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Post COVID Pulmonary Fibrosis: What, Why and Whom?

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Abstract: ***Post COVID-19 pulmonary fibrosis is a new condition which is being recognized increasingly in few patients of COVID diseases. Though the actual prevalence is still unknown, but more patients are being detected of having this condition with increasing number of cases. Patients usually present with persistent shortness of breath even after recovery from other COVID related symptoms. The HRCT shows organizing pneumonia, traction bronchiectasis and ground glass opacities (GGOs). Injury to Type II Pneumocytes by the virus may be the inciting event. The treatment of the condition is still unknown, but various drugs have been tried.***

Keywords: Idiopathic Pulmonary Fibrosis (IPF), Non Specific Interstitial Pneumonia (NSIP, Organizing Pneumonia (COP), Bronchiolitis Obliterens Organizing Pneumonia (BOOP), Organizing Pneumonia, Pneumocytes, Epithelial Type II Pneumocyte Dysfunction, Epithelial Type II Pneumocyte Dysfunction

1. Introduction

As per natural law- healing occurs following an injury. But excessive healing response often leads to scars. Lungs are the main harbors for flourishing and nourishing the SARS-COV-2 virus in COVID-19. So this battlefield bears the burden of injuries. With the increasing number of cases many new facets of this disease are being discovered. One such is the post COVID pulmonary fibrosis. This article is all about that: revealing the mechanisms of fibrosis, identifying the risk candidates and formulating a possible approach to such patients.

But before going to the lung pathology of COVID-19 and fibrosis, we should first know how and why fibrosis occurs in lungs in response to various injuries? Because such a knowledge is required to predict the type of fibrosis. Different injuries may act differently in lungs and may produce different phenotypes of fibrosis. The classical examples are the diverse spectrum of Interstitial Lung Diseases (ILD) or as currently termed Diffuse Parenchymal Lung Diseases (DPLD).

The classification of DPLD is always confusing, but overall this condition may occur due to known or unknown causes of injuries. The unknown causes are called Idiopathic. The Idiopathic DPLD can further be divided into 3 basic groups as per duration of onset or specific etiology. They are –

1) **Chronic Fibrosing varieties:** Idiopathic Pulmonary Fibrosis (IPF) and Non Specific Interstitial Pneumonia (NSIP)
2) **Acute/ subacute varieties:** Acute Interstitial Pneumonia (AIP) and Cryptogenic Organizing Pneumonia (COP) or previously known as Bronchiolitis Obliterens Organizing Pneumonia (BOOP)
3) **Smoking related:** Respiratory Bronchiolitis Interstitial Lung disease (RB-ILD) and Desquamative Interstitial Pneumonia (DIP).

All the classifications described above are clinico-radiological- pathological classification. This classification we should know to predict the type of pulmonary fibrosis that develops following an injury.

The main caveat of the above classification is too much dependence to the radiology pattern and considering the respective pathological patterns as distinct entities and separate diseases. **In fact most of the above conditions are a continuous spectrum or different mixture of only two distinct primary pathologies- first is Organizing Pneumonia and second is alveolar collapse.** We need to know the things with a little detail to understand the type of response after COVID. We will start from the basic, that is the structure of the alveolar units of lungs.

Alveolar area

The alveoli are the gas exchanging area of the lungs. So they are very thin for effective gas exchange and easy diffusion of Oxygen and CO2. The 'blood-air' barrier may be as little as 0.2 micron thick. A thin basement membrane separate the air and blood in the alveoli. The vascular side of the basement membrane contains very thin endothelial cells and the alveolar side contains the alveolar epithelium or also called Pneumocytes. There are 2 types of Pneumocytes, Type I and Type II. Type I Pneumocytes are simple squamous epithelial cells and form over 90% of alveolar surface area. The edges of the adjacent Type I cells overlap and form tight junction to avoid any spillage from vascular side. The Type II Pneumocytes contribute to only 10% of the surface area of the alveoli. They are rounded cells and protrude from alveolar surface. They have two important functions. The Type I Pneumocytes when damaged can't self proliferates or regenerate. The Type II cells proliferate and differentiate into Type I cells. Second important function of type II Pneumocytes is that they secrete surfactants. The surfactants lower the surface tension of the alveoli. The surface tensions of alveoli are very high because of minute structure of alveoli. Increased gravitational pressure further tends to collapse the alveoli in the dependent part. All these things oppose the expansion of alveoli during inspiration and promote the collapse of the alveoli in expiration. The detergent like action of surfactant prevents this phenomenon and makes ventilation more efficient and smooth.

