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EDITORIAL COMMENT

Targeting Interleukin-1 and Interleukin-6

The Time Has Come to Aggressively Address Residual Inflammatory Risk*

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With the publication of CANTOS (the Canakinumab Anti-inflammatory Thrombosis Outcomes Study) in 2017, the cardiovascular community received proof of principle that therapeutic targeting of interleukin-1 and interleukin-6 to the C-reactive protein (CRP) pathway of innate immunity can significantly reduce major adverse cardiovascular event rates (1). Although the benefits of interleukin-1β inhibition in CANTOS were observed in the absence of any effects on low-density lipoprotein cholesterol (LDLC), the cardiovascular protection from canakinumab was identical in magnitude to that observed in major trials of PCSK9 inhibition. Furthermore, on-treatment levels of the inflammatory biomarkers interleukin-6 and high-sensitivity CRP (hsCRP) were powerful predictors of efficacy after inflammation-lowering therapy in a manner fully parallel to that of on-treatment levels of LDLC following lipid-lowering therapy (2,3). CANTOS thus provided the first hard evidence in 40 years of an effective therapy for atherosclerosis not directly related to cholesterol reduction, blood pressure, or coagulation.

Although CANTOS was a secondary prevention trial, there is considerable interest in addressing residual inflammatory risk in the setting of acute coronary ischemia. From a biomarker perspective, both interleukin-6 and hsCRP have repeatedly proven effective for risk prediction, not only in primary prevention and stable coronary disease, but also in acute coronary syndromes (4). By contrast, comparatively little is known about plasma levels of interleukin-1β itself, in part because its measurement is more complex and less well suited for epidemiologic investigation. Nonetheless, information about circulating interleukin-1β could provide important insights into the pathophysiology of acute plaque rupture and, by extension, atherosclerotic progression. In one recent example, interleukin-1β levels were associated with increased mortality in the setting of heart failure (5), an endpoint also reduced by interleukin-1β inhibition in CANTOS (6).

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In this issue of the *Journal*, Silvain et al. (7) present intriguing data regarding interleukin-1β as a biomarker of risk in the prospective ePARIS registry of 1,398 patients with recent ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (PCI) (7). In brief, interleukin-1β concentration measured at the time of PCI was associated with all-cause mortality at 90 days (adjusted hazard ratio [HR]: 1.47 per 1-SD increase; 95% confidence interval [CI]: 1.16 to 1.87) in a nonlinear manner, such that the highest baseline tertile of interleukin-1β was associated with the highest mortality rates at 90 days (adjusted HR: 2.78; 95% CI: 1.61 to 4.79) and 1 year (adjusted HR: 1.93; 95% CI: 1.21 to 3.06). Importantly, the effects

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remained significant after adjustment for LDLC and troponin. Moreover, the risks of short- and long-term cardiovascular mortality increased nearly 8-fold among those with levels of both interleukin-1β and hsCRP in the top tertile of each distribution at baseline (HR: 7.9; 95% CI: 3.2 to 20.0).

One interpretation of the ePARIS data is that the magnitude and intensity of the acute phase response during coronary hypoxia correlates with larger infarct size and worse clinical outcomes. If so, it is perhaps not surprising that a combination of 2 markers that increase with the acute-phase response provide greater utility than either alone. However, it has been known for more than 20 years that elevations of hsCRP precede acute ischemia (8) and, thus, that inflammation begets plaque rupture and is a cause as well as a result of coronary hypoperfusion. Subsequent studies simultaneously evaluating coronary and systemic blood for inflammatory biomarker changes after acute plaque rupture support this biology (9). In the current data, the impact of interleukin-1β levels was independent of troponin, indicating that infarct size alone is not a simple explanation of these important observations.

Measurement of interleukin-1β is unlikely to become commonplace in clinical settings. No standardized clinical assays for interleukin-1β exist; research assays differ considerably, with wide variation; and many individuals have interleukin-1β levels that cannot be ascertained at all. In the ePARIS study, interleukin-1β levels were below the limit of assay detection in more than a third of the individuals enrolled. Furthermore, even in these provocative data, the difference between interleukin-1β levels between those alive and dead at 90 days was small and of borderline significance (5.2 vs. 4.4 pg/ml; $p = 0.048$). By contrast, and consistent with a wide body of prior evidence, differences between those alive and dead at 90 days for hsCRP were large and highly significant (27.3 vs. 5.4 mg/l; $p < 0.00001$). It is unfortunate that data on interleukin-6 are not available because this biomarker may well be superior in the setting of acute coronary syndromes, both for prognosis and for the selection of interventional versus conservative therapy (10). However, what these data do provide is further insight into the processes driving acute plaque rupture that go beyond lipids alone. Most important, the current data reaffirm that the time has come for direct targeting of the interleukin-1-to-interleukin-6 pathway in acute coronary ischemia.

For the clinical and research communities, the crucial question at hand is to discern which of several targets in the canonical pathway of NLRP3 to interleukin-1 to interleukin-6 to CRP can be altered to maximize cardiovascular benefit and minimize infectious risk. Several oral NLRP3 inhibitors are in development that, in addition to inhibiting the activation of interleukin-1β, can also be anticipated to inhibit the activation of interleukin-18, an effect we have recently shown likely to be advantageous rather than harmful (3). At the same time, multiple agents that target interleukin-1α and interleukin-1β exist, and novel ones are in development; of particular interest, these agents have efficacy in the treatment of lung cancers, where inflammation in the tumor microenvironment is a prominent feature (11). An abundance of genetic and biologic data point directly to interleukin-6 as a highly attractive target (12,13), and of current interleukin-6 inhibitors, at least 1, ziltikevimab, is being developed solely for atherosclerosis, an exciting and important development. Enticing endpoint reduction data have also been presented for colchicine, an agent the inhibits microtubule polymerization and may indirectly affect NLRP3 function (14). If confirmed in the ongoing LoDoCo2 (Low Dose Colchicine-2) and other endpoint trials, colchicine could become an inexpensive anti-inflammatory for cardiovascular disease prevention. Clinicians will need to be cautious with colchicine among those with renal dysfunction, for whom use can be contraindicated.

Finally, and perhaps of greatest importance, the ePARIS registry data published in this issue of the *Journal* further support the hypothesis that all patients with atherosclerosis may soon be treated with combination lipid-lowering and inflammation-inhibiting agents (15). Rapid progress is taking the cardiovascular community in this exciting direction, either with highly targeted bispecific monoclonal antibodies or with simple combination oral agents, such as colchicine and statin therapy. In the cardiac catheterization laboratory where the current data from Silvain et al. (7) derive, invasive cardiologists may soon find themselves injecting powerful systemic anti-inflammatory agents at the time of primary PCI (13,15). The time has clearly come to aggressively address residual inflammatory risk.

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