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Statins and PCSK9 inhibitors: What is their role in coronavirus disease 2019?

Fotios Barkas, Haralampos Milionis, Georgia Anastasiou, Evangelos Liberopoulos * 

Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Ioannina, Greece

ABSTRACT

Statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors interfere with several pathophysiological pathways of coronavirus disease 2019 (COVID-19).

Statins may have a direct antiviral effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by inhibiting its main protease. Statin-induced up-regulation of angiotensin-converting enzyme 2 (ACE2) may also be beneficial, whereas cholesterol reduction might significantly suppress SARS-CoV-2 by either blocking its host-cell entry through the disruption of lipid rafts or by inhibiting its replication. Available human studies have shown beneficial effects of statins and PCSK9 inhibitors on pneumonia and sepsis. These drugs may act as immunomodulators in COVID-19 and protect against major complications, such as acute respiratory distress syndrome and cytokine release syndrome. Considering their antioxidative, anti-arrhythmic, antithrombotic properties and their beneficial effect on endothelial dysfunction, along with the increased risk of mortality of patients at high cardiovascular risk infected by SARS-CoV-2, statins and PCSK9 inhibitors might prove effective against the cardiovascular and thromboembolic complications of COVID-19.

On the whole, randomized clinical trials are needed to establish routine use of statins and PCSK9 inhibitors in the treatment of SARS-CoV-2 infection. In the meantime, it is recommended that lipid-lowering therapy should not be discontinued in COVID-19 patients unless otherwise indicated.

Introduction

At the end of 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of a cluster of pneumonia cases in Wuhan, in the Hubei Province of China and finally declared as pandemic in February 2020 [1]. Until 30 May 2020, a total of 5,775,043 cases of coronavirus disease 2019 (COVID-19) and 361,220 deaths were confirmed worldwide [1]. SARS-CoV-2 is a beta-coronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus, using an identical receptor, namely angiotensin-converting enzyme 2 (ACE2), for cell entry [2]. Although the majority of SARS-CoV-2 infections are mild to moderate, 14% of patients develop severe disease (dyspnea, hypoxia, or >50% lung involvement on imaging within 24–48 h) and 5% critical disease (respiratory failure, shock, multi-organ dysfunction). Mortality rates range from 0.9 to 12% depending on the population under study [1,3]. Cardiovascular disease, diabetes, hypertension, dyslipidemia, chronic lung and kidney disease, cancer, obesity and smoking have all been associated with severe disease and increased mortality [4,5].

SARS-CoV-2 infection has been associated with downregulation of ACE2 receptors and a cytokine storm characterized by increased release of interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and tumor necrosis factor (TNF)-α [6]. The activation of these pathways lead to COVID-19 major complications related with high mortality rates, such as acute respiratory distress syndrome (ARDS) and secondary hemophagocytic lymphohistiocytosis, as well as cardiovascular complications, including myocarditis, heart failure, myocardial infarction and arrhythmias [3,6–8]. Coagulopathy and thromboembolic events, such as stroke, pulmonary embolism and deep vein thromboses, have also been described in patients with COVID-19 [9,10].

Currently, there are no well-established effective therapies to treat SARS-CoV-2 [11]. Only dexamethasone has been shown to significantly reduce 28-day mortality in patients with critical COVID-19 [12,13]. Remdesivir, a novel nucleotide analogue, has been proposed in hospitalized patients with severe COVID-19 requiring low-flow supplemental oxygen, given the potential reduction in time to clinical improvement [12–16]. However, the World Health Organization recommends against...
the use of remdesivir [13]. The rapidly expanding knowledge regarding its virology points to a number of potential drug targets. A plethora of randomized trials investigate possible therapeutic options against COVID-19 [11]. In this context, drugs used in every day clinical practice are being considered. As a matter of fact, there is evidence that statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors could interfere with several pathophysiological pathways in COVID-19 (Fig. 1). The aim of the present review was to describe these pathways and evaluate the potential role of these drugs in the management of patients infected with SARS-CoV-2.

**SARS-CoV-2 virology**

Statin therapy has been previously described to reduce Ebola infectivity through the inhibition of viral glycoprotein processing, as evidenced by decreased ratios of the mature glycoprotein form to precursor form in statin-treated cells [17]. Similarly, it has been argued that statins could reduce SARS-CoV-2 infectivity by inhibiting its main protease, which plays an important role in the proteolytic maturation and thus in virus replication (Fig. 1) [18]. A recent experimental study showed that statins, particularly pitavastatin, had a binding affinity to SARS-CoV-2 main protease which was more potent than that of protease or polymerase inhibitors [18].

