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Review Article

Nintedanib as an Antifibrotic in Post Covid Lung Fibrosis: Are we Really Overestimating?

Shital Patil, MD FCCP[1*], Neel Tandel MD[2], Omprakash Bhangdia MD[3], Gajanan Gondhali MD[4]
[1]Professor, Pulmonary Medicine, MIMSR Medical College, Latur, India
[2]Junior Resident, Radiodiagnosis, MIMSR Medical College, Latur, India
[3]Professor, Radiodiagnosis, MIMSR Medical College, Latur, India
[4]Professor, Internal Medicine, MIMSR Medical College, Latur, India

***Corresponding Author:** Shital Patil
Professor, Pulmonary Medicine, MIMSR Medical College, Latur, India

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Abstract: Antifibrotics were exuberantly used to treat post covid lung complications. Lung is the primary target organ in COVID-19 disease with diverse clinical and radiological presentations and outcome. It has caused minimal to moderate lung disease in some patients and in some cases caused deadly acute respiratory distress syndrome (ARDS). COVID-19 disease caused lung damage by direct virus induced alveolar damage, cytokine induced alveolar and vascular damage and microvascular thrombosis resulting into acute hypoxic respiratory failure. COVID-19 pneumonia evolved over period of three weeks in cases with ARDS as natural course of illness. Usually, ARDS resolves by fibrosis or resolution as final outcome. Similarly, in COVID-19 recovered cases of advanced disease or those suffering from ARDS are having post covid lung disease. Lung fibrosis is final radiological outcome of COVID-19 pneumonia documented in proportionately majority of cases. Post COVID lung fibrosis is considered as worrisome radiological complication observed during early phase of pandemic. Antifibrotics such as Nintedanib and Pirfenidone were used to treat post covid lung complications such as fibrosis. Both drugs were shown good antifibrotic property in clinical trials for fibrotic lung disease and observed positive outcome in restoring lung parenchyma. Time trends of final radiological outcome has evolved over months with or without treatment with antifibrotics and steroids. Importantly, Post covid lung fibrosis resolved more than fifty percent cases in six months and nearly in all cases after one year. Thus, antifibrotics were used irrationally in fibrosing lung condition of reversible type. Actually, we have overestimated post covid lung fibrosis and overtreated with antifibrotics.

Keywords: COVID-19, ARDS, Pneumonia, Post covid lung fibrosis, Post covid sequelae, antifibrotics.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged viral pathogen that leads to coronavirus disease-2019 (COVID-19). A large proportion of infected COVID-19 cases have very mild symptoms such as loss of taste or smell, fever, fatigue, and dry cough - or are completely asymptomatic. However, in about 14% of the cases, acute respiratory distress syndrome (ARDS) can develop which is a potentially fatal condition [1]. Pulmonary fibrosis is an interstitial lung disease (ILD) that is characterized by progressive scarring of the lung tissue, impacting lung function, and leading to impaired gas exchange and difficulty breathing [2]. Currently, the incidence of pulmonary fibrosis is increasing significantly [3]. The development of pulmonary fibrosis is associated with many risk factors, such as aging, smoking, genetic predisposition, and exposure to occupational dust and asbestos [4]. The risk of mortality is increased in patients with pulmonary fibrosis owing to a lack of effective therapies to halt disease progression [5]. Pulmonary fibrosis has been linked to viral pneumonia, such as coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, it is thought to be uncommon [6-8]. COVID-19 may cause atypical pneumonia that progresses to acute lung injury and acute respiratory distress syndrome (ARDS). The symptoms associated with COVID-19 range from mild upper respiratory tract involvement to severe ARDS requiring long-term oxygen therapy due to pulmonary

fibrosis [9]. The risk of mortality in COVID-19 patients with pulmonary fibrosis increases as pulmonary fibrosis is a progressive disease that leads to respiratory failure and is associated with a poor prognosis; lung transplantation is the only treatment demonstrated to improve outcomes [10]. Few studies have documented progressive, persistent and resolving type in short time follow up of three to six months [11].

