The cytokines interleukin 1 (IL1) and tumour necrosis factor \( \alpha \) (TNF\( \alpha \)) are produced acutely as part of host defence in response to microbial infection, inflammation, and tissue injury.\(^1\)\(^2\) Overexpression of these cytokines, however, has been implicated in the pathogenesis of several human diseases—notably, rheumatoid arthritis (RA) and other chronic inflammatory disorders, including Crohn’s disease. Accordingly, agents capable of blocking these cytokines have been sought for their potential clinical use. Advances made in the laboratory looking at cytokine regulation as a means of reducing immune cell activity have been rapidly translated into the clinical setting. The efficacy and safety of several biological agents that block either IL1 or TNF\( \alpha \) have now been established in controlled clinical trials, mostly in patients with RA but also in Crohn’s disease.\(^3\)\(^4\)

The efficacy of TNF blocking agents etanercept and infliximab confirms a large body of experimental evidence that implicated TNF\( \alpha \)s in the pathogenesis of chronic inflammatory diseases. In addition, a large amount of experimental evidence supports a role for IL1 in these disorders. Moreover, in each clinical trial, a significant percentage of patients did not respond adequately to the TNF blockers, suggesting that TNF\( \alpha \) alone cannot explain the pathogenesis of chronic inflammatory disease. Further, a role for IL1 in RA is supported by results of controlled clinical trials of anakinra, a recombinant human IL1 receptor antagonist (IL1Ra).\(^5\)\(^6\) This paper will focus on blocking IL1 as a therapeutic strategy for human disease.

**STRUCTURE AND FUNCTION OF IL1 AND RELATED MOLECULES**

IL1 exists in two forms—IL1\( \alpha \) and IL1\( \beta \).\(^7\) Each is produced by a separate gene as a 31 kDa precursor protein, termed proIL1\( \alpha \) and proIL1\( \beta \), respectively. The proIL1\( \alpha \) forms are subsequently cleaved by specific cellular proteases, including IL1 converting enzyme to mature 17 kDa proteins. IL1\( \beta \) is generally located intracellularly or expressed on the cell surface; it is believed to function as an autocrine messenger. In contrast, IL1\( \beta \) is released from the cell and produces its effects by acting on other cells. IL1Ra is the third member of the IL1 family; it is produced and secreted as a 17 kDa protein by almost all cells that express IL1.\(^8\) Although each of the IL1 family members has a distinct amino acid sequence, their three dimensional structures are related, and consequently, each can bind with high affinity to IL1 receptors located on target cells.

The members of the IL1 family can bind to two distinct IL1 receptors, termed type I (IL1RI) and type II (IL1RII).\(^9\) Binding of IL1\( \alpha \) or IL1\( \beta \) to IL1RI leads to receptor activation and subsequent intracellular signal transduction and cellular responses (fig 1). In contrast, IL1RII contains a short cytoplasmic domain and is unable to transduce an intracellular signal in response to IL1 binding. Therefore, IL1RI is the receptor that mediates the biological actions of IL1, whereas IL1RII is a decoy receptor that may serve to buffer the effects of excessive IL1 concentrations. The extracellular domains of both receptors are found in the circulation in both healthy and disease states, where these soluble fragments may also function to buffer the actions of IL1. Whereas IL1\( \alpha \) and IL1\( \beta \) may be considered as agonists at the IL1RI, the third member of the IL1 family, IL1Ra, functions as a competitive receptor antagonist. IL1Ra blocks binding of IL1\( \alpha \) and IL1\( \beta \) to IL1RI, thereby preventing IL1RI activation and inhibiting the biological actions of IL1 (fig 1).

IL1 produces a variety of biological actions that appear conserved across species.\(^7\)\(^8\) Systemic injection of recombinant IL1 elicits fever, increased slow wave sleep, anorexia, hypotension, leucopenia, and thrombocytopenia. IL1 stimulates the hypothalamic-pituitary-adrenal axis, leading to production of adrenocorticotropic hormone, growth hormone, vasopressin,

Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IL1, interleukin 1; IL1Ra, IL1 receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PGE\(_2\), prostaglandin E\(_2\); RA, rheumatoid arthritis; sIL1R, soluble IL1 receptor; TNF\( \alpha \), tumour necrosis factor \( \alpha \)
and somatostatin. IL1 influences haemopoiesis by increasing production of colony stimulating factors and stem cell factors and by acting synergistically with these factors to augment production of granulocytes and platelets. IL1 may also protect the haemopoietic progenitors against the damaging effects of radiation and cytotoxic drugs. IL1 stimulates production of acute phase proteins by the liver, including IL6, fibrinogen, complement components, and various clotting factors. IL1 also protects against infection in normal and compromised animals provided that it is present before the onset of the pathological process.

