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The advantages of drug treatment with statins in patients with SARS-CoV-2 infection

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Summary On 11 March 2020 the World Health Organization (WHO) declared a status of global pandemic caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019, COVID-19). The pandemic is currently underway, and to date has caused approximately 2.42 million deaths worldwide. The first vaccines have recently been licensed; however, research continues to identify therapeutic agents to prevent serious complications, such as anti-inflammatory, immunomodulatory, anticoagulant or antiviral agents authorized for other therapeutic indications. Epidemiological evidence shows that advanced age and comorbidities, such as diabetes, heart disease, and dyslipidemia may represent COVID-19 risk factors. In particular, in patients with hypercholesterolemia treated with statins, it is recommended that treatment should not be discontinued if COVID-19 infection occurs. The pleiotropic effects of statins are well known. In this brief review, we propose that the use of statins can potentially protect against SARS-CoV-2-induced tissue damage and improve lung function in COVID-19 patients through several pleiotropic effects. Pleiotropic effects of statins that may be a significant benefit in patients with hypercholesterolemia treated with statins and COVID-19 positive. Recent evidence shows promising results.

Keywords Hypercholesterolemia · Pleiotropic effect · Comorbidities · Pandemic · Pharmacotherapy

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Introduction

SARS-CoV-2 (COVID-19)

In November 2019 a new coronavirus was identified as the cause of a number of severe pneumonia cases in Wuhan, China. The virus designated as coronavirus-2 is responsible for severe acute respiratory syndrome, SARS-CoV-2 (coronavirus disease 2019, COVID-19). The virus has rapidly spread worldwide. In March 2020, the World Health Organization (WHO) proclaimed the status of a global pandemic by COVID-19, to date there are about 2.42 million deaths and 109 million infected persons [1]. The SARS-CoV-2 is an RNA (ribossinucleid acid) virus similar to SARS-CoV (responsible for the 2003 outbreak) for about 80% of the viral genome [2]. In vitro studies confirmed that the virus penetrates human cells by binding to the protein angiotensin conversion enzyme 2 (ACE-2), which is part of the renin-angiotensin system (RAS) [3] and is considered a possible receptor of the protein. It is also known that patients infected with this virus have changes and variations in the concentrations of the enzyme components of RAS [4, 5] during illness days. A SARS-CoV-2 infection may have an asymptomatic or symptomatic course. In a percentage of cases, however, the infection has a course consisting of an initial asymptomatic or slightly symptomatic phase and subsequent phases characterized by a generalized inflammatory state that causes multiorgan tissue lesions and respiratory distress syndrome [6]. The generalized inflammatory state responsible for

severe lesions is caused by an overactivation of the components of the host inflammatory/immune system characterized by a sudden and high release of cytokines, an event called a cytokine storm that leads to severe and sometimes fatal tissue damage. Since a few months the first vaccines have been authorized, in the case of a positive COVID-19 case ongoing treatments for other diseases should be continued to avoid serious complications [7–11].

Clinical manifestations

The SARS-CoV-2 is transmitted from person to person. In most cases the incubation period is about 5 days after exposure and in some cases it can be as long as 15 days [12]. Bilateral interstitial pneumonia seems to be the most frequent serious manifestation of infection characterized by coughing and dyspnea [13]. The infection may also have a totally asymptomatic or slightly asymptomatic course; however, the manifestation of upper respiratory tract symptoms, myalgia and fatigue, diarrhea, and disturbances of the sense of smell are common [14]. Epidemiological evidence shows that fever is present in about 90% of hospitalized COVID-19 patients [13]. In some studies, smell and taste disorders have been reported in about 50% of COVID-19 positive patients [14, 15]. A smaller percentage of COVID-19 positive patients experience gastrointestinal symptoms, such as nausea and diarrhea [16]. Cases of dermatological reactions such as rashes and hives have also been reported [17]. A SARS-CoV-2 infection can cause several serious complications: acute respiratory distress syndrome (ARDS) is the major complication in COVID-19 positive patients [16]; however, in addition to the respiratory system, other organs may also be affected, particularly the cardiovascular system. Epidemiological data report cases of acute cardiac lesions from COVID-19 [18]. Thromboembolic complications including pulmonary embolism have also been reported [19]. Some cases reported liver lesions caused by COVID-19 [20]. The presence of lesions of the lungs and other organs such as the heart or liver appears to be caused by direct or indirect damage of the virus. As described above SARS-CoV-2 uses the entry receptor ACE-2, a protein expressed in several tissues, in type II pneumocytes, heart cells, liver cholangiocytes [21], which may be responsible for direct tissue damage caused by the virus; however, in the most severe stages of COVID-19 infection, a cytokine storm [22] can be generated that is responsible for organ lesions, in particular the formation of fibrotic tissue, such as pulmonary fibrosis, myocardial fibrosis, or liver fibrosis observed in some cases of COVID-19. [23, 24].

