EDITORIAL

Targeting Inflammation in Coronary Artery Disease

Robert A. Harrington, M.D.

For more than 20 years, our understanding of the biology of atherosclerosis has incorporated the so-called inflammatory hypothesis.[1,2] Inflammatory cells and signals drive the healing response to vascular injury, allowing the initiation and growth of atherosclerotic plaque. Inflammatory reactions probably increase plaque instability, possibly resulting in plaque rupture, fissuring, or erosion and setting up the substrate for the thrombotic response that causes myocardial damage or infarction. Yet, no strictly antiinflammatory drugs are used to treat patients with coronary artery disease. Effective cardiovascular drugs with antiinflammatory effects, such as aspirin and statins, predominantly exert therapeutic benefits by means of mechanisms other than inflammation. Intriguing results from JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) showed that, among patients with an elevated level of high-sensitivity C-reactive protein, a nonspecific inflammatory marker, a statin resulted in a lower risk of cardiovascular events than placebo.[3] However, because the level of low-density lipoprotein (LDL) cholesterol was also lowered from baseline in statin-treated patients, it was impossible to conclude that altering the inflammatory state was responsible for the clinical benefit.

Canakinumab, a human monoclonal antibody against interleukin-1β, is approved for use in systemic juvenile idiopathic arthritis and cryopyrin-associated periodic syndromes.[4] The inhibition of interleukin-1β lessens inflammation by down-regulating a variety of markers involved in autoimmunity. Canakinumab has been or is being evaluated in several conditions in which autoimmunity and inflammation play key mechanistic roles.

Ridker and colleagues now report in the *Journal* the primary results of the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS).[5] The trial randomly assigned patients with a previous myocardial infarction and an elevated level of high-sensitivity C-reactive protein to receive one of three doses of canakinumab or placebo, administered subcutaneously every 3 months. Patients had an average age of 61 years, had multiple cardiac risk factors, and had a history of frequent revascularization and aggressive use of secondary prevention medications, including approximately 90% of the patients being treated with a statin. As compared with placebo, canakinumab reduced the high-sensitivity C-reactive protein level from baseline in a dose-dependent fashion by 3 months and sustained it throughout the dosing period, with no reduction in the LDL cholesterol level. The 150-mg dose reached statistical significance with regard to a lower incidence of the primary end point (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) than was observed with placebo, although the modest overall effect was completely driven by a lower incidence of myocardial infarction. The effect of the 300-mg dose looked similar, but this dose level did not achieve statistical significance because of the complexities of testing multiple doses against placebo. In an analysis in which the data for the three doses of canakinumab were combined, significantly more deaths from infection occurred in patients who received canakinumab than in those who received placebo. The investigators noted an intriguingly lower risk of cancer mortality with canakinumab than with placebo, and so there was a neutral effect on overall mortality.

The design of CANTOS was modified in two ways after enrollment had begun. The trial began with 150-mg and 300-mg doses of canakinumab; a 50-mg dose was later added at the request of regulatory bodies. The investigators originally intended to enroll 17,200 patients, but the sponsor decided, reportedly on the basis of financial considerations and without access to data, to decrease the sample size to 10,000. The investigators therefore extended the follow-up to allow for the accumulation of an adequate number of events; longer follow-up typically helps to uncover and even accentuate benefit when dealing with a chronic disease such as coronary atherosclerosis. Neither of these in-trial decisions is likely to affect the interpretation of the trial, but transparency in describing such issues is important.

Despite the scientific and clinical excitement associated with having a new mechanism of action to attack in the treatment of coronary artery disease, a better understanding of the risks and benefits of this form of therapy is needed. Given that there was no observed effect on cardiovascular mortality in this trial, more information about the details of the myocardial infarctions (infarct size, Q-wave vs. non–Q-wave, and spontaneous or procedure-related) is needed to better assess the clinical benefit of canakinumab. We also need additional information about the fatal infections encountered in CANTOS. Furthermore, any discussion of the use of canakinumab in patients with a previous myocardial infarction must consider cost. Given monthly for approved indications, canakinumab is priced at approximately $200,000 per year in the United States.[6] Such pricing may be suitable for rare diseases, but not for a common indication such as coronary artery disease, even if given every 3 months.

Now that an agent targeting inflammation and autoimmunity has been shown to provide clinical benefit, the field is opened to further investigation to find agents that exert more substantial benefit than was seen in CANTOS and perhaps to find agents that do not increase the risk of death from infection as was seen with canakinumab. For example, an ongoing trial sponsored by the National Heart, Lung, and Blood Institute is testing whether low-dose methotrexate can effectively and safely reduce the risk of cardiac events among patients with a previous myocardial infarction who have diabetes or the metabolic syndrome.[7]

CANTOS has helped move the inflammatory hypothesis of coronary artery disease forward scientifically. However, the modest absolute clinical benefit of canakinumab cannot justify its routine use in patients with previous myocardial infarction until we understand more about the efficacy and safety trade-offs and unless a price restructuring and formal cost-effectiveness evaluation supports it.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Department of Medicine, Stanford University, Stanford, CA.

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