Editorial

Statins and COVID-19: emerging evidence on the safety and efficacy of statins in COVID-19

Shweta Kapur, Prateek Lohia^

Department of Internal Medicine, Wayne State University, Detroit, MI, USA

Correspondence to: Prateek Lohia. Department of Internal Medicine, Wayne State University, 4201 St Antoine, UHC 5C, Detroit, MI 48201, USA. Email: plohia@med.wayne.edu.

Comment on: Chow R, Lee J, Noh H, *et al.* The association between statin and COVID-19 adverse outcomes: national COVID-19 cohort in South Korea. Ann Palliat Med 2022;11:1297-307.

Submitted Apr 07, 2022. Accepted for publication Apr 18, 2022.
doi: 10.21037/apm-22-442
View this article at: https://dx.doi.org/10.21037/apm-22-442

The widespread morbidity and mortality caused by the current global pandemic of COVID-19 have motivated researchers around the world to explore ways to combat its wrath. From vaccine development at unprecedented speed to the mobilization of resources to best tackle the surges, significant efforts in medical innovation are being made at different levels. One such domain being actively investigated is the possible role of existing drugs such as statins in COVID-19 treatment. Statins are widely prescribed lipid-lowering drugs known for their pleiotropic effects. Over a quarter of the population over the age of 40 years is estimated to be using statins in the United States (1).

COVID-19 can trigger cytokine storm and endothelial injury has been noted to play a role in hyperinflammation and procoagulant state seen in COVID-19, triggering microthrombosis and macrothrombosis (2-4). Statins are known for their immunomodulatory, anti-inflammatory, antithrombotic, and vasculoprotective effects (5-10) and thereby may contribute to limiting inflammation and thromboembolism in COVID-19. Several other mechanisms might also explain the possible role of statins in COVID-19, namely modulating SARS-CoV-2 entry by acting on ACE2 and CD147 receptors and lipid raft engagements (11), inhibiting the MDY-88 gene and thereby inhibiting the NF-kb pathway preventing marked inflammation (12,13). High triglycerides and low high-density lipoproteins have also been reported to be associated with worse outcomes in COVID-19 (14). So, statins may protect against severe disease progression via lipid profile improvement.

The study by Chow *et al.* (15) published in the current issue of the Annals of Palliative Medicine explores the association between pre-hospitalization statin use and adverse clinical outcomes in hospitalized COVID-19 patients using a national cohort from South Korea. The authors identified statin users from the database by selecting patients who had received prescriptions for statins in the 240 days before hospitalization for COVID-19. Overall, the study reports no significant association between statin use and the primary outcome, which was a composite of mortality, intensive care unit (ICU) admission, mechanical ventilation use, and cardiovascular outcomes. Interestingly, the presence of hypertension modified this association, and a protective role of antecedent statin use was noted for the patients with a history of hypertension. The authors also conducted extensive sensitivity analyses by varying the statistical methods, changing the exposure window, and including both non-hospitalized and hospitalized COVID-19 patients to validate their findings. These sensitivity analyses were generally consistent with the main results supporting the safety of statins. Some of the sensitivity analyses also demonstrated the protective association between statins and the primary outcome, mortality, and ICU admission.

This observational study joins the growing literature endorsing the safety of statins in COVID-19. However, the uniqueness of this study by Chow *et al.* lies in the

^ ORCID: 0000-0003-4148-9597.

population-based cohort used in the study. It captured more than 92% of all COVID-19 patients over the age of 40 years in South Korea. In some of the sensitivity analyses, this study included almost 98% of the entire population of South Korea, over the age of 40 years old, infected with COVID-19. Though authors have done a commendable job with thorough analysis and use of methodologies to minimize bias, the inherent flaws of an observational study design prevail. Lack of information about adherence to the statin prescription, the intensity of statins, continuation of statins in the hospital, along with the lack of racial diversity in the study population cannot be negated.

