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EDITORIAL COMMENT

Will Reducing Inflammation Reduce Vascular Event Rates?*

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Twenty years ago, investigators in the Physicians Health Study reported that measurement of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) predicted future risk of heart attack and stroke in apparently healthy individuals independent of traditional risk factors, and that the anti-inflammatory agent aspirin reduced vascular events in direct proportion to underlying hsCRP levels (1). Soon thereafter, similar effects for hsCRP were observed in women: inflammation was found to be a stronger predictor of cardiovascular events than low-density lipoprotein (LDL) cholesterol (2,3). With the further discovery that statins have clinically relevant anti-inflammatory effects (4), a series of clinical trials demonstrated that the benefits of statin therapy related both to lowering cholesterol and lowering inflammation (5–8). These observations led to the JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial in which 17,802 apparently healthy men and women with LDL cholesterol levels <130 mg/dl (median 108 mg/dl) who were at elevated cardiovascular risk because of hsCRP levels >2 mg/l were randomly allocated to rosuvastatin 20 mg daily or placebo (9). In that trial, when compared with placebo, rosuvastatin resulted in a 54% reduction in myocardial infarction ($p = 0.0002$), a 48% reduction in stroke ($p = 0.002$), a 47% reduction in the need for arterial revascularization procedures ($p < 0.0001$), and a 20% reduction in all-cause mortality ($p = 0.02$). The concept that "lower is better" for hsCRP, as well as LDL cholesterol, was subsequently confirmed in the independent IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial (10).

The foregoing findings proposed a diagnostic role for hsCRP and influenced prevention guidelines worldwide. They did not, however, provide proof that inflammation is causal in atherosclerosis. That proof could come only from randomized trials that reduce inflammation in the absence of lipid lowering. To address this possibility, 2 large-scale trials were launched in 2011, the 7,000-patient National Institutes of Health-funded CIRT (Cardiovascular Inflammation Reduction Trial) (NCT01594333) and the 10,000-patient industry-funded CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) (NCT01327846). CIRT is currently enrolling post-myocardial infarction patients or patients with multivessel coronary disease into a randomized double-blind, placebo-controlled trial of low-dose methotrexate (target dose 20 mg weekly). Low-dose methotrexate is a widely used systemic anti-inflammatory agent, has few drug interactions, and is associated with lower vascular event rates in observational studies of patients with rheumatoid arthritis and psoriatic arthritis. CANTOS, however, is complete and has formally proven the inflammatory hypothesis of atherosclerosis. In brief, canakinumab, which is an anti-inflammatory monoclonal antibody that targets interleukin-1β, was found to reduce the primary endpoint of myocardial infarction, stroke, or cardiovascular death by 15% with no change in LDL cholesterol but with large concomitant reductions in hsCRP (11). Moreover, in a demonstration of the importance of inflammation in multiple systemic disorders, inhibition of interleukin-1β in CANTOS also reduced incident lung cancer and lung cancer mortality by more than one-half in a dose-dependent manner (12).

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Colchicine represents another potentially useful agent for investigating the inflammatory hypothesis of atherogenesis. Colchicine is a microtubule inhibitor with anti-inflammatory properties that is used to treat gout and pericarditis and that also reduces downstream production of hsCRP. In a preliminary open-label trial of 532 patients that was conducted in Western Australia, low-dose colchicine showed promise for secondary prevention (13). On that basis, 2 double-blind, placebo-controlled trials are under way: LoDoCo2 (Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease) (N = 3,000; ANZCTR126140000093684) and COLCOT (Colchicine Cardiovascular Outcomes Trial) (N = 4,500; NCT02551094).

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In parallel with these outcome trials, the imaging community has sought to provide surrogate markers for atherosclerosis and vascular inflammation. The examples have included demonstration of interval change in the plaque volume by intravascular ultrasound, noninvasive coronary computed tomography angiographic evidence of reduction in necrotic core volume (represented as low-attenuation plaque [LAP] volume), and resolution of inflammation on fluorodeoxyglucose positron emission tomography imaging to track statin efficacy (8,14,15). In this issue of *iJACC,* Vaidya et al. (16) present computed tomography angiographic data from an observational study of 40 patients with recent acute coronary syndromes to suggest that colchicine favorably modifies vulnerable coronary plaque. Over a mean follow-up period of 1 year, colchicine was found to reduce LAP volume in these patients in a manner that correlated with reductions in hsCRP. This finding is provocative because LAP is considered to be an imaging marker for instability and a predictor of adverse cardiovascular events (17). By contrast, Vaidya et al. (16) report little if any effect of colchicine on total atheroma volume, a finding suggesting plaque modification and stabilization. A significant limitation of the current study is the lack of randomization, and hence it was subject to both confounding and bias; the control patients were derived from a general cardiology clinic and were likely to differ in important ways from the patients with acute coronary syndrome who were given colchicine. Future studies in prospective settings will thus be needed to address the potential utility of LAP volume as a surrogate for clinical outcomes trials.

Although imaging-verified change in plaque composition (including LAP or inflammation) should be intuitively more informative than the interval change in the percentage of atheroma volume in response to therapeutic intervention, it is likely that no imaging modality would succeed as a validated surrogate for hard clinical events. History is replete with various examples, such as from ILLUSTRATE (A Coronary IVUS Study to Compare Torcetrapib/Atorvastatin to Atorvastatin Alone in Subjects With Coronary Heart Disease) and ILLUMINATE (A Study Examining Torcetrapib/Atorvastatin and Atorvastatin Effects on Clinical CV Events in Patients With Heart Disease) to Dal-Plaque (A Study of the Effect of RO4607381 on Atherosclerotic Plaque in Patients With Coronary Heart Disease) and Dal-Outcomes (Effects of the Cholesterol Ester Transfer Protein Inhibitor Dalcetrapib in Patients with Recent Acute Coronary Syndrome) (18). As the most recent example, magnetic resonance imaging of the carotid arteries and aorta failed to demonstrate statistically significant effects of canakinumab on measures of vascular structure and function despite evidence of hsCRP reduction (19). Nonetheless, imaging is likely to serve as a useful tool for understanding the pathophysiologic mechanisms of atherogenesis and the role of new drugs in interference with these mechanisms and as a method to de-risk drug development. Imaging and change therein are the only means to study the change in disease process at gross and subcellular levels in a living patient (20). Studies such as that by Vaidya et al. (16) underscore the importance of imaging platforms. After the presentation of CANTOS (10,11) recently, the search for a valid imaging surrogate predictive of drug effects will likely accelerate.

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