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Coronavirus 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has had significant impacts worldwide since its emergence in December, 2019. Despite a high recovery rate, there is a growing concern over its residual, long-term effects. However, because of a lack of long-term data, we are still far from establishing a consensus on post-COVID-19 complications. The deposition of excessive extracellular matrix (ECM), known as fibrosis, has been observed in numerous survivors of COVID-19. Given the exceptionally high number of individuals affected, there is an urgent need to address the emergence of fibrosis post-COVID-19. In this review, we discuss the clinical relevance of COVID-19-associated fibrosis, the current status of antifibrotic agents, novel antifibrotic targets, and challenges to its management.

Keywords: COVID-19; SARS-CoV-2; Fibrosis; Extracellular matrix; Antifibrotic agents

Introduction

COVID-19 first emerged in December 2019 in Wuhan, China, and was declared a pandemic by the WHO on 11 March, 2020. It is caused by a novel virus, named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV) because of its striking resemblance to SARS-CoV. By mid-2022, more than 6.36 million people had died from COVID-19 and more than 558 million active cases had been reported. SARS-CoV-2 primarily affects the pulmonary organs, although multiple organs can also be affected. The virus causes infections from mild cold, fever, and acute inflammation to severe acute respiratory distress syndrome (ARDS). Associated symptoms include headache, generalised weakness, vomiting and diarrhoea, and lower respiratory tract infection-related symptoms, such as dry cough and dyspnoea. In the acute phase, SARS-CoV-2 infection drastically increases the production of proinflammatory cytokines, resulting in severe lung damage, fibrosis and multiorgan dysfunction. However, one of the biggest concerns arises from the emergence of post COVID-19 fibrosis. Xu et al. provided early evidence that SARS-CoV-2 infection causes upregulation of the mRNA levels of fibrosis drivers, such as angiotensin-converting enzyme 2 (ACE2), transforming growth factor-β1 (TGFβ1), connective tissue growth factor (CTGF), and fibronectin 1 (FN1). Later, it was established that around one-third of patients demonstrated SARS-CoV-2-associated pulmonary fibrosis. The established fibrosis causes further deterioration of the already-compromised pulmonary functions in survivors of COVID-19. In addition, COVID-19 infection affects not only the lungs, but also other organs, such as liver and kidney, among others. However, because of the limited treatment options, the management of organ fibrosis in survivors of COVID-19 remains a challenge. Therefore, a clear understanding of fibrosis progression is essential for fibrogenesis management in survivors of COVID-19, which would decrease the global health burden associated with the pandemic.
COVID-19-associated fibrosis: Clinical relevance

COVID-19 infection primarily affects the lungs, resulting in pneumonia, or ARDS-like conditions, in severe cases. ARDS is observed in almost 40% of cases. Despite a high recovery rate, 70–80% of patients do not recover fully and present with at least one symptom, even after becoming COVID-19 free. Given the wide impact of the disease, even a minor proportion of patients affected by fibrosis-like conditions warrants investigation of this condition. COVID-19-affected lungs develop fibrosis primarily as a result of viral- and immune-mediated mechanisms. In response to lung injury, persistent inflammation initiates fibrotic signalling, leading to compromised organ functions. Typical imaging features of fibrosis include ground glass opacities (GGOs), consolidation patterns, reticulations, and mixed lesions, as observed on computerised tomography (CT) scans. In addition, these CT scan results are correlated with histopathological findings, such as interstitial oedema, inflammatory infiltration, fibrin deposition, alveolar oedema, hyaline membrane deposition, diffuse alveolar damage, necrotizing and non-necrotizing vasculitis, capillary congestion, and collagen deposition.7,8

Although COVID-19 infection primarily affects the lungs, the hyperactivated immune response increases the risk of multiple organ failure. Apart from lungs, COVID-19 infection also affects kidney function.9,10 SARS-CoV-2 can directly infect kidney cells and induced fibrosis in human-induced pluripotent stem cell-derived kidney organoids.11 Meta-analysis studies showed that severe acute kidney injury (AKI) is a primary cause of mortality in patients with COVID-19,12 resulting from acute renal failure, increases in plasma creatinine, and rhabdomyolysis suggestive of severe renal injury.13,14 Given the abundance of ACE2 in renal cells and its utilisation by the virus to gain entry to host cells, it is suggested that COVID-19 infection activates the renin–angiotensin–aldosterone system (RAAS) to enhance levels of angiotensin II, a profibrotic agent. Histopathological findings from clinical samples show tubular injury, obstruction of the peritubular and glomerular capillary loops, lymphocytic endotheliolitis, and viral inclusion particles, which can aggravate fibrosis progression in the kidneys.