What happens when the alveoli are injured?

When the alveoli are injured it can respond in limited ways. The response depends on the structures mainly involved in the injuries. The three main alveolar structures may be

injured, though injury is not often limited to that sole structure.

1) Type I Pneumocyte injury: As this is the most abundant structural component of the alveoli they are primary targets of many insults. Injury to Type I Pneumocytes causes denudation and exposure of the underlying basement membrane due to necrosis and sloughing of these Pneumocytes. The degraded proteins of the cells along with inflammatory exudates form the hyaline membrane. This fills up the alveoli. It heralds the acute exudative phase of Pneumonia. It is followed by organizing phase with migration of fibroblasts and formation of loose Organizing fibrosis. This phase is often called 'Organizing Pneumonia' by the pathologists.

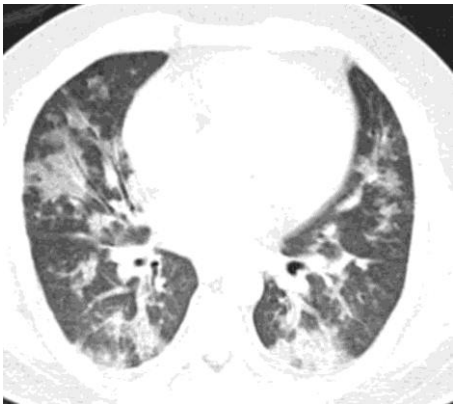

Figure 1: Organizing pneumonia

So 'Organizing Pneumonia 'is a mechanism of lung injury repair when Type I Pneumocytes are mainly damaged. The cause may be known, like Streptococcus Pneumonia, or radiation or when unknown called 'Cryptogenic Organizing Pneumonia '(COP). If the lung involvement is extensive and bilateral involving all the five lobes then it is called Acute Respiratory Distress Syndrome (ARDS). If the cause of ARDS is not known it is called Acute Interstitial Pneumonia (AIP). The pathological changes of ARDS/ AIP is known as Diffuse Alveolar Damage (DAD), but basically it is nothing but widespread alveolar consolidation and extensive 'Organizing Pneumonia '. The exudates are often engulfed by alveolar macrophages gradually and the Organizing portion thins out, but still remaining in the alveoli, and this may produce a diffuse ground glass like opacities in HRCT thorax. They are now called a 'NSIP' pattern, which is basically a healing phase of Organizing Pneumonia.

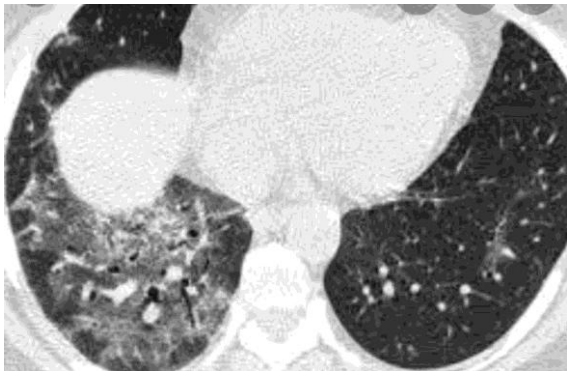

Figure 2: NSIP pattern

If the portion of the Organizing exudate becomes incorporated into the alveolar wall, it causes thickeing of the basement membrane and fibrosis. It is evident as increased Reticular shadows in HRCT thorax. As the fibroblasts contract within a fibrosis there is some volume loss of lungs. The broncho – vascular bundles lie in the centre of the secondary pulmonary lobule and the pathogen either comes through the airway or carried with blood, so the distribution of this type of injury is often centrilobular or centrifugal in nature. But during the cleaning phase the debris are removed either centrally by blood vessels or peripherally by lymphatics of the secondary pulmonary lobule. So they try to aggregate either centrally or peripherally as depicted in the picture. These types of fibrosis often are responsive to steroid, as seen in case of COP.

