International Scholars Journals

African Journal of Infectious Diseases Research. ISSN 2756-3340, Vol. 9(2), pp. 001-005, March, 2022. Available Online at www.internationalscholarsjournals.com © International Scholars Journals

Review Article

Adjunctive use of statins in pandemic politics

Jamshid Tabeshpour and Mehri Bemani Naeini*

[1]Department of Pharmacy, Damghan Branch, Islamic Azad University, Damghan, Iran

[2]Department of Nanotechnology, Pharmaceutical Technology Institute, Mashhad, Iran

Received: 04-Jan-2022, Manuscript No. AJIDD-22-59611; Editor assigned: 07-Jan-2022, Pre QC No. AJIDD-22-59611 (PQ); Reviewed: 21-Jan-2022, QC No. AJIDD-22-59611; Revised: 07-Mar-2022, Manuscript No. AJIDD-22-59611 (R); Published: 15-Mar-2022.

ABSTRACT

Since antiviral agents and vaccines are unavailable in all countries, we should determine whether other available agents could yield clinical benefits for treatment and prophylaxis of pandemic disease. Drug repurposing, an effective drug discovery strategy from existing drugs, shortens the time and diminish the cost compared to de novo drug discovery. An achievable but effective treatment is needed, particularly by FDA-approved medications. SARS-CoV-2-induced disease is associated with a boosted cardiovascular disease and induces proinflammatory cytokines. Statins show immunomodulatory effects, and could be useful in the control of life-threatening infections and proinflammatory cytokine dysregulation which confirmed by reduced rates of hospitalization and death in patients. Statins are globally distributed and cheap. They might be one of the most valuable agents that could alter the course of this pandemic. We have inadequate supplies of antiviral agents, and antiviral resistance might limit their usefulness against viruses. Millions of people will have to wait many months or more for availability of supplies of pandemic vaccines. Also, obtaining sufficient supplies of pandemic vaccines with antigen-sparing technologies to meet global demand may be inaccessible. Research in the operative vaccines and antiviral drugs development, has been time consuming. Statins effectiveness to alleviate the inducing influence of SARS-CoV-2 on the immune system merits assessment, such we certainly do require to consider randomized trial evidences in prophylaxis and treatment.

Keywords: Statins, SARS-CoV-2, COVID-19, Inflammation, Immunity

INTRODUCTION

After SARS-CoV-2 started spreading around the world, physicians observed that the infection often lead to a hyper inflammatory state accompanied by myocardial injuries and thrombotic events [1]. That was the rational that researchers use statins as a potential therapy. Beneficial pleiotropic effects of statins are including anti-inflammatory, immunomodulatory, anti-thrombotic and a direct microbicidal effect [2-4], which may have potential positive role in the prevention and treatment of community-acquired pneumonia. Pneumonia reveals a wide range of severity, from asymptomatic or mild illness at one end to severe sepsis or septic shock and mortality at the other. Despite of the necessity of an acceptable inflammatory response for combat against cause of disease, disproportionate inflammation can cause ongoing local and systemic impairment. Because of this, adjuvant therapy for pneumonia that can modify the immune response has become a progressively relevant approach.

Diverse adjuvant treatment alternatives for pneumonia have recently been offered. Promising treatment choices include statins, corticosteroids, and macrolides and Toll-like receptor antagonists [5]. Reperfusion injury of importance, in patients, it will be desirable that cardiovascular disorders and related consequences improved with the continuation of statin therapy and, also de novo initiation of statin.

Patients with pneumonia are at increased risk for cardiac injuries secondary to augmented inflammatory cytokines which could induce increased thrombosis [6,7], plaque instability [8] and stimulate consumption show to be useful in preventing viral infection of COVID-19. Since several studies have reported increased cardiovascular events in patients with pneumonia and similarly, in COVID-19 infection [9-15], the beneficial effect of statins in reducing the risk of cardiac events, due to their anti-inflammatory function, as well as their lipid-lowering effects may be proposed [16].

