

Statin therapy in COVID-19 infection

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causal agent of the current pandemic of coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a positive-sense single-stranded RNA betacoronavirus sharing genetic similarities with the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV).¹ SARS-CoV-2 enters the cells mainly through angiotensin-converting enzyme 2 (ACE2), and triggers an intense inflammatory host response, sometimes leading to a life-threatening acute respiratory distress syndrome (ARDS).¹ Several randomized controlled trials (RCTs) are investigating the safety and efficacy of various antiviral and immunosuppressive agents. Still, many of these drugs have serious adverse effects, and may not be readily available in some healthcare settings, such as in low-income countries.

In this paper we support the rationale for the use of statins, a class of drugs with widespread availability and an optimal tolerability profile, as an add-on treatment for COVID-19 patients, on the basis of their known immunomodulatory properties.

Besides their lipid-lowering activity, statins exert pleiotropic effects on inflammation and oxidative stress, contributing to their beneficial impact on cardiovascular diseases. Statins modulate the immune response at different levels, including immune cell adhesion and migration, antigen presentation, and cytokine production. Moreover, they restore the vascular redox balance by reducing reactive oxygen species and increasing antioxidants, and ameliorate nitric oxide bioavailability, endothelial function, and integrity. Most of these effects depend on statin-mediated inhibition of the production of isoprenoids, which are fundamental constituents of small GTPases (such as Ras, Rho, and Rac), and on consequential down-regulation of redox-sensitive proinflammatory transcriptional factors such as NF- κ B.²

Statins have proven to be beneficial as an add-on therapy in patients with different autoimmune inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and graft-versus-host disease).² Statins have also been evaluated as an

immunomodulatory treatment in various infectious diseases. Although observational studies have reported improved outcomes in patients with community-acquired pneumonia or sepsis receiving statins,^{3,4} most RCTs on inpatient statin treatment in sepsis or ventilator-associated pneumonia failed to demonstrate a beneficial effect.⁴ On the other hand, statin therapy appears promising in the context of viral infections. Avian influenza viruses induce an intense host response characterized by a cytokine storm, which can sometimes lead to ARDS.³ Few large observational studies have reported the effectiveness of statin treatment in reducing influenza-related hospitalizations and deaths.³ Further, a recently completed RCT (ClinicalTrials.gov number, NCT02056340) showed a significant improvement of symptoms in statin-naïve patients hospitalized for seasonal influenza receiving atorvastatin 40 mg compared with placebo. An association between outpatient statin use and reduction in disease severity among patients hospitalized during the 2009 H1N1 pandemic has also been demonstrated.³ Some authors have therefore advocated statin use as an immunomodulatory therapy for viral infections with potential for epidemics and pandemics.³ Although no RCT has yet investigated this hypothesis, statins [together with angiotensin receptor blockers (ARBs)] were effective in targeting the host response and preventing endothelial barrier damage in patients infected with Ebola virus during the recent Ebola outbreak in West Africa.⁵

Similar to avian influenza viruses, betacoronaviruses cause severe respiratory illnesses by triggering an intense proinflammatory host response. Some immunomodulatory therapies have indeed proven beneficial in patients with SARS, MERS, and COVID-19; for example, tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, was effective as a supportive therapy in selected COVID-19 patients.¹ SARS-CoV-1 interaction with Toll-like receptors on the host cell membrane significantly increases the expression of the *MYD88* gene, whose product activates NF- κ B, thereby triggering inflammatory pathways.⁶ Notably, inhibition of NF- κ B resulted in reduced lung infection and increased survival in a murine model of SARS-CoV-1 infection.⁷ Experimental models have demonstrated that statins stabilize MYD88 levels after a proinflammatory trigger such as hypoxia.⁸ Moreover, in

murine cells, atorvastatin 0.1 μ M (corresponding to the plasma concentration obtained with a daily dose of \sim 40 mg in humans) significantly attenuated NF- κ B activation within 48 h.⁹ (Figure 1). Based on this evidence, the use of a statin as an immunomodulatory treatment for COVID-19 patients may deserve consideration.

Statins also interfere with ACE2 signalling. After initial entry through ACE2, SARS-CoV-2 down-regulates ACE2 expression, possibly facilitating the initial infiltration by innate immunity cells and causing an unopposed angiotensin II accumulation, leading to organ injury.¹ Statins, as well as ARBs, are known to experimentally up-regulate ACE2 via epigenetic modifications.⁵ (Figure 1). Since an increase in ACE2 might prove beneficial for COVID-19 patients, RCTs with recombinant human ACE2 or ARBs are currently underway,¹ and there is biological plausibility to investigate statins too.⁵

Cardioprotective actions of statins should also be taken into consideration in the setting of SARS-CoV-2 infection. Observational studies have found that elderly people with cardiovascular comorbidities are more likely to be infected with SARS-CoV-2 and to develop severe symptoms.¹ In addition, there is evidence of direct cardiovascular involvement in some cases of COVID-19.¹ Furthermore, the lipid-lowering action of statins could treat the hyperlipidaemia associated with the use of protease inhibitor-based antiretroviral and immunosuppressive drugs in COVID-19 infection. Statin therapy has proven effective in improving hyperlipidaemia in patients with human immunodeficiency virus receiving protease inhibitor treatment¹⁰ and in patients with rheumatoid arthritis receiving tocilizumab (Figure 1).² Most statins undergo 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; therefore, starting with a lower dose of statin and monitoring creatine kinase and transaminases would be advisable in these cases.

