# Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy

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**In December, 2019, reports emerged from Wuhan, China, of a severe acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the end of April, 2020, over 3 million people had been confirmed infected, with over 1 million in the USA alone, and over 215 000 deaths. The symptoms associated with COVID-19 are diverse, ranging from mild upper respiratory tract symptoms to severe acute respiratory distress syndrome. The major risk factors for severe COVID-19 are shared with idiopathic pulmonary fibrosis (IPF), namely increasing age, male sex, and comorbidities such as hypertension and diabetes. However, the role of antifibrotic therapy in patients with IPF who contract SARS-CoV-2 infection, and the scientific rationale for their continuation or cessation, is poorly defined. Furthermore, several licensed and potential antifibrotic compounds have been assessed in models of acute lung injury and viral pneumonia. Data from previous coronavirus infections such as severe acute respiratory syndrome and Middle East respiratory syndrome, as well as emerging data from the COVID-19 pandemic, suggest there could be substantial fibrotic consequences following SARS-CoV-2 infection. Antifibrotic therapies that are available or in development could have value in preventing severe COVID-19 in patients with IPF, have the potential to treat severe COVID-19 in patients without IPF, and might have a role in preventing fibrosis after SARS-CoV-2 infection.**

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## Introduction

In December, 2019, the first reports emerged of a novel severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) in Wuhan, China.[1] The virus, which causes atypical pneumonia progressing to acute lung injury and acute respiratory distress syndrome (ARDS) in some individuals, was named COVID-19 and spread rapidly through other provinces in China. Before long the remainder of the world was affected and on March 11, 2020, WHO assigned to COVID-19 a pandemic status.

Initial reports from China,[2,3] which were later substantiated by data from Northern Italy,[4] suggested that the demographic most severely affected by COVID-19 was elderly men, and other poor prognostic factors included a history of smoking and the presence of comorbidities.[2,3] Of the 1099 patients with confirmed COVID-19 in the Chinese study by Guan and colleagues,[2] 173 had severe disease. In this group, the median age was 52 years, 100 (57·8%) were male, 41 (23·7%) had a history of hypertension, 28 (16·2%) had diabetes mellitus, and ten (5·8%) had coronary artery disease. Of 67 patients who were admitted to intensive care, required mechanical ventilation, or died, the median age was 63 years, 45 (67%) were male, and 39 (58%) had a comorbidity, of which the most common was hypertension affecting 24 (36%) individuals. This description of the group in whom SARS-CoV-2 infection is most lethal is also highly representative of patients suffering with idiopathic pulmonary fibrosis (IPF). IPF characteristically affects men in their seventh or eighth decade of life,[5] commonly with comorbidities such as hypertension, diabetes, and ischaemic heart disease, and with a history of cigarette smoke exposure.[6]

IPF is a progressive disease in which lung function inexorably declines, leading to respiratory failure and eventually death with lung transplantation being the only treatment that improves outcomes.[7] The incidence of IPF is rising and the disease is estimated to affect 3 million people worldwide.[8,9] A large proportion of patients with IPF are treated with one of the two available antifibrotic drugs, pirfenidone and nintedanib, that have been shown

### Key messages

- COVID-19 leads to a wide spectrum of respiratory diseases with an extremely high incidence of acute respiratory distress syndrome.
- The risk factors for severe COVID-19 are shared with idiopathic pulmonary fibrosis (IPF), suggesting that this group of patients will be at increased risk of severe COVID-19.
- The burden of fibrotic lung disease following SARS-CoV-2 infection is likely to be high; therefore, given the scale of the pandemic, the global burden of fibrotic lung disease will probably increase considerably.
- There is therapeutic rationale for the use of licensed antifibrotic therapy in acute exacerbations of IPF, including those triggered by viral infection.
- Available antifibrotic therapies have broad antifibrotic activity regardless of aetiology, and these drugs might have a role in attenuating profibrotic pathways in SARS-CoV-2 infection.
- Novel antifibrotic strategies have a range of antiviral and epithelial protective effects in models of acute and viral-induced lung injury.
- Previous coronavirus outbreaks have been associated with substantial postviral fibrosis and physiological impairment. Close follow-up of patients after COVID-19 is essential.
- There is an urgent need for therapies that mitigate severe COVID-19 and clinical trials of antifibrotic molecules should be considered.