On a cellular level, IL1 regulates the expression of numerous genes that are involved in inflammatory and immune responses. For example, IL1 increases expression of intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells, which facilitate leucocyte entry into inflammatory sites. IL1 also induces expression of enzymes which play a part in the synthesis of proinflammatory mediators, such as nitric oxide, prostaglandins, and platelet activating factor. IL1 triggers T and B lymphocyte activation, leading to generation of numerous cytokines, increased antibody production, and expansion of specific T cell clones. In joints, IL1 stimulates chondrocytes to release collagenase and other proteolytic enzymes involved in cartilage degradation. IL1 also stimulates the differentiation of osteoclast progenitors and subsequently contributes to the activation of mature osteoclasts, leading to bone resorption. Finally, IL1 triggers growth factor release, leading to proliferation of fibroblasts and smooth muscle cells.

In normal homoeostasis, the actions of IL1 are maintained in balance by IL1Ra, other natural IL1 inhibitors, such as IL1RII and circulating soluble IL1RI and IL1RII, as well as a network of anti-inflammatory cytokines. However, increased IL1 production has been reported in a variety of disease states, including autoimmune diseases, infection, solid tumours, leukaemia, Alzheimer’s disease, trauma, haemodialysis, ischaemic myocardial infarction, asthma, and graft versus host disease. In RA, for example, systemic and synovial fluid concentrations of IL1 are raised, and they correlate with disease severity and histological features. IL1Ra levels are also increased in many patients with RA, but they may not be sufficient for keeping IL1 activity in balance.

ANIMAL MODELS
Role of IL1Ra
The importance of IL1Ra in homoeostasis can be gleaned from studies of knockout mice in which the IL1Ra gene was deleted. Inflammatory erosive arthritis developed spontaneously in mice with a BALB/c genetic background, but it occurred at a much lower incidence in mice with a C57BL background. The polyarthropathy was characterised by pannus invasion of the articular surface and histological evidence of marked synovial and periarthicular inflammation, resembling the inflammatory changes typically seen in RA. Evidence of autoimmune disease was suggested by the presence of antibodies against type II collagen, immunoglobulins, and double stranded DNA. The expression of IL1 and several other proinflammatory cytokines was also increased, reflecting an imbalance in the normal cytokine network. In another study, deletion of the IL1Ra gene led to development of lethal arteritis with aneurysm formation. Arterial inflammation was found at branch points and flexures of the aorta as well as its primary and secondary branches. Histologically, massive infiltration of neutrophils, macrophages, and CD4+ T lymphocytes was found in these arterial lesions.

Neutralising anti-IL1Ra antibodies have also been used to evaluate the role of endogenous IL1Ra in acute inflammatory states. For example, immune colitis in rabbits depends on production of IL1 in the colon and is ameliorated by exogenous administration of IL1Ra. This model is characterised by neutrophil and eosinophil infiltration, crypt abscess formation, epithelial cell degeneration, mucous depletion, and mucosal necrosis. Colonic IL1 levels increase initially before
the onset of inflammation, and then 48 hours later, IL1Ra levels rise, preceding a significant decline in IL1 and resolution of the colonic inflammation. However, administration of anti-IL1Ra resulted in exacerbation and prolongation of the colonic inflammation, and it proved lethal in six of 18 animals. In contrast, all control animals survived. Moreover, colonic IL1 levels were significantly increased by anti-IL1Ra treatment. This study suggests that endogenous IL1Ra plays a protective role against inflammatory insults.