Considering that statins and inhibitors of the renin-angiotensin–aldosterone system (RAAS) up-regulate ACE2 receptors [19], concerns were initially raised as to a possible adverse impact on COVID-19 [20]. However, a recent case-population study including 1139 COVID-19 cases and 11,390 controls showed that RAAS inhibitors do not increase the risk of COVID-19 patients requiring admission to hospital when compared with users of other antihypertensive drugs (adjusted odds ratio, OR: 0.94, 95% confidence interval, CI: 0.77–1.15) [21]. Likewise, another meta-analysis of 4 studies (n = 8990 patients with COVID-19) revealed a significantly reduced hazard for fatal or severe disease with the use of statins (hazard ratio, HR: 0.70, 95% CI: 0.53–0.94) compared to non-use of statins in COVID-19 patients [22]. Therefore, fear that ACE2 overexpression could increase SARS-CoV-2 host-cell entry is not substantiated. On the contrary, ACE2 up-regulation may be beneficial rather than harmful in SARS-CoV-2 infected patients due to an increase in the catalysis of ‘bad’ angiotensin II and the production of ‘good’ angiotensin 1–7 [20].

Even though we lack reports on the effects of PCSK9 inhibitors against SARS-CoV-2, previous evidence suggests that PCSK9 might...
interfere with the pathogenesis of viral infections, such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV) [23,24]. In-vitro and in-vivo studies have shown that PCSK9 or a more active membrane-bound form of the protein (PCSK9-ACE2) potentially reduce membrane infectivity through the down-regulation of putative liver HCV receptors, namely CD81 and low-density lipoprotein receptors (LDL-R) [25].

Another study revealed that HCV enhanced LDL-R expression and decreased PCSK9 expression in order to facilitate viral propagation [25]. On the other hand, a human cohort showed that HCV and HIV co-infection was associated with both high PCSK9 levels and increased LDL-R [26]. Consequently, there were concerns as to whether PCSK9 inhibitors actually increase the risk of viral infections and especially hepatitis C. An experimental study showed that PCSK9 inhibition with alirocumab had no effect on CD81 and did not result in increased susceptibility to HCV entry [27]. Likewise, FOURIER and ODYSSEY OUTCOMES, the two major randomized clinical trials (RCTs) evaluating cardiovascular outcomes with the use of PCSK9 inhibitors over a period of 2–3 years, showed no differences regarding the rates of incident HCV between evolocumab or alirocumab and placebo (0.02% vs 0.00% and 0.01% vs 0.01%, respectively) [28,29]. Elevated liver enzymes are frequently noticed in COVID-19 patients [7]. Therefore, relevant studies could evaluate whether PCSK9 inhibitors have a direct effect on SARS-CoV-2 entry at least in liver cells.

Lipid rafts, i.e. membrane microdomains enriched with cholesterol, sphingolipids, and associated proteins, are involved in the process of viral infections [30]. Cholesterol is an essential component of lipid rafts and interferes with various aspects of virus life-cycle, especially viral entry [31]. The successful internalization of enveloped viruses, including many coronaviruses, requires the presence of cholesterol in either the viral and cellular membranes or both [31]. In this context, an experimental study investigated the impact of drug-induced cholesterol depletion from cells or virions on porcine delta-coronavirus infection (PDCoV) [32]. Treatment with methyl-β-cyclodextrin (MβCD) diminished PDCoV infection in a dose-dependent manner, whereas the addition of exogenous cholesterol to MβCD-treated cells or virions moderately restored PDCoV infectivity. In addition, the pharmacological sequestration of cellular or viral cholesterol efficiently blocked both virus attachment and internalization [32]. Likewise, an experimental study has shown that drug-mediated cholesterol depletion of lipid rafts reduces the expression of viral structural proteins and consequently impairs the attachment of coronavirus infectious bronchitis virus to the cell surface [33]. Indeed, a recent study suggested 3 different cholesterol-dependent pathways of SARS-CoV-2 host-cell entry and infectivity [9]. First, loading cells with cholesterol enhances endocytic SARS-CoV-2 host-cell entry by increasing the total number of viral entry points. Secondly, the cholesterol concomitantly traffics ACE2 to the viral entry site where SARS-CoV-2 docks to properly exploit cell entry and interferes with various aspects of virus life-cycle, especially viral entry [31].

