

Review Article

Rationale of Using Common Antifibrotic Therapy in Post COVID Fibrosis

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Abstract:

Different mechanisms of lung injury in COVID-19 have been described, like viral to immune-mediated mechanisms. Lung injury can be either subsequent to chronic inflammation or an idiopathic and genetically influenced process. Pulmonary fibrosis can occur with acute lung injury & a known sequela to ARDS. However, persistent radiological abnormalities after ARDS are of little clinical significance and have dwindled with protective lung ventilation.

Pulmonary fibrosis is associated with permanent pulmonary architectural distortion and irreversible lung dysfunction. Available clinical, radiographic, and autopsy data has indicated that pulmonary fibrosis is central to severe acute respiratory distress syndrome (SARS) and MERS pathology, and current evidence suggests that pulmonary fibrosis could also complicate infection by SARS-CoV-2

The aim of this review is to explore the current literature on the pathogenesis of lung injury in COVID-19 infection, its risk factors & to find out the possible effective therapy within the existing medication. After literature review, we conclude that, currently there are no approved therapies for SARS COV2. Trials are based on drugs that are already approved for other diseases, have acceptable safety profiles or have been effective in animal studies against the other two highly pathogenic coronaviruses. Apart from the potent use of antivirals to reduce the viral effects, the use of antifibrotic therapies could also be under consideration based on the pulmonary fibrotic disease observed after COVID-19 recovery.

Pirfenidone and Nintedanib are the two approved anti fibrotic drugs for Idiopathic Pulmonary Fibrosis (IPF). Despite having different modes of action, both are effective in attenuating the rate of lung function decline and are widely considered to improve life expectancy.

Key Words: COVID-19, Fibrosis, Antifibrotic



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Introduction

An outbreak of the novel coronavirus nCoV-19 (SARS-CoV-2), responsible for the coronavirus disease-19 (COVID-19), was first reported in Hubei province, China, on December 31, 2019. It has rapidly spread globally with approximately 3 million confirmed infections and 200,000 deaths within

the first four months.¹ Similar to the etiological agents in previous human coronavirus outbreaks (severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)), SARS-CoV-2 primarily affects the respiratory system. Clinical, radiographic, and autopsy reports of pulmonary fibrosis were commonplace following SARS and MERS, and current evidence suggests pulmonary fibrosis could complicate infection by SARS-CoV-2.² Pulmonary fibrosis is also a known sequela of severe and/or persistent damage to the lung from other causes such as connective tissue disorders, chronic granulomatous diseases, medications, and respiratory infections.³

Fibrosis could be viewed as a consequence of a disordered wound healing process and may be directly related to the

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severity of an inciting event. Various mechanisms of lung injury in COVID-19 have been described, with both viral and immune-mediated mechanisms being implicated.⁴ Apart from these, additional factors could predispose individuals to severe lung injury and lead to an increased risk of mortality or pulmonary fibrosis in survivors. In this review, we discuss the pathological mechanisms involved in the development of fibrosis and explore the pathogenesis of lung injury in COVID-19 infection and review reports of pulmonary fibrosis following previous and current human coronavirus outbreaks. In addition, we review the evidence in support of the risk factors for the development of lung fibrosis following COVID-19 infection and putative risk mitigation strategies.^{4,5}

Methodology

We searched thoroughly relevant articles using PubMed and Cochrane Library up to 30 November 2020, for all studies related to COVID-19, SARS, and MERS, focusing to acute lung injury and pulmonary fibrosis, using a combination of standardized search terms. Cohort studies, cross-sectional studies, and randomized controlled trials were identified and screened for relevance. Articles on the mechanisms of acute lung injury, pulmonary fibrosis, and SARS-CoV-2-induced pulmonary damage, in addition to reports on pulmonary fibrosis following SARS, MERS, and COVID-19 as well as predictors of pulmonary fibrosis, were selected for a full-text review.

Pulmonary fibrosis in COVID-19

Pulmonary fibrosis is a known sequela to ARDS. Although pulmonary fibrosis can occur in the absence of a clear-cut inciting agent, it is more commonly associated with severe lung injury. Various mechanisms of lung injury in COVID-19 have been described, with both viral and immune-mediated mechanisms being implicated. Apart from these, additional factors could predispose individuals to severe lung injury and lead to an increased risk of mortality or pulmonary fibrosis in survivors.⁵

An initial phase of lung injury is followed by acute inflammation as well as an attempt at repair. This process can result in the restoration of normal pulmonary architecture, or it may lead to pulmonary fibrosis with architectural distortion and irreversible lung dysfunction. The repair process involves regeneration by native stem cells and connective tissue deposition to replace areas of defect. Alveolar macrophages play a central role in this process by phagocytizing alveolar debris and the production of cytokines and growth factors involved in the repair process. The process of repair involves angiogenesis, fibroblast activation, and collagen deposition.⁶

