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Antifibrotics for COVID-19 related lung fibrosis: agents with benefits?

To the Editor

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an exponentially spreading pandemic with more than 36 million confirmed cases and over one million deaths worldwide, all within ten months of its first case in Wuhan, China [1]. The brunt of the infection affects the respiratory system and may range in presentation from an asymptomatic infection to severe acute respiratory distress syndrome (ARDS). Although more than 25 million cases have been reported to have recovered globally [2], an alarming upcoming trend is that of the long-term sequelae of COVID-19, the most devastating of which is pulmonary fibrosis. Referral for up to 10–15% of non-critically ill moderate to severe COVID-19 patients is sought in view of varying degrees of fibrotic change in the lungs in the authors' growing experience. Irrespective of the underlying etiology, pulmonary fibrosis notoriously jeopardizes the patient's functional capacity, confers chronic respiratory insufficiency, and consequently, compromises quality of life. Due to dearth of conclusive data, it may not be presently possible to compute the actual prevalence of COVID-19 lung fibrosis. However, given the enormity of the pandemic and its predominant and wide range of effects on the lungs, a significant burden of post-COVID-19 pulmonary fibrosis is anticipated [3]. Therefore, long-term follow-up studies will be desperately needed to address this issue.

The pathogenesis of pulmonary fibrosis involves alveolar epithelial damage triggered by genetic predisposition, unchecked chronic inflammation, viral infections, or ARDS. This happens due to the overexpression of pro-inflammatory cytokines (i.e. tumor necrosis factor-alpha, interleukins), proliferation and persistence of pro-fibroblastic cells and mediators (i.e. fibroblasts, transforming growth factor-beta, fibroblast growth factor, platelet derived growth factor), and resultant activation of the profibrotic pathway. Excess collagen and extracellular matrix replace normal lung tissue and produce architectural distortion typical of interstitial pulmonary fibrosis. Recent reports suggest that these mediators are likely implicated in COVID-19 lung fibrosis as well, as suggested by their increased serum levels in these patients [4–6].

The typical sequence of events in COVID-19 patients developing pulmonary fibrosis consists of an upper respiratory viral prodrome, atypical pneumonia, and ARDS culminating in fibrosis. Fibrosis may begin during or after the acute infectious episode and is more likely to develop in patients with a prolonged severe illness due to a cytokine storm, in those with pre-existing lung conditions, and in the elderly. No definitive profibrotic mechanisms are known in COVID-19 patients; however, pulmonary fibrosis in fatal COVID-19 cases characteristically shows the histological picture of diffuse alveolar damage and microthrombosis. Other proposed mechanisms driving fibrosis in these patients include a cytokine storm-related hyperimmune response triggered by the SARS-CoV-2 antigen, severe acute lung injury, fibrosing organizing pneumonia, and drug induced- and/or artificial ventilation-induced lung damage. It may not always be possible to identify which mechanism is at work in a particular patient. Further, even after the virus gets cleared in patients who

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have recovered from COVID-19, it does not necessarily mean that fibrosis may not ensue. However, COVID-19-related lung fibrosis is supposedly not a progressive fibrosing interstitial lung disease (PF-ILD).

In the landmark placebo-controlled INBUILD trial, nintedanib was administered to patients who had progressive pulmonary fibrosis due to a wide variety of interstitial lung diseases (ILDs). The drug intervention was associated with a reduction in FVC decline (about 60%) thereby concluding that nintedanib appears to inhibit fibrogenesis across a broad range of pulmonary diseases [7]. Somewhat similar effects were observed with pirfenidone in another phase-2 randomized controlled trial [8]. An autopsy study of ARDS patients noted that longer the disease duration, greater were the chances of fibrosis [9]. Such patients may benefit from antifibrotic drugs if introduced early in the disease course before the need for mechanical ventilation emerges. These studies potentially imply that the early use of antifibrotics in COVID-19 lung fibrosis may possibly reduce immune-mediated fibrotic lung changes. However, other aspects of lung damage like inflammation and thrombosis must also be optimally addressed to maximize the potential benefit.

In light of these facts, the question that is currently puzzling clinicians around the world is whether antifibrotics indicated for other PF-ILDs would be of any benefit in COVID-19 patients developing lung fibrosis. Available anti-fibrotic medications like pirfenidone and nintedanib approved for use in PF-ILDs like idiopathic pulmonary fibrosis (IPF) and scleroderma-interstitial lung disease have broad anti-fibrotic activity irrespective of the underlying etiology. Importantly, the similar cytokine profiles in IPF and COVID-19 possibly suggest similar pathogenic mechanisms of lung fibrosis in both diseases, thus implying the likely utility of antifibrotics used in IPF for COVID-19 patients also, in whom they may be expected to prevent occurrence and/or progression of fibrosis. Therefore, it would be interesting to explore their full potential role, if any, in such patients to fulfil the urgent but largely unmet need for such therapies. Nevertheless, their use must not be outside of experimental studies, and the optimal timing of initiation, dosage, and duration of treatment must be determined.

No evidence currently exists to support empirical off-label use of antifibrotics in COVID-19 patients. Thus, well-designed, prospective, randomized clinical trials of these drugs in this group of patients are warranted. Until conclusive evidence builds up, these patients may probably best be offered aggressive pulmonary rehabilitation, possibly an extended course of low dose steroids on a case-by-case basis, and a trial of antifibrotic agents within a study protocol with periodic assessment of lung function and chest imaging. It is also likely that quite a few of these patients may have their lung changes resolved with time, possibly over a period of months. Such trends were also evident in previous coronavirus outbreaks where spontaneous but gradual resolution of fibrotic sequelae was observed [10, 11].

To conclude, limiting the development of post-COVID-19 lung fibrosis is expected to be a challenge in view of the blistering disease course and the ongoing search for effective antivirals, anti-inflammatory agents, and immunomodulatory therapies. Even a small degree of fibrosis in these patients, especially in the elderly who may quite commonly have other preexisting respiratory comorbidities, may be sufficient to significantly compromise their lung function and quality of life. Insightful evidence on therapeutic options for the treatment of this dangerous disease may bring about a landmark change in its management and, consequently, reduce these devastating sequelae.

Conflict of interest

None declared.

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