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Physiopathology and prospectives for therapeutic treatment of pulmonary fibrotic state in COVID-19 patients

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ABSTRACT

The COVID-19 global pandemic has caused about 4,30 Mln deaths. Recently the first vaccines have been licensed, representing the most powerful weapon available to stop the pandemic. The COVID-19 viral infection in the most severe cases can cause severe lung lesions with the presence of fibrotic tissue. Even among cured individuals, the presence of pulmonary fibrotic tissue may be the major cause of long-term complications of COVID-19 requiring antifibrotic therapeutic treatment even in the post-COVID-19 infection phase to accelerate the healing process and fully recover lung function. This article reviews the fibrogenic mechanism of SARS-CoV-2-induced viral damage and the antifibrotic treatments indicated to treat sequelae post COVID-19 infection.

1. Background

In November 2019, a sudden surge of patients admitted to hospitals in Wuhan, China, due to severe pneumonia of viral origin was identified (Wang et al., 2020a). The rapid exponential increase in the number of cases suggested the possibility of human-to-human transmission (Huang et al., 2020; Li et al., 2020a). On January 7, 2020, Chinese scientists isolated a new coronavirus from samples taken from the airways of hospitalized patients (Zhu et al., 2020). This viral agent has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Islam and Iqbal, 2020). The World Health Organization (WHO) declared this new viral disease a global public health emergency on January 30, 2020, and subsequently declared SARS-CoV-2 global pandemic status (COVID-19) on March 11, 2020 (Guarner, 2020). To date, data record 400 Mln infected and 4,30 Mln deaths worldwide. SARS-CoV-2, following spike (S) protein binding, penetrates host cells via attachment to the angiotensin-converting enzyme-2 (ACE2) receptor. After endocytosis, the viral RNA genome is released into the host cell. ACE-2 is expressed in numerous tissues; therefore, it is believed that SARS-CoV-2 can penetrate and infect several target organs, from the lungs to the heart, liver, and testes (Zhou et al., 2020a). Transmission occurs from human to human (Wang et al., 2020b). The onset of the first symptoms of the disease has been reported within a period of 14 days after exposure to the virus. Current epidemiologic evidence indicates that the highest

morbidity affects individuals of advanced age and with preexisting comorbidities. Because of the urgency and rapidity of action, treatments used to treat infection have been experimental and mostly indicated to avoid serious complications (Shi et al., 2020; Yang et al., 2020). Recently, the first vaccines have been licensed, using mRNA, viral vector and protein subunit methods (Vitiello et al., 2020a; Vitiello and Ferrara, 2020a). Pulmonary fibrosis caused by SARS-CoV-2 is an important clinical consequence of COVID-19 infection. Pulmonary fibrosis is also a common sequela of COVID-19 patients in recovery, compromising quality of life in some cases. Evidence has shown that cytokines involved in the development of pulmonary fibrosis are increased in severe COVID-19 patients, this suggests that pulmonary fibrosis plays an important role in the development of severe disease in COVID-19 patients.

1.1. SARS-CoV-2 and pulmonary fibrosis

Evidence shows that COVID-19 viral infection can exacerbate preexisting respiratory diseases, particularly pulmonary fibrose (PF). A direct pathophysiologic relationship between COVID-19 viral infection and stable or progressive fibrosis is not entirely clear, although some data suggest a potential fibrosis caused by the infection, even after recovery from the virus (Zhou et al., 2020b; Naik and Moore, 2010). Fibrosis may take a course as a stable disease in response to infection, or progressive

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also characterized by periods of rapid exacerbation. COVID-19 can cause lung lesions with the presence of fibrotic tissue even after virus eradication. The fibrotic lung condition may be associated with a thickening of the alveolar walls obstructing the normal physiology of gas exchange and decreasing lung function. COVID-19 patients with symptomatic and then cured disease are at increased risk of developing fibrotic disease and long-term damage (George et al., 2020a). Therefore, it is critical to know the pathophysiological pathways activated by COVID-19 to identify the most effective targeted treatments to accelerate resolution and the healing process (Vitiello and Ferrara, 2021b; Vitiello et al., 2020b). Although to date, the genetic predisposition that makes some individuals more susceptible to severe COVID-19 infection than others is still unclear, in view of the very high number of infected individuals, the best therapeutic strategies to treat the current infection, but also the post-infection sequelae, must be identified.

