receptors has also proved to be effective (TABLE 1), and the soluble decoy receptor rilonacept (Arcalyst; Regeneron) and the anti-IL-1β neutralizing monoclonal antibody canakinumab (Ilaris; Novartis) have now been approved. Other therapeutic approaches, including IL-1α neutralization, a therapeutic vaccine targeting IL-1β and a chimeric IL-1Ra, are in early clinical trials (TABLE 1). In addition, orally active small-molecule inhibitors of IL-1 production, such as caspase 1 inhibitors, have been developed and are being tested[2,3].

Box 1

Examples of conditions treated with IL-1 blockade

Joint, bone and muscle diseases*

- Rheumatoid arthritis; ankylosing spondylitis
- Erosive osteoarthritis of the hand
- Recurrent multifocal osteomyelitis
- Traumatic knee injury; relapsing polychondritis

Hereditary systemic autoinflammatory diseases*‡

- Familial Mediterranean fever (FMF)
- Cryopyrin-associated periodic syndrome (CAPS)
- TNF receptor-associated periodic syndrome (TRAPS)
- Hyper-IgD syndrome (HIDS)
- Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA)
- Deficiency of interleukin-1 (IL-1) receptor antagonist (DIRA)

Systemic inflammatory diseases*

- Systemic juvenile idiopathic arthritis
- Adult-onset Still’s disease
- Schnitzler syndrome
- Behcet’s disease
- PFAPA
- SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome
- Macrophage activation syndrome

Common inflammatory diseases*

- Gout; pseudogout
- Type 2 diabetes
- Hidradenitis suppurativa

- Systolic heart failure; cardiac remodelling
- Dry eye syndrome
- Pustular psoriasis; neutrophilic dermatoses

* See Supplementary information S1 for a referenced and expanded list. ‡ See TABLE 2.

By specifically blocking IL-1, we have learned a great deal about the role of this cytokine in inflammation and, equally importantly, reducing IL-1 activity has lifted the burden of a broad spectrum of inflammatory diseases for many patients[4]. Furthermore, blocking IL-1 activity has provided proof of concept for diseases that were not considered to be inflammatory, such as type 2 diabetes[5], heart failure[6,7] and loss of hearing[4,8–11]. The largest randomized, placebo-controlled trial ever designed in anti-cytokine therapeutics is presently underway: the CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study), which is evaluating whether IL-1β neutralization will reduce the risk of myocardial infarction, stroke and cardiovascular deaths in high-risk patients[12]. In addition, two large trials of IL-1 blockade in type 1 diabetes, one with anakinra and the other with canakinumab, are nearing completion. In this Review, we examine the diseases for which IL-1 blockade has become the standard of therapy, and also examine the rationale for ongoing trials.

IL-1 synthesis, processing and release

IL-1α

The IL-1α precursor is constitutively present in the cells of healthy individuals. 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 IL-1α precursor is found within the entire endothelium of the vasculature, as well as in membrane fragments termed ‘apoptotic bodies’[13]. These membrane fragments are active in inducing neutrophil infiltration[13] in several inflammatory conditions of the blood vessels, termed vasculitis[14]. As the IL-1α precursor is active, the presence of IL-1α in health is like a loaded gun. Under disease conditions, IL-1α moves to the cell’s surface membrane where it can activate adjacent cells bearing the IL-1 receptor[15,16]. During ischaemia, however, cell death by necrosis takes place and the IL-1α precursor is released[17–19]. This is the first step in sterile inflammation (FIG. 1) and therefore IL-1α is sometimes classified as an alarmin, requiring no time for synthesis and being ready to function as soon as it leaves the dying cell in the first few hours following an ischaemic or injurious event. This early ischaemic inflammation is dominated by neutrophil accumulation at the site of injury. As shown in FIG. 1, IL-1 orchestrates several pathways involved in the destructive actions of the invading neutrophil, also extending neutrophil survival[20]. As shown in FIG. 2, resident tissue macrophages and infiltrating blood monocytes become the prominent cells in the inflammatory process and account for the role of IL-1β in the days following the ischaemic event.

IL-1β

In contrast to IL-1α, IL-1β is not present in cells from healthy individuals and requires a series of intracellular events before the cytokine can trigger inflammation. IL-1β is a product of a limited number of cells, such as blood monocytes, tissue macrophages and dendritic cells. The rate-limiting step in the production of IL-1β is its transcription. The stimulus can be a microbial product but cytokines such as tumour necrosis factor (TNF), IL-18, IL-1α or IL-1β itself can induce IL-1β transcription[21]. In fact, IL-1 self-induction is part of the mechanism of autoinflammation. The IL-1β precursor is inactive (FIG. 2), requiring intracellular cleavage by caspase 1, a cysteine protease. Caspase 1 itself requires activation,

which occurs following the assembly of a complex of intracellular proteins termed the inflammasome[22,23], the components of which were characterized by the late Juerg Tschopp. Once activated by the inflammasome, caspase 1 processes IL-1β, removing the amino-terminal amino acids to release mature, active IL-1β.

IL-1 in disease

Criteria for IL-1-mediated disease

The best evidence for a pathological role of either IL-1α or IL-1β in a disease comes from specific blockade of IL-1 activity, as correlations of the levels of any cytokine with disease severity do not establish causality. Even in the most severe IL-1-mediated inflammatory diseases, IL-1β levels in the circulation increase only fivefold[24], and IL-1α — being intracellular or part of cell membranes — is usually not measurable in the circulation. Even with low levels (pg per ml) of IL-1β, impressive clinical responses with anakinra, rilonacept or canakinumab have been reported in several diseases.

The importance of IL-1 as a master cytokine in inflammation has also been demonstrated by studies of infants born with a loss-of-function mutation in the naturally occurring endogenous IL-1Ra. These infants succumb early in life to overwhelming sterile inflammation of the skin, joints and bone, with large numbers of infiltrating neutrophils and high levels of IL-17 (REFS 25,26). The condition is called deficiency of interleukin-1 receptor antagonist (DIRA), and daily treatment with anakinra rapidly reverses the inflammation and prevents a lethal outcome. Although DIRA is an extreme example of reduced levels of functional endogenous IL-1Ra, mutations in the promoter of IL-1Ra are associated with decreased serum levels and an increased risk of type 2 diabetes[27].

Autoinflammatory and autoimmune disease

Autoinflammatory disease can be defined as increased inflammation that is mediated predominantly by cytokines of the innate immune system, particularly IL-1β, without the presence of — or association with — autoantibodies or autoreactive T lymphocytes but with a significant host predisposition[28]. In autoimmune diseases the defect seems to be more pronounced in the adaptive immune system than in the innate immune system. However, given the various interactions and similarities between the innate and adaptive immune systems, they cannot be viewed as completely separate entities but more as two ends of a continuum of inflammatory and immunological diseases. In autoimmune diseases, blocking TNF can be highly effective (TABLE 2). In autoinflammatory diseases, however, neutralization of TNF is not effective (such as in gout), and in some cases it can even exacerbate the condition. In autoinflammatory diseases, the release of IL-1β from monocytes is often elevated, but in the same cells the production of TNF is not different from that of healthy controls. As shown in TABLE 2, there are several therapeutic options for the treatment of autoimmune diseases. There have been no trials of IL-1 blockade for the treatment of Crohn’s disease, psoriasis or multiple sclerosis, although preclinical studies do suggest a role of this cytokine in these diseases.

Classic autoinflammatory diseases

Classic autoinflammatory diseases are chronic, debilitating syndromes[29]. They are rare genetic disorders but the clinical inflammatory manifestations as well as the haematological and metabolic abnormalities are common to most inflammatory diseases and are characterized by recurrent episodes of systemic and local inflammation. The frequency, duration and severity of these episodes vary; in some cases the inflammatory episodes seem almost continuous but the attacks can often resolve spontaneously only to reoccur a few weeks or several months later. Typically, patients suffer from recurrent fevers, generalized

fatigue, diffuse pains in the muscles and joints, inflammation in the lining of the lungs and peritoneal cavity, loss of appetite and poor sleep. Symptoms also include gastrointestinal disturbances and skin rashes. Neutrophilia and elevated levels of acute-phase proteins are present during the episodes.

What accounts for the inflammation? Blood monocytes from patients with autoinflammatory diseases release more IL-1β than cells from healthy individuals[8,30–34]. Some autoinflammatory conditions are hereditary and due to mutations in the intracellular proteins that control caspase 1, the enzyme that converts IL-1β into an active cytokine before its release from the cell. With increased secretion of IL-1β, there is greater inflammation.

Familial mediterranean fever

Familial Mediterranean fever (FMF) is perhaps the most well-known autoinflammatory disease. Starting in childhood or adolescence, patients with FMF suffer lifelong, recurrent bouts of fevers and pain in the lining of the abdomen. This pain mimics acute appendicitis and most patients have had abdominal surgery before FMF is diagnosed. The genetic mutation was identified in the Mediterranean fever (*MEFV*) gene, a previously unknown gene encoding a protein that was given the name pyrin (derived from the Greek word ‘pyr’ for fire)[35]. The term pyrexia is sometimes used to describe the fever observed in FMF. A French consortium suggested the name ‘marenostrin’ because most patients with FMF are from the Mediterranean region, but the term pyrin is now accepted. Wild-type pyrin is required to keep a tight control over the activation of caspase 1 as well as the processing and release of active IL-1β, whereas a mutation in pyrin results in a loss of this control, thus leading to greater release of IL-1β[36].

Cryopyrin-associated periodic syndrome

In patients with cryopyrin-associated periodic syndrome (CAPS), single-amino- acid mutations are found in a protein that was originally called cryopyrin[37]; the clinical manifestations of the disease are triggered by exposure to cold temperatures, hence the term ‘cryo’. Following exposure to cold temperatures, even air-conditioned rooms, patients develop fever and systemic symptoms (resembling FMF); the causative protein had already been called pyrin, hence the protein was renamed cryopyrin. The commonly used term for the protein is NLRP3 but the name cryopyrin remains in use. Before mutation analysis was available, three clinical variants of disease manifestations were recognized: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome and neonatal-onset multisystem inflammatory disease (NOMID; also called chronic infantile neurologic cutaneous and articular syndrome). It is now clear that CAPS is a continuum of diseases, with severity ranging from the mildest form (FCAS) to the most severe (NOMID), and with overlap between the clinical phenotypes. In Muckle–Wells syndrome, patients develop progressive loss of hearing and lose kidney function owing to secondary amyloidosis. Children with NOMID suffer from total body rashes, destruction of the joints, hearing loss and chronic sterile inflammation in the brain. In fact, these children are thought to have learning and emotional problems, which resolve with IL-1 blockade[4,8].