***Corresponding author.** Mehri Bemani Naeini, E-mail: Bemani.naeini1@gmail.com.

LITERATURE REVIEW

Mechanistic insights and clinical relevance

Perhaps, it was difficult to accept the hypothesis that treatment could be operative without killing the virus, yet numerous studies have shown that the host response could be altered in ways that leads to survival improvement while producing no change in virus replication. Immunomodulatory agents can target non-virus-infected cells and organs. They help maintenance of pulmonary endothelial integrity, trigger early mitochondrial biogenesis or modify immunometabolism [17]. Statins have shown to be a potent vaccine adjuvant against influenza [18]. In preclinical models, by decreasing protein prenylation, statins increased antigen retention, presentation and T cell activation, which completely protected mice and cynomolgus monkeys against influenza HA1 infection [19]. Thus, the approach of manipulating statin-mediated host immunity to viral diseases opens a new window for specific targeting of downstream products of the mevalonate pathway. However, statin therapy appears to have pleiotropic effects including attenuation of chronic low-grade inflammation and modulation of TLR activity. Statins through abolition of TLR4 expression and regulation of the TLR4/Myd88/NF-κB signaling pathway may slow the progression of atherosclerosis and other inflammatory diseases [20]. In addition, investigators discuss several potential mechanisms through which statins could be improving outcomes among patients with COVID-19: preventing endothelial dysfunction (a shared feature of a number of virus infections); lowering blood pressure, reduction of inflammation; plaque stabilization; and antithrombotic effects, and in sum help to stabilization of underlying conditions that can raise the risk of serious illness from COVID-19. Statins also remove cholesterol from the outer membranes of cells. Of note, this evidence has been uncovered that removing cholesterol from cell membranes significantly prevents the coronavirus attachment, entry and replicate [21]. Cell Entry happens through viral spike proteins attachment to cell's Angiotensin-Converting Enzyme 2 (ACE2) receptors. These receptors sit in a lipid raft, a part of the cell's membrane that contains cholesterol, proteins like ACE2, and other fats and proteins. In summary, it is proposed that some of the pleiotropic properties of statins such as the inhibition of CD147 expression and function, disruption of lipid rafts, activation of autophagy, and reduction of both the inflammation and the coagulation activation and endothelial function improvement are linked to the protection against infection and replication of SARS-CoV-2 in host cells [22]. Statins offer lung protection in critically ill patients by reducing lung inflammation and injury, as well as their endothelial cell stabilizing characteristics and hence decreases the need for ventilator support [23,24]. Also, in previous studies, preliminary findings from epidemiological study have also proposed that statin consumption was associated with reduction in influenza-related pneumonia, acute myocardial infarction, and stroke [25]. Statins may also prevent a viral-induced acute coronary syndrome by stabilizing atherosclerotic plaques [26], as well as prevent Acute Kidney Injury (AKI) [27]. Both acute cardiac injury and AKI are predictors of COVID-19-related mortality and statin treatment may inhibit these complications and consequently, increase survival. In addition, an in-silico molecular modeling investigation by Wang et al. to identify approved drugs targeting SARS-CoV-2 recognized rosuvastatin as the sixth potentially functional medication that may have clinical efficacy in COVID-19 [28].

Plagiarized Statins also remove cholesterol from the outer membranes of cells. Liverpool COVID-19 drug interactions [29]. If monitored, atorvastatin seems to be relatively safe at submaximal doses. Also, pravastatin, rosuvastatin, and pitavastatin show to have the benign safety profiles among statins when co-administered with ART and may not require dose adjustment [30]. The anti-inflammatory and immunomodulatory functions of statins on the host immune response to acute lung injury are becoming progressively manifest. Also, clinical studies included patients with influenza virus infection or bacterial pneumonia, rather than coronaviruses previously performed [31,32], while some reports have revealed that statins may be effective in people with MERS-COV (other beta coronavirus like the current SARS-CoV-2), and currently, in patients with COVID-19 infection (meta, cohorts) [33]. The hypothesis of probable effectiveness of statins on coronavirus could be evaluated in large, prospective, randomized trials. Unfortunately, these studies might not be considerable, because patients enrolled in the trials are younger, rather than older, and have experienced properly few hospitalizations or mortality owing to respiratory disorders [34-39].

