PHARMACOTHERAPY

LETTERS TO THE EDITOR

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 overexpression[7] and underrexpression of *MyD88* gene[8] 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 hypoxia[10] and mitigate NF-κB activation,[11] so some investigators hypothesized the idea of using statins for the treatment of MERS-CoV infection[12] 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.[17] The findings on the effects of statin on community-acquired[18] and ventilator-associated pneumonia[19, 20] are conflicting as well.

Finally, for the COVID-19 outbreak, although some US hospitals included statins in COVID-19 treatment[6] and some proposed their use for this condition,[13] some others worry regarding statin-induced increase in IL-18 and deterioration of SARS-CoV-2–induced ARDS and mortality.[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.[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.[23] Myalgia, increased creatine phosphokinase, rhabdomyolysis, and acute kidney injury occur in patients with COVID-19 as well.[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.[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.[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.[24, 25]

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 guidance-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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