Role of IL1
The role of IL1 in various disease models in animals has been inferred by the protective effects of recombinant IL1Ra, soluble IL1 receptors (sIL1R), and neutralising antibodies to IL1α and IL1β. Blocking the effects of endogenous IL1 with these agents improved survival in mice and rabbits injected with endotoxin; reduced shock in rabbits and baboons with bacteremia; reduced the incidence and severity of inflammatory arthritis in mice, rats, and rabbits; reduced colonic inflammation in rats and rabbits; decreased the severity of graft versus host disease and prolonged survival of cardiac allografts in mice; inhibited experimental autoimmune encephalomyelitis in mice and ischemic brain injury in rats; diminished the late phase asthmatic response and airway hyperreactivity in guinea pigs; reduced lung injury in rats; decreased glomerulonephritis in rats; and inhibited streptozotocin induced diabetes in mice.

Table 1

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Disease</th>
<th>Evidence from clinical trials and in vitro experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>1 Rheumatoid arthritis</td>
<td>IL1Ra in the treatment of RA alone and in combination with methotrexate</td>
</tr>
<tr>
<td>Probable</td>
<td>1 Septic shock</td>
<td>Mixed results from 4 studies using IL1Ra</td>
</tr>
<tr>
<td></td>
<td>2 Graft versus host disease</td>
<td>Preliminary results with IL1Ra promising</td>
</tr>
<tr>
<td>Experimental</td>
<td>1 Alzheimer’s disease</td>
<td>In vivo studies showing overexpression of IL1 and increased risks in subjects with IL1α allelic polymorphism</td>
</tr>
<tr>
<td></td>
<td>2 Atherosclerosis</td>
<td>Higher levels of IL1β in the aorta of patients with aortoiliac occlusive disease and aneurysms</td>
</tr>
<tr>
<td></td>
<td>3 Adult T cell leukaemia</td>
<td>Increased IL1 receptors on T cells</td>
</tr>
<tr>
<td></td>
<td>4 Multiple myeloma</td>
<td>Homing of myeloma cells to marrow and osteolytic lesions of biological actions of IL1</td>
</tr>
<tr>
<td></td>
<td>5 Asthma</td>
<td>IL1 levels higher in asthmatics than in normal controls</td>
</tr>
</tbody>
</table>

Plasma IL1β concentrations averaged 120 pg/ml, which was two times higher than the levels found in a group of healthy volunteers. However, plasma IL1β did not correlate with disease severity or mortality risk. In comparison, plasma TNFα was also significantly raised in the patients with septic shock, and these levels correlated with disease severity based on APACHE scores. Plasma levels of the two cytokines were unrelated.

Rheumatoid arthritis
As noted previously, plasma and synovial fluid concentrations of IL1β are raised in patients with RA, and they correlate with disease activity and histological features. Moreover, expression of high concentrations of human IL1β in a rabbit knee joint produced clinical and histological features characteristic of RA. These features included synovial hypertrophy and hyperplasia; profound increases in leukocyte infiltration; high levels of cartilage breakdown products in joint fluid; reduced synthesis of extracellular matrix components; and systemic manifestations, such as fever, raised erythrocyte sedimentation rate (ESR), and weight loss. Histological analysis showed that the synovium had attached to cartilage and subchondral bone within the first week of IL1β overexpression, and initial evidence of cortical bone erosion was seen at this time. In the second week, pannus invasion of cartilage and subchondral bone resulted in severe erosions of cortical bone, and thereafter, the pannus encroached into the bone marrow.

Atherosclerosis
Chronic inflammatory cells are found in the adventitia and media of abdominal aortic aneurysms as well as aortic occlusive disease. Infra-renal aortic biopsy specimens obtained from surgical patients with these conditions showed substantially higher IL1β production than specimens obtained from cadaveric donors. IL1β production averaged 908 pg/ml and 604 pg/ml for specimens from patients with abdominal aortic aneurysm and aortic occlusive disease, respectively, as compared with 100 pg/ml for the specimens from the cadaveric donors. Lipopolysaccharide augmented IL1β production in a concentration dependent manner, with maximal effects achieved at a concentration of 5 µg/ml. In contrast, TNFα production was low in all aortic specimens, and lipopolysaccharide did not stimulate it. These findings suggest that inflammatory infiltrates found in patients with abdominal aortic aneurysms or aortic occlusive disease produce IL1β, which probably contributes to the underlying pathological sequelae.