Post covid lung predictors and pathophysiology:

The first reports of a novel coronavirus SARS-CoV-2 came from Wuhan, China, in December 2019. As this highly transmissible virus spread rapidly across the globe, it quickly overwhelmed medical and critical care resources, becoming a leading cause of morbidity and mortality worldwide. Due to the high prevalence of respiratory failure and the need for mechanical ventilation in patients with severe manifestations of the disease, there has been increasing concern about the pulmonary sequelae, most notably pulmonary fibrosis (PF) [2]. Given that survivors of COVID-19 who develop persistent pulmonary disease will require long term specialty care, all clinicians have a vested interest in understanding and mitigating the various risk factors associated with post-COVID-19 pulmonary fibrosis (PCPF). Potential contributing etiologies for PCPF include viral pneumonia and pneumonitis [12-18]; ARDS from COVID-19 pneumonia and COVID-19 related sepsis [16-21]; trauma due to prolonged mechanical ventilation (MV) [21-24]; thromboembolism [17, 19, 25, 26]; hyperoxia [18, 19, 27, 28]; and dysregulations in the immune response [29-34]. Pathophysiology of post covid lung fibrosis is well established and follows same pathway of ARDS due to any cause such as injury, inflammation, exaggerated inflammation, repair and fibrosis. Post covid lung fibrosis (PCLF) or Post covid pulmonary fibrosis (PCPF) pathway is shown in Figure 1 [35]. There has been some discussion on P-SILI (patient-self-induced lung injury), a form of lung injury that is thought to occur early in ARDS, in which strong spontaneous breathing effort may contribute to lung damage, and there has been debate on if this should affect timing of intubation [36, 37].

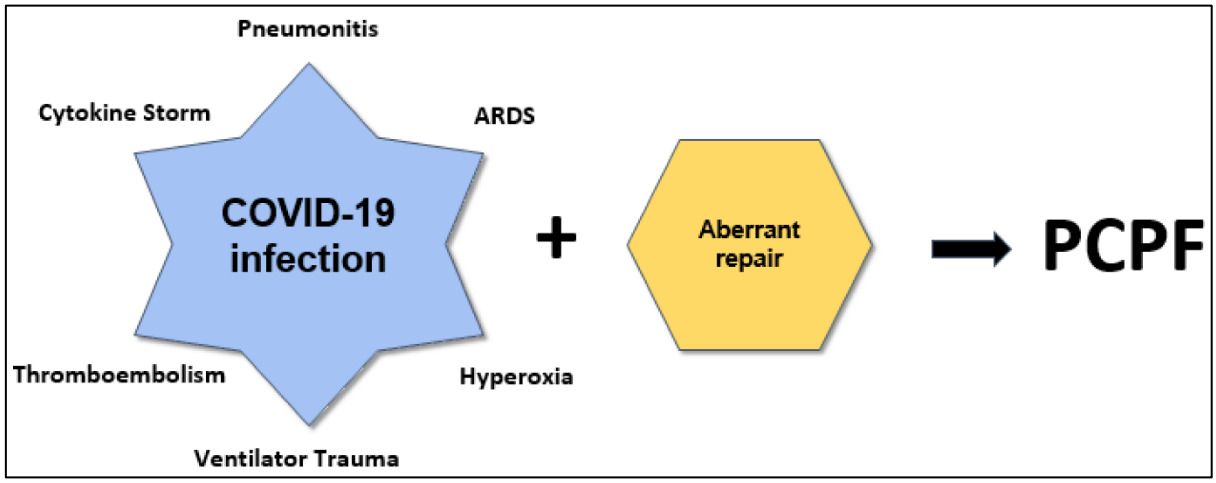

Figure 1: Injury → Inflammatory response → Repair → Fibrosis

Post-ARDS Pulmonary Fibrosis:

By contrast, in ARDS survivors there is extensive literature documenting the correlation of physiologic and radiologic data with health-related quality of life (HR-QOL), as well as pulmonary-specific measures. Survivors may have various pulmonary abnormalities including restriction, which may be due to neuro-muscular weakness (NMW) and deconditioning more so than parenchymal injury. Burnham *et al.*, showed the radiographic changes and physiologic measures correlated well with patient's symptoms and reduced pulmonary function months after diagnosis in a number of acute lung injury (ALI)/ARDS survivors [38]. These patients tended to have low diffusing capacity for carbon monoxide (DLCO) supporting direct pulmonary injury impacting gas exchange [39]. Common variables for fibrotic lung disease following viral respiratory failure are advanced age, prolonged duration of mechanical ventilation, and worsened initial radiographic changes, all of which are consistent with a baseline more severely ill population. The underlying pathophysiology is likely multifactorial, with the largest contributions coming from mechanical ventilation induced trauma to the lungs, as well as aberrant reparative processes. In response to viral mediated lung damage, dysregulation of epidermal growth factor receptor (EGFR) signaling may lead to a prolonged and exaggerated wound healing response, leading to fibrosis [40].