As another viral target of the virus, the liver is also affected by COVID-19. Clinical studies reported hepatocellular injury in 14–53% of patients hospitalised with severe COVID-19.15–17 In another study, 43 out of 99 patients with COVID-19 demonstrated varying degrees of liver damage along with increased levels of liver injury markers.18 In addition, elevated bilirubin levels in patients hospitalised with COVID-19 were also linked with severe alterations of liver function.19,20 Although it is not known whether such liver damage was due to COVID-19 or to drug exposure, ACE2 expression in the liver suggests that this is an organ affected by COVID-19.21 Another study demonstrated that ACE2 occurs in cholangiocytes and that liver damage could be the result of the specific involvement of these cells rather than of hepatocytes.22 A recent study showed that 65% of individuals infected with COVID-19 had an increased liver fibrosis index (FIB-4).5 Thus, given such evidence, a new paradigm involving severe liver fibrosis in COVID-19 warrants research attention.

Basic mechanisms of fibrosis

The establishment of fibrotic scars is a result of an uncontrolled wound-healing process. In normal wound healing, inflammatory pathways are activated in response to injury, resulting in the activation of wound-healing signals followed by the apoptotic death of activated fibroblasts or myofibroblasts. However, in fibrotic reactions, the wound-healing process never comes to a halt, primarily because of the persistent nature of the injury. The release of inflammatory cytokines/chemokines and growth factors from immune cells activates fibrotic signalling to cause interstitial fibrosis.23 In addition, paracrine signalling from injured cells fuels the recruitment of inflammatory cells and help to remodel the ECM. In addition, the reduced activity of matrix metalloproteinases (MMPs), which are matrix-degrading enzymes, aggravates this process and results in the formation of a highly stable ECM-rich matrix. Clinical cases of COVID-19 have also shown symptoms of remodelled matrices rich in collagens.24 Despite no concrete evidence of long-term pulmonary fibrosis in survivors, this remodelling and developed fibrosis compromise organ function and, thus, requires research attention. The intricate relationship between inflammation, cytokine storm and fibrosis is detailed in Fig. 1.

Myofibroblasts

Fibroblasts are one of the most dominant cells in the interstitial matrix and help to maintain the structural support and rigidity by secreting ECM components. However, activated fibroblasts, also known as myofibroblasts, secrete excessive ECM, increasing tissue stiffness and forming a scar. Myofibroblasts acquire mesenchymal characteristics, such as increased actin stress fibres and vimentin fibres, induced transcription factors (Snail1 and Slug), and increased motility, among others. In addition, myofibroblasts have microfilament bundles, which form a fibronexus, a specialised adhesion complex that connects the internal microfilaments of myofibroblast with fibronectin in the extracellular environment. This bridging helps these cells to produce and transmit contractile forces to the surrounding ECM, which can be strengthened by collagen deposition under fibrotic conditions.25 The myofibroblast population is well correlated with fibrosis severity and, accordingly, strategies to reduce the myofibroblast population or inhibit their activation are beneficial in reducing fibrosis. The clinical presentation of patients with severe COVID-19 also includes excessive proliferation of myofibroblasts,26,27 suggestive of their crucial involvement in fibroprogression in these patients.

Epithelial–mesenchymal transition

Epithelial–mesenchymal transition (EMT) is one of the basic programs primarily activated during the initial stages of life. However, EMT reactivation is observed in multiple disorders, particularly in cancer and fibrosis. EMT activation leads to the transformation of epithelial cells to a mesenchymal subtype through a series of events. When the EMT program is activated, epithelial cells start to lose cell–cell junctions, causing them to detach from the basement membrane, gain migratory properties, and overexpress mesenchymal markers. This transformation
favours the deposition of ECM proteins secreted by activated fibroblasts/myofibroblasts. Although the contributing role of epithelial cells to EMT program has been a topic of debate because of the involvement of several cell types, there is evidence that EMT program activation is crucial for fibrogenesis, irrespective of the cell type involved. It is now believed that epithelial cells mainly undergo partial EMT activation during fibrosis. The major players involved in EMT program and deposition of fibrotic matrix are shown in Fig. 2.

