

Editorial

Post COVID 19 Lung fibrosis: “Jumping out of the fire in to the frying pan” How to avert the crisis?

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When entire world rejoicing on Eve of the new year 2020, an acute atypical respiratory ailment known as the severe acute respiratory syndrome caused by the novel coronavirus, flared up in Wuhan, China in weird circumstances, later rapidly spread to other part of the world like a firestorm due to its unacquainted behavior in the human body & fluctuating management guideline.

A SARS disease usually spread through the micro droplet, typically consists of three phases when virus entered the body: viral multiplication, hyperactivity of immune system, and destruction of lung parenchyma,(1) forbye pathology of the lung is associated with diffuse alveolar damage, which is characterized by an initial acute inflammatory exudative phase associated with edema, hyaline membranes, and interstitial acute inflammation, followed by an organizing phase with loose organizing fibrosis mostly within the alveolar septa, besides this lymphopenia, hemophagocytosis in the lung, and white-pulp atrophy of the spleen is also manifested in SARS patients which supports cytokine deregulation and in severe cases, may bring about tissue hyper inflammation, fibrosis, lung collapse, multi-organ dysfunction, and patient death .(2, 3)

Thille et al. published the report of 159 autopsies from patients with ARDS, reveal that the probability of fibrosis gets exponentially increased from 4% to 61 % with the severity and duration of diseases in follow-up from 1st week to 3rd week. Additionally, 47% of patients had impaired Diffusing Capacity of the lungs for carbon monoxide (DLCO) as well as 25% had reduced total lung capacity (TLC).(4) Similarly in another study conducted by Polak et al. highlighted diffuse alveolar damage (DAD) in 85% as well as fibrotic pattern in 22% with honeycombing in 7% of biopsy and autopsy report of 131 study subjects.(5)

Studies have shown that bilateral interstitial pneumonia is associated with the presence of fibrotic tissue caused by excess collagen in the pulmonary interstitium with hyper-inflammation. (6) Patients with severe diseases showed lymphopenia with the reduction in peripheral blood T-cells as well as increased plasma concentrations of pro-inflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1 α , and tumor necrosis factor (TNF)- α .(7,8) Similarly hyperactive inflammatory state in the most severe stages of COVID-19 infection, caused by the cytokine storm, is probably the major culprit of pulmonary fibrosis within the lungs, more over injury occurs to the lung endothelium, epithelial cells, and bronchoalveolar capillaries leading to elevated vascular permeability, disseminated intravascular coagulation, focal demarcation of hemorrhages, and proteinaceous exudates within alveolar spaces responsible for severe and in some cases fatal lung lesions which gives the lungs an appearance of bi-lateral ground-glass opacity during computed tomography (CT) scans.(1,9)

The pathophysiological analogy between IPF and COVID-19 suggests a similar pathogenetic mechanism of pulmonary fibrosis; therefore, it is hypothesized that drugs useful for the treatment of IPF could also be useful for patients with COVID-19.(10,11) In fact, existing data indicate that pirfenidone has both antifibrotic as well as anti-inflammatory properties which mitigate the proliferation of fibroblasts as well as accumulation of extracellular matrix in response to cytokine growth factors such as TGF- β and PDGF.(12) Recently it has been cited that pirfenidone significantly inhibits TGF- β 1-induced fibronectin synthesis. Down-regulation of profibrotic gene expression and collagen secretion as well as reduction of over expression of TGF- β in inflammatory conditions plays a crucial role in the antifibrotic activity of pirfenidone, besides this, it also inhibits collagen I fibril formation lead to a reduction in collagen fibril bundles. It has been shown that pirfenidone has pleiotropic actions on both the immune system and extracellular matrices (ECM), such as hyaluronan, a major component of the ECM that regulates tissue injury and repair. (13) Recently, the up-regulation of RGS2 has been suggested as a novel mechanism of amelioration of pulmonary fibrosis with pirfenidone

treatment. Surprisingly, it has been shown that pirfenidone inhibits the AT1R/p38 MAPK pathway, decreased angiotensin-converting enzyme (ACE), angiotensin II, and angiotensin II type 1 receptor expression, and strongly enhanced liver X receptor- α expression. This will not only protect cells from developing fibrosis but also decrease the entrance of the COVID-19-SARS virus into cells by decreasing the ACE receptor expression.(14)

Although the therapeutic efficacy of pirfenidone in pulmonary fibrosis induced by SARS-CoV-2 is still being demonstrated, few recent studies proposing to use the FDA-approved anti-fibrotic therapies (nintedanib NCT04338802 and pirfenidone NCT04282902) for idiopathic pulmonary fibrosis (IPF) in COVID-19 patients.(5,15,16)Pirfenidone and Nintedanib are available only in oral form hence cannot be used in intubated patients, therefore, an inhaled formulation of pirfenidone is under evaluation in patients with COVID-19 (NCT04282902).(17-19)The current literature proposed that antifibrotic intervention can be used in combination with anti-inflammatory drugs to limit the damage produced by the cytokine storm and avoid the death of the patient, however in the chronic phase, when the patient is saved and cured of the infection, pirfenidone can be used to eliminate residual complications, such as fibrotic tissue in the lungs.(20-22)

Therefore early measures to cease the progression of fibrotic changes in the COVID 19 case may help prevent permanent disability among the affected population also mitigate the global burden of DALY loss in the future. Although before incorporating anti-fibrotic medication in the standard guideline of COVID 19 management, need more clinical trials globally in different strata to evaluate its risk-benefit criteria's among SARS Cov2 infected population to validate its use by the eminent scientific societies as well as the World health organization.

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