Direct Trauma from Mechanical Ventilation and post covid lung fibrosis:

A postulated role of prolonged mechanical ventilation-induced lung injury (VILI) in PF has been outlined by several authors [24]. Although mechanical ventilation (MV) is the most important supportive therapy for ARDS, it can cause or worsen lung injury which is referred to as VILI [24]. A significant proportion of patients with COVID-19 require MV as a supportive treatment and in one study of 5700

hospitalized COVID-19 patients, 20% required MV [41]. ARDS causing respiratory failure is a frequent cause of morbidity and mortality in COVID-19 patients and often is the reason they need MV [42, 43]. The initial inflammatory injury of ARDS to the lung may be augmented by mechanical forces of MV [44]. VILI presents similarly to and is clinically indistinguishable from ALI/ARDS [45]; thus, it is difficult to determine cause and effect and whether the virus, the disease process (ARDS), or the treatment (MV) is the culprit for any ensuing and persistent lung injury [45, 46].

Thromboembolism and post covid lung fibrosis:

In addition to causing a clinical array of respiratory-related disorders, COVID-19 has also been shown to result in a profoundly prothrombotic state leading to both micro- and macro-thrombotic disease [10]. At present, the specific pathophysiology underlying this hypercoagulable state remains unclear; proposed mechanisms include a combination of hyperinflammatory processes triggering thrombo-inflammation; dysregulation of complement, fibrinolytic and plasminogen systems; and viral-mediated endothelial cell injury [47]. However, this is not specific to COVID-related ARDS; ARDS in general is associated with pulmonary thrombosis and it is not clear that COVID-related ARDS has more or less thrombosis than non-COVID related ARDS.

Thromboembolism and hypercoagulability may be implicated in pathogenesis of pulmonary fibrosis. Epidemiologic observations have supported this possibility [17, 25, 26]. A large cohort study showed that the incidence rates of ILD were higher in patients with a history of venous thromboembolism or pulmonary embolism than in control patients [48]. A possible mechanism would be pulmonary emboli leading to lung injury and damage, triggering or contributing to fibrosis [48]. Grosse *et al*., evaluated the spectrum of cardiopulmonary histopathology of COVID-19 based on non-minimally invasive autopsies, and their findings revealed different stages of DAD in all fourteen patients assessed, with the presence of thrombotic/thromboembolic vascular occlusions in an overwhelming majority (11/14) [49]. Thus, pulmonary artery thrombi in COVID-19 may be attributable to dysregulation of the inflammatory and reparatory mechanisms as a result of DAD. Prior autopsy series from patients infected with SARS-CoV-1 seem to support this theory as the authors considered fibrin microthrombi in small pulmonary arteries as a common finding of DAD, however, this is a common finding in autopsies of patients with ARDS from other disease states and may simply be a reflection of illness severity.

Pro-Inflammatory State and post covid lung fibrosis:

Another mechanism more recently hypothesized as a potential contributor to the immune dysregulation and hypercoagulable state found in COVID-19 patients are neutrophil extracellular traps (NETs) [50]. Activated neutrophils have the unique ability to form NETs, which are weblike structures rich in host DNA, modified histone proteins, and granule proteins such as neutrophil elastase (NE) and myeloperoxidase (MPO). Initially discovered for their role in bactericidal activities, NETs are now hypothesized to be involved in a variety of infectious and non-infectious processes that lead to lung damage, thrombosis, and fibrosis. Interestingly, NETs have been found in the airways and pulmonary microcirculation of COVID-19 patients, but were not detected in the lungs of patients who died of other causes [50]. Further investigation is required to more specifically elucidate whether NETs are directly involved in the formation of pulmonary micro-thrombi, but it is possible that under hyper-inflammatory conditions such as those induced by severe COVID-19 infection, NETs could represent a mechanism by which neutrophils contribute to thrombus formation, host-system repair dysregulation, and subsequent pulmonary fibrosis formation. A possible mechanism by which NETs may contribute to PCPF is that in advanced stages, NETs could be replaced by collagen networks [50, 51].