TNF receptor-associated periodic syndrome

TNF receptor-associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by mutations in TNF receptor type 1 (TNFR1; also known as TNFRSF1A)[38]. The mutations result in an inability of the receptor to be inserted normally into the cell membrane, which is at first sight contradictory with an inflammatory phenotype. Research so far has shown that the mutated receptor accumulates inside the cells, which causes increased synthesis of IL-1 through increased activation of reactive oxygen species and possibly other pathways[39,40]. Patients experience recurrent bouts of fever with local and

systemic inflammation, which was initially thought to be due to a lack of circulating soluble TNF receptors but has now been shown to be mediated by IL-1.

Hyper-IgD Syndrome

Hyper-IgD syndrome (HIDS) is a genetic (autosomal recessive) autoinflammatory disorder characterized by 4 to 6 days of fever, muscle aches, a skin rash, painful mouth ulcers and swollen lymph nodes. The disease is caused by mutations in the enzyme mevalonate kinase, resulting in mevalonate kinase deficiency. Several intracellular pathways of protein modification have linked mevalonate kinase deficiency to the control of IL-1 production[41], including activation of caspase 1 (REF. 42). Mevalonate kinase deficiency *per se* is linked to a phenotypic continuum of disease, ranging from isolated fever episodes (that is, HIDS) to a more severe phenotype of fever episodes in combination with cerebellar ataxia, learning disabilities, anaemia, liver damage and developmental delay, which can result in early death.

IL-1-mediated inflammatory conditions

Acute-onset ischaemic diseases

IL-1-mediated inflammation contributes to the catastrophic events of acute ischaemic diseases. These include myocardial infarction, stroke, liver and kidney failure as well as acute lung injury, each with rapid loss of function. In the case of myocardial infarction and thrombotic stroke, the ischaemic event is triggered by a sudden blockage of a blood vessel owing to the formation of a clot initiated by an atherosclerotic plaque rupture. The blockage results in poor supply of oxygen (hypoxia) and death of the cells supplied by the blood vessel (FIGS 1,2). Death of heart muscle can be fatal, and death of brain cells results in loss of motor skills as well as cognitive functions. In the case of acute kidney failure and acute lung injury, the hypoxic event can be due to an episode of extremely low blood pressure: for example, resulting from a large loss of blood from multiple trauma. Loss of lung function may be fatal, and loss of kidney function requires dialysis. Acute toxic effects take place in liver failure caused by alcohol poisoning or overdosing of acetaminophen.

There are many animal studies demonstrating an essential role for IL-1 following ischaemic injury of the heart[43], lung[44], liver[45], kidney[46] and brain[47]. Inflammation following an ischaemic event is characterized first by infiltration of neutrophils, followed by accumulation of myeloid precursors into the surrounding ischaemic area, often termed the penumbra (FIGS 1,2). 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 tissue and loss of function; however, the cells in the penumbra of inflammation are salvageable.

Heart remodelling following ST segment elevation myocardial infarction

Patients who have had an acute myocardial infarction, which is characterized by an elevation of the ST segment on the electrocardiogram (known as ST segment elevation myocardial infarction; STEMI), have a high risk of death owing to an extensive area of heart muscle damage. With modern emergency approaches to re-establish the patency of the blocked coronary artery, more patients survive after STEMI, but in the weeks and months that follow, some patients progress to heart failure owing to loss of viable heart muscle from the infarction and enlargement of the heart. Patients are also at a high risk of a second heart attack. IL-1-induced inflammation has a role in this process, as blocking IL-1 in animal models of acute myocardial infarction improves heart function in comparison with untreated animals[43,48]. The subsequent heart failure that develops can be debilitating even with the optimal therapies presently used.

Chronic heart failure has reached epidemic levels owing to the increase in cardiovascular events associated with the growing prevalence of type 2 diabetes. The physiological effect of IL-1 on the heart is twofold: first, IL-1 weakens the heart by directly suppressing the contractile force of cardiac muscle; second, IL-1-mediated inflammation in the heart attracts IL-1-producing cells from the bone marrow, which produce IL-1 and other inflammatory mediators contributing to cell death of cardiac muscle. The plasma from patients with modest to severe heart failure contains biologically active IL-1, as injection of the plasma into healthy mice results in suppression of the contractile force of the mouse heart[7].

Diabetes

There are two types of diabetes: type 1 diabetes is an autoimmune disease driven by T lymphocytes that kill the insulin-producing cells, resulting in the necessity of daily injections of insulin. In type 2 diabetes, obesity and inactivity lead to insulin resistance, with secondary failure of the insulin-producing β-cells to adapt to the increased insulin demand. In both types of diabetes, very low (picomolar) concentrations of IL-1β have been shown to be selectively toxic for insulin-producing pancreatic β-cells (reviewed in REF. 49).

High glucose concentrations stimulate IL-1β production from the β-cell itself[50], thus implicating a selfdestructive role for IL-1β autoinflammation by the β-cell and the recruitment of immune cells via IL-1β-driven chemokines (reviewed in REF. 51). Moreover, the deposits of islet amyloid may activate IL-1β production from infiltrating blood monocytes, which contributes further to β-cell loss[52]. Furthermore, steady-state levels of *IL1B* mRNA are 100-fold higher in β-cells of patients with type 2 diabetes[51] compared to non-diabetic individuals. The IL-1β can come from the β-cell itself, but it can also come from blood monocytes that infiltrate the islet. Obesity is a high risk factor for type 2 diabetes, and caspase 1-dependent IL-1β production has been demonstrated in macrophages isolated from human adipose tissue[53]. Others have reported similar data on the role of caspase 1-dependent IL-1β production in adipose tissue[54]. In diabetic mice, administration of a caspase 1 inhibitor reduces insulin resistance, and mice deficient in caspase 1 exhibit improved insulin sensitivity[53]. IL-1α and IL-1β exert the same toxic effects on insulin-producing β-cells and it is unclear to what extent IL-1α has a role in patients with type 2 diabetes. Thus, type 2 diabetes is characterized by progressive loss of β-cells owing to IL-1-mediated inflammation, which may also underlie the mechanism of insulin resistance[55].

Gout and pseudogout

Although gout is caused by the formation of crystals of uric acid in the joints, pseudogout is due to the deposition of phosphate crystals. Both conditions are inflammatory diseases of the joints, which become swollen, warm and painful. The inflammation is due to the accumulation of large numbers of neutrophils in the joint space. *In vitro* studies indicate that uric acid crystals stimulate IL-1β production but on closer examination fatty acids are also required. The ability of fatty acids to augment the uric-acid-mediated production of IL-1β is consistent with the well-known association of overnutrition with gout[56].

Osteoarthritis

In animal models of osteoarthritis as well as *in vitro* studies on human chondrocytes (cartilageproducing cells), IL-1β results in reduced synthesis of proteoglycan, which comprises the flexible matrix of cartilage. In addition, IL-1 induces the synthesis of matrix metalloproteinases and the release of nitric oxide, both of which contribute to the loss of functional cartilage (reviewed in REF. 57). This concept has been confirmed in *ex vivo* studies in human cartilage explants[58]. Blocking IL-1β reduces the destructive processes of cartilage in mice, rabbits, pigs, dogs and particularly in horses.

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease, but like all autoimmune diseases there is an inflammatory component that is driven by IL-1. Blocking IL-1 with anakinra in patients with rheumatoid arthritis reduces the migration of inflammatory cells into the joint[59]. In rheumatoid arthritis there is a progressive loss of cartilage in the joints, resulting in narrowing of the joint space and increased pain due to the loss of a 'cushion' provided by the cartilage. However, after 48 weeks of anakinra treatment, joint damage is considerably reduced[60]. The joint-salvaging properties of IL-1 blockade are also likely to be due to the inhibition of osteoclasts, as osteoclast activating factor was identified as IL-1β[61].

Chronic systemic inflammatory conditions

There are several chronic inflammatory diseases that are refractory to standards of therapy such as glucocorticoids, various immunosuppressive drugs and TNF blockers. A genetic basis for these diseases has yet to be found. Nevertheless, they are responsive to monotherapy with IL-1-blocking agents, often with a rapid and sustained improvement. Adult-onset Still's disease is characterized by recurrent fevers, prominent neutrophilia, rash, systemic inflammation and arthritis with unusually high C-reactive protein (CRP) and ferritin levels. Some patients respond initially to non-steroidal anti-inflammatory drugs (NSAIDs) but then develop resistance to glucocorticoid therapy. Anti-TNF drugs and methotrexate are ineffective. There is a similar disease in children: systemic juvenile idiopathic arthritis (SJIA). Onset can be at a very young age and treatment with glucocorticoids retards normal growth. Another childhood disease, although unrelated, is the syndrome of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA). Treatment varies and includes long-term use of antibiotics, often without any considerable benefit, although tonsillectomy may reduce the frequency of attacks. The cause is unknown but recurrent attacks last throughout childhood, becoming less frequent after puberty. A genetic analysis of PFAPA has not been completed but studies have revealed increased production of IL-1-induced chemokines[62].

Schnitzler syndrome is a debilitating systemic inflammatory disease that is characterized by repeated bouts of fever, chronic skin rash and a gammopathy, which can progress to haematopoietic malignancies. For patients with Schnitzler syndrome, there is an increased risk of developing Waldenström macroglobulinaemia, a dreaded long-term complication. The systemic and local inflammatory manifestations of Schnitzler syndrome can be completely controlled with anakinra[63–67] or canakinumab[68], but it remains unknown whether long-term treatment will prevent the haematological changes. Behçet's disease is another debilitating systemic inflammatory disease that affects nearly all organs and tissues, resulting in inflammation of the blood vessels (vasculitis) and a hypercoagulation state[69]. Patients suffer from oral, gastrointestinal and genital ulcers, but more worrisome is the sight-threatening panuveitis and retinal vasculitis, both of which respond to anti-IL-1β antibody treatment[69].

Another painful disease is idiopathic recurrent pericarditis, which is characterized by chronic substernal chest pain due to inflammation in the pericardium — the fibrous sac that surrounds the heart. Pericarditis develops in some patients following a viral infection and is usually successfully treated with NSAIDs and glucocorticoids. However, not all patients respond to this regimen and some go on to have recurrent bouts of inflammation. Anakinra treatment provides a prompt cessation of symptoms[70].

Macrophage activation syndrome (MAS) is a lifethreatening disease in patients with acute infection of Epstein–Barr virus or cytomegalovirus, but is also observed in patients with lymphoma or lupus[71]. MAS also occurs in patients with SJIA[72]. The disease results in bone

marrow suppression and hepatitis, and is often fatal. The cause is unknown but the rapid reversal of the syndrome in response to intravenous administration of anakinra suggests that IL-1 has a pathological role[73–76].