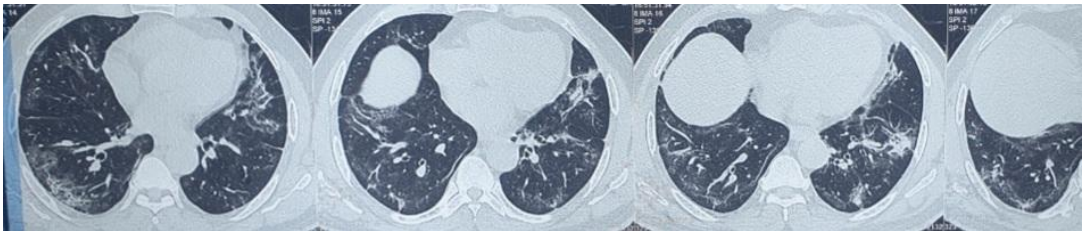

Figure 3: Organizing phase

2) Type II Pneumocyte injury: Injury to these cells often leaves long lasting consequences. As Type I Pneumocytes cannot replicate and Type II Pneumocytes differentiate and produce Type I Pneumocytes, injury to Type II Pneumocytes lead to incomplete renewal of primary alveolar structure. So targeted deletion of Type II Pneumocytes [1, 2, 3] is sufficient to incite a fibrotic response in the lungs. In addition the lack of surfactant release cause collapse of the alveoli. As the surface tension is more in the periphery or basal portion of the lungs, the collapse and associated fibrotic changes are more detected in the basal and peripheral portion of the lungs. Damage to Type II Pneumocytes invariably associated with damage of Type I Pneumocytes and so some evidence of Organizing Pneumonia is also evident here. In fact presence of organizing exudates within the alveoli help to keep the alveoli open, otherwise it completely collapses. If due to some reasons the depletion of Type II Pneumocytes become permanent then the collapse progresses and it progress from periphery to central region or centripetally. The collapsed alveoli surrounding the Respiratory Bronchiole in the centre of secondary pulmonary lobule put a traction on the bronchiole wall and causes bronchiolectasis and bronchiectasis, also known as traction bronchiectasis, if the pull increases further due to more collapsed alveoli then the respiratory bronchiole becomes round in shape, as they lack

any cartilagenous support. Agglomeration of many such rounded Respiratory Bronchioles produces the appearance of honeycombing in CT thorax.

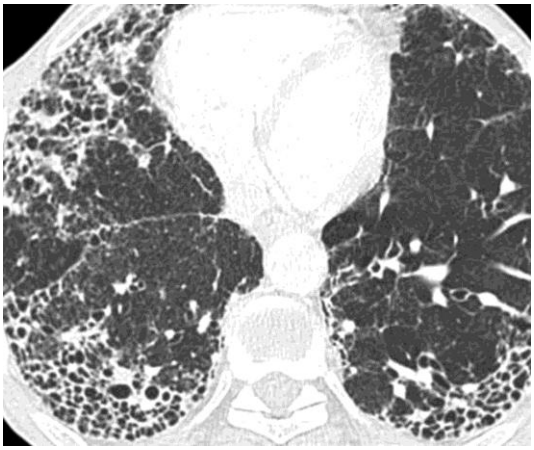

Figure 4: IPF/UIP

This is pathologically termed as Usual Interstitial Pneumonia (UIP). Many known injuries either from airway side (like, asbestosis) or blood side (like, Rheumatoid arthritis) may damage specifically the Type II Pneumocytes and produce UIP like changes. When the cause of UIP is not known, it is called Idiopathic Pulmonary Fibrosis or IPF. This kind of fibrosis responds poorly with steroid but showed better responses to antifibrotic drugs like Pirfenidone or Nintedanib.