Risk factors in COVID-19 patients

Epidemiological evidence has shown that the severity of viral infection can vary greatly from subject to subject depending on various factors. As described in fact, some individuals may be totally asymptomatic, others may represent cases with a severe course, and in some cases fatal. The risk of serious complications from COVID-19 is increased in older people and/or with pre-existing diseases, in particular pulmonary, cardiac, metabolic diseases and weakening of the immune system may represent an important risk factor. Pulmonary diseases such as COPD (chronic obstructive pulmonary disease), asthma, cystic fibrosis can make the respiratory tract vulnerable to serious injuries from COVID-19 [25]. Diseases such as diabetes and obesity may reduce the efficiency of the immune system, heart diseases such as ischemic heart disease or heart failure may make the heart susceptible to serious injury from COVID-19, considering that SARS-CoV-2 itself may cause damage to cardiac tissue. The presence of hypercholesterolemia can also be a risk factor. The development of atherosclerosis may predispose to acute coronary syndrome, a COVID-19 infection may further complicate the scenario and increase the risk of myocardial ischemia [26–28].

Statins

The inhibitors of hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, the statins, have been used for many years with undoubted therapeutic efficacy in the management of hyperlipidemia and in the prevention of atherosclerotic vascular diseases, in particular acute coronary syndromes [29, 30]; however, the therapeutic benefits of statin treatment are not only related to lowering endogenous cholesterol, suggesting that other effects and mechanisms come into play. Numerous experimental and clinical trials in recent years have led to the widely accepted scientific concept of pleiotropic effects of statin treatment independent of HMG-CoA inhibition, including restoration of endothelial dysfunction, stabilization of atherosclerotic plaques, regulation of angiogenesis, antifibrotic, antithrombotic and antifibrotic effects [31]. The pleiotropic effects of statins may result in potential therapeutic benefits in the patient under treatment and COVID-19 positive, particularly for properties in thrombotic manifestations that may occur in the more severe stages of SARS-CoV-2 infections. (Fig. 1).

Pleiotropic effects of statins and COVID-19

Reducing LDL (Low Density Lipoprotein) and cardiovascular protective effects

The therapeutic efficacy of statin treatment and associated pleiotropic effects can indirectly preserve or reduce cardiac damage that can occur in severe COVID-19 patients [18]. Well-known epidemiological evidence indicating the protective effect of statin treatment on the cardiovascular system is also po-

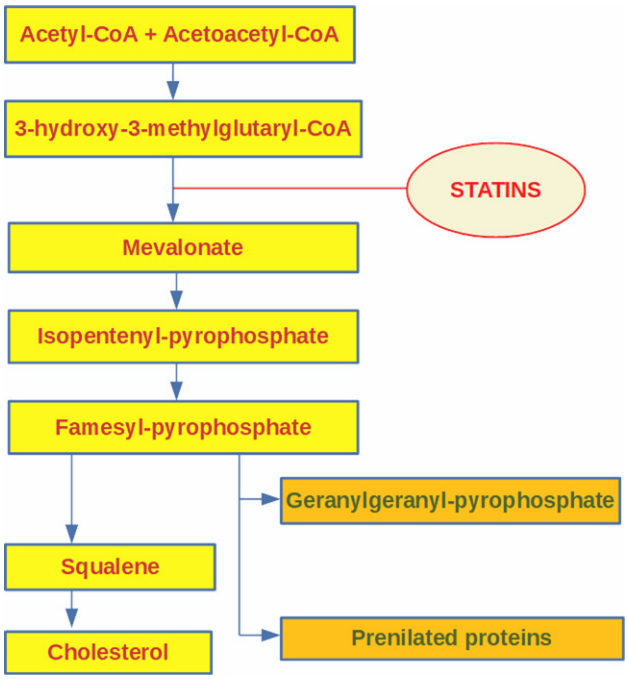

Fig. 1 Mechanism of action of statins on the reduction of circulating cholesterol