**TGFβ1**

TGFβ1, a cytokine involved in an array of physiological functions, is mainly secreted by immune cells and generally present in plasma and ECM proteins. The abnormal activation of TGFβ signalling has been associated with fibrosis. Following injury, inflammatory and epithelial cells produce numerous profibrogenic mediators, including TGFβ1. Induced TGFβ1 signalling directly activates fibrotic responses through downstream canonical and non-canonical signalling. The former is mediated by the activation of Smad proteins. Phosphorylation of Smad2/3 leads to the formation of a complex with Smad4, which, after nuclear translocation, induces the transcription of fibrotic genes, such as SNAI1, SLUG, and Zeb1. By contrast, non-canonical signalling involves three different pathways: ERK1/2, p38, and AKT. TGFβ1 can affect multiple pathways implicated in fibrogenesis, such as myofibroblast proliferation, EMT activation, ECM expansion, inflammation, and induction of transcription factors.

**Matrix metalloproteinases**

MMPs are members of a family of extracellular endopeptidase that are mainly involved in the degradation of ECM substrates. The family has 25 members with contrasting effects on the establishment of fibrotic ECM. However, in general, MMPs have a proteolytic effect on ECM substrates. By contrast, tissue inhibitors of metalloproteinases (TIMPs) can block the catalytic activity of MMPs. Hence, the net effect on ECM is the result of the differ-

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**FIGURE 1**

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, cytokine storm, and fibrosis induction. Pulmonary infection with SARS-CoV-2 can result in the activation of immune responses and inflammatory pathways, leading to an exaggerated release of cytokines in acute manner, also known as a cytokine storm. Once the virus enters the cell, it releases its genetic material into the cytoplasm and causes pyroptotic cellular injury, which activates paracrine signalling in nearby cells. The affected cells, nearby cells, and tissue macrophages release cytokines/chemokines, giving rise to a cytokine storm. By contrast, when the virus is absorbed in the systemic circulation, it can directly affect other organs, such as liver, heart, and kidneys. The increased immune response along with inflammation results in the induced transcription of fibrotic genes causing organ fibrosis. Abbreviations: ACE2, angiotensin-converting enzyme 2; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern.
ence in the expression of MMPs versus that of TIMPs. MMP2 is activated in liver fibrosis and it highly expressed on myofibroblasts. However, Mmp2−/− mice showed a higher degree of fibrosis compared with wild-type, suggesting the anti-fibrotic behaviour of MMP2. In addition, expression of MMP9 is downregulated in fibrotic rigidities. By contrast, MMP9 is profibrotic in nature, as shown in experimental fibrosis. Patients with COVID-19 also showed dysregulated levels of MMP2/MMP9. In line with this, targeting of MMPs has been suggested for COVID-19 management. However, because of the contradictory roles of MMPs under different disease conditions, it will be necessary to thoroughly dissect the involvement of MMPs before reaching any firm conclusion.

Inflammation

Inflammation is an integral component of fibrosis, given the causal link between inflammation and established fibrosis. The persistent activation of inflammatory pathways leads to uncontrolled wound healing, resulting in establishment of fibrotic foci. The exaggerated immune response mediated by sudden release of circulating proinflammatory cytokines, also called a ‘cytokine storm’, is an influential proinflammatory mechanism involved in the pathogenesis of COVID-19 and its associated complications. The activation of immune responses after SARS-CoV-2 infection results in increased recruitment of inflammatory cells, such as macrophages, monocytes, and neutrophils, which results in the massive release of cytokines. Patients with COVID-19 have demonstrated induced levels of multiple cytokines/chemokines, including IL2, IL7, IP10, MIP1α, MCP1, and TNFα. Given the stringent role of proinflammatory pathways in COVID-19-associated abnormalities, several therapeutic strategies have been proposed, such as steroids, monoclonal antibodies, JAK inhibitors, and NLRP3 inflammasome inhibitors. The partial success of anti-inflammatory agents in COVID-19 suggests that regulating proinflammatory mechanisms could be helpful to both contain the virus-mediated damage and provide antifibrotic effects.

