General review • 10.2478/pneum-2024-0014 • 72 • 2023 • 90-96

Pneumologia

Nintedanib: beneficial agent in post-COVID-19 Pulmonary Fibrosis

Victoria Țau[1], Andreea Zabară Antal[1,2,*], Paula Vasilache Antohi[1], Ioana Adelina Stoian[1,2], Adriana Loredana Pintilie[1], Antigona Carmen Trofor[1,3], Radu Adrian Crișan-Dabija[1,3]

[1]Clinical Hospital of Pulmonary Diseases Iași, 700116 Iasi, Romania
[2]Doctoral School, Faculty of Medicine, University of Medicine and Pharmacy "Grigore T. Popa", 700115 Iași, Romania
[3]Pulmonary Department, Faculty of General Medicine, University of Medicine and Pharmacy "Grigore T. Popa," 700115 Iași, Romania

Abstract

English:

The pandemic of the coronavirus disease 2019 (COVID-19) has affected millions of people worldwide. Patients can develop a lot of different manifestations, from asymptomatic form to severe acute respiratory distress syndrome (ARDS). Pulmonary fibrosis, as a primary cause of mortality, is the main consequence of lung injury caused by acute respiratory distress syndrome. Unfortunately, effective treatment for pulmonary fibrosis has not yet been found; that's why we found an essential anti-fibrotic agent in the early acute phase of severe COVID-19 to fight the infection outcomes. This narrative review presents the therapeutic strategy and the importance of fighting pulmonary fibrosis to help patients worldwide protect themselves against severe and fatal viral infections. To prevent long-term sequelae and early mortality, it's necessary to test the efficacy of anti-inflammatory drugs.

Keywords

Coronavirus • lung fibrosis • Immune response • Respiratory syndrome • anti-fibrotic agent • Nintedanib

Eficiența nintedanib-ului în fibroza pulmonară post-COVID-19

Rezumat

Romanian:

Pandemia COVID-19 a afectat milioane de oameni în întreaga lume. Pacienții pot dezvolta o multitudine de manifestări diferite, de la forma asimptomatică la sindromul de detresă respiratorie acută severă (ARDS). Fibroza pulmonară, ca principală cauză a mortalității, reprezintă principala consecință a leziunilor pulmonare cauzate de sindromul de detresă respiratorie acută. Din păcate, încă nu s-a găsit un tratament eficient pentru fibroza pulmonară; de aceea, am identificat un agent anti-fibrotic esențial în faza acută timpurie a COVID-19 sever pentru a combate consecințele infecției. Această recenzie narativă prezintă strategia terapeutică și importanța combaterii fibrozei pulmonare pentru a ajuta pacienții din întreaga lume să se protejeze împotriva infecțiilor virale severe și fatale. Pentru a preveni sechelele pe termen lung și mortalitatea precoce, este necesar să se testeze eficacitatea medicamentelor antiinflamatoare.

Cuvinte-cheie

Coronavirus • fibroză pulmonară • răspuns imun • sindrom respirator • agent anti-fibrotic • Nintedani

1. Introduction

The global pandemic, declared in December 2019 as a novel coronavirus, was recognized to be the cause of a cluster of patients with pneumonia [1]. COVID-19 was declared a global pandemic on March 11, 2020 [2]. The structure of SARS-CoV-2 is very similar to that of the severe acute respiratory syndrome (SARS) virus; both infect pulmonary epithelial

*Corresponding author: Andreea Zabară Antal
E-mail: zabara-antal_andreea@d.umfiasi.ro

cells by a simple mechanism of binding to the receptor of angiotensin-covering enzyme 2 (ACE2). The most severe complication, including ARDS, is death. As of December 2022, 650 million COVID-19 cases and more than 6.6 million associated deaths have been reported globally [3].

The clinical manifestations of COVID-19 include cough, fever, dyspnoea, and respiratory pain. The infection can develop into severe respiratory complications, such as pneumonia or acute lung injury. There are a lot of comorbidities that cause higher mortality, such as cardiovascular disease, diabetes Mellitus, hypertension, obesity, chronic lung disease, chronic liver disease, chronic kidney disease, smoking, and malignancy. All of them contribute to ARDS, a syndrome related to an overactive innate immune response. The neutrophils and macrophages become hyperactive and release pro-inflammatory cytokines, causing cytokine storm and severe immune cell inflammation in the lung. Pulmonary fibrosis is mediated by the regulatory cells (Tred) that become dominant to generate a sequel to ARDS in the later stage. ARDS is a respiratory disorder.