tentially useful in cases of severe COVID-19 infection; however, the clinical significance of the pleiotropic effects of statins in the cardiovascular system remains controversial and has yet to be fully clarified, given the enormous benefits of cholesterol reduction in the prevention of cardiovascular events. As described above, cardiac lesions can occur in severe COVID-19 positive patients, in particular cases of acute coronary syndrome (SCA), arrhythmia, edema, pericarditis, acute heart failure have been reported. An SCA can be a serious complication caused by COVID-19 infection in patients without or with pre-existing cardiovascular risk factors. The basic mechanism by which COVID-19 causes these effects remains questionable. It has been proposed that COVID-19 may induce a prothrombotic state, as supported by high levels of factor VIII, fibrinogen and d-dimer [32, 33]. Some interesting evidence associates antithrombotic properties to the statins. In addition, statins can have a reducing effect on cardiac fibrosis, hypertrophy, and pathologic remodeling in response to angiotensin II (Ang II) in a Rho/ROCK dependent manner [34–36]. Increased ROCK (Rho-associated protein kinase) activity is observed in patients with hypertension, pulmonary hypertension, metabolic syndrome, dyslipidemia, acute coronary syndrome (CAD), coronary vasospasm, left ventricular hypertrophy (LVH), and in heart failure with reduced systolic function [37–39]. The ROCK inhibition is a candidate for mediating pleiotropy of statins. The effect of statins on the myocardium mediated by RhoA and ROCK is of paramount importance because both lead to increased apoptosis and increased fibrosis, which could lead to development of LVH and heart failure. Endothelial dysfunction can be caused by hypercholesterolemia and is characterized by reduced bioavailability of endothelial nitric oxide (NO). Endothelial NO is important for vasodilation, platelet aggregation, vascular smooth muscle proliferation and leukocytic endothelial interactions. Statins increase endothelial NO production, in part by increasing endothelial NO synthase (eNOS) [40, 41]. Statins increase the bioavailability of NO, which increases myocardial blood flow under hypoxic conditions and inhibits interleukin 6 (IL-6), IL-8 and the adhesion molecule of vascular cell-1 (VCAM-1). In vitro studies show that statins reduce mitochondrial dysfunction and death of cardiomyocytes [42]. Several studies have described a protective effect of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) against ventricular arrhythmia and sudden cardiac death. Statins reduce inflammation, a known risk factor for sudden death and ventricular arrhythmia [43, 44]. An overactive inflammatory state, as may occur in severe COVID-19 phases, alters the autonomic tone measured by heart rate variability, which may partly explain these associations of inflammation and arrhythmic outcomes. Statins have documented effects on autonomic activation, improving heart rate variability and desensitizing myocytes to beta-adrenergic stimulation [45].

Anti-inflammatory and immunomodulatory effects

Recently numerous in vitro and in vivo evidence has associated direct anti-inflammatory effects that are not mediated by their hypocholesterolemic activity. The evidence is further supported by observations that statin treatment lowers the C-reactive protein (CRP), a marker of inflammation, regardless of the lipid-lowering effect [46, 47]; however, there are still many aspects to be clarified on the anti-inflammatory effect of statins. Some studies showed that statins inhibit leukocyte recruitment. The activity on leukocyte migration is probably related to the reduction of chemokines and IL-6 cytokine [48]. In addition, statin treatment can improve NO release from the endothelium and downregulatee endothelial P-selectin [49]. An increasing amount of in vitro and in vivo evidence associates the antispasmodic effects of statins with the key concept of modulation of the leukocyte adhesion cascade. Based on these considerations, statins inhibit both acute and chronic cholesterol-inhibiting inflammation independently by exerting their anti-inflammatory effect by interfering with the adhesion and transendothelial migration of leukocytes to sites of inflammation. In addition, it seems that the inhibition of the activation of the integrins is related to the reduced geranylgeranylation of Rho [50]. By blocking the activity of Rho GTPase the statins prevent ICAM-1 expression in endothelial cells [51]. Other evidence shows that by inhibiting the geranylgeranylation of Rho GTPase the statins induce the

expression of eNOS[52–55]. Finally statins are associated with cytokine and chemokine release inhibition effects by regulating nuclear receptors, proliferator of the activated peroxisome receptor α (PPAR-α) and PPAR-γ. Other studies indicated that statins could modulate the adhesion of leukocytes by interfering with the path of nuclear factor κB (NF-κB) [56, 57]. In the most severe stages of COVID-19 infection a hyperactive and generalized inflammatory state may be responsible for the most severe complications, in this direction the pleiotropic anti-inflammatory effects, particularly in endotheliitis by statins, could prove to be therapeutically effective [58–61].

