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.
REVIEW ARTICLE

Statins in COVID-19: Is there any foundation?∗

Marcos M. Lima Martínez a,b,*, Miguel A. Contreras c, Waleska Marín d, Luis D’Marco e

a Unidad de Endocrinología, Diabetes, Metabolismo y Nutrición, Anexo Centro Médico Orinoco, Ciudad Bolívar, Venezuela
b Departamento de Ciencias Fisiológicas, Universidad de Oriente, Núcleo Bolívar, Ciudad Bolívar, Venezuela
c Centro Médico El Valle, Nueva Esparta, Venezuela
d Servicio de Oftalmología, Hospital Universitario de Caracas, Caracas, Venezuela
e Hospital Clínico Universitario INCLIVA, Departamento de Nefrología, Valencia, Spain

KEYWORDS
Statins; COVID-19; Inflammation; Renin; Angiotensin

Abstract Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causal agent of coronavirus disease 2019 (COVID-19). Acute respiratory distress syndrome is the main cause of death from COVID-19 and occurs due to an exaggerated inflammatory response that causes the release of pro-inflammatory cytokines such as interleukins and tumor necrosis factor-alpha (TNF-α). Statins are lipid lowering drugs with pleiotropic effects. They have shown benefit in the management of inflammatory and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis. Furthermore, due to their immunomodulatory properties, they have been used in the treatment of various infectious diseases such as community-acquired pneumonia and influenza. In this review we analyze the pathophysiological foundations that support the use of statins as an adjunctive treatment in patients with COVID-19.
© 2020 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Arteriosclerosis.

PALABRAS CLAVE
Estatinas; COVID-19; Inflamación; Renina; Angiotensina

Estatinas en COVID-19: ¿existe algún fundamento?

Resumen El coronavirus tipo 2 del síndrome respiratorio agudo grave (SARS-CoV-2) es el agente causal de la enfermedad por coronavirus 2019 (COVID-19). El síndrome de distress respiratorio agudo constituye la principal causa de muerte por COVID-19 y ocurre por una respuesta inflamatoria exagerada que provoca la liberación de citocinas proinflamatorias como interleucinas y factor de necrosis tumoral alfa (TNF-α). Las estatinas son fármacos hipolipemiantes con efectos beneficiosos demostrados en la inmunorregulación y en enfermedades autoinmunes, como lupus eritematoso sistémico, artritis reumatoide y esclerosis múltiple. Por ello, han sido utilizados en el tratamiento de enfermedades infecciosas como la neumonía adquirida en la comunidad y la influenza. En esta revisión analizamos las bases patofisiológicas que respaldan el uso de las estatinas como tratamiento adyuvante en pacientes con COVID-19.

© 2020 Publicado por Elsevier España, S.L.U. en nombre de la Sociedad Española de Arteriosclerosis.

DOI of original article: https://doi.org/10.1016/j.arteri.2020.06.003
Please cite this article as: Lima Martínez MM, Contreras MA, Marín W, D’Marco L. Estatinas en COVID-19: ¿existe algún fundamento? Clin Invest Arterioscler. 2020;32:278–281.
* Corresponding author.
E-mail address: marcoslimamedical@hotmail.com (M.M. Lima Martínez).

2529-9123 © 2020 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Arteriosclerosis.
pleiotrópicos. Han demostrado beneficio en el manejo de enfermedades inflamatorias y autoinmunores como el lupus eritematoso sistémico, la artritis reumatoide y la esclerosis múltiple. Además, debido a sus propiedades inmunomoduladoras se han utilizado en el tratamiento de diversas enfermedades infecciosas como neumonía adquirida en la comunidad e influenza. En esta revisión analizamos los fundamentos fisiopatológicos que apoyan el uso de estatinas como tratamiento coadyuvante en pacientes con COVID-19.

© 2020 Publicado por Elseiver España, S.L.U. en nombre de Sociedad Española de Arteriosclerosis.

Introduction

In December 2019, an outbreak of acute respiratory disease characterized by fever, dry cough and shortness of breath occurred in China. A new coronavirus was later identified, termed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). Acute respiratory distress syndrome (ARDS) is the leading cause of death from COVID-19 and occurs as a consequence of an exaggerated inflammatory response that causes the release of pro-inflammatory cytokines such as interleukins and tumour necrosis factor-alpha (TNF-α). Therefore, the use of anti-inflammatory agents has been proposed in the treatment of these patients.

