EDITORIAL COMMENT

Imaging to Assess the Effect of Anti-Inflammatory Therapy in Aortic and Carotid Atherosclerosis*

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A considerable body of experimental and clinical evidence has implicated inflammation in the pathogenesis of atherosclerosis and its complications, such as plaque disruption and thrombosis (1,2). Because elevated levels of atherogenic (containing apolipoprotein B-100) lipoproteins play a major role in initiation and progression of inflammation and atherosclerosis, the primary therapeutic target for atherosclerosis involves interventions such as statins that reduce circulating levels of atherogenic lipoproteins. Although attractive, interventions directly targeting inflammatory pathways remain largely unproven.

In this issue of the Journal, Choudhury et al. (3) presented the results of a multicenter investigation of the effects of the anti-inflammatory agent canakinumab, an interleukin (IL)-1β inhibitor, on arterial structure and function as assessed by magnetic resonance imaging (MRI) in patients with clinical evidence of atherosclerosis and either type 2 diabetes or impaired glucose tolerance. We congratulate the investigators for this international MRI study of both carotid arteries and aorta in 189 qualified subjects. The collaborative effort demonstrated that canakinumab did not reduce atherosclerotic burden nor improve arterial function significantly compared to placebo during a 12-month period, even though the drug did significantly decrease circulating levels of inflammatory markers, both high-sensitivity C-reactive protein (hsCRP) and IL-6.

These results are disappointing in view of IL-1β’s previously established role in inflammation and atherogenesis and its favorable effects on inhibiting IL-1β signaling in animal models of atherosclerosis (4,5). What could explain the lack of effect on atherosclerosis burden and vascular function despite a compelling hypothesis? Among the possible explanations are poor subject selection; limits of the imaging methodology; suboptimal endpoints, suboptimal dosing, and inadequate duration of treatment; and even the possibility of an incorrect hypothesis.

SUBJECT AND ENDPOINT SELECTION

Enrolled patients had clinically high-risk atherosclerotic vascular disease, with 90% having coronary artery disease, 22% a history of stroke, and 69% diabetes of ≥5 years’ duration. They were also treated with standard-of-care medications for cardiovascular disease and diabetes: 95% were on antiplatelet agents, 98% were on a statin, and 73% were on an angiotensin-converting enzyme inhibitor; 63% had a glycosylated hemoglobin ≤7%, and the average hsCRP was 1.8 mg/l. The problem is that aggressive standard therapies may have made it difficult to demonstrate effectiveness of incremental therapy with canakinumab.

It is unclear in the current study how many subjects had carotid lesions with advanced plaque features, such as a lipid-rich necrotic core (LRNC). In a similar population in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global...
Among a subset of 113 participants in the CPC (Carotid Plaque Composition by MRI during Lipid Lowering) study, 46 were identified to have lipid-rich necrotic core (LRNC) at baseline and 67 were without. Percent wall volume decreased significantly over 2 years of intensive lipid therapy in LRNC(+) subjects, but did not change in subjects without LRNC. LRNC(+) had lipid-rich necrotic core; LRNC(-) did not have lipid-rich necrotic core.

Data from the CPC study, with a larger sample size, showed that percent wall volume (PWV) decreased significantly from 46.6 ± 1.1% to 44.5 ± 1.0% (p < 0.001) over 2 years of lipid therapy in 46 subjects with LRNC at baseline, but did not change (36.7 ± 0.6% vs. 36.3 ± 0.5%) in 67 subjects without LRNC (Figure 1).

Further, Du et al. (17) recently showed that 4 years of statin therapy resulted in continued decrease in LRNC and an increase in fibrous tissue without significant change in PWV. These data suggested that plaque burden measurement alone is unable to reveal complex tissue composition changes, including LRNC reduction and increase in fibrous tissue and calcium content during extended statin therapy.

**NEOVASCULARIZATION, PERMEABILITY, AND INFLAMMATION**

Inflammatory cells, such as monocyte macrophages, appear to enter plaques from the luminal side as well as from the adventitial vasa vasorum via neovascularization. Studies have shown that neovascularature and macrophage content are topographically and statistically associated (18,19). New microvessels are immature, fragile, and leaky, and express cellular adhesion molecules, resulting in the accumulation of inflammatory cells, local extravasation of plasma proteins, and ultimately the accumulation of erythrocytes, an indication of IPH (20). In addition to 18F-fluorodeoxyglucose positron emission tomography, as the authors have suggested, dynamic contrast-enhanced (DCE) MRI using gadolinium agents can assess plaque perfusion arising from the adventitial vasa vasorum. Kinetic modeling of DCE-MRI can assess elevated vascularity (Vp = partial plasma volume) and vascular permeability (Ktrans).

Because Vp and Ktrans also associate with inflammation, DCE-MRI has been used to characterize plaque inflammation (24,25). Kerwin et al. (19) reported a
correlation of 0.8 between $V_p$ estimated by kinetic modeling of DCE-MRI and histological measurements of neovessel areas in subjects undergoing carotid endarterectomy. Both $V_p$ and $K^{trans}$ correlated with plaque macrophage content. DCE-MRI also has been shown in multicenter studies to have excellent reproducibility across scanner platforms (26).

DCE-MRI was used to investigate changes in vasa vasorum in the CPC subjects. Dong et al. (27) reported a drop in adventitial $K^{trans}$ from 0.085 to 0.067 min$^{-1}$ ($p = 0.02$) after 1 year of intensive lipid therapy. This decrease in $K^{trans}$ was independent of LRNC and PWV reduction (27). Longer duration of statin therapy was associated with decreased carotid plaque vascularity in the AIM-HIGH carotid MRI substudy (28). Given that both fluorodeoxyglucose positron emission tomography and $K^{trans}$ are indirect measures of plaque inflammation, it might be interesting to consider a study that uses both to better understand their role in vascular inflammation. Thus, measurement of these indexes of inflammation could have provided additional insights into the effects of anti-inflammatory therapy in atherosclerosis.

The authors discussed some of the possible reasons for the observed discordance between changes in circulating inflammatory markers (hsCRP and IL-6 levels) and vascular response (no significant reduction in carotid and aorta wall areas or improvement of aorta distensibility). In the CPC study, we found that LRNC regression varied during lipid-altering therapy. LRNC can be partially depleted after 3 years in some, but not all, subjects on intensive lipid therapy. Five subjects developed new measurable LRNC during the 3 years, but only 1 of these 5 had measurable LRNC at 3 years (16). The heterogeneity of changes in LRNC during intensive lipid therapy suggested an individualized vascular response to a given therapy, which is consistent with findings in recent clinical trials with low-density lipoprotein cholesterol (LDL-C) lowering (29–31) showing that not everyone benefits equally for any given reduced LDL-C level. For example, in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial (29), overall, the lower levels of LDL-C achieved on therapy were associated with better outcomes; however, 33% of subjects treated with simvastatin plus ezetimibe to a mean LDL-C level of 54 mg/dl continued to develop cardiovascular events over 7 years. Identifying individuals with increased residual cardiovascular risk, despite intensive statin therapy, remains an unmet clinical need.

Future imaging studies are warranted to evaluate the link between individualized vascular response to therapy, in addition to clinical risk factors and biomarkers, and subsequent vascular events. If verified, this link might improve residual cardiovascular risk prediction and potentially guide further therapy.

Notwithstanding these negative results, we eagerly await the results of the ongoing event-based CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial, which is also evaluating targeted IL-1β inhibition with canakinumab (32).

**REFERENCES**


**KEY WORDS** interleukin, lipid lowering, lipid-rich necrotic core, magnetic resonance imaging