Antiviral effects

Some studies have attributed direct cholesterol-dependent or non-cholesterol-dependent antiviral effects to statin treatment. In fact, in this direction, many studies suggested that statins, due to their pleiotropic properties, may be beneficial for the treatment of viral infections and their complications. Some evidence has shown that statins can exert direct antiviral effects, blocking the intracellular production of cholesterol and intervening directly on the infectious cycle of viruses [62]. Moreover, as described above statins reduce geranylgeranyl pyrophosphate (GGP) and farnesyl pyrophosphate isoprenoids, which are necessary for the prenylation of proteins such as Rho and Ras GTPase; in particular the latter proteins are associated to the regulation of the life cycle of viruses. This evidence has been supported by some studies that have shown that statins may have some antiviral potential against HCV (hepatitis C virus). In fact, statins have been shown to block viral replication against HCV when used in association with interferon [62–64]. By reducing the availability of cholesterol, statins may represent possible candidates to interfere with virus fusion and entry into host cells. How much this evidence can also be associated with an anti-SARS-CoV-2 activity is to be demonstrated. A suggested mechanism could be that membrane cholesterol reduction prevents normal ACE2-spike interactions.

Antifibrotic effects

Many studies have suggested that statins have antifibrotic effects on liver and lung tissue and decrease portal hypertension. One of the antifibrotic mechanisms of statins is the reduction of proinflammatory mediators, as described above, which can induce tissue fibrosis; however, it seems that other pathways are involved. In particular, the reduction and decrease in activity of profibrotic factors such as TGFβ1 (Transforming growth factor β1), CTGF (Connective tissue growth factor) and PDGFβ (platelet-derived growth factor-β) are associated with statins. Moreover, by decreasing the RhoA pathway and its downstream Rho-kinase effector, collagen synthesis and liver fibrosis are reduced. Finally, a greater availability of statin-mediated NO causes a decrease in intrahepatic resistance and portal pressure [65, 66]. The hyperactive inflammatory state caused by COVID-19 infection may also be responsible for the formation of fibrotic tissue, in particular pulmonary fibrosis that could cause serious complications. Characteristics of pulmonary fibrosis pathogenesis are cell proliferation, collagen deposition and differentiation of fibroblasts into the profibrogenic phenotype of myofibroblasts, these processes are mainly mediated by connective tissue growth factor (CTGF), an autocrine growth factor induced by TGF-b1. Some evidence suggests that statins could modify the critical determinants of profibrogenic mechanisms and potentially prevent pulmonary parenchymal remodeling associated with the formation of myofibroblasts by inhibiting the expression of the *CTGF* gene after TGF-b1 induction [67, 68].

Antithrombotic effects

Treatment with statins has been associated with antiplatelet and anticoagulant effects, independent of cholesterol lowering. A decrease in platelet activity is through an increase in NO, which is a powerful inhibitor of platelet aggregation. In addition, the administration of statins has been shown to decrease the expression and activity of tissue factor (TF) in monocytes and macrophages [69]. Thrombomodulin acts as a cofactor of thrombin in the process of activation of protein C (APC), which proteolytically inactivating the activated factors V and VIII plays an anticoagulant role. The statins have been shown to increase the expression of anticoagulants TM (thrombomodulin), APC (activated protein C) [70].

Increasing ACE-2

The intracellular input receptor used by SARS-CoV-2 is the angiotensin-conversion of enzyme 2 (ACE-2), expressed in pulmonary, hepatic and cardiac tissue. The ACE-2 is an important regulatory enzyme in the renin-angiotensin system (RAS), catalyzing the conversion of angiotensin II (AT-II) to angiotensin 1–7 (AT 1-7). The AT 1–7 oppose the effects induced by AT-II, with antioxidant, anti-inflammatory, antifibrotic and vasodilator action. It is also known that SARS-CoV-2 infection in the most severe stages causes a reduction in ACE-2. This effect can increase the likelihood of lung injury, which can be fatal in some cases. Ultimately, ACE-2 plays a dual role in COVID-19 infection, the first as a protector against the damaging effects of hyperinflammatory response, the second as an input receptor for SARS-CoV. Statins have been the first choice in the treatment of hypercholesterolemia for years. Studies have shown an increase in ACE-2 expression after statin treatment. Important questions

arise. If statins increase ACE-2, can they be a risk factor for SARS-CoV-2 infection? Or, in severe stages of infection, can the increase in ACE-2 be an additional protection value? To date, it is not clear how clinical results in patients with COVID-19 are affected by the use of statins, alone or in combination with ACE inhibitors and ARBs (angiotensin receptor blocker). Well-structured clinical studies are needed [71–73].