Several observational studies in the recent past have demonstrated the safety of statins in COVID-19 (16-19). Some studies have identified reduced mortality among statin users in patients hospitalized with COVID-19. The intensity response relationship of statins has also been explored: pointing to a protective effect of statins in COVID-19 only at moderate and high intensities (17). Currently, 17 registered randomized clinical trials (RCTs) are looking at the role of statins in COVID-19 (20). The majority of these RCTs are looking at the role of high-intensity statins. The results from a recent INSPIRATION-S trial reported no statistically significant reduction in adverse clinical outcomes with statin use during hospitalization among ICU patients with COVID-19 (21). However, this trial was underpowered. Also, antecedent statin users were excluded from this RCT and the patients enrolled were started on statins upon admission to the ICU which might be too late in the disease process to affect the outcomes. They also reported the protective effect of statins in patients who presented to the hospital within 7 days of symptom onset. This finding, along with the multiple other reports of the association between antecedent statin use and reduced mortality in COVID-19, might point towards the beneficial role of statins in the early phase of the disease (17,19,22,23). Another RCT, although with a small sample size, reported that high-intensity atorvastatin therapy (40 mg per day) reduced the duration of hospitalization in COVID-19 patients (24). The same RCT also reported a significant decrease in the C-reactive protein levels in the patients who received atorvastatin therapy compared to the control group, with a large effect size by the sixth day of therapy. In the light of current literature, the safety of statins in COVID-19 seems to be evident; however, more evidence is warranted to prove their efficacy in reducing the severity of adverse clinical outcomes in COVID-19. The results from other RCTs are awaited and will hopefully shed more light on the possible efficacy of statins in COVID-19 treatment. Large-scale, well-designed, and adequately powered RCTs can elucidate the role of statins in COVID-19 and might pave way for innovations in the treatment of acute viral infections.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Palliative Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-442/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Gu Q, Paulose-Ram R, Burt VL, et al. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. NCHS Data Brief 2014;(177):1-8.
2. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7.
3. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med 2020;383:120-8.

4. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020;41:3038-44.
5. Totura AL, Whitmore A, Agnihothram S, 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:e00638-15.
6. Stroes ES, Koomans HA, de Bruin TW, et al. Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication. Lancet 1995;346:467-71.
7. Holm T, Andreassen AK, Ueland T, et al. Effect of pravastatin on plasma markers of inflammation and peripheral endothelial function in male heart transplant recipients. Am J Cardiol 2001;87:815-8, A9.
8. Greenwood J, Mason JC. Statins and the vascular endothelial inflammatory response. Trends Immunol 2007;28:88-98.
9. Zeiser R. Immune modulatory effects of statins. Immunology 2018;154:69-75.
10. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. Circ Res 2017;120:229-43.
11. Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, et al. Statins: Could an old friend help in the fight against COVID-19? Br J Pharmacol 2020;177:4873-86.
12. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, et al. Inhibition of NF-κB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. J Virol 2014;88:913-24.
13. Sheahan T, Morrison TE, Funkhouser W, et al. MyD88 is required for protection from lethal infection with a mouse-adapted SARS-CoV. PLoS Pathog 2008;4:e1000240.
14. Masana L, Correig E, Ibarretxe D, et al. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep 2021;11:7217.
15. Chow R, Lee J, Noh H, et al. The association between statin and COVID-19 adverse outcomes: national COVID-19 cohort in South Korea. Ann Palliat Med 2022;11:1297-307.
16. Zhang XJ, Qin JJ, Cheng X, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. Cell Metab 2020;32:176-187.e4.
17. Lohia P, Kapur S, Benjaram S, et al. Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with propensity score matching. J Clin Lipidol 2021;15:451-9.
18. Lohia P, Kapur S, Benjaram S, et al. Statins and clinical outcomes in hospitalized COVID-19 patients with and without Diabetes Mellitus: a retrospective cohort study with propensity score matching. Cardiovasc Diabetol 2021;20:140.
19. Gupta A, Madhavan MV, Poterucha TJ, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun 2021;12:1325.
20. Talasaz AH, Sadeghipour P, Aghakouchakzadeh M, et al. Investigating Lipid-Modulating Agents for Prevention or Treatment of COVID-19: JACC State-of-the-Art Review. J Am Coll Cardiol 2021;78:1635-54.
21. INSPIRATION-S Investigators. Atorvastatin versus placebo in patients with covid-19 in intensive care: randomized controlled trial. BMJ 2022;376:e068407.
22. Chacko SR, DeJoy R 3rd, Lo KB, et al. Association of Pre-Admission Statin Use With Reduced In-Hospital Mortality in COVID-19. Am J Med Sci 2021;361:725-30.
23. Daniels LB, Sitapati AM, Zhang J, et al. Relation of Statin Use Prior to Admission to Severity and Recovery Among COVID-19 Inpatients. Am J Cardiol 2020;136:149-55.
24. Davoodi L, Jafarpour H, Oladi Z, et al. Atorvastatin therapy in COVID-19 adult inpatients: A double-blind, randomized controlled trial. Int J Cardiol Heart Vasc 2021;36:100875.

Cite this article as: Kapur S, Lohia P. Statins and COVID-19: emerging evidence on the safety and efficacy of statins in COVID-19. Ann Palliat Med 2022;11(4):1157-1159. doi: 10.21037/apm-22-442

