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EDITORIAL COMMENT

PCSK9: The Nexus of Lipoprotein Metabolism and Inflammation in COVID-19*

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Coronavirus disease-2019 (COVID-19) is caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and is associated with pathologic inflammation and thrombosis. Most COVID-19 therapeutics have focused on direct immune modulation and suppression of pathologic inflammation. Although cardiovascular disease (CVD) and lipid-related risk factors are associated with worse outcomes in COVID-19, there is a paucity of randomized clinical trials (RCTs) of lipid-modulating therapies in COVID-19. In several observational cohort studies of patients hospitalized with COVID-19, statin use was associated with a reduction in clinical events and lower mortality.[1,2] Mechanistically, lipid-modulating therapy may limit inflammation and thrombosis in COVID-19 through antiviral, anti-inflammatory, immunomodulatory, rheologic, and antithrombotic effects.[3]

In 2003, the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9) was identified and linked to familial hypercholesterolemia (FH). PCSK9 regulates low-density lipoprotein receptor (LDLR) recycling, and loss-of-function PCSK9 variants are associated with low circulating levels of low-density lipoprotein cholesterol (LDL-C), and a reduced risk of coronary artery disease.[4,5] These mechanistic insights motivated the development of monoclonal antibodies that inhibit PCSK9, reducing hepatic LDLR degradation and increasing LDLR activity, resulting in striking reductions of LDL-C and improved clinical outcomes in patients with atherosclerotic cardiovascular diseases (ASCVD). In randomized placebo-controlled clinical trials using PCSK9 monoclonal antibodies (PCSK9 mAbs), the reductions in ASCVD events are strongly correlated with the magnitude of LDL-C lowering. Although the role of PCSK9 on LDL-C is clear, the contribution of PCSK9 inhibition (PCSK9i) in mediating inflammation has hitherto been limited to experimental studies and an ex vivo study in human mononuclear cells, and the clinical trials with PCSK9 mAb have not shown any changes in high-sensitivity C-reactive protein (hs-CRP) levels.[6,7] hs-CRP, a hepatically synthesized acute phase reactant, has proved to be an important marker of systemic inflammation, but hs-CRP does not capture all of the dimensions of an inflammatory response. Circulating and stress-induced biomarkers may be necessary to fully capture physiologic and pathologic immune responses.

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This issue of the *Journal of the American College of Cardiology* includes a randomized, double-blind, placebo-controlled, multicenter trial (IMPACT-SIRIO 5)[8] that was designed to evaluate the efficacy of a single subcutaneous dose of the PCSK9 mAb evolocumab on death or need for intubation at 30 days in 60 patients hospitalized for severe COVID-19 infection. Eligibility for the trial included adults hospitalized for acute COVID-19 infection verified by real-time polymerase chain reaction, associated pneumonia with radiologic features characteristic of COVID-19, and impaired oxygenation. The investigators hypothesized that PCSK9i interferes with interleukin (IL)-6-mediated inflammatory pathways and therefore treatment with

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a PCSK9 mAb would reduce the hyperinflammation that contributes to adverse outcomes in patients with COVID-19 infection. The main secondary endpoint was change in IL-6 levels from baseline to 7 and 30 days, and a relevant inclusion criterion required an elevated IL-6 level. Treatment with evolocumab reduced death or need for intubation within 30 days by −30% (95% CI: −54.40% to −6.59%). Patients with more severe systemic inflammation (as determined by IL-6 levels) had larger reductions in mortality with PCSK9i. The authors are to be commended on conducting an RCT of a lipid-modulating therapy in patients hospitalized with severe COVID-19 illness. Several unresolved issues require consideration for future trial of PCSK9i in COVID-19. In addition to inflammation, adverse outcomes in acute COVID-19 can involve thrombosis and hyperviscosity that affects the arteries, veins, and microvasculature.[9] This report does not provide data on clinical, imaging, or autopsy findings indicative of thrombosis.

In addition to adding to our clinical arsenal against COVID-19, this study builds on the expanding knowledge of PCSK9 dynamics and reignites the debate on: 1) how to capture inflammation independently from hs-CRP; and 2) the mechanisms through which PCSK9i dually modulates lipoprotein metabolism and inflammation. Regarding the former, clinical trials of PCSK9i have found no effects on hs-CRP levels, leading to the conclusion that the clinical benefits of PCSK9i are primarily through reducing LDL-C levels. Although no data are available on hs-CRP in IMPACT-SIRIO 5, the benefits of PCSK9i was greatest in those with elevated IL-6 levels (with a greater reduction in IL-6 levels compared with placebo), strongly suggesting that PCSK9i can directly modulate inflammation in COVID-19. Even though the presented study is small and hypothesis generating, the striking improvement in COVID-19–associated events with the use of PCSK9i suggests that either acute lower LDL or LDL-independent effects can modulate inflammation in COVID-19. These results are congruent with mechanistic studies suggesting that PCSK9i can favorably modulate multiple inflammatory pathways. Outside of COVID-19, post hoc analyses of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial found that relative benefit of PCSK9i was consistent regardless of baseline level of hs-CRP and that PCSK9i had no effects on hs-CRP levels.[10] The apparent disconnect between results from mechanistic studies with those from observational clinical studies using hs-CRP as a global marker of inflammation has to date not been resolved. Whether the clinical results of IMPACT-SIRIO 5 are due to LDL or LDL-independent effects are beyond the scope of this small hypothesis-generating clinical trial. Regardless of the specific mechanisms, the effects of PCSK9i on inflammation and clinical outcomes in COVID-19 are provocative and warrant further investigation, and ongoing studies of lipid-modulating therapies in COVID-19 will further illuminate the connection between lipoprotein metabolism and inflammation.

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