Inflammation and Cardiovascular Disease
Role of the Interleukin-1 Receptor Antagonist

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Inflammation plays an important role in the development and progression of a variety of cardiovascular conditions, most notably coronary atherosclerosis and congestive heart failure. A number of inflammatory molecules have been implicated in these processes, including interleukin-1 (IL-1). The IL-1 gene family consists of 3 proteins, IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra). IL-1α and IL-1β exert their similar effects by binding to the IL-1 type I receptor. The IL-1 type II receptor also binds IL-1α and IL-1β but acts as a decoy receptor and is not involved in signal transduction, thereby counterbalancing the inflammatory effects of IL-1α and IL-1β. IL-1ra is an endogenous inhibitor of IL-1α and IL-1β, which competitively binds to the IL-1 type I receptor without activating it.

This cascade promotes atherosclerosis and plaque destabilization. IL-1 and other proinflammatory cytokines have also been implicated in the progression of heart failure, as a result of their negative inotropic effects and deleterious effects on left ventricular remodeling. Another important mechanism by which IL-1 may enhance atherogenesis and exacerbate left ventricular dysfunction is by contributing to endothelial dysfunction. IL-1 stimulates release of endothelin-1, a potent vasoconstrictor, and IL-1 stimulates inducible nitric oxide synthase, which increases the formation of reactive oxygen species and reactive nitrogen species (eg, nitrotyrosine), which leads to oxidative and so-called nitrosative stress and endothelial dysfunction (Figure). The important role of IL-1 in the development and progression of atherosclerosis has been highlighted by preclinical studies demonstrating less atherosclerosis in IL-1 knockout or IL-1 type I receptor knockout mice. Moreover, IL-1ra–deficient mice are more prone to neointima development after endothelial injury and more prone to atherogenesis. Administration of IL-1 to porcine coronary arteries leads to neointimal formation, whereas balloon angioplasty results in increased levels of IL-1β at the injured segment of the porcine coronary artery but not at uninvolved sites. Treatment of balloon-injured or stented porcine coronary arteries with IL-1ra reduces neointimal formation.

In clinical studies, IL-β has been found in greater concentration in atherosclerotic human coronary arteries. An association between certain IL-1ra gene polymorphisms and the presence and extent of coronary disease, as well as the occurrence of restenosis after coronary stenting, has also been identified. One of the body’s responses to acute inflammatory processes, such as acute coronary syndromes, is to upregulate IL-1ra. For example, patients with acute coronary syndromes have been shown to have significantly greater concentrations of IL-1ra than those with stable coronary disease or with no coronary disease. Indeed, because of its early release at sites of ruptured plaque, even before myocardial necrosis has occurred, IL-1ra was found to be elevated in patients presenting with ST-segment elevation myocardial infarction earlier than traditional markers of necrosis.

Anakinra
Anakinra is a nonglycosylated, recombinant form of human IL-1ra that, like endogenous IL-1ra, competitively inhibits IL-1 by binding the IL-1 type I receptor. A commercially available form of anakinra (Kinere) was approved by the US Food and Drug Administration in 2001 for treatment of patients with rheumatoid arthritis on the basis of studies demonstrating its efficacy as monotherapy; a subsequent trial evaluating its role in combination with anti-tumor necrosis factor agents is underway.
factor-α therapy did not show additional benefit over anti-tumor necrosis factor-α alone, which suggests some overlap in the deleterious inflammatory effects of these 2 cytokines.17,18 Anakinra is administered as a once-daily subcutaneous injection; it is rapidly absorbed, with a peak plasma concentration within hours; and it is cleared by the kidneys. It is well tolerated, with the primary side effect being injection site reactions. Serious infections are rare but increased with anakinra compared with placebo in patients with rheumatoid arthritis.19 Given the strong link between IL-1 and coronary artery disease and the favorable experience with anakinra in patients with rheumatoid arthritis, interest has grown in applying anti-IL-1 therapy with anakinra to patients with cardiovascular disease.20

