

Statin Withdrawal and Treating COVID-19 Patients

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Abstract

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Abstract

Most but not all observational studies of statin treatment of COVID-19 patients suggest that treatment improves outcomes. However, almost all observational studies fail to consider what cardiovascular investigators have known for 15-20 years: withdrawing statins after hospital admission has detrimental effects on patient outcomes. Continuing (or starting) statin treatment after hospital admission consistently improves COVID-19 patient outcomes, whereas discontinuing treatment does not. Thus, observational studies of the effectiveness of statin treatment of COVID-19 patients must consider the consequences of statin withdrawal.

Key words: COVID-19, statin treatment, statin withdrawal, mortality

Introduction

The COVID-19 pandemic has caused worldwide social, economic and political disruption. Its pathogenesis is largely due to extensive disruption of innate and adaptive immunity, altered interferon responses, and coagulation abnormalities that lead to microvascular immunothrombosis. Many of these changes are caused by endothelial dysfunction.¹

Antiviral treatments for COVID-19 have been only marginally effective. Antibody treatments (convalescent plasma and monoclonal antibody preparations) for severe disease have also been disappointing. Some investigators have suggested repurposing drugs that are already licensed for use against other diseases.² Some of these drugs target the host response to infection, not the virus itself. One of these drugs is dexamethasone, which improves survival in COVID-19 patients who require oxygen treatment but not in those who do not require oxygen.³

Cardiovascular drugs have also attracted interest because many of them (including statins) affect endothelial dysfunction.⁴ Experts recommend continuing statin treatment in COVID-19 patients who are already being treated.⁵ This recommendation is based largely on numerous observational studies that suggest continuing treatment is safe. Nonetheless, most of these studies are based on outpatient-documented treatment. Because they do not consider the effects of statin withdrawal after hospital admission, their estimates of statin effectiveness are likely to be imprecise. It is unclear whether investigators recognize that statin withdrawal could be a problem.

Methods

The study is based on a PubMed search conducted on April 20, 2021 using the search terms “statin withdrawal” (510 references) and “COVID-19, statins” (197 references). Citations for articles on statin treatment of COVID-19 patients and statin withdrawal are available as supplementary information.

Results

At least 32 individual observational studies have evaluated the effectiveness of outpatient statin treatment on the outcomes of COVID-19 patients admitted to hospital (supplementary information). These studies have used a variety of methods to reach different conclusions about the effectiveness of treatment. Seventeen reports conclude that statins reduce the occurrence of severe disease (e.g., ICU admission) or mortality.^{S1-S17} Nine reports conclude that statins might not be effective, but at least they are not harmful.^{S18-S26} Six others conclude that statin treatment is actually associated with harm.^{S27-S32} Seven meta-analyses of these studies (based largely on outpatient information) provide varying estimates of statin effectiveness.^{S33-S39} In contrast, eight observational studies show that in-hospital statin treatment is uniformly effective in reducing COVID-19 mortality (Table 1).^{S40-S47}

None of the individual studies based on outpatient-documented treatment has mentioned the possibility of statin withdrawal after hospital admission. Moreover, none of the seven meta-analyses and only one of eight studies of in-hospital statin treatment has cited any reference on the detrimental effects of statin withdrawal.

Discussion

The difference between the conflicting findings of outpatient-documented statin treatment and the uniform findings that inpatient treatment reduces COVID-19 severity and mortality is critically important. Documentation of statin treatment based only on outpatient information does not take into account the effects of statin withdrawal after hospital admission. If statins are withdrawn, their beneficial effects on the host response are rapidly reduced.⁶ For example, cardiovascular investigators who studied patients hospitalized with acute myocardial infarction 15-20 years ago found that those who had been treated with statins as outpatients and whose statins were continued after hospital admission had lower mortality rates than those who had never received statins.⁷ The same benefit was seen in those who were started on statin treatment after hospital admission. However, those who had been treated with statins as outpatients but whose treatment was withdrawn after hospital admission had greater mortality than what was seen in never-treated patients.

Studies by cardiovascular investigators suggest that the effectiveness of statin treatment on the severity and

mortality of COVID-19 can be accurately determined only by evaluating in-hospital treatment. This has been confirmed in two studies that compared continuing versus not continuing statin treatment after hospital admission (Table1).^{8,9}

Remarkably, all of the 32 studies based on outpatient-documented statin treatment failed to consider the possible effects of statin withdrawal after hospital admission. For example, in one study outpatient statin treatment was associated with decreased mortality, but only 77% of outpatient-treated patients continued statin treatment after hospital admission.¹⁰ The investigators concluded that statin treatment was protective, but this was likely an underestimate because statins were withdrawn in 23% of hospitalized patients. In another study of 247 statin-treated patients, 46% of treatments were initiated after hospital admission and yet 29% of all statin treatments were later discontinued because of elevated liver function or creatine kinase tests.¹¹

This is not to say that outpatient statin treatment is unimportant. In studies reporting that outpatient-documented statins were effective, many patients probably had their treatment continued after hospital admission. Outpatient statins could also reduce the likelihood of developing symptomatic COVID-19¹² and might even prevent the development of “long COVID”. Clinical findings clearly indicate that statin treatment should be continued in COVID-19 patients with cardiovascular diseases after hospital admission.⁵ No study has yet shown that statins should be used to treat *all* hospitalized COVID-19 patients.