Macrophages

Macrophages are one of the earliest cells to reach the site of injury to prepare for repair and wound healing. Locally released signals, such as damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), chemokines, cytokines, and other chemotactic proteins trigger macrophage recruitment at the injury site. Macrophages then release several types of cytokine and other secreted factors necessary to remodel the matrix. Macrophage infiltration appears to be one of the most commonly observed processes in almost all types of fibrotic reaction. In addition, the degree of macrophage infiltration closely associates with the extent of fibrosis. Broadly, there are two subtypes of macrophage based on their phenotypes: classically activated M1 and alternatively activated M2 macrophages. Inflammatory agents, such as IFNγ and lipopolysaccharide (LPS), activate proinflammatory M1 macrophages, whereas IL4/13 induce the M2 phenotype. However, macrophage polarisation, a term given to the phenotypic conver-
sion of the M1 subtype to M2, is associated with the profibrotic activity of macrophages. On a broader scale, the change from an M1 to an M2 subtype was demonstrated to induce fibrosis by releasing profibrotic mediators, such as TGFβ, IGF1, FGF2, and PDGF.40

**Therapeutic options for fibrosis management**

Despite a continuous increase in the number of patients with fibrosis, only limited therapeutic agents are available for their management. Only two drugs are currently approved for the pulmonary fibrosis: nintedanib and pirfenidone.

Pirfenidone works by inhibiting expression of multiple fibrotic and inflammatory mediators, primarily TGFβ1, TNFα, IL1β, and IL6. Inhibition of TGFβ1 and its downstream signalling by pirfenidone blocks fibroblast proliferation, myofibroblast differentiation, and, ultimately, collagen deposition. It can also upregulate Regulator of G-protein Signaling 2 (RGS2) to inhibit thrombin-dependent collagen deposition. Furthermore, it can be helpful in COVID-19 because of its broad-spectrum activity, including inhibition of CTGF, PDGF, TNFα, and reactive oxygen species. In addition, it can also downregulate the expression of ACE2 receptors, which are used by SARS-CoV-2 to gain cellular entry, thereby making it a valuable drug to use to inhibit viral entry. Furthermore, the anti-inflammatory activity of pirfenidone, notably against TNFα and the NLRP3 inflammasome, might also inhibit the cytokine storm. A recent trial reported that 4 weeks of treatment with pirfenidone improved lung inflammation and interstitial damage, and reduced the duration of hospitalisation, suggesting it as a viable drug for cases of severe COVID-19.42 Furthermore, 2 months of pirfenidone therapy improved dyspnoea and fibrosis symptoms, helping the patient to return to daily activities by the seventh month of treatment.13 Deupirfenidone (LYT-100), a deuterium-substituted analogue of pirfenidone, is in a clinical trial (NCT04652518) for its efficacy against post-acute COVID-19 respiratory diseases.

Nintedanib is an ATP-competitive inhibitor of receptor tyrosine kinase and has also proved to be beneficial in the management of COVID-19-associated pulmonary function decline.44,45 A recent report showed that six months of nintedanib treatment reduced pulmonary fibrosis and restored lung functions, as shown by a reduced Borg score, improved total lung capacity, diffusive lung capacity for carbon monoxide (DLCO), CT scoring, and a 6 min walk test score.46 The adverse events reported included mild dysphagia, frontal headache, and upper-extremity numbness, which eventually resolved a few weeks after treatment without causing any treatment discontinuation. Furthermore, two ongoing clinical trials (NCT04619680 and NCT04338802) aim to investigate the potential of nintedanib against COVID-19 associated pulmonary fibrosis.

In addition, various other investigational agents are in clinical trials for the management of fibrotic conditions, as detailed in Table 1.

**Novel pharmacological targets for COVID-19-associated fibrosis**

Although various pharmacological targets have already been proposed for the management of fibrosis, these are oriented mainly toward the management of COVID-19 infection. Here, we discuss novel targets for the prevention/resolution of the underlying fibrotic matrix to aid the management of interstitial fibrosis (Fig. 3).