3) Injury to the basal membrane: The above two types of Pneumocytes injuries are always associated with some basal membrane injuries. The extent of basal membrane injuries may drive the inflammation; as in ARDS an extensive basal membrane injury occurs. The basal membrane injury turns the alveoli more porous and inflammatory exudates pour within the alveoli. The pathogen also gets a chance to invade the endothelium and blood stream.

The amount of fibrosis after any insult depends on the amount of damage. In ARDS both Type I and Type II Pneumocytes are damaged along with basal membrane. Organizing Pneumonia, collapse, fibrosis are all evident in this case.

What happens in COVID-19?
The SARS-CoV-2 virus attaches to the ACE2 receptors of host cell. The pathogenesis can be divided into 3 phases [4]

1) **The upper airway phase**: The virus attaches to the ciliated and secretary cells of upper airway, replicate their but doesn't incite an adequate immune response [5]. Though the patient is infective but mostly asymptomatic.
2) **The conducting airway phase:** The virus now trickles lower down into the lungs affecting the Bronchi or Bronchioles. They probably infect the ciliated but not the mucous cells [6]. More immune response is mounted and patient may have some symptoms like cough. But the Keratin 5 expressing Basal cells of the conducting airways are not affected [6]. These cells are progenitor cells or stem cells for conducting airway epithelium. They adequately repair the conducting airway epithelium.
3) **The Alveolar phase**: Now the virus affects the Type II Pneumocytes of alveolar surface, as these cells have abundant ACE2 receptors. Type I Pneumocytes are also shown to be affected by the virus in primate model [6, 7]. The extent of damages to these cells determines the clinical course and subsequent healing procedure.

The Alveolar phase of COVID-19:
The stages can be broadly divided into two phases- the early and late pulmonary phase [4]

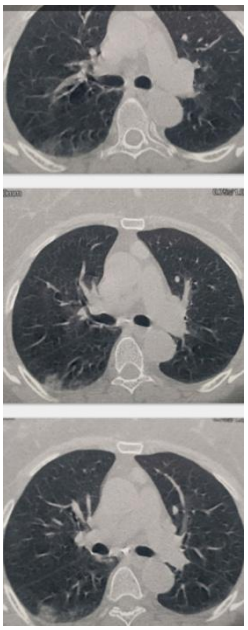

Figure 5: Early GGO in Right base

The early pulmonary phase- The early involvements of peripheral and basal areas of the lungs are obvious from above discussions. The involvement of Type II Pneumocytes by the virus and subsequent destruction leads to alveolar collapse, focal alveolar flooding [8]. These are due to loss of surfactant and fibrin exudates due to alveolar damage. But the reason for continuous perfusion and loss of hypoxic vasoconstriction in these fluid filled or collapsed alveoli, is a great mistery. It may be due to an interference with local or central hypoxic vasoconstriction response, due to local production of vasodilators like Nitric Oxide (NO) or Prostaglandin (PGI2). The infected Type II Pneumocytes will be among the first responder to initiate a stronger immune response. The infected cells will propagate the virus and the viral particles will spill over the adjacent alveoli through the pores of Kohn. There will be additional migration of fibroblasts and inflammatory cells into the alveolar lumen and appositional atelectasis and loss of gas units. The loss of Type II cells means loss of progenitor cells for Type I Pneumocytes. That often leads to aberrant healing with fibrosis and may lead to permanent scarring in few cases.