Clinical evidence and COVID-19 patients

Several studies have compared the outcomes of COVID-19 infections in patients who take statins with those who do not. The results have been encouraging, generally suggesting that statin use does not cause worsening health outcomes. Notably, in some studies, statin use was associated with fewer deaths. One retrospective observational study showed that statin use in hospitalized subjects with COVID-19 was associated with a lower risk of all-cause mortality and a favorable recovery profile. Because of the nature of such retrospective studies, these findings should be interpreted and considered with due caution; however, these data also provide evidence supporting the safety of statins as monotherapy or in combination with ACEi/ARBs in patients with COVID-19 [74]. Another retrospective observational study showed slower progression to death associated with atorvastatin in patients with COVID-19 [75]. The current preliminary results suggested a 30% reduction in fatal or severe disease and discredited the suggestion of harm with statin use in patients with COVID-19. Much remains to be determined about the statin regimen for the treatment of COVID-19, although available evidence suggests that moderate to high intensity statin treatment may be effective [76]. Another retrospective study showed that statin use during the 30 days before hospitalization for COVID-19 was associated with a lower risk of developing severe COVID-19 and a faster recovery time among patients without severe disease [77]. Another retrospective study showed that in patients with hyperlipidemia, statin use was independently associated with fewer ICU admissions. This supports the current practice of continuing statin prescribing in patients with COVID-19 [78] but although the results of these studies are interesting and important, they cannot answer the question of whether statins can treat COVID-19 [79]. Recent evidence has also associated novel PCSK-9 (Proprotein convertase subtilisin/kexin type 9) inhibitors with cardiovascular pleiotropic effects; one might speculate that their long-term use before infection may also play a protective role.

Interactions of statins and COVID-19

Statins are drugs well tolerated at the common doses used in the treatment of hypercholesterolemia; however, like any drug, they are not free from potential adverse reactions. The patient with severe COVID-19 is a complex patient, who may have organ lesions, in particular liver and kidney with modified statin metabolization and excretion, increased circulating concentrations, and increased risk of inducing adverse reactions, such as myotoxicity and rhabdomyolysis. Rhabdomyolysis may further create kidney damage [80].

In addition, old COVID-19 patients may have further decreased liver and kidney clearance, making the scenario more complicated. In addition, as described above, a potential increase in ACE-2 concentration caused by statin treatment could represent a COVID-19 risk factor, as the virus would find a higher amount of transmembrane cellular input receptor. In this direction, however, there is no certain epidemiological evidence and studies are necessary. Moreover, most of the available statins are substrate for the cytochrome P450 (CYP) system, in particular 3A isoenzymes and P-glycoproteins (P-gp). Antivirals used in the COVID-19 positive patient (e.g. lopinavir, darunavir) are potent inhibitors of CYP3A and P-gp, and their concomitant administration can cause a marked increase in statin exposure with potential toxic effects [81]. The patient with COVID-19 infection, is a complex patient, the benefit/risk ratio of the pharmacological agents used must be carefully monitored avoiding any adverse reactions that may complicate the scenario [82–86].

Conclusion and perspectives

Statins are drugs of undoubted therapeutic efficacy and with a good tolerability profile. Current guidelines recommend not to stop treatment in cases of COVID-19 positivity. The pleiotropic effects of statins can represent an added value in patients on statin treatment of hypercholesterolemia and COVID-19 positive. Well-structured epidemiological studies are necessary to generate further evidence on this topic.

These effects include combating SARS-CoV-2-induced inflammation and cytokine storm, inhibition of cellular trafficking through the autophagy pathway, mediation of ACE-2 expression, and decreased extracellular matrix biosynthesis and scar formation in COVID-19 patients. Our current work may have some different results from those reported in the study in China, probably because of differences in the number (limitation of our current study) and genetic background of patients involved. Although we could not demonstrate a significant association between statin use and a reduction in COVID-19 mortality, our results are promising and clinically relevant and warrant the need for prospective randomized controlled trials and large retrospective studies in large and diverse patient populations to further evaluate the potential beneficial therapeutic effects of statin treatment on clinical symptoms and mortality rates associated with COVID-19. We hypothesize that long-term statin use

prior to infection could represent a strong adjuvant therapeutic strategy but clinical studies are needed.

Author contribution Antonio Vitiello: conceptualization, writing original draft, methodology. Francesco Ferrara: writing, review and editing, supervision, validation.

Conflict of interest F. Ferrara and A. Vitiello declare that they have no competing interests.

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