The most significant risk factor for developing ARDS is septicemia. The key in the pathophysiology of symptomatic bacteremia due to bacterial infection is PMN. TH17 immune reaction with PMN overactivity begins the pathogenesis of ARDS.

The stages in the development of ARDS

There are three stages in the development of ARDS [4]. The first one is the exudative phase, which includes the damaged alveolar capillary endothelium and type I pneumocytes inducing the loss of the alveolar barrier function and accumulation of protein-rich edema fluid in interstitial alveolar spaces that contribute to atelectasis, followed by intrapulmonary shunting and hypoxia [5]. The microvascular occlusion leads to increased alveolar dead space and pulmonary hypertension. The second stage is proliferative, and a good part of patients recover, but some of them suffer from progressive lung injury and early fibrosis initiated by fibrosis markers. This is an organizing phase with loose organizing fibrosis, mainly within the alveolar septa, and type II pneumocyte hyperplasia. The third is the fibrotic stage, when several patients may require mechanical ventilators to maintain respiratory function [6]. On the upper respiratory tract, this virus can bind to the angiotensin-converting enzyme two receptors [7], increasing angiotensin2, neutrophils and macrophages, and direct endothelial injury [8]. Angiotensin 2 is also responsible for regulating collagen1 and transforming growth factor-β (TGF-β), the primary factor in fibrosis. Metalloproteinases are subjected to an uncontrolled production and injury of epithelial and endothelial during the inflammatory phase of ARDS. VEGF and cytokines such as IL-6 and TNFα are also implicated in the fibrotic process. It remains why specific individuals can recover from such an insult. In contrast, others develop an accumulation of fibroblasts and myofibroblasts and excessive collagen deposition, resulting in progressive pulmonary fibrosis.

The most crucial role of macrophages or monocytes, which can exert a proinflammatory or an antiinflammatory effect based on the microenvironment in different stages, is also well established. Abnormal immune mechanisms initiate and promote pulmonary fibrosis, possibly due to a cytokine storm.

The consequences of ACE2 engagement in virus infection leading to fibrosis

The critical role in maintaining blood pressure homeostasis and leap balance, which is also incriminated in acute lung diseases such as ARDS, is the system renin-angiotensin. The RAS is involved in pulmonary fibrosis and particularly the following actions of angiotensin I (Ang I), which is divided by angiotensin-converting enzyme (ACE) into angiotensin II (Ang II). In this manner, Ang II advances inflammatory and fibrotic answers through the Ang II type 1 receptor (AT1R) [9]. The other potency in the RAS requires a split of Ang I into Ang (1-9), forgiven by the angiotensin-converting enzyme 2 (ACE2), and counteracts the ACE arm.

More recent circumstances of Ang (1-9) result in a depreciation of inflammation and fibrosis through the Mas receptor. Subsidiary, ACE2 reacts on Ang II by converting it into an Ang (1-7) peptide, reducing inflammation. The ACE2 thus functions as a negative regulator of the angiotensin system [9]. The guest access of SARS-CoV-2 is adjudged through binding to membrane-anchored ACE2, like SARS-CoV in SARS. Supplementary, the transmembrane protease serine 2 (TMPRSS2) and certainly coupled proteases, e.g., ADAM17, advance SARS-CoV-2 entry by ACE2 division, which includes viral absorption, inclusion to activating the S protein of the virus for membrane fusion [10]. Soluble ACE2 has two particularities, one of which is protection by binding the coronavirus, impeding endocytosis. In patients with severe COVID-19 infection, the ACE2 has been seen to be increased in injured lung tissue compared to healthy lung tissue, along with augmented plasma levels of ACE2 [11]. Soluble ACE2, increased, can be favorable with downstream action of Ang (1-7) containing inflammation and fibrosis, including membrane-bound ACE2, which is also regulated in smokers, older people, and diabetes, allowing the virus with the richness of access points. The patient's high risk of severe disease can be explained by adipocytes from abdominal fat, which have an expressed ACE2, which may serve as a cistern for SARS-CoV-2.

