International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(REVIEW ARTICLE)

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Post Covid-19 pulmonary fibrosis: A review article

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International Journal of Biological and Pharmaceutical Sciences Archive, 2022, 04(01), 040–045

Publication history: Received on 22 June 2022; revised on 09 August 2022; accepted on 11 August 2022

Article DOI: https://doi.org/10.53771/ijbpsa.2022.4.1.0048

Abstract

COVID-19 also known as Coronavirus disease 2019 is an infectious disease caused by the highly contagious pathogen SARS-CoV-2.Various studies have found that 70–80% of patients who recovered from COVID-19 continue to have at least one or more symptoms even after being pronounced COVID-free. Pulmonary fibrosis is a severe respiratory illness consequence. It is defined by the lungs' failure to repair the injured alveolar epithelium, the persistence of fibroblasts, and the excessive deposition of collagen and other extracellular matrix components. An initial phase of lung injury is followed by acute inflammation and an effort at healing. Oxygen toxicity and ventilator-induced lung injury are two iatrogenic variables that may contribute to the fibrosis seen in survivors of severe COVID19 pneumonia. Based on scientific evidence and demographic findings, Pirfenidone and Nintedanib, used alone or in combination with anti-inflammatory agents and this combination is effective in preventing serious complications during COVID-19 infection. Pirfenidone inhibits TGF-β stimulated collagen synthesis and the synthesis of tumor necrosis factor, interferon-gamma, interleukin- 1beta, and interleukin-6 resulting in anti-inflammatory action. Depending on the concentration, pirfenidone has been demonstrated to have antioxidant capabilities. Nintedanib saw inhibitory action on pro-fibrotic mediators like platelet-derived growth factor and fibroblast growth factor, transforming growth factor-beta, and vascular endothelial growth factor. Who were already taking antifibrotic therapy saw a reduction in the number of acute exacerbations of IPF. Thus, Nintedanib and Pirfenidone both drugs slowed down the progression of Lung Fibrosis in patients over 18yr of age. However, more studies are required for usage of antifibrotics in Non- IPF patients.

Keywords: COVID-19; Post covid-19 pulmonary fibrosis; Pirfenidone; Nintedanib

1. Introduction

COVID-19 also known as Coronavirus disease 2019 is an infectious disease caused by the highly contagious pathogen SARS-CoV-2. Coronaviruses (CoVs). have been linked to major illness outbreaks in East Asia and the Middle East over the last two decades. In 2002 and 2012, the severe acute respiratory syndrome (SARS). and the Middle East respiratory disease (MERS). first appeared. On December 12, 2019, Wuhan City, Hubei Province, China, reported the discovery of Novel CoV (previously known as 2019-nCoV). the World Health Organization (WHO). declared a Public Health International Emergency on January 31, 2020,on February 29, 2020, it was classified as a high-risk disease, and on March 11, 2020, it was declared a pandemic.(1,2). The International Committee on Taxonomy of Viruses (ICTV). has proposed that this virus be designated/named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).(1). SARS-CoV-2 is an enclosed virus with a single strand positive-sense RNA genome ranging from 26 to 32 kilobases in length and a diameter of 50–200 nm. It has the ability to survive for several days in the environment.(2). Wuhan, China, was the epicenter of the disease, which eventually spread to Italy, the United States, and Brazil. Following then, it has impacted approximately 215 countries/territories in less than six months, resulting in nearly 0.75 million human deaths.(2). COVID-19 has a less severe pathophysiology than previously known human CoVs, but it has a greater

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transmission competence, as evidenced by the growing number of confirmed cases around the world (1). The incubation time of SARS-CoV-2 is predicted to be 3– 7 days (range, 2–14 days)., indicating that the virus has a protracted transmission period.(3).

Coronaviruses are members of the Coronaviridae family of viruses (subfamily Coronavirinae)., which is part of the Nidovirales order. Alphacoronavirus (-CoV)., Betacoronavirus (-CoV)., Gammacoronavirus (-CoV)., and Deltacoronavirus (-CoV). are the four genera that make up the Orthocoronavirinae subfamily. δ- and γ -CoVs infect birds while both α- and β-CoV genera infects mammals.(1,3). SARS-CoV-2 is the seventh member of the human-infecting CoV family. SARS-CoV and MERS-CoV are responsible for atypical pneumonia, while four human CoVs (HCoV-229E, HCoV-NL63, HCoVOC43, and HCoV- HKU1). can cause a wide spectrum of upper respiratory tract infections (common cold). (3). The SARS-CoV-2 spike has a 10–20-fold higher affinity for human ACE2 than the SARS- CoV spike, making it easier to transfer from human to human.(3). The receptor-binding domain (RBD). of spike protein interacts with the ACE2 (angiotensin-converting enzyme 2). membrane protein of human cells, causing viral fusion and entrance (4). SARS-CoV-2 replicates quickly once it enters alveolar epithelial cells, triggering a robust immunological response that results in cytokine storm syndromes and pulmonary tissue destruction (3). Hypercytokinemia, also known as cytokine storm syndromes, is a set of illnesses characterized by the unregulated production of pro- inflammatory cytokines. It is a leading cause of ARDS and multiple organ failure (3).