to slow the rate of lung function decline.[10,11] Given the rapid global spread of the COVID-19 pandemic, and with efforts largely focused on the management of the most acutely unwell patients with COVID-19 pneumonia, the IPF clinical and research communities have had little time to collect sufficient data to thoroughly evaluate the potential risks and benefits of initiating and continuing antifibrotic therapy in this setting. To our knowledge, there are as yet no data reporting the incidence or mortality of SARS-CoV-2 infection in patients with IPF. Given that the risk factors for poor outcomes in SARS-CoV-2 infection are common in this patient group, who are further debilitated by reduced pulmonary reserve, it is possible that the prognosis is even worse for patients with IPF than for the general population.

In this Personal View, we address the role of antifibrotic therapy in patients with IPF who contract SARS-CoV-2 infection and the scientific rationale for their use or discontinuation. We also consider the potential novel role of antifibrotic therapy in the management of patients without IPF who develop COVID-19 pneumonia, acute lung injury, and ARDS. Finally, we consider the fibrotic consequences for patients who survive COVID-19-related ARDS.

## Conventional antifibrotic therapy in patients with IPF who are infected with SARS-CoV-2

Pirfenidone and nintedanib are antifibrotic drugs that, despite having differing modes of action, are similarly effective in attenuating the rate of lung function decline by about 50%.[10,11] These therapies are widely considered to improve life expectancy,[12,13] perhaps by as much as 2·5 years.[14] Considering that median historical survival estimates for this condition are 3 years from diagnosis,[15] akin to many cancers,[16] any decision to withhold treatment must be carefully considered.

Acute exacerbations are the most devastating complication of IPF, having an in-hospital mortality rate of greater than 50%.[17] There is biological and epidemiological support for the concept that acute exacerbations of IPF could be triggered by respiratory viral infections. Wootton and colleagues[18] found that a small proportion of patients with acute exacerbation of IPF had evidence of viral infection, including coronavirus infection (human coronavirus OC43). Acute exacerbations of IPF are also more common in the northern hemisphere's winter and spring months,[19,20] supporting the theory that they might be mediated by respiratory tract infections. Pirfenidone is a pyridone with a poorly understood mechanism of action and nintedanib is a tyrosine kinase inhibitor. Although both drugs have pleiotropic effects, neither is immunosuppressive per se, and so there is no rationale for their discontinuation in the face of viral or bacterial infection. Of relevance, data from the INPULSIS II study[11] showed that treatment with nintedanib reduced the time to first acute exacerbation. Although this result was not replicated in the INPULSIS I study,[11] there remains the suggestion that nintedanib could reduce the incidence of acute exacerbation of IPF. Future studies analysing the effect of the COVID-19 pandemic on the incidence of acute exacerbation of IPF will be informative in establishing the postulated link with viral infection.

As of April, 2020, pirfenidone and nintedanib are commercially available only in oral form and so cannot be used in patients who are intubated and mechanically ventilated, clearly restricting their use in those individuals with severe COVID-19 on the intensive care unit (ICU). An inhaled formulation of pirfenidone is under evaluation in patients with COVID-19 (NCT04282902). Further, pirfenidone should be avoided if patients have an estimated glomerular filtration rate of less than 30 mL/min per 1·73 m². Although only 12 (1·6%) of 752 patients in the cohort reported by Guan and colleagues[2] had a creatinine concentration of 133 µmol/L or higher, this proportion rose to six (4·3%) of 138 patients with severe COVID-19, and data from Wuhan showed that of 52 patients admitted to the ICU, 15 (28·8%) developed acute kidney injury and nine (17·3%) required renal replacement.[3] These data imply that patients with mild SARS-CoV-2 infection are less likely to experience renal dysfunction, but with increasing severity of COVID-19 disease this renal dysfunction might become an important consideration when considering antifibrotic therapies. Both pirfenidone and nintedanib can be associated with hepatotoxicity, and liver dysfunction is common in patients infected with SARS-CoV-2. Elevated concentrations of liver enzymes were observed in 168 (22%) of 757 patients with confirmed COVID-19 and 56 (39%) of 142 patients with severe disease.[2] Concomitant use of antibiotics for superimposed bacterial infection is likely to heighten the risk of liver dysfunction, and so in the context of a hospitalised patient who has IPF and severe COVID-19 with deranged liver function tests, temporarily withholding antifibrotic therapy pending resolution of liver dysfunction might be necessary, although this should be assessed on a case-by-case basis.