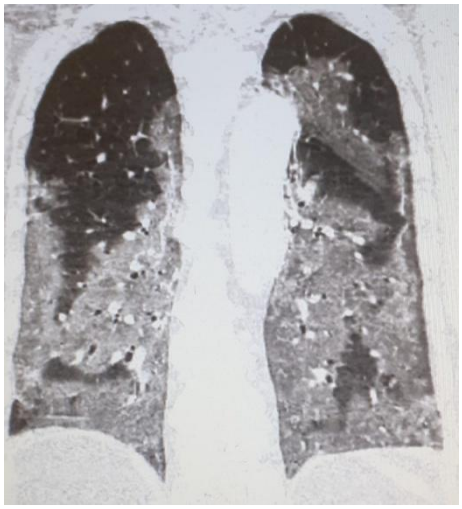

Figure 6: Late pulmonary phase of COVID

The late pulmonary phase: This is characterized by more extensive involvement of both lungs due to continuous spread. There is Diffuse Alveolar Damage (DAD) with alveolar exudates, hyaline membrane, interstitial inflammation this is followed by the Organizing phase. Pulmonary Fibrosis is a known sequela of ARDS due to extensive destruction of Type I, Type II Pneumocytes along with the basement membrane and also the capillary endothelium.

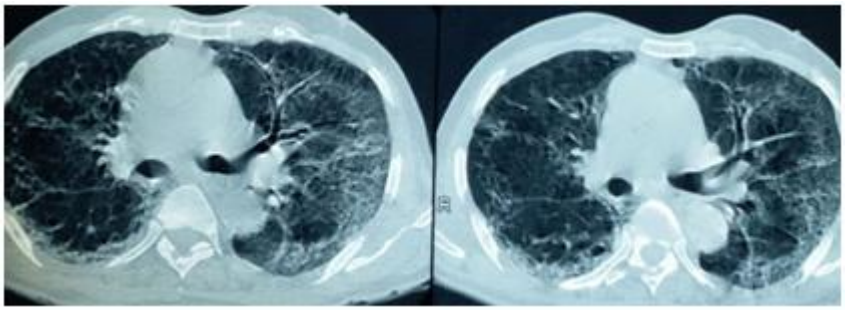

Figure 7: Post COVID fibrosis

Who are at risk of developing fibrosis?

As evident from the discussion both Organizing Pneumonia and alveolar Collapse are possible in COVID-19, due to damage of both Type I and Type II Pneumocytes. So the chances of developing fibrosis are more with COVID-19. But certain factors will influence the outcome, like

1) Extent of involvement of the alveolar units- the more the involvement, the more will be the chances of fibrosis
2) The repair mechanisms- The effective repair mechanisms will minimize the chances of fibrosis. The Organizing Pneumonia is cleared by alveolar macrophages. If fully cleared and Type II Pneumocytes regenerate, the healing process may not lead to any scarring. But if the Organizing Pneumonia gets embedded in the alveolar wall and epithelial cells grow over this, it will lead to thickeing of the basement membrane and scarring. If the regeneration of Type II Pneumocytes are not complete, it may lead to fibrosis and scarring. Few people will be at risk of developing IPF in the long term, who have an 'Epithelial Dysfunction'.

Epithelial Type II Pneumocyte Dysfunction

This model often leads to IPF as has been already mentioned [1]. But the transient loss of Type II Pneumocytes will not lead to IPF like changes. If the Type II Pneumocyte depletion is permanent or if there are dysfunctional Type II Pneumocytes, it may lead to IPF like changes. Such things often occur in patients who develop IPF. A few of reasons are responsible for such permanent depletion of Type II Pneumocytes.