Statin use could be beneficial in the management of COVID-19, since SARS-CoV-2 infection is mediated by the interaction of the SARS-CoV-2 spike protein with angiotensin-converting enzyme 2 (ACE2) [34]. Analyses restricted to events occurring before a cardiovascular event showed that pneumonia occurred in 203 participants treated with rosuvastatin and 250 on placebo (HR: 0.81, 95% CI: 0.67–0.97) [37]. On the other hand, RCTs have not confirmed any benefit on inpatient statin treatment in sepsis or ventilator-associated pneumonia (VAP) [38,39]. In a placebo-controlled study with 1002 patients with suspected VAP who required invasive mechanical ventilation for more than two days, treatment with simvastatin had no effect on 28-day mortality (HR: 1.45, 95% CI: 0.83–2.51) [39]. In line, a meta-analysis of 14 RCTs (n = 2628) suggested that statin therapy cannot be recommended for sepsis management, since no difference was noticed regarding 30-day all-cause mortality (risk ratio, RR: 0.96, 95% CI: 0.83–1.10) [38].

Statins have been considered promising in the context of viral infections. Available evidence derived from observational studies supports the efficacy of statin therapy in reducing hospitalizations and deaths related with influenza and Ebola [40,41]. In a retrospective case-control study of 1520 patients with laboratory-confirmed influenza (H1N1), prior statin therapy was associated with a 28% reduction in the severity of illness (adjusted OR: 0.72, 95% CI: 0.38–1.33) [42]. Likewise, a multi-state observational study showed that administration of statins prior to or during hospitalization reduced mortality risk in patients infected with influenza (adjusted OR: 0.59, 95% CI: 0.38–0.92) [43]. All evidence considered, statins could be considered to be ‘used against’ COVID-19 and future RCTs are needed to confirm this theory.

There are limited data regarding the effect of PCSK9 inhibitors on infections and sepsis. According to an analysis from 10,924 black participants tested for PCSK9 loss-of-function (LOF) variants in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, the presence of PCSK9 variants was not associated with infection risk (adjusted HR: 0.68, 95% CI: 0.38–1.25) or sepsis among those hospitalized for a serious infection (adjusted OR: 7.31, 95% CI: 0.91–58.7) [44]. In phase II RCTs, upper respiratory infection, such as nasopharyngitis and cough, were more frequent in the PCSK9 inhibitor group compared with placebo [45–48]. Nevertheless, FOURIER and ODYSSEY OUTCOMES found no increase in infection or sepsis risk [28,29].

**Innate immunity**

Apart from their cholesterol-lowering effect, statins and PCSK9 inhibitors exert pleiotropic effects and favorably affect inflammation and oxidative stress [49,50]. Experimental studies have linked both drug classes with the modulation of immune response at different levels, such as immune cell adhesion and migration, antigen presentation and cytokine production (Fig. 1) [49,50].

Statins inhibit the rate-limiting enzyme of the mevalonate pathway leading to reduced levels of its downstream products, which are critical for geranylgeranylation or farnesylation of GTPases (hydrolyses of nucleotide guanosine triphosphate) mediating multiple steps in the immune response, such as cell migration, activation, signaling and cytokine production [49]. In addition, statins have been demonstrated to suppress the expression of toll-like receptor (TLR) leading to an immune response shift towards anti-inflammatory response [51]. Experimental evidence demonstrated that statins stabilize the levels of myeloid differentiation primary response 88 (MyD88) after a proinflammatory trigger, such as hypoxia, and attenuate the activation of NF-xB (nuclear factor kappa-light-chain-enhancer of activated B cells) [52]. These effects could be beneficial in the management of COVID-19, since SARS-CoV-1 interaction with TLR on the host cell-membrane significantly increases MyD88 gene expression, which in turn attenuates the activation of NF-xB inflammatory pathway [53]. Notably, NF-xB inhibition has been associated with reduced lung infection and increased survival in a murine model of SARS-CoV-1 infection [54].

In addition to the conventional role of LDL-Rs in cholesterol clearance, these receptors are involved in the hepatic clearance of endotoxins, such as lipopolysaccharide (LPS) from the bloodstream during sepsis [55,56]. Therefore, LDL-R up-regulation by statins and PCSK9
inhibitors could increase endotoxin clearance and inhibit the initiation of an unbridle systemic inflammatory response in sepsis (Fig. 1) [55,56].