Alzheimer’s disease
IL1 has been thought to have a role in Alzheimer’s disease on the basis of its overexpression in the brains of afflicted
patients; its ability to induce excessive expression of the β-amylloid precursor protein; and its ability to activate astrocytes to produce a number of important proteins related to Alzheimer’s disease, including S100β, IL6, α-antichymotrypsin, and apolipoprotein E. Notably, the number of activated microglia that overexpress IL1 has been correlated with the number of β-amyloid plaques. Moreover, a specific IL1β gene polymorphism in allele 2 appears to triple the risk of Alzheimer’s disease, with the onset of disease occurring at an earlier age. A further increase in risk is seen in patients carrying allele 2 polymorphisms in both the IL1α and IL1β genes.

Cancer
The transformation of normal cells into malignant ones is a multifactorial process that very probably occurs over many years. IL1 may have a facilitative role in the process of tumorigenesis, inasmuch as it stimulates the proliferation of some tumour cells. For example, human IL1α and IL1β stimulate the proliferation of adult T cell leukaemia cells that were freshly isolated from patients with leukaemia. These cells contained higher levels of IL1 receptor than normal T cells. Notably, the growth of these freshly isolated leukaemia cells appeared to depend on an autocrine effect of IL1α, because proliferation was suppressed by the addition of anti-IL1α. In multiple myeloma, the biological actions of IL1 are consistent with clinical features of disease, including osteolytic bone lesions and homing of myeloma cells to the bone marrow. It remains to be determined whether IL1 production in a pre-myeloma state is a critical factor in progression to active myeloma.

Asthma
The ability of IL1 to stimulate granulocytes, lymphocytes, endothelial cells, epithelial cells, and haemopoietic cells is of potential relevance to the aetiology of asthma. IL1β levels found in the bronchoalveolar lavage fluid of patients with symptomatic asthma were higher than those found in normal volunteers as well as asymptomatic patients. Moreover, expression of both IL1β and IL1Ra in bronchial epithelium of patients with asthma was significantly raised relative to healthy volunteers. Notably, the percentage of macrophages that produced IL1β was significantly higher in the submucosa of patients with asthma than volunteers.

EFFICACY OF BLOCKING IL1 IN VARIOUS DISORDERS
The activity of IL1 may be reduced by several distinct pharmacological interventions—some are non-selective, such as fish oils and corticosteroids, whereas others selectively target IL1, such as anakinra and sIL1R. To date, anakinra is the only selective intervention that has been shown in controlled clinical trials to be effective and well tolerated in the treatment of a specific human disorder, RA.

Non-selective interventions
Fish oil
The production of IL1 as well as TNFα by peripheral blood mononuclear cells of healthy volunteers was reduced by a six week dietary supplementation with the n-3 polyunsaturated fatty acids found in a fish oil concentrate. Notably, production of these cytokines remained diminished even 10 weeks after the end of the supplementation period, but returned to baseline by 20 weeks. It should be recognised that the fish oil supplement also impacts other proinflammatory mediators, including cyclo-oxygenase and lipoxygenase products. The clinical benefit of a fish oil supplement in RA has been evaluated in a clinical setting. Nevertheless, this intervention is effective in animal models of disease, such as collagen induced arthritis, as described in a previous section.

Selective interventions
Anti-IL1 monoclonal antibody
The use of neutralising antibodies to IL1α or IL1β, has not been evaluated in a clinical setting. Nevertheless, this intervention is effective in animal models of disease, such as collagen induced arthritis, as described in a previous section.

Soluble IL1 receptor
The effect of soluble recombinant IL1RI was evaluated in healthy volunteers given an experimental endotoxin...
infusion.\textsuperscript{44} Soluble IL1RI significantly reduced IL1\textbeta concentrations, but it also significantly reduced IL1Ra levels. Notably, at a high dose, soluble IL1RI was associated with significantly raised levels of TNF\alpha, IL8 cell-associated IL1\textbeta, and C reactive protein (CRP). Although treatment reduced the severity of chills, soluble IL1RI did not alter the endotoxin induced changes in body temperature, systemic haemodynamics, or leucocyte or platelet counts. The increase in inflammatory mediators and absence of a discernable anti-inflammatory effect may be due to the neutralisation of IL1Ra by soluble IL1RI treatment.

