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Treatment of Inflammatory Diseases with IL-1 Blockade

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Abstract

Background.—Autoinflammatory diseases are distinct from autoimmune diseases. Whereas autoinflammatory diseases are due to dysfunctional T-cells and B-cells, autoinflammatory diseases are due to overproduction of macrophage cytokines particularly interleukin-1 beta (IL-1β). A causative role for IL-1 in autoinflammatory diseases is derived from clinical studies blocking the IL-1 receptor or neutralizing monoclonal antibodies or soluble receptors.

Methods.—A review was performed of clinical trials in autoinflammatory diseases using the IL-1 receptor antagonist (anakinra), the soluble IL-1 receptor (rilonacept), antibodies to IL-1β (canakinumab, gevokizumab) and anti-IL-1α (xilonix).

Findings.—Anakinra blocks the IL-1 Receptor type 1 (IL-1R1) and therefore blocks the activities of both IL-1α and IL-1β. Off-label use of anakinra is common for a broad spectrum of inflammatory diseases. Neutralization of IL-1β is used to treat hereditary autoinflammatory diseases but also atherosclerosis. Rilonacept reduces arterial wall inflammation in patients with chronic kidney disease. Neutralization of IL-1α has prolonged life in patients with advanced metastatic colorectal cancer. Compared to other cytokine blocking therapies, reducing the activities of IL-1 has an excellent safety record.

Conclusions.—Blocking IL-1 therapies can be used to treat a wide-spectrum of acute and chronic inflammatory diseases.

Keywords

innate immunity; anakinra; canakinumab; xilonix; rilonacept; cancer

Introduction

The interleukin-1 (IL-1) family consists of 11 cytokines and 10 receptors. The IL-1 family is divided into three subfamilies (Figure 1). Of these, IL-1β and IL-1α are the most inflammatory members and are studied for their role in autoinflammatory diseases. IL-18, a

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member of the family, also plays a role in autoinflammatory inflammatory diseases but because IL-18 induces IFNγ, IL-18 is also studied for its role in autoimmune diseases. Monotherapy specifically blocking IL-1α, IL-1β or IL-18 activities results in a rapid and sustained reduction in disease severity. Although initially studied for the treatment of rare hereditary autoinflammatory diseases, blocking IL-1 activities is also effective in treating common autoinflammatory conditions such as heart failure and acute flares of gout. Ongoing trials target a broad spectrum of new indications, including cancer, atherosclerosis and hearing loss. Three IL-1-targeted agents have been approved: the IL-1 receptor antagonist, anakinra, a soluble decoy receptor, rilonacept, and a neutralizing monoclonal anti-interleukin-1β antibody, canakinumab. In addition, a monoclonal antibody directed against the IL-1 receptor and a neutralizing anti-IL-1α are in clinical trials.

Autoinflammatory and Autoimmune disease

Autoinflammatory diseases are associated with overactive innate inflammation and can be defined as increased inflammation mediated predominantly by IL-1, without the association with autoantibodies or autoreactive T lymphocytes (1). In autoimmune diseases, the adaptive immune system is dysfunctional. 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 TNFα is effective but blocking several cytokines of T-cell origin is also effective. In autoinflammatory diseases, neutralization of TNFα is not effective (such as in gout), or can even exacerbate the condition. In autoinflammatory diseases, the release of IL-1β from the monocyte is often elevated, but in the same cells the production of TNFα is not different from that of healthy controls.

Classic, hereditary autoinflammatory diseases

The classic autoinflammatory diseases are chronic, debilitating syndromes (2). They are rare genetic disorders, but the clinical inflammatory manifestations as well as the hematologic and metabolic abnormalities are common, 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 re-occur a few weeks or several months later. Typically, patients suffer from recurrent fevers, generalized fatigue, diffuse pains in muscles and joints, frank inflammation in the linings of the lungs and peritoneal cavity, loss of appetite and poor sleep. Symptoms also include gastrointestinal disturbances and skin rashes. Neutrophilia and elevated acute phase proteins are present during the episodes.

What accounts for the inflammation? Blood monocytes from patients with autoinflammatory diseases release more IL-1β compared to cells from healthy persons (3–8). Some autoinflammatory conditions are hereditary and due to mutations in the intracellular proteins that control caspase-1, the enzyme that converts IL-1β to an active cytokine prior to release from the cell. With increased secretion of IL-1β, there is greater inflammation.

Familial Mediterranean Fever.

Familial Mediterranean Fever (FMF) is perhaps the most known autoinflammatory disease. Starting in childhood or adolescence, FMF patients suffer life of recurrent bouts of fevers and pain in linings of the abdomen. This pain mimics acute appendicitis and most patients have had abdominal surgery before the diagnosis of FMF is made. The genetic mutation was identified in the *MEFV* gene (after Mediterranean Fever), a previously unknown gene encoding for a protein that was given the name 'pyrin' from the Greek 'pyros' for fire (9). The term pyrexia is sometimes used for fever, as in the fever in FMF. A French consortium suggested the name 'marenostrin' because most patients with FMF are from Mediterranean Sea region. Wild-type pyrin is required to keep a tight control over activation of caspase-1 and the processing and release of active IL-1β whereas the mutation in pyrin results in a loss of this control with greater release of IL-1β (10).

Cryopyrin Associated Periodic Syndrome (CAPS).

In CAPS patients, single amino acid mutations are found in a protein that was originally called "cryopyrin" (11) because the clinical manifestations of the disease are triggered by exposure to cold, hence "cryo". Following exposure to cold, even air-conditioned rooms, these patients develop fever and systemic symptoms (resembling FMF), in which the causative protein had already been called "pyrin", hence the name "cryopyrin". The commonly used term for the protein is NLRP3 (Nucleotide-binding domain and Leucine-rich Repeat Pyrin containing 3) but the name CAPS remains. Before mutation-analysis was available, three clinical variants of disease manifestations were recognized: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome and Neonatal Onset Multi Inflammatory Disease (NOMID, also called CINCA). It is now clear that CAPS is a continuum of diseases with severity from mildest form (FCAS) to most severe NOMID, with overlap between the clinical phenotypes. In Muckle-Wells Syndrome, the patients develop progressive loss of hearing and lose kidney function due to secondary amyloidosis. In children with NOMID there are 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 (6, 12).

