Review Article

Exploring the common pathophysiological links between IPF, SSc-ILD and post-COVID fibrosis

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ABSTRACT

In coronavirus disease 2019 (COVID-19) patients, dysregulated release of matrix metalloproteinases occurs during the inflammatory phase of acute respiratory distress syndrome (ARDS), resulting in epithelial and endothelial injury with excessive fibroproliferation. COVID-19 resembles idiopathic pulmonary fibrosis (IPF) in several aspects. The fibrotic response in IPF is driven primarily by an abnormally activated alveolar epithelial cells (AECs) which release cytokines to activate fibroblasts. Endoplasmic reticulum (ER) stress is postulated to be one of the early triggers in both diseases. Systemic sclerosis (SSc) is a heterogeneous autoimmune rare connective tissue characterised by fibrosis of the skin and internal organs. Interstitial lung disease (ILD) is a common complication and the leading cause of SSc-related death. Several corollaries have been discussed in this paper for new drug development based on the pathogenic events in these three disorders associated with pulmonary fibrosis. A careful consideration of the similarities and differences in the pathogenic events associated with the development of lung fibrosis in post-COVID patients, IPF patients and patients with SSc-ILD may pave the way for precision medicine. Several questions need to be answered through research, which include the potential role of antifibrotics in managing IPF, SSc-ILD and post-COVID fibrosis. Many trials that are underway will ultimately shed light on their potency and place in therapy.

KEY WORDS: IPF, post-COVID fibrosis, SSc-ILD

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has been associated with respiratory symptoms ranging from mild to severe. Severe pneumonia and acute respiratory distress syndrome (ARDS) leading to death occur in susceptible individuals. In spite of recovering from COVID, many patients with moderate to severe COVID continue to have symptoms such as cough and dyspnoea (long COVID-19 syndrome). Important post-COVID-19 complications include the development of pulmonary fibrosis, which has been observed to occur in patients in the intensive care unit (ICU) who develop ARDS.[1] These patients remain hypoxaemic, although they are given adequate treatment. Imaging studies have demonstrated fibrotic changes in the form of traction bronchiectasis, architectural distortion and septal thickening, similar to the changes seen in other fibrotic

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lung diseases.[2] The correlates for the severity of fibrosis are advanced age, comorbid diseases, severity of lung disease, length of ICU stay and mechanical ventilation.[3] Post-COVID fibrosis may occur in non-ICU patients also.

Acute inflammation occurs in lungs after acute injury or infection. It can lead to epithelial and endothelial damage, reduced integrity of these tissues and finally results in oedema, migration of leucocytes and angiogenesis. Healing of the tissue injury through apoptotic and phagocytic pathways helps restore normal tissue architecture. But the persistent presence of radiation, allergens or toxic chemicals is associated with a dysregulated healing response resulting in a pathogenic fibrosis. Thus, the trio of inflammation, tissue damage and tissue regeneration acts in concert to lead to fibrosis in the lung tissues.[4]

Two other diseases commonly associated with lung fibrosis include idiopathic pulmonary fibrosis (IPF) and interstitial lung disease (ILD) associated with systemic sclerosis (SSc-ILD). Little is known about the common mediators that play a role in the development of fibrosis in these three disorders. The question arises if there is a common pathogenic pathway linking these disorders. A study of the common pathogenic mediators and events of these three diseases can provide an insight into preventive measures and can also provide a guide for new drug development targets against the devastating complication of pulmonary fibrosis.

Pulmonary fibrosis has a significant negative impact on the quality of life of the patient. Hence, prevention and effective symptomatic management of this complication will be an important step in reducing the morbidity and mortality in patients at risk of developing pulmonary fibrosis.