There is anecdotal evidence of an increased risk of acute pulmonary embolism in patients with COVID-19 and anticoagulant therapy might be associated with improved outcomes in patients with severe COVID-19 and coagulopathy.[21] This observation has relevance to patients prescribed nintedanib, as this drug confers a theoretically increased risk of bleeding when concomitantly administered with full-dose anticoagulation. In this context, the balance of risk and benefit is likely to tip in the direction of withholding antifibrotic therapy, particularly in the acutely unwell patient with low physiological reserve. Unfortunately, in a proportion of patients with IPF who contract SARS-CoV-2 infection, the patient and their medical team might consider escalation to intensive care to not be in their best interests, and that the focus should be on palliative care. In this setting, antifibrotic therapy could be withdrawn in some cases to minimise the side-effects of pharmacotherapy.

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

The rationale for using antifibrotic therapy is based on the spectrum of pulmonary fibrotic disease observed in COVID-19, ranging from fibrosis associated with organising pneumonia to severe acute lung injury, in which there is evolution to widespread fibrotic change.[22] In fatal cases of COVID-19, pulmonary fibrosis is generally present at autopsy,[23] with anecdotal reports of severe fibrotic organising pneumonia. In some cases, abnormal immune mechanisms initiate and promote pulmonary fibrosis, possibly as a consequence of a cytokine storm.[23,24] However, diffuse alveolar damage, which is the defining feature of ARDS, has been the characteristic histological feature in fatal COVID-19 cases[23,25] with the added observation of microvascular thrombosis.[23]

Although it might be unrealistic to separate these profibrotic pathways in individual patients, in whom there is a variable mixture of immunologically mediated damage and classical acute lung injury, antifibrotic therapy could provide value in inhibiting both broad pathways. However, this hypothesis must be advanced with important caveats, all of which need to be addressed if existing antifibrotic agents are to be applied in the current pandemic. These drugs do not address the immune dysregulation of SARS-CoV-2 infection, nor can they be expected to attenuate the prothrombotic aspects of this complex pathogenic process. If antifibrotic therapy is to have a role, it is likely to take the form of inclusion in combination regimens, once effective anti-inflammatory treatments have been identified. Combination therapy could, in principle, address major anti-inflammatory and antifibrotic pathways while attenuating their fibrotic consequences.

A further uncertainty relates to the rapidity with which antifibrotic agents act. Antifibrotic therapies are exclusively used in chronic fibrotic disorders—mostly in IPF but also for progressive pulmonary fibrotic disease in disorders other than IPF.[26,27] Outcomes have generally been evaluated at 1 year follow-up, with changes in forced vital capacity (FVC) being the uniform primary endpoint. However, it is striking that in pivotal trials of nintedanib, both in IPF (the INPULSIS trials)[11] and in other non-IPF disorders (the INBUILD trial),[26] early separations in FVC trends between treatment and placebo groups were shown, with significant differences at 4–6 weeks. No similar early trends exist in the pirfenidone data, but FVC separations were evident at 3 months in the ASCEND trial.[10] A decline in FVC occurs slowly in chronic fibrotic lung disease and, thus, the observed early separation of FVC trends seem to indicate that antifibrotic agents attenuate profibrotic pathways shortly after their introduction. However, it might be overly optimistic to expect these agents to add value in ventilated patients, in whom the opportunity for effective treatment has already passed. The use of antifibrotic therapy in COVID-19 might be contingent on the identification of biomarkers early in the disease course to identify patients with a poor prognosis who are likely to progress to pulmonary fibrosis and acute lung injury.