Therapeutic strategies for IL-1 blockade

Aspirin and NSAIDs such as ibuprofen are the first line of drugs to treat inflammatory conditions but they may be associated with gastrointestinal disturbances and bleeding. Treatment with glucocorticoids such as prednisone is also commonly prescribed for many inflammatory conditions as well as several autoimmune diseases and allograft transplantation, but chronic use is known to result in opportunistic infections, metabolic disturbances, hypertension and loss of bone and skin integrity. Similarly, immunosuppressive therapies, which are often used to treat autoimmune diseases, increase the risk of opportunistic infections as well as cancer. By contrast, if the disease is identified as being responsive to an IL-1-blocking agent, specifically targeting IL-1 can be highly effective without causing gastrointestinal disturbances, opportunistic infections or metabolic derangements. Three IL-1-targeting agents have now been approved and more are being actively pursued (TABLE 1).

Targeting the IL-1 receptor

IL-1Ra

The IL-1 receptor is expressed in nearly all tissues and its antagonism prevents receptor binding of either IL-1α or IL-1β. Anakinra, the recombinant form of the naturally occurring IL-1Ra, was the first selective IL-1Ra to receive approval from the US Food and Drug Administration (FDA). Approved in 2001 to treat rheumatoid arthritis, anakinra has since proved to be efficacious in a broad spectrum of diseases (BOX 1; Supplementary information S1 (table)) and is currently undergoing several clinical trials (TABLE 3). It remains unresolved how much of the efficacy of anakinra is due to the blocking of IL-1α and how much to the blocking of IL-1β. Intravenous administration of anakinra is preferred in acute-onset conditions owing to its ability to prevent either IL-1α or IL-1β activity, its long history of safety even at blood levels 100-fold higher than those achieved following a subcutaneous dose and the fact that blood levels fall within hours of treatment stoppage.

Chimeric IL-1Ra–IL-1β

Eleven Biotherapeutics has developed a chimeric molecule of the natural IL-1Ra with IL-1β, and the initial clinical trial will investigate the topical application of this molecule to treat refractory dry eye syndrome. This syndrome is due to a dysfunction of the meibomian gland, which secretes the oily meibum to prevent the drying of the surface of the eye. Dry eye syndrome disables daily functions such as reading and driving, and is the most common ophthalmic condition in the developed world. Topical application of anakinra is effective[77]. The chimeric IL-1Ra (EPI-005) occupies the IL-1 receptor with a greater affinity and duration than anakinra.

IL-1 receptor-blocking antibody

IL-1 receptor antibodies block IL-1-mediated signal transduction. One such antibody — AMG108 — was tested in patients with rheumatoid arthritis and exhibited excellent safety but was only marginally more effective in relieving symptoms than anakinra. AMG108 — administered parenterally, not intra-articularly — has shown efficacy in the treatment of osteoarthritis[78]. AMG108 was licensed to AstraZeneca and MedImmune, and is now termed MEDI-78998.

IL-1-neutralizing strategies

Soluble IL-1 decoy receptors

Rilonacept is a unique molecule constructed by recombinant technology; the two chains of the IL-1 receptor, which extend outside the cell membrane, are fused to each other, forming a 'trap' that neutralizes either IL-1α or IL-1β. Rilonacept received FDA approval for the treatment of CAPS in 2008 and is currently being investigated in several other indications (TABLE 4).

Anti-IL-1β antibodies

There is a large body of evidence supporting the rationale for specifically targeting IL-1β with neutralizing antibodies so that IL-1α may still participate in host defence. First, IL-1β secreted from the cell is produced at one site and affects tissues at a distant site, whereas IL-1α is not secreted and acts locally. For example, IL-1β produced in adipose tissue in patients with type 2 diabetes is likely to affect insulinproducing cells in the pancreatic islets[53]. Second, blood monocytes from patients with various autoinflammatory diseases release more IL-1β than monocytes from healthy individuals[8,33]. Third, IL-1β induces itself in autoinflammatory diseases and so neutralizing IL-1β reduces the production of IL-1β several weeks after cessation of therapy[21,69]. This has been clinically recognized, with prolonged efficacy extending beyond the presence of the IL-1 blocker[79,80]. Fourth, the amount of IL-1β that is produced or circulates in autoinflammatory diseases is low: for example, in the pg per ml range and only fivefold higher than in healthy individuals[24]. Therefore the dose of antibody needed to treat an IL-1β-mediated disease is low and easy to titrate to each disease. For example, the improvement in glycaemic control with gevokizumab (Xoma; Servier), which lasted for over 90 days, was achieved following a single dose (0.03 mg per kg) of the drug[79].

Owing to its specificity and long half-life, neutralization of IL-1β is emerging as an optimal strategy for some chronic diseases and being tested in several trials (TABLE 5). Canakinumab, which was approved by the FDA in 2009 for the treatment of CAPS, is a human monoclonal antibody that specifically targets IL-1β. Canakinumab is currently in trials for several indications (TABLE 5), including type 1 diabetes and chronic obstructive pulmonary disease. However, the largest trial of any anti-cytokine drug is the CANTOS trial, which is testing whether neutralizing IL-1β will reduce cardiovascular events in high-risk patients. The trial is examining 17,200 individuals using three doses of the antibody in a placebocontrolled, randomized design in 146 centres. The basis for the trial is the observation that CRP levels are reduced following the administration of the IL-1β-neutralizing antibodies canakinumab[81] and gevokizumab[79] in patients with type diabetes who are taking statins. In addition to canakinumab, other anti-IL-1β antibodies, namely gevokizumab and LY2189102, are in multiple clinical trials (TABLE 5).

Anti-IL-1α antibodies

Inflammation resulting from ischaemic damage is likely to be initiated by the release of the IL-1α precursor from dying cells and results in the infiltration of neutrophils at the ischaemic site (FIG. 1). A role for IL-1α in chronic diseases is currently being investigated in several trials (TABLE 5). In most epithelial cell tumours, including breast and lung cancer, IL-1α is present and is released upon cell death. A neutralizing monoclonal IL-1α antibody, MABp1, has been developed by Xbiotech and is currently being tested in type 2 diabetes, advanced cancer, cancer cachexia, leukaemia, severe psoriasis, occlusive vascular disease and scarring acne vulgaris.

Other IL-1-targeting agents

The soluble IL-1RI has been tested in Phase I and Phase II clinical trials in patients with rheumatoid arthritis, graftversus- host disease (GVHD) and HIV-1 infection[82–84]. However, the trials were halted because the expected therapeutic benefit was not observed, as soluble IL-1RI preferentially binds to IL-1Ra and thus creates an iatrogenic reduction in endogenous levels of IL-1Ra.

Therapeutic vaccines that induce the production of endogenous antibodies targeting epitopes on specific endogenous molecules have demonstrated efficacy and safety in humans in several settings. CYT-013 is a novel vaccine targeting IL-1β, for which a Phase I clinical trial has been initiated in patients with type 2 diabetes[83].

Orally active small molecules that target the release of active IL-1β have also been developed, including two caspase 1 inhibitors: pralnacasan (VX-740) and VX-765. As pralnacasan was effective *in vitro* and in several animal models, the drug was tested in a clinical trial in rheumatoid arthritis; however, the outcome of the trial has not been reported. VX-765 has been administered to six patients with Muckle–Wells syndrome, resulting in a 40–70% decrease in markers of inflammation as well as a significant reduction in recurrent fevers and arthritis[85]. VX-765 is being tested in patients with treatmentresistant partial epilepsy, with apparent success. A third trial is underway (Phase IIb; ClinicalTrials.gov identifier: NCT01501383). The rationale for testing a caspase 1 inhibitor in epilepsy is based on studies showing that IL-1 blockade prevents seizures in animal models[86–89].

The activation of caspase 1 by the inflammasome, with the subsequent release of IL-1β, requires a reduction in the levels of potassium inside the cell. This process is controlled by the ATP receptor P2X purinergic receptor 7 (P2X7) and therefore small-molecule inhibitors of P2X7 have been developed and tested in humans. In patients with rheumatoid arthritis, the P2X7 inhibitor AZD9056 resulted in a significant clinical improvement in joint inflammation but there was no reduction in CRP levels[90]. Another P2X7 inhibitor, CE-2245354, has been tested in a Phase IIa trial in rheumatoid arthritis (ClinicalTrials.gov identifier: NCT00628095) but the drug was not effective[91]. Furthermore, GSK1482169 has been investigated in a Phase I trial (ClinicalTrials.gov identifier: NCT00849134) using *ex vivo* release of endotoxin-induced IL-1β from blood obtained from treated healthy individuals[92]. The drug did not suppress IL-1β release unless a large amount of exogenous ATP was added. Overall, oral inhibitors of P2X7 do not seem to be effective in rheumatoid arthritis but it remains unclear whether these inhibitors would be effective in treating IL-1β-driven autoinflammatory diseases such as gout and CAPS.

Clinical trials of IL-1-targeting agents

Stroke

In a randomized, double-blind, placebo-controlled Phase II study of intravenous anakinra (given within 6 hours of onset of ischaemic stroke), clinical scores improved in association with a significant reduction in serum levels of IL-6 and CRP as well as neutrophilia, each of which is known to correlate with poor outcome[93]. In strokes resulting from subarachnoid haemorrhage, a higher dose of intravenously administered anakinra (10 mg per kg per hour) achieved results within 45 minutes[94], with a concentration of the antagonist (in ventricular cerebral spinal fluid) that is neuroprotective in animal models[94]. The higher dose of 10 mg per kg per hour reduced both peripheral and ventricular concentrations of IL-6 in the cerebral spinal fluid, demonstrating an anti-inflammatory effect in the brain. A Phase II study is currently underway to determine whether subcutaneously administered anakinra has a similar effect to intravenously administered anakinra in patients with subarachnoid

haemorrhage. The advantages of subcutaneously administered anakinra include an increased half-life and ease of administration, and it has been used extensively in other conditions.

Anakinra is the optimal IL-1-targeting agent for stroke because of its small size and proven ability to enter the brain and suppress inflammation in patients who have had a stroke[93]. If the Phase II trial of subcutaneously administered anakinra in subarachnoid haemorrhage is shown to reduce the motor and cognitive consequences of brain injury, it would provide an easily administered and safe treatment for acute stroke, which could potentially be started in the ambulance. A Phase II trial has been initiated in diabetic ketoacidosis (diabetic coma) to reduce acute brain swelling. The dose of intravenously administered anakinra in this trial is the same as that used in over 1,200 patients with septic shock[95].

Cardiac remodelling

In the initial trial, patients who had an acute myocardial infarction were treated with the standard of therapy (angioplasty and stent placement) and the following day they were randomized to 14 days of anakinra treatment or placebo. After 12 weeks, left ventricular enlargement in the anakinra group was significantly reduced compared to placebo-treated patients[6] and correlated with reductions in serum levels of CRP. After 18 months, 60% of placebo-treated patients had developed heart failure; by contrast, none of the anakinra-treated patients developed heart failure. A Phase III expanded trial of the same design is underway and expected to be completed in 2012 (TABLE 3).