COVID-19–related lung fibrosis

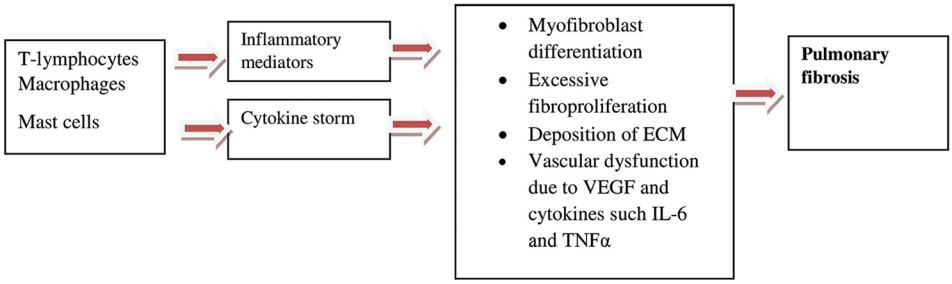
SARS CoVid 2 infection primarily targets the epithelial cells and also lung fibroblasts.[1] Lung fibroblasts respond to activation by inciting agents such as cigarette smoke as well as to cues received from leucocytes and epithelial cells. Hence, the inflammatory mediators in SARS-CoV-2 infection could activate myofibroblast differentiation and lead to deposition of extracellular matrix (ECM).[1]

COVID-19 resembles IPF in several aspects. Endoplasmic reticulum (ER) stress is postulated to be one of the early triggers in both diseases. Similar angiotensin type 2 (AT2) cytopathic changes may occur in both disorders, such as damage to DNA leading to arrest in a transient, damage-induced progenitor state and senescence-associated secretory phenotype. In the SARS-CoV-2 infection, the cytokine storm may be an additional mediator of damage. The cytokine storm is mediated by T lymphocytes and macrophages, with a large contribution from mast cells.[4,5] The ER stress induced in the AT2 cells activates host immune response and alveolar cytopathic changes in both the disorders[6] [Figure 1]. Extensive deposition of eosin-positive collagenous materials has been seen in autopsies of COVID-19–affected lung compared to normal lung tissues.[6]

In COVID-19 patients, dysregulated release of matrix metalloproteinases occurs during the inflammatory phase of ARDS, resulting in epithelial and endothelial injury with excessive fibroproliferation. Vascular dysfunction (due to vascular endothelial growth factor [VEGF] and cytokines such as interleukin [IL]-6 and tumour necrosis factor [TNF]-α) is the trigger for switch from ARDS to fibrosis[7-14] [Figure 1].

IPF-related lung fibrosis

IPF is considered to be a chronic, progressive lung disease of unknown aetiology. IPF commonly affects elderly patients over 60 years of age.[15] Patients suffering from IPF have lung function decline, and death ensues within approximately 3 years of diagnosis. Periods of transient clinical stability may ensue, but continued progression of the disease is expected to occur.[15,16] IPF was once considered to be a chronic inflammatory process,[17] but recent evidence has made researchers propose that



New drug development corollaries for COVID -19 related pulmonary fibrosis

1. Do antifibrotics have role to play in prevention and treatment of post-COVID fibrosis?
2. Development of specific mast cell stabilizers to prevent cytokine storm?

Figure 1: Pathogenic events in pulmonary fibrosis in SARS-CoV-2 infection

the fibrotic response in IPF is driven primarily by an abnormally activated alveolar epithelial cells (AECs) which release cytokines to activate the fibroblasts.[16] This initiates aberrant epithelial–fibroblast communication, induction of matrix-producing myofibroblasts and considerable ECM accumulation and remodelling of lung interstitium.[18] IPF is typified by the progressive and fatal accumulation of fibroblasts and ECM in the lung, leading to distortion of the lung architecture and reduction in lung function. IPF is caused by aberrant or exuberant wound-healing processes resulting in pathological fibrosis. The environmental stimuli that trigger IPF are yet to be identified, but available evidence suggest a role of injury to the alveolar epithelium. Repeated epithelial injury and the ensuing AEC death may lead to a series of events such as the migration, proliferation, activation and myofibroblast differentiation of fibroblasts, resulting in the accumulation of these cells and the ECM. These activated fibroblasts cause additional AEC injury and death, thus creating a vicious cycle of profibrotic epithelial cell–fibroblast interactions [Figure 2].