It must also be stressed that the use of antifibrotic therapy in COVID-19 can be based only on extrapolation from chronic lung disease. In this regard, there are suggestive data that relate to both 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 efficacy of antifibrotic therapy in different pulmonary fibrotic disorders

Before 2019, nintedanib and pirfenidone had been studied exclusively in IPF. However, it has become increasingly apparent that distinct patient subgroups in other interstitial lung diseases show relentless disease progression, similar to IPF, despite traditional treatments (eg, corticosteroids and mycophenolic acid) used to suppress immune dysregulation. These patient subsets, amalgamated as the progressive fibrotic phenotype, were not able to access antifibrotic drugs confined by regulators to patients with IPF. With this background, patients with progressive pulmonary fibrosis in a wide variety of interstitial lung disorders were combined in the placebo-controlled INBUILD trial of nintedanib,[26] an approach similar to that in basket oncological trials. In the landmark publication, active treatment was associated with a reduction in FVC decline of about 60%. Importantly, treatment effects were shown to be strikingly similar within each of the five core disease groups, one of which consisted of patients with connective tissue disease-associated interstitial lung disease.[28] In this subgroup, pathogenetic profibrotic pathways driven by immune dysregulation might have similarities to those pathways in SARS-CoV-2 infection. Whether or not this speculation is confirmed, the key conclusion from the INBUILD study was that nintedanib therapy appears to inhibit fibrogenesis across a wide range of pulmonary disorders. In a parallel study of pirfenidone therapy in unclassifiable interstitial lung disease and idiopathic non-specific interstitial pneumonia,[27] the choice of home spirometry as the primary endpoint might have led the study to not meet its prespecified criteria for success, but a key secondary endpoint—FVC trends measured in pulmonary function laboratories—was equivalent to the primary endpoint in the INBUILD trial,[26] and the pirfenidone treatment effects were similar to those of nintedanib. These trials potentially suggest that antifibrotic therapy, when used early in SARS-CoV-2 infection, might have major benefits in reducing fibrotic damage driven by immune dysregulation. However, to have a major impact on outcome, interventions must also address the serious issue of acute lung injury.

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

From the outset, it must be acknowledged that data in this area are suggestive but inconclusive, in part because acute lung injury is difficult to study. Putative treatment benefits with antifibrotic therapy in reducing the prevalence of acute exacerbations of IPF were observed in patients already established on antifibrotic therapy.[11] The applicability of these data to COVID-19 depends on the rapidity of action of antifibrotic drugs and their introduction before severe acute lung injury has supervened (ie, before assisted ventilation).

In IPF, acute exacerbations have an almost uniformly poor outcome. This phenotype has the clinical, imaging, and histological characteristics of diffuse alveolar damage (ie, ARDS), overlaid on features of IPF. In the INPULSIS IPF trials of nintedanib,[11] there were strong trends towards a reduction in the frequency of acute exacerbations when the two trials were pooled. However, in the pooled analysis, investigator-defined frequency of acute exacerbations were not significantly different between nintedanib and placebo. The widespread uncertainty about this finding relates to the small number of events: the difference was significant in only one of the two trials. Some credibility is added by the fact that significance increased when the pooled adjudicated analysis was confined to episodes judged by an expert panel to be genuine acute exacerbations, despite the reduction in numbers of events. Although these observations were merely suggestive, they do at least provide a theoretical basis for the early use of antifibrotic therapy in COVID-19.

Much the same can be argued from data in small cohorts of patients with IPF undergoing resection of lung cancer, a frequent trigger of fatal acute exacerbations in IPF. In three Japanese studies, perioperative pirfenidone therapy was given to patients 4 weeks before surgery and for a variable time afterwards. Clinical outcomes were compared between patients receiving and not receiving pirfenidone, although these evaluations were neither placebo controlled nor randomised. Treatment with pirfenidone was associated with significant reductions in both postoperative mortality[29] and acute exacerbations.[30,31]

In summary, we hypothesise that a clinical trial of antifibrotic therapy in COVID-19 before ventilation is warranted. Formal controlled evaluation is essential to assess unexpected adverse effects, even though existing antifibrotic agents have not, in general, exhibited life-threatening toxicity. In advancing this argument, we stress that there is currently no basis for empirical off-licence treatment. The assumptions made in this Personal View are that antifibrotic therapy has a very rapid effect, that treatment benefits in other forms of lung fibrosis will be applicable to fibrosis triggered by severe viral infection, and that efficacy might depend on the combination with anti-inflammatory treatment.

