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Pharmacological agents modifying the renin angiotensin and natriuretic peptide systems in COVID-19 patients

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SARS-CoV-2 (COVID-19) infection

Coronaviruses (CoV) are a large family of viruses that cause illnesses ranging from the common cold to more severe diseases. A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans. The new virus was subsequently named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease caused by the virus is coronavirus disease 2019 (COVID-19). The new coronavirus SARS-CoV-2 (COVID-19) is responsible for the current global pandemic [1]. In December 2020, vaccinations began in Europe. To date, forms of treatment are experimental [2]. The COVID-19 infection has caused 2 million deaths [3]. The infection is described in three phases: the first asymptomatic or slightly symptomatic, the second moderately severe characterized by a pulmonary inflammatory state, the third very severe characterized by a generalized inflammatory state affecting all tissues causing multiorgan dysfunction. In the more severe stages of infection, COVID-19 lung lesions are characterized by diffuse alveolar damage with irregular inflammatory cellular infiltration [4, 5].The literature data not only identify COVID-19 viral infections as a respiratory disease, but in more severe cases there may be involvement of other organs, such as the heart and liver, contributing to the development of serious complications [6]. Pharmacological treatment of the infection involves the use of antivirals, anticoagulants and immunomodulants [7–10]. In the most severe stages of infection, a generalized inflammatory state induced by a cytokine storm results in multiorgan dysfunction and tissue injury. The SARS-CoV-2 penetrates cells using the S protein through the angiotensin-converting enzyme receptor 2 (ACE-2) widely present in respiratory mucosa epithelial cells and other tissues. ACE-2 is also a conversion enzyme with a key role in the renin-angiotensin system (RAS) [11].

Cardiovascular complications

Patients with cardiovascular disease (CVD) have an increased risk of severity and mortality from COVID-19 infection [12]. Pulmonary and acute cardiac injury are the main severe clinical manifestations observed in patients infected with SARS-CoV-2 during the late phase of infection [13]. Numerous clinical evidence confirms that the severity of COVID-19 is pronounced in patients with a prevalence of underlying CVD, and in many of these patients the virus causes severe myocardial injury [14], including myocardial dysfunction, cardiomyopathy, arrhythmia, heart failure, and increased risk of thrombosis [6, 15, 16].

Cytokine storm

It is known that COVID-19 not only causes viral pneumonia but can also affect the cardiovascular and other systems. The most severe stages of COVID-19 infection are characterized by a hyperinflammatory state caused by a cytokine storm [17]. The term indicates the role of the immune system in producing an uncontrolled and generalized inflammatory response. This uncontrolled inflammatory response

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can be the cause of multiorgan dysfunction and responsible for severe lung injury and cardiac damage [18]. Cardiovascular complications of COVID-19 infection include acute coronary syndrome, pulmonary thromboembolism, myocarditis and potential arrhythmic effects. Several studies show that tumor necrosis factor (TNF-α) plays a central role in the depression of myocardial contractility through various time-dependent mechanisms with an inotropic adverse effect [19, 20]. Interleukin-6 (IL-6) is a powerful mediator of myocardial depression, which in turn improves the cardiodepressant effects of TNF-a and IL-1. The inotropic negative effect of IL-6 is the result of JAK2/STAT3 mediated activation of nitric oxide synthases, inducible isoform (iNOS). IL-1 also produces a prolonged decrease in myocardial contractility [21–23]. Finally, IL-18 stimulates proinflammatory cytokines with known cardiodepressant effects, such as TNF-a, IL-1a, IL-1b, IL-6. Through different mechanisms of action, the proinflammatory cytokines described above mediate contractile dysfunction and myocytic cardiac apoptosis with cardiac damage [24–26].