**Notch signalling**

Notch is a well-known signalling pathway that involves four Notch transmembrane receptors. Notch signalling has an important role in embryonic development and cell-cell communication. Activated Notch signalling promotes myofibroblast proliferation in the fibrosis of various organs, including lungs, liver, kidney, and heart.50 In addition, Notch signalling also promotes EMT activation, leading to phenotypic transition of epithelial cells to a mesenchymal subtype, further aggravating fibrogenesis.51 Increased Notch expression correlates with structural fibrotic anomalies in the lungs.52 A preclinical study showed the induction of Notch signalling in SARS-CoV-2 infection in macaques.53 Using computational tools, another study also suggested a link between Notch2 signalling and SARS-CoV-2 infection.54 Although no studies have performed direct manipulation of Notch signalling in SARS-CoV-2 infection, there might be an indirect link with Notch signalling because of the crucial role of Furin and ADAM17 in COVID-19 infection.55

**Wnt/β-catenin**

Wnt/β-catenin is involved in the regulation of various crucial cellular events,56 whereas abnormal Wnt/β-catenin signalling is implicated in inflammation, fibrosis, and cancer.57 Wnt ligands control immune cell modulation, inflammatory response, and tissue damage and repair.58 The upregulation of Wnt/β-catenin is observed in lung injury and ARDS.59 Given that Wnt/β-catenin signalling is crucial for the renewal of taste bud cells and taste perception,60 the loss of taste and smell observed in some patients with COVID-19 suggests a direct involvement of Wnt/β-catenin in COVID-19 infection. Furthermore, the increased release of TGFβ activates Wnt/β-catenin signalling and increases risk of pulmonary infection and fibrosis in COVID-19.61 Taylor et al. analyzed samples from patients with COVID-19 and observed alterations in the expression of nine genes that directly interact with either Wnt or β-catenin in the signalling pathway.62 This suggests that genetic or pharmacological blockade of Wnt/β-catenin as a useful therapeutic approach for the management of COVID-19-associated complications and fibrosis.

**Lysyl oxidase**

Lysyl oxidase (LOX) enzymes belong to a family of copper-dependent, amine oxidase enzymes that has five members (LOX and LOXL1–4). Their primary function is to crosslink collagen and elastin molecules, resulting in the formation of highly interlinked ECM. Given their crucial role in collagen stabilisation, these enzymes have attracted research attention. The dysregulated levels of these enzymes have been observed in the fibrosis of multiple organs, including lungs, kidneys, liver, heart, and pancreas. In addition, a non-competitive monoclonal antibody against LOXL2 (sintuzumab) was investigated for its efficacy in patients with idiopathic pulmonary fibrosis (IPF), although the results were not promising.63 Nevertheless, it is evi-
dent that these enzymes are involved in the establishment of fibrotic foci and targeting them could limit fibrosis progression.64 An in silico study proposed interactions between LOX protein and ORF8 of COVID-19.65 Thus, the influential role of LOX proteins in fibrosis warrants their exploration for the management of COVID-19 and associated fibrosis.

**Hedgehog pathway**

The Hedgehog (Hh) pathway is essential for proper embryonic development, organogenesis, homeostasis, and regeneration. Disrupted Hh signalling contributes significantly to the progression of cancer and fibrosis. Hh activation can induce fibrosis in preclinical66,67 and clinical settings.68 Baratella et al. suggested

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**TABLE 1**

Molecules in clinical trials for pulmonary fibrosis, COVID-19-induced fibrosis, and associated conditions.6