Statins are lipid-lowering drugs but are also known for their anti-inflammatory and antioxidant effects. As yet, there are no randomised controlled clinical trials that have demonstrated the benefit of statins in patients with COVID-19. However, a multinational observational study involving over 8000 hospitalised patients with COVID-19 showed that the use of statins was associated with improved survival rate in these patients. In addition, statins have shown benefit as immunomodulatory drugs in several infectious diseases, including community-acquired pneumonia and influenza.

In this review we will address the rationale behind the judicious use of statins in COVID-19 patients.

The renin-angiotensin system

The renin-angiotensin system (RAS) is an elegant cascade of vasoactive peptides that orchestrates key processes in human physiology. Angiotensinogen is a glycoprotein of 452 amino acids produced in the liver and circulates as a biologically inactive peptide. Through the action of renin, angiotensinogen is split into a decapetide called angiotensin (Ang) I and this in turn is converted by the angiotensin converting enzyme (ACE) into an octapeptide called Ang II, which, by acting on the Ang type 1 receptor (AT1-R), exerts vasoconstrictive and oxidative effects and at lung level induces bronchial smooth muscle contraction, fibroblast proliferation, alveolar epithelial cell apoptosis and increased vascular permeability.

In 2000, two independent groups identified a new ACE homologous enzyme, which they named angiotensin-convetering enzyme 2 (ACE2). This enzyme is 42% homologous with ACE, but with different biochemical activities. ACE2 when hydrolysed to Ang I generates Ang (1–9); however, the catalytic activity of ACE2 is 400 times higher over Ang II than over Ang I and leads to the formation of Ang (1–7) with vasodilatory properties through the Mas receptor (MAS-R). Thus, the RAS works as a dual endocrine system in which vasoconstrictive/proliferative actions and vasodilatory/antiproliferative actions are regulated by a balance between ACE and ACE2 (Fig. 1).

Interaction between SARS-CoV-2 and the renin angiotensin system

Viral infections depend on the virus entering the cell and using the host’s cellular machinery to replicate multiple copies that will subsequently infect more cells. The coronaviruses SARS-CoV-1 and SARS-CoV-2 enter host cells using ACE2 as a receptor. ACE2 is expressed in type 1 and type 2 alveolar epithelial cells and has two fractions: a soluble and a membrane-bound fraction.
Moreover, ADAM (ACE2, S-protein) virus infection results in a loss of ACE2 on the cell surface and therefore prevents the degradation of Ang II into Ang (1–7), which could contribute to the lung damage and fibrosis associated with COVID-19.

SARS-CoV-1 and SARS-CoV-2 express in their shells a protein called S-protein that contains a receptor-binding region that binds with high affinity to the extracellular domain of ACE2, causing membrane fusion and internalization of the virus through endocytosis. The internalization of ACE2 by SARS-CoV-2 results in a loss of ACE2 on the cell surface and thus prevents the degradation of Ang II into Ang (1–7), which could contribute to the lung damage and fibrosis associated with COVID-19.

Coronavirus and inflammation

Toll-like receptors (TLRs) are a family of proteins that act as sensors and help the immune system discriminate between foreign and domestic elements. SARS-CoV-1 and, presumably, SARS-CoV-2 interact with TLRs on the host cell membrane and increase the expression of the primary myeloid differentiation response gene 88 (MyD88), which in turn activates nuclear factor kappa B (NF-κB), eventually promoting an inflammatory cascade that increases lung damage (Fig. 2).

In the coronavirus causing Middle East acute respiratory syndrome (MERS-CoV) it was observed that increased expression of the MyD88 gene was associated with increased mortality. Moreover, in a murine model of SARS-CoV-1 it was shown that inhibition of NF-κB resulted in less lung damage and increased survival, and therefore this mechanism appears to be of particular importance in coronavirus infection.

Pathophysiological basis for the use of statins in COVID-19

Statins exert pleiotropic effects and there are at least 4 reasons that support the use of statins in patients with COVID-19:

1) Experimental models have shown that statins preserve normal levels of MyD88 during hypoxia, thereby inhibiting NF-κB activation, exerting an anti-inflammatory effect.

2) Statins are able to induce positive regulation of ADAM17 through epigenetic pathways, thus increasing levels of soluble ACE2, stimulating on the one hand the protective system of Ang (1–7) and MAS-R, thus decreasing pulmonary fibrosis and exerting a cardioprotective effect; on the other hand, soluble ACE2 could bind to SARS-CoV-2, preventing its fusion with the host cell membrane and therefore inhibiting viral replication.