| | Inhibits viral infection or disease | Inhibits experimental acute lung injury | Inhibits IL-1 or IL-1 effects | Inhibits IL-6 |
|---|---|---|---|---|
| Nintedanib | Not described | Not described | Yes[38,39] | Yes[40,41] |
| Pirfenidone | Not described | Yes[42] | Yes[43,44] | Yes[42] |
| αvβ6 integrin blockers and knockout mice | Yes[45,46] | Yes[47,48] | Yes[48] | Yes[49] |
| Gal-3 inhibitor and knockout mice | Yes[50,51] | Yes[51,52] | Yes[51] | Not described |
| Autotaxin inhibitor | Not described | Not described | Not described | Yes (skin);[53] not described |
| Lysophosphatidic acid inhibitor (BMS-986020; SAR100842) | No | Yes[54] | Not described | Yes (skin)[53] |
| JNK inhibitor | Yes[55-58] | Yes[59] | Not described | Yes |
| mTOR pathway modulator | Yes[60] | Yes[61] | Yes[61] | Yes[43] |
| SAP (also known as PTX2) | Yes[60,62,63] | Yes[64] | Not described | Not described |
| AT2R inhibitor | Not described | Yes[65,66] | No[44] | Yes[65] |

*Table:* **Potential link between antiviral mechanisms and antifibrotic drugs**

## Novel antifibrotic drugs for the treatment of severe COVID-19

There has been an enormous increase in the number of compounds being assessed for the treatment of pulmonary fibrosis, many with effects on the immunoinflammatory system. Indeed, a number of early antifibrotic studies focused on key antiviral proteins, such as IFN-β and IFN-γ.[32,33] Subsequent studies have found that exogenously administered as well as endogenously produced interferon might induce pulmonary vasculopathy,[34–36] and this finding is important given that pulmonary vascular disease could play an important role in severe COVID-19 disease. Indeed, circulating IFN-γ and CXCL10 concentrations are raised in patients with severe COVID-19.[37] Furthermore, much of the data generated in preclinical studies for antifibrotic therapy include use of the bleomycin animal model of pulmonary fibrosis. There are numerous issues with this strategy for research into IPF therapies, not least because this model is of the fibrotic response following acute lung injury, rather than the de-novo progressive fibrosis. However, acute lung injury and ARDS are the major cause of mortality in COVID-19. Therefore, it is possible that antifibrotic therapies developed for chronic fibrotic lung diseases using bleomycin models might actually be beneficial in COVID-19, both in the acute phase of the illness and in preventing long-term complications. There are two important issues to consider when trying to determine whether a novel antifibrotic drug would be harmful or beneficial in the context of SAR-CoV-2-related illness (table). First, what is the effect of antifibrotic molecules on viral internalisation and replication? And second, what is their effect on mitigating the cytokine storm that seems to be responsible for complications in severe COVID-19 such as ARDS?

A major target for antifibrotic therapies is the TGF-β pathway. There are a number of drugs in development

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that target various molecules in this pathway, including those against αvβ6 integrin (BG00011 [Biogen, Cambridge, MA, USA]; PLN-74809 [Pliant Therapeutics, San Francisco, CA, USA]) and galectins (TD139 [Galecto Biotech, Copenhagen, Denmark]). These are particularly interesting candidates because the SARS-CoV-2 spike protein contains an Arg-Gly-Asp integrin-binding domain and a number of coronaviruses contain an N-terminal galectin fold,[67] raising the possibility that therapies that inhibit integrins or galectins might be of benefit in treating COVID-19 (figure). There are some experimental data to support the use of these three drugs in viral-induced lung injury. Mice that do not express the αvβ6 integrin or treated with an αvβ6 blocking antibody are protected from a number of viral infections, including influenza and sendai virus.[45,46] Strategies to block the αvβ6 integrin have been protective in in-vivo models of acute lung injury.[47,48] Reassuringly, given the role of TGF-β in immunity and host defence, inhibiting epithelial integrins does not appear to increase the risk of viral infection in several animal models.[45–47,68] Furthermore, IL-1, which has been identified as a key component of the cytokine storm in COVID-19 and other viruses, might mediate its affects through Arg-Gly-Asp binding integrins.[69] Similarly, there is a well described role for galectins in viral infections. Gal-3 is upregulated in lung epithelial cells after influenza A infection and promotes binding to *Streptococcus pneumonia*.[50] Following H5N1 influenza infection, Gal-3 knockout mice do not have lower viral loads than control mice but do have reduced pulmonary inflammation,[51] and are protected from bleomycin and TGF-β-induced lung injury and fibrosis.[52]

