Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Are statins safe in patients with COVID-19?

As of early May, there were over 1.1 million confirmed cases of the 2019 novel coronavirus disease (COVID-19) and over 65,000 COVID-19–related deaths in the United States. The number of cases continues to rise, and there are concerns about a second wave of infections later this year. Risk factors for serious complications and death from COVID-19 include older age, hypertension, diabetes, and cardiovascular disease (CVD).[1] Many of these individuals who are at high risk of serious complications and death from COVID-19 are likely taking a statin or have a definite indication for one. A hyperinflammatory response to the novel coronavirus plays a key role in causing the severe complications from COVID-19. Data from China where the outbreak began show that cardiac involvement is common among patients hospitalized with COVID-19 and contributes up to 40% of the deaths related to the virus.[2] Statins lower LDL cholesterol, improve CVD outcomes, and have anti-inflammatory properties independent of their lipid-lowering effects. In patients with severe infections, plasma levels of cholesterol including HDL and LDL cholesterol are reduced and the levels correlate with the severity of the disease.[3] The potential impact of further lowering of cholesterol with a statin in a patient with COVID-19 is unknown. We are now in an era of COVID-19, and our patients and referring clinicians will ask whether statins are safe in patients with or at risk for COVID-19 and whether statins can reduce the complications of COVID-19.

Statins have anti-inflammatory effects and may have beneficial effects on the immune system. Toll-like receptors (TLR) are a family of sensor proteins that play a key role in the innate immune system. They can detect viruses and other pathogens and activate immune cell responses that suppress viral replication. On activation, TLR recruit the adapter proteins MyD88 and TIRF. MyD88 activates the transcription and induction of inflammatory cytokines, whereas TRIF activates several kinases, which suppress genes that activate the inflammatory response. A balance between both the MyD88- and TRIF-driven pathways is needed to provide the body with the most effective defense against viral infections. Animal studies have shown that mice deficient in the adaptor protein TRIF were more susceptible to infection, developed more serious complications, and had higher mortality when infected with severe acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus (MERS-CoV) than wild-type mice.[4] The findings were like those seen in human patients with poor disease outcomes after infection with severe acute respiratory syndrome coronavirus or MERS-CoV, other coronaviruses like COVID-19. In a rat model, atorvastatin has been shown to inhibit the mRNA and protein expression of TLR and reduce downstream inflammation and oxidative stress, providing at least a mechanistic rationale for studying the effect of statins in viral infections such as COVID-19.[5]

Observational studies of statins in patients with viral infections have suggested some positive results. In one study of 3043 patients with laboratory-confirmed influenza, 33% received statins.[6] Statin-treated patients were older and more likely to be men and have CVD. Patients who received statins before or during their hospitalization had a decreased odds of death after controlling for confounding variables. In another larger retrospective cohort study of individuals who had received an influenza vaccination, over 1.2 million statin users were matched with nonusers to evaluate the effect of statins on hospitalizations and death related to influenza.[7] The use of a statin was associated with a small protective effect against hospitalization for pneumonia, 30-day pneumonia death, and all-cause death. This apparent protective effect was substantially attenuated after multivariate adjustment for confounding variables. In both studies, there was no evidence of harm associated with statin therapy.

Serum levels of total cholesterol, LDL cholesterol, and HDL cholesterol fall in patients with active viral infections. In a recent study from Wenzhou China, total cholesterol, LDL cholesterol, and HDL cholesterol were 25%, 41%, and 20% lower, respectively, in patients with COVID-19 infection compared with healthy age-matched controls.[3] These findings were confirmed in another recent study from China.[8] In that study, the level of LDL cholesterol was inversely correlated with the levels of C-reactive protein and interleukin-6 and the more severe the disease, the lower the LDL cholesterol. This raises at least a minor concern about further lowering of LDL cholesterol with statins in patients with acute COVID-19 infection. To date, no studies have been published confirming the safety of statins in patients infected with COVID-19. However, there is some suggestive evidence that statins are safe in the setting of infection with COVID-19 and other coronaviruses such as Ebola or MERS. A preliminary uncontrolled

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trial report from Sierra Leone claimed improvement in survival in Ebola patients given a generic statin and an angiotensin receptor blocker.[9] Animal studies conducted to understand the mechanism of MERS infection provide a rationale for a possible benefit of statin therapy.[5] In a recent analysis of 8910 total patients hospitalized with COVID-19, the 860 patients taking statins at the time of admission had greater odds of survival and discharge from the hospital than the nonstatin users.[10] However, unrecognized covariates could have played a role, including the possibility that some of the sicker patients may have discontinued statins shortly before hospital admission. These studies should be interpreted with caution because they provide marginal evidence. However, at least statins appear generally safe in patients at risk for coronavirus infections or in the early stages of infection.

When starting a patient on a statin in the era of COVID-19, patients may develop side effects from the statin that mimic the symptoms of COVID-19. Statins may lead to muscle-related symptoms, and muscle symptoms have been described with COVID-19. However, fever, cough, and shortness of breath, which are more common presenting symptoms of COVID-19, do not occur with statins and should allow the clinician a means to distinguish between symptoms of COVID-19 and statin-associated side effects, as will more access to rapid testing to exclude or confirm acute COVID-19 infection.

Statins have been shown to be safe and improve CVD outcomes. In the era of COVID-19, statins should continue to be prescribed when indicated by current guidelines. Because patients with underlying CVD are at increased risk of serious complications and death from COVID-19, reducing the burden of CVD in our patients should improve outcomes in those who become infected with COVID-19. On the other hand, the shortest period over which reduction of cardiovascular events has been observed with statin treatment is about 8 weeks.[11] Symptomatic or survival benefit has not been confirmed for statin treatment over shorter periods in any clinical setting. Rhabdomyolysis has occurred in severely ill COVID-19 patients, and COVID-19–induced liver dysfunction may also change statin metabolism leading to myopathic peripheral blood levels. Weakening of stressed respiratory muscles is possible. Whether statin therapy should be continued in COVID-19 patients sick enough to be hospitalized is uncertain. Current data suggest, however, that statins are safe and might provide benefit in the setting of uncomplicated COVID-19.

Although there are no randomized clinical trials with statins on risk of infection or complications with COVID-19, the observational evidence along with that from patients infected with other coronaviruses provide support for the safety of statins in the era of COVID-19. Once vaccines are available, COVID-19 may no longer be a health care issue; however, CVD will remain, and our conviction to reduce CVD risk in our patients with statins must not waver.

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