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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Perspective

Potential role of statins in COVID-19

Ken Cheah Hooi Lee*, Duu Wen Sewa, Ghee Chee Phua

Department of Respiratory and Critical Care Medicine, Singapore General Hospital

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ABSTRACT

Patients with COVID-19 infection have an increased risk of cardiovascular complications and thrombotic events. Statins are known for their pleiotropic anti-inflammatory, antithrombotic and immunomodulatory effects. They may have a potential role as adjunctive therapy to mitigate endothelial dysfunction and dysregulated inflammation in patients with COVID-19 infection.

Highlights

- Statins have anti-inflammatory effects including augmentation of ACE2 expression.
- Statins have an antithrombotic effect.
- Statins may improve endothelial function in patients with COVID-19 infection.

Main Text

The novel coronavirus 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 4.2 million people and caused more than 280,000 deaths worldwide as of 12 May 2020. Apart from concern about progressive respiratory failure, emerging data suggest that COVID-19 patients are also at increased risk of cardiovascular complications and thrombotic events, including acute pulmonary embolism, deep vein thrombosis, and ischemic stroke. Understanding the mechanism of infection and pathophysiology of the disease will provide useful guidance on therapeutic and preventive strategies that avoid these complications.

Angiotensin-converting-enzyme 2 (ACE2) is the receptor that allows SARS-CoV-2 to gain entry into host cells. Alveolar epithelial type II cells account for 83% of ACE2-expressing cells in the lung (Zhang et al., 2020). The ACE2 receptor is also expressed in extrapulmonary tissues such as the heart, vasculature, brain, gastrointestinal tract, and kidneys. ACE2 is an important counter-regulatory enzyme in the renin-angiotensin system, catalyzing the conversion of angiotensin II (AT II) to angiotensin-(1-7). AT-(1-7) opposes the effects induced by AT II, which left unopposed lead to increased oxidative stress, inflammation, and fibrosis.

Infection with SARS-CoV-2 causes downregulation of ACE2. This increases vulnerability to the damaging effects of AT II, which is thought to be responsible for the lung injury that is seen in many COVID-19 patients. The dual roles played by ACE2 as a protector against the harmful effects of the hyperinflammatory response, and as the receptor for SARS-CoV, has caused controversy regarding the use of medications such as ACE-inhibitors (ACE-I) and angiotensin-receptor blockers (ARBs). These concerns stem from experimental animal models that demonstrate these drugs cause an up-regulation of ACE2 expression and activity in heart and kidney tissue (Ferrario et al., 2005a; Ferrario et al., 2005b). This means patients on these drugs might be at an increased risk of more severe COVID-19 infection.

Nonetheless, increased ACE2 may confer protection against more severe lung injury in patients who have been infected (Imai et al., 2005; Kuba et al., 2005). Results from several recent observational studies, however, do not support an association between these drugs and more severe COVID-19 infection (Mehra et al., 2020; Reynolds et al., 2020; Mancia et al., 2020). The European Society of Cardiology, American College of Cardiology and American Heart Association recommend continuing ACE-I and ARB treatment in COVID-19 patients (De Simone, 2020; Bozkurt et al., 2020). COVID-19 patients who are already on statin therapy should also continue treatment if not contraindicated (ESC guidance, 2020).

Statins are known for their pleiotropic anti-inflammatory effects, including augmentation of ACE2 expression and inhibition of the Toll-like receptor (TLR)-MYD88-NF-κB pathway in vitro (Chansrichavala et al., 2009). Studies in patients with cardiovascular disease have demonstrated reduced C-reactive protein (CRP), providing convincing evidence of the anti-inflammatory benefits

* Corresponding Author:Department of Respiratory and Critical Care Medicine, 20 College Road, Singapore 169856
E-mail address: ken.lee.c.h@singhealth.com.sg (K.C.H. Lee).

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of statins independent of their cholesterol-lowering effects (Albert et al., 2001). In COVID-19 patients, the same anti-inflammatory activity might improve outcomes in those patients with increasingly severe illness, worsening respiratory failure, and increasing D-dimer and IL-6 levels: all factors associated with increased mortality (Kruger et al., 2013; Ruan et al., 2020; Wu et al., 2020). Earlier studies suggested the possible effectiveness of statin therapy in decreasing influenza-related hospitalizations and deaths. During the 2009 H1N1 pandemic, statin therapy was associated with reduced disease severity among hospitalized patients (Fedson, 2013). Two observational studies reported a 41% and 59% reduction in 30-day all-cause mortality, respectively, associated with the use of statins in hospitalized patients with influenza infections (Vandermeer et al., 2012; Laidler et al., 2015). The first study suggested that statins might be useful for treating hospitalized influenza patients (Vandermeer et al., 2012), while the other concluded that statins should not be used as an adjunct treatment to improve survival due to unmeasured confounding in the study (Laidler et al., 2015). Nonetheless, these encouraging findings have led some to advocate statins as an immunomodulatory treatment for viral infections that have the potential to cause pandemics (Fedson, 2013; Fedson, 2016).

