Statins as candidate therapeutic agents for coronavirus disease 2019 (COVID-19)

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Statins are 3-hydroxy-3-methyl glutaryl (HMG)-coenzyme A (CoA) reductase inhibitors, acting on the rate-limiting enzyme for the conversion of HMG-CoA to L-mevalonate to reduce cholesterol biosynthesis. Apart from reducing cardiovascular events by lowering low-density lipoprotein cholesterol concentrations, pleiotropic cholesterol-independent functions of statins, including immunomodulatory and anti-inflammatory effects, are increasingly recognized. The current coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),¹¹ has caused >500,000 deaths worldwide as of July 2, and it continues to spread without specific antiviral therapies. Statins, with potential antiviral functions as a host-directed therapy (HDT), could be a safe means of improving outcomes for patients with COVID-19.²³

Clinical Evidence

Statin use reduces viral infection and improves clinical outcomes in patients with influenza,⁴ human immunodeficiency virus (HIV), and other viruses.³ It markedly and dose-dependently reduces mortality from influenza.⁴ Studies on patients with HIV found that statins reduce viral copies and lower markers of inflammation, including high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor-α (TNF-α).⁵

Among all COVID-19 patients, 60.7% show CRP ≥10 mg/L, rising to 81.5% in those with severe disease.⁶ RNAemia, immune dysregulation, and elevated serum cytokines, such as interleukin (IL)-6, IL-10, and TNF-α, have been observed and might indicate disease severity.⁷ Another finding was that coexisting cardiovascular diseases are more frequent in patients with severe disease and are associated with poor prognosis for COVID-19.⁸ Since statins show antiviral, anti-inflammatory, and immunomodulatory effects, they might be effective for COVID-19 treatment and reducing cardiovascular events in those with underlying cardiovascular diseases.³ However, more clinical studies are needed to decide whether statin treatment should be started for patients without underlying cardiovascular diseases.

Although statins have a well-established, safe therapeutic profile, their use is not risk-free. Side effects include rhabdomyolysis, statin-induced necrotizing autoimmunity, new onset diabetes mellitus, and potential hemorrhagic stroke, which appear to be dose-dependent for common types of statins.⁹ Meanwhile, patients with COVID-19 might show serum creatine kinase ≥200 U/L (13.7% of patients) and rhabdomyolysis (0.2%),⁶ suggesting that statin use could increase myopathy frequency. In addition, studies on influenza have found that statin use reduces the effectiveness of vaccines against medically attended acute respiratory illness.⁹ As such, the potential side effects of statins during future COVID-19 vaccination should be considered. Another concern is that statin-induced IL-18 production might increase COVID-19 severity via cytokine storms⁴¹⁰ but this is unconfirmed.

Pre-clinical evidence

Antiviral function

SARS-CoV-2 is a member of the betacoronavirus (β-CoVs), similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).¹¹ Ongoing virological studies on SARS-CoV-2 have shown that angiotensin converting enzyme 2 (ACE2) is a receptor bound by SARS-CoV-2 for cell entry,¹² similar to that with SARS-CoV, which uses spike glycoproteins (S protein) on the viral envelope for binding. Depleting cholesterol in ACE2-expressing cells decreases ACE-S protein binding by
50%, indicating that decreased cholesterol levels in host cells might inhibit SARS-CoV-2 replication, as lipid rafts and cholesterol are required for SARS-CoV entry into host cells. Such inhibitory effects on CoV entry could be restored by the addition of exogenous cholesterol. In addition, statins inhibit HMG-CoA reductase, resulting in reduced mevalonate synthesis and suppressed cholesterol production. [3] and cholesterol is required by viruses for replication. [2] For example, influenza virus causes infected cells to produce lipid droplets, potentially as materials for their lipid components, but this can be effectively inhibited by atorvastatin, resulting in reduced viral replication. [14]