Anakinra

Early clinical studies with anakinra focused on endotoxaemia, septic shock, and steroid resistant graft versus host disease. Infusion of anakinra significantly reduced endotoxin induced neutrophilia in a study of 14 healthy male volunteers; however, other endotoxin induced symptoms, including fever and tachycardia, were unaffected.\textsuperscript{45} Plasma cytokine levels were reduced non-significantly with anakinra treatment in this study. Anakinra infusion reduced 28 day mortality of patients with sepsis syndrome in a phase II, dose finding, open label study of 99 patients.\textsuperscript{46} However, in two large, double blind, placebo-controlled multicentre trials, anakinra treatment did not provide a significant survival advantage for patients with sepsis syndrome or septic shock.\textsuperscript{47} In a preliminary evaluation of 17 patients with steroid resistant graft versus host disease after bone marrow transplantation, anakinra infusion led to an improvement in acute disease of at least one grade in 63% of evaluable patients.\textsuperscript{48} Complete resolution occurred in two patients during anakinra treatment and in an additional patient after treatment.

The feasibility of delivering anakinra by subcutaneous injection to patients with RA was demonstrated in a three week dose ranging and dose frequency study.\textsuperscript{49} Once daily administration was well tolerated and showed better clinical activity than dosing every three or seven days. These findings prompted a clinical evaluation of anakinra monotherapy in patients with active RA.\textsuperscript{50} In this multicentre study, 472 patients with disease duration for 0.5–8 years were randomly assigned to receive anakinra 30 mg, 75 mg, or 150 mg or placebo once daily by subcutaneous injection for 24 weeks. Patients discontinued any previous disease modifying antirheumatic drug treatment before starting anakinra, but they were allowed to continue to receive NSAIDs and corticosteroids. Patients who completed the initial 24 week treatment were eligible to continue receiving IL1Ra for a second 24 week period.

The primary efficacy variable was the ACR 20% composite index.\textsuperscript{51} After 24 weeks, IL1Ra 150 mg enabled a significantly greater percentage of patients to achieve this level of clinical response as compared with placebo (43% vs 27%; p=0.014). In addition, treatment with any anakinra dose was significantly more effective than placebo (p=0.020). The benefit of anakinra treatment was evident on all measures in the ACR composite index, including swollen and tender joint counts, patient and doctor global assessments, pain, disability, ESR, and CRP.

Figure 2: Effect of IL1Ra on radiographic progression of RA. Serial hand radiographs at baseline and after 24 weeks were evaluated by the Genant method for patients treated with placebo (n=78) or IL1Ra 30 mg (n=86), 75 mg (n=83), or 150 mg (n=79). Statistical significance versus placebo is shown above each histogram. From Jiang Y, Genant HK, Watt I, Cobry M, Brennihan B, Altschun B, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 2000;43:1001–9. Copyright © 2000 Wiley-Liss Inc. Reprinted by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.

Also in this study, hand x ray pictures were taken at baseline and after 24 weeks of treatment, and evaluated by the Genant and Larsen methods (fig 2).\textsuperscript{52} According to the Genant evaluation, radiographic progression was significantly slowed by any anakinra treatment as compared with placebo (p=0.0004), with benefits evident on both bone erosions (p=0.0097) and joint space narrowing (p=0.0003) (fig 2). In the Larsen evaluation, the erosive joint count was significantly reduced by any anakinra treatment as compared with placebo (p=0.005). The benefit of anakinra on joint space narrowing was maintained during the 24 week extension period, but a further slowing of erosions became evident during this period with continued anakinra treatment.

Anakinra was evaluated in combination with methotrexate in another 24 week, double blind, placebo controlled, multicentre study of patients with RA.\textsuperscript{53} This study included 419 patients who had active RA despite receiving methotrexate for at least six months, including stable weekly doses of 12.5–25 mg for the past three months before enrolment. Patients were randomly assigned to receive placebo or one of five different daily doses of anakinra: 0.04, 0.1, 0.4, 1.0, or 2.0 mg/kg. All patients continued to receive their regular methotrexate dose. After 24 weeks, anakinra treatment produced significantly higher ACR 20 response rates than placebo (p=0.0036). The anakinra 1.0 mg/kg group had the highest response rate (42%), which was significantly greater than the 23% response rate with placebo (p=0.021) (fig 3). In addition, the two highest anakinra doses significantly reduced
disability as determined by the Health Assessment Questionnaire (p<0.01).