TNF-Receptor Associated Periodic Syndrome.

TNF-Receptor Associated Periodic Syndrome (TRAPS) is an autosomal dominant disease caused by mutations in the TNF-receptor type 1 (13). 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 reactive oxygen species activation and possibly other pathways (14, 15). Patients experience recurrent bouts of fever with local and systemic inflammation, initially thought to be due to a lack of circulating soluble TNFα receptors, but now shown to be an IL-1-mediated disease.

Hyper-IgD Syndrome.

Hyper-IgD Syndrome (HIDS) is a genetic, (autosomal recessive) autoinflammatory disorder characterized by 4–6 days of fever, muscle aches, a skin rash, painful mouth ulcers and swollen lymph nodes. The disease is caused by mutations in the enzyme termed 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(16), including activation of caspase-1 (17). Mevalonate kinase deficiency *per se*, is linked to a phenotypic continuum of disease ranging from isolated fever episodes (i.e. Hyper-IgD Syndrome) to a more severe phenotype of fever episodes in combination with cerebellar ataxia, mental retardation, anemia, liver damage and developmental delay which can result in early death.

Common Inflammatory Diseases due to Autoinflammation.

As described above, specific missense mutations in diseases such as FMF and CAPS result in periodic fevers with systemic and local inflammation. These diseases do not involve T-lymphocytes, which are characteristically the effector cells in autoimmune diseases. There are other acute and chronic inflammatory diseases such as gout, pericarditis and heart failure, which are not autoimmune diseases but rather autoinflammatory syndromes. In autoinflammatory diseases, the effector cell is a myeloid cell, characteristically a monocyte or macrophage (18). Because of the safety and relative short duration, anakinra can be used as a diagnostic as well as a treatment for patients refractory to glucocorticoid treatment with undefined autoinflammatory signs and symptoms (19).

Gout, a uniquely IL-1β mediated disease.

Worldwide, osteoarthritis dominates as the cause of painful joints followed by gouty arthritis. By comparison, rheumatoid arthritis accounts for a marginally small number of subjects with painful joints. Nevertheless, the systemic effects of rheumatoid arthritis garner considerable interest in the pathogenesis and treatment of the disease. It is often overlooked that gout is also a systemic disease but also hyperuricemia even in patients without. Gout is the tip of the iceberg for the systemic manifestation isolated hyeruricemia. Subjects with hyperuricemia are in a state of chronic inflammation. For example, there are ample studies linking hyperuricemia with morbidity and mortality associated with hypertension, atherosclerosis, chronic kidney disease and type 2 diabetes (20–22). Soluble urate suppresses the level of the IL-1 Receptor antagonist (IL-1Ra), the natural inhibitor of IL-1β. As a result, IL-1β levels increase and blood monocytes from subjects with hyperuricemia release more IL-1β compared to monocytes from subjects without elevated uric acid (23). Transcriptomic analysis of urate primed monocytes revealed broad increased mTOR signaling and decreased autophagic activity (24). Acute attacks of gouty arthritis are highly responsive to anakinra (25–32), rilonacept (33–37) or canakinumab (38, 39).

Anakinra following an acute myocardial infarction.

The first study examined the effect of anakinra in patients who had suffered a ST-elevated myocardial infarction (STEMI) and had received optimal standard of care. Standard treatment includes anti-coagulation, catherization of the affected coronary arteries and

placement of stents. In that study, anakinra treatment was initiated at 100 mg subcutaneously following stent placement and continues for two weeks (40, 41). Seventy-two hours after the acute event, CRP reaches peak levels and correlates with the degree of inflammation due to the ischemic event as well as to the size of the infarcted myocardium. Anakinra treatment resulted in a significant reduction in the medium level of CRP of 256 in the placebo group to 75 mg/L in patients receiving anakinra (41). Thus, despite optimal standard of care for the acute event, anakinra administered after the event exerts a beneficial effect in reducing the progressive inflammation and damage to the myocardium. From animal studies, the infiltration of neutrophils and monocytes into the penumbra of the ischemic area likely contribute to further damage; anakinra treatment significantly reduces the infiltration (42).

Twelve weeks following the myocardial infarctions, patients were assessed for heart function such a left ventricular ejection fraction. Compared to the placebo-treated group, anakinra treated patients exhibited improved functional status, but did not reach statistical significance (41). A second trial was performed with 30 patients (41). Again, anakinra reduced CRP levels 72 hours after the myocardial infarction ($p=0.002$). After 10–14 weeks, cardiac function was evaluated and the reduction in CRP correlated with a reduction in left ventricular end-systolic volume (41). In both trials, the development of new onset New York Heart Association Grade III and IV heart failure was assessed. When the two trials were compared, the overall reduction in the development of heart failure was 30% in the placebo-treated groups compared to 5% in the anakinra group ($p=0.035$) (41).

Anakinra treatment of heart failure in patients on optimal standard of care.

Additional studies examined the effect of anakinra on heart failure in patients with poor exercise tolerance and signs of systemic inflammation. In a clinical trial, seven patients with heart failure and markers of systemic inflammation despite standard of care treatment received 100 mg of anakinra daily for 14 days. There was a statistically significant improvement in oxygen consumption compared to baseline measurements and a decrease in carbon dioxide (43). This first study established a role for treating patients with anakinra for refractory heart failure.