Immunological dysregulation, also known as the “cytokine storm”, may be a significant contributor to multiorgan dysfunction [15]. Many cytokines have been reported at elevated levels in COVID-19 cases, including IL1-β, IL-6, IL-7, IL-8, and tumor necrosis factor-α (TNF-α). Elevated proinflammatory cytokines correlate with disease severity [52, 53]. The immune induced mechanism of PF is important to address. Immune-related damage contributes to COVID related ARDS [12-17]. Also, transforming growth factor beta (TGF-β) is a cytokine thought to be a crucial mediator of initiation and progression of fibrosis and remodeling [54]. Its expression is increased in animal models of PF and in human lungs with IPF [55]. IL- 6 and IL-16 are other cytokines that may also be implicated in lung or other organs’ fibrosis [56, 57].

Impact of CT severity on Post COVID Lung Fibrosis:

CT severity as the best visual marker of severity of COVID-19 pneumonia which can be correlated with inflammatory markers as IL-6, ferritin, CRP, LDH, D-dimer and lymphopenia, lymphocyte platelet ratio, and it will help in triaging cases in casualty and help in targeting interventions in indoor units accordingly to have successful treatment outcome [29-34]. CT severity classification done according to anatomical involvement of lung parenchyma in both lungs in different lobes and segments. As CT severity increases the lung involvement is also increases. Thus, CT severity score more than 12/25 was associated with lung fibrosis and is correlated well with inflammatory markers [29-34]. A large single center study involving more than 6000 cases with long covid symptoms has documented post covid fibrosis in significant number if

cases at three months following discharge form hospital [58]. Authors have mentioned CT severity is good predictor of requirement of interventions in indoor unit during hospitalization and very well correlated with inflammatory markers. Higher the CT severity, there will be more lung parenchymal necrosis and inflammatory burden which exaggerate lung inflammation and more synergistic effect on lung healing with altered repair resulting into fibrosis [29-34, 58]. Authors have also documented that reversible nature of post covid lung fibrosis with antifibrotics mediations such as Nintedanib and pirfenidone. In their study, follow up HRCT thorax done at one year before labelling as reversible nature of post covid lung fibrosis [29-34, 59].

Does decreased oxygenation status or hypoxia during hospitalization triggers post covid lung fibrosis or these are two sides of same coin?

Prolonged hypoxia's effect on the development of interstitial pulmonary fibrosis is not specific to COVID-19 but well-documented in the literature [60-62]. Some studies have suggested a link between hypoxia and the development of pulmonary fibrosis, citing the aberrant interplay between hypoxia, fibroblast formation, and extracellular matrix (ECM) deposition. This been supported by studies showing that hypoxia-inducible factor 1-alpha, (HIF-1-alpha), is implicated in initiation and progression of multiple types of tissue fibroses [60].

Hypoxia has documented important trigger for post covid lung fibrosis. Hypoxia resulting from more advanced lung parenchymal disease as per CT severity which is very well correlated with advanced interventions requirement in intensive care units such as high flow nasal canula (HFNC), non-invasive ventilation (NIV) and invasive mechanical ventilation (MV) [29-34]. Oxygenation status was proportional to disease severity and inflammatory burden. Thus, COVID-19 cases with hypoxia are indirect marker for future post covid lung fibrosis irrespective of interventions [29-34]. Authors have documented interventions in intensive care unit has significant association with reversal of hypoxia and inflammatory burden. But this will have minimal effect on final radiological outcome as post covid lung fibrosis [29-24].

By the same token, hyperoxia or prolonged exposure to excessively high amounts of supplemental oxygen has also been documented to lead to PF (DAD histopathology) [63]. This is difficult to mitigate in COVID patients with profound hypoxemia who are susceptible to the more acute effects of tissue hypoxia, but this mechanism is worth considering, especially with regards to growing understanding of what constitutes acceptable oxygen levels in this illness [64].

Does Inflammatory makers analysis during and during follow up predicts post covid lung fibrosis?