The current management of patients with COVID-19 infection remains mostly supportive. The most severe cases often require mechanical ventilation, and standard approaches to managing acute respiratory distress syndrome (ARDS) of any cause are often used to treat these patients. However, increasing data suggest the respiratory failure that develops in COVID-19 infection differs from that in other ARDS patients in many ways (Rello et al., 2020). Features including relatively good lung compliance despite poor oxygenation, the lack of pulmonary vasoconstriction with resultant significant shunting, and thrombotic microangiopathy (Gavriilaki and Brodsky, 2020; Tang et al., 2020; Fogarty et al., 2020) suggest that vascular endothelial dysfunction plays a vital role in the pathogenesis of COVID-19 infections (Varga et al., 2020). Statin treatment might improve endothelial and vascular function in these patients. In fact, a combination of statin/ARB treatments was used in an unconventional and poorly documented experience to target the host response and prevent endothelial barrier damage in Ebola patients during the outbreak in West Africa (Fedson and Rordam, 2015; Fedson, 2018). A similar approach might be considered for patients with severe COVID-19 infection since both statins and ARBs upregulate ACE2 activity and counter endothelial dysfunction (Fedson et al., 2020).

Markedly elevated D-dimer levels and high incidence of thrombotic complications recently reported in critically ill COVID-19 patients have raised concerns about increased thrombogenicity in these patients (Dolhnikoff et al., 2020; Klok et al., 2020). One study reported a 31% cumulative incidence of thrombotic complications among 184 patients with COVID-19 pneumonia admitted to an intensive care unit despite standard pharmacological thromboprophylaxis (Klok et al., 2020). Some centers recommend prophylactic anticoagulation for all patients with COVID-19 infection, and therapeutic anticoagulation to be strongly considered for patients deemed to be at high risk for coagulopathy. Others have proposed thrombolytic treatment in refractory cases of hypoxia (Poor et al., 2020). The role of statins in managing venous thromboembolism has been explored in previous studies. The JUPITER trial, which studied relatively healthy patients with high CRP levels, reported a significantly decreased rate of deep vein thrombosis in those who received rosuvastatin compared to placebo (Glynn et al., 2009). Another study found statin therapy was associated with a 50% reduction in recurrent pulmonary embolism (Biere-Rafi et al., 2013). Several mechanisms have been proposed to explain the antithrombotic effects of statin treatment, including reduced tissue factor expression, decreased platelet aggregation, and increased thrombomodulin expression on endothelial cells (Arsian et al., 2008).

The negative outcomes from randomized controlled trials of statin treatment in mechanically ventilated ARDS and sepsis patients (Grimaldi et al., 2016) have contributed to the reluctance to consider statins as adjunctive treatment in patients with COVID-19 infection. These may be due to the heterogeneity of statin treatment effects caused by suboptimal patient selection. Safety concerns about statin treatment (liver injury, myotoxicity, and rhabdomyolysis-related kidney injury) might also be factors. These conditions may occur more frequently in patients with severe COVID-19 infection (Li and Fan, 2020). Furthermore, most statins undergo hepatic metabolism by the hepatic isoenzyme CYP3A4. Concomitant administration of statins with antiviral agents in COVID-19 randomized controlled trials that are CYP3A4 inhibitors may increase the risks of these adverse effects. Careful monitoring of creatine kinase levels and liver function would be advised in such instances. Considering other adjunctive therapies that are being tested (e.g., corticosteroids, where there are concerns about delayed viral clearance and other side effects, or anticoagulation and thrombolytic therapies that are associated with significant bleeding risks), the potential for adverse effects of statin treatment appear more tolerable.

To conclude, we believe that statins might mitigate the effects of COVID-19 infection in selected patients based on our understanding of its associated coagulopathy, endothelial dysfunction, and dysregulated inflammation. However, in the absence of reliable evidence, the role of statins remains uncertain, and this undoubtedly contributes to the hesitancy to administer a yet unproven treatment. Phase 3 trials should be considered to determine which COVID-19 patients may benefit from statin therapy, and the type and dose of statin to be given.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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