After the initial entry through ACE2, SARS-CoV-2 down-regulates ACE2 expression, possibly facilitating the initial infection by innate immunity cells and causing an unopposed angiotensin II accumulation, leading to organ injury [8]. Therefore, ACE2 up-regulation induced by statins and RAAS could ameliorate the cytokine release in COVID-19. To this end, statins and ACE inhibitors were recently associated with reduced mortality in hospitalized patients with COVID-19 [19,20].

Considering the well-known effects of statins on subclinical inflammation, their use as immunomodulatory treatment against cytokine storm in COVID-19 patients may deserve consideration. Of course, the question remains whether tackling subclinical inflammation would be sufficient to prevent such a major inflammatory response, as a cytokine storm. Despite the lack of RCTs in COVID-19, statins have been shown to be effective in targeting the host response and preventing endothelial barrier damage in patients infected with Ebola [41]. It has also been suggested instead that statins act beneficially in ‘hyper-inflammatory’ ARDS patients, as defined by increased biomarkers of inflammation, coagulation and endothelial activation [57]. Indeed, a large multicenter, placebo-controlled randomized trial of simvastatin for ARDS (HARP-2) showed that 28-day mortality was lower in the hyper-inflammatory subphenotype patients treated with simvastatin compared with placebo (32% vs 45%, p = 0.008) [57]. Moreover, human PCSK9 LOF genetic variants were associated with improved survival in septic shock patients and a decrease in inflammatory cytokine response both in septic shock patients and in healthy volunteers after LPS administration [58].

Finally, it has been recently proposed that the persistent inflammation happening in COVID-19 adversely affects the anti-inflammatory, antioxidant and immunomodulatory function of high-density lipoproteins (HDL) which could contribute to pulmonary inflammation [59]. In addition, the impaired HDL function associated with increased lipid oxidation could result in the over-activation of innate immune scavenger receptors [59,60]. Considering their beneficial effect on the quantity and quality of HDL [61–63], statins and PCSK9 inhibitors could ameliorate the cytokine release syndrome in COVID-19.

Cardiovascular complications

Could statins and PCSK9 inhibitors protect against the cardiovascular complications of COVID-19? There is strong evidence of direct cardiovascular involvement in COVID-19, such as acute coronary syndrome, arrhythmia, myocarditis, pericarditis and heart failure [64]. Hypoxemia is a putative mechanism underlying the increased risk of cardiovascular disease complications in COVID-19 [64]. Pulmonary parenchymal inflammation and edema caused by SARS-CoV-2 infection interferes with alveolar gas exchange, thereby resulting in ventilation/perfusion imbalance and hypoxemia, which not only affects respiratory function, but also impairs systemic metabolism and vital organ functions, including the heart [64]. Moreover, down-regulation of ACE2 receptors by SARS-CoV-2 leads to inflammation and multi-organ failure [8]. In addition, immune over-reactivity can potentially destabilize atherosclerotic plaques and explain the development of acute coronary syndromes [65]. The ‘cystine storm’ induced by SARS-CoV-2 activates T cells and macrophages which may infiltrate infected myocardium, resulting in severe myocarditis and subsequent heart failure [65]. Moreover, the viral infection itself may cause direct cardiac myocyte damage, leading to myocardial dysfunction and arrhythmogenesis [65].

In addition to their immunomodulating properties, statins and PCSK9 inhibitors exert direct antioxidative and antithrombotic properties, since their use has been experimentally associated with improved endothelial function, reduced oxidative stress, less platelet adhesion and increased atherosclerotic plaque stability [50,66]. Available evidence suggests that statins may protect against arrhythmias and heart failure (Fig. 1) [67,68]. Therefore, both drug classes could ameliorate the endothelial dysfunction, instability of the atherosclerotic plaque and myocardium inflammation or fibrosis induced by COVID-19 and protect against its cardiovascular complications.

Finally, patients at high cardiovascular risk, such as elderly people with cardiovascular comorbidities or patients diagnosed with familial hypercholesterolemia are more likely to develop severe COVID-19 [8,69]. Likewise, such patients are likely to be at increased long-term risk of an atherothrombotic event following COVID-19 [8,69]. In this context, lipid-lowering therapy in patients at high cardiovascular risk should not be discontinued during infection and, because of their possible increased ASCVD risk, could even be intensified following recovery from COVID-19 [70,71]. Of note, the potential advantages of intensifying lipid-lowering therapy for such patients after COVID-19 epidemic and the potential disadvantages of a lack of intensification, should be explored in future epidemiological investigations.