In clinical era, a combination use of statins and angiotensin receptor blockers, during the Ebola virus disease epidemic in Sierra Leone, led to improved outcomes and augmented survival [40]. In 2017, in a study, it was found that people taking statins on admission to the hospital for community-acquired pneumonia were less likely to die than people not taking statins [41]. .In 2018, it was reported that statin use improved outcomes in patients with a hyper-inflammatory subtype of Acute Respiratory Distress Syndrome (ARDS) [42]. Furthermore, observational studies and meta-analyses of cohort studies showed a benefit of long-term use of statins on SARS-CoV-2 associated mortality and disease severity [43-68]. Also, several reports did not show any significant effect or even found unwanted results [69-81]. However, beneficial effects of statins on inflammation, vascular function, and cardiac and pulmonary function, intensely support the continuation of their use in COVID-19 patients. Clinical trials are assessing to confirm the potential role of statins alone or in combination with other drugs such as colchicine, nevibolol, folic acid, ruxolitinib or lopinavir/ritonavir. The results of these trials will elucidate the effectiveness of statins in COVID-19 outcomes [82,83]. Certainly, these studies are not free from limitations and these are related to their retrospective nature and to the restricted sample size, which could have limited the significance of their findings. Given the study design, we cannot suppose causality of statins on mortality and it should be deliberated hypothesis generating.

DISCUSSION

Results suggest that statin users with COVID-19 have a greater baseline risk mainly driven by more advanced age and a high burden of cardiovascular comorbidities, which might in theory disguise a potential protective effect of statins in this particular subset of patients. Statin users were older had diabetes of longer duration, and more hypertension, heart failure and chronic obstructive pulmonary disease, as well as more macro vascular and micro vascular complications than non-users of statins. The majority of analyses concerning mortality risk during COVID-19 have thus far indicated a beneficial or neutral effect of statin use.

CONCLUSION

In the next global pandemic outbreaks, physicians who live in parts of the world without vaccine companies or antiviral stockpiles will have little for suggestion to their patients. Patients receiving statins may possibly have more stable, well-controlled illness and may show lower acute pathologic events such as plaque rupture. These patients may also have a greater survival in a severe disease condition. Statins are already commonly produced and distributed throughout the world and are used by millions of persons on a year-round basis. Furthermore, statins are already being produced as generics in a number of developing countries. In developing countries, the low cost of generic statins, compared with prevailing antiviral agents, will be notable. Although this comparison may not be correct, it can be acceptable in an emergency. The scientific rationale for considering statins as treatment and prophylaxis of pandemic influenza is convincing enough to authorize public health policy to use them. Due to low cost, safety, and worldwide accessibility, generic statins as therapeutic alternative could become crucially vital for provoking the pandemic. They are able to greatly reduce the disparity that in this condition, separate developed and developing countries. They could become the available key agents to alter a globally unprecedented health crisis at any time. Ideally, these medications should be generically produced, and extensively available in developing countries. Research on statins and other agents might also have applicability for other serious virus diseases, such as severe acute respiratory syndrome and Human Immunodeficiency Virus infection and Acquired Immunodeficiency Syndrome (HIV/AIDS) [83].

AUTHORS CONTRIBUTION

Authors conceived the subject matter and contributed to write the original draft and revised the first draft for approval the final version of paper.

CONFLICT OF INTEREST

We have no conflict of interest to declare.