An open-label trial of anakinra has been completed in patients with poorly compensated heart failure who are receiving the standard of therapy[7]. Entry criteria for this trial were as follows: left ventricular ejection fraction less than 40%, and elevated serum CRP levels greater than 2 mg per l. After 14 days of anakinra treatment (at a dose of 100 mg), cardiopulmonary exercise performance testing was carried out, showing an improvement in peak oxygen consumption and ventilation efficiency; serum levels of CPR decreased by 84%. In addition, serum IL-1β and IL-6 levels fell by 90% and there was a statistically significant reduction in the neutrophil count. There was no effect on serum levels of TNF[7]. These data are similar to those observed in patients with rheumatoid arthritis who were treated for 30 days with anakinra; during this time there was an improvement in the left ventricular function of patients[96]. In a related study, a single subcutaneous dose of anakinra increased blood flow after 3 hours. Overall, these improvements in heart function are also consistent with animal models showing that IL-1 suppresses the myocardium (reviewed in REF. 7). The reduction in levels of IL-1β and IL-6 suggests that poorly compensated systolic heart failure is mediated by IL-1 and falls into the class of autoinflammatory diseases.

A randomized, placebo-controlled Phase II pilot study is underway (TABLE 3) in patients who have heart failure with preserved ejection fraction. After 14 days of either anakinra or placebo, the primary end point will be assessed for peak oxygen consumption compared to the baseline. Secondary end points include exercise performance, cytokine biomarkers and heart failure symptoms.

Type 1 diabetes

Picomolar concentrations of IL-1β have been shown to be selectively toxic for insulin-producing pancreatic β-cells (reviewed in REF. 49); furthermore, in rat and mouse models of spontaneous type 1 diabetes, IL-1 blockade reduced the incidence and severity of the disease[49,97].

In a Phase II trial in children, a 28-day-long treatment with anakinra, starting within 1 week of the onset of diabetes, substantially lowered insulin use 1 and 4 months after diagnosis

compared to insulin use in historically untreated patients[98]. Although repeated courses of IL-1 blockade would probably be necessary, the chronic use of anakinra or canakinumab appears to be safe in children with autoinflammatory diseases[11,99]. IL-1 blockade in type 1 diabetes may therefore keep islet inflammation at bay and reduce insulin use, with fewer episodes of high or low blood sugar. In an open-label trial of 1 week of anakinra treatment in patients with long-standing type 1 diabetes, increased insulin sensitivity was observed[100].

Placebo-controlled, randomized Phase II trials of anakinra (TABLE 3) and canakinumab (TABLE 5) in patients with new-onset diabetes are nearing completion. In the anakinra trial (termed anti-interleukin-1 in diabetes action; AIDA), individuals with newly diagnosed (within the past 3 months) type 1 diabetes received 100 mg of subcutaneously administered anakinra or placebo daily for 9 months. The primary end point was β-cell function, assessed by measuring C-peptide levels following a standardized 2-hour mixed-meal challenge. Secondary end points included insulin requirement, percentage insulinfree remission and 2-hour glucose levels after an oral glucose load. Similarly, in the canakinumab trial, individuals received monthly subcutaneous injections of 2.0 mg per kg of canakinumab or placebo for 12 months, beginning 3 months after diagnosis. All groups received standard intensive diabetes treatment (with insulin and dietary management) and have been followed for 1–3 years. The primary end point will be levels of C-peptide following a mixed-meal test after 1 year of canakinumab or placebo treatment. The secondary outcome will measure immunological markers and metabolic changes.

Type 2 diabetes

Clinical proof of a role for IL-1 in the pathogenesis of type 2 diabetes can be found in the randomized, placebo-controlled, 13-week study of anakinra, in which improved insulin production and glycaemic control was associated with decreased CRP and IL-6 levels[5]. Unexpectedly, in the 39 weeks following the treatment, anakinra responders used 66% less insulin to maintain the same glycaemic control to their baseline requirements[27]. This observation suggests that blocking IL-1β even for a short period restores the function of β-cells or possibly allows for partial β-cell regeneration. These findings of anakinra treatment in patients with type 2 diabetes have been confirmed using anti-IL-1β monoclonal antibodies. In a Phase I/II placebo-controlled trial, a single dose of gevokizumab[79] resulted in a statistically significant decrease in levels of haemoglobin A1C — a standardized marker of the amount of high blood sugar during the preceding month. There was also an increase in insulin production 90 days after the single treatment and a decrease in levels of CRP and cytokines. Anakinra treatment has also increased insulin sensitivity in pre-diabetic patients with metabolic syndrome[55]. Gevokizumab treatment also reduced fatigue in patients with type 2 diabetes[101], as did anakinra in patients with Sjögren's syndrome[102].

Two similar Phase I/II trials were carried out using canakinumab[103] and LY2189102 (REF. 104). In both anti-IL-1β trials, a statistically significant decrease in haemoglobin A1C levels was observed. A Phase II trial of canakinumab evaluated patients on metformin (the standard of therapy) for improvements in impaired glucose tolerance[103]. Mean peak insulin levels and total insulin production following a single dose (150 mg) of canakinumab were significantly higher than in placebotreated patients[103]. Anakinra has also been evaluated in a Phase II trial in obese non-diabetic patients with metabolic syndrome. Levels of CRP and circulating leukocytes were decreased and the glucose disposition index significantly increased after anakinra treatment, reflecting improved β-cell function[55]. These data are consistent with the trials of gevokizumab, LY2189102 and anakinra, demonstrating that blocking the IL-1 receptor or neutralizing IL-1β improves insulin secretion.

Studies of the neutralizing, naturally occurring, antihuman IL-1α antibody MABp1 (TABLE 5) will test a role of IL-1α in type 2 diabetes. In this Phase I/II trial, a single subcutaneous

injection of the antibody will be assessed for changes in haemoglobin A1C levels as well as CRP and insulin production. A preliminary study has been published on the effect of this antibody in patients with cancer cachexia[105].

Type 2 diabetes-associated atherosclerosis

A large body of preclinical data reveals that IL-1 has a role in the progression of atherosclerosis[106–108]; as type 2 diabetes increases the risk of cardiovascular events, blocking IL-1β activity in these patients may also reduce the incidence of myocardial infarction and stroke. The largest trial of an anti-cytokine drug is the CANTOS trial, a Phase III study testing whether canakinumab will reduce the risk of cardiovascular events in patients with type 2 diabetes who have high CRP levels despite receiving optimal statin therapy[12]. Secondary end points include prevention and improvement of diabetes. The rationale for CANTOS is based on the consistent decrease in CRP levels observed with anakinra, canakinumab or gevokizumab in patients with type 2 diabetes. The anti-IL-1α monoclonal antibody MABp1 is also being tested in a Phase II trial in patients with peripheral vascular disease (TABLE 5).

Arthritis and joint diseases

In several controlled studies with and without methotrexate (reviewed in REF. 109) (BOX 1; Supplementary information S1 (table)), anakinra significantly reduced disease severity, improved quality of life and decreased radiographic evidence of joint space narrowing in rheumatoid arthritis[60,110,111]. Because of its short half-life, daily subcutaneous injections of anakinra are required, sometimes resulting in local skin reactions, although these are usually resolved within 14 days. TNF blockers dominate the field of biologics for rheumatoid arthritis; however, there are many patients in whom TNF blockers fail or are contraindicated (for example, because of the risk of infection) and such patients require alternative biologics (TABLE 2). Anakinra is effective in patients who fail to benefit from TNF blockers, although there has been no direct comparison of the outcome of an IL-1-blocking therapeutic with any of the growing list of biologics presently used for treating rheumatoid arthritis (TABLE 2). However, 1 year of anakinra therapy — alone or in combination with methotrexate — seems to have a similar efficacy to other biologics[60,112–115].

Similarly to anakinra, canakinumab reduces disease severity in patients with new-onset rheumatoid arthritis, including patients who fail to benefit from anti-TNF therapies[116]. Novartis has suspended further trials of canakinumab in rheumatoid arthritis, perhaps because of the increasing number of competitive agents. Unlike anakinra, however, the long-term benefit of preservation of joint function and possible prevention of bone erosions with canakinumab remains unstudied.

Patients with recurrent attacks of gouty arthritis, who are unable to use colchicine and other standards of therapy, often require steroids to control disease flares. When treated with anakinra, rilonacept or canakinumab, a rapid, sustained and remarkable reduction in pain as well as objective signs of reduced inflammation have been observed in Phase II and III trials[117–127]. Even gout of the lumbar spine responds to anakinra[128]. The effect of IL-1 blockade appears to be superior to that of steroids and results in prolonged periods without flares. Pseudogout is also highly responsive to anakinra[119,125].

The routine (daily) use of subcutaneously administered anakinra (at a dose of 100 mg) improved pain and swelling in an aggressive form of erosive osteoarthritis of the hand[129]. When injected intra-articularly in patients with knee osteoarthritis[130,131], anakinra exhibited a dose-dependent reduction in pain scores but the benefit did not extend beyond 1 month[131]. With a molecular weight of 17,000 Da, the short-lived benefit of anakinra may be due to its

brief duration in the joint space. Systemic treatment of osteoarthritis with an IL-1 receptor antibody (AMG108) was carried out and a modest improvement was reported, particularly in those patients who had high pain levels at enrolment[78]. The optimal trial to investigate the efficacy of IL-1 blockade in osteoarthritis would involve the intra-articular injection of an IL-1β antibody or an IL-1 receptor-blocking antibody[132]. An ongoing Phase II trial of intra-articularly administered canakinumab in osteoarthritis (TABLE 5) may prove to be more efficacious than systemic treatment. As in all trials of osteoarthritis, the primary outcome is an improvement in the visual acuity composite score of pain and swelling.

Classic autoinflammatory diseases

A common feature of nearly all hereditary autoinflammatory syndromes is a rapid and sustained responsiveness to monotherapy with IL-1 blockade, regardless of whether the therapeutic agent is anakinra, rilonacept or canakinumab[8,29,80,133]. In some patients, an increased dose of the IL-1 blocker is needed but it is not uncommon to increase the dose of an anti-cytokine for treating rheumatoid arthritis, Crohn's disease or psoriasis.

In patients with FMF, daily oral colchicine is the mainstay of treatment but in some patients colchicine is not well tolerated or the dose is insufficient to prevent the attacks. It is important to reduce the attacks of FMF in order to avoid kidney failure resulting from secondary amyloidosis. In several case reports, treatment with anakinra or canakinumab in colchicine-resistant patients has been highly effective in reducing the number and severity of attacks[134–141] (BOX 1; Supplementary information S1 (table)).

