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Letter to Editor

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Anti-fibrotic drugs dealing with pulmonary fibrosis after COVID-19-associated acute respiratory distress syndrome

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus which is responsible for coronavirus disease (COVID-19), uses an angiotensin-2-converting enzyme (ACE2) as a cell receptor in humans. Initially, there is interstitial lung damage after infection, and then parenchymal lesions appear, which if not managed appropriately could worsen. Available data suggests that around 40% of patients with COVID-19 develop acute respiratory distress syndrome (ARDS), and 20% of these patients who develop ARDS require invasive and advanced modes of ventilation[1]. Cytokine storm, severe inflammation leading to injury to the lung parenchyma, oxidative stress, presence of reactive oxygen species damage, and increased permeability of the vascular bed are responsible for the development of ARDS. If the patient recovers from this insult, the affected areas of the lungs will manifest as fibrosis on imaging. Pulmonary fibrosis develops after the acute event due to the destruction of the lung parenchyma, persistence of fibroblasts and myofibroblasts, deposition of the extracellular matrix and collagen, and also in the presence of predisposing factors like smoking, elderly age and underlying immunosuppression[2].

The prevalence of post-COVID-19 fibrosis is not clear yet but around one-third of patients developing severe ARDS had fibrosis. It has been reported that around 47% of patients had impaired diffusing capacity of the lungs for carbon monoxide, and 25% had reduced total lung capacity which is an alarming number[3]. Once the pandemic gets under control, clinicians would be facing the challenge of managing symptomatic patients with lung fibrosis secondary to COVID-19 infection.

To date, definitive treatment of COVID-19 is not clear although several modalities have been used with variable success. Corticosteroids, anti-viral agents, immunomodulatory agents like hydroxychloroquine sulphate, serotherapy, inflammation inhibitors (tocilizumab), anticoagulation, and plasma therapy have been used at different phases of diseases with variable efficacy[4].

Pirfenidone and nintedanib are two agents approved for treating patients with idiopathic pulmonary fibrosis (IPF) and are referred to as an anti-fibrotic drug. Pirfenidone is an orally administered, pyridine compound approved for patients with mild to moderate IPF. The drug is well tolerated and has been shown to improve progression-free survival in IPF[5]. Nintedanib is a multiple tyrosine kinase inhibitor that acts through the inhibition of profibrotic mediators like platelet-derived growth factor, fibroblast growth factor, transforming growth factor (TGF)-β, and vascular endothelial growth factor, thereby reducing fibroblast activity and thus limits the progression of IPF[6]. In experimental studies, pirfenidone has exhibited favorable properties like anti-inflammatory and anti-fibrotic effects, anti-apoptotic effects, and downregulation of ACE receptor repression which has however not yet been tested or validated in COVID-19 patients. Table 1 shows the mechanism of action of both pirfenidone and nintedanib and how they can have potentially beneficial effects in preventing or interfering with lung fibrosis after COVID-19 ARDS.

At present, there is an ongoing research where nintedanib and pirfenidone are being evaluated in patients with moderate to severe COVID-19. In a phase 2 trial (The stage of a clinical trial studying a drug or biological product, based on definitions developed by the U.S. Food and Drug Administration), nintedanib ethanesulfonate soft capsule 150 mg/12 h orally for 8 weeks is being compared with empty capsules (https://clinicaltrials.gov/ct2/show/NCT04338802). A phase 3 trial is ongoing to evaluate the safety and efficacy of adding pirfenidone 2 tablets thrice daily for 4 weeks or more, which

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Table 1. Mechanism of action of pirfenidone in general and its possible advantages in preventing pulmonary fibrosis in COVID-19 patients after ARDS.

Drugs	Mechanism of action	Role in preventing fibrosis in COVID-19 patients
Pirfenidone (5-methyl-1-phenyl-1H-pyridin-2-one)	(1) Inhibits fibroblast, epidermal, platelet-derived, and transforming beta-1 growth factors; (2) Modulates expression of pro-fibrotic factors and proinflammatory cytokines, and potentially suppresses the production of reactive oxygen species.	(1) Anti-inflammatory effects; (2) Anti-fibrotic effects; (3) Anti-oxidant; (4) Free oxygen radical scavenger.
Nintedanib (6-methoxycarbonyl-substituted indolinone)	(1) Inhibits multiple receptor tyrosine kinases and non-receptor tyrosine kinases (vascular endothelial growth factor receptor, fibroblast growth factor receptor, platelet-derived growth factor receptor, and colony-stimulating factor 1 receptor tyrosine kinases; (2) Inhibits all 3 subtypes of vascular endothelial growth factor receptor.	(1) Antiangiogenesis; (2) Antifibrotic effects; (3) Induces apoptosis.

will be compared with ongoing standard treatment of COVID-19 in severe or critical COVID-19 patients (https://www.clinicaltrials.gov/ct2/show/study/NCT04282902).

The results of these two clinical trials could be very important for the progress of fibrosis after COVID-19 ARDS in survivors and to provide a better quality of life to these patients. Further studies would be required to know the timing of initiation, dose, and duration of therapy with pirfenidone or nintedanib. It would be interesting to see if researchers could consider combining both drugs in these patients owing to their different mechanisms of action.

To conclude, once the efficacy and feasibility of antifibrotic medications are established, their use along with other supportive treatment modalities could reduce the respiratory issues resulting from pulmonary fibrosis as a consequence of COVID-19 ARDS.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

A.S.N.: Concepts, design, the definition of intellectual content, manuscript preparation, manuscript review; S.K.P.: Definition of intellectual content, manuscript editing; P.K.K.: Literature review, manuscript review; A.C.: Literature review, manuscript review.

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