1.2. Pathophysiology of pulmonary fibrotic/inflammatory state by SARS-CoV-2

Bilateral interstitial pneumonia caused by COVID-19 infection is associated with the presence of fibrotic tissue caused by excess collagen (fibrosis) in the pulmonary interstitium with hyperinflammation present. SARS-CoV-2 infection in its most severe stages is characterized by a generalized hyperinflammatory state, induced by a cytokine storm, causing pulmonary and multi-organ injury. This massive and sudden release of proinflammatory cytokines, such as tumor necrosis factor alpha TNF- α and interleukin-1-beta (IL-1 β) causes acute inflammatory fibrotic lung disease. At this stage of infection COVID-19, activated macrophages

contribute to the induction of neutrophil recruitment (Ye et al., 2020) contributing to the generation of reactive oxygen species (ROS). This response is useful in eliminating the virus, but in excess and abnormal can result in tissue damage (Deng et al., 2020; Herbert et al., 2020). In addition, activation of fibroblasts deposits collagen to repair tissue damage. However, even when the fibroblast response is unregulated it can cause increased thickness, stiffness, and alteration of the normal structure of the lung pathways. Some evidence shows that the formation of fibrotic lung tissue in severe COVID-19 patient is also caused by an excess of chemokines (Blanco-Melo et al., 2020). Moreover, activated macrophages and fibroblasts produce large amounts of TGF β which produces increased extracellular matrix, collagen deposition, and subsequent increase in tissue stiffness. From a molecular point of view, other mechanisms are responsible for the formation of pulmonary fibrotic tissue in COVID-19 patients. In particular, SARS-CoV-2 penetrates cells through the ACE-2 receptor, this is expressed in alveolar pneumocytes. ACE2 is a regulator of the renin-angiotensin system (RAS). The RAS system consists of a classical ACE-dependent pathway and a nonclassical ACE-2-dependent pathway. In severe stages of COVID-19 infection, a dysregulated RAS system may contribute to excessive production of Ang II, synthesized by the classical ACE-dependent pathway, with profibrotic, and inflammatory effects. In contrast, the non-classical ACE-2 pathway appears to be reduced, with decreased production of antifibrotic and anti-inflammatory mediators such as Ang (1-7) and Ang (1-9) (Vitiello and Ferrara, 2020; Vitiello et al., 2021a). Increased Ang II causes activation of tumor necrosis factor- α (TNF α), interleukin (IL)-6, TGF β , and increased recruitment of neutrophils and macrophages, which are critical factors in a fibrotic response. However, the increase in these described