| S. no. | Drug | Indication | Mechanism of action | Status | Clinical trial identifier |
|-------|------|------------|---------------------|--------|--------------------------|
| 1     | Pirfenidone | COVID-19-induced pulmonary fibrosis (PF) | Inhibits TGFβ | Phase II | NCT04607928 |
| 2     | Nintedanib | COVID-19-induced PF | Inhibits FGFRs, PDGFRs, and VEGFRs | Phase II | NCT04338802 |
| 3     | Deupirfenidone (Lyt-100) | COVID-19-induced PF | Inhibits IL6, TNFα, and TGFβ | Phase II | NCT04652518 |
| 4     | Fuzheng Huayu | COVID-19-induced PF | Inhibits hematopoietic stem cell activation and inflammation | Phase II | NCT04279197 |
| 5     | Sirolimus | COVID-19 pneumonia or post-COVID fibrosis | Inhibits T lymphocyte activation | Phase II/III | NCT04948203 |
| 6     | Canrenoate potassium | COVID-19-induced PF | Minocorticoid receptor antagonist | Phase IV | NCT04912011 |
| 7     | Longidaze (bovhyaluronidase azoxymer) | COVID-19-induced PF | Hyaluronic acid degradation | NA | NCT04645368 |
| 8     | Collagen-polyvinylpyrrolidone | Cytokine storm | Decreases inflammation and TGFβ | Phase I/II | NCT04517162 |
| 9     | Antibiotic monocyte (MON002) | COVID-19-induced PF | Clears partially degraded collagen fragments | Phase I/II | NCT04805086 |
| 10    | Treamid | COVID-19 pneumonia | Metal ion chelator | Phase II | NCT04527354 |
| 11    | Tetrandrine | COVID-19 | Calcium channel blocker | Phase II | NCT04308317 |
| 12    | Genistein nanoparticles (BIO300) | COVID-19 | Inhibits tyrosine kinase and topoisomerase II | Phase II | NCT04482595 |

**Antifibrotic agents under clinical trials**

| S. no. | Drug | Indication | Mechanism of action | Status | Clinical trial identifier |
|-------|------|------------|---------------------|--------|--------------------------|
| 1     | HZN-825 | IPF, diffuse cutaneous scleroderma | Lysophosphatidic acid receptor 1 antagonist | Phase II | NCT05032066 |
| 2     | Pamrevlumab | IPF | Monoclonal antibody against CTGF | Phase III | NCT03955146 |
| 3     | Taladegib | IPF | Hh pathway inhibitor | Phase II | NCT04968574 |
| 4     | Lansoprazole | IPF | Proton pump inhibitor | Phase III | NCT04965298 |
| 5     | TRK-250 | IPF | Single-strand long-chain nucleic acid against TGFβ1 | Phase I | NCT03727802 |
| 6     | Inhaled nitric oxide | IPF | Soluble guanylate cyclase activator | Early Phase I | NCT05052229 |
| 7     | Vismodegib | IPF | Hh inhibitor | Phase I | NCT02648048 |
| 8     | GLPG1690 | IPF | Autotaxin inhibitor | Phase II | NCT02738801 |
| 9     | N-acetylcysteine | IPF | Antioxidant | Phase III (PRECISIONS trial) | NCT04300920 |
| 10    | CC-9001 | IPF | JNK inhibitor | Phase II | NCT03142191 |
| 11    | Autoantibody reductive therapy | IPF | Reduces autoantibodies | Phase II | NCT03286556 |
| 12    | Umbilical cord mesenchymal stem cells | COPD | Immunomodulation | Phase I | NCT05016817 |
| 13    | Saracatinib | IPF | Inhibits Src and Bcr-Abl tyrosine kinase | Phase II | NCT04598919 |
| 14    | Belumosudil | Systemic sclerosis | Inhibits ROCK2 | Phase II | NCT02688647 |
| 15    | ORIN1001 | IPF | Inhibits IRE1 | Phase I | NCT04643769 |
| 16    | Jaktinib | IPF | Inhibits JAK1–3 | Phase II | NCT04312594 |
| 17    | Morphine | IPF-associated cough | Opioid cough suppressant | Phase III | NCT04429516 |
| 18    | BMS-986278 | IPF | LPA1 antagonist | Phase II | NCT04308681 |
| 19    | Ifenprodil (NP120) | IPF and associated cough | NMDA antagonist | Phase II | NCT04318704 |
| 20    | GKT137831 | IPF | Dual-selective inhibitor of αVβ6 and αVβ1 | Phase II | NCT04396756 |
| 21    | PLN-74809 | IPF | Inhibits Galectin-3 | Phase II | NCT03832946 |
| 22    | GB0139 | IPF | Inhibits NOX1/4 | Phase II | NCT03865927 |

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**Source:** [https://www.clinicaltrials.gov.](https://www.clinicaltrials.gov.)
the involvement of Shh signalling in patients with COVID-19-related pneumomediastinum, a rare complication of ARDS. In addition, the involvement of the Hh pathway in multiple physiological functions highlights a possible role in COVID-19-associated fibrosis. Hence, targeting Hh signalling could lead to the development of clinically effective therapies for the management of COVID-19-associated complications.