Patients with acute decompensated heart failure are hospitalized and present a therapeutic challenge. These patients have signs of systemic inflammation in addition to being in refractory heart failure while on standard of care. Thirty patients with acute decompensated heart failure, ejection fraction less than 40% and elevated CRP were randomized to receive either anakinra or placebo (44). Upon entering the trial, patients received either 100 mg anakinra or placebo twice daily for 3 days followed by 11 days of once daily dosing. Three days into the trial, CRP decreased by 61% in the anakinra group compared to the placebo treated group ($p=0.004$) (44). The authors concluded that IL-1 receptor blockade reduced the systemic inflammation in these patients but the study was not powered to determine a clinical benefit.

In these trials, patients are treated with anakinra for 14 days and although clinical and objective data indicate a functional improvement and reduced inflammation, it is possible that a more prolonged course of anakinra treatment would result in greater benefit for these patients. Patients hospitalized with an episode of acute decompensated heart failure have a

high incidence for repeated hospitalizations for recurrent bouts of heart failure. Therefore, a trial was performed comparing treatment with 100 mg of daily anakinra of two and 12 weeks duration in patients discharged from the hospital following an episode of acute decompensated heart failure. In this study, a placebo treated group was also included. Patients treated with 12 weeks of anakinra exhibited improved aerobic capacity, ventilatory efficiency, quality of life and reduced readmission rates compared to placebo but also compared to patients treated with two weeks of anakinra (45).

Treating refractory idiopathic pericarditis with anakinra.

Pericarditis can be a manifestation of an inherited auto-inflammatory disorder such as TRAPS, FMF and CAPS (46, 47). Patients with Adult Onset Still Disease (AOSD) also have bouts of pericarditis (48) that respond to anakinra. However, there is no genetic association with idiopathic pericarditis, which most often develops after a viral illness. A summary of case reports that anakinra was highly effective in treating these patients was published in 2011 (49) and since that report a large number of studies have established the rapid and sustained benefit of anakinra, particularly in patients refractory to colchicine (50–62). A recent review of anakinra treatment for idiopathic pericarditis concluded that the disease is an example of IL-1-driven autoinflammation (45). Treating pericarditis with etanercept or infliximab has not been successful and in some reports anti-TNFα treatment for Crohn's Disease has worsened the disease (63, 64).

Acute thrombotic stroke.

Anakinra was administered to patients admitted to the hospital within 6 hours of the signs of an acute thrombotic stroke (65). The dose, 2 mg/kg/hour for 72 hours, was the same dose used to treat septic shock. The trial in 34 patients was randomized and placebo controlled. Compared to placebo-treated controls, peripheral CRP, neutrophils and IL-6 levels were lower in patients treated with anakinra (65). Although the study was not powered for significant improved neurological outcome, the subgroup of patients with cortical infarcts performed better compared to the placebo group.

Intravenous anakinra was also administered to patients with subarachnoid hemorrhage due to aneurysmal rupture (66). Within 72 hours of the onset of symptoms, six patients received a bolus infusion of 500 mg of anakinra, followed by a steady infusion of 10 mg/kg/hour for 24 hours. Seven patients received placebo infusions. At 24 hours, CSF levels for IL-6 were reduced in the anakinra group compared to those patients receiving placebo at 24 hours ($p=0.06$) (66). In a related study, 25 patients with a cerebral ventricular drain in place as part of treatment for a subarachnoid bleed received increasing doses of intravenous anakinra (67). First, the patients received a bolus dose of anakinra (100 mg to 500 mg) followed by a four-hour infusion of anakinra from 1 to 10 mg per kilogram per hour. Plasma and CSF levels of anakinra were monitored. The objective of the study was to establish the dose regimen of peripheral anakinra that resulted in a CSF level of anakinra of 100 ng/mL within 45 minutes of the onset of the infusion. A concentration of 100 ng/mL is 100-fold greater that that measured in the CSF of children treated for 3 months with 100 mg of daily subcutaneous anakinra (6). This concentration (100 ng/mL) was deemed neuroprotective based on rats subjected to brain ischemia (68). In humans, CSF levels of 100 ng/mL were

achieved with the highest regimen, that is, a bolus of 500 mg followed by 4 hours of anakinra at 10 mg/kg/hour (67, 69). The authors concluded that anakinra passively enters the brain in patients with a subarachnoid hemorrhage. Given these data, this regimen of anakinra for patients with cerebral vascular accidents such as thrombotic strokes and subarachnoid hemorrhages would provide reduced inflammation at the site of the lesion such as reduced infiltration of neutrophils and edema. Whether reduced IL-1-mediated inflammation will result in improved neurological outcomes remains to be determined in randomized, placebo-controlled blinded studies.

Traumatic brain injury.

Traumatic brain injury is a major cause of death worldwide in persons under the age of 40 years. An even greater number are left with severe disabilities, which results in a significant economic cost. A trial randomized, open-labeled trial was performed comparing 5 days of 100 mg subcutaneous anakinra to placebo in 20 patients with diffuse traumatic brain injury within the previous 24 hours. After a 6-hour monitoring period, patients received either anakinra or placebo. A central microdialysis was in placed in each patient as part of standard of care. Patients were intubated and were receiving ventilatory support. During the 6 hour monitoring period, the mean level in the CSF was 78 pg/mL but rose to 138 pg/mL 12 hours after the first dose of anakinra (70). In general, inflammatory cytokines in the CSF were lower in patients treated with anakinra; of these, macrophage-derived chemoattractant-1 (MDC-1) was significantly lower on days 1–5 ($p=0.05$) compared to patients treated with the placebo. On the 5^{th} day of anakinra treatment, mean MDC-1 was 1.04 pg/mL compared to 45.4 pg/mL in the placebo group (70). The study was too small to detect clinic improvement, although the marked decrease in CSF levels MDC-1 represents a beneficial CNS effect of anakinra. Treatment earlier and longer would likely result in improved clinical outcomes.