Role of Fibroblasts in Pulmonary Fibrosis in Coronavirus Disease

Fibroblasts are the “effector” cells in fibroproliferation. They are mesenchymal cells found in every tissue in the body, playing a vital role in structural support as well as tissue repair following injury. They secrete and regulate the extracellular matrix (ECM).⁷ Fibroblasts are found in the alveolar interstitium.⁸ Following alveolar injury, fibroblast migration to the site of the injury is stimulated by fibroblast growth factor (FGF), PDGF, TGF- α , and chemokines. Fibroblasts proliferate and differentiate into myofibroblasts under the influence of EGF, PDGF, TGF- α , and IL-1⁷ Fibroblasts synthesize collagen, fibronectin, and ECM ground substance. In addition to ECM synthesis, myofibroblasts play an additional role in the inflammatory response by secreting IL-1, IL-6, IL-8, and monocyte chemoattractive protein-1 (MCP-1). In addition, mediators of the repair process such as VEGF and TGF- β are secreted by myofibroblasts.⁹

Myofibroblasts produce denser but more disorganized ECM than fibroblasts and persist longer at the site of injury. Due to the presence of α -smooth muscle actin, they are able to contract irreversibly leading to a spatial reorganization of collagen fibrils, an important feature of fibrogenesis [9]. Other proposed origins of myofibroblasts include pulmonary interstitium pericytes, epithelial mesenchymal transition, and endothelial mesenchymal transition.¹⁰ Epithelial/endothelial to mesenchymal transition occurs via a molecular reprogramming of epithelial/endothelial cells to acquire biological properties of mesenchymal cells.^{11,12} Through this process, alveolar epithelial cells lose their markers such as surfactant proteins, mucin, adhesion molecules (E-cadherin and claudin), and cytoskeletal proteins.^{13,14} These markers are replaced by mesenchymal cell markers such as α -smooth muscle actin, vimentin, and fibronectin.¹⁵

Role of Cytokines

Macrophage activation during the acute immune response occurs through two pathways known as the classical (M1) and the alternative (M2) pathways. The M1 pathway is initiated by the interaction of PAMPs and DAMPs with macrophage receptors in the innate immune response and stimulation by interferon- γ from the T-cell adaptive response. This pathway leads to the production of reactive oxygen species, antimicrobial products, and proinflammatory cytokines responsible for the initial phase of acute inflammation. The M2 pathway is triggered by the effect of IL-4 and IL-13 produced by T-lymphocytes and other cells. This pathway leads to the production of cytokines and growth factors involved in the tissue repair process. It also inhibits the inflammatory process by decreasing the M1 pathway and plays a central role in the formation of scar tissue.¹⁶

In a study of 62 patients by Zhou et al., fibrotic changes were seen in 21 (33.9%) patients, with this finding more likely to occur in advanced-phase disease (8-14 days after the onset of symptoms) than early phase of the disease (d+7 days after the onset of symptoms). Similarly, Pan et al. reported fibrotic changes on the chest CT scan of 11 out of 63 patients taken during the acute illness.¹⁷

These imaging findings are supported by autopsy reports. Reports on 4 patients who died of COVID-19 pneumonia reveal features of diffuse alveolar damage with areas of consolidation by fibroblastic proliferation and deposition of ECM and fibrin in the alveolar spaces. Similarly, lung explants from 3 patients who had lung transplant for end-stage ARDS show extensive fibrosis of the lungs. The finding of fibrotic changes early in the disease suggests an attempt at repair following pulmonary injury. It is however too early in the process of the disease to determine if this finding would resolve with time or progress to fixed pulmonary fibrosis.

4. Risk Factors for Pulmonary Fibrosis following SARS-CoV-2 Infection :

a. Age:

Lung fibrosis is reported more often in individuals with advanced age. The median age for the diagnosis of idiopathic pulmonary fibrosis is 65 years, and it rarely occurs before 50 years. The exact reason for this association is unknown; however, older people are more susceptible to both SARS and MERS similar to SARS-CoV-2 infection and are more likely to have severe symptoms.^{18,19}

b. Illness Severity:

According to the World Health Organization, 80% of SARS-CoV-2 infections are mild, 14% develop severe symptoms, and 6% will become critically ill. Factors associated with increased disease severity include comorbidities such as hypertension, diabetes, and coronary artery disease. Laboratory findings of lymphopenia, leukocytosis, and elevated lactate dehydrogenase (LDH) correlate with increased disease severity. Serum LDH level has been used as a marker of disease severity following acute lung injuries. It is an indicator of pulmonary tissue destruction and correlates with the risk of mortality. Peaked LDH level was found to significantly correlate with the risk of pulmonary fibrosis following MERS-CoV infection. Similarly, a follow-up study at 6 months after discharge in SARS patients shows a significant relationship between elevated levels of LDH during acute illness and an increased risk of developing pulmonary fibrosis.²⁰

c. Length of ICU Stay and Mechanical Ventilation:

COVID19 severity is closely related to the length of ICU stay. Mechanical ventilation poses an additional risk of

ventilator-induced lung injury (VILI). VILI is an acute lung injury arising from or exacerbated by mechanical ventilation.