Natriuretic peptide system and Covid-19

Natriuretic peptides are a family of structurally related hormonal factors. Atrial natriuretic peptide (ANP) and type B natriuretic peptide (BNP) are secreted by the atria and cardiac ventricles. Type C natriuretic peptide (CNP) is the most highly expressed natriuretic peptide in the brain but is also highly expressed in chondrocytes and endothelial cells. Neutral neprilysin endopeptidase (NEP) is the enzyme that metabolizes natriuretic peptides. Natriuretic peptides mediate different physiological effects through interaction with specific guanylyl cyclase receptors (GCr) that induce intracellular production of cGMP [27, 28]. The main physiological effects are natriuresis/diuresis and peripheral vasodilation, inhibition of the RAS and sympathetic nervous system (SNS). In particular, some studies have demonstrated an antifibrotic and anti-inflammatory action associated with natriuretic peptides. The CNP, through selective binding to the transmembrane receptor GCr (guanylyl cyclase receptors), mediates different biological effects in various organs. CNP is expressed in a wide variety of tissues, such as vascular endothelium, heart, bones and adrenal glands [29, 30]. CNP plays an important role in the regulation of local vascular tone, and has been shown to have primarily cardioprotective, antihypertrophic and antifibrotic effects [31]. Recently, CNP has been shown to have protective effects against inflammation and also regulates the secretion of inflammatory cytokines. In the inflammatory phase, cytokine expression levels are high and exert a profibrotic activity through the activation and proliferation of fibroblasts. In association with evidence of antifibrotic and antihyperproliferative effects, studies also show direct antifibrotic effects mediated by the action of natriuretic peptides. In particular, some studies associate the BNP peptide with an important inhibitory effect on NALP3 (Nacht Domain-, Leucine-Rich Repeat-, and PYD-Containing Protein 3) inflammasome activation, which is related to NF-kB downregulation and BNP-induced ERK1/2 activation [32, 33]. The data indicate a powerful anti-inflammatory and immunomodulatory role for this peptide. BNP is synthesized as a prehormone (proBNP), upon release into the bloodstream it is divided in equal proportions into biologically active BNP and biologically inactive NT-proBNP. Stress and myocardial damage are the main release stimuli for BNP and NT-proBNP, studies have shown that increased cytokines and an inflammatory state are important additional factors inducing hormone secretion. BNP and NT-proBNP are important biomarkers for the evaluation of cardiac function. As described, cardiac lesions are a common condition among patients hospitalized with COVID-19 [34]. A recent study has shown that the NT-proBNP marker has increased significantly in more severe cases of COVID-19, suggesting a relationship between high plasma levels of NT-proBNP, cardiac damage and risk of death in patients with severe COVID-19. The explanation for the increase in NT-proBNP in severe COVID-19 is probably due to cardiac complications resulting from up-regulation of the RAS, cytokine cascade and systemic inflammation. In particular, cytokine storm could probably play an important role in cardiac damage and in the increase of NT-proBNP [35–38].

RAS and COVID-19

Several studies have shown that the variation in the RAS can be related to SARS-CoV-2 infection at all stages of severity. The ACE-2 has been identified as receptors, which are the sites of viral entry into in epithelial lung cells. Certainly, RAS activation is known to change in conditions, such as COPD, asthma, during viral infections and in smokers, showing that the system is related to proper lung and airway function [39, 40]. The evidence suggests that the physiological balance of the RAS system and especially between ACE/ACE-2 is probably altered by SARS-CoV-2 viral infection. This RAS imbalance is likely to play a role in pulmonary injury and activation of the inflammatory state. Studies in SARS-CoV-2 patients have shown that the expression of ACE-2 has a rapid increase in the first few hours of viral infection and then begins a rapid reduction in lung tissue when the patient enters the more severe stages of infection [41, 42]. This suggests that ACE-2 has a protective effect and when it decreases there is a worsening of the inflammatory lung state. In addition, it is noted that angiotensin II (Ang II), Ang 1–7 and Ang 1–9 have different biological effects. In fact, the biological effects of Ang II are vasoconstriction, myocardial hypertrophy, interstitial

fibrosis, endothelial dysfunction, increased inflammatory state and oxidative stress biological effects that, if altered, can cause serious complications in a patient with SARS-CoV-2 infection; however, it is important to note that all these biological effects are mediated by AT-1 receptors (AT-1r). ACE-2 can reduce the negative effects of Ang II through several mechanisms, for example through the conversion of Ang II to Ang 1–7 [43, 44]. Ang 1–7 has opposite biological effects to Ang II through the Mas receptor (MASr) and Ang II type II receptors (AT-2r). MASr stimulation has anti-inflammatory and antifibrotic effects [45, 46]. All the considerations expressed suggest a therapeutic pharmacological solution with the action to increase the concentration of circulating natriuretic peptides, decrease the concentration of NT-proBNP, increase the RAS through the ACE-2 axis with a greater synthesis of Ang 1–7 and Ang 1–9 with antifibrotic and anti-inflammatory effects, and decrease the effects of Ang II on the AT-1 receptor [47, 48].

Sacubitril/valsartan

Potential cardiovascular effect benefits in COVID-19 patients

Sacubitril is a NEPi, valsartan an angiotensin II receptor antagonist (ARB). Based on the above considerations, the association sacubitril/valsartan could bring therapeutic benefits to the patient with COVID-19 and cardiac involvement. The use of the sacubitril/valsartan association could be of clinical benefit for several reasons, in particular the antagonism of AT-1 receptor mediated by valsartan would lead to increased AT-2 receptor occupation by Ang II with antifibrotic, anti-inflammatory, antihyperproliferative and vasodilator effects with potential benefits on both pulmonary lesions caused by fibrotic tissue and cardiac damage caused by COVID-19. In addition, the actions of Ang-II on the AT-1r, which mediates vasoconstrictive, profibrotic and hyperproliferative effects, are blocked [49–51]. Finally, Ang II can cause increased inflammation through the production of IL-6, TNF-α and other inflammatory cytokines mediated by AT-1. Antagonism of AT-1 r leads to a compensatory increase of ACE-2 with a protective role [52, 53]. In fact, ACE-2 synthesizes Ang 1–7 and Ang 1–9 with known anti-inflammatory, vasodilator, antifibrotic and antihyperproliferative effects. Finally, after ARB administration the response to hypertrophic growth induced by TNF-a is significantly attenuated ([54–57]; Fig. 1).