Treatment of epilepsy with IL-1 blockade.

A role for IL-1 in seizure disorders is based on the innovative studies of Vezzani and Barfai (71). Although IL-1α is found in brain astrocytes and microglia, the data indicate that IL-1β contributes to epileptic seizures. Indeed, there was a clinical trial of an oral caspase-1 inhibitor (VX-765, NCT01048255) in subjects refractory to standard anti-epilepsy drugs. In that trial, 48 people received 900 mg of VX-765 three times each day and 12 people received placebo for six weeks followed by a six week post-treatment observation period. Although the primary endpoint was safety and tolerability, decreased seizure rates were less in the treatment arm. For example, 13–19% of the treatment group was seizure-free during the last two weeks compared to 0–9% in the placebo group. During the first two weeks of the follow-up period, there was a 19–31% decrease in the seizure rate of the treatment arm compared to 0–9% in the placebo arm.

Several studies have focused on febrile seizures since these are the most common type of seizure activity. Using an animal model for febrile seizures, an agonist role for IL-1β and an antagonist role for endogenous IL-1Ra in the hippocampus have been reported (72). Other studies have examined circulating cytokines in patients with recurrent seizures and find elevated levels of IL-6, IL-1Ra in the post-ictal period (73). In one study, elevated IL-1β has also been observed in the intracellular-ictal period in patients with recurrent temporal lobe

epilepsy (74). Some studies have reported polymorphisms in IL-1α, IL-1β and IL-1Ra that are associated with subjects who develop epilepsy as adults (75–79).

Anakinra has been administered a young patient with a severe seizure disorder termed febrile infection-related epilepsy syndrome. This syndrome, which often follows an infectious encephalopathy, has a high mortality rate and there are few treatment options. The patient had recurrent seizures each day, which be came increasing less and even ceased while being treated with daily subcutaneous anakinra (80). When anakinra was stopped, seizures resumed only to decrease again upon restarting. CSF cytokines decreased with anakinra treatment.

Anakinra for MAS (Macrophage Activation Syndrome).

The pathogenesis of MAS has been the topic of increasing reports (81) and the incidence of MAS is likely underestimated. For example, there are case reports of MAS in patients with Ebola virus, parasitic and influenza infections (82, 83). The use of anakinra in MAS is primarily in patients with systemic juvenile idiopathic arthritis (sJIA). Similar to sJIA, some patients with Adult Onset Still's Disease (AOSD) also develop MAS. There are several reports of anakinra use in sJIA and AOSD. Although canakinumab is approved for sJIA, anakinra is commonly used in these patients, possibly because anakinra also reduces the activity of IL-1α. Patients with sJIA or AOSD and treated with anakinra or canakinumab can develop MAS while on therapy. In some cases, the dose of anakinra is increased with clinical improvement.

What is the role for IL-1 in MAS? IL-1 acts at several levels related to the signs and symptoms of MAS. Fever and the increase hepatic ferritin are IL-1 mediated since IL-18 does not cause fever (84, 85), does not induce PGE2 (86) and dose not induce hepatic acute phase proteins (87). A critical role for IL-1 in MAS is the induction of IL-18. The endothelium contains constitutively preformed IL-18 precursor (88) and IL-1 induces the release of IL-18. High levels of IL-18 reported in MAS are not of myeloid origin but rather are derived from the IL-1-activated endothelium. IL-1-induced myocardial suppression is mediated by IL-18 (88, 89). IL-1 mediates the fever, hyperferritimia, coagulopathy and the production of IL-18. Also shown, IL-18 likely mediates the hypersplenism, elevated IFNγ, hypertriglyceridemia and hypotension of MAS. With high levels of IL-18-dependent IFNγ, there is macrophage activation and hemophagocytosis, which characterizes MAS.

Anakinra treatment of MAS as a manifestation with septic shock.

There were three randomized, placebo-controlled trials of anakinra to reduce all cause 28-day mortality in patients with a diagnosis of septic shock (90–92). Nearly 2,000 patients were enrolled in these trials. The first trial was dose-response open labeled trial (91). The second trial tested two doses, 1 mg/kg/hour for 72 hours compared to 2 mg/kg/hour for 72 hours (92). This trial revealed that survival increased over placebo when the patient enrolled in the trial had a greater than 24% risk of death but did not reach statistical significance. The third trial was performed in 91 centers world-wide but stopped at mid-way as the likelihood of reaching a statistically significant endpoint was low (90). A re-analysis of the data from the third trial was performed subsequently (93). The analysis revealed that patients with

fever, disseminated intravascular coagulation, hepatobiliary dysfunction, cytopenias, and hyperferritinemia were features of MAS. Data were available for 763 adults from the original study cohort, randomized to receive either anakinra or placebo. Concurrent hepatobiliary dysfunction/disseminated intravascular coagulation was noted in 43 patients (5.6% of total; 18–75 years old; 47% women). Treatment with anakinra improved 28-day survival: 65.4% anakinra vs. 35.3% placebo), with hazard ratio for death 0.28 (0.11–0.71; p = 0.0071) (93).

Is atherosclerosis an autoinflammatory disease?

For at least three decades, a role for cytokine-mediated inflammation in the arteries, particularly the coronary and carotid arteries, has been the subject of basic as well as pre-clinical studies. The first clinical testing of such a concept was the use of anakinra in patients with rheumatoid arthritis and cardiovascular disease (94, 95). In those studies, anakinra treatment resulted in improved in endothelial and coronary aortic function as well as left ventricular myocardial deformation.

Background of the CANTOS trial.