REFERENCES

1. Iraklis C Moschonas, Alexandros D Tselepis (2021). SARS-CoV-2 infection and thrombotic complications: a narrative review. J Thromb Thrombolysi. 52:111-123.
2. Kwak B (2000). Statins as a newly recognized type of immunomodulator. Nat Med. 6:1399-1402.
3. Steiner S (2005). Simvastatin blunts endotoxin-induced tissue factor in vivo. Circulation. 111:1841-1846.
4. Catron DM (2004). *Salmonella enterica* serovar Typhimurium requires nonsterol precursors of the cholesterol biosynthetic pathway for intracellular proliferation. Infect Immun. 72:1036-1042.
5. Meijvis S (2012). Treatment with anti-inflammatory drugs in community-acquired pneumonia. J Intern Med. 272:25-35.
6. Danesh J (1998). Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. Jama. 279:1477-1482.
7. Mendall M (1997). Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart. 78:273-277.
8. Ramirez J (2008). Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. Clin Infect Dis. 47:182-187.
9. Shin W, A Szuba and SG Rockson (2002). The role of chemokines in human cardiovascular pathology: enhanced biological insights. Atherosclerosis. 160:91-102.
10. Corrales-Medina VFM Madjid and DM Musher (2010). Role of acute infection in triggering acute coronary syndromes. Lancet Infect Dis. 10:83-92.
11. Musher DM (2007). The association between pneumococcal pneumonia and acute cardiac events. Clin Infect Dis. 45:158-165.
12. Perry TW (2011). Incidence of cardiovascular events after hospital admission for pneumonia. Am J Med. 124:244-251.
13. Corrales-Medina (2009). Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. Medicine. 88:154-159.
14. Yende S (2011). Elevated hemostasis markers after pneumonia increases one-year risk of all-cause and cardiovascular deaths. PloS one. 6:22847.
15. Naeini MB (2021). A meta-meta-analysis: Evaluation of meta-analyses published in the effectiveness of cardiovascular comorbidities on the severity of COVID-19. Obes Med. 22:100323.
16. Radenkovic D (2020). Cholesterol in relation to COVID-19: should we care about it? J Clin Med. 9:1909.
17. Fedson DS (2013). Treating influenza with statins and other immunomodulatory agents. Antiviral Res. 99:417-435.
18. Bird L (2018). Statins as adjuvants. Nat Rev Immunol 18:669-669.
19. Xia Y (2018). The mevalonate pathway is a druggable target for vaccine adjuvant discovery. Cell. 175:1059-1073.
20. Bahrami A (2018). Effect of statins on toll-like receptors: a new insight to pleiotropic effects. Pharmacol Res. 135:230-238.
21. Katsiki NM Banach and DP Mikhailidis (2020). Lipid-lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic. Arch Med Sci. 16:485-489.
22. Torres-Pena JD. N Katsiki and P Perez-Martinez (2021). Could statin therapy be useful in patients with coronavirus disease 2019 (COVID-19)? Front Cardiovasc Med. 8:775749.
23. Subir RJD (2020). Research, and reviews, pros and cons for use of statins in people with coronavirus disease-19 (COVID-19). Diabetes Metab Syndr. 14:1225-1229.
24. Song SL (2020). Statin use is associated with decreased risk of invasive mechanical ventilation in COVID-19 patients: a preliminary study. Pathogens. 9:759.
25. Enserink M (2005). Old drugs losing effectiveness against flu; could statins fill gap? Science. 309:1976-1977.
26. Madjid M (2020). Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. 5:831-840.