In the NOMID variant of CAPS, there is neurological involvement including aseptic meningitis, elevated intracranial pressure, deafness and growth retardation. Anakinra is highly effective in treating each of the manifestations of the syndrome, particularly in reversing the local and systemic symptoms as well as the loss of hearing and neurological abnormalities associated with CAPS (BOX 1; TABLE 2; Supplementary information S1 (table)). Rilonacept[133] and canakinumab[80,142–144] are equally effective and both received initial approval for the treatment of CAPS. A report of a 2-year follow-up of canakinumab treatment in 166 patients with CAPS revealed the long-term efficacy of canakinumab in decreasing the number and severity of episodes. There were few side effects[145], even in previously severely affected patients with neurological abnormalities. Sensorineural deafness is a common manifestation of CAPS, as are other neurological abnormalities. Loss of hearing is partially reversible with IL-1 blockade, and is more effective in this regard when started soon after the first manifestations of the disease[9,142,146].

For the treatment of HIDS, several case reports have demonstrated the success of IL-1 blockade in reducing the frequency and severity of the attacks[41,147–152] (BOX 1; Supplementary information S1 (table)). An observational study in a group of patients with HIDS showed that IL-1 can directly abrogate an attack if started early enough[147].

TRAPS was initially thought to be a TNF-mediated disease resulting from the failure of the TNF receptor to insert itself into the cell's membrane. Indeed, TRAPS was initially treated with the TNF inhibitor etanercept (Enbrel; Pfizer), with some benefit, but treatment with IL-1 blockers is substantially more effective than with TNF inhibitors[153–155]. In fact, blocking TNF with infliximab (Remicade; Centocor Ortho Biotech) worsens the disease[156].

Chronic inflammatory diseases

There is a growing list of chronic inflammatory disorders without a known genetic basis, in which reducing IL-1 activity can be highly effective. For example, treating idiopathic recurrent pericarditis with immunosuppressive agents, anti- TNF antibodies, NSAIDs, intravenous gamma globulin or high-dose glucocorticoids often results in partial remissions,

whereas anakinra or canakinumab provide complete remission in all reported cases[70,157–159]. Although most chronic inflammatory conditions without a known basis can be controlled with glucocorticoids, monotherapy with IL-1 blockade can provide improved control without the metabolic and gastrointestinal side effects. In children, glucocorticoids retard growth and development, and treating SJIA with anakinra or canakinumab allows for reduced glucocorticoid dosing and a return to normal as well as accelerated growth[33,99,160,161].

In patients with adult-onset Still's disease, monotherapy with anakinra is highly effective and has become the standard of therapy, particularly in prednisone-refractory disease[162–166] (BOX 1; Supplementary information S1 (table)). The juvenile form of Still's disease, named SJIA, is the severe form of juvenile idiopathic arthritis. As in the adult form, IL-1 contributes substantially to inflammation, and several reports describe a remarkable efficacy of anakinra in patients who are refractory to steroids, methotrexate and TNF blockers[33,161,167]. Several trials with IL-1β neutralization in SJIA are underway, and blocking IL-1β with canakinumab has been reported[99,168] (TABLES 4,5).

Patients with Schnitzler syndrome are treated with anakinra, which results in rapid improvement, often within hours, and complete remission within days[63–67]. Indeed, the Schnitzler syndrome international registry, which collects data on patients with Schnitzler syndrome, reports nearly 100% efficacy with anakinra. Canakinumab has exhibited similar efficacy[68] and various clinical trials are currently being undertaken to study this in more detail.

Treatment of seven patients who had acute, sight-threatening panuveitis associated with Behçet's disease (which was resistant to azathioprine and cyclosporine) with a single dose of gevokizumab resulted in complete resolution of intraocular inflammation and return of vision within 4 to 21 days[146]. There is an ongoing expanded controlled study of gevokizumab in Behçet's disease (TABLE 5).

Smouldering or indolent myeloma

As reviewed recently[169], the link between chronic inflammation and malignant transformation includes IL-1. The incidence of multiple myeloma — a bone marrow cancer that is nearly always fatal — continues to increase each year. A non-malignant stage called 'monoclonal gammopathy of undetermined significance' progresses to a pre-cancerous stage called 'smouldering or indolent myeloma', which involves IL-1β production[170]. Owing to IL-1β-driven inflammation in the microenvironment of the bone marrow, stromal cells release large amounts of IL-6, which in turn promotes the survival and expansion of pre-myeloma cells[171]. It was reasoned that in the indolent stages of multiple myeloma, blocking IL-1β would reduce IL-6 activity[172]. Therefore, patients with smouldering or indolent myeloma who were at a high risk of progressing to multiple myeloma were selected with the clinical objective of slowing or preventing progression to active disease. During 6 months of treatment with anakinra, CRP levels decreased in most but not all patients, in conjunction with decreased myeloma cell proliferation. After 6 months of anakinra treatment, a low dose of dexamethasone was added. Of the 47 patients who received anakinra with dexamethasone, progression-free disease was observed over 3 years, and in eight patients it was observed over 4 years[172]. Given the increasing incidence of multiple myeloma in the ageing population, an option of anti-IL-1β therapy as an early intervention in the indolent stages of the disease might have a substantial impact on the management of this fatal cancer.

Angiogenesis has a pathological role in many malignancies. Animal models as well as *in vitro* data demonstrate that IL-1β is a key cytokine in angiogenesis (reviewed in REF. 173). IL-1β neutralization reduces the production of IL-6 as well as the pro-angiogenic chemokine

IL-8. IL-1β also has a role in the angiogenic process of macular degeneration[174]. It appears that the use of anti-IL-1β therapy may augment the anti-angiogenic effects of antibodies directed against vascular endothelial growth factor[175].

GVHD

In patients who received a stem cell transplant and developed full-blown GVHD, blocking IL-1 with anakinra reduced disease severity[176]. Similar findings were reported using soluble IL-1RI[83]. Of the three phases of GVHD — immunization, proliferation and targeting of tissue by graft T cells — IL-1 is important in at least the first two phases[177]. IL-1 has a role at the level of the acute inflammatory manifestations of GVHD rather than during the immunological development of the disease.

New indications

Mental impairment and hearing loss

Patients with CAPS exhibit various neurological abnormalities, such as aseptic leptomeningitis, reflecting IL-1-mediated inflammation in the brain. In a study of patients with CAPS, 92% had headaches with features of migraine, 54% had sensorineural deafness and 46% had papilloedema[142]. In clinical trials of CAPS patients receiving anakinra, rilonacept or canakinumab, near-complete resolution of symptoms has been reported[4,8,80,133,142,145,178]. Children with severe CAPS show manifestations of elevated intracranial pressure and are believed to suffer from learning disabilities. However, both mental and hearing impairments are reversed or improved upon treatment not only with anakinra[4,8,9,179–181] but also with specific neutralization of IL-1β with canakinumab[80,143–145,182].

A sudden or progressive loss of hearing associated with vertigo is called Ménière's disease, but it has no known pathogenesis. Patients are treated with a course of glucocorticoids, but this often fails to have a significant benefit; moreover, those not responding to glucocorticoid therapy fail to show an elevation in levels of the soluble IL-1β decoy receptor. In addition, peripheral blood monocytes from patients with the disease release more IL-1β than monocytes from unaffected individuals[183]. A related disease termed 'autoimmune inner ear disease' can also be characterized as progressive sensorineural hearing loss with dysregulation of IL-1β[183–185]. A Phase II randomized, placebo-controlled trial of anakinra in autoimmune inner ear disease is underway (TABLE 3).

Amyloidosis

Amyloidosis is a destructive process for several organs owing 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[186]. Left untreated, IL-1-mediated diseases such as FMF and CAPS may result in kidney failure resulting from amyloid deposits, which can be fatal if transplantation is not performed. However, in clinical trials of anakinra (TABLE 3), rilonacept (TABLE 4) and canakinumab (TABLE 5), reductions in SAA levels are associated with improved kidney function, and transplantation can thus be avoided[136,138,187–190].

Multiple sclerosis and neuromyelitis optica

Patients without multiple sclerosis who are being treated with TNF blockers may have clinical and magnetic resonance imaging (MRI) evidence of brain demyelinization, and patients with active multiple sclerosis may have exacerbations of their disease[191]. In a cohort of 104,000 patients with rheumatoid arthritis (87% females), those patients without a history of multiple sclerosis or optic neuritis who were treated with anti-TNF agents had an

adjusted rate ratio of 1.31 (of developing evidence of demyelinization), whereas those treated with anakinra had a rate ratio of 0.80 (REF. 192). Levels above 1.0 indicate 'more disease severity' whereas levels below 1.0 indicate 'less disease severity'. The lower disease level of anakinra is consistent with preclinical reports of a protective effect of IL-1 blockade in mice that are exposed to allergic autoimmune encephalitis, the model for multiple sclerosis, as reviewed in REF. 193. Also, interferon-β (IFNβ) — which is widely used to treat multiple sclerosis — induces IL-1Ra production in microglia, and IL-1Ra levels are increased in the serum of patients with progressive multiple sclerosis during IFNβ therapy. Thus, there is a clear rationale for a clinical trial of anakinra in multiple sclerosis.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by a progressive loss of motor neurons, resulting in death within a few years of diagnosis. The pathogenesis of ALS is associated with mutations in superoxide dismutase 1 (SOD1); a misfolding of this protein results in increased neuroinflammation. In a mouse model of mutant SOD1 as well as in patients with ALS, IL-1β levels are elevated[194]. Deficiency in caspase 1 (or IL-1β) or treatment with anakinra extended the lifespan of SOD1-transgenic mice and attenuated inflammatory pathology[194]. Furthermore, in a case study of a patient who was treated with anakinra for acquired cold urticaria there was an improvement in the early manifestations of ALS[195]. Therefore, there may be a rationale for treating ALS with IL-1β blockade[196]. Indeed, a Phase II trial (TABLE 3) is currently underway using anakinra to treat patients with early stages of ALS.

Inflammation in haemodialysis

A role for IL-1 in the systemic and local inflammation observed in haemodialysis has been a topic of many studies[197]. Patients with end-stage renal disease on maintenance haemodialysis have an increased risk of all-cause mortality as serum albumin levels fall. In a randomized, placebo-controlled trial in which patients were given anakinra for 4 weeks, there was a 23% increase in mean albumin levels in the anakinra arm compared with a 6% increase in the placebo arm[198]. In addition, markers of systemic inflammation — such as CRP and IL-6 levels — fell significantly[198]. Extending the duration of IL-1 blockade would determine whether treatment improves survival.