Authors have documented that the follow-up inflammatory markers titer during hospitalization as compared to entry point normal inflammatory markers such as CRP, Ferritin, D-dimer, IL-6 and LDH has significant association in post-covid lung fibrosis during follow up assessment at three months [29-34]. They have specifically mentioned that a small fraction of nonsevere patients developed into severe cases in the first 2 weeks after symptom onset. Therefore, health care institutions should also pay close attention to the mild patients, identify progressors early, and provide appropriate treatment to reduce mortality [29-34].

Authors have documented that the Follow-up inflammatory markers titer during hospitalization during hospitalization as compared to entry point abnormal inflammatory markers such as CRP, Ferritin, D-dimer, IL-6 and LDH has significant association in post-covid lung fibrosis during follow up assessment at three months [29-34]. Authors have documented that serial inflammatory markers measurement of during hospitalization irrespective of entry point level has very well correlation with outcome and requirement of interventions in intensive care setting, which will indirectly help in predicting future risk of development of post covid lung fibrosis in majority of cases required aggressive interventions like high flow nasal canula, BIPAP/NIV, ECMO, Invasive mechanical ventilation irrespective of inflammatory markers level reaching to cytokine storm. Serial measurements also predict chances of lung fibrosis in these patients as cytokine induced lung damage resulted in lung necrosis and resultant lung fibrosis [11-17]. Few studies have documented inflammatory markers analysis after few months of follow-up is not very good predictor of post covid lung fibrosis especially after one year duration [58]. Authors have mentioned that retrospective analysis of cases required ventilatory support, poor oxygenation status and four-fold raised inflammatory markers were key pointers for post covid lung fibrosis [29-34, 58].

Why post covid lung fibrosis outcomes were different during different COVID-19 waves?

Genetic makeup of corona virus was determining factor for overall outcome different waves COVID-19 as in first was classical 'Wuhan variant virus' and second one was mutant 'Delta variant' corona virus; and third wave 'omicron variant'. Delta variant was deadly mutant documented in second wave which was associated with increased morbidity and mortality. In all the waves, covid pathophysiology were same i.e., immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues [65]. Rapidly evolving pneumonia or 'accelerated acute respiratory distress syndrome' (a-ARDS) was more commonly documented in second wave and more number of patients were

presenting with similar syndrome in second wave with time interval of less than a week, with rapidly deteriorating radiological and clinical-laboratory parameters like increased CT severity score, worsened oxygenation, increased inflammatory markers like CRP, IL-6, Ferritin, LDH, D-dimer, decreased leucocyte and platelet counts [65]. Post-COVID lung fibrosis and mucormycosis were two deadlier complications documented during the evolution of COVID-19 pneumonia, predominantly in the second wave as compared to the first wave across the country. Rational for the occurrence of both the complications was not clear, post-COVID fibrosis was documented more commonly in the second wave and related to more virulent nature of mutant Delta variant virus as compared to Wuhan variant of the first wave [66].

Although mortality documented in COVID-19 is less as compared to SARS and MERS, various variants evolved during COVID-19 disease have different trends of mortality. Importantly why the second wave "delta" variant of COVID-19 has highest mortality as compared to first wave variant, and negligible in third wave omicron variant, is still unknown. Maybe, genetic makeup of coronavirus was the determining factor for overall outcome in the first and second wave different variants of coronavirus with genetic mutations; which was associated with increased morbidity and mortality in comparison to currently ongoing omicron variant with negligible mortality [67]. Pulmonary involvement was predominant over extrapulmonary in second wave with delta variant, pulmonary and extrapulmonary proportionately similar in first wave Wuhan variant and predominant extrapulmonary with minimal pulmonary involvement was commonly documented in third wave omicron variant [66, 67]. This diverse presentation is documented all over the world but rational for heterogeneous scenario needs further research.

Various myths regarding Post covid lung fibrosis have been documented during routine care of these cases in post covid care settings [67]. Survivors of critically ill COVID-19 disease cases were seeking attention regarding doubtful role of remdesivir and steroids in their illness during hospitalization and these rational treatment options for Covid are the link towards post covid lung fibrosis [67]. This was real myth, and steroids and remdesivir are the only scientifically proven treatment options along with anticoagulants during this pandemic and we have saved millions of lives with these lifesaving medications [68]. Social media has played a crucial role in spreading wrong message regarding doubtful role of Remdesivir in COVID-19 and these non-scientific comments and statements spread without available research has created misunderstanding in majority of recovered cases, especially in those facing "long COVID" manifestations.

