Review Article

The potential role of Statins in the treatment of COVID-19

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The recent COVID-19 pandemic has become a great challenge for the world with 52.5 million affected and 1.2 million deaths, as of 12th November 2020. Globally, the health care system has been under immense pressure in terms of the availability of Medicare, medical equipment, and medical personnel. Although, there is no effective and proven antiviral-or combination drug that is specifically made to treat COVID-19 or fend off its severe complication i.e. acute respiratory distress syndrome, symptomatic treatment and treatment of clinical manifestation with available drugs and agents still remains the sole option to treat COVID-19 and its associated complications.

Repurposing drugs is quicker and unmistakably more prudent than beginning advancement without any preparation, and many medication targets are shared across infections. Generally, there have been a few striking medication repurposing triumphs (e.g., sirolimus for lymphangioleiomyomatosis, thalidomide for multiple myeloma), yet there are likewise a significant number of difficulties, for example, prioritizing drug candidates, choosing the fitting investigation plan and endpoints, and rivaling off-label use. Repurposing of drugs can help us fight this pandemic and can easily come to the aid of failing health care systems.

COVID-19 causes acute respiratory distress syndrome (ARDS) and multi-organ failure via the cytokine storm. In patients infected with COVID-19, the respiratory epithelial cells, dendritic cells, and macrophages produce an increased number of Interferons (IFNs), pro-inflammatory cytokines (IL-1 beta, IL-6 and TNF), and chemokines (CCL-2, CCL-3 and CCL-5) causing a cytokine surge followed by the attraction of chemokines and eventual infiltration of inflammatory cells such as neutrophils and monocytes ultimately leading to lung injury **[**1**]**. Subsequently, COVID-19 also causes endothelial inflammation, complement activation, thrombin formation, platelets, and leukocyte recruitment resulting in thrombotic complications such as deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke **[**2**]**.

Data from the past suggests the efficacy of statins in decreasing fatality rate in ARDS caused by avian influenza viruses (AIVs) and a simultaneously decreased mortality in MERS-CoV by dysregulation of myeloid differentiation primary response 88 (MYD88) pathway **[**3,4**]**. The anti-inflammatory effects of statins also include augmentation of the ACE-2 expression **[**5**]**.

Furthermore, an RCT conducted during the 2009 H1N1 pandemic also demonstrated a reduction in disease severity and significant improvement in a patient receiving atorvastatin 40 mg compared with the placebo **[**6**].** Even, some authors have encouraged the use of Statin in viral infections that carries a potential for epidemic and pandemic **[**6**]**. Moreover, studies mainly observational have demonstrated a benefit in patients with pneumonia and decreasing pulmonary inflammation, a lipopolysaccharide challenge (LPS) in healthy human also demonstrated that subjects taking simvastatin 40 mg for 4 days attenuate the inflammatory systemic response **[**7**]**.

Statins attenuate TLR mediated NF-kappa B activation causing several anti-inflammatory effects **[**8**].** They also tend to interfere with the activation of the clotting system and the coagulation cascade via decreasing tissue factor, thrombin, factor Va, oxidized LDL increasing thrombomodulin and protein C. Antithrombotic effects of statins brought about by inhibiting platelet activation have also been documented **[**9**]**.

As the severe acute respiratory syndrome coronavirus (SARS-CoV) has demonstrated engagement with Toll-like receptors present on the host cell membranes and increased expression of the MYD88 gene ultimately triggering NF-κB and activating inflammatory pathways, statins can be very helpful to counter this. Since statins are known inhibitors of MYD88 and can also play a role in stabilizing MYD88 levels, they, therefore, suggest their role in

protecting COVID-19 patients from progression to the overwhelming inflammatory responses **[**10**]**.

As statins are known to experimentally up-regulate ACE-2 expression, their role warrants rigorous assessment by Randomized control trials (RCTs). However, statins do down-regulate CD-147 expression which is a major entry regulator in pulmonary cells. Moreover, autophagy activation, weakening of both the coagulation activation and the inflammatory response suggest the possible therapeutic effects of statins in COVID-19 as a co-adjuvant or add-on therapy **[**11**]**. With the advent of this pandemic, multiple observational studies have demonstrated the need to address hypercholesterolemia, a major risk factor associated with increased mortality **[**12**]**, in COVID-19 patients. Several randomized control trials (RCT) have illustrated the benefit of using statins in severely affected COVID-19 patients **[**13-15**]**. Recently, a meta-analysis involving 8,990 patients showed decreased mortality by 30% **[**16**].**

Although, some safety concerns in the patients taking a statin should be taken into account in terms of using statins as an add-on in treating COVID-19, including the patient's LDL level. As suggested by some retrospective studies a low level of LDL can have a pernicious effect on the COVID-19 manifestation and prognosis **[**17**]**. Another challenge in treating patients of COVID-19 with statins is the concomitant use of antiviral therapy i.e. lopinavir/ritonavir with statins [18]. Lovastatin and Simvastatin are contraindicated along with statin use due to increased risk of rhabdomyolysis. Other statins, including atorvastatin and rosuvastatin, generally have a safe-profile and should be given in lowest dose possible while the patient is taking lopinavir/ritonavir **[**18].

In summary, we hypothesize the mitigation of COVID-19 manifestations in certain patients on basis of our understanding of the resulting coagulopathy, endothelial dysfunction, and disrupted inflammation. The appropriate therapeutic regimens for COVID-19 are yet to be established but the effect of statins in reducing mortality of patients is noteworthy and to further validate their efficacy larger observational studies or ideally, randomized controlled trials (RCT) need to be conducted. Observational evidence from patients infected with other coronaviruses supports the potency and safety of statins amid COVID-19. COVID-19 may no longer remain a health care issue once the approved vaccines are readily available; regardless, cardiovascular disease (CVD) will, and this should not hamper our struggle in understanding more about the mechanisms of these drugs.

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