Safety issues with IL-1 blockade

IL-1 and host defence against infection

Anakinra has a remarkable record of safety[109,199]. It is estimated that over 150,000 patients have received anakinra, and some patients with rheumatoid arthritis have taken it daily for over 10 years[60,200]. In the 1990s there were three controlled trials of anakinra in patients with life-threatening septic shock who received 3 days of high-dose intravenously administered anakinra (2 mg per kg per hour)[201–203]. In each trial, anakinra reduced all-cause 28-day mortality compared to placebo-treated patients, particularly in patients with bacteria in the blood and the highest risk of death[202,203]. However, none of the anti-cytokine agents, including anakinra, reached statistical significance for reducing all-cause 28-day mortality; this is thought to be due to the heterogeneity of patients with septic shock.

As with all biologics, the occurrence of routine bacterial infections does increase with IL-1 blockers but what distinguishes IL-1-based therapeutics from other agents is the lack of opportunistic infections. A broad spectrum of opportunistic infections occur with chronic use of immunosuppressive drugs such as glucocorticoids and cyclosporine for the treatment of autoimmune diseases. Opportunistic infections occur with TNF-blocking therapies, and progressive multifocal leukoencephalopathy is a risk factor in patients treated with rituximab

(Rituxan; Biogen Idec/Genentech/Roche) or natalizumab (Tysabri; Elan/Biogen Idec). Owing to the indolent and dangerous nature of these infections, host defences against opportunistic organisms as well as routine bacterial infections have since become a major concern for all anti-cytokine agents. Reactivation of latent *Mycobacterium tuberculosis* in patients receiving anti-TNF therapies can be 25 times higher than in untreated individuals[204] and is often the disseminated form of the organism, similar to that observed in patients with HIV-1 infection. *M. tuberculosis* infection also occurs in patients treated with TNF blockers who have no evidence of prior exposure to the organism.

By contrast, opportunistic infections in patients treated with anakinra are rare[205], including in populations that are at a high risk for reactivation of *M. tuberculosis* infections[200]. There is a single case study of a 77-year-old man with severe rheumatoid arthritis and a history of pulmonary tuberculosis who developed reactivation 23 months after starting anakinra treatment[206]. Despite testing each patient, using tuberculin, for previous exposure to *M. tuberculosis* before beginning any anti-cytokine drug, reactivation continues to occur in patients and can be as high as 9.3% — with the notable exception of anakinra[207].

During controlled trials of anakinra, canakinumab and rilonacept, there were more viral-type upper-airway infections than in placebo-treated patients, but such infections are reported with all biologics. Although upper-airway infections are not life threatening, bacterial infection with organisms such as *Streptococcus pneumoniae* and *Streptococcus aureus* are of concern in any patient receiving a biologic. Rapidly progressive bacterial infections are always a possibility with IL-1-blocking therapies and therefore patients need to be aware of this. However, anakinra is administered to patients with chronically active infections[208–210]. In patients with chronic hidradenitis suppurativa due to *S. aureus*-infected apocrine glands, anakinra treatment resolves the inflammatory nature of the disease without increasing the extent of infection[210–212]. In addition, in patients with chronic granulomatous disease — an inherited condition with multiple bouts of fungal, Gram-positive and Gram-negative bacterial infections — treatment with anakinra reduces the severity of inflammatory bowel disease and granulomas associated with the disease without exacerbating infection[208]. With the life-long use of IL-1-blocking therapies, we do not know how such a reduction in IL-1 activity will affect natural defences against cancer, although to date there are no indications of an increased risk of cancers with IL-1 blockade. The use of anti-IL-1β monoclonal antibodies and the soluble IL-1 receptor rilonacept is relatively recent compared to the experience with anakinra, but there has been no unexpected increase in the occurrence of infections beyond those observed for anakinra.

Effects of IL-1 on haematopoiesis

One of the more salient properties of IL-1 is its ability to increase circulating neutrophil numbers (reviewed in REF. 1). The injection of only 3 ng per kg of IL-1β into humans results in neutrophilia[213]. To shorten the nadir in neutrophils following chemotherapy for bone marrow transplantation, low doses of either IL-1α or IL-1β have been administered as haematopoietic factors, and increased neutrophilic responses were consistently reported (reviewed in REF. 1). Neutrophilia is perhaps the most characteristic finding in many IL-1-mediated inflammatory diseases, particularly in the autoinflammatory disease setting. Thus, a response to IL-1 blockade is heralded by a reduction in circulating neutrophil counts as an indication of efficacy, and has been observed even in patients with osteoarthritis[78] or chronic heart failure[7]. In healthy individuals, intravenous infusions of anakinra (at a dose of 10 mg per kg) did not affect peripheral neutrophil counts[214]. In the rare cases of neutropaenia being less than 500 mm^3, neutrophil counts rapidly rise upon cessation of treatment.

Future directions

Blocking IL-1 in an unclassified inflammatory condition can be viewed as both a diagnostic as well as a targeted therapy for IL-1-mediated inflammation, in contrast to the nonspecific nature of glucocorticoids and immunosuppressors. Anakinra offers the ideal option as it has been used in several diseases (BOX 1; TABLE 3; Supplementary information S1 (table)), prevents the activity of both IL-1β and IL-1α, has an excellent safety profile, can be administered subcutaneously or intravenously and has good tissue penetration, particularly into the central nervous system. The short half-life of 6 hours affords an additional safety benefit and allows for short-term use. For example, in patients with periodic autoinflammatory diseases such as FMF or gout, prodromal symptoms can alert the patient to initiate anakinra treatment to avert an impending attack. Owing to the protracted half-life of antibodies targeting either IL-1α or IL-1β, these antibodies are not ideal as a test for IL-1-mediated inflammation and would result in unnecessarily sustained IL-1 blockade for a short-term need. Nevertheless, because of the long half-life of these antibodies, we anticipate increased use of anti-IL-1β or anti-IL-1α drugs in the treatment of some chronic diseases. For inflammatory conditions in which both IL-1α and IL-1β contribute to the disease, anakinra would be the preferred treatment.

A future direction for the development of IL-1- targeting agents will be the expansion of indications. Based on the responses with anakinra in patients with hidradenitis suppurativa[210–212], there will be a trial of anti- IL-1α as well as anti-IL-1β therapy in severe, scarring acne vulgaris (TABLE 5). Expansion of new indications will be based on preclinical data. For example, a mouse model of sickle cell disease has revealed a role for IL-1, and the primary end points in a trial for an IL-1 blocker in patients with sickle cell crisis include reduced pain and prevention of ischaemic organ damage[215]. The ischaemia that occurs in transplanted organs may also benefit from IL-1 blockade. Similarly, the observation of elevated serum IL-1 activity during the menstrual cycle[216] provides a rationale for testing anakinra in patients with endometriosis[217].

Increasing the levels of endogenous IL-1Ra confers protection in mouse models of epilepsy. In patients with epileptic seizures, an imbalance between IL-1β and IL-1Ra levels in the brain, favouring IL-1β, is thought to account for the inflammation[86,218], and an oral caspase 1 inhibitor is undergoing a third clinical trial to reduce the release of IL-1β in this setting. As intravenous infusions of anakinra penetrate the central nervous system[8,94], there is a rationale for testing anakinra in patients with poorly controlled seizures following spinal cord or traumatic brain injury. Indeed, a controlled trial of anakinra in thrombotic stroke revealed a beneficial effect[93] and a trial is underway to test the efficacy of anakinra in subarachnoid bleeding (TABLE 3). Other inflammatory conditions of the central nervous system may also benefit from anakinra testing. For example, there is an ongoing trial of intravenously administered anakinra in children with diabetic ketoacidosis (TABLE 3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

IL-1 receptor antagonist (IL-1Ra)	A naturally occurring protein that is structurally similar to interleukin-1 (IL-1), and inhibits IL-1α and IL-1β activity by blocking the IL-1 receptor
Monoclonal antibody	A type of antibody that recognizes and binds to a single specific epitope of the antigen of interest. For example, canakinumab is a monoclonal antibody that binds to a specific location on interleukin-1β (IL-1β). Monoclonal antibodies are used clinically to neutralize cytokines and cytokine receptors
Chimeric	Composed of two unrelated components. A fusion of the naturally occurring interleukin-1 receptor antagonist (IL-1Ra) with IL-1β is an example of a chimeric molecule
Caspase 1	An intracellular enzyme that cleaves the inactive interleukin-1β (IL-1β) precursor to form an active molecule. Caspase 1 is activated by the inflammasome
Type 2 diabetes	Diabetes resulting from the loss of insulin-producing cells by an inflammatory process. Type 2 diabetes is an autoinflammatory disease caused by interleukin-1 (IL-1)-mediated inflammation
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcome Study: a trial testing canakinumab for lowering the risk of myocardial infarction, stroke and cardiovascular deaths in high-risk patients
Type 1 diabetes	Diabetes resulting from the loss of insulin-producing cells following an immune attack. Type 1 diabetes is an autoimmune disease
IL-1α precursor	Interleukin-1α (IL-1α) is first synthesized in the cell as a larger molecule, termed a precursor. The IL-1α precursor is active, but undergoes shortening to form a more active molecule, often called the ‘mature’ protein
Alarmin	A term used to describe an active molecule (such as interleukin-1α) that is ready to induce inflammation
Tumour necrosis factor (TNF)	A highly inflammatory cytokine that has overlapping properties with interleukin-1
Autoinflammation	An inflammatory process by which more inflammation arises from endogenous products of inflammation. For example, interleukin-1 (IL-1) induces more IL-1
IL-1β precursor	Interleukin-1β (IL-1β) is first synthesized in the cell as a larger molecule, termed a precursor. It undergoes shortening to form a more active molecule, often called the ‘mature’ protein
Inflammasome	An assembly of intracellular proteins that activate caspase 1
Deficiency of interleukin-1 receptor antagonist	(DIRA). An inherited disease caused by a mutation in the interleukin-1 receptor antagonist (IL-1Ra). DIRA is a systemic and lethal disease present at birth
Gout	A disease caused by the formation of crystals of uric acid in the joints, particularly in the foot. It is highly painful and associated with overnutrition