The design of the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial was published in 2011 (96) and based on a reduction in circulating CRP in inflammatory diseases such as gout and several hereditary diseases upon treatment with anti-IL-1β monoclonal antibodies (reviewed in (18)). However, anakinra treatment had already been used in a randomized, placebo-controlled study in Type 2 diabetics; this trial was published in the New England Journal of Medicine in 2007. In that trial, after 4 and 13 weeks, anakinra significantly reduced CRP, IL-6 and the level of glycated hemoglobin (97). In many ways, the data from the anakinra trial served as a rationale for the CANTOS trial because Type 2 diabetics are comprise a large number of the high-risk population for a second cardiovascular event. Thus, a Phase 2b trial was performed using a dose-response of canakinumab of 5, 15, 50 and 150 mg monthly for 4 months in 556 Type 2 diabetics being treated with standard of care doses of statins but with CRP >2 mg/L. The median percentage reductions in CRP were 52, 66, 69, and 72, respectively, compared to 2.9 in the placebo group (98). As anticipated, IL-6 levels were also significantly reduced in the study. In many, ways the data from Phase 2b canakinumab study was similar to those of the 2007 anakinra trial (97). Another trial in Type 2 diabetic patients specifically used a neutralizing antibody to IL-1β, gevokizumab (99). That trial similarly reported the reductions in CRP. Therefore, at the time of the initiation of CANTOS trial, blocking IL-1 with anakinra or specifically IL-1β in Type 2 patients at risk for a second cardiovascular event was established.

CANTOS achieves its primary and secondary endpoints.

The role of low density lipoprotein (LDL) in the pathogenesis of atherosclerosis has been the basis for drug development for several decades. Lowering plasma LDL with statins has proven efficacy in reducing myocardial infarctions and deaths. However, the atherosclerotic process includes a significant role for cytokine-mediated arterial inflammation and IL-1β has been the most studied cytokine for its detrimental role in the formation of the atherosclerotic lesion (100). The CANTOS trial was a world-wide study in 10,000 patients who had survived a previous myocardial infarction or stroke but despite standard of care

with statin therapy, continued to have a level of CRP greater than 2 mg/L; this level of CRP is a biomarker for risk of a second cardiovascular event (101). The primary endpoint of the trial was the first occurrence of a fatal or nonfatal myocardial infarction or non-fatal stroke. This is also defined as a three-point MACE. The first secondary end points included hospitalization for unstable angina that required rapid revascularization. There was another secondary endpoint; did IL-1β neutralization reduce the incidence of new-onset type 2 diabetes in patients with prediabetes at the time of randomization? Thus the CANTOS trial tested the hypothesis that IL-1β was causative in the atherosclerotic process, which resulted in a cardiovascular event.

Three doses were used; 50 mg, 150 mg, and 300 mg of canakinumab or Placebo administered 4 times a year for 4 years. The decrease in CRP was dose dependent. Importantly, canakinumab did not reduce lipid levels and this observation provides the conclusion that inflammation, and particularly IL-1β-induced inflammation, is as important as lowering LDL in reducing cardiovascular events. The reduction in a composite of cardiovascular events met the primary endpoint. The hazard ratios as compared with placebo were 0.85 (0.74 to 0.98; P=0.021) in subjects receiving 150 mg and 0.86 (0.75 to 0.99; P=0.031) in the 300 mg group. The reduction in the 50 mg dose was not statistically significant. The secondary endpoint of hospitalization for unstable angina and rapid angioplasty was reduced compared to placebo treated patients (Hazard Ratio of 0.83; 95% confidence level 0.73 to 0.95; P=0.005).

Is hearing loss as an autoinflammatory syndrome.

Sensorineural deafness is a prominent characteristic of persons with Muckle-Wells syndrome and persons with mutations in NLRP3 (102). The first reports of efficacy of anakinra to improve hearing in were in patients with Muckle-Wells syndrome (103) and several other reports subsequently followed (47, 104–111). In general, the reversal in sensorineural deafness with anakinra treatment was unexpected and signified the concept that hearing loss in autoinflammatory diseases was due to a reversible chronic inflammatory response and not due to loss of neuronal function. Thus early treatment is more likely to be beneficial (112). The autoinflammatory syndromes are gain-of-function mutations of NLRP3 and are autosomal dominant diseases. A recent study reported tow families with a missense mutation (Arg918Gln) in NLRP3 as the cause of autosomal-dominant sensorineural hearing loss (113). Treatment of one family member with IL-1β blockade reversed the systemic inflammation. However, treatment of the other family revealed that hearing loss was present without systemic inflammation (113). Thus local macrophages in the cochlea may release IL-1β, which leads to the hearing loss. It is also likely that somatic mutation in NLRP3 may account for other hearing-lose disorders.

Autoinflammation in Cancer: the role of IL-1 in the progression of cancer

IL-1 and the tumor microenvironment.

In the tumor microenvironment, one considers the role of IL-1 from the infiltrating myeloid cells as well as IL-1 production from the tumor cell or both. In addition, the production of IL-1Ra from the infiltrating myeloid cells is of considerable relevance. It is also possible that

tumors also produce IL-1Ra. In health, the IL-1α precursor is found in nearly all epithelial cells such as the entire gastrointestinal tract, the epithelial cells of the lung, the ductal epithelium of the breast, prostatic cells, the hepatocyte and lining of the bladder and the renal epithelium. Therefore, tumors originating from these cells will contain the IL-1α precursor. Melanoma cells, B –cells of lymphomas, Hodgkin's cells and the plasma cell of multiple myeloma contain the IL-1β precursor as reviewed in (114). In general, the level of IL-1α or IL-1β often correlates with poor outcomes (115). The level of IL-1β in the tumor microenvironment may be from the tumor cell itself but more likely to be from infiltrating myeloid cells, such as monocytes, neutrophils, dendritic and Natural Killer (NK) cells. T-cells are often present in the tumor and can be a source of either IL-1α or IL-1β. Regardless of whether IL-1 is of tumor cell origin or from infiltrating bone marrow-derived cells, IL-1 plays a major role in inducing angiogenesis (116–118). As the tumor increases in size due to neovascularization, IL-1 induction of matrix metalloproteinases facilitates the entry of tumor cells into the circulation and result in local or distant metastasis. IL-1 itself is a growth factor for malignant cells but IL-1 also induces growth factor production from resident stromal cells. For example, in multiple myeloma, IL-1β from the plasma cell in the bone marrow induces IL-6 from the stromal cells; IL-6 is a growth factor for plasma cells.