Evaluation of Post COVID Lung fibrosis during follow-up:

Post-COVID-19 pulmonary fibrosis is defined as the presence of persistent and different fibrotic tomographic changes identified on follow-up, often combined with impairment in pulmonary function tests. During follow-up in post covid care settings, clinical, radiological, laboratory and lung function assessment were key steps during evaluation of Post covid lung fibrosis. Clinical assessment includes symptoms of cough, shortness of breath, chest discomfort & oxygen saturation, vital parameters at rest and during ambulation. Oxygen saturation and stable heart rate after ambulation is considered as best marker of improvement in these cases. Laboratory assessment of anemia is important in these cases with tachycardia with borderline oxygen saturation during routine walk. Pulmonary functions test & 6-Minute walk test is performed during routine follow-up for more precise assessment of pulmonary and cardiopulmonary status respectively [69, 70]. Pulmonary functions abnormality in post-COVID-19 pneumonia cases has been documented and should be assessed cautiously to have successful treatment outcome. Restrictive lung disease is the predominant lung function impairment in post-COVID 19 recovered lung pneumonia cases. Age above 50 years, male gender, diabetes, High CT severity, longer duration of illness, proper timing of initiation of BIPAP/NIV therapy, has documented significant impact on post-COVID lung functions at 12 weeks assessment [70].

Post covid lung: is it fibrosis (PCLF) or sequel (PCLS)?

Initially after first wave of COVID-19 pandemic, many covid survivors in intensive care units those required oxygen supplementation, ventilatory support or high flow nasal canula, longer hospital stay, high CT severity were documented post covid lung fibrosis. The development of pulmonary fibrosis is considered one of the key concerns regarding COVID-19 pulmonary sequelae as it is associated with architectural distortion of the lung parenchyma and overall impairment of lung function resulting in decreased quality of life [8, 58]. The pathogenic progression of pulmonary fibrosis post-COVID-19 is yet to be fully illuminated; however, it is thought to be multifactorial. Whatever the cause, fibrosis is considered to be due to the abnormal healing of the injured lung parenchyma. In COVID-19 patients, possible sources of injury include cytokine storm due to improper inflammatory response, bacterial co-infections, and thromboembolic events causing microvascular damage and endothelial dysfunction [71]. According to the literature, pulmonary fibrosis can develop right after discharge or several weeks later [8].

Post covid lung fibrosis at any stage ranging from minimal lung parenchymal abnormalities as parenchymal bands to reticular opacities and complete

architectural distortion with or without tractional bronchiectasis and honeycombing shown near complete resolution in one to two years. Authors have also mentioned role of anti fibrotics in some cases and some cases were treated with short course of steroids. Authors have mentioned that some cases shown complete recovery without treatment with steroids and antifibrotics. Thus, post covid lung abnormalities or lung fibrosis is completely reversible process [8, 58, 71].

Post covid lung fibrosis is considered as 'health issue of great concern' initially in post pandemic phase of first wave, and due to its resolving nature over time period; now considered as 'sigh with relief' due to its reversible pathophysiology. Post covid sequel is minimal residual effects of COVID-19 lung disease irrespective of disease severity in past. We recommend to use term post covid sequel over post covid lung fibrosis.

Is there a role for antifibrotic therapy with Nintedanib or Pirfenidone?

Pulmonary fibrosis is one of the fatal complications in severe or critical COVID-19 patients [72, 73]. Based on the resemblance of pulmonary fibrosis' pathophysiological mechanisms between IPF and COVID-19 infection, it is considered that IPF regimens could be beneficial in COVID-19 pneumonia treatment. The clinical rationale of using antifibrotic therapy in COVID-19 patients is to prevent complications of ongoing infection, stimulate the recovering phase, and control the fibroproliferative processes [74]. Many early antifibrotic studies had concentrated on immunomodulatory system involvement, such as IFN-β and IFN-ɣ. However, the novel antifibrotic therapies should be focused on the fibrotic response following acute lung injury (ALI) rather than the new fibrotic lesions [75]. At Present, there is no evidence that Nintedanib or pirfenidone affects the severity of COVID symptoms. Furthermore, the side effects of these drugs are similar, in part, to those of COVID (e.g., diarrhea, fatigue, loss of appetite), which can hamper early diagnosis and worsen clinical manifestations [55]. Acute complications are some of the most serious IPF consequences, and the rate of in-hospital lethality for this condition exceeds 50%. Such acute IPF complications may be caused by respiratory viral infections. Although both antifibrotic agents have pleiotropic effects, neither of them is immunosuppressive. Thus, there is no evidence supporting the suspension of their use during an ongoing viral infection.