In a follow-up study of 27 patients who had mechanical ventilation for ARDS, 110–267 days after extubation, 23 (85%) had pulmonary fibrosis with a significant relationship to the duration of pressure-controlled inverse-ratio ventilation ($P < 0.001$).²¹

d. Smoking

Epidemiological studies show a high incidence of familial and sporadic IPF in smokers when compared to nonsmokers. Smoking is associated with chronic oxidative stress, increased expression of inflammatory cytokines, and interstitial lung fibrosis. A systematic review by Vardavas and Nikitara shows that smokers were 1.4 times more likely (RR = 1.4, 95% CI: 0.98–2.00) to have severe symptoms of COVID-19 and 2.4 times more likely to need ICU admission and mechanical ventilation or die compared to nonsmokers (RR = 2.4, 95% CI: 1.43–4.04).²²

e. Chronic Alcoholism:

Clinical and experimental studies show it causes glutathione depletion, chronic oxidative stress, inflammation, and induction of TGF- β in the lungs, thereby increasing the risk of acute lung injury and pulmonary fibrosis. By increasing the risk of lung injury and expression of TGF- α , a potent fibroproliferative cytokine, chronic alcohol abuse could potentially increase the chance of developing pulmonary fibrosis.^{23,24}

5. Is there a role for antifibrotic therapy ?

Currently, there are no approved therapies for SARS COV2. Trials are based on drugs that are already approved for other diseases, have acceptable safety profiles or have been effective in animal studies against the other two highly pathogenic coronaviruses.

Steroid, specially Dexamethasone are widely using to control inflammation as well as to stop cytokines storm in some patients.

Tocilizumab, an immunosuppressive drug, mainly used for the treatment of rheumatoid arthritis are also in focus to stop Cytokines Storm. But has been failed to prove any benefit of increase survival in COVID pneumonia.²⁵

Antifibrotic Drugs:

Pirfenidone and Nintedanib are the two approved antifibrotic drugs for IPF. Despite having different modes of action, are both effective in attenuating the rate of lung function decline and are widely considered to improve life expectancy.^{26,27}

Apart from the potent use of antivirals to reduce the viral effects, the use of antifibrotic therapies could also be under

consideration based on the pulmonary fibrotic disease observed after COVID-19 recovery.

Pirfenidone exerts antifibrotic, antioxidative and antiinflammatory properties. pirfenidone reduces LPS-induced acute lung injury and subsequent fibrosis by suppressing NLRP3 inflammasome activation .

The current literature is suggestive that any potential antifibrotic intervention should be considered within the first week of ARDS onset & before starting Mechanical Ventilations.

- Pirfenidone is a pyridone that is 2-pyridone substituted at positions 1 and 5 by phenyl and methyl groups respectively. An anti-inflammatory drug used for the treatment of idiopathic pulmonary fibrosis. It has a role as a non-narcotic analgesic, a non-steroidal anti-inflammatory drug and an antipyretic.²⁷
- Nintedanib is an orally active small molecule tyrosine kinase inhibitor that has been evaluated in large clinical trials for the treatment of IPF .The polypharmacology of nintedanib on the receptors for FGF, PDGF and VEGF, and on non-receptor kinases like Src results in a broad inhibitory activity on the downstream signalling cascades of fibroblasts and myofibroblasts and, potentially also on cells involved in angiogenesis in the lung.²⁶

Effective Antifibrotic for IPF can prevent Covid-19 fibrosis

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 showed that treatment with Nintedanib reduced the time to first acute exacerbation of IPF. Putative treatment benefits with antifibrotic therapy in reducing the prevalence of acute exacerbations of IPF were observed in patients already established on antifibrotic therapy.²⁷

In the INPULSIS trials on Nintedanib, there were strong trends towards a reduction in the frequency of acute exacerbations of IPF when the two trials were pooled.[26]

In the INBUILD trial on Nintedanib in other non-IPF disorders The primary end point was the change in FVC . Trends between treatment and placebo groups were shown, with significant differences at 4–6 weeks.²⁷

In the ASCEND trial Of Pirfenidone , A decline in FVC occurred slowly in both chronic fibrotic lung disease and Idiopathic Pulmonary Fibrosis.^{28,29}

Acute exacerbation of IPF has the clinical, imaging, and histological characteristics of diffuse alveolar damage mimicking ARDS.³⁰ 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 leading to diffuse alveolar damage(ARDS), threatens for Mechanical Ventilation has supervened

Conclusion :

The COVID-19 pandemic is bringing huge economic, social, and health-care challenges. In this context, it is important to try , predict and prepare for these challenges.

Many of the epidemiological risk factors and biological processes that lead to this Novel viral-induced ARDS and finally Lung fibrosis.

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.

Finally , we hope that ,this evidence-based discussion will help the respiratory and critical care communities to work together for further research on well designed studies of antifibrotic therapies for severe COVID-19 pneumonia.

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