The advanced binding chances for the virus, intercession with ACE2 activity, and its advantageous anti-inflammatory and antifibrotic effects proved the weak prognosis and risk

of developing pulmonary fibrosis. This opposite benefits the ACE-/Ang II arm, pressing into enhanced inflammation and fibrosis. To counter the molecular events increased in COVID-19 infection over ACE2 binding and following events, the RAS plays a crucial function in the pathogenesis of COVID-19 and other lung diseases.

The effect of molecules in the pathogenesis of pulmonary fibrosis

Between infection, Covid-19 and IPF have changed the balance of the RAS and the levels of VEGF and IL-6. The mechanism of activating the ACE-/Ang II arm is the increase of IL-6 and the reactive oxygen species (ROS). This attacks the TGF-β pathway, which is familiar to be highly included in fibrosis. Known as regulators of the inflammatory and fibrotic response in IPF, COVID-19, IL-6, and IL-1 subscribe to the severe cytokine storm. In extreme cases of COVID-19, IP-10, MCP-3, and IL-1 RA, like an inflammatory mediator, connect to ARDS to activate various immune cells and counter pulmonary fibrosis.

In IPF, we found increased expression of CXCL13 and matrix metallopeptidase 7 (MMP7) as a predictive marker for IPF. At the end of these determinations, coronaviruses depend on host MMPs and other proteases, such as TMPRSS2, for cell penetration, survival, and replication, better implicating pathways in pulmonary fibrosis and COVID-19.

Fibrosis caused by chronic inflammation

It is acknowledged that chronic inflammation influences the tissue microenvironment and mostly, seen in the severe phase of COVID-19, causes fibroblastic stimulation and increased generation of extracellular matrix components, MMPs, and tissue inhibitors of MMPs, which help to counteract the injuries provoked by inflammation, including ROS, proteases, and other constructive molecules. The saving response increases the condensation of the parenchyma and induction of fibrosis in COVID-19—this method modifies the biomechanics of the lung and, consequently, lung function. Like in IPF, these events may cause chronic pulmonary fibrosis, showing a wooden tissue with less compliance. The most important thing is that fibrosis can spoil biomechanical properties as it improves tissue damage, even though it is inhomogeneously ubiquitous in the lungs. In agreement with this, the response of the cells to the environment that makes part of the stringent IPF lung tissue involves particular cellular responses being included in disease progression. This self-propagating cellular response towards the non-flexible microenvironment produces the accumulation of extracellular matrix proteins that contain deposition of glycosaminoglycans. This is an essential switch in the amount and structure of glycosaminoglycans in IPF; precisely, highly sulfated heparan sulfate was observed in the border zone between highly fibrotic areas and more normal structures of the distal lung. The processes like altered cellular activity and further propagation of fibrosis participate, besides the changes in glycosaminoglycans, the release of development of factors like TNF-α, IL-6, and TGF-β.

Imaging changes observed at CT of post-covid pulmonary fibrosis

On computer tomography (CT), lung fibrosis represents ground-glass opacities, interstitial thickening, irregularity of the interface, and bands throughout the lung parenchyma [7]. We see many results in a review that compared the initial and worst-state Ct imaging to look over the process of COVID-19 pneumonia and imaging marks that suggest the genesis of fibrosis. They may be from a simple ground-glass opacity, noticed as the most common CT features in COVID-19 pneumonia, to a ground-glass opacity consolidation, interstitial thickening, crazy paving, irregular interface, and parenchymal band in bilateral lower lobes with peripheral distribution. On worst-state CT imaging, more segments and a big lesion diameter of progression were involved. Compared to initial CT, worst-state CT evidenced irregular interface and parenchymal band. After a while, the typical features such as interstitial thickening and crazy paving can disappear, but evidence of fibrosis, such as irregular interface and parenchymal band, were still manifest. These reactions indicate that the quirky interface and parenchymal band may have been demonstrated during COVID-19 pneumonia, while part of them was finally resolved. Even if many other lesions were gradually absorbed, only ground-glass opacity rests like an exception of residual form of pulmonary fibrosis. In conclusion, we show that pure ground-glass opacity, with consolidation, interstitial thickening, crazy paving, irregular interface, and parenchymal band, were the most common CT features in COVID-19. Patients with severe clinical conditions and with high inflammatory indicators can develop fibrosis. The formation of early pulmonary fibrosis can be demonstrated by irregular interface and parenchymal band.