Nintedanib and Pirfenidone:

Nintedanib and pirfenidone are antifibrotic medicines that, despite different mechanisms of action, are equally efficacious in inhibiting the reduction of respiratory function by ~50% and increase the life expectancy of IPF (idiopathic pulmonary fibrosis) patients by 2.5 years on average [76]. Nintedanib (6-methoxycarbonyl-substituted indolinone) is an oral therapeutic used for the treatment of IPF and a second-line treatment for non-small cell lung adenocarcinoma. In 2020, this drug was approved for the treatment of advanced chronic fibrotic interstitial lung diseases.

Lung fibroblasts from IPF patients and in vivo models demonstrate that the antifibrotic activity of Nintedanib is associated with the inhibition of pro-fibrotic mediators, including platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF). Nintedanib binds to the intracellular ATP pockets of the corresponding receptors, which leads to the inhibition of pro-fibrotic signaling and the attenuation of the proliferation, migration, and differentiation of fibroblasts as well as extracellular matrix component secretion [77].

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is an oral antifibrotic agent with multiple effects such as the regulation of pro-fibrotic and pro-inflammatory cytokine cascades and the inhibition of fibroblast proliferation and synthesis of collagen, which is a standard therapy for lung cancer and moderate IPF [78]. Pirfenidone decelerates fibrosis by inhibiting pro-fibrotic and pro-inflammatory cytokine cascades, including TGF-β signaling, which plays a central role in IPF pathogenesis [79]. Pirfenidone blocks TGF-β-stimulated collagen production, inhibiting the activation of HSP47 and Col1 genes. In in vitro and in vivo studies, pirfenidone showed an anti-inflammatory effect by suppressing the production of tumor necrosis factor-α (TNF-α), interferon gamma (IFN-γ), interleukin-1beta (IL-1β), and interleukin-6 (IL-6). Pirfenidone was also shown to have antioxidant properties; depending on the concentration, it blocked NADPH-dependent microsomal lipid peroxidation in the liver. Based on in vivo models, it was determined that pirfenidone suppresses TGF-β-associated fibroblast differentiation in the lungs [79]. As of April 2020, pirfenidone and Nintedanib have been commercially sold only in an oral form, and therefore have limited use among patients undergoing artificial lung ventilation. However, in December 2020, pirfenidone was used in patients with COVID-induced severe ARDS; the compound was administered through a nasogastric tube [80]. In February 2020, a clinical trial was initiated to evaluate the safety and efficacy of pirfenidone in new coronavirus patients >18 years old. During the four-day trial, the authors assessed the dynamics of damaged lung areas using chest CT scans, oxygenation, changes in blood gas content, and quality of life according to the King's Brief Interstitial Lung Disease (K-BILD) questionnaire. Moreover, the researchers analyzed the mortality rate, clinical manifestation dynamics (dyspnea and coughing), blood parameters such as lymphocyte counts, viral nucleic acid, and markers of inflammation in the blood [81].

Another clinical trial of pirfenidone in patients with fibrotic changes after COVID was launched in August 2020 [82]. The established inclusion criteria selected (1) adults older than 18, (2) who had verified SARS-CoV-2 infection (3) that led to severe pneumonia and ARDS (4) with convalescence and/or clinical and radiological signs of pulmonary fibrosis on a high-resolution CT (HRCT) scan (with fibrotic changes of no less than 5% after recovery). This trial aimed to study how pirfenidone affected COVID-induced fibrotic changes, the level of forced vital capacity (FVC) of the lung, if it lowered oxygen uptake during exercise, increased exercise tolerance during the 6-min walking test (6MWT), requests for hospitalization (general as well as associated with respiratory disease), requests for emergency or outpatient care due to respiratory diseases, lung transplants, and mortality.