The beneficial effects of NEPi are attributable to the decrease in the degradation of natriuretic peptides. Natriuretic peptides cause vasodilation by stimulating the guanylate cyclase receptor to produce cGMP. In addition, as already mentioned, natriuretic peptides also exert anti-inflammatory, antifibrotic and antihypertrophic effects. In particular, some evidence shows directly mediated anti-inflammatory effects. During this period doubts have emerged as to whether the increase in ACE-2 caused by ARB could be a risk factor for COVID-19 infection. To date, there is no evidence suggesting that the current treatment should be discontinued [58]. The pharmacological treatment of

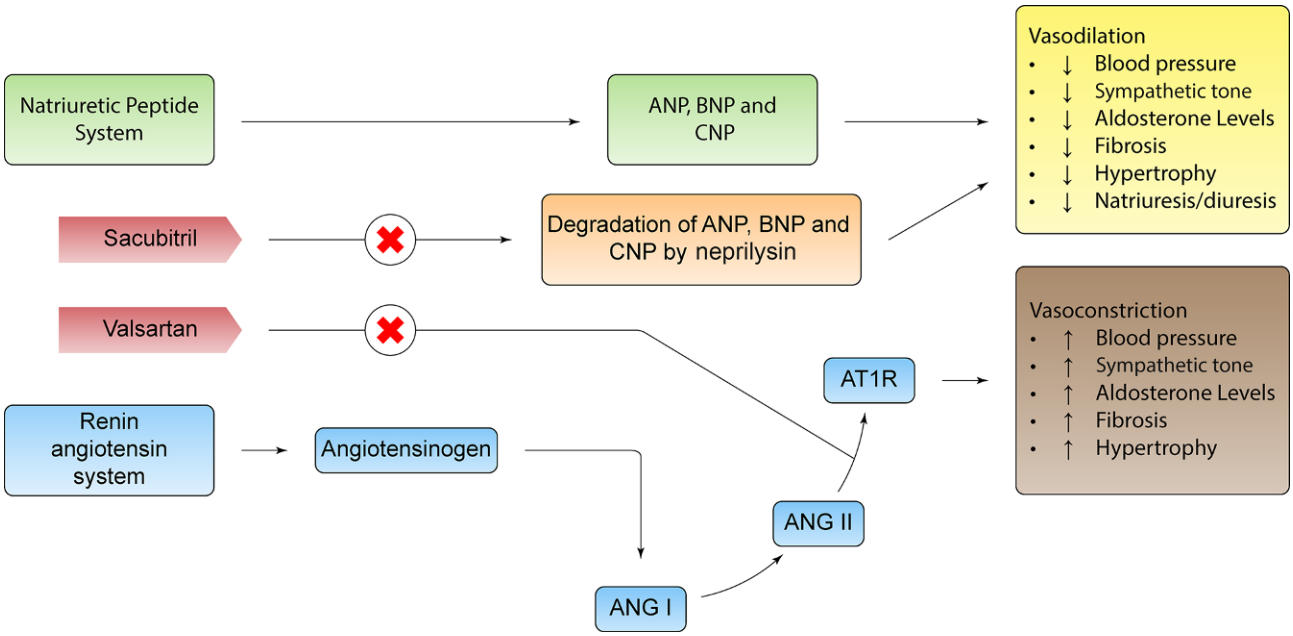

Fig. 1 Mechanism of action: sacubitril/valsartan association is neprilysin inhibitor and angiotensin II receptor blocker type-1 (AT-1 r). The complementary cardiovascular benefits of sacubitril/valsartan are attributed to the increase in neprilysin-degraded peptides and the simultaneous inhibition of the effects of angiotensin II. *ANP* atrial natriuretic peptide, *BNP* B-type natriuretic peptide, *CNP* C-type natriuretic peptide, *ANG I* Angiotensin I, *ANG II* Angiotensin II

the severe covid 19 patient should be carefully monitored and the safety profile of the therapeutic agents evaluated [59, 60].

Conclusion

On the basis of the evidence described and in relation to the hypotheses suggested the use of the sacubitril/valsartan association in patients with COVID-19 and cardiac involvement could be of therapeutic benefit, with cardioprotective, anti-inflammatory and antifibrotic effects able to reduce the damage caused by COVID-19 on the cardiovascular system, through an increase in the natriuretic peptide system and a decrease in the effects of Ang-II mediated by the AT-1 receptor. Well-structured clinical studies are required to confirm these hypotheses [61].

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

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