Considerations for Statin Therapy in Patients with COVID-19

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The current coronavirus pandemic is an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is the third coronavirus outbreak during the current century, after the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses.1

Acute respiratory distress syndrome (ARDS) is an immunopathologic event and the main cause of death following COVID-19. The main mechanism of ARDS is uncontrolled systemic inflammatory response and cytokine storm following the release of proinflammatory cytokines (e.g., interferons [IFNs], interleukins [ILs], tumor necrosis factor [TNF]-α) and chemokines.2, 3 Therefore, some Chinese researchers proposed or used anti-inflammatory agents in the treatment regimen of patients with COVID-19.3, 4

Statins are well known for their anti-inflammatory effects,5 and some hospitals included them in the COVID-19 treatment protocol.6 Here, we summarize the main points that should be considered before incorporating this class of drugs in a COVID-19 treatment regimen.

Potential Mechanistic Effects/Adverse Effects of Statins on ARDS

Toll-like receptors (TLRs), a family of sensor proteins, assist the immune system to discriminate between “self” and “non-self.” In a mice model, researchers demonstrated that TLR signaling through TRIF adaptor protein mitigate ARDS as a main cause of death in SARS-CoV disease.7 Gene expression of myeloid differentiation primary response 88 (MyD88) acts downstream of TLRs and is induced by SARS-CoV infection.7 Both overexpression7 and underexpression of MyD88 gene8 were related to increased mortality after MERS-CoV infection. Downstream of TLRs-MyD88 pathways, NF-κB is activated by coronavirus infections. In a mice model, inhibition of NF-κB improved lung infection and survival after SARS-CoV infection.9 Statins preserve MyD88 at normal levels during hypoxia10 and mitigate NF-κB activation,11 so some investigators hypothesized the idea of using statins for the treatment of MERS-CoV infection12 and COVID-19.13 But animal studies have shown that aberrant inhibition of TLR adaptor TRIF or MyD88 signals results in severe lung damage and death.7, 14 This may be due to the compensatory activation of other innate immune factors. In addition, animal studies on SARS-CoV and MERS-CoV infections revealed that abolished TLR pathway leads to increased viral load that persists for a longer time and increases the risk of human-to-human transmission.7, 14 Therefore, statins, by the potential to stop TLR and NF-κB signaling, carry the potential risk of exacerbating compensatory immune signals and poor disease outcome. Although some human and animal studies have shown lung injury improvement of statins via their anti-inflammatory effects,15, 16 a retrospective analysis of the findings of a multicenter clinical trial on the efficacy of rosuvastatin against infection-induced ARDS showed higher IL-18 level

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and mortality in statin-treated patients.\textsuperscript{17} The findings on the effects of statin on community-acquired\textsuperscript{18} and ventilator-associated pneumonia\textsuperscript{19, 20} are conflicting as well.

Finally, for the COVID-19 outbreak, although some US hospitals included statins in COVID-19 treatment\textsuperscript{6} and some proposed their use for this condition,\textsuperscript{13} some others worry regarding statin-induced increase in IL-18 and deterioration of SARS-CoV-2–induced ARDS and mortality.\textsuperscript{21}

Considerations in Real Situation

We have to notice that patients with common comorbidities, including hypertension, cardiovascular diseases, and diabetes, are at greater risk for SARS-CoV-2 infection and its related ARDS and mortality.\textsuperscript{22} Most of these patients are taking statins routinely based on diabetes and cardiovascular guidelines. There is no evidence for discontinuing statins in these patients during the COVID-19 episode.

Common Adverse Effects Between COVID-19 and Statins

Although usually well tolerated, statins may cause myotoxicity in some patients. Features of statin-induced myotoxicity differ from those of myalgia (more common) to myopathies and rarely rhabdomyolysis. Rhabdomyolysis can cause acute kidney injury.\textsuperscript{23} Myalgia, increased creatine phosphokinase, rhabdomyolysis, and acute kidney injury occur in patients with COVID-19 as well.\textsuperscript{2} In addition, some risk factors such as advanced age and liver and kidney impairments are common between statin-induced myopathies and infection with SARS-CoV-2.\textsuperscript{2, 23} Thus, initiating statins in patients with COVID-19 may increase the risk and severity of myopathies and acute kidney injury. Furthermore, statin therapy and COVID-19 both increase liver enzymes that are hard to differentiate from each other, if statin therapy starts at the episode of COVID-19.\textsuperscript{2}

Drug Interaction Between Statins and Antiviral Agents for COVID-19 Treatment

Most available statins are substrate for the cytochrome P450 (CYP) system, especially 3A isoenzymes and P-glycoproteins (P-gp). Protease inhibitors (e.g., lopinavir, darunavir) and their pharmacokinetic enhancers (ritonavir and cobicistat) are potent inhibitors of both CYP3A and P-gp, and their concomitant administration results in markedly increased statin exposure and adverse effects. Coadministration of simvastatin or lovastatin with ritonavir/cobicistat-boosted protease inhibitors should be avoided. Maximum daily doses of 20 mg for atorvastatin and 10–20 mg for rosuvastatin have been proposed in patients receiving ritonavir/cobicistat-boosted protease inhibitors.\textsuperscript{24, 23}

Conclusion

Taken together, although there is an urgent need for finding safe and available options for treatment of COVID-19 and its related fatal ARDS, we must balance our expectation from these immunomodulatory drugs against the potential of disease exacerbation by these agents. We recommend guideline-directed continuation of statin therapy among COVID-19 patients with a history of atherosclerotic cardiovascular disease or diabetes. We recommend guideline-directed initiation of statin in patients with COVID-19 who show acute cardiac injury. But, de novo initiation of statin therapy for management of COVID-19 episode can be done only as a clinical trial, not routinely.

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