1) **Stem cell exhaustion-** A reduction in total number of Type II Pneumocytes, which behave as a stem cell or progenitor cell of alveolar epithelium, will lead to ineffective repairs of alveolar injuries and subsequent fibrosis [9].
2) **Increased apoptosis of Type II Pneumocytes-** The genetic mutations may lead to increased apoptosis of Type II Pneumocytes and depletion [10]. Endoplasmic Reticulum (ER) stress- ER is an important cellular organelle that facilitates the folding and trafficking of proteins to ensure quality control of proteins required for cellular homeostasis. In situations that overwhelm the protein folding capacity of the ER, the unfolded protein response (UPR) is activated. When UPR is prolonged or severe the cell undergoes apoptosis [11]. There are multiple factors which increase the ER stress, like, aging, environmental factors, viral infections, and smoking. The increased ER stress of Type II Pneumocytes will cause a premature apoptosis. So these people will be at increased risk for progression to IPF.
3) **Dysfunctional Type II Pneumocytes-** Hyperplastic and hypertrophic Type II Pneumocytes ate often found in the fibroblastic foci in organizing phase. But they often have impaired renewal capacity [12]. In IPF this dysfunctional phenotype often is the driver of fibrosis [13].
4) **Cellular senescence and aging-** Cellular senescence is one of the signatures of aging process. A major contribution to Cellular senescence is lung fibrosis due to Telomere shortening [14, 15]. The Telomere protects the ends of the chromosomes from replicative loss. Thus the

Telomere maintains the replicative potential of stem cells and progenitor cells [16]. Both aging and smoking are associated with Telomere shortening and regenerative ability of Type II Pneumocytes [17].So post COVID pulmonary fibrosis will be more florid in **elderly patients and in smokers**. Patients with extensive lung involvement also have higher chances of fibrosis. Patients with established ILD like IPF, may have accelerated lung fibrosis.

Biomarkers of potential fibrosis in COVID patients:

There are still no sensitive Biomarkers which can predict the development of fibrosis in COVID-19 [18]. Though several readily available and few experimental Biomarkers are identified, which can predict the fibrosis to some extent. They are serum LDH, hs-CRP and lymphocyte count [19]. The increase in LDH reflects tissue destruction and is regarded as a common sign of cell damage. In patients with severe pulmonary interstitial disease, the increasing LDH is significant and is one of the most important prognostic markers of lung injury [20]. Previous studies in ARDS have also detected few experimental biomarkers in BAL fluid. They are N-terminal pro-peptide of Type III Collagen, C-terminal pro-peptide of Type I Collagen, TGF Beta and alveolar fibroblasts and fibrocytes [21].

Prevalence of Post COVID pulmonary fibrosis:

Though this clinical entity is now well recognized in COVID patients, but any large scale prevalence data are lacking. The prevalence of post COVID pulmonary fibrosis will be apparent in time. Early analysis from hospital discharge of COVID patients suggests that more than a third of the recovered patients had developed fibrosis in lungs. 47% of patients had impaired Diffusing Capacity or DLCO and 25% reduced Total Lung Capacity (TLC) [22]. These values were even worse in severe patients. Previous work in ARDS (any cause) had shown that pulmonary fibrosis develops 4% of patients with disease duration of less than a week, in 24% patients with a disease duration between 1 to 3 weeks and in 61% of patients with a disease duration of more than 3 weeks [23]. Though ARDS occurs only a subset of patients of COVID-19 (may be less than 5%), but still it will be a huge number considering the magnitude of the pandemic.

Treatment of post COVID pulmonary fibrosis

As like the prevalence data the treatment of this condition is not streamlined yet. But based on the above discussion we can formulate some hypothesis to treat this condition.

1) Subtle fibrosis in young asymptomatic patients may resolve with time and should not require any treatment.
2) Subtle fibrosis in symtomatic patients will need an observation. If the dyspnoea is out of proportion to fibrosis other causes should be ruled out like – Pulmonary thromboembolism, pulmonary hypertension, or any underlying cardiac dysfunction.
3) A Complete Pulmonary Function Test with TLC, RV and DLCO can predict the functional restrictive severity in such patients.
4) If the HRCT depicts a severe fibrosis, the nature of fibrosis should be followed in symptomatic patients. A limited low dose CT with just lung window will be helpful in such scenario, if available.
5) If the abnormalities are of predominant 'Organizing Pneumonia' or 'NSIP' type, a course of oral steroid may be helpful. The duration and dose should be clinically decided.
6) If more traction bronchiolectasis or Reticular shadows suggestive of Interstitial thickening and alveolar collapse, like UIP/IPF are visible, a course of Pirfenidone or Nintedanib may be tried.