Thromboembolic complications

COVID-19 has been associated with coagulation abnormalities and increased incidence of venous thromboembolic disease [9,10]. Statins and PCSK9 inhibition could be beneficial in COVID-19 patients at increased thromboembolic risk. In a post-hoc analysis of JUPITER, rosuvastatin significantly reduced the occurrence of symptomatic venous thromboembolism by 43% compared with placebo (HR: 0.57, 95% CI: 0.37–0.86) [72]. An analysis of FOURIER and ODYSSEY OUTCOMES reported lower rates of venous thromboembolism in subjects treated with PCSK9 inhibitors compared with placebo (HR: 0.69, 95% CI: 0.53–0.90) [73].

Endothelial dysfunction

It has been suggested that the non-pulmonary complications of COVID-19 could be attributed to profound endothelial dysfunction and injury [74]. Indeed, a case series in New York showed that ~30% of COVID-19 patients with electrocardiographic signs indicating active ischemia had no obstructive coronary artery disease and thus, microvascular dysfunction was considered as the likely cause of ischemia [75]. Moreover, SARS-CoV-2 isolation from cardiac autopsy samples was not associated with immune cells infiltration, as observed in myocarditis [76]. Therefore, the virus seems to primarily affect the endothelium, resulting in secondary myocardial inflammation and dysfunction. The mechanisms involved in the systemic endothelitis in COVID-19 include the activation of the renin angiotensin system and angiotensin II type 1 receptor, the increase of reactive oxygen species (ROS), the activation of NF-kB reducing nitric oxide (NO) production and the activation of several cytokine receptors, such as TNF-a and IL-6 [74]. In turn, endothelial dysfunction itself impairs organ perfusion by disrupting the balance between vasoconstriction and dilatation, increases inflammation and leads to a pro-thrombotic state in both larger and smaller vessels by favoring tissue factor production and platelet activation [74]. In this setting, statins might be helpful by reducing oxidized LDL levels and NADPH oxidase activity, which decreases reactive oxygen species (ROS), by affecting the NF-kB transcription or by improving the coupling of endothelial NO synthase [74]. Independently of NO, statins also prevent the expression of tissue factor in endothelial cells, thus protecting against blood coagulation and platelet activation [77].

Likewise, accumulating evidence suggests that coronary endothelial dysfunction and vascular inflammation are associated with increased PCSK9, with the NF-kB signaling pathway playing a pivotal role in PCSK9-mediated vascular inflammation [78]. The Effect of Evolocumab on Coronary Endothelial Function (EVOlved) study demonstrated that evolocumab rapidly improved coronary endothelial function in individuals with stable pro-inflammatory states (HIV and dyslipidemia) but without coronary artery disease [79]. It could be speculated that PCSK9 inhibitors could also protect against the systemic endotheliitis in SARS-CoV-2 infected patients [79].
Safety of statins and PCSK9 inhibitors in COVID-19

On admission, a considerable proportion of patients infected with SARS-CoV-2 exhibit severe kidney injury (SARI) (16.0–36.6%) along with elevated levels of creatine kinase (13.7%) and aminotransferases (32–46%) [80–82]. Statin therapy might prove beneficial in AKI in such patients, considering their pleiotropic effects in this setting [83,84]. Myalgia, myositis and increase of aminotransferase serum levels are adverse events taken into consideration in patients treated with statins [85] and physicians should be cautious in COVID-19 patients with relevant symptoms and laboratory abnormalities.

Drugs with a potential viricidal effect, such as chloroquine/hydroxychloroquine, protease inhibitors (lopinavir-ritonavir, darunavir-cobicistat), remdesivir and azithromycin are being used in treatment protocols of COVID-19 patients [11]. Most statins undergo a hepatic metabolism through CYP3A4, and concomitant administration of CYP3A4 inhibitors currently used in COVID-19, such as ritonavir and cobicistat, could increase the risk of muscle and liver toxicity. Low-dose statin treatment and monitoring create kinase and transaminases is advised.

PCSK9 inhibitors have reportedly low rates of adverse effects and drug interactions [86] and their use appears safe in the setting of COVID-19.

Conclusion

Available evidence seems to support the hypothesis that statins and PCSK9 inhibitors favorably interfere with several pathways in COVID-19. Considering the need for effective therapeutic strategies to address cases of COVID-19 ranging from mild to severe, further research may be warranted to evaluate potential benefits with these agents. Nonetheless, their well-established cardioprotective effects should prompt physicians to maintain lipid-lowering therapy when treating patients infected with SARS-CoV-2.

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