SAFETY OF IL1Ra

IL1Ra has been generally safe and well tolerated when given by continuous infusion to healthy volunteers and patients with septic syndrome or by daily subcutaneous injection to patients with RA. In a phase I study, administration of anakinra to healthy men by a three hour continuous intravenous infusion at doses of between 1 and 10 mg/kg did not produce clinically significant changes in complete blood counts, mononuclear cell phenotypes, blood chemistry profiles, or serum iron or cortisol levels. In patients with steroid resistant acute graft versus host disease, anakinra was given by a continuous intravenous infusion at doses of 400–3200 mg daily for seven days. A reversible rise of liver transaminases was seen in two of 17 patients, but the enzyme levels returned to normal after completion of anakinra treatment. In patients with severe sepsis, anakinra was delivered by a 100 mg intravenous bolus followed by a 72 hour continuous infusion at a rate of 2 mg/kg/h. Clinical and laboratory adverse event rates were comparable for the IL1Ra and placebo groups. The frequency of microbial superinfections was not increased by anakinra treatment, nor was the resolution of infection delayed by such treatment when appropriately covered by antibiotics.

In RA, monotherapy with anakinra was delivered by a daily subcutaneous injection at doses of 30 mg, 75 mg, or 150 mg. Injection site reactions were the most common adverse event, occurring in 50%, 73%, and 81% of patients at the three respective anakinra doses as compared with 25% of patients in the placebo group. These events were generally mild, usually characterised by some erythema and induration, and usually resolved after 2–3 weeks. At the highest anakinra dose, 5% of patients withdrew owing to injection site reactions as compared with 1–3% in the other groups (fig 4). Infections and allergic reactions occurred at a comparable rate in the anakinra and placebo groups. When anakinra was given in combination with methotrexate, injection site reactions were again the most common adverse event, occurring in 63% of patients receiving the highest anakinra dose (2 mg/kg) as
compared with 19% with placebo (fig 4). In these groups, the withdrawal rate due to injection site reactions was 10% and 3%, respectively. Other adverse events, including infections, were reported at a comparable rate with anakinra and placebo.

The Anakinra safety database, presented in public forum at the FDA Arthritis Advisory Committee in August 2001, has generally revealed an acceptable profile for just under 3000 subjects who have participated in controlled clinical trials. The incidence of serious infections appears to be higher (1.8% v 0.7%) in all patients receiving the 100 mg daily dose. This figure is largely driven by a safety study of 1400 patients where serious infections (those requiring admission to hospital) were noted in 2.1% of anakinra subjects compared with 0.4% of controls. Post hoc analysis of risk factors for serious infections in this study indicates that risk is higher in anakinra subjects either receiving corticosteroids or with a history of asthma or pneumonia.

There is limited information available on the safety of anakinra taken with other biological agents. A small open label 24 week study of anakinra employed upon a background of etanercept treatment showed serious infections in 7% of the 58 patient combination study; leucopenia was seen more frequently, and two patients with neutrophil counts below 1000/mm³ developed subsequent serious infections. The current package insert for anakinra urges extreme caution in the use of anakinra in combination with TNF inhibitors. To date there have been no reports of reactivation tuberculosis for anakinra subjects in clinical trials.

CONCLUSION

A large body of experimental evidence implicates IL1 in the pathogenesis of a variety of human disorders. Many therapeutic interventions either directly or indirectly reduce the biological activities of IL1, and some of these agents, including anakinra, anti-IL1, and sILIR, were effective in a wide range of animal disease models. Nevertheless, translation of these promising preclinical observations into the clinical setting has been a difficult undertaking. On the basis of controlled clinical trials with anakinra, it is now evident that blocking the effects of IL1 contributes to reduction in the symptoms of RA. Treatment with anakinra slowed radiographic disease progression. Moreover, addition of anakinra to existing methotrexate treatment safely reduced signs and symptoms of active disease. Nevertheless, preliminary observations from a small open study on the concomitant use of anakinra with biological induced TNF blockade indicate extreme caution should be exercised until larger and more definitive studies are available. These studies illustrate the clinical use of anakinra in the management of RA. The role of anakinra in the treatment of other disorders, in which IL1 has been implicated to be of pathogenic relevance, still needs to be defined by controlled clinical investigations. Finally, the long term effects of IL1 blockade, especially in combination with other biological agents, need to be evaluated, particularly its safety, because these diseases are chronic and continuous treatment will be required.

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IL-1 antagonists in human diseases


Potential therapeutic uses of interleukin 1 receptor antagonists in human diseases

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