The duration of such antifibrotic therapy should be decided from previous studies. In both INPULSIS and INBUILD trials of Nintedanib in IPF and non-IPF patients of lung fibrosis, an early improvement of FVC were seen after 4 to 6 weeks [24]. So this drug can be used for that period and patient should be evaluated for response [25]. In ASCEND trial of Pirfenidone such significant improvements in FVC were noted after 3 months [26]. So this drug should be given for atleast 3 months before evaluating the response. The role of IL-1 in the pathogenesis of IPF is well described [27]. The inhibition of IL-1 with Anakinra has the potential to prevent the development of post COVID pulmonary fibrosis, at least theoretically. The role of anti IL-6 is less clear. IL-6 is generally considered a pro-fibrotic molecule [28, 29]. But experimental studies have suggested that inhibiting IL-6 in the early phase of lung injury promotes fibrosis and inhibition in the later phase of injury ameliorate fibrosis [30]. Nintedanib has been shown to reduce the BAL concentration of IL-1 Beta and Pirfenidone reduces serum and lung IL-6 concentrations in murine models of Pulmonary fibrosis [31]. So both of them provide a biological rationale for use of these drugs in COVID-19 associated fibrosis. There are suggestive data on potential benefit of these drugs in prevention of Acute Lung Injury (ALI). The application of this knowledge in COVID-19 depends on the rapidity of action of these antifibrotic drugs and initiating these before assisted ventilation or even before onset of ALI. A small cohort of patients in 3 Japanese studies with IPF, undergoing resection of lung cancer, which is a frequent trigger of fatal acute exacerbation of IPF with DAD pattern, a preoperative Pirfenidone therapy were given to patients 4 weeks before surgery and for a variable time afterwards. Clinical outcomes were compared between those receiving Pirfenidone or not. The treatment with Pirfenidone was associated with significant reductions in both prospective mortality [32] and acute exacerbation of IPF [33, 34]. Whether such therapy will be applicable for COVID or not is still not known. The current literatures suggest that any potential antifibrotic therapy should be considered within the first week of ARDS. But the use should be personalized as per clinical decision. One advantage of these antifibrotic drugs are they are safe, do not cause immune dysregulation and do not have immuno-suppressing effects. But Nintedanib theoretically has increased risk of bleeding when used with full dose anticoagulantion. An inhaled form of Pirfenidone is already under evaluation in COVID-19 (NCT04282902). Another drug Aviptadil, which is a VIP agonist, and prevents Type II Pneumocytes apoptosis, may be a promising drug, but will need more research [35].

2. Conclusion

Post COVID pulmonary fibrosis is a increasingly recognized condition in COVID-19. Damage to Type II Pneumocytes is a trigger to such fibrosis. During extensive involvement of lungs the Type I Pneumocytes and the basal membrane are also damaged. The extent of fibrosis will depend on severity of lung injury. But the persistence of fibrosis is related to effectiveness of the repair mechanisms. A low reserve of Type II Pneumocytes may cause permanent lung scarring. Elderly, smokers and patients with known history of Pulmonary fibrosis are at increased risk for post COVID pulmonary fibrosis. Certain biomarkers are available which can predict the fibrosis. The treatment will depend on the nature of fibrosis. While many patients will require no treatment, few patients will be benefitted from steroids, especially those with a pattern of Organizing Pneumonia. Patients with more like UIP patterns will be benefitted from antifibrotic drugs. Whether early initiation of antifibrotic drugs, in high risk patients with high chances of ARDS, will prevent subsequent fibrosis, is an intriguing thought. In future definitely we will have more knowledge to answer and treat this condition more efficiently.

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