Third, statins also inhibit the downstream production of lipid isoprenoid intermediates such as farnesyl pyrophosphate and geranyl-geranyl pyrophosphate, which are crucial for host-cell protein prenylation functions. [3,15] During prenylation, isoprenoids are required for G protein subunits such as Ras, Rab, Rho, Rac, and Rap, as their activation induces host cell proliferation or inflammatory factor production. [3] For example, statins directly inhibit HIV via Rho pathway downregulation. [16] Defined as detectable serum SARS-CoV-2 viral loads, RNAemia was observed in patients with COVID-19 and can trigger cytokine storms, which was associated with increased IL-6 levels and poor prognosis. [7] Statins might decrease the risk of RNAemia and reduce respiratory viral loads, which might help suppress transmission. [17]

**Anti-inflammatory function**

In clinical practice, the uncontrolled hyperproduction of cytokines and chemokines such as IL-6, IL-8, TNF-α, interferon (IFN), C-C motif chemokine 8, and C-X-C motif chemokine ligand 10 (CXCL10) can have disastrous interferon (IFN), C-C motif chemokine 8, and C-X-C motif chemokine ligand 10 (CXCL10) can have disastrous consequences. In an in vitro study, imbalanced host responses to SARS-CoV-2 have been reported, as inhibited innate antiviral defense coexists with the excess release of inflammatory cytokines, especially IL-6, which is in line with highly elevated IL-6 in COVID-19 patients. [7,18] Statins can markedly reduce pro-inflammatory cytokines and chemokines by targeting multiple functions of virus-infected host cells. [19] For example, Rho proteins can increase levels of pro-inflammatory cytokines such as TNF-α and IL-6 via nuclear factor-kB (NF-kB) signaling. [3,15] Statins can reduce IL-6 synthesis by inhibiting NF-kB and Rho pathways. [20] To inhibit virus-induced cytokine storms, immunosuppressive therapy has been proposed, with tocilizumab (blocking IL-6 receptors) suggested to treat severe cases. Despite their anti-inflammatory effects, statins have not been investigated for applications to COVID-19.

**Immunomodulatory function**

Statins could inhibit major histocompatibility complex (MHC)-II mediated T-cell activation, affect the ability of phagocytes and lymphocytes, and influence lymphocyte proliferation. Since an increase in this ratio indicates poor prognosis for patients with COVID-19, statins might be helpful as simvastatin decreased CD4+/CD8+ ratio. [22] In addition, lovastatin can attenuate ambient particulate matter-induced recruitment and activation of alveolar polymorphonuclear leukocytes and macrophages, reduce local inflammatory responses, and facilitate foreign particle clearance from lung tissues. [22] However, decreased T-cell numbers might reduce earlier viral clearance and could be associated with severe cases, thus possibly worsening COVID-19 disease. [23] Third, elevated levels of ACE2 are associated with reduced disease severity in patients and animal models with ARDS, [24,25] whereas atorvastatin could upregulate ACE2 activity in rat models.

Although the effects of statins, as an HDT, are antiviral, anti-inflammatory, and immunomodulatory, which will help clinicians design serum or viral biomarkers for statin therapy in COVID-19 patients, these effects are always seen together. We noticed that although high-dose statins might be more effective against viral infections, [4,26] the effects might vary depending on the type of statin, dose, treatment duration, and disease severity; this will need to be carefully assessed to avoid exacerbating COVID-19 or producing deleterious side effects. Unfortunately, no large-scale clinical trial has provided direct evidence regarding the use of statins for COVID-19 patients, indicating the necessities of further in-depth analysis on COVID-19, including pre-clinical and clinical studies.

In summary, statins might be useful in inhibiting SARS-CoV-2 replication, suppressing the release of inflammatory factors, and reducing local pulmonary immune responses, thus attenuating cytokine storms and reducing damage to lung tissue, but this warrants further clinical studies.

**Conflicts of interest**

None.

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