We can see that about 25% of patients who have ARDS will manifest on pulmonary function tests in the next six months as a progressive restrictive lung disease [8]. Prolonged illness caused by ARDS can be a significant risk factor for progression to fibrosis.

Patients with post-ARDS fibrosis show a lack of progression in pulmonary function in comparison to idiopathic pulmonary fibrosis. Another difference between post-COVID and idiopathic fibrosis is the absence of acute exacerbations.

IPF vs post-COVID fibrosis

IPF is a progressive disease, described as an irrevocable decline in lung function, responsible for respiratory failure

and, finally, death. There is a single treatment that improves outcomes, and it is transplantation. The incidence of IPF is rising, and the disease is estimated to affect 3 million people worldwide [12, 13]. Two antifibrotic drugs, pirfenidone and nintedanib, are the best treatment in the fight against IPF. Due to the rapid and global spread of COVID-19 infection and the effort to treat severe COVID-19 pneumonia patients, IPF research communities have had little time to collect sufficient data and evaluate the risks and benefits of initiating antifibrotic therapy in this case.

Due to the rapid and global spread of COVID-19 infection and the effort to treat severe COVID-19 pneumonia patients, IPF research communities have had little time to collect sufficient data and evaluate the risks and benefits of initiating antifibrotic therapy in this case. As yet, no data reports the incidence or mortality of SARS-CoV-2 infection in patients with IPF. The prognosis may be even worse for patients with IPF than for the general population, considering risk factors common in this patient group with debilitated reduced pulmonary reserve. This review provides an overview of pulmonary fibrosis resulting from COVID-19 infection, addressing the possible ongoing treatments to prevent early mortality and prolong survival.

Antifibrotic therapy in patients with IPF who are infected with SARS-CoV-2

Pirfenidone and nintedanib are antifibrotic drugs that, in defiance of having various ways of action, are likewise substantial in reducing the rate of lung function decline by about 50% [14,15]. These therapies generally upgrade life expectancy by as much as 2.5 years. Given median historical survival estimates for this condition are three years from diagnosis, like many cancers, any decision to manage must be prudently considered. The most damaging complication of IPF is acute exacerbations and in-hospital death, with a greater than 50%. These acute exacerbations of IPF could be activated by respiratory viral infections, which can include coronavirus, which is also more common in the northern hemisphere's winter and spring months.

Pirfenidone is a pyridone with an imperfectly comprehended mechanism of action, and nintetanib is a tyrosine kinase inhibitor. Both drugs have pleiotropic effects, and neither is immunosuppressive; that's why they are not reasonable for stopping in the face of viral or bacterial infection. A pertinence data from the INPULSIS II study showed that treatment with nintedanib reduced the time to the first acute exacerbation. Even if this result was not reproduced in the INPULSIS I study, the conclusion suggests that nintedanib could diminish the incidence of acute exacerbation of IPF. As of April 2020, pirfenidone and nintedanib are commercially available only in oral form; that's why they can't be used in intubated and mechanically ventilated patients. In patients with COVID-19, an inhaled formulation of pirfenidone is under evaluation. Onward, pirfenidone should be repealed if the patients have an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m2. A study by Guan and colleagues shows us that patients with mild COVID-19 infection are less likely to try renal dysfunction. Still, with the augmenting severity of COVID-19 disease, this renal dysfunction can become of great attention when considering anti-fibrotic therapies. Both pirfenidone and nintedanib can be linked with hepatotoxicity, and liver dysfunction is present in patients infected with SARS-CoV-2. Raised concentrations of liver enzymes were noticed in 168 (22) of 757 patients with confirmed COVID-19 infection and 56 (39%) of 142 patients with severe disease. Liver dysfunction will increase considerably in the case of simultaneous use of both antifibrotics over a bacterial superinfection. That way, if a hospitalized patient has both pathologies IPF and severe COVID-19 with degraded liver function tests, it is necessary to stop antifibrotic treatment in favor of liver dysfunction temporarily.

