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EDITORIAL COMMENT

Cardiovascular Risk Reduction in Patients With Chronic Kidney Disease

Potential for Targeting Inflammation With Canakinumab*

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Despite current therapeutic strategies involving control of hyperglycemia, dyslipidemia, proteinuria, and blood pressure, cardiovascular (CV) morbidity and mortality remain unacceptably high in patients with chronic kidney disease (CKD). There is therefore an important need to identify novel agents to target other pathophysiological mechanisms leading to CV and CKD progression, including cell signaling components of inflammation. The proinflammatory state in patients with CKD contributes to all phases of atherothrombosis, including early cell adhesion and endothelial dysfunction, matrix and collagen degradation, smooth muscle cell proliferation, increased platelet reactivity, plaque rupture, thrombosis, and development of vascular calcification, thereby promoting CV risk. From a clinical perspective, high-sensitivity C-reactive protein (hsCRP) is an inflammatory biomarker that has been used to identify individuals at elevated CV risk (1). Suppression of hsCRP in response to statin treatment is linked with CV protection in secondary CV prevention studies and in otherwise healthy patients with low low-density lipoprotein (LDL) cholesterol levels who participated in the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) and JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trials. Similarly, the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering Trial), IMPROVE IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial), CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure), ASCOTT (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm), and A to Z (Aggrastat to Zocor Trial) statin trials demonstrated that plasma hsCRP lowering reduced CV risk by a similar magnitude compared with LDL cholesterol lowering. These observations provide the rationale to examine the role of suppressing inflammation with other agents targeting non-LDL pathways to reduce CV risk. Because statins reduce both inflammatory markers and LDL cholesterol, trials with lipid-lowering therapies cannot determine the relative contributions of decreases in LDL cholesterol versus the effects on inflammatory or prothrombotic pathways.

Elucidating the role of anti-inflammatory therapies is additionally important because of the deleterious effect of inflammation on CKD progression, including glomerular filtration rate (GFR) loss and albuminuria, which further contribute to CV risk. Although inflammation is recognized as a contributing factor in the pathophysiology of CKD progression, studies examining the impact of antifibrotic and anti-inflammatory agents have yielded neutral results or were stopped as a result of significant adverse effects (2). The identification of safe, effective therapies that suppress inflammation in the setting of CKD, and that also mitigate CV or renal risk, may be crucial to reduce morbidity and mortality associated with CKD further.

Beyond hsCRP, interleukin (IL)-1β is a proinflammatory factor associated with atherosclerosis and CV risk in humans. IL-1β expression is limited in

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healthy individuals, but it is markedly increased in blood monocytes, tissue macrophages, and dendritic cells after exposure to infectious agents and inflammatory cytokines (i.e., tumor necrosis factor-α, IL-18, IL-1α, and IL-1β) (3). To become biologically active, pro-IL-1β requires proteolytic cleavage by caspase-1- or IL-1-converting enzymes (ICEs). Caspase-1 is a protease that is processed by the Nod-like receptor protein 3 (NLRP3) inflammasome, a process promoted by a large variety of cytosolic danger signals, such as reactive oxygen species, adenosine triphosphate, osmotic pressure, uromodulin, biglycan, extracellular histones, oxalate, uric acid, or cholesterol crystals. The resulting IL-1β activation promotes chronic inflammatory conditions, such as atherosclerosis (4), whereas blockade of IL-1β is associated with CV protection (**Figure 1**). For example, in a phase IIB trial, IL-1β selective antagonism for 4 months with canakinumab, a human monoclonal antibody, resulted in sustained reductions in fibrinogen, IL-6, and CRP without affecting lipid levels in patients with type 2 diabetes (5). Therefore, canakinumab provides a method to target the inflammatory hypothesis for atherothrombosis specifically without confounding lipid-lowering effects in patients with and without CKD, a concept that was first addressed in the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study). The study was conducted as an intent-to-treat analysis in 10,061 adult patients with a history of myocardial infarction and systemic inflammation (elevated hsCRP >2 mg/ml). Canakinumab lowered hsCRP and IL-6 levels in a dose-dependent manner, whereas LDL cholesterol levels were unaffected. In the CANTOS cohort with stable coronary artery disease patients, 90% of participants were statin users. Canakinumab treatment at 150 mg daily for 3.7 years reduced the risk of the primary 3-point major adverse cardiovascular events endpoint compared with placebo (hazard ratio: 0.85; $p = 0.021$), and also reduced the secondary 4-point major adverse cardiovascular events (addition of hospitalization for unstable angina requiring urgent revascularization; hazard ratio: 0.83; $p = 0.0005$) (6). The main effect of canakinumab was driven by a lower incidence of myocardial infarction. Importantly, there was no effect on overall mortality, possibly because of an increased incidence of fatal infection in the context of lower cancer mortality.

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In this issue of the *Journal,* Ridker et al. (7), in a post hoc analysis of CANTOS, report that in patients with moderate CKD (estimated GFR <60 ml/min/1.73 m^2), and a high overall rate of CV events, canakinumab reduced the risk of major adverse cardiovascular events. In addition to demonstrating CV benefit, this analysis is of interest because canakinumab was safe and well tolerated in patients with CKD. Although the precise mechanisms responsible for CV protection with canakinumab are not yet clear, the largest benefit was observed in patients with a robust anti-inflammatory response to the first dose, a finding strongly suggesting that reducing inflammation played a role in CV protection. Comparable effects were also observed in patients with baseline albuminuria and in those with diabetes. Thus, the CV benefit observed with IL-1β inhibition in this cohort of patients with earlier stages of CKD may also set the stage for future research in patients with diabetes or more advanced renal disease including stages 3B and 4, who tend to exhibit exaggerated proinflammatory states.

Despite strong evidence linking inflammation to CKD progression and the positive impact on CV outcomes, there were no significant benefits on CKD progression in CANTOS. It is, however, important to recognize that CKD progression was not the primary goal of the study, nor was the cohort enriched with other renal factors such as albuminuria or accelerated GFR decline to maximize the chance of capturing renal endpoints. Accordingly, although the results of CANTOS do not support the presence of robust renal protective effects, they do not rule out the possibility of potential renal protective effects in higher-risk patients exhibiting greater degrees of renal function impairment, albuminuria, and hence inflammation (**Figure 1**).

The data from CANTOS may have additional implications for reducing renal and CV endpoints in certain high-risk groups, such as patients with heart failure or diabetes. In fact, cardioprotective effects were observed among patients in the CANTOS post hoc analysis when they were stratified by the presence or absence of type 2 diabetes. The high-glucose milieu in diabetes may have synergistic effects with chronic low-grade inflammation and oversecretion of IL-1β, thereby contributing to insulin resistance, endothelial dysfunction, and diabetes-related CV disease (8). In patients with diabetes, CV and CKD risk is attenuated with newer antihyperglycemic therapies, including sodium-glucose co-transporter 2 (SGLT2) inhibitors (EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], CANVAS [CANagliflozin cardiovascular Assessment Study] Program trials) and glucagon-like peptide (GLP)-1 receptor agonists (LEADER [Liraglutide Effect and