The first clinical trial of Nintedanib started in April 2020. A single-center, randomized, placebo-controlled trial on the efficacy and safety of Nintedanib for the treatment of lung fibrosis in patients with moderate and severe COVID symptoms was initiated. The cohort included patients 18–70 years old suffering from fibrosis of both lungs after recovery from COVID. The primary efficacy endpoint was the FVC measurement after eight weeks of therapy; the secondary endpoints were DLCO levels, 6MWT parameters, and HRCT eight weeks after therapy [83].

Phase III trial of Nintedanib began in October 2020 [84]. The study included patients 18–89 years old and verified to have had COVID (positive PCR or serologic test results within the previous 2–6 months), with radiological signs (CT) of fibrosis (>10% of lung capacity) and DLCO ≤ 70%. The primary objective is to assess the efficacy of Nintedanib in the retardation of lung fibrosis progression in COVID survivors expressed as FVC levels in 12 months compared to placebo. The authors aim to compare the rate of DLCO decrease after 6 and 12 months, exercise tolerance after 12 months, the increase in fibrotic changes (HRCT) after 12 months, and health-related quality-of-life changes; to evaluate dyspnea dynamics, changes in depression and anxiety levels, biomarkers of lung damage, lung hypertension and inflammation, rate of lung hypertension after 12 months compared to the moment of inclusion; to assess the link between genetic predisposition (MUC5B polymorphism) and lung fibrosis in COVID survivors, and the safety of the compound.

The third clinical trial of Nintedanib (phase IV; in progress since November 2020) is aimed at investigating the influence of Nintedanib on slowing down lung fibrosis in patients over 18 years old, with infiltrates or progressive lung damage appearing on chest X-rays or CTs not less than 4 weeks after the emergence of the first symptoms, and an FVC ratio below 80% or DLCO less than 50% of normal values [85]. Primary endpoints include FVC change in 180 days compared to the initial value. Secondary endpoints are death at 90 and 180 days after trial inclusion due to respiratory causes; a visual evaluation of the chest by CT scan; changes according to St. George's Respiratory Questionnaire (SGRQ), K-BILD, Leicester Cough Questionnaire (LCQ), and others.

Data indicate a higher risk of thromboembolia of the pulmonary artery in COVID patients. Anticoagulant therapy may improve outcomes in patients with severe COVID and coagulopathy [86]. This observation is relevant to individuals receiving Nintedanib, as it is likely that this drug may increase the risk of bleeding when used together with anticoagulants. In this case, antifibrotic therapy can be suspended to minimize the side effects of pharmacotherapy [76]. Additionally, pirfenidone and Nintedanib may contribute to hepatotoxicity, while patients infected with SARS-CoV-2 often experience liver dysfunction. Elevated levels of liver enzymes were observed in 168 out of 757 patients (22%) with confirmed COVID and in 56/142 (39%) patients with severe symptoms [87]. The simultaneous use of antibiotics can increase the likelihood of liver dysfunction, which may be mitigated by a temporary suspension of antifibrotic therapy for in-hospital IPF patients with severe COVID and abnormal hepatic function tests until the levels of key liver function indicators are normalized [76].

CONCLUSIONS

Post covid lung fibrosis is commonly documented and overestimated during COVID-19 pandemic and distressed patients and pulmonologists globally. Patients with a greater risk for post-COVID-19 pulmonary fibrosis include those who are older, male, and smokers and have comorbidities. The pathogenesis of post-COVID-19 pulmonary fibrosis is partially known and likely multifactorial. Tomographic features identified in pulmonary fibrosis secondary to COVID-19 include the presence of architectural distortion, reticular opacities, traction bronchiolectesis, ground-glass opacities, mosaic attenuation, and honeycombing. Strategies to reduce the severity and progression of post-COVID-19 are unclear.

Antifibrotics such as Nintedanib and Pirfenidone were used to treat post covid lung complications such as fibrosis. Both drugs were shown good antifibrotic property in clinical trials for fibrotic lung disease and observed positive outcome in restoring lung parenchyma. Time trends of final radiological outcome has evolved over months with or without treatment with antifibrotics and steroids. Importantly, Post covid lung fibrosis resolved more than fifty percent cases in six months and nearly in all cases after one year. Thus, antifibrotics were used irrationally in fibrosing lung condition of reversible type. Actually, we

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