Above all, we can be concerned that many other studies were dedicated to the immunomodulatory response, like IFN-β and IFN-γ, in the antifibrotic system. In addition to this fact, the new antifibrotic therapies should emphasize the fibrotic response following acute lung lesions rather than the new lesions [16]. Based on the structure of SARS-CoV-2 spike proteins, particularly the Arg-Gly-Asp integrin-binding domain and the N-terminal galectin fold, it is the base of novel drugs in preventing COVID-19 infection [16]. Pirfenidone inhibits TGF-β-induced fibronectin synthesis and has antifibrotic and anti-inflammatory properties, used to diminish the accumulation of inflammatory cells, fibroblast proliferation, and cytokine production and secretion [17]. Nintedanib is the second antifibrotic drug approved by the FDA for IPF treatment; it's a tyrosine kinase inhibitor with a role in fibroblast growth factor, platelet-derived growth factor, and VEGF, and stopping the cascades of fibroblasts and myofibroblasts, further to a potential effect of pulmonary angiogenesis [17]. Nintedanib lowers the collapse of FVC in IPF, eventually decreasing the disease progression with benefits seen in the IMPULSES trial. VEGF inhibition causes reduced platelet activity and leukocyte adhesion; that's why nintedanib should be used carefully due to the increased risk of bleeding and thrombosis. Meanwhile, the PDGF stoppage affects platelet production, possibly accompanied by thrombocytopenia [18]. Both drugs, approved by the FDA in 2014, have different mechanisms of action that reduce the rate of lung function decrease and enhance life expectancy.

Anticoagulant therapy can improve life expectancy and reduce the risk of pulmonary embolism in patients with severe COVID-19 infection. The simultaneous administration

of nintedanib with the total dose of anticoagulant confers a significant risk of bleeding. Due to the fact calculation of the risk-benefit balance, antifibrotic treatment is stopped in favor of anticoagulant therapy during severe degradation.

The antifibrotic therapy in patients without IPF in the treatment of COVID-19

The argument for utilizing antifibrotic therapy is established on a variety of pulmonary fibrotic diseases remarked in COVID-19, progressing from fibrosis connected with pneumonia to severe acute lung injury; there is progression to global fibrotic change. Sever fibrotic pneumonia is present at autopsy in fatal COVID-19 infections. Occasionally, abnormal immune mechanisms begin and advance pulmonary fibrosis, which is feasible because of cytokine storm [19]. Anyway, diffuse alveolar damage, which is the determining characteristic of ARDS, has been a histological mark in fatal COVID-19, with vascular thrombosis replacement. Although it seems surreal to treat both fibrosis pathologies and immunologically mediated lesions in classical acute lung injury, this goal can be achievable and inhibit both processes. Although this postulation must be progressed with warning, all of them must be directly attested. Antifibrotic agents are to be applied in the current pandemic. In this complex pathogenic process, antifibrotic treatment is unrelated to immune dysregulation of infection and does not alleviate prothrombotic aspects. If antifibrotic treatment is implemented in practice, it follows an important role, being included in combined regimens once anti-inflammatory treatments have been identified. Combination therapy, antifibrotic and anti-inflammatory, could solve two significant consequences while reducing the sequels of fibrosis.

The speed of action of antifibrotic agents remains another enigma. In IPF and other progressive pulmonary fibrotic diseases, antifibrotic therapies are specifically utilized. The results of this treatment have been highlighted over a year of use by tracking changes in vital capacity (FVC). It remains astonishing that in studies with the use of nintedanib in both IPF (INPULSIS trials) and other non-IPF disorders (INBUILD trial), vital function capacity revealed a difference at 4-6 weeks compared to placebo. With preferential use of pirfenidone, such early tendencies were not observed, but the increase in FVC was at three months in the ASCEND trial. The decrease in FVC in chronic fibrotic lung disease is shown, so treatment should be introduced as early as possible so that antifibrotic agents attenuate profibrotic pathways shortly after their activation. It's unknown how effective it is in ventilated patients, to whom the adequate opportunity has already passed. The use of antifibrotic therapy depends on identifying biomarkers at the beginning of disease evolution to find patients with severe prognoses with evolution to fibrosis and acute lung injury. Antifibrotic treatment in COVID-19 therapy is based on extrapolation from chronic lung disease. In this aspect, there are indicative data that connect two major profibrotic pathways: immunologically mediated damage and acute exacerbations in patients with IPF, who have the histological, imaging, and clinical profile of acute lung injury.

