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Editorial

Post-COVID Pulmonary Fibrosis: A Medical Quagmire?

It seems that the world spent the last two years like the ancient king *Trishanku* of the Vedic epic *Ramayana*, suspended upside down in a state of limbo between the heaven and the hell for his unnatural desire to go to the heavens alive. It now looks like a bad dream which unfortunately is not yet over. The rapid spread of the pandemic COVID-19 due to the Corona virus (SARS-CoV-2) was partly contained by drastic control measures including lock-downs, curfews and almost complete ban on travel and other human activities. But the virus is notorious for mutations and several variants of concern have emerged which are responsible for 2nd and 3rd wave of the pandemic. India also suffered from a severe second wave during April-May 2021 after a relative quiescence from the first wave in October 2020. The third wave is already threatening at the doors.

Post-COVID Pulmonary Fibrosis

COVID-19 infection due to SARS-CoV-2 not only continues to attack with new strains and variants, many of those who were afflicted with the infection during the last two years continue to suffer from the residual damage to the lungs and other systems.[1-3] Those with severe disease have persisted with imaging abnormalities, such as ground-glass opacities (GGOs), consolidation and reticulation and architectural distortion.[4] Traction-bronchiectasis and honey-combing are often considered as definite radiological evidence of residual fibrosis. Presence of these structural radiological abnormalities is variously labeled as post-COVID lung fibrosis (PC-LF), post-COVID interstitial lung disease (PC-ILD), or post-COVID diffuse lung disease (PC-DLD).[5] The condition is often accompanied with functional disability and lung function impairment.[6] Arterial oxygen de-saturation, initially demonstrable after exercise, may be present even at rest in patients with significant disease. In severe cases, it leads to a state of respiratory crippling with inability to even move in the bed and high dependence on oxygen.

Of several post-COVID problems, post-COVID pulmonary fibrosis (PC-PF) or PC-ILD is one of the most serious problems.[1,2,7,8] Both treatment and natural history of PC-PF are not yet established. The incidence of PC-PF is quite significant; in some clinical studies, the incidence rate of impaired diffusion capacity (DLCO) which is possibly the most objective, functional parameter persistent lung damage is reported to exceed 30%.[9,10] There are also some observational reports on the high incidence of post-COVID problems and their management from India, even though there is lack of clinical and follow-up data.[7,11,12]

Puzzling Questions?

Every pulmonary physician is now most frequently confronted by patients with multiple questions about the treatment – the choice of drugs and how long to use; is it progressive or whether the respiratory disability is going to revert to a normal situation; will the disability persist in the same severity and whether it can cause death? As of today, we do not know definite answers to most of these questions. In any case, the disease is rather novice, it is a bit early to comment upon the long term prognosis and natural history of COVID-19 infection. Also, there is a complexity of interactions of disease specific molecular pathways as well as treatments between coexisting IPF or ILD and COVID-19, such as in patients with severe COVID-19 who are at serious risk of pulmonary fibrosis.[13]

One can take some cues from the previous epidemic due to the Severe Acute Respiratory Syndrome (SARS) caused by a SARS-associated coronavirus (SARS-CoV-1) in 2003, which however, was not as widespread as the COVID-19 due to SARS-CoV-2.[14] About 20% of the cases of SARS due to CoV-1 with initial fibrotic lung damage had shown significant progression of fibrosis in the following 5-10 years afterwards.[9] It is important to note that most SARS-CoV-1 patients with fibrotic lung damage had recovered within the first year and then remained healthy thereafter. On the other hand, persistence of lung damage had lead to both long-term disability and even death. There is no proven treatment as yet. Lung transplantation remains the only hope for severely damaged end-stage lungs. Good success has been reported with this modality in selected patients.[15,16] Not all patients of PC-LF need lung transplantation. Moreover, the option is infeasible in a large number of cases, especially in the low and middle income countries.

Different drugs have been used for medical prevention and treatment of PC-PF. Glucocorticoids are useful in the presence of persistent post-COVID inflammatory lung disease.[17] Antifibrotic drugs,

like pirfenidone and nintedanib, have been tried based on the previous experience with their use and demonstrable benefits for fibrotic interstitial lung diseases, in particular the idiopathic pulmonary fibrosis (IPF).[9] As of today, there is no randomised controlled trial on such a treatment. There is, however, a biological plausibility as well as availability of some evidence from observational data on the use of glucocorticoids and antifibrotic agents.

Besides the choice of drug(s), duration of treatment is another important issue. We do not know the end-point of therapy. It is quite likely that the continued use of these drugs is futile after fibrosis is established. Lung fibrosis in PC-PF is more like a post-inflammatory healing progress than the continued 'injury and repair' mechanism of IPF or other progressive fibrosing illnesses. In spite of some clinical and behavioural similarities, PC-PF is not IPF in its several pathogenetic mechanisms. It is, therefore, important not to extend the treatment decisions without the availability of well collected data.[9,21]

Caught in a Quagmire

Presently, we are caught in a quagmire which we can neither avoid nor escape. We do not know the answers for most of the questions and find solutions thereof. It is quite likely that improvement in respiratory disability and functional parameters observed in a large number of patients is attributable more to the respiratory physiotherapy and compensatory mechanisms than to the use of drugs. It is akin to the case of other chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) where exercise and other components of respiratory rehabilitation have shown proven benefits and significantly improve the lung function. Similar benefits of respiratory rehabilitation have been reported in survivors of acute respiratory distress syndrome following severe influenza-A pneumonitis.[22] It is again a bit early to comment upon the efficacy of respiratory rehabilitation programmes in PC-PF.

One needs a large body of data to answer most of the obvious questions faced by the clinicians in their day-to-day practice. The time factor and appropriate study-design are essential for any meaningful conclusions. Unfortunately, the COVID-19 pandemic has not allowed that kind of 'luxury' to the investigators. Most of the recommendations till date are based more on opinions and observations than on the proved scientific rationale. Nonetheless, the clinical decisions with respect to treatment of individual patients cannot wait. One keeps on managing patients with the hope that the truth may lie somewhere in-between what is being done and what will prove to be correct. It is somewhat akin to the old adage of half-truths about medical teaching:

"Medical teachers know that half of what they teach is wrong — the trouble is that they donot know which half!"

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