27. Yoshida T and M Hayashi (2017). Pleiotropic effects of statins on acute kidney injury: involvement of Krüppel-like factor 4. Clin Exp Nephrol. 21:175-181.
28. Farag A (2020). Identification of atovaquone, ouabain and mebendazole as FDA approved drugs Tar-geting SARS-CoV-2 (version 4). Biol Med Chem.
29. Katsiki N, MBanach and DP Mikhailidis (2020). Lipid lowering therapy and renin-angiotensin-aldosterone system inhibitors in the era of the COVID-19 pandemic. Arch Med Sci. 14:485-489.
30. Feinstein MJ (2015). A systematic review of the usefulness of statin therapy in HIV-infected patients. Am J Cardiol 115:1760-1766.
31. Mortensen EM (2005). The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. Respir Res. 6:82.
32. Papazian L (2013). Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. Jama. 310:1692-1700.
33. Yuan S (2015). Statins may decrease the fatality rate of Middle East respiratory syndrome infection. M Bio. 6:01120-01125.
34. Unit ES (2005). Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 366:1267-1278.
35. Jacobson JR (2004). Cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Respir Cell Mol Biol. 30:662-670.
36. Jacobson (2005). Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. Am J Physiol Lung Cell Mol Physiol. 288:1026-1032.
37. Pirat A (2006). Pretreatment with simvastatin reduces lung injury related to intestinal ischemia-reperfusion in rats. Anesth Analg. 102:225-232.
38. Tisoncik JR (2012). Into the eye of the cytokine storm. Microbiol Mol0 Biol Rev. 76:16-32.
39. Ishikawa T (2012). Clinical preparedness for cytokine storm induced by the highly pathogenic H5N1 influenza virus. J Pharmacogenomics Pharmacoproteomics. 3: 131.
40. Fedson DS and OM Rordam (2015). Treating Ebola patients: a 'bottom up' approach using generic statins and angiotensin receptor blockers. Int J Infect Dis. 36:80-84.
41. Grudzinska FS (2017). Statin therapy in patients with community-acquired pneumonia. Clin Med (Lond). 17:403-407.
42. Calfee CS (2018). Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. Lancet Respir Med. 6:691-698.
43. Tan WYT (2020). Statin use is associated with lower disease severity in COVID-19 infection. Sci Rep. 10:17458.
44. Daniels LB (2020). Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. Am J Cardiol. 136:149-155.
45. Gupta A (2021). Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun. 12:1325.
46. Saeed O (2020). Statin Use and In-Hospital Mortality in Patients with Diabetes Mellitus and COVID-19. J Am Heart Assoc. 9:e018475.
47. Song SL (2020). Statin use is associated with decreased risk of invasive mechanical ventilation in COVID-19 patients: a preliminary study. Pathogens. 9:759.
48. Pal R (2021). Statin use and clinical outcomes in patients with COVID-19: An updated systematic review and meta-analysis. Postgrad Med J. 98:354-359
49. Chacko SR (2021). Association of pre-admission statin use with reduced in-hospital mortality in COVID-19. Am J Med Sci. 361:725-730.
50. Wu CC (2021). Statin use is associated with a decreased risk of mortality among patients with COVID-19. J Clin Med. 10:1450.
51. Fan Y (2020). Association of statin use with the in-hospital outcomes of 2019-coronavirus disease patients: A retrospective study. Front Med (Lausanne). 7:584870.
52. Zein A (2021). Statin and mortality in COVID-19: a systematic review and meta-analysis of pooled adjusted effect estimates from propensity-matched cohorts. Postgrad Med J. 98:503-508.
53. Shadid H (2021). Statin use may be associated with decreased severity of Covid-19J. Am Coll Cardiol. 77:3185-3185.
54. Kow CS and SS Hasan (2020). Meta-analysis of effect of statins in patients with COVID-19. Am J Cardiol. 134:153-155.
55. Torres-Pena JD (2021). Prior treatment with statins is associated with improved outcomes of patients with COVID-19: Data from the SEMI-COVID-19 registry. Drugs. 81:685-695.
56. Khan A (2021). Statin for pneumonia and influenza - systematic review and meta-analysis to inform policy to mitigate COVID-19. SSRN. 32.
57. Masana L (2020). Effect of statin therapy on SARS-CoV-2 infection-related mortality in hospitalized patients. Eur Heart J Cardiovasc Pharmacother. 8:157-164.
58. Ikari Y (2021). Association between statin use prior to admission and lower coronavirus disease 2019 (COVID-19) severity in patients with cardiovascular disease or risk factors. Circ J. 85:939-943.
59. Permana H (2021). In-hospital use of statins is associated with a reduced risk of mortality in coronavirus-2019 (COVID-19): systematic review and meta-analysis. Pharmacol Rep. 73:769-780.
60. Kollias A (2021). Statin use and mortality in COVID-19 patients: Updated systematic review and meta-analysis. Atherosclerosis. 330:114-121.
61. Lohia P (2021). Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with propensity score matching. J Clin Lipidol. 15:451-459.