The benefits of antifibrotic therapy in the prevention of acute lung injury

Because acute lung injury is challenging to study, data from this field are suggestive but somewhat inconclusive. In patients already established on antifibrotic therapy, the benefit of this therapy was observed. The earlier the antifibrotic drug is introduced (before assisted ventilation), the faster its speed of action is, the better its effect and benefit will be observed.

In IPF, acute exacerbations have an almost uniform, weak effect. Diffuse alveolar lesions are superimposed on those of IPF, having the same clinical, imaging, and histological properties. In the INPULSIS IPF trials of nintedanib, a significant reduction of acute exacerbations was evident. These data can serve with certainty as the theoretical basis for the early antifibrotic treatment of COVID. The same data can be used in the case of patients with IPF and atypical resection in lung cancer to reduce the rate of acute exacerbations. Because antifibrotic therapy has a very rapid effect, its effectiveness still depends on the combination with anti-inflammatory treatment.

COVID-19, ARDS, and pulmonary fibrosis

Due to the high percentage of deaths from pulmonary fibrosis, studies have been conducted for antifibrotic treatment in patients who survive ARDS in the acute phase. Notably, in an autopsy study of 159 patients with ARDS, fibrosis was noted in three of 82 patients with a disease duration of less than one week and 14 of 23 patients with a disease duration of greater than three weeks; these data reveal that antifibrotic treatment should be introduced as early as the first week of ARDS. Some patients who develop ARDS will experience residual long-term consequences of lung function seen on CT scans [20]. Evidence of restrictive pulmonary disease in 25 % of survivors was observed in the group of patients with CT imaging changes, as well as those with reduced vital functional capacity and pulmonary diffusion for carbon monoxide. During the acute ARDS phase, multiple aberrant pathways are interconnected, such as mediators releasing matrix metalloproteinases that will cause epithelial and endothelial damage and uncontrolled fibroproliferation [21]. The critical component of switching from ARDS to fibrosis, with VEGF and cytokines like IL-6 and TNFα involved, is vascular dysfunction. It remains uncertain why some patients

can recover, and others develop pulmonary fibrosis through uncontrolled cell proliferation and accumulation of fibroblasts and myofibroblasts, which are deposited excessively alongside collagen and other components of the extracellular matrix.

Another critical factor in the complicity of COVID-19 infection is the use of interleukin therapy for severe boring, including anakinra or anti-IL-6 therapies. The role of IL-6 therapies in preventing fibrosis from COVID019 infection is less clear than the role of IL-1 in IPF pathogenesis. Even though IL-6 is a profibrotic molecule, it is believed that using antileukotriene therapy in the early stages has a profibrotic effect, rather than in the later stages [22]. Using nintedanib has been shown to attenuate IL-1β concentrations, bronchoalveolar lavage, and pirfenidone to reduce serum and pulmonary IL-6 concentrations, which provides biological thinking for pirfenidone use in COVID-19. Due to the globality of the COVID-19 pandemic and the number of people requiring invasive ventilation, post-COVID-19 fibrosis is becoming a fundamental problem. What could lead to a worsening of pulmonary fibrosis is the long-term effect of anti-interleukin therapy. Finally, the interstitial lung disease community should unite to investigate and find an effective treatment for post-COVID-19 fibrosis.

2. Conclusion

Patients with COVID-19, in severe cases, may develop lung fibrosis. A significant long-term complication, added by risk factors like advanced age with limited function and preexisting comorbidities, such as diabetes, cardiovascular disease, hypertension, and obesity, includes patients in a category with reduced exercise tolerance.

The two antifibrotic drugs, pirfenidone, and nintedanib, have been sufficiently studied in progressive pulmonary fibrosis, and the benefit of nintedanib has been evident with increased prevalence. Both drugs have been used in IPF antifibrotic treatment. However, neither has sufficiently demonstrated their result in the context of acute exacerbations or ARDS. Nintedanib may reduce rates of exacerbations of interstitial lung disease, which respiratory viruses might cause. Antifibrotic drugs, such as Nintedanib and Pirfenidone, are under clinical trials. Yet, this theme should become as encouraging as possible for rehabilitation and improving the quality of life in such patients.