In IPF, the development of pulmonary fibrosis is attributed to the interaction of platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) with pulmonary mesenchymal cells.[19] TGF-β is present in cells such as fibroblasts and in AECs, macrophages, bronchial epithelium and ECM. TGF-β plays a critical role in the development of IPF. Other growth factors implicated in promoting the profibrogenic process of the lung after injury include VEGF and epidermal growth factor (EGF). In IPF, impaired tissue homeostasis releases pro-inflammatory cytokines and metalloproteinases, referred to as the 'secretory phenotype related to ageing' (SPRA).[20] Promoters of premature aging in IPF include oxidative stress, DNA damage telomere deficiency and mitochondrial dysfunction. Decreased ability of bone marrow-derived mesenchymal stem cells (BMSCs) to proliferate and mature also contributes to fibrosis.[20]

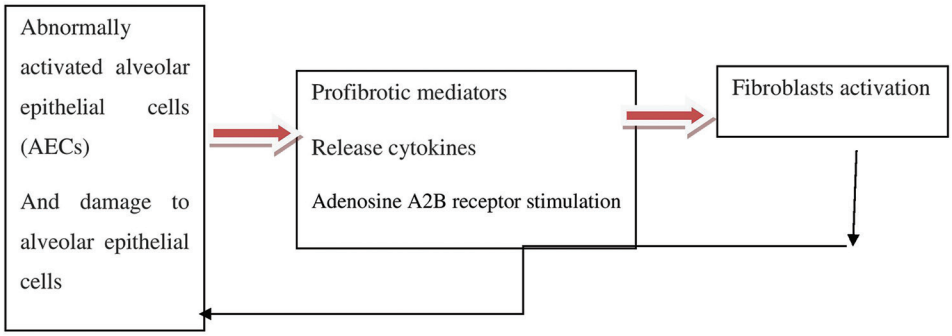
Chemokines (TNF-α and TGF-β) released lead to cellular and ECM interactions, causing fibrosis and disease progression. Activated myofibroblasts deposit an increased amount of altered ECM components, destroying normal alveolar architecture and disrupting gas exchange.[18] Abnormal ECM deposition leads to the progression of IPF. Changes in ECM composition lead to an alteration of the cell behaviour, and a positive feedback loop ensues between fibroblasts and aberrant ECM, leading to fibrosis.[18] Fibroblasts from the lungs of IPF patients have demonstrated an increased production of fibronectin.[20]

Another factor that drives the differentiation of pulmonary fibroblasts is the adenosine A2B receptor stimulation. It has been implicated in the development of lung fibrosis related to IPF.[20,21]

The occurrence of aberrant lung remodelling with bronchodilation of alveolar tissue is also important in IPF fibrosis progression. Abnormal activation of airway basal cells of the conducting airways up to the respiratory bronchioles may lead to re-epithelisation of damaged alveolar epithelium and bronchodilation of alveolar spaces.

SSc-ILD–related fibrosis

Systemic sclerosis is a rare heterogeneous autoimmune connective tissue characterised by fibrosis of the skin and internal organs. ILD is a common complication and the leading cause of SSc-related death.[22] SSc-ILD may occur within 10 years of diagnosis in patients with limited or diffuse cutaneous subtypes of SSc.[17]



New drug development corollaries for IPF:

1. An "anti-aging" agent that kills senescent type II alveolar epithelial cells can lead to prevention of lung fibrosis in IPF.
2. Targeting TGF-beta effects can help modulate the development of fibrosis
3. The development of A2B receptor antagonists may represent a therapeutic option in IPF

Figure 2: The vicious cycle of profibrotic epithelial cell–fibroblast interactions in IPF. IPF = idiopathic pulmonary fibrosis

Vascular injury is an early event in the pathogenesis of SSc-ILD and is associated with an increased formation of alveolar capillaries, circulating endothelial cells and expression of endothelin-1. Immune complexes (ICs) can activate human monocytes and thus promote lung fibroblast migration due to osteopontin (OPN) secretion, which is enhanced by autocrine monocyte colony stimulating factor (MCSF) and IL-6 activity [Figure 3].

