Inflammation as a Therapeutic Target To Improve Vascular Function in Kidney Disease

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Cardiovascular disease is a leading cause of morbidity and mortality in patients with CKD. Chronic inflammation and oxidative stress are postulated to link cardiovascular disease and CKD and may be part of a vicious cycle, with CKD leading to increased inflammation and subsequently more rapid loss of renal function. Several mechanisms have been posited to connect CKD with chronic inflammation. These include impaired cytokine clearance, with higher levels of circulating cytokines and inflammatory markers in those with CKD. Inadequate dietary antioxidant intake and excessive free-radical production contribute to oxidative stress, causing further renal and systemic injury, and driving an amplifying loop among oxidative damage, inflammation, and CKD. Chronic inflammation in CKD likely damages the vascular endothelium over time, resulting in dysfunction and ultimately atherosclerosis. This inflammation-mediated endothelial damage may be the crux of the CKD–inflammation–cardiovascular disease diathesis, and disrupting this malignant axis is a crucial goal.

The IL-1 cytokine system plays an important role in systemic inflammation, vascular injury, and kidney disease. Integral to the IL-1 system are inflammasomes, wheel-like cytosolic protein complexes that respond to various danger signals by facilitating release of IL-1α and IL-1β. These cytokines subsequently bind ubiquitous IL-1 receptors, thereby activating neutrophils and endothelial cells, augmenting reactive oxygen species production, and inducing acute-phase response protein release. Agents targeting the IL-1 system (either IL-1 inhibitors or IL-1 receptor antagonists) have proven to be effective in some systemic inflammatory diseases, such as gout, rheumatoid arthritis, and adult-onset Still disease. Rilonacept is a soluble decoy receptor protein that acts by binding to IL-1α and IL-1β, thereby preventing activation of IL-1 receptors, and has regulatory approval for treatment of a rare group of genetic inflammatory syndromes.

In this issue of the Journal of the American Society of Nephrology, Nowak et al. report a pilot trial of IL-1 inhibition and its effect on vascular function in persons with nondialysis-dependent CKD. This study enrolled 42 adults with stage 3 or 4 CKD (mean eGFR, 38±13 ml/min per 1.73 m²), mostly attributed to diabetic or hypertensive nephropathy, with chronic inflammation (high-sensitivity C-reactive protein [hsCRP], 2–30 mg/L). Participants were on stable antihypertensive, diabetic, and statin therapy before enrollment. Equal numbers were randomized to the IL-1 inhibitor rilonacept or placebo for 12 weeks. Participants in the treatment arm received an initial subcutaneous injection of 320 mg rilonacept, followed by weekly 160 mg injections for the remainder of the study; those in the placebo arm underwent the same regimen with inert injections. The primary end points were changes in a measure of endothelial function (brachial artery flow-mediated dilation [FMDBA]) and large artery stiffness (aortic pulse-wave velocity [aPWV]), assessed at 4-week intervals. FMDBA in the treatment arm showed an absolute 1.1% increase from baseline to 12 weeks, compared with an absolute 0.9% decrease in the placebo arm (P<0.01). There was no significant change in aPWV in the treatment or placebo group. Several secondary end points were assessed. Systemic inflammation, as reflected by hsCRP level, decreased by >50% in the rilonacept group (P<0.01) but other markers (IL-6, IL-1Ra, IL-18, and IL-18 binding protein) were not lowered with the treatment. A supraphysiologic dose of the superoxide scavenger ascorbic acid was given in a subgroup of participants to test whether it differentially affected FMDBA on the basis of treatment status. The point estimate showed greater effect in...
the placebo arm, suggesting reduced oxidative stress with rilonacept, but the result did not achieve the prespecified statistical significance level. Five persons in the rilonacept group and two in the placebo group sustained any adverse event, and two participants in the rilonacept group discontinued treatment because of adverse reactions.

Despite being a pilot study, the improvements noted with vascular function, inflammatory markers, and oxidative stress are exciting. It is notable that most participants in both arms were already receiving therapies that might improve endothelial dysfunction (renin-angiotensin system blockers and statins), suggesting IL-1 inhibition has a beneficial effect on top of the standard treatment options. The reduced response to supraphysiologic dose ascorbic acid infusion and the reduced NADPH oxidase expression in the rilonacept-treated group support reduced vascular oxidative stress as a mechanism through which the agent acted. FMDBA assesses endothelial function by ultrasonographically measuring brachial artery dilation in response to shear stress from increased blood flow. FMDBA tends to decrease with decline in kidney function and is an appropriate surrogate end point of interest. aPWV assesses aortic stiffness by measuring the velocity of a pressure wave generated by left ventricular contraction, with a stiffer aorta causing a faster wave. The lack of effect on aPWV is not surprising, as such a short duration of therapy is unlikely to change arterial structural characteristics, such as calcification and collagen alterations that determine aPWV.

However, our initial enthusiasm over a positive result from a well-conducted trial targeting vascular dysfunction in an at-risk population must be tempered. Could the apparent effect of rilonacept on endothelial function be because of a type 1 error? The results are fragile, given the small number of participants, and the decrease in FMDBA in the placebo arm suggests a chance exaggeration of comparative treatment effect. FMDBA showed an absolute decrease of 0.9% over 12 weeks in the placebo arm (from 3.4% to 2.5%); although FMDBA is expected to decrease over time in CKD population, this was exceptionally rapid. The beneficial effects seen here need to be tested in larger trials, ultimately assessing clinical end points rather than surrogate outcomes. This is critical, as many agents with promising mechanisms of action and positive results from early trials are ultimately found wanting when tested rigorously in larger studies, with bardoxolone methyl a particularly disappointing recent example in CKD.5

Although IL-1 inhibition and IL-receptor antagonists have been studied in patients with rheumatologic illnesses, such investigations are limited in CKD. Hung et al. demonstrated that several inflammatory biomarker levels declined in maintenance hemodialysis patients receiving the IL-1 receptor antagonist anakinra for 4 weeks.6 In those with rheumatoid arthritis, an IL-1 receptor antagonist exerted more potent benefit in those with preexisting cardiovascular disease.7 In the study by Nowak et al., the participants’ cardiovascular disease status was unclear, and future studies should address whether presence of cardiovascular disease modifies the effects of IL-1 inhibition in CKD.4 An ongoing trial is examining whether a monoclonal antibody IL-1β inhibitor can decrease cardiovascular events in participants with coronary artery disease and inflammation (hsCRP≥2 mg/L).8 However, as is often the case, patients with CKD are excluded, necessitating dedicated trials in this population. Nowak et al. report safety data for 12 weeks; however, longer follow-up is needed to establish the safety of IL-1 inhibition in CKD.4

Well-conducted randomized trials are sorely needed in nephrology.9 IL-1 antagonism has the potential to become an important strategy to improve vascular function in the CKD population. Additional studies confirming these findings and evaluating clinical effectiveness (on both cardiovascular and renal outcomes) and safety end points in CKD are needed. Ultimately, if rilonacept is shown to be safe and effective in reducing adverse outcomes in CKD, thorough health economic scrutiny will be necessary, as applying this expensive medication to a high-prevalence disease would pose a large burden to health care payers. The road to improving outcomes for our CKD patients is long, difficult, and filled with dead ends, but Nowak et al. have taken another important step forward.

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REFERENCES


See related article, “IL-1 Inhibition and Vascular Function in CKD,” on pages 971–980.