Two recent network analyses of protein–protein interactions identified that mTOR might be an anti-SARS-CoV-2 target and that rapamycin could be repurposed for this indication (figure).[70,71] mTOR is an emerging target in IPF, with genetic support for the mTOR pathway identified in a large-scale genome-wide association study[72] and studies with PI3K inhibitors showing promise in IPF.[73,74] Moreover, the mTOR inhibitor rapamycin is a well established treatment for lymphangioleiomyomatosis[75] and is commonly used in transplant medicine. In an experimental animal model of H1N1 influenza, rapamycin in combination with oseltamivir reduced viral replication and the NLRP3 inflammasome.[60]

PRM-151 (Roche, Basel, Switzerland) is an analogue of SAP (also known as PTX2), which is a member of the pentraxin family of proteins that includes CRP and PTX3, and has shown promising results in a phase 2 trial for IPF.[62] The pentraxins are major acute phase response proteins with key roles in inflammation and immunity.[63] SAP has been shown to bind influenza A virus and prevent viral internalisation[64] and to inhibit influenza infection both in vitro and in vivo (figure).[76–78] In addition, injection of recombinant SAP reduces inflammation 7 days following bleomycin-induced lung injury in mice.[79] The mechanism of action of SAP might be via

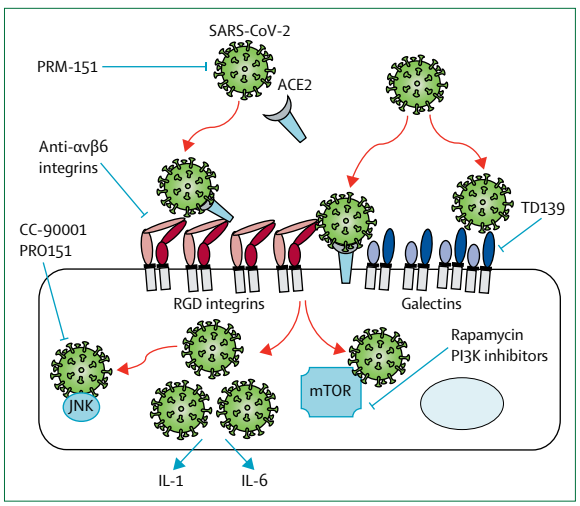


***Figure:*** **Potential mechanisms through which novel antifibrotic drugs could prevent the development of severe SARS-CoV-2 infection**
SARS-CoV-2 binds ACE2 in the alveolar lumen or on alveolar epithelial cells, and CD98 or RGD-binding integrins potentially facilitate cellular entry. Once within the cell, SARS-CoV-2 might use JNK and mTOR pathways for viral replication, which could activate the NLRP3 inflammasome to secrete IL-1 and IL-6 promoting severe disease. RGD=arg-gly-asp. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

suppression of JNK family signalling (figure),[80] which has also been therapeutically targeted in IPF (CC-90001; Celgene, Summit, NJ, USA). This selective JNK1 inhibitor has been shown to prevent fibrosis in some experimental animal models,[55,59,81] and also inhibits sepsis-induced lung injury.[56] H5N1 influenza infection leads to upregulation of cytokines such as TNFα, IFN-β, and IL-6 via phosphorylation of JUN, and genetic targeting of JNK1 improved survival and reduced bronchoalveolar lavage cytokines in mice.[57] Furthermore, JNK family inhibition impairs synthesis of H5N1 viral RNA,[58] and SARS-CoV-2 has been shown to stimulate pro-inflammatory pathways via JNK signalling pathways.[82] In studies with dengue virus, which is also a positive-sense, single-stranded RNA virus, in a viral animal model, a JNK inhibitor reduced viral liver injury and markers of severe disease, such as leucopenia and cellular apoptosis.[83]

