

Use of Statins in COVID-19 Treatment: Multiple Pathways but Minimal Evidence

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Abstract

Coronavirus disease-2019(COVID-19) is an emerging viral infection of public importance and it is caused by a beta coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). So far, it has affected about 15 million individuals and over 600 000 patients have died from it. The virus is novel and there is no approved specific therapy for the infection. This has led to the trial of different drugs to reduce the morbidity and mortality of the infection. Statins are primarily used to lower cholesterol. They also have other pleiotropic effects such as anti-inflammatory, anti-thrombotic, immunomodulatory and antiviral effects. Coincidentally, the processes that statins antagonize are the mechanisms underlying the pathogenesis of COVID-19. Therefore, it has been suggested that statins should be considered as an adjunct in the treatment of COVID-19. In the new era of evidence-based medicine, there is a need to examine the level of evidence available to support the clinically beneficial effect of statins in COVID-19 treatment. This literature review explores the strength and volume of evidence for the usage of statins in COVID-19. However, as at the time of writing this review, the evidence base is very scanty. The most quoted evidence available is a retrospective study which is a low level of evidence. Therefore, it can be concluded that there are various mechanisms identified by which statins could be useful in the treatment COVID-19. However, the evidence for their recommendation as adjuncts for COVID-19 treatment is very weak.

Keywords: Statins; COVID-19; Mechanisms of statin; Evidence for statin in COVID.

Introduction

The coronavirus disease 19 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. It was first reported in Wuhan, China but later spread to many parts of the world [2]. The World Health Organization (WHO) has declared COVID-19 as a pandemic [3]. The early clinical features that have been reported from multiple

sources include fever, malaise, nasal discharge, dry cough, sore throat, breathlessness, loss of taste and smell and digestive symptoms [4]. Later on, the patient may develop acute respiratory distress syndrome or septic shock and die from it. A recent meta-analysis found that hypertension, cardiovascular disease and diabetes mellitus in 17.1, 16.4, and 9.7%

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respectively of patients with COVID-19 [5]. Currently there are no widespread approved therapies specific for COVID-19 but different medications direct acting antivirals (DAAs), host-targeted antivirals, Hydroxychloroquine, Azithromycin, steroids, vitamins C and D and zinc are being prescribed for treating based on few observational studies in an attempt to reduce morbidity and mortality [6]. None of these, so far, has met globally acceptable satisfactory clinical outcomes. Therefore, efforts are on-going to identify the medications that can give significant and reproducible clinical outcomes. This has led to the consideration of the use of statins. Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are widely used in the treatment of dyslipidaemia [7]. They are well tolerated and have excellent safety records. Examples include simvastatin, atorvastatin, rosuvastatin, lovastatin, pravastatin and fluvastatin. It has however been reported extensively that statins also have other non-lipid effects, the so called 'pleiotropic effects' [8]. Some of these mechanisms are recognized as potential pathways for which the use of statins to treat COVID-19 is being proposed.

Aim and methods

The aim of this review article is to highlight the various pathways that could explain why statins might be beneficial in the treatment of COVID-19 and to explore the literature for evidences supporting the use of statins in the treatment of COVID-19.

Relevant articles were gotten from biomedical databases such as PubMed, Google scholar, Science direct, African Journals Online (AJOL) as well as the grey literature using search terms such as 'statins, COVID 19', 'mechanisms of statins,

COVID 19', 'COVID 19, evidence for statin use' and 'COVID 19, statin trials'. The selected articles were adjudged independently to be of adequate quality and relevant to the topic by the authors.

Use of statins for treating COVID-19: the mechanisms

Anti-inflammatory mechanism

Recent publications highlight that the various phases of COVID-19 are characterized by varying severity of inflammatory responses [9]. Studies on the use of statins in patients with cardiovascular disease that used an inflammatory marker called C-reactive protein (CRP) demonstrated a reduction in this inflammatory marker. This suggests that statins also have anti-inflammatory properties apart from their cholesterol-lowering effects [10]. The anti-inflammatory properties of statins, by blocking several molecular mechanisms, including nuclear factor kappa B (NF- κ B) and nucleotide binding domain-like receptor protein 3 (NLRP3) inflammasomes, could limit the cytokine storm in severe COVID-19 patients which is linked to fatal outcome [11].

Immunomodulatory mechanism

There are substantial reports on the complex immune dysregulation caused by SARS-CoV-2 and this causes cytokine storm leading to increased risk of death [12]. In contrast, here is also significant evidence that statins may modulate immune responses [13]. Statins inhibit the expression of class II major histocompatibility antigens (MHC-II) on human macrophages, endothelial cells, and smooth muscle cells (SMC) stimulated by interferon γ (IFN γ) [14]. Another

immunomodulatory effect of statins is a selective blocking of the β_2 integrin expressed on the surface of leukocytes and, when activated, binds to intercellular adhesion molecule 1 (ICAM-1).

Antithrombotic effect

Patients with COVID-19 infection have been reported to have a higher incidence of cardiovascular disorders and thromboembolic phenomenon [15]. A study that measured D-dimer as a marker of thrombotic events reported elevated levels of this marker in patients with COVID-19 who were admitted into the intensive care units [15]. This suggests that these patients are more prone to thrombotic events. Statins have been reported to demonstrate antithrombotic effect by interfering with the different components of the clotting system and the coagulation cascade [16]. Some of the mechanisms which have been proposed to explain this antithrombotic effects of statins include interfering with platelet aggregation, inhibiting the expression of tissue factor and increased expression of a physiological anticoagulant called thrombomodulin on endothelial cells [16].

Antiviral mechanism

Following the infection of SARS-CoV-2, the viruses bind specific receptors which are found in the bilayer of the cell membrane which is rich in cholesterol. These areas are sometimes described as the lipid rafts. These lipid rafts play a vital role in the packaging of vesicles responsible for the concentration of the virus replication factors thereby destabilizing the replication phase of the coronavirus. Statins act on the cell membrane bilayer by reducing the concentration of cholesterol present in it. This process will reduce the aggregation of the specific receptors that the virus interact

with thereby reducing the tendency of the cell from being invaded by the virus there by protecting the host [17].

Evidence for statins usage in COVID-19

Despite the observations that statins have mechanisms of actions that might support their usage in the treatment of COVID-19, the evidence to back it up is very scanty. As at the time of writing this review, there are no published results of meta-analyses, systematic reviews or clinical trials to support the usage of statins in COVID-19. Statins have been documented to have beneficial effects, as adjunctive therapy, against influenza virus, Ebola virus and Zika virus infections [18]. The most quoted evidence supporting the use of statins in COVID-19 as adjunctive therapy was a retrospective study done in Hubei province, China [19]. The study involved 13 981 COVID-19 patients out of whom 1219 patients were on statins. 28 day mortality was better among patients on statins (5.2% vs 9.4%). This gave a 42% reduction in risk of death for COVID-19 patients on statins. There was also a greater reduction in inflammatory markers (interleukin 6, C-reactive protein and neutrophils) among COVID-19 patients on statins compared to those without statins.

Conclusion

Statins are readily available, inexpensive and well tolerated medications whose primary roles are cholesterol lowering but they also have non-lipid effects. Among the documented non-lipid effects include their anti-inflammatory, anti-thrombotic, immunomodulatory and antiviral effects. These make statins a potential adjunctive drug in the treatment of COVID-19. However, the level and volume of evidence for this purpose is limited. Randomized

clinical trials will be needed to substantiate the role of statins as adjunctive COVID-19 potential therapy.

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