Cardiologists have known for 15-20 years that combination treatment with a statin and an ACE inhibitor (ACEI) or an angiotensin receptor blocker (ARB) is more effective than treatment with any of these agents alone.^{4,13} In COVID-19 patients, a propensity score-matched case-control study has recently shown that combination treatment with a statin and an ACEI or an ARB was more effective than single agent treatment and was associated with a 3-fold reduction in the odds of 28-day hospital mortality (OR = 0.33, 95% C.I. 0.17-0.69, $p = 0.002$).¹⁴

There is a solid scientific and clinical rationale for repurposing statins and other widely available, inexpensive generic drugs to treat the host response to COVID-19 and other pandemic diseases.^{2,4} Unfortunately, only 7% of the prospective clinical trials of COVID-19 treatments listed on ClinicalTrials.gov are focused on these drugs.¹⁵ Most of them are single center studies and only a few are evaluating statins, ACE inhibitors, or ARBs. To my knowledge, no randomized controlled trial of combination treatment has been planned or is underway.

In the absence of clinical trials of these treatments, physicians will have to rely on the findings of observational studies alone. For this reason, any study that seeks to determine the effectiveness of statin treatment (either by itself or in combination with other drugs) for COVID-19 patients must consider the consequences of statin withdrawal after hospital admission.

References

1. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease, *Eur Heart J*. 2020;41:3038-3044. doi: 10.1093/eurheartj/ehaa623
2. Martin JH, Head R. A pharmacological framework for integrating treating the host, drug repurposing and the damage response framework in COVID-19. *Br J Clin Pharmacol*. 2021 Mar;87:875-885. doi: 10.1111/bcp.14551
3. Jensen MP, George M, Gilroy D, Sofat R. Beyond dexamethasone, emerging immuno-thrombotic therapies for COVID-19. *Br J Clin Pharmacol*. 2021 Mar;87:845-857. doi: 10.1111/bcp.14540
4. Fedson DS. Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola. *Ann Transl Med*. 2016;4:421. doi: 10.21037/atm.2016.11.03
5. Iqbal Z, Ho JH, Adam S, et al. Managing hyperlipidaemia in patients with COVID-19 and during its pandemic: An expert panel position statement from HEART UK. *Atherosclerosis*. 2020;313:126-136. doi: 10.1016/j.atherosclerosis.2020.09.008

6. Cubeddu LX, Seamon MJ. Statin withdrawal: clinical implications and molecular mechanisms. *Pharmacotherapy*. 2006;26:1288-1296. doi: 10.1592/phco.26.9.1288
7. Fonarow GC, Wright RS, Spencer FA, et al. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. *Am J Cardiol*. 2005;96:611–616. doi: 10.1016/j.amjcard.2005.04.029
8. Torres-Pena JD, Perez-Belmonte LM, Fuentes-Jimenez F, et al. Prior treatment with statins is associated with improved outcomes of patients with COVID-19: Data from the SEMI-COVID-19 Registry. *Drugs*. 2021 Mar 29;1-11. doi: 10.1007/s40265-021-01498-x
9. Memel ZN, Lee JJ, Foulkes AS, Chung RT, Thaweethai T, Bloom PP. Statins are associated with improved 28-day mortality in patients hospitalized with SARS-CoV-2 infection. *medRxiv*. 2021 Apr 6;2021.03.27.21254373. doi: 10.1101/2021.03.27.21254373
10. 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 Feb 26;12:1325. doi: 10.1038/s41467-021-21553-1
11. McCarthy CP, Murphy S, Jones-O'Connor M, et al. Early clinical and sociodemographic experience with patients hospitalized with COVID-19 at a large American healthcare system. *EclinicalMedicine*. 2020;26:100504. doi: 10.1016/j.eclinm.2020.100504
12. De Spiegeleer A, Bronselaer A, Teo JT, et al. The effects of ARBs, ACEis, and statins on clinical outcomes of COVID-19 infection among nursing home residents. *J Am Med Dir Assoc*. 2020 Jul;21:909-914.e2. doi: 10.1016/j.jamda.2020.06.018
13. Koh KK, Sakuma I, Shimada K, Hayashi T, Quon MJ. Combining potent statin therapy with other drugs to optimize simultaneous cardiovascular and metabolic benefits while minimizing adverse events. *Korean Circ J*. 2017;47:432-439. doi: 10.4070/kcj.2016.0406
14. Byttebier G, Belmans L, Alexander M, et al. Hospital mortality in COVID-19 patients in Belgium treated with statins, ACE inhibitors and ARBs. *Hum Vaccin Immunother*. 2021;to be published.
15. Varshney AS, Wang DE, Bhatt AS, et al. Characteristics of clinical trials evaluating cardiovascular therapies for Coronavirus Disease 2019 registered on ClinicalTrials.gov: a cross-sectional analysis. *Am Heart J*. 2021;232:105-115. doi: 10.1016/j.ahj.2020.10.065

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