IL-1 in the systemic response to cancer.

Although levels of circulating IL-1β or IL-1α are low and often below the level of quantification in cancer (119), the systemic response to cancer reveals that the inflammation of cancer is due, in part, to IL-1. In two studies treating patients with metastatic colorectal cancer with a neutralizing antibody to IL-1α, the levels of IL-6 fall consistently as do the platelet counts (120, 121). Not unexpectedly, the inflammation of cancer increases the levels of circulating of IL-1Ra (114). In several studies, the levels of IL-1Ra reflect IL-1 driven inflammation, as is the case with non-cancer inflammation such a patients with coronary artery inflammation (122). However, in some cancers, the expected elevated levels of IL-1Ra are low, as reviewed in (114)

Anakinra to treat pre-multiple myeloma.

The first study to use a IL-1 blocking therapy to treat cancer is in patients with a diagnosis of pre-myeloma stage. Anakinra treatment was assessed in patients with smoldering or indolent myeloma, and first reported by Lust and co-workers in 2009 (123). The treatment was the standard dose of 100 mg daily of anakinra plus a weekly low dose of 20 mg of oral dexamethasone. The rationale for using anakinra in these patients is to reduce progression to overt myeloma, a consistently fatal disease even with advanced chemotherapeutics and bone marrow transplantation. The mechanism of action of IL-1 blockade is based on data that IL-1β released from bone marrow plasma cell induces IL-6 production from marrow stromal cells; futhermore, IL-6 is a growth factor for the malignant plasma cell (124). Since the amount of IL-1β released from malignant plasma cells is low, anakinra would reduce IL-6 with greater efficacy compared to neutralizing IL-6. In addition, experimental data revealed that although anakinra was highly effective in reducing IL-1β induced IL-6 *in vitro*, adding dexamethasone resulted in the death of the plasma cells (123–125).

A follow-up assessment of the treated cohort of patients has recently been reported (126). A reduction in serum C-reactive protein (CRP) level of 40 or greater percent from baseline was used as a biomarker of response to anakinra. Of the 47 patients, 22 patients did not have this a 40% fall in CRP; the median progression free survival was 11 months. However, in 25 patients with a fall in CRP of 40% or greater, the median progression free survival was 104 months ($p<0.001$). Moreover, the median overall survival of the responders has not been reached whereas the overall survival of those patients without a 40% reduction in CRP was 7.9 years $p<0.001$).

The clinical assessment of patients with smoldering myeloma includes a therapeutic intervention or a “wait and see” approach. Since the progression to active myeloma in many patients is 6 months to one year, blocking IL-1 with anakinra is a strategy for preventing progression of the disease. Each of the 47 patients in the study met established criteria for smoldering myeloma or indolent myeloma (126). Patients who did progress had statistically significant evidence of more active disease at time of enrollment. The standard of care for active multiple myeloma often is autologous bone marrow transplantation, but not in older patients. Therefore, when considering the overall survival in the 47 patients, the data include those with transplantation. In the 25 patients with a CRP decrease of 40% or greater and without bone marrow transplantation, many remain without progression to active disease. As such, a universally fatal disease is held at bay by daily anakinra and a weekly low dose of dexamethasone. It is possible that anakinra therapy in those without a 40% fall in CRP (considered non-responders) began anakinra therapy at a time when progression had already advanced. In contrast, anakinra when anakinra was started at an earlier stage of the disease, the Progression Free Survival and as well as Overall Survival was significantly greater.

Anakinra for solid tumors.

Despite a considerable number of reports in various animal models of solid tumors, there has been limited use of anakinra to treat solid tumors. Models of breast cancer are of particular interest based on data that the level of IL-1β in biopsies and excised tumors from patients with hormone receptor negative breast cancer correlate with poor prognosis (127). A polymorphism in the IL-1β gene (rs1143627) has been proposed to relate to increased breast cancer risk but a meta analysis of several studies reveals the polymorphisms is not a risk factor (128).

How much of anakinra therapy is blockade of IL-1α activity?

Because IL-1α and IL-1β can play a role in augmenting immune recognition, a prevailing, but misunderstood concept, is that blocking IL-1β or IL-1α would contribute to the immunosuppression of cancer and be contraindicated. However, reversing the immunosuppression of cancer has been validated with blocking CTLA4 and PD-1. Therefore, there is less reluctance to neutralize an immunostimulatory cytokine such as IL-1α. In what may be landmark milestone studies, patients with refractory, endstage cancer and losing weight received a course of neutralizing human anti-human IL-1α(129). Within the treated population, a significant number of patients responded with an increase in lean body mass (LBM), decreased constitutional symptoms and extended life compared to non-responders.

The study, albeit small, is the first to specifically neutralize IL-1α, a highly inflammatory member of the IL-1 family. It is a unique contribution for many reasons, particularly in end stage cancer patients. Since blocking the IL-1 receptor with anakinra or neutralizing IL-1β with canakinumab or rilonacept (reviewed in (18)) is without symptom side-effects, it was not unexpected that there were no symptom side-effects with anti-IL-1α. Importantly, the study evokes an examination of likely mechanisms, which could account for the objective and constitutional endpoints. First, the data demonstrate that treatment reduces systemic inflammation since a fall in circulating IL-6 levels remains one of the most consistent observations of blocking IL-1 (18). The source of the inflammatory trigger is likely the tumor itself, as all cancer cells of epithelial cell origin contain IL-1α in its precursor form. Inflammation also is due to invading stromal cells into the tumor microenvironment. As tumors out grow their vascular supply, they become necrotic, the IL-1α precursor is readily released and triggers local production of chemokines, which facilitate an influx of neutrophils and monocytes(18). Unlike precursor of IL-1β, the IL-1α precursor is fully active(130). Neutralization of local IL-1α likely reduces the infiltration of tumor-associated macrophages and myeloid derived suppressor cells, which contribute to the immunosuppression cancer mediated by inflammation (131).