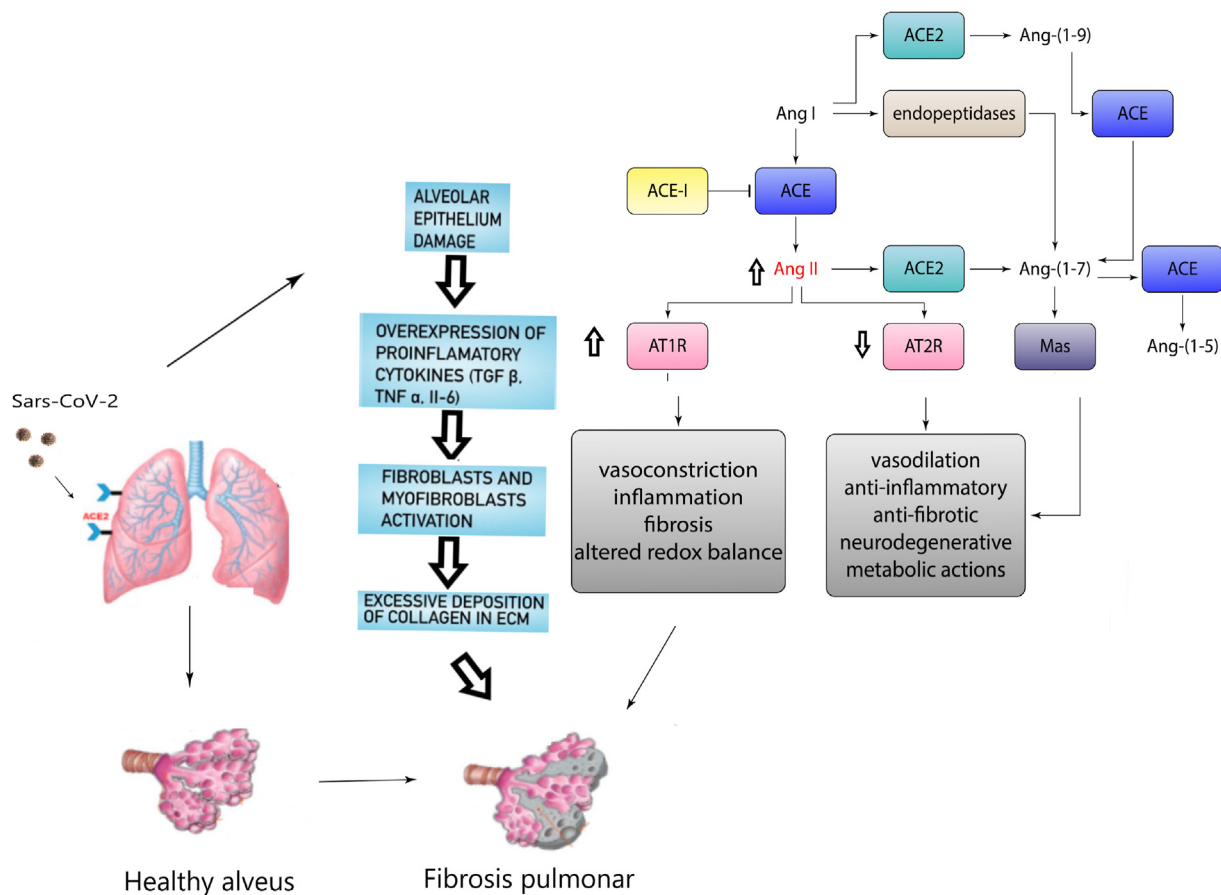


Fig. 1. Schematic representation of fibrotic tissue caused by COVID-19 infection and RAS system dysregulation: SARS-CoV-2 penetrates lung cells via ACE-2. In the most severe stages of infection the hyperactive inflammatory state, recruitment and activation of macrophages, fibroblasts and neutrophils, decrease of ACE-2 and overproduction of Ang II cause inflammation, deposition of extracellular matrix, formation of fibrotic tissue.

proinflammatory factors, increased Ang II, and activation of downstream mediated pathways should be carefully considered and evaluated even after recovery from COVID-19 (Fig. 1).

In the most severe phases of the infection, a generalized inflammatory state induced by the cytokinetic cascade may appear, and in parallel a state of systemic hypercoagulability characterized by the tendency of venous, arterial and microvascular thrombosis. In these subjects high levels of D-dimer and fibrinogen alterations, a slight prolongation of the prothrombin time are frequently detected. The consequent damage to the alveolar epithelium causes the release of pro-inflammatory cytokines and excessive deposition of collagen, with the formation of fibrotic tissue (Fig. 1). Several studies also show ARDS in the lungs and microangiopathic, hemorrhagic and thrombotic phenomena with widespread alveolar damage.

The direct viral damage at the endothelial level is determinant in the hyperactivation of coagulation (Varga et al., 2020). The damage to the endothelium can cause circulatory dysfunction, vasoconstriction, with consequent ischemia and inflammation of the microcirculation. In addition, the inflammatory state itself is an important trigger for the coagulation cascade. Finally, the platelet component of coagulation is also activated during COVID-19 infection. In autopsy lung tissue, the abundant presence of megakaryocytes suggests a correlation with the finding of widespread small platelet-rich thrombi. Platelets, in fact, can promote an immune-mediated response causing tissue infiltration and, in critical phases, thrombocytopenia. The latter is essentially always present in severe pictures of COVID-19 disease (Pick et al., 2017; Moreau et al., 2007). This shows that the mechanism of pulmonary fibrosis in COVID-19 is different from that in IPF and other fibrotic lung diseases.