In conclusion, statins are low-cost, extensively tested, well-tolerated drugs that are less likely to be affected by a shortage in a health crisis such as the current COVID-19 pandemic, even in low-income countries, where treatment with more expensive drugs may not be implemented. Adjuvant treatment and continuation of pre-existing statin therapy could

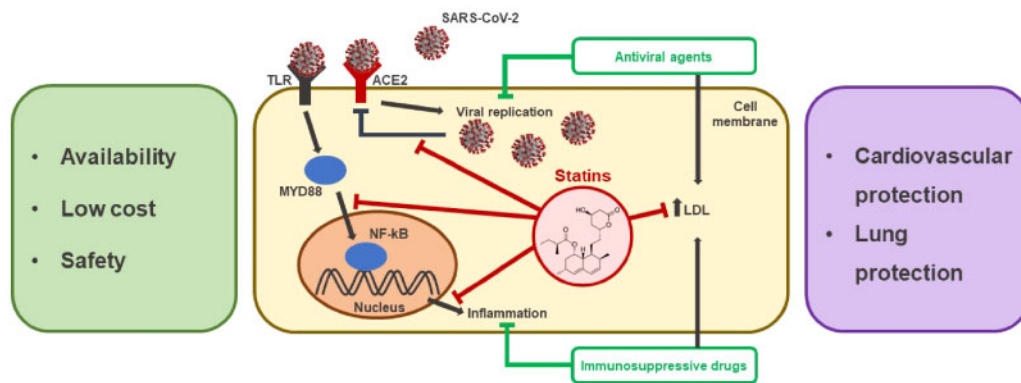


Figure 1 Molecular mechanism of actions and proposed advantages of statins in COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), enters the cell through angiotensin-converting enzyme 2 (ACE2). Once in the cell, SARS-CoV-2 causes ACE2 down-regulation, thus reducing its protective effects on various tissues. Coronaviruses are known to induce a proinflammatory host response via the activation of the Toll-like receptor (TLR)–MYD88–NF- κ B pathway. Statins are available worldwide, and are low-cost, safe drugs with lipid-lowering and immunomodulatory effects. In experimental models, statins inhibit the MYD88–NF- κ B proinflammatory pathway and promote ACE2 up-regulation. Through these mechanisms, statins may prove beneficial in COVID-19 patients. Statins may also counteract hyperlipidaemia caused by some antiviral and immunosuppressive treatments currently used for COVID-19.

improve the clinical course of patients with COVID-19, either by their immunomodulatory action or by preventing cardiovascular damage. This hypothesis should warrant consideration for phase III clinical trials.

Conflict of interest: none declared.

References

- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.1286.
- Zeiser R. Immune modulatory effects of statins. *Immunology* 2018;**154**:69–75.
- Fedson D, Fedson DS. Treating influenza with statins and other immunomodulatory agents. *Antivir Res* 2013;**99**:417–435.
- Pertsov B, Eliakim-Raz N, Atamna H, Trestioreanu AZ, Yahav D, Leibovici L. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults—a systematic review and meta-analysis. *Clin Microbiol Infect* 2019;**25**:280–289.
- Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *mBio* 2020;**11**:doi: 10.1128/mBio.00398-20.
- Totura AL, Whitmore A, Agnihotram S, Schäfer A, Katze MG, Heise MT, Baric RS. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. *mBio* 2015;**6**:e00638-15.
- DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeno JM, Fernandez-Delgado R, Fett C, Castaño-Rodríguez C, Perlman S, Enjuanes L. Inhibition of NF- κ B-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. *J Virol* 2014;**88**:913–24.
- Yuan X, Deng Y, Guo X, Shang J, Zhu D, Liu H. Atorvastatin attenuates myocardial remodeling induced by chronic intermittent hypoxia in rats: partly involvement of TLR-4/MYD88 pathway. *Biochem Biophys Res Commun* 2014;**446**:292–297.
- Chansrichavala P, Chantharakri U, Sritara P, Chaiyaroj SC. Atorvastatin attenuates TLR4-mediated NF-kappaB activation in a MyD88-dependent pathway. *Asian Pac J Allergy* 2009;**27**:49–57.
- Eckard AR, McComsey GA. The role of statins in the setting of HIV infection. *Curr HIV/AIDS Rep* 2015;**12**:305–312.

Vincenzo Castiglione^{1†}, **Martina Chiriaco**^{1,2†}, **Michele Emdin**^{1,3}, **Stefano Taddei**², and **Giuseppe Vergaro**^{1,3*}

¹Institute of Life Science, Scuola Superiore Sant'Anna, Pisa, Italy; ²Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; and ³Fondazione Toscana Gabriele Monasterio, Pisa, Italy

*Corresponding author; Scuola Superiore Sant'Anna Piazza Martiri della Libertà, 33, 56127 Pisa, Italy. Tel: +39 050 3153396, Fax: +39 050 3152277, Email: vergaro@ftgm.it

†These authors contributed equally.