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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Potential role of statins in COVID-19
Ken Chee Hooi Lee*, Duu Wen Sewa, Ghee Chee Phua
Department of Respiratory and Critical Care Medicine, Singapore General Hospital

A R T I C L E   I N F O
Article history:
Received 12 May 2020
Received in revised form 27 May 2020
Accepted 28 May 2020

A B S T R A C T
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.

© 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 counterregulatory 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...
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 therapy 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 (Gavrilaki 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 Nordam, 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.

**Funding**

Funding information is not available.

**Ethical approval**

Ethical approval is not required for the preparation of this manuscript.

**Author Contributions**

All authors participated in the conception, analysis, and writing of this manuscript.

**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.

**References**

Albert MA, et al. PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286(1):56–70, doi:http://dx.doi.org/10.1001/jama.286.1.56.

Arsian F, Pasterkamp G, de Klein JP. Unraveling pleiotropic effects of statins: bit by bit, a slow case with perspective. Circ Res 2008;103(4):334–6, doi:http://dx.doi.org/10.1161/CIRCRESAHA.108.182220.

Biere-Rafi S, et al. Statin treatment and the risk of recurrent pulmonary embolism. Eur Heart J 2013;34(24):1800–6, doi:http://dx.doi.org/10.1093/eurheartj/eht046.

Bozkurt B, Kovacs R, Harrington B. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.
Chansrichavala P, et al. Atorvastatin attenuates TLR4-mediated NF-kappaB activation in a MyD88-dependent pathway. Asian Pac J Allergy 2009;27:49–57.

De Simone G. Position statement of the ESC Council on hypertension on ACE-inhibitors and angiotensin receptor blockers. 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang.

Dollnhofer M, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost 2020.; doi:http://dx.doi.org/10.1111/jth.14844.

ESC guidance. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. 2020. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance.

Fedson DS. Treating influenza with statins and other immunomodulatory agents. Antiviral Res. 2013;99(3):417–35, doi:http://dx.doi.org/10.1016/j.antiviral.2013.06.018.

Fedson DS. Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola. Ann Transl Med 2016;4(21):421, doi:http://dx.doi.org/10.21037/atm.2016.11.03.

Fedson DS. What treating Ebola means for pandemic influenza. J Public Health Policy. 2018;39(3):268–82, doi:http://dx.doi.org/10.1057/s41271-018-0138-8.

Fedson DS, Rordam OM. Treating Ebola patients: a ‘bottom up’ approach using generic statins and angiotensin receptor blockers. Int J Infect Dis 2015;36:80–4, doi:http://dx.doi.org/10.1016/j.ijid.2015.04.019.

Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. mBio 2020;11(2):e00398-20, doi:http://dx.doi.org/10.1128/mBio.00398-20.

Ferrario CM, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005a;111(20):2605–10, doi:http://dx.doi.org/10.1161/CIRCULATIONAHA.104.510461.

Ferrario CM, et al. Effects of renin-angiotensin system blockade on renin angiotensin-(1–7) forming enzymes and receptors. Kidney Int 2005b;68(5):2189–96, doi:http://dx.doi.org/10.1111/j.1523-1755.2005.00675.x.

Fogarty H, et al. COVID-19 coagulopathy in Caucasian patients. Br J Haematol 2020.; doi:http://dx.doi.org/10.1111/bjh.16783.

Gavrilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. Br J Haematol 2020., doi:http://dx.doi.org/10.1111/bjh.16783.

Glynn RJ, et al. A randomized trial of rosvastatin in the prevention of venous thromboembolism: the JUPITER trial. N Engl J Med 2009;360(18):1851–61, doi:http://dx.doi.org/10.1056/NEJMoa0902241.

Grimaldi D, et al. Failure of statins in ARDS: the quest for the Holy Grail continues. Minerv Aneriostesia 2016;62(11):1230–4.

Imai Y, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436(7047):112–6, doi:http://dx.doi.org/10.1038/nature03712.

Klok FA, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Throm Res 2020., doi:http://dx.doi.org/10.1016/j.thromres.2020.04.013.

Kruger P, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med 2013;187(7):743–50, doi:http://dx.doi.org/10.1164/rccm.201209-1718OC.

Kuba K, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11(8):875–9, doi:http://dx.doi.org/10.1038/nm1267.

Laidler MR, et al. Statin treatment and mortality: Propensity score-matched analyses of 2007–2008 and 2009–2010 laboratory-confirmed influenza hospitalizations. Open Forum Infect Dis 2015;2(1):ofv028, doi:http://dx.doi.org/10.1093/ofid/ofv028.

Li J, Fan J. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol 2020;8(1):13–7, doi:http://dx.doi.org/10.14281/JCTH.2020.00019.

Mancia G, et al. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med 2020;NEJMoa2006923, doi:http://dx.doi.org/10.1056/NEJMoa2006923.

Mehra MR, et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med 2020;NEJMoa2009621, doi:http://dx.doi.org/10.1056/NEJMoa2007621.

Poor HD, Ventetuolo CE, Tolbert T. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombosis. medRxiv 2020., doi:http://dx.doi.org/10.1016/j.crvi.2020.

Rello J, et al. Clinical phenotypes of SARS-CoV-2: Implications for clinicians and researchers. Eur Respir J 2020;55(5):2001028, doi:http://dx.doi.org/10.1183/13993003.01028-2020.

Reynolds HR, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020;NEJMoa2008975, doi:http://dx.doi.org/10.1056/NEJMoa2008975.

Ruan Q, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846–8, doi:http://dx.doi.org/10.1007/s00134-020-05991-x.

Tang N, et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Thromb Haemost 2020;18(4):844–7, doi:http://dx.doi.org/10.1111/j.1476-9458.2019.02255.x.

Vandemere ML, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis 2012;205(1):13–9, doi:http://dx.doi.org/10.1093/infdis/jir531.

Varga Z, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet 2020;395(10234):1417–8, doi:http://dx.doi.org/10.1016/S0140-6736(20)30937-5.

Wu C, Chen X, Cai Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;e2009974, doi:http://dx.doi.org/10.1001/ jamanetworkmedicine.2020.0994.

Zhang H, et al. Angiotensin-converting enzyme (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;46(4):586–90, doi:http://dx.doi.org/10.1007/s00134-020-05985-9.