2. Risk factors of pulmonary fibrotic/inflammatory state by SARS-CoV-2

Some evidence shows that certain risk factors such as age, severity of COVID-19 disease, use of mechanical ventilation, and smoking may contribute more to the development of pulmonary fibrosis (Ojo et al., 2007). Elderly patients are more likely to develop severe symptoms from COVID-19. Laboratory evidence indicates that elevated lactate dehydrogenase (LDH) levels correlate with increased disease severity and risk of developing pulmonary fibrosis. LDH is an indicator of lung tissue destruction and correlates with mortality risk. Severe COVID-19 patients may require intensive care. Mechanical ventilation may be an additional risk factor for ventilator-induced lung injury (VILI). Ventilator-induced lung injury is an acute lung injury resulting from or exacerbated by mechanical ventilation that leads to the release of proinflammatory mediators, presence of pulmonary fibrosis, and increased mortality. In a follow-up study of 27 patients undergoing mechanical ventilation for ARDS, 110–267 days after extubation, 23 patients (85%) had pulmonary fibrosis with a significant relationship to duration of ventilation (Ojo et al., 2007).

2.1. Pulmonary fibrotic state post COVID-19 infection

To date, there is open debate whether individuals recovered from COVID-19 infection with sequelae, may present with irreversible airway damage with the presence of progressive post-infection fibrose or reversible damage that with appropriate therapy may recur. Other outbreaks caused by similar viruses such as MERS or SARS-CoV suggest that post-infection pulmonary fibrose could be a problem. Epidemiologic evidence indicates that 33% of patients recovered from MERS had pulmonary fibrose in the postinfection setting (Varga et al., 2020). Studies of SARS-CoV have indicated that 27.8%–62% of patients infected with SARS-CoV showed decreased lung function and increased fibrose (Das et al., 2017; Chan et al., 2003). In a 15-year follow-up from the 2003 SARS outbreak, 9% of study participants experienced fibrose after infection, and this percentage decreased within 1 year and remained stable until a 15-year follow-up in 2018 (Hui et al., 2005b). The study

found that most patients recovered from interstitial damage and functional decline within 2 years of rehabilitation. What proportion of COVID-19 patients developed pulmonary fibrose remains speculative and should not be assumed without an appropriate prospective study. A study shows (Zhang et al., 2020) Lung lesions in 64.7% of discharged patients were completely absorbed after 4 weeks of follow-up. This indicated that lung damage caused by COVID-19 might be reversible for common COVID-19 patients. It also suggested that the prognosis of non-severe patients is favorable, and clinical intervention should be conducted in time to prevent common COVID-19 patients from worsening into severe patients. Many studies have shown that the most common abnormality of lung function in survivors discharged with COVID-19 is impaired diffusion capacity, followed by restrictive ventilatory defects, both of which are associated with disease severity (Liu et al., 2020; Nusair, 2020). The cytokine storm that occurs in the most severe stages of infection can lead to the initiation and promotion of pulmonary fibrosis. Dysregulated release of matrix metalloproteinases, VEGF, and cytokines cause epithelial and endothelial damage in the airways. In particular, some individuals develop progressive pulmonary fibrosis induced by the accumulation of fibroblasts excessive collagen deposition.

2.2. Molecular biomarkers

Pulmonary fibrosis has been identified as the major cause of lung dysfunction in patients who survived severe SARS-CoV-2 infection. Thus, there is an urgent need to identify biomarkers for early detection of post COVID-19 infection patients at risk of developing persistent lung fibrosis with subsequent risk of mortality. Probably the data and knowledge acquired on the pathophysiological mechanisms of lung fibrosis can also be used to identify post-COVID-19 patients at higher risk of persistent fibrotic lung damage by directing the best choices of drug treatment. A number of noninvasive, serologic biomarkers may be important to rapidly detect tissue remodeling and fibrosis, and subsequent decline in lung function (Mo et al., 2020). In the absence of pathology, the extracellular matrix (ECM) in the airways separates capillaries from the alveolar space and allows gas diffusion. In the presence of fibrotic tissue, the ECM expands limiting this function. The fibrotic ECM is composed of fibronectin and collagen types I, III, and VI (Leeming et al., 2021). An important tool to prevent COVID-19 development of pulmonary fibrotic tissue is to understand the effects of COVID-19 infection on pulmonary ECM remodeling using appropriate markers. Neoepitope technology is useful to detect the generation of newly formed epitopes of collagens and other ECM proteins that form during fibrosis (Karsdal et al., 2017; Sand et al., 2016). These neoepitope markers may be associated with the progression of Pulmonary Fibrosis in COVID-19 patients. The value of D-Dimer may also be considered, in severe COVID-19 patients there is dysregulation of coagulation.

