

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pandemic: Is Sequela the Bigger Threat?

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To the Editor,

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has been affecting the population worldwide for over six months now. Despite having a recovery rate of about 80%, around 32 to 55% of patients continue to have one or more symptoms at the 60-day follow-up period.¹

While long-term follow-up studies of coronavirus disease (COVID-19) patients are still underway, post-COVID-19 pulmonary fibrosis is one such complication being faced by clinicians worldwide. The exact prevalence of post-COVID-19 fibrosis is not known, but it has been reported in more than one-third of recovered patients.² Search from previous severe acute respiratory syndrome and Middle East respiratory syndrome epidemic has revealed length of intensive care unit stay, disease severity, hypertension, diabetes, smoking, and advanced age to be predictors of development of fibrosis.

Antifibrotics nintedanib and pirfenidone had been studied exclusively in idiopathic pulmonary fibrosis (IPF). The putative role in post-COVID fibrosis has been from the extrapolation of their role in chronic IPF. There are many caveats associated with the possible role of these drugs in mitigating fibrotic changes after COVID-19. The profibrotic pathway is a result of a variable mixture of immunologically mediated damage and classical acute lung injury.³ Antifibrotic therapy does not affect the immune dysregulation pathway, hence a combination with other anti-inflammatory drugs could be a rational approach.

Another problem is the formulation of antifibrotics. Both nintedanib and pirfenidone are available in oral preparation. The unpredictable absorption in critically ill patients and difficulty administering to patients on a ventilator along with delayed metabolism in patients having deranged liver function enzymes are some of the problems.

A further problem is the rapidity of action of these drugs. Patients treated for IPF are generally followed yearly to monitor the progress by evaluating the pulmonary function tests, especially forced vital capacity.⁴

In the current scenario, we do not have sufficient data on how well the patients have fared after treatment with these antifibrotics.

The optimal timing of initiating therapy also warrants some attention. There are no recommendations for prophylactic initiation of antifibrotic therapy in COVID-19 patients. The benefit

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of antifibrotics is doubtful once the fibrotic changes are already established. Early experimental models have shown that starting antifibrotics in the early phase of lung injury promotes fibrosis and initiation in the later stages of injury at the onset of fibrotic phase might ameliorate fibrosis.⁵

Multiple profibrotic pathways lead to fibrosis. Apart from immunomodulatory pathway, there is evidence that vascular dysfunction involving vascular endothelial growth factor and tumor necrosis factor- α is a key component leading to fibrosis. The commonly used antifibrotics do not target every pathway leaving some profibrotic pathways to perpetuate despite ongoing therapy.

As the current pandemic, unfortunately, continues to flourish, clinicians worldwide are being confronted with new challenges. Post-COVID pulmonary fibrosis is one such dreadful sequela without any proven therapy. Many of the current antifibrotics have therapeutic potential for treating post-COVID fibrosis; long-term results are still awaited. We sincerely hope that issues associated with the current antifibrotics addressed in this commentary will open avenues for further research.

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