Several diverse cells such as myofibroblasts, fibroblasts, endothelial cells and T lymphocytes are involved in inflammatory activation. Lymphocyte activation, release of cytokines and autoantibody production modulate the immunological response.[23] The distinctive features of ILD in SSc include endothelial lesions, fibroblast proliferation and differentiation of normal lung fibroblasts to a myofibroblast phenotype, and activation of coagulation proteases such as thrombin.[24]

A common feature of both IPF and SSc-ILD is the activation of macrophages with a similar chemokine expression and similar T-cell profiles (Th2-increased T_{regs}, Th22, Th17, increased ratio of CD4 to CD8 T cells).[25]

They differ in their the B-cell profiles and T-cell chemokine profiles (IL-4, IL-5, IL-10 and IL-17 for IPF and IL-4, IL-5, IL-6, IL-10, IL-13 and IL-22 for SSc-ILD).[26] In SSc-ILD, myofibroblasts are the chief effector cells in ECM remodelling.[27] The chemokine IL-6 plays a critical role in SSc by enhancing collagen synthesis through fibroblast stimulation, myofibroblast differentiation and inhibiting the secretion of metalloproteinase.[26]

DISCUSSION

Common proposed pathogenic link: IPF, SSc-ILD & post-COVID fibrosis

Alveolar epithelial injury is considered to be the first step in the pathogenesis of fibrosis in IPF, SSc-ILD and post-COVID fibrosis. An endothelial injury may occur in SSc-ILD. There may be an acute injury in case of COVID-19 or a chronic injury in IPF and SSc-ILD. The next step is the migration of fibroblasts and their subsequent proliferation. These fibroblasts then transform into myofibroblasts.

Simultaneously, the interstitial pericytes, epithelial–mesenchymal transition and endothelial mesenchymal transition increase the myofibroblasts' recruitment. Fibroblast migration is facilitated by Fibroblast growth factor (FGF), TGF-β, IL-1, IL-6 EGF & PDGF, in IPF, SSc ILD and post-COVID fibrosis as well. The next step in the pathogenesis of fibrosis in these disorders is collagen deposition by the myofibroblasts, resulting in progression of lung fibrosis. These are the common links unfurled currently in IPF, SSc-ILD and post-COVID fibrosis.

In the pre-COVID era, fibrosis of lungs was chiefly associated with a wide array of disorders grouped under ILD, where the common features were chronic inflammation in the lungs and varying degrees of lung fibrosis.[2] With the onset of the COVID-19 pandemic, a significant increase in the number of patients with complications of pulmonary fibrosis is expected globally.

Both stable and progressive fibrotic lung disease are associated with significant morbidity and impaired quality of life [Figure 4]. Alveolar epithelial injury is one of the primary initiating mechanisms of pulmonary fibrosis, but activated fibroblasts are the primary effector of the disease.[28]

Clinical correlates of pathogenic events to be considered when selecting drugs for disorders associated with lung fibrosis

For the management of COVID-19, repurposing of drugs has been the earliest approach adopted with varying degrees of success. Currently, our understanding about the pathogenic mechanism involved in post-COVID fibrosis is evolving.

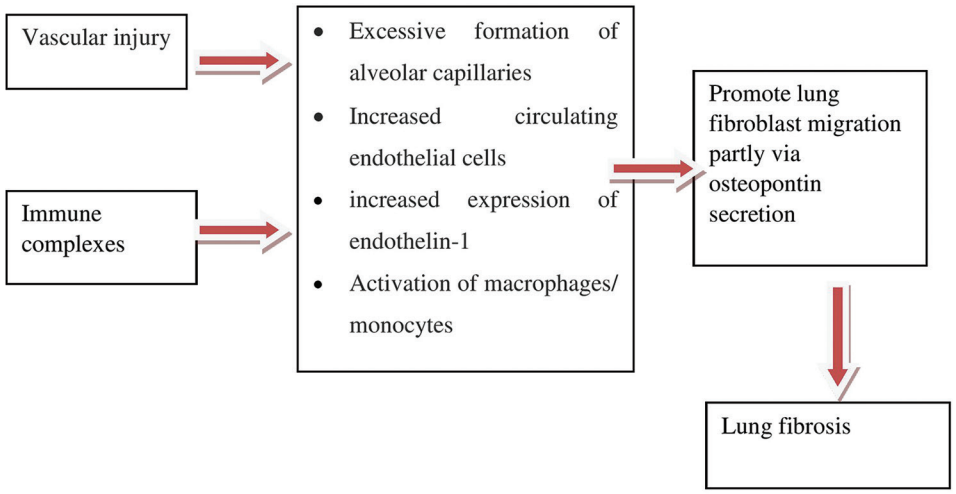


Figure 3: Development of lung fibrosis in SSc-ILD. SSc-ILD = interstitial lung disease associated with systemic sclerosis