A study stratified a sample of 239 patients with pulmonary fibrosis during hospitalization according to their degree of pulmonary fibrosis at discharge, biological marker and their clinical characteristics were analyzed. Patients with and without pulmonary fibrosis had statistically significant differences in age, IL-6 levels, % lymphocytes, aspartate transaminase (AST), albumin, CRP/albumin ratio, and platelet/lymphocyte ratio, suggesting that these abnormal clinical indicators may be related to pulmonary fibrosis (Karsdal et al., 2020).

Antifibrotic treatment post COVID-19 infection needs to be undertaken in a timely manner in order to accelerate the healing process and resume full lung function.

2.3. Pharmacological treatment of COVID-19 pulmonary fibrosis

The management of drug treatments of the severe COVID-19 patient is complex. The benefit/risk ratio of the pharmacologic agents used should be carefully monitored (Zubairi et al., 2018; Ferrara, 2020). Appropriate use of medications may reduce the risk of severe COVID-19

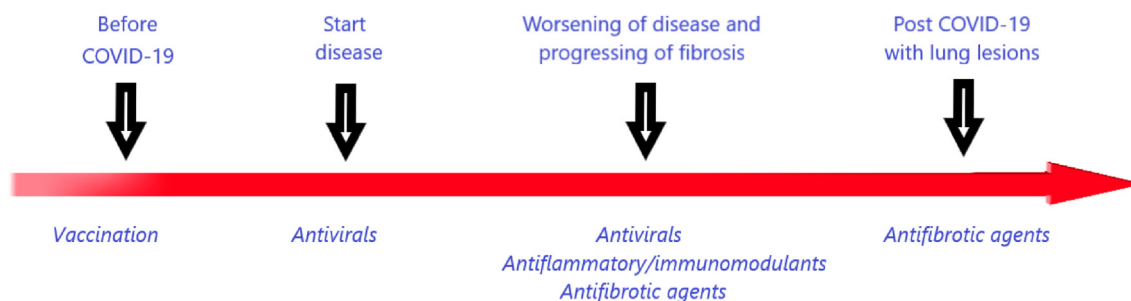


Fig. 2. Schematic view on timing of drug treatment to avoid/reduce pulmonary fibrotic tissue formation by COVID-19.

complications and postinfection sequelae. To date, no fully proven epidemiological evidence is available for the treatment of post COVID 19 infection pulmonary fibrose, in this direction various treatment strategies are being evaluated. It has been proposed that the appropriate use of antivirals, antifibrotics (Vitiello et al., 2020c, 2021b), and anti-inflammatory agents reduces the risk of developing pulmonary fibrose. However, among the antivirals and anti-inflammatory drugs, it is yet to be fully elucidated which of them has the greatest efficacy in preventing lung remodeling and fibrosis. Synthetic glucocorticoid drugs and interleukin inhibitors (eg, Tocilizumab, Sarilumab) used in severe phases of COVID-19 infection, by reducing the hyperactive and generalized inflammatory state may indirectly also prevent the formation of fibrotic lung tissue (Vitiello et al., 2021c). Same rationale for use also applies to colchicine. The use of large doses of glucocorticoid drugs could worsen hyperglycemia and contribute to proximal myopathy, which in turn would delay patients' mobility and rehabilitation (Ferrara and Vitiello, 2021a). Pirfenidone and nintedanib, are drugs used for the treatment of Idiopathic Pulmonary Fibrosis (IPF) (Vitiello et al., 2021d; Ferrara et al., 2020c). They are drugs with pleiotropic, antifibrotic, antioxidant, and anti-inflammatory effects that can be used in the acute phase of COVID-19 infection and in the pharmacological treatment of the post COVID-19 pulmonary fibrotic state, for a better and faster healing process (Ferrara and Vitiello, 2021b; Vitiello and Ferrara, 2021c). In particular, pirfenidone possesses anti-inflammatory activity by suppressing the activation of the NLRP3 inflammasome. Probably the use of pirfenidone immediately at the onset of acute respiratory syndrome from SARS-CoV-2 may prevent more consequences such as pulmonary fibrosis (Ferrara et al., 2020a,b; Ferrara and Vitiello, 2020; Haschke et al., 2013; Hui et al., 2005a; Khan et al., 2017). In addition, it should be considered that both of these antifibrotic drugs require at least 1–3 months to demonstrate a clinical efficacy effect. This has been demonstrated in the INBUILD, and INPULSIS studies (Wells et al., 2020; Crestani et al., 2019). Thus, the time of initiation of antifibrotic treatment is critical; adding them at a late stage in patients requiring ventilatory support may not be optimal. Patients with the most severe ARDS are best suited for anti-fibrotic therapy. Such patients will generally require prolonged ventilation with high oxygen requirements, and perhaps antifibrotics along with steroids (which have already become the standard of care) could play a role in preventing or delaying the fibrosis that many of these patients will develop. Another interesting line of research to prevent and reduce the pulmonary fibrotic state in post COVID-19 infection patients is to act on the RAS system. As described above, decreased expression of ACE-2 and increased synthesis of Ang II may result in inflammatory and profibrotic effects. Several agents under consideration could include soluble recombinant human ACE2 (hrsACE2) with a dual mechanism of action anti COVID-19, 2 binds the viral spike protein neutralizing SARS-CoV-2, and minimizes damage to multiple organs, including the lungs, kidneys, and heart, by reducing Ang II concentrations and increasing conversion to Ang (1–7) with anti-inflammatory antioxidant and antifibrotic effects. Another novel approach in this direction is the use of the ACE2-like enzyme (Ferrara and Vitiello, 2021c; Monteil et al., 2020). An example of such experimental agents is B38-CAP. B38-CAP shares structural

