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Considerations for statin therapy in patients with COVID-19

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Current coronavirus pandemic named 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 severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses.[1]

Acute respiratory distress syndrome (ARDS) is an immunopathologic event and main cause of death following COVID-19. The main mechanism of ARDS is uncontrolled systemic inflammatory response and cytokine storm following release of proinflammatory cytokines (such as interferons (IFN), interleukines (IL), tumor necrosis factor (TNF)-α) and chemokines.[2-3] So, 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 main points that should be considered before incorporating this class of drugs in COVID-19 treatment regimen.

Potential mechanistic effects/adverse effects of statins on ARDS

Toll-like receptors (TLR), a family of sensor proteins, assist immune system to discriminate between "self" and "non-self". In mice model, Totura *et al* 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 over-expression[7] and under-expression 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 mice model, inhibition of NF-κB improved lung infection and

survival after SARS-CoV infection.[9] Statins preserve MyD88 at normal level during hypoxia[10] and mitigate NF-κB activation[11], therefore some investigators hypothesized the idea of using statins for 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 longer time and increase risk of human to human transmission.[7,14] So, 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 by their anti-inflammatory effects.[15-16], a retrospective analysis of the findings of a multicenter clinical trial on efficacy of rosuvastatin against infection-induced ARDS showed higher IL-18 level 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 COVID-19 outbreak, although some US hospitals included statin 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 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 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] So, initiating statin 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 cytochrome (CYP) 450 system especially 3A isoenzymes and P-glycoproteins (P-gp). Protease inhibitors (*e.g.* lopinavvir, 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 20mg for atorvastatin and 10-20mg 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 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 clinical trial not routinely.

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