RT-qPCR (reverse transcription quantitative PCR). is a nucleic acid sequence-based molecular biological diagnosis technique. Thus, SARS-CoV-2 nucleic acid can be detected in nasopharyngeal and oropharyngeal swabs, faeces, sputum, or blood samples using RT-qPCR or viral gene sequencing (3).

2. Pulmonary fibrosis after covid-19

The development of pulmonary fibrosis is a rare complication of the novel coronavirus disease 2019 (COVID-19). Post-COVID was initially identified in the context of a survey of lasting COVID-19 symptoms conducted by the Patient-Led Research Collaborative, a citizen's scientist group, in the spring of 2020 (5). Various studies have found that 70–80 percent of patients who recovered from COVID-19 continue to have at least one or more symptoms even after being pronounced COVID-free (5). It is believed that 10% to 35% of patients who do not require hospitalization develop post-COVID symptoms, regardless of co-morbidities, but rates of up to 80% have been documented among hospitalized patients and patients with severe diseases (5). Pulmonary fibrosis is a severe respiratory illness consequence (6). Patients with SARS who required ICU hospitalization had considerably less restricted lung function six months after disease onset than those who received ward-based care (7). The corona virus has a higher prevalence of severe interstitial pneumonia, ARDS, and multi-organ failure in high-risk populations such as the elderly or those with many comorbidities. Although the pulmonary system is the primary target of SARS-CoV-2, it can also affect the gastrointestinal, endocrine, and cardiovascular systems (8).

Cough, dyspnea, fever, sore throat, chest pain, palpitations, cognitive deficits, myalgia, neurological symptoms, skin rashes, and diarrhea are among the symptoms that people with extended COVID encounter; some also have persistent or intermittent low oxygen saturations (5). Patients affected with pulmonary fibrosis commonly complain of dry cough, fatigue, and dyspnea. Weight loss is expected with physical deconditioning (8). Dyspnea and impaired exercise tolerance were recorded in 10–40% of hospitalized COVID-19 patients for 2–4 months following discharge, whereas 65.6 percent of patients admitted to the intensive care unit had new or worsening dyspnea. Chest pain has been recorded in up to 22% of COVID-19 patients two months following hospital release. Olfactory and gustatory impairment can last longer than one month, affecting up to 11% and 9% of patients six months after discharge from the hospital, respectively, and up to 9% and 3.7 percent of patients eight months following mild COVID-19, respectively (7).

The majority of SARS-COV-2 patients had bilateral ground glass opacities with or without consolidation, with a preference for the lower lobes. Long-term lung damage, particularly fibrotic interstitial lung disease, may develop following virus clearance. Pulmonary fibrosis is a genetically predisposed, age-related fibroproliferative illness that can be idiopathic, although chronic inflammation may also play a role in the pathogenesis of lung fibrosis. It has been discovered that 40% of COVID-19 patients develop ARDS, amongst these population 20% are severe (9).

The pathogenesis of pulmonary fibrosis is complicated, with age, smoking, viral infection, drug exposure, and genetic predisposition all playing a role (8). Diffuse alveolar damage (DAD). is a pathological characteristic of ARDS that is defined by an initial acute inflammatory exudative phase with hyaline membranes, followed by an organizing phase and fibrotic phase (10). Pulmonary fibrosis is defined by the lungs' failure to repair the injured alveolar epithelium, the persistence of fibroblasts, and the excessive deposition of collagen and other extracellular matrix (ECM). components (8). A cytokine storm induced by an abnormal immune mechanism may cause the onset and progression of pulmonary

fibrosis (10). During an acute immunological response, macrophages are activated by two pathways known as the classical (M1). and alternative (M2). pathways. The interaction of PAMPs and DAMPs with macrophage receptors in the innate immune response, as well as stimulation by interferon-y from the T-cell adaptive response, initiate the M1 pathway. This pathway produces reactive oxygen species, antimicrobial compounds, and proinflammatory cytokines, which are responsible for the acute phase of inflammation. T-lymphocytes and other cells release IL-4 and IL-13, which activate the M2 pathway (11).

