LETTER TO EDITOR

Pulmonary Fibrosis in COVID-19 Recovered Patients: Problem and Potential Management

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Sir,

About 17 million people worldwide have recovered from COVID-19 till date, but concerns of long-term pulmonary complications still remain. Other genetically similar strains of the Coronaviridae family like the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) have caused pulmonary manifestations akin to COVID-19.

A 15-year follow-up study on healthcare workers who were infected with SARS-CoV identified that pulmonary fibrosis (38%) and femoral head necrosis (14%) were the most severe sequelae.[1] The pulmonary interstitial damage gradually decreased with time and mostly recovered within 2 years. The femoral head necrosis was non-progressive and partially reversible and was most likely induced by large doses of steroid therapy. Pulmonary fibrosis was also seen in 33% of patients in an early follow-up study of patients who recovered from MERS pneumonia.[2] In both the epidemics, pulmonary fibrosis involved multiple lobes and was associated with older age, greater duration of disease, ICU stay, higher chest radiographic deterioration patterns, and peak lactate dehydrogenase levels.[3,4]

Interstitial pneumonia is a common feature of COVID-19 and can be complicated by acute respiratory distress syndrome (ARDS). Pulmonary fibrosis is a recognized sequela of ARDS. An autopsy study on 159 patients with ARDS revealed that the incidence of fibrosis increased from 4% in the first week to 61% in more than three weeks, indicating that initiation of any possible intervention for fibrosis should be considered within the first week of onset of ARDS.[5] Even a small degree of residual fibrosis could result in considerable morbidity in older patients and patients with preexisting pulmonary conditions. Pulmonary postmortem findings in patients with COVID-19 also showed fibrotic changes in patients with severe and longer duration of the disease.[6]

Given the magnitude of the epidemic, the burden of post-COVID-19 fibrosis is likely to be high. Early analysis of patients with COVID-19 revealed that 47% of patients had impaired gas transfer consistent with pulmonary fibrosis or associated vasculopathy.[7] It is still unclear why only a certain proportion of patients recover and why some progress to pulmonary fibrosis. Dysregulated release of matrix metalloproteins during the inflammatory phase of ARDS causes epithelial and endothelial injury with fibroproliferation.[8] Some of the key mediators involved in the fibrotic process are transforming growth factor β (TGF-β), tumor necrosis factor α (TNF-α), and various growth factors. Several drugs have been suggested extrapolating from its efficacy in the treatment of chronic fibrotic disorders like idiopathic pulmonary fibrosis (Table 1). Based on evidence from the previous and current coronavirus epidemics, in patients with a high likelihood of developing fibrotic sequelae (old age, coronary heart disease, lymphopenia on admission, elevated interleukin levels, prolonged ICU stay, raised LDH levels, history of smoking, and chronic alcoholism), antifibrotic therapy may be considered. Clinical trials regarding the safety and efficacy of these drugs in the context of COVID-19 are the need of the hour.

Multiple strategies could be adopted to address this potential problem: effective antiviral treatment, dedicated outpatient clinics to follow up recovered patients, identification of patients at risk for long-term complications, serial chest imaging/PFT, and referral to rehabilitation centers. The British Thoracic Society has suggested a detailed clinical assessment, chest X-ray, and pulmonary function tests at 12 weeks of discharge along with a timely referral to a specialist in the presence of evidence of interstitial lung disease.[15] As the number of patients recovering from COVID-19 is increasing exponentially over the months, the long-term pulmonary sequelae are not to be ignored. Every center can therefore make plans and algorithms so that a timely diagnosis can be made and appropriate clinical care delivered, thereby possibly preventing the second wave of associated morbidity due to this overwhelming pandemic.

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Table 1: Summary of potential antifibrotic therapies in COVID-19 patients

Treatment modality	*Mechanism of action*	*Evidence as antifibrotic*	*Antiviral mechanisms*	*Evidence in COVID-19*
Pirfenidone	Regulates TGF-β and TNF-α *in vitro* Inhibits fibroblastic proliferation and collagen synthesis	Pooled analysis of CAPACITY and ASCEND trials—reduces the rate of progression in IPF at 1 year[9]	Inhibits IL-1, IL-6, and acute lung injury Downregulates expression of ACE receptor[10]	Ongoing clinical trial evaluating its efficacy and safety in severe and critical coronavirus infection Identifier: NCT04282902
Nintedanib	Tyrosine kinase inhibition—FGFR-1, PDGFR, and VEGFR-2 (profibrotic mediator) inhibition	INPULSIS trial and INBUILD trial—reduces the rate of decline in pulmonary function in IPF[11]	Inhibits IL-1 and IL-6	Ongoing clinical trial evaluating its efficacy and safety in the treatment of pulmonary fibrosis in moderate to severe COVID-19 Identifier: NCT0433802
Tetrandrine	Interferes with TGF-β signaling	Possible role in rat studies; attenuated airway inflammation and remodeling	Inhibits IL-1	Ongoing clinical trial evaluating its role on survival rate in COVID-19 Identifier: NCT04308317
Rapamycin	mTOR inhibitor	Idiopathic and radiation-induced pulmonary fibrosis[12]	Improved outcome in severe H1N1 pneumonia Role of mTOR signaling in MERS-CoV infection Antifungal property	No current evidence
Spironolactone	Inhibition of mineralocorticoid receptor Decrease in extracellular matrix turnover	Attenuates bleomycin-induced pulmonary fibrosis	Antioxidant; Alleviates acute pneumonia caused by lipopolysaccharides No evidence in postviral fibrosis	No current evidence
BG00011 (Biogen)	Anti-Avb6 integrins	Possible role in IPF—limited evidence and safety concerns[13]	No evidence	No current evidence
PRM-151	Recombinant human pentraxin—decreases the production of TGF-β	Possible role in IPF and bleomycin-induced fibrosis[14]	Prevents influenza virus internalization and infection *in vivo* and *in vitro*; Inhibits IL-6	No current evidence

TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; mTOR, mammalian target of rapamycin; IPF, idiopathic pulmonary fibrosis.

Authors' Contributions

Dr. Bhavana Kayarat helped in search strategy and drafting of the manuscript; Dr. Puneet Khanna contributed to conceptualization and editing; and Dr. Soumya Sarkar assisted in study selection, data extraction, drafting of the manuscript, and editing.

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