On March 30, 2020, Vicore Pharma submitted a clinical trial application for C21 (an agonist of AT2R) in IPF and this drug has been given approval for a phase 2 study in COVID-19 (EudraCT 2017-004923-63). The role of angiotensin in SARS-CoV-2 is well documented, if somewhat poorly understood understood.[84] Membrane bound ACE2 is the primary receptor for SARS-CoV-2, but is shed into the serum by ADAM17 where it acts to catalyse the hydrolysis of Ang II to Ang 1–7. This cleavage prevents the harmful effects of Ang II, which the conventional AT1R inhibitors, the artans, exploit in the treatment of hypertension. The role of AT1R inhibitors in COVID-19 is controversial, with studies suggesting that these treatments might increase ACE2 concentrations.[85]

However, a study has shown that the risk of severe COVID-19 was significantly decreased in patients who took AT1R blockers before hospitalisation compared with patients who took no drugs (odds ratio 0·343, 95% CI 0·128–0·916, p=0·025).[86] Generally, AT2R is thought to have antagonistic effects to AT1R signalling;[87] however, C21 has been shown to have anti-inflammatory properties in experimental animal models of acute lung injury and the role of C21 in viral infection is not known (table).

Potential antifibrotic therapies might have beneficial effects in the treatment of COVID-19 through a range of different mechanisms, such as preventing viral uptake and replication, inhibiting viral signalling, and through beneficial effects on the renin–angiotensin system (figure). Although there is clearly much work to be done before these drugs could be considered safe, let alone beneficial in the context of COVID-19, the medical community should be reassured that there is biological rationale to suggest that antifibrotic therapies might have potential as novel therapeutics for severe COVID-19.

## COVID-19, ARDS, and pulmonary fibrosis

Although many patients who develop ARDS survive the acute phase of the illness, a substantial proportion die as a result of progressive pulmonary fibrosis.[88] Importantly, in an autopsy study of 159 patients with ARDS, fibrosis was noted in three (4%) of 82 patients with a disease duration of less than 1 week, 13 (24%) of 54 patients with a disease duration of between weeks 1 and 3, and 14 (61%) of 23 patients with a disease duration of greater than 3 weeks, suggesting that to be effective, any potential antifibrotic intervention should be considered within the first week of ARDS onset.[89] A substantial proportion of patients who develop ARDS will experience residual long-term impairment of lung function and CT evidence of pulmonary fibrosis,[90,91] with anterior reticulation the dominant abnormality in as many as 85% of survivors.[92] The extent of reticulation on CT correlates with quality of life and lung function measures of pulmonary restriction, such as FVC and the diffusion of the lung for carbon monoxide, with approximately 25% of survivors exhibiting physiological evidence of restrictive lung disease.[93] Multiple aberrant host pathways interconnect to result in pulmonary fibrosis in a subset of individuals who develop ARDS.[94] Important mediators include the dysregulated release of matrix metalloproteinases during the inflammatory phase of ARDS, which causes epithelial and endothelial injury[95,96] and unchecked fibroproliferation. Canonical profibrotic pathways regulated by TGF-β[47] are important, and there is evidence that vascular dysfunction is a key component of the switch from ARDS to fibrosis, with VEGF[97] and cytokines such as IL-6 and TNFα implicated.[88] It remains unclear why certain individuals are able to recover from such an insult, whereas in others there is a shift to unchecked cellular proliferation with the accumulation of fibroblasts and myofibroblasts and the excessive deposition of collagen alongside other components of the extracellular matrix to result in progressive pulmonary fibrosis.