At some point, this local inflammation must become systemic in order to account for one of the clinical endpoints of the study, the association of increased survival (19.3 months) with increased LBM in patients with colorectal cancer compared to 6.6 months in those who failed to increase LBM. The association of non-cancer chronic inflammation with loss of LBM is well established and IL-1 can directly induce muscle protein breakdown (132). The study also reports a reduction in fatigue, which is consistent with the use of anakinra in patients with inflammatory diseases unrelated to cancer (reviewed in(18)). In the early 1990's either IL-1β or IL-1α was administered to patients with suppressed bone-marrow due to chemotherapy in order to stimulate hematopoiesis; although effective, picomolar concentrations of IL-1α was toxic with fever, severe fatigue, loss of appetite, myalgias and frank hypotension (133). Since picomolar concentrations of IL-1α induce these symptoms, demonstrating elevated circulating IL-1α should not be a criterion for the rationale of blocking IL-1α in cancer. IL-1α is also present on platelets and may account for the systemic effects such as elevated IL-6. In fact, the longstanding reports of platelet involvement in metastasis, which would include platelet-endothelial cell interaction (134), may now be, in part, understood by neutralization of IL-1α. This study is the first clinical evidence that endogenous IL-1α-induced IL-6 contributes to the thrombocytosis in cancer (133).

Additional possible mechanisms of action with neutralization of IL-1α include decreased angiogenesis (116) and decreased immunosuppression (135). IL-1α neutralization also includes direct anti-tumor properties by inhibition of tumor growth. With IL-1α presence in non-cancerous as well as cancerous cells and given the broad inflammatory properties of IL-1α, no one mechanism accounts for the study's observations (129). We are left questions. Is refractory endstage cancer with progressive loss in LBM sufficient to initiate treatment with IL-1α neutralization? Given the near total lack of side-effects, the long-term safety of IL-1 blockade (18) and the efficacy of MABp1, there are few reasons to withhold treatment in this population. Would neutralizing IL-1α exhibit a greater efficacy if used earlier as an

adjunct during chemotherapy? For example, would neutralizing IL-1α potentiate the anti-tumor effect of tyrosine kinase inhibitors? Since we know that IL-1 induces myeloid suppressor cells(131), would neutralizing IL-1α be beneficial if used in combination with anti-CTLA4 or anti-PD-1?

CANTOS reveals a role for IL-1β in the progression of cancer.

Patients considered for entry into the CANTOS trial with a known cancer were not enrolled. The 10,061 patients were randomized to receive 50, 150, 300 mg of canakinumab or Placebo every 3 months. However, during the 4 year duration, these subjects were evaluated for a diagnosis of cancer by oncologists blinded to the whether the patients were treated with canakinumab or the Placebo. The first observation was remarkable; there were 196 cancer deaths in the study but in patients receiving the 300 mg dose, there was 51% reduction in death from any cancer ($p=0.0009$) (136). The baseline CRP levels in those patients who were determined to have lung cancer was 6.0 mg/L compared to 4.2 mg/L in patients with no CRP ($p<0.0001$). Similarly, the baseline IL-6 in the cancer group was 3.2 pg/ml compared to 2.6 pg/mL in those without a diagnosis of cancer ($p<0.0001$). The incidence of lung cancer diagnosis was reduced by 67% in patients receiving the 300 mg dose ($P=0.00008$). In this group of patients with lung cancer, treatment with the 300 mg dose of canakinumab reduced fatal lung cancer by 77% (0.0002).

Can autoinflammation explain cancer progression?

The reduction in the incidence and survival of cancer demonstrated in the CANTOS trial reveals the role of IL-1 driven inflammation and the progression of cancer. As listed in Table 1, there are several known inflammatory properties of IL-1, which mediate cancer progression. A fundamental concept in autoinflammation is that regardless of the initiating event, as inflammation increases the production of IL-1 also increases and contributes to more inflammation. From Table 1, cancer progression from its early stages of vascularization and local spread to invasion into the circulation and lymphatics suggest autoinflammatory mechanisms independent of T or B cell function. The suppression of acquired immune responses in cancer is specific for the neoantigens of the tumor but the IL-1-driven immunosuppression is non-specific and therefore due to autoinflammation. The data from the CANTOS trial as well as anti-IL-1α treatment of advanced metastatic cancer support the concept that IL-1 blockade a safe, non-toxic, durable checkpoint inhibitor, reversing the immunosuppression of cancer-induced inflammation Would reversing the immunosuppression of cancer by the toxic, checkpoint inhibitors be better served when used in combination with IL-1 blockade? Would treating very early cancer with IL-1 blockade monotherapy prevent cancer progression?

Conclusions.

Blocking IL-1 therapies can be used to treat a wide-spectrum of acute and chronic inflammatory diseases, including cancer, due to autoinflammation.