similarity with ACE2. In vitro evidence shows that the recombinant B38-CAP protein catalyzes the conversion of angiotensin II to Ang 1–7. Finally, another approach in this direction is the administration of Ang-derived plasma (1–7) in COVID-19-positive patients. Several clinical trials are underway to confirm these interesting hypotheses (Kuba et al., 2005; Minato et al., 2020; Vitiello and Ferrara, 2021b, Vitiello and Ferrara, 2021a). Thus, the identification of biomarkers from the onset of COVID-19 infection is urgently needed to identify patients who are likely to progress to pulmonary fibrose. The use of anti-inflammatory and antibiotic therapy should be tailored with careful monitoring of the benefit/risk profile of the agents used (Fig. 2).

One of the most promising therapeutic approaches in the treatment of post COVID-19 pommel fibrosis is stem cell therapy (MSC) (Li et al., 2020b). Infection with COVID-19 triggers an exaggerated exaggerated immune reaction in the body by producing large amounts of various inflammatory factors including several cytokines, chemokines, and immunoreactive cells. MSC therapy could prevent the triggering of the cytokine storm by the activated immune system, and the reparative properties of stem cells could promote endogenous repair (Vitiello et al., 2021e; Vitiello and Ferrara, 2021d). In addition, novel antifibrotic therapies may include molecules that block integrins and galectins in the TGF-beta pathway, and also act to inhibit viral infection (George et al., 2020b). Another treatment in Covid-19 are PDE4 inhibitors (PDE4i). These have recently been suggested as promising molecules to beat the severe inflammation in Covid-19 by acting to block the infiltration of neutrophils, monocytes, and lymphocytes and to reduce the production of inflammatory cytokines and chemokines from these cells and the lung epithelium (Bridgewood et al., 2020). Finally, those who have had significant respiratory disease may benefit from pulmonary rehabilitation.

3. Conclusions

Severe acute infection occurring in the airways of severe COVID-19 patients is a disease that can lead to pulmonary fibrosis and permanent disability.

There are few options available for its treatment. The most important factor in limiting pulmonary fibrosis is early, timely antiviral treatment and elimination of the causative viral agent, and anti-inflammatory treatment with glucocorticoids directed at reducing the inflammatory state that generates pulmonary fibrosis. In addition, antifibrotic therapies consisting of pirfenidone, nintedanib, and promising MSC therapy may be considered. In addition, another important line of research is the use of molecules that act on the RAS system. Well-structured clinical trials are needed to generate additional and urgent evidence in this direction.

Ethical approval

Not applicable

Consent to participate

Not applicable

Consent to publish

The authors consent to the publication of the manuscript

Authors contributions

AV: Conceptualization, Writing - original draft, Methodology, Writing - original draft. FF: Writing - review & editing, Supervision, Validation. All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used

Founds

None

Availability of data and materials

Full availability of data and materials.

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The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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