Author Contributions

Conceptualization, V.T. and R.C.-D.; methodology, I.G.-C. and O.M.; validation, A.Z.-A., R.C.-D, ; investigation, V.T., and R.C.-D. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

This study did not involve humans. It is a narrative review of published literature in the field.

Data Availability Statement

The data published in this research are available on request from the first author and corresponding author. Relevant references document all information provided in this review.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Hosseini, E.S.; Kashani, N.R.; Nikazad, H. The novel coronavirus Disease-2019 (COVID-2019): Mechanism of action, detection and recent therapeutic strategies. *Virology.* **2020**. 551:1-9.
2. Cucianotta, D.; Vanelli, M. WHO declares COVID-19 a pandemic. *Biomed*. 2020;91:157–160.
3. Huang, C.; Wang, Y.; Li, X.; Clinical features of patients infected with 2019 nocel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. DOI:10.1016/s0140-6736(20)30183-5
4. Kong, S.L.; Lim, B.; et al.; Elucidating the molecular physiopathology of acute respiratory distress syndrome in severe acute respiratory syndrome patients. *Virus Res*. 2009;145(2):260–269.
5. Lee, E.J.; Lim, J.Y.; Lee, S.Y.; el al. The expression of HSPs, anti-oxidants, and cytokines in plasma and bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. *Clin Biochem*. 2012;45(6):493–498.
6. Li-Jane, S.; Chun-Chun Yang,; Min-Tser, L.; et al; An importan call: call Suggestion of using IL-10 as therapeutic agent for

COVID-19 with ARDS and other complications. *Virulence*. 2023; doi.org/10.1080/21505594.2023.2190650
7. Wigen, J.; Lofdahl, A.; Bjermer, L.; el al,; Converging pathways in pulmonary fibrosis and Covid-19 – The fibrotic link to desease severity. *Respir Med X*. 2020;2;100023,
8. McDonald, L.T.; Healinh after COVID-19: are survivors at risk for pumonary fibrosis? *Am J Phusiol Lung Cell Mol Physiol*. 2021;320:0–65.
9. Furuhashi, M.; Moniwa, N.; Takizawa, H.; Potential differential effects of renin-angiotensin system inhibitors on SARS-CoV-2 infection and lung injury in COVID-19. *Hypertens. Res*. 2020;43:837–840.
10. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; SARS-CoV-2 cell entry depends on ACE2 and TMPRESS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271–280 e278.
11. Zhang, H.; Shang, W.; Liu, Q.; infection, China : 2020. Clinical Characteristics of 194 Cases of COVID-19 in Huanggang and Taian.
12. Nalysnyk, L.; Cid-Ruzafa, J.; Rotella, R.; Esser, D.; Incidence and prevalence of idiopathic pulmonary fibrosis: a literature review. *Eur Respir Rev.* 2012;21:355–361.
13. Hutchinson, J.; Fogarty, A.; Hubbard, R.; McKeever, T.; Global incidence and mortality of idiopathic pulmonary fibrosis: a system review. *Eur Respir J.* 2015;46:795–806.
14. King TE, Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2083–2092.
15. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2071–2082.
16. George, P.M.; Wells, A.U.; Jenkins, R.G.; Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med*. 2020;8:807–815.
17. Seifirad, S.; Pirfenidone: a novel hypothetical treatment for COVID-19, Seifirad S. *Med Hypotheses*. 2020;144: 110005.
18. Grześk, G.; Woźniak-Wiśniewska, A.; Błażejewski, J.; Górny, B.; The interactions of nintedanib and oral anticoagulants-molecular mechanisms and clinical implications, *Int J Mol Sci*. 2020;22:282.
19. Zhang, T.; Sun, LX.; Feng, R.E.; [Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019] *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43:e040.
20. Herridge, M.S.; Tansey, C.M.; Matté, A.; et al. Functional disability five years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364:1293–1304.
21. Burnham, E.L.; Janssen, W.J.; Riches, D.W.; Moss, M.; Downey, G.P.; The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. *Eur Respir J*. 2014;43:276–285.
22. Le, T.T.; Karmouty-Quintana, H.; Melicoff, E.; et al. Blockade of IL-6 trans signaling attenuates pulmonary fibrosis. *J Immunol*. 2014;193:3755–3768.