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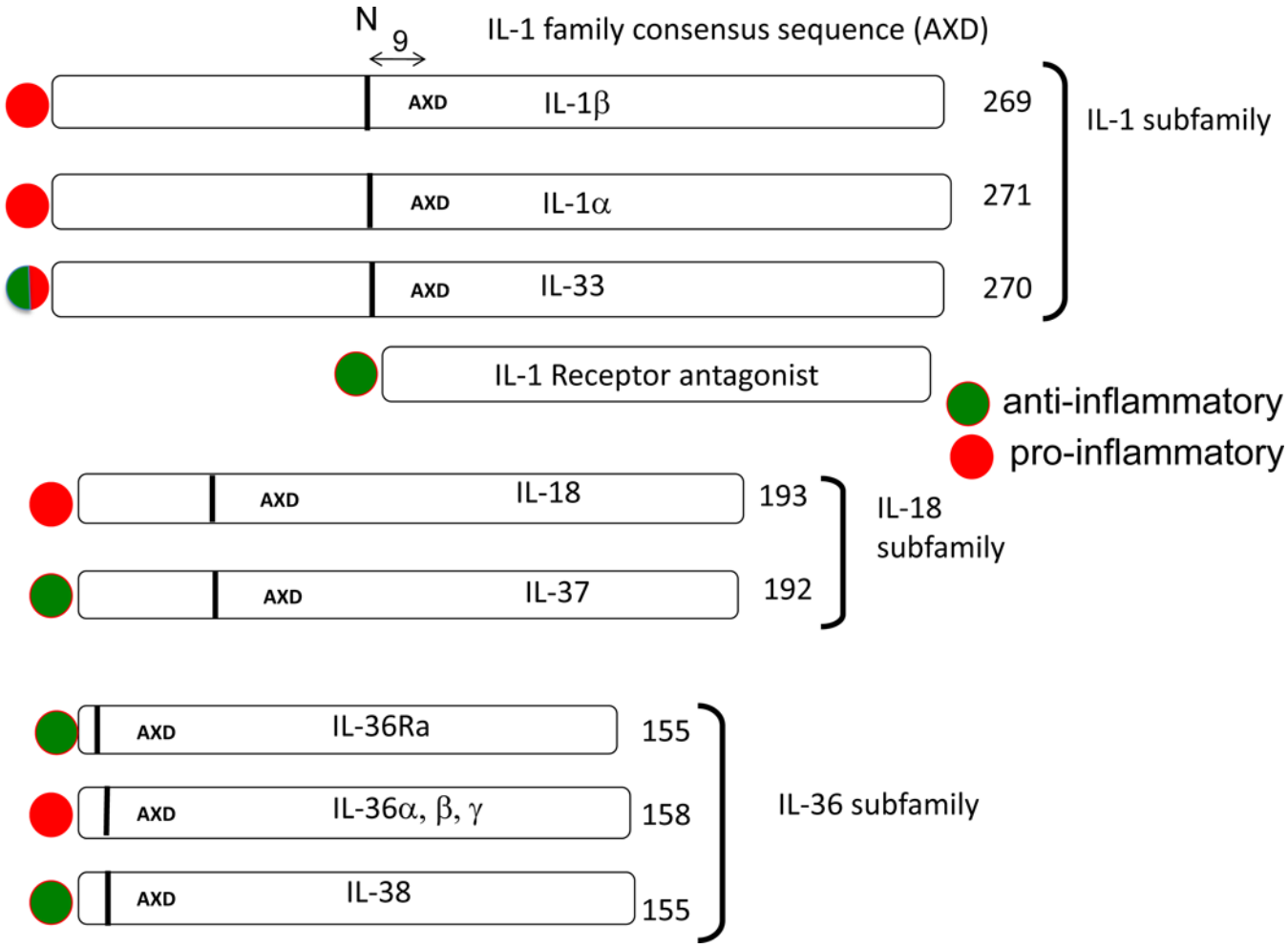

Figure 1. The 3 subfamilies of the IL-1 family.

The lengths of the precursors are shown with the number of amino acids indicated at the end of each cytokine. The location of IL-1 family consensus sequence AXD is indicated in each precursor. In consensus sequence AXD, the A is an aliphatic amino acid, X is any amino acid and then D is always aspartic acid. The aspartic acid D is not the aspartic acid for the recognition of caspase-1 cleavage. Nine amino acids preceding the AXD site is a vertical bar. The vertical bar indicates the location of the optimal N-terminus. The processing enzymes of the precursors that result in an optimal N-terminus differ for each member. Some members of the IL-1 family have more than one AXD site thus creating an alternative N-terminus, for example IL-37 (137). The N-terminus affects the dimensional structure of the cytokine and therefore receptor binding and activity (138). In the case of IL-1β, nine amino acids preceding the AXD site is the caspase-1 cleavage site at amino acid 117. The IL-1 family members with proinflammatory properties are indicated by a red circle whereas a green circle represents cytokines that are anti-inflammatory. IL-1Ra is a unique member of the IL-1 family and highly homologous to IL-1β. IL-1Ra precursor has a classic signal peptide, is processed in the Golgi and readily secreted. There is an intracellular form of the

IL-1Ra generated by alternate splicing. Intracellular IL-1Ra plays a role inside the cell (139). Because IL-1Ra has a signal peptide and is readily secreted, there is no AXD site.

Table 1

IL-1-mediated Mechanisms of Cancer Promotion

Angiogenesis, IL-1-dependent VEGF production, increased VEGFR
Generation of Myeloid-derived Suppressor Cells (MDSC)
Elevated IL-8 and chemokines, including monocyte chemotaxis (for MDSC)
Migration of endothelial precursors into tumors
Increased basic FGF, PDGF, IL-6 and other stromal growth factors
Neutrophil accumulation in tumor
Growth factor production (GM-CSF, FGF, IL-6, IL-1, chemokines)
Thrombocytosis, platelet-derived IL-1α
Induction of matrix metalloproteinases (MMP) for local spread
Cyclooxygenase (increased PGE2) for immunosuppression
Immunosuppression (increased PD-l ligand and CTLA-4)
Low IL-1Ra circulating levels due to high uric acid levels
Increased endothelial tissue factor for coagulopathy
Increased ICAM-1, increased VCAM-1 for local and metastatic tumor spread