Cardiovascular Effects of Anakinra

In this issue of Circulation, Ikonimidis and colleagues21 evaluate the immediate and short-term effects of anakinra on coronary flow; left ventricular, aortic, and endothelial function; and mediators of inflammation. In 23 patients with rheumatoid arthritis and no known coronary artery disease or ischemia on stress imaging, the investigators administered a single dose of anakinra or placebo, in a double-blind fashion, and at 48 hours gave the other treatment. Three hours after anakinra, coronary flow reserve and aortic function measured with transthoracic echocardiography, left ventricular function assessed with tissue Doppler echocardiography, and endothelial function examined with flow-mediated brachial artery dilation all improved significantly compared with 3 hours after placebo. The investigators also found that malondialdehyde and nitrotyrosine, markers of oxidative and nitrosative stress, respectively, decreased significantly after anakinra, as did the inflammatory marker IL-6 and the vasoconstrictor endothelin-1.

In a second part of the study, the 23 patients with rheumatoid arthritis all received daily injections of anakinra for 30 days. Nineteen separate patients with rheumatoid arthritis who were matched for age, sex, and disease activity received prednisolone for 30 days, and 23 age- and sex-matched patients without rheumatoid arthritis or cardiovascular disease served as normal control subjects. After 30 days, the patients treated with anakinra had significantly improved coronary flow, left ventricular function, endothelial function, and markers of inflammation such that they were similar to the normal control subjects. There was a significant correlation between changes in the inflammatory biomarkers and improvement in vascular function and left ventricular function.

A few limitations of this study should be highlighted. The investigators included patients with rheumatoid arthritis and specifically excluded patients with coronary artery disease. It is not clear that these findings can be extrapolated to those in whom they would be most relevant, those without rheumatoid arthritis and with coronary artery disease. In patients with existing cardiovascular disease, the IL-1—dependent changes in vascular function and left ventricular function may be irreversible. Moreover, can the positive findings in this study be explained in part by the fact that it did include patients with active rheumatoid arthritis, who had a heightened inflammatory milieu as evidenced by higher levels of inflammatory markers at baseline compared with the control group? If this is the case, where is the IL-1 coming from? Is it being produced locally in presumably normal coronary vessels, or more likely, is it coming from inflamed joints via blood?22 Other limitations include the small sample size and the lack of randomization of the second part of the study that evaluated the short-term effects of anakinra. Before the clinical relevance of these findings can be appreciated fully, a similar but larger and randomized study will need to be performed that would include patients without rheumatoid arthritis and with coronary artery disease.

Clinical Implications and Future Directions

Despite the above limitations, the study by Ikonimidis and colleagues21 provides fundamental information regarding the beneficial effects of anti-IL-1 therapy with anakinra on vascular and left ventricular function in patients with rheumatoid arthritis and without coronary artery disease. It will be necessary to reproduce these findings in patients with coronary disease and document a reduction or improvement in clinical end points. Fortunately, more data will be forthcoming from the MRC-ILA-HEART study, a randomized, placebo-controlled, multicenter study comparing 14 days of anakinra therapy to placebo in patients presenting with non–ST-segment elevation myocardial infarction.20 The primary end point will be the effect of treatment on C-reactive protein levels, with clinical events as secondary end points. The rapid antiinflammatory effect of anakinra makes it an attractive intervention for other cardiac conditions, such as ischemia-reperfusion injury, whereas its antirenostotic properties suggest the possibility of an anakinra-eluting coronary

![Diagram](http://circ.ahajournals.org/)

**Figure.** Potential roles of IL-1 and IL-1ra in atherosclerosis. The binding of IL-1 to the IL-1 type I receptor results in a proinflammatory response implicated in the development and progression of endothelial dysfunction, atherosclerosis, and plaque instability. IL-1ra competitively inhibits IL-1 by binding to the IL-1 type I receptor. The IL-1 type II receptor is a decoy receptor, which inhibits IL-1 by binding to it without causing a proinflammatory response. iNOS indicates inducible nitric oxide synthase.
Disclosures

References


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