Familial Mediterranean fever (FMF)	A systemic and local inflammatory disease characterized by recurrent bouts of fever and painful inflammation in the linings of the abdominal and chest walls of the body. FMF is an inherited disease
Cryopyrin-associated periodic syndrome (CAPS)	A grouping of three syndromes: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome and neonatal-onset multi-inflammatory disease (NOMID). CAPS is an inherited autoinflammatory disease
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3. Also called cryopyrin. This protein participates in the activation of caspase 1 and is a component of the inflammasome
Amyloidosis	A destructive process caused by the deposition of amyloid fibrils. In inflammatory diseases, the condition is termed secondary amyloidosis
TNF receptor-associated periodic syndrome (TRAPS)	An inherited disease caused by a mutation in the tumour necrosis factor (TNF) receptor; patients suffer from debilitating recurrent bouts of fever with local and systemic inflammation. TRAPS is an autoinflammatory disease
Hyper-IgD syndrome (HIDS)	A genetic autoinflammatory disorder that is associated with high levels of immunoglobulin D in the blood. The disease is caused by a mutation in the enzyme mevalonate kinase. Patients experience 4–6 days of fever, muscle aches, a skin rash, painful mouth ulcers and swollen lymph nodes
ST segment elevation myocardial infarction (STEMI)	A type of heart attack characterized by an elevation of the ST segment on the electrocardiogram. STEMI is the most dangerous type of heart attack
Insulin resistance	A metabolic abnormality that is commonly present in type 2 diabetes, in which elevated blood insulin levels are ineffective in transporting glucose into the cells
Pseudogout	Clinically similar to goutp; a disease caused by the formation of phosphate crystals in the joints
Osteoarthritis	The most common cause of arthritis (painful joints). Osteoarthritis is due to loss of the cartilage that cushions the joints. Proteoglycans comprise the flexible matrix of cartilage
Rheumatoid arthritis	An autoimmune disease resulting in inflammation of the joints, in which the synovial membrane is thickened with inflammatory cells. Rheumatoid arthritis is a systemic disease affecting nearly all organs and is distinct from osteoarthritis, which affects only the joints
Glucocorticoids	The preferred name for cortisone-like drugs. Also known as steroids. Prednisone is a synthetic glucocorticoid
C-reactive protein (CRP)	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

Non-steroidal anti-inflammatory drugs (NSAIDs)	Oral drugs that are used to treat many inflammatory conditions. Ibuprofen is an example of an NSAID
Gammopathym	The presence of elevated levels of a monoclonal antibody in the circulation. Gammopathies are part of multiple myeloma and Schnitzler syndrome
Panuveitis, Inflammation in the eye	usually in either the front chamber (anterior uveitis) or the rear chamber (posterior uveitis). Uveitis reduces visual acuity and may result in blindness
Graft-versus-host disease	A disease that occurs in patients following bone marrow transplantation, in which the newly transplanted donor bone marrow attacks the intestinal and skin cells of the recipient patient
Ejection fraction	A term used to describe the amount (percentage) of blood that is pumped from the left ventricle of the heart. Patients with heart failure have a low (less than 40%) ejection fraction and therefore have limited physical ability
Sensorineural deafness	Loss of hearing due to the inability of the cholear organ to sense vibrations and convert the vibrations into neural signals
Multiple myeloma	A uniform form of cancer in which there is uncontrolled overproduction of antibody-producing cells that crowd the bone marrow's normal function to produce red blood cells, platelets and white blood cells
Angiogenesis	Growth of blood vessels. In cancer, angiogenesis provides growing tumours with a blood supply. Drugs that inhibit angiogenesis are used to treat cancer

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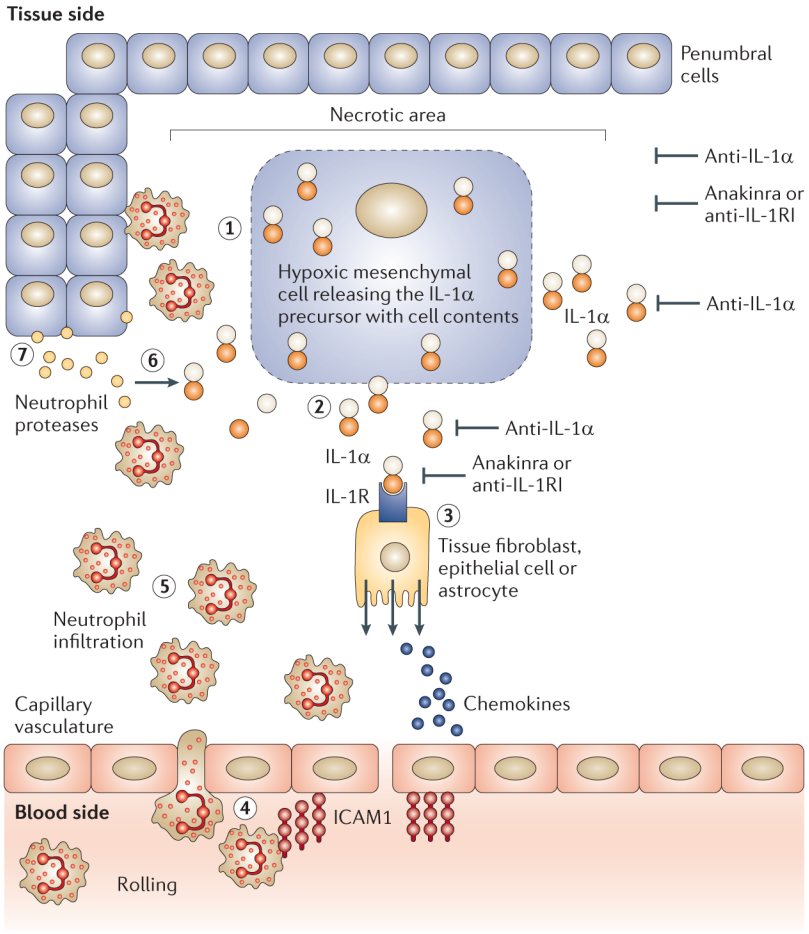


Figure 1. Initiation of sterile inflammation by IL-1α following an ischaemic event

Step 1: in the necrotic area, dying cells lose membrane integrity. Step 2: dying cells release their contents, including the interleukin-1α (IL-1α) precursor. Anti-IL-1α antibodies neutralize IL-1α at this step. Step 3: IL-1α binds to IL-1 receptor type I (IL-1RI) on nearby resident fibroblasts, epithelial cells or in brain astrocytes, releasing chemokines and establishing a chemokine gradient. Anakinra or anti-IL-1RI antibodies block this step. The chemokine gradient facilitates the passage of blood neutrophils into the ischaemic area. Step 4: capillaries in the ischaemic tissues express intercellular adhesion molecule 1 (ICAM1). Circulating blood neutrophils roll on the endothelium, adhere to ICAM1 and enter the ischaemic tissue via diapedesis. Step 5: the number of neutrophils in the area of the necrotic event increases; the presence of local IL-1 prolongs the survival of neutrophils at this step. Step 6: neutrophil proteases cleave the extracellular IL-1α precursor into mature, more active forms. Step 7: neutrophils scavenge dying cells and release proteases that contribute to the destruction of penumbral cells.

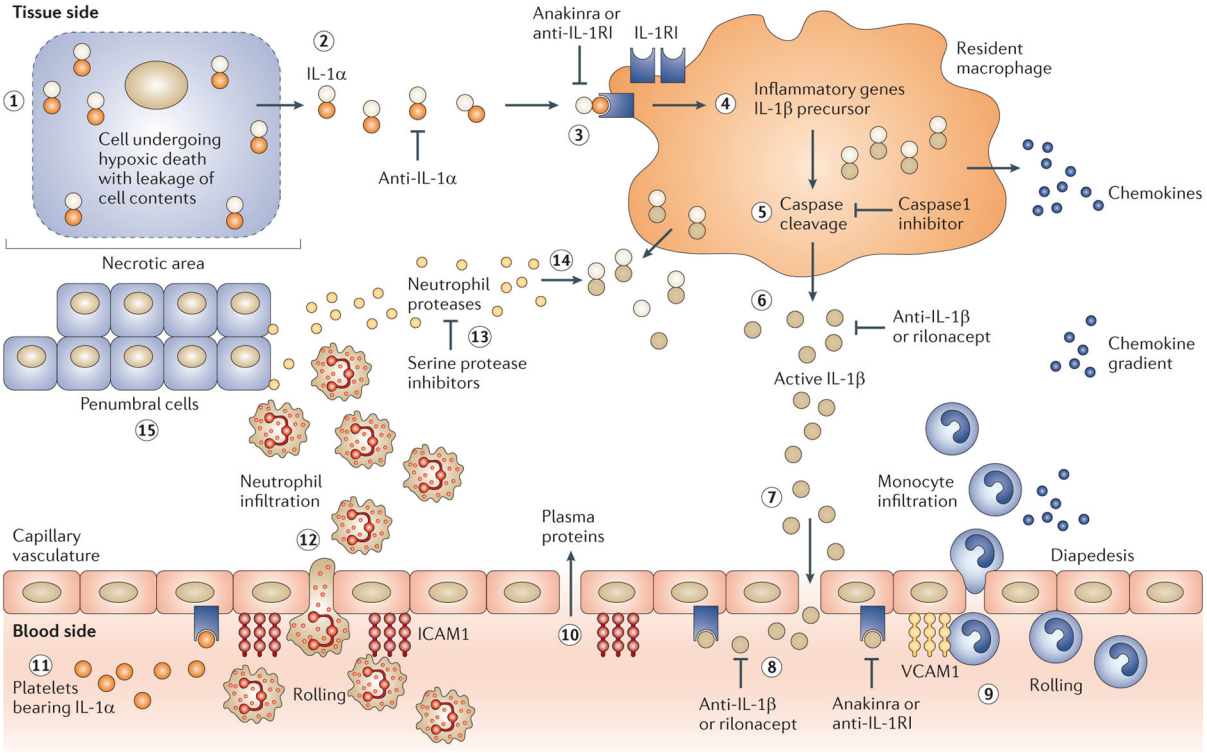
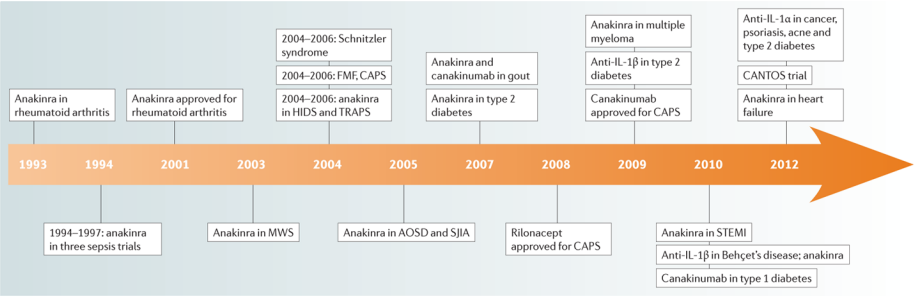


Figure 2. Role of IL-1 β in sterile inflammation

Step 1: following an ischaemic event, cells undergo hypoxic damage, lose membrane integrity and the dying cell releases cell contents (see FIG. 1). Step 2: the preformed interleukin-1α (IL-1α) precursor is released. Anti-IL-1α antibodies neutralize IL-1α at this step. Step 3: IL-1α binds to IL-1 receptor type I (IL-1RI) on nearby resident macrophages. Anakinra or anti-IL-1RI antibodies prevent IL-1α activity at this step. Step 4: triggered by the binding of IL-1α to IL-1RI, resident macrophages synthesize inflammatory genes as well as the IL-1β precursor. Step 5: the IL-1β precursor undergoes intracellular processing by caspase 1. Caspase 1 inhibitors prevent the processing of IL-1β at this step. Step 6 involves the secretion of active IL-1β. Rilonacept or antibodies of IL-1β neutralize IL-1β in the extracellular compartment at this step. Step 7: with the breakdown of vascular integrity in the necrotic area, IL-1β gains access to the vascular compartment. Step 8: IL-1β binds to IL-1RI on capillaries and induces vascular cell adhesion molecule 1 (VCAM1). Step 9: blood monocytes roll along the endothelium and bind to VCAM1, followed by their migration into the ischaemic tissue via diapedesis. Increasing numbers of monocytes become a source of increased production of IL-1β. Step 10: opening of the endothelial junction results in capillary leak, with the passage of plasma proteins into the ischaemic area. Step 11: platelet-derived IL-1α binds to the endothelial IL-1RI and induces the expression of intercellular adhesion molecule 1 (ICAM1). Step 12: large numbers of neutrophils enter the tissue space and the presence of local IL-1 prolongs the survival of neutrophils. Step 13: neutrophil proteases are released. Step 14: the IL-1β precursor released into the extracellular space is cleaved by serine proteases to generate active IL-1β. Natural inhibitors of serine proteases such as α1 antitrypsin prevent the extracellular processing of the IL-1β precursor. Step 15: increasing numbers of neutrophils surround the necrotic area, scavenging dead cells and debris. Damaging neutrophilic proteases attack and injure penumbral cells, resulting in increased loss of function of the organ undergoing the ischaemic event. Blocking IL-1 cannot restore the necrotic tissue but reduces the loss of penumbral cells.