**Integrins**

Although ACE2 was identified as the primary receptor for SARS-CoV-2 binding and cell entry, recent evidence also suggests the involvement of other pathways, such as integrins. These are heterodimers used by animal cells as transmembrane linkers between the ECM and the cellular actin cytoskeleton. The spike (S) protein of SARS-CoV-2 has an arginine-glycine-aspartate (RGD) motif, which suggests the involvement of integrins in viral entry. The RGD sequence found in ECM proteins, including fibronectin and laminin, acts as a cell attachment site and helps to bind these ECM components with their integrin receptors. Integrin signalling is involved in fibrogenesis and demonstrates two-way interactions with TGFβ. Depletion of αv-integrins in hepatic stellate cells and myofibroblasts protected mice from CCl4-induced liver fibrosis. In addition, several viruses use RGD motifs to bind with the ECM domain of integrins and gain entry to host cells. Furthermore, Sigrist et al., discussed the possibility of integrins as a route for host cell entry by SARS-CoV-2. To further strengthen the case for the effectiveness of integrin blockers, the recovery from COVID-19 was reported in a patient with multiple sclerosis who was treated with natalizumab (an α4 integrin antagonist) and who then demonstrated negative results in five consecutive microbiological studies. Such evidence suggests that protection could be provided by integrin blockers and highlights inhibition of integrins as potential therapeutic targets for COVID-19-associated fibrosis.

**COVID-19-associated fibrotic complications: Reality or myth?**

The clinical relevance of fibrotic disorders in COVID-19 is clear. Previous SARS-CoV and Middle East respiratory syndrome (MERS)-CoV pandemics have taught us that the residual effects of the infection can persist for years. Studies have shown a
significant persistence of abnormalities in survivors of COVID-19, raising the concerns of long-term residual effects. One case study revealed pulmonary abnormalities in the form of septal thickening and traction bronchiectasis suggestive of progressive pulmonary fibrosis post infection. Carfi et al. reported the persistence of symptoms in patients with COVID-19 and suggested that continue monitoring of patients is necessary even after recovery. A significant proportion of patients with SARS-CoV-2 pneumonitis had inflammatory lung disease and functional deficits at 4 weeks after discharge. A recent report demonstrated that 72% (85 out of 118) patients showed fibrotic-like changes and 42% (49/118) showed GGOs on a 6-month follow-up chest CT. Similarly, another 6-month follow-up study also demonstrated similar results whereby 40 of 114 participants with severe COVID-19 pneumonia showed fibrotic-like symptoms, while the remaining 74 participants showed either complete radiological resolution, residual GGOs, or interstitial thickening. Li et al., reported abnormal lung functions in more than half of a total of 462 patients after 90 days from onset. They found that 62.03% of patients developed pulmonary fibrosis after >120 days, whereas 48.98% of patients showed a reversal of fibrosis. Schwensen and associates documented the development of fatal lung fibrosis even after eradication of COVID-19. When the CT scans were compared, it was observed that the patients developed characteristic fibrotic symptoms in previously healthy lungs. Another study reported the development of fibrotic-like changes correlated with lung function, cough, and measures of frailty, 4 months after hospitalisation. A 6-month-long follow-up study also reported fibrotic-like changes in the lungs of more than one-third of survivors of severe COVID-19.

However, there is also evidence to suggest that COVID-19-associated complications can resolve with time. Although SARS-CoV-2 shares 79.5% and 50% genomic homology with SARS-CoV and MERS-CoV, respectively, predicting a similar type of persistence in COVID-19 as seen with the former two would not be appropriate. Available evidence also points to the ‘self-resolution’ nature of COVID-19-associated complications, including fibrosis, which can spontaneously reverse during the recovery phase. A 4-week follow-up study of 51 patients suggested significant resolution of pulmonary abnormalities post infection. The patients showed varying percentages of improvement in different parameters, such as focal GGOs, multiple GGOs, reticular patterns, and consolidation and septal thickening suggestive of gradual recovery of pulmonary functions. However, the follow-up period was short (up to 4 weeks), which might have affected the results because the development of reversible fibrosis occurs over a period of time. A large population cohort study of 8 256 161 patients reported that the risk of COVID-19 in patients with asthma was relatively small. Furthermore, the risk of death in patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) was far lower than the risk of death from other causes, suggesting a lower risk of pulmonary fibrosis in COVID-19. In addition, the landscape of immunological and inflammatory events, such as circulating lymphocytes, monocytes, and concentration of inflammatory mediators, which show exaggerated levels in acute cases, also reduces during the recovery phase. Moreover, clinical assessment of patients with COVID-19 at 1 year post discharge revealed a significant decline in immune cell infiltration and improvement in CT abnormalities compared with 3–6-months post discharge, demonstrating a long-term resolution of lung pathology. However, the contradictions observed among studies add to the complexity of establishing a direct association between COVID-19 and the persistence of fibrotic symptoms. Nevertheless, this should not compromise the search for a potential antifibrotic drug useful for the management of fibrosis of diverse organs.