3) Statins could directly affect SARS-CoV-2 by binding to the main protease of the virus, in a similar way to protease inhibitors.

4) Statins are effective in the treatment of hyperlipidaemia associated with the use of antiretrovirals as protease inhibitors or immunosuppressive drugs that could be used in the management of patients with COVID-19.

Safety of statins in patients with COVID-19

There are insufficient studies to date on the effect of SARS-CoV-2 on the liver, but it is plausible that it also uses ACE2 to enter these cells. In fact, COVID-19 is associated with abnormal liver tests in 15%–53% of patients, the most common abnormality being elevated aminotransferases (AST and ALT), with occasional increases in alkaline phosphatase and total bilirubin.

Statins are associated with mild and transient elevation of aminotransferases in 1%–3% of patients and increases of three times the upper normal limit only in 0.7% of cases. We highlight one study that compared 342 patients with liver profile abnormalities and 1437 patients with no abnormalities who started treatment with statins, and observed no statistically significant differences between the groups in the development of severe liver disease, and therefore use of statins in patients with COVID-19 could be safe.

Conclusions

Statins are well-studied, low-cost, and generally well-tolerated drugs that could be used as adjuvant treatment...
in patients with COVID-19 due to their immunomodulatory, anti-inflammatory and cardioprotective effects. Randomised controlled clinical trials are required to confirm these hypotheses.

**Funding**

This research study has received no specific support from public sector agencies, commercial sector, or non-profit entities.

**Conflict of interests**

The authors have no conflict of interests to declare.

**References**

1. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265-9.
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
3. Zeiser R. Inmune modulatory effects of statins. Immunology. 2018;154:69-75.
4. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. 2020;382:e102, http://dx.doi.org/10.1056/NEJMc2007621.
5. Fedson DS. Treating influenza with statins and other immunomodulatory agents. Antiviral Res. 2013;99:417-35.
6. Garnacho-Montero J, Barrero-Garcia I, Gómez-Prieto MG, Martín-Loeches I. Severe community-acquired pneumonia: current management and future therapeutic alternatives. Expert Rev Anti Infect Ther. 2018;16:667-77.
7. Lima MM, Nuccio JC, Villalobos M, Torres C, Balladares N. Sistema renina angiotensina y riesgo cardiometabólico. Revisión. Rev Venez Endocrinol Metab. 2010;8:3–10.
8. Yan T, Xiao R, Lin G. Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: a double-edged sword? FASEB J. 2020;34:6017-26.
9. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Staglino N, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res. 2000;87:E1–9.
10. Tippins SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem. 2000;275:33238-43.
11. Vadugananathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382:1653-9.
12. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2, and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:271-80.
13. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol. 2020;318:H1084-90.
14. Totura AL, Whitmore A, Agnihotram S, Schäfer A, Katze MG, Heise MT, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio. 2015;6:e00638-715.
15. Sheahan T, Morrison TE, Funkhouser W, Uematsu S, Akira S, Baric RS, et al. MyD88 is required for protection from lethal infection with a mouse adapted SARS-CoV. PLoS Pathog. 2008;4:e1000240.
16. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeño JM, Fernández-Delgado R, Fett C, et al. Inhibition of NF-κB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. J Virol. 2014;88:913-24.
17. Chansrichavala P, Chantharaksri U, Sritara P, Chaiyaroj SC. Atorvastatin attenuates TLR4-mediated NF-kappaB activation in a MyD88-dependent pathway. Asian J Allergy Immunol. 2009;27:49-57.
18. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating with severe COVID-19 infection. mBio. 2020;11:e00398-420, http://dx.doi.org/10.1128/mBio.00398-20.
19. Castiglione V, Chiriacò M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. Eur Heart J Cardiovasc Pharmacother. 2020, http://dx.doi.org/10.1093/ehjcvp/pva042.
20. Reiner Z, Hatamipour M, Banach M, Pirro M, al-Rasadi K, Jamialahmadi T, et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. Arch Med Sci. 2020;16:490-6.
21. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40:998-1004.
22. Newman CB, Preiss D, Tober JA, Jacobson TA, Page RL 2nd, Goldstein LB, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019;39:e38-81.
23. Chaisani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology. 2004;126:1287-92.