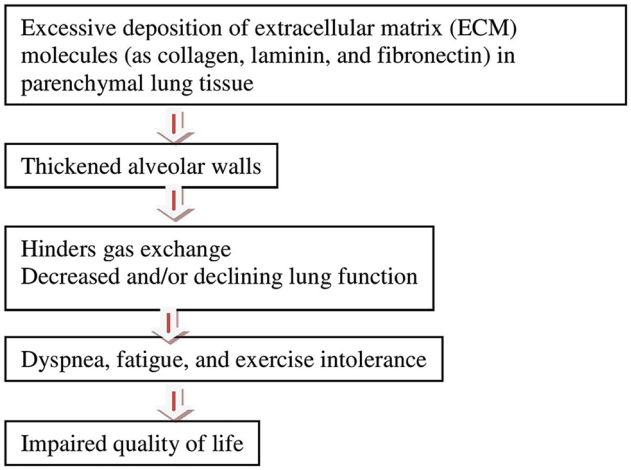


Figure 4: Pathogenic events in COVID-19 leading to impaired quality of life in the patients. COVID-19 = coronavirus disease 2019

Since ILDs are presumed to be inflammatory disorders, especially in the early phase, corticosteroids and immunosuppressants have been tried as treatments for ILDs. Subsequently, drugs are categorised based on whether they were immunomodulatory or antifibrotic drugs.[29] Immunomodulator drugs used include corticosteroids, cyclophosphamide, mycophenolate mofetil and monoclonal antibodies such as rituximab. Tocilizumab has been used for the treatment of SSc-ILD and refractory SSc-ILD.[29] Haematopoietic stem cell transplant (HSCT) is a new treatment option for patients with severe SSc-ILD or SSc-ILD that is refractory to standard therapy and may not develop complications after transplantation. Lung transplant is an option for selected patients with refractory disease.[30]

Antifibrotic drugs for management of IPF include pirfenidone and nintedanib. These drugs are effective in slowing disease progression.[29] Currently, antifibrotics are the only approved drugs in the management of ILD. Physicians treating patients with long COVID syndrome with lung fibrosis have been prescribing antifibrotic drugs such as pirfenidone and nintedanib.

Pirfenidone is an oral antifibrotic agent which has been approved for the treatment of IPF.[31] Pirfenidone controls the activity of the diverse cytokines such as TGF-β and TNF-α. Pirfenidone inhibits proliferation of fibroblasts and synthesis of collagen and reduces markers of fibrosis.[32] Pirfenidone at a dose of 2403 mg/day reduces disease progression, as reflected by lung function, exercise tolerance and progression-free survival, in patients with IPF. Pirfenidone has an acceptable tolerability and has improved survival rates in IPF patients. In the ASCEND trial, 278 IPF patients were treated with 2403 mg/day of pirfenidone for 52 weeks. The pirfenidone-treated group demonstrated 45.1% lesser decline in the forced vital capacity (FVC) from baseline, compared to the control group. The CAPACITY, RECAP and PASSPORT studies included patients treated with 2403 mg/day of pirfenidone, and the patients continued treatment for a long term. In the PASSPORT study, one-third of IPF patients treated with pirfenidone in real-life settings were still under treatment, 2 years after initiation.[31,33] An Indian study by Dhooria *et al*.[34] demonstrated an 81% reduced risk of death with 2403 mg/day dose of pirfenidone, compared with a lower dose. An integrated safety analysis from five clinical trials demonstrated that pirfenidone is generally well tolerated.