62. Chow R (2021). The protective association between statins use and adverse outcomes among COVID-19 patients: a systematic review and meta-analysis. MedRxiv. 16:0253576.
63. Onorato D (2021). Protective effects of statins administration in european and North American patients infected with covid-19: a meta-analysis. Semin Thromb Hemost. 47:392-399.
64. Marić I (2021). Decreased mortality rate among COVID-19 patients prescribed statins: data from electronic health records in the US. Front Med. (Lausanne). 8:639804.
65. Bonilla HMG (2021). Effect of Statin In Hospitalized Patients with Covid 19. J Am Coll Cardiol. 77:3171-3171.
66. Diaz-Arocutipa C (2021). Statins reduce mortality in patients with COVID-19: an updated meta-analysis of 147 824 patients. Int J Infect Dis. 110:374-381.
67. Wu KS (2021). The use of statins was associated with reduced COVID-19 mortality: a systematic review and meta-analysis. Ann Med. 53:874-884.
68. Chow R, EH Prsic and HJ Shin (2021). Cost-effectiveness analysis of statins for treatment of hospitalized COVID-19 patients. MedRxiv.
69. Hariyanto TI and A Kurniawan (2020). Statin therapy did not improve the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 14:1613-1615.
70. Mitacchione G (2021). Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy. J Clin Lipidol. 15:68-78.
71. Butt JH (2020). Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. BMJ open. 10:044421.
72. Oh TK Song and YT Jeon (2021). Statin therapy and the risk of COVID-19: a cohort study of the national health insurance service in South Korea. J Pers Med. 11:116.
73. Hariyanto TI and A Kurniawan (2021). Statin and outcomes of coronavirus disease 2019 (COVID-19): a systematic review, meta-analysis, and meta-regression. Nutr Metab Cardiovasc Dis. 31:1662-1670.
74. Russo V (2021). Preadmission statin therapy and clinical outcome in hospitalized patients with COVID-19: An italian multicenter observational study. J Cardiovasc Pharmacol. 78:94-100.
75. Lee HY (2021). Beneficial effect of statins in COVID-19-related outcomes-brief report: A national population-based cohort study. Arterioscler Thromb Vasc Biol. 41: 175-182.
76. Cariou B (2021). Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: Results from the CORONADO study. Diabetes Metab. 47:101202.
77. Scheen AJ (2020). Statins and clinical outcomes with COVID-19: Meta-analyses of observational studies. Diabetes Metab. 47:101220.
78. Peymani P (2021). Statins in patients with COVID-19: a retrospective cohort study in Iranian COVID-19 patients. Transl Med Commun. 6:3.
79. Ayeh SK (2021). Statin use is associated with more severe COVID-19 disease in hospitalized patients. SSRN Electr J.
80. Yetmar ZA (2021). Association between chronic statin use and 30-day mortality in hospitalized patients with COVID-19. Mayo Clin Proc Innov Qual Outcomes. 5:442-446.
81. Strandberg TE and M Kivimäki (2021). Increased mortality risk associated with statins in the CORONADO study. Diabetes Metab. 47:101250.
82. Rodriguez-Nava (2020). Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. Crit Care. 24:429.
83. Boettiger DC. (2021). Maintenance of statin therapy among people living with HIV. AIDS. 35:567-574.