Timeline.

IL-1-blocking agents in various disease states

The timeline highlights the testing of interleukin-1 (IL-1)-blocking agents in various but not all indications. AOSD, adult-onset Still's disease; CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcome Study; CAPS, cryopyrin-associated periodic syndrome; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; MWS, Muckle–Wells syndrome; SJIA, systemic juvenile idiopathic arthritis; STEMI, ST segment elevation myocardial infarction; TRAPS, TNF receptor-associated periodic syndrome.

Table 1

Agents available or under study for reducing IL-1 activity

Agent	Availability	Mechanism of action	Company	Refs
Anakinra	Approved	Receptor antagonist for IL-1RI	Swedish Orphan BioVitrum (see Supplementary information S1 (table))	–
Rilonacept*	Approved	Soluble IL-1 receptor that binds IL-1β>IL-1α>IL-1Ra	Regeneron	91,102
Canakinumab	Approved	Neutralizing anti-IL-1β IgG1 mAb	Novartis	60,76,93, 112,142
Gevokizumab	Phase II	Neutralizing anti-IL-1β IgG2 mAb	Xoma	59, 119
LY2189102	Phase II	Neutralizing anti-IL-1β IgG1 mAb	Lilly	77
MABp1	Phase I/II	Neutralizing anti-IL-1α IgG1 mAb	XBiotech	78
MEDI-8968	Phase II/III	Blocking antibody to IL-1RI	MedImmune	18
CYT013	Phase I	Therapeutic vaccine targeting IL-1β	Cytos Biotechnology	–
sIL-1RI‡	Halted	Binds IL-1Ra>IL-1α>IL-1β	Amgen	63,64,65
sIL-1RII§	Halted	Binds IL-1β complex with soluble IL-1RAcP	Amgen	–
EBI-005	Phase I/II	Chimeric IL-1Ra–IL-1β	Eleven Biotherapeutics	–
CMPX-1023	Preclinical	Alphabody	Complix	–
VX-765	Phase II	Oral caspase 1 inhibitor Vertex	Vertex	–

IgG1, immunoglobulin G1; IL-1, interleukin 1; IL-1Ra, IL-1 receptor antagonist; IL-1RAcP, IL-1 receptor accessory protein; IL-1RI, IL-1 receptor type I; mAb, monoclonal antibody.

*A soluble decoy receptor; composed of extracellular domains of IL-1RI fused to the extracellular domains of IL-1RAcP.

‡Soluble IL-1RI; composed of extracellular domains of IL-1RI; binds to IL-1Ra, IL-1α and IL-1β in decreasing order of affinity: IL-1Ra>IL-1α>IL-1β.

§Efficacy depends on the binding of IL-1β with soluble IL-1RAcP; binds to IL-1β, IL-1α and IL-1Ra in decreasing order of affinity: IL-1β>IL-1α>IL-1Ra.

Table 2

Autoimmune versus autoinflammatory diseases

Dysfunctional cells	Dominant cytokines	Disease examples	Options for biologics
Autoimmune diseases			
T- and B lymphocytes	TNF, IL-6 and IL-17	• Rheumatoid arthritis • Crohn's disease • Psoriasis • Multiple sclerosis	• TNF blockers • Anti-IL-6 receptor mAb • Anti IL 12/IL 23 mAb • Anti-IL-17 mAb • CTLA4 immunoglobulin • Rituximab; anakinra
Autoinflammatory diseases			
Monocytes macrophages	IL-1α and IL-1β	• Hereditary diseases: CAPS; FMF; TRAPS; HIDS; PFAPA • Common (non-hereditary) diseases: adult and juvenile Still's disease Schnitzler syndrome; hidradenitis suppurativa; gout; pseudogout; type 2 diabetes	• Anakinra • Rilonacept • Canakinumab • Gevokizumab • LY2189102 • Anti-IL-1α mAb • Anti-IL-1 receptor mAb • Oral caspase 1 inhibitors

CAPS, cryopyrin-associated periodic syndrome; CTLA4, cytotoxic T lymphocyte antigen 4; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; IL-1α, interleukin-1α; mAb, monoclonal antibody; MI, myocardial infarction; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; TNF, tumour necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

Table 3

Ongoing trials with anakinra

Study name	Phase	ClinicalTrials.gov identifiers
Amyotrophic lateral sclerosis	Phase II	NCT01277315
Steroid-resistant autoimmune inner ear disease	Phase I/II	NCT01267994
Inflammation following subarachnoid haemorrhage	Phase II	NA*
Severe atopic dermatitis	Phase I	NCT01122914
Post-MI (myocardial infarction) cardiac remodelling-2	Phase III	NCT01175018
Heart failure with preserved ejection fraction	Phase II	NCT01542502
Decompensated systolic heart failure	Phase II	NCT01300650
Left ventricular function in coronary artery disease	Phase II	NCT01566201
Pulmonary artery hypertension	Phase I/II	NCT01479010
Insulin secretion/sensitivity in type 2 diabetes	Phase II	NCT01285232; NCT00928876
Diabetic ketoacidosis coma (brain swelling)	Phase II	NCT01477476
Postoperative incisional pain	Phase II	NCT01466764
Behçet's disease	Phase II	NCT01441076
Chronic kidney and cardiovascular disease	Phase I	NCT00897715
Hidradenitis suppurativa	Phase II	NCT01558375; NCT01516749
Osteoarthritis of the knee (intra-articular)	Phase II	NCT00110916

*Information not available.

Table 4

Trials with soluble interleukin-1 decoy receptor (rilonacept)

Study name	Phase	ClinicalTrials.gov identifiers
Ongoing trials		
Familial Mediterranean fever	Phase II	NCT00582907
Juvenile idiopathic arthritis in children	Phase II	NCT00534495
Type 1 diabetes safety study	Phase I	NCT00962026
Systemic sclerosis	Phase II	NCT01538719
Muckle–Wells syndrome	Phase II	NCT01045772
Completed trials		
Cryopyrin-associated periodic syndrome	Phase II	NCT00288704
Artery function in atherosclerosis	Phase II	NCT00417417
Dialysis-dependent chronic kidney disease	Phase I	NCT000609544
Prevention of gout flares	Phase II/III	NCT01459796; NCT00856206; NCT00610363
Adult-onset Still's	Phase II	NCT00094900
Schnitzler syndrome	Phase II	NCT01245127

Table 5

IL-1 blockade with trials of anti-IL-1 monoclonal antibodies*

Study name (Phase)	ClinicalTrials.gov identifiers
Anti-IL-1β trials	
Early and established rheumatoid arthritis	NCT00487825; NCT00784628; NCT00505089; NCT00619905; NCT00619905; NCT00424346; NCT00471198; NCT00380744
Gout flares in patients refractory to standard treatment (or contraindicated)	NCT00798369; NCT00819585; NCT01362608; NCT00927810; NCT01431638; NCT01080131; NCT01029652; NCT01470989; NCT01356602; NCT00663169; NCT01194921; NCT01160016; NCT01593527
Polymyalgia rheumatica	NCT01364389
Osteoarthritis of the knee (intra-articular)	NCT01160822
Systemic-onset juvenile idiopathic arthritis	NCT00426218; NCT00889863; NCT00886769
Schnitzler syndrome	NCT01276522; NCT00504595
Familial Mediterranean fever	NCT01148797; NCT01088880
Cryopyrin-associated periodic syndrome	NCT01576367; NCT01105507; NCT00991146; NCT01302860; NCT00685373; NCT00770601; NCT01213641; NCT00465985; NCT00487708
Hyper-IgD syndrome	NCT01303380
TNF receptor-associated periodic syndrome	NCT01242813
Type 2 diabetes	NCT01068860; NCT00605475; NCT00900146; NCT01144975; NCT00541983; NCT01066715; NCT00513214; NCT00942188
Type 2 pre-diabetic state	NCT00995930
Proliferative diabetic retinopathy	NCT01589029
Wet age-related macular degeneration	NCT00503022
Arterial function in atherosclerosis in type 2 diabetes	NCT00995930
Cardiovascular risk reduction in type 2 diabetes (CANTOS trial)	NCT01327846
Chronic obstructive pulmonary disease	NCT00581945
Type 1 diabetes	NCT01322321; NCT00998699
Urticarial vasculitis	NCT01170936
Pyoderma gangrenosum	NCT01302795
Dry eye syndrome	NCT01250171
Acne vulgaris	NCT01498874
Anti-IL-1α trials‡	
Moderate to severe acne vulgaris (Phase II)	NCT01474798
Moderate to severe plaque psoriasis (Phase II)	NCT01384630
Reducing restenosis in peripheral artery revascularization (Phase II)	NCT01270945
Subjects with advanced haematological malignancies (Phase I)	NCT01260545
Dose escalation in patients with advanced cancer (Phase I)	NCT01021072
Patients with type 2 diabetes (Phase I)	NCT01427699

CANTOS, Canakinumab Anti-inflammatory Thrombosis Outcome Study; IL-1, interleukin-1; TNF, tumour necrosis factor.

* Includes the following monoclonal antibodies neutralizing IL-1β: canakinumab, gevokizumab and LY2189102.

[≠]All studies using MABp1, a naturally occurring monoclonal antibody neutralizing IL-1α.