Nintedanib is an intracellular inhibitor of multiple tyrosine kinases, including the VEGF, FGF and PDGF receptors. The results of the Phase II TOMORROW trial, a randomised, double-blind, placebo-controlled trial involving 432 patients with IPF, indicated that 12 months of treatment with 150 mg of nintedanib twice daily reduced the decline in FVC, decreased the frequency of acute exacerbations and preserved health-related quality of life.[35] INPULSIS Phase III studies were randomised, double-blind, placebo-controlled, parallel-group studies conducted at 205 sites in 24 countries across several continents such as the Americas, Europe, Asia and Australia. These studies demonstrated that in patients with IPF, nintedanib reduced the decline in FVC, indicating a slowing of disease progression.[18] But nintedanib was frequently associated with diarrhoea, which led to discontinuation in less than 5% of patients.[17] Real-world data confirms the findings of earlier clinical trials. Recent real-world studies also suggest that nintedanib stabilises lung function till lung transplantation.[36] In the INBUILD trial, the efficacy of nintedanib was evaluated in patients with progressive fibrosing ILD (PF-ILD). Study results demonstrated reduction in FVC decline akin to older published trials. An important aspect to consider is the fact that the benefits were observed regardless of the interstitial pattern on high-resolution thoracic computed tomography. The relative reduction observed with a usual interstitial pattern (UIP) was 61%, while in the patients with non-UIP, the relative reduction was about 49%. The results were consistent regardless of the underlying aetiology of ILD.[37,38] In patients with SSc-ILD, nintedanib demonstrated a consistent reduction in the rate of decline of FVC by 44% over a period of 52 weeks compared to placebo.[39]

In the open-label INJOURNEY trial, the efficacy and safety of nintedanib with add-on pirfenidone was evaluated versus nintedanib alone in patients with IPF. The IPF patients enrolled in the study completed a 4–5-week run-in with nintedanib 150 mg twice daily. They were randomised to either of the two treatment groups, namely, nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times daily) or nintedanib 150 mg twice daily alone for 12 weeks. The primary end point evaluated the on-treatment gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were observed in 69.8% patients treated with nintedanib with add-on pirfenidone and in 52.9% patients treated with nintedanib alone. The mean change in FVC at the end of treatment

compared to the baseline was −13.3 ml in patients treated with nintedanib with add-on pirfenidone (n = 48) and −40.9 ml in patients treated with nintedanib alone (n = 44). These findings need to be evaluated through further clinical trials.[40]

Currently, there are few ongoing trials of nintedanib and pirfenidone in post-COVID fibrosis ranging from 4 to 52 weeks and from 4 to 28 weeks, respectively. The trial results will provide insights into the efficacy of antifibrotics in preventing as well as treating fibrosis in moderate to severe COVID-19 patients. The study by Umemura *et al*.[41] enrolled 30 patients with COVID-19 for a period of 28 days. Significantly shorter length of mechanical ventilation (MV) was observed in the nintedanib group. Also, in this study, computed tomography volumetry showed that the percentages of high-attenuation areas were significantly lower in the nintedanib group on weaning from MV (38.7% vs. 25.7%, P = 0.027), thus proving the role of nintedanib in minimising lung injury.

CONCLUSION

Several corollaries have been discussed in this paper for new drug development based on the pathogenic events. New drug development will have to be based on modulating the pathogenic events. Targets for new drugs to prevent or treat pulmonary fibrosis can be defined by studying the pathogenic events involved in lung fibrosis of the three disorders discussed. A careful consideration of the similarities and differences in the pathogenic events associated with the development of lung fibrosis in post-COVID patients, IPF patients and patients with SSc-ILD may pave the way for precision medicine.

Several questions need to be answered through research, which include the potential role of antifibrotics in post-COVID fibrosis and mast cell stabilisers' role in modulating COVID-19–related pulmonary fibrosis. Some recent evidence confirm the role of antifibrotics in minimising COVID-related lung injury, and many trials are underway, which will ultimately shed light on their potency and place in therapy.

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Conflicts of interest

Dr. Rajesh Swarnakar has no conflict of interest to declare. Dr. Neeraj Markandeywar and Dr. Suyog Mehta are full-time employees of Sun Pharma Laboratories Limited. Dr. Yogesh Garje is a full-time employee of Sun Pharmaceutical Industries Limited.

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