**Pitfalls and future directions**

Despite concrete evidence of fibrosis development in patients with COVID-19, we are still far from knowing whether to use antifibrotic therapy for COVID-19-associated fibrosis. There have been concerns raised over the use of antifibrotic agents in different conditions. One of the first questions associated with the use of antifibrotic therapy in COVID-19 is whether we should administer antifibrotic drugs at all, given the self-resolving nature of COVID-19-associated fibrotic-like reactions. In addition, fibrosis is generally regarded as an irreversible process and antifibrotic therapy is mainly used to slow functional decline. Hence, antifibrotic therapy is unlikely to be a definitive cure for established fibrosis, limiting the use of these agents. In addition, both available drugs are given by oral route, which hampers their use in patients critically ill with COVID-19. Furthermore, complications associated with these drugs reduce their usefulness for the management of COVID-19-associated fibrotic complications. For instance, the two replicate 52-week, randomised, double-blind, Phase III trials (INPULIS-1 and INPULIS-2) documented that nintedanib showed incidence rates of 61.5 and 63.2%, respectively. By contrast, a long-term safety trial with pirfenidone (PAASPORT) observed that, out of 1009 patients, 73.4% experienced adverse drug reactions, most commonly nausea (20.6%) and fatigue (18.5%), with a treatment discontinuation rate of 28.7%. In addition, pirfenidone is also contraindicated in renal failure, which needs to be kept in mind. Furthermore, continuous mutations of the virus further complicate the picture, resulting in changes to the transmissibility, virulence and clinical presentation of the infection, which make it difficult to choose therapeutic options and other measures.

Another major concern is the impaired wound-healing process in the patients undergoing antifibrotic treatment. Theoretically, long-term treatment with antifibrotic agents is expected to impair the overall wound-healing capabilities of the body. However, there are no reports for such observations in clinical settings and it remains is highly unlikely. In fact, patients taking pirfenidone up to 1 month before transplant showed no symptoms of impaired wound healing. In addition, pirfenidone, as an immunosuppressant, also increases the risk of infections and superinfections. From the lessons of cancer research, antifibrotic treatment is suspected to enhance the cellular growth of tissues and disrupt tissue homeostasis. However, there is a lack of data on the mentioned complications associated with the use of antifibrotic drugs, although these could be a major concern in patients with COVID-19 complications. However, these adverse events can be easily managed with suitable approaches.
and, thus, the effectiveness of antifibrotic agents in COVID-19-associated complications cannot be ignored.

Concluding remarks
The significant improvement in pulmonary functions following treatment with antifibrotic agents indicates the viability of these agents. Numerous studies have shown their effectiveness in ameliorating fibrosis-like conditions and improving the quality of life of patients. Given the benefits of antifibrotic agents, it makes more sense to add these agents to therapeutic regimen for COVID-19. In addition, the relatively safer profiles of these drugs also strengthen their case. However, it is advisable to monitor liver and kidney functions closely to avoid compromising patient health. A temporary suspension, dose reduction, and a judiciously prepared antifibrotic regimen could be beneficial for patients with COVID-19. Currently, there is uncertainty over the use of antifibrotic agents in COVID-19. However, with an increasing number of clinical trials and comprehensive studies, it is possible that the underlying pathological mechanisms will become clearer. Nevertheless, the timely regulation of fibrosis progression will lead to positive outcomes and will improve the quality of life of survivors of COVID-19.

Data availability
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Declaration of interests
None declared by authors.

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