The prevalence of post-COVID-19 fibrosis will become apparent in time, but early analysis from patients with COVID-19 on discharge from hospital suggests a high rate of fibrotic lung function abnormalities. Overall, 51 (47%) of 108 patients had impaired gas transfer and 27 (25%) had reduced total lung capacity. This was much worse in patients with severe disease.[98] Until mature data are available, it is important to draw on the experience of previous coronavirus outbreaks. Although the global outbreak of SARS in 2003, caused by SARS-CoV,[99] affected far fewer individuals than the current COVID-19 pandemic, there are clear parallels. In a study of 75 patients who were consecutively hospitalised and met criteria for SARS, as defined by fever with a temperature of 38°C or higher, cough or shortness of breath, and new pulmonary infiltrates, the frequency of ARDS was 20% by week 3 of admission.[100] Patients requiring admission to ICU with SARS had significantly more restricted lung function at 6 months after disease onset than those 6 months following ward-based treatment.[101] Across the entire cohort and regardless of whether ICU admission was required, impairment of gas diffusion was observed in 17 (16%) and abnormal chest radiographs were present in 33 (30%) of SARS survivors.[101] In an early follow-up study of patients with SARS, 15 (62%) of 24 patients had CT evidence of pulmonary fibrosis at a mean follow-up duration of 37 days after hospital discharge.[39] Patients at higher risk of developing post-SARS fibrosis were older and more likely to have required ICU care than patients without post-SARS fibrosis. In a follow-up study of 36 patients surviving Middle East respiratory syndrome coronavirus infection, 12 (33%) had radiographic evidence of pulmonary fibrosis; these patients were older and had longer ICU admissions.[102] Given approximately 30% of survivors of SARS and Middle East respiratory syndrome experienced persistent radiological and physiological abnormalities consistent with fibrotic lung disease, the repercussions of COVID-19 could include a large cohort of individuals with pulmonary fibrosis and persistent and potentially progressive physiological impairment. Long-term follow-up studies will be required to establish the true prevalence of post-COVID-19 fibrosis.

A further complicating factor in the COVID-19 pandemic is that many patients around the world will be receiving anti-interleukin therapies for severe disease, including anakinra or anti-IL-6 therapies, either through participation in clinical trials (NCT04332913; NCT04322773; NCT04331795; NCT04315298; NCT04324021) or as off-licence therapies.[103] Although the role of IL-1 in the pathogenesis of IPF is well described,[38] and inhibiting IL-1 could possibly prevent the development of post-COVID-19 fibrosis, the role of anti-IL-6 strategies is less clear. Although IL-6 is generally considered to be a profibrotic molecule,[42,104,105] an experimental study with the bleomycin model of pulmonary fibrosis suggested that inhibiting

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### Search strategy and selection criteria

References for this Personal View were identified through searches of PubMed, Google, Google Scholar, and pre-print servers (ChinaXiv, medRxiv, bioRxiv, arXiv) for articles published from Jan 1, 1991, to April 30, 2020, with the terms "IPF", "SARS", "MERS", "coronavirus", "COVID-19", "acute exacerbation", "acute lung injury", "ARDS", "anti-fibrotic", "viral infection", "IL1", "IL6", "integrin", "galectin-3", "mTOR", "JNK", "PTX2", "SAP", "AT2R", "nintedanib", and "pirfenidone". English language articles from these searches and relevant references cited in those articles were reviewed.

IL-6 in the early phase of lung injury promotes fibrosis and that inhibition in the later stages of injury at the onset of the fibrotic phase might ameliorate fibrosis.[106] Nintedanib has been shown to attenuate bronchoalveolar lavage concentrations of IL-1β,[107] and pirfenidone reduces serum and lung IL-6 concentrations in murine models of pulmonary fibrosis, providing further biological rationale for the use of pirfenidone in COVID-19.[108]

Given the scale of the COVID-19 pandemic and the number of people requiring invasive ventilation worldwide, post-COVID-19 fibrosis is likely to be a substantial problem. The effects of anti-interleukin therapy in the long term, although potentially beneficial, are completely unknown and could lead to worse fibrosis. Ultimately, the interstitial lung disease community should pull together to investigate the long-term consequences of COVID-19 and develop evidence-based strategies to deal with this emerging problem.

## Conclusion

The COVID-19 pandemic is bringing huge economic, social, and health-care challenges. As the wave of viral infection recedes, other problems will emerge that will need to be addressed. In this context, it is important to try and predict and prepare for these challenges. Many of the epidemiological risk factors and biological processes that lead to viral-induced ARDS are shared with IPF. In addition, many of the current and emerging antifibrotic drugs could have therapeutic potential for treating severe COVID-19 and preventing the long-term fibrotic consequences that might follow this pandemic. Ultimately, we hope the observations highlighted in this Personal View will help the respiratory and critical care communities to work together on well designed studies of antifibrotic therapies for severe COVID-19 pneumonia.

**Contributors**

All authors did the literature search and drafted sections of the manuscript. RGJ combined and edited the drafts, prepared the figures, and supervised the manuscript. All authors subsequently revised the manuscript.

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