This route results in the synthesis of cytokines and growth factors that are important in tissue healing. It also reduces the M1 pathway, which suppresses the inflammatory process, and it is essential in the creation of scar tissue (11). Inflammatory mediators such as Transforming growth factor-beta (TGF-)., vascular endothelial growth factor (VEGF)., interleukin 6 (IL-6). and tumour necrosis factor-alpha (TNF-). play critical roles in the fibrotic cascade (21). The tissue factor-dependent extrinsic pathway is the most common mechanism by which the coagulation cascade is activated locally in the lungs of pulmonary fibrosis patients (12).

An initial phase of lung injury is followed by acute inflammation and an effort at healing. The high affinity binding of the SARSCoV2 viral spike protein to the angiotensin converting enzyme2 (ACE2). receptor has been found to downregulate the ACE2 receptor level. ACE2 is thought to play a protective role in lung fibrosis. Reduced ACE2 expression leads to increased angiotensin II (ANG II). levels. ANG II is a powerful vasoconstrictive peptide that plays a direct role in the development of inflammation and fibrosis. ANG II is essential in the fibrotic process, signaling cellular and molecular events that result in the development of lung fibrosis (13). The following are the cellular and molecular signaling events of ANG ll that lead to the development of abnormal wound healing and pulmonary fibrosis: I production of proinflammatory cytokines such as interleukin 6 (IL6). and IL8, (ii). production of reactive oxygen species among infected alveolar cells, and (iii). activation of TGF-β1, which leads to proliferation, migration, and differentiation of fibroblasts into myofibroblasts, with the collagen and fibronectin deposition (12). This process may result in the restoration of normal pulmonary architecture, or it may result in pulmonary fibrosis with architectural distortion and irreversible lung impairment (11). Compared to non-smokers, smokers are 1.4 times more likely to develop severe COVID-19 symptoms, 2.4 times more likely to require ICU admission and mechanical ventilation, and times more likely to die. COVID-19 problems are more likely in people who drink excessively (10). Oxygen toxicity and ventilator induced lung injury are two iatrogenic variables that may contribute to the fibrosis seen in survivors of severe COVID19 pneumonia (VILI). (13).

On radiography, fibrotic abnormalities of the lungs have been observed in COVID-19 patients as early as 3 weeks following the onset of symptoms (12). Ground glass opacities (GGOs). with or without consolidation, crazy-paving pattern, interstitial thickening, and parenchymal bands that are mostly bilateral with a preference for the lower lobe periphery are all radiologic imagingfindings in COVID19 pneumonia (13). Each of the five lung lobes was visually graded from 0 to 5 as follows: 0, no engagement; 1,5% involvement; 2,25% involvement; 3,26–49% involvement; 4,50–75% involvement; 5, >75% involvement. The overall CT score was the sum of the individual lobar scores, and it varied from 0 (no involvement). to 25 (complete involvement). (maximum involvement). In this work, we assessed the existence of fibrotic or non-fibrotic patterns using a qualitative measure that was closely related to the previously established semi-quantitative score. Patients with a score greater than 5 were judged to have a fibrotic pattern (14). C reactive protein (CRP). was thought to be a systemic inflammatory measure linked to infection severity. All hospitalized patients had abnormalities in their chest CT scans, which are characterized by grinding glass- like and consolidation regions in 98 percent of cases reporting bilateral lung limitation due to bilateral interstitial pneumonia (13). Because HRCT of the lung is more sensitive than chest x- ray, it can be used to distinguish between different ILDs, determine the amount and severity of disease activity, and, most significantly, diagnose disease, especially in patients who have no or minor change on chest radiography. Early symptoms include patchy, primarily peripheral subpleural reticular opacities and mild honeycomb alterations (12). Pulmonary function testing is helpful in determining the presence of functional impairment in pulmonary fibrosis, as well as tracking the disease's progression and response to treatment. In pulmonary fibrosis, lung capacities such as total lung capacity (TLC)., functional residual capacity (FRC)., and residual volume are diminished. Because of the reduction in lung volume, forced expiratory flow rates (FEV1). and forced vital capacity (FVC). may be reduced, but the FEV1/FVC ratio remains unchanged (12). People who are older are more likely to develop lung fibrosis. Idiopathic pulmonary fibrosis is diagnosed at a median age of 65 years, and it rarely occurs before the age of 50. Comorbidities include hypertension, diabetes, and coronary artery disease have been linked to increased disease severity. Lymphopenia, leukocytosis, and elevated lactate dehydrogenase (LDH). levels in the blood associated with greater disease severity (11). Following acute lung injury, serum LDH levels have been utilized as a measure of disease severity. When compared to non-smokers, smokers are 1.4 times more likely to develop severe COVID-19 symptoms, 2.4 times more likely to require ICU admission and mechanical ventilation, and 2.4 times more likely to die (10).

3. Treatment management

There are 11 medicines, two technologies, and one vaccination in clinical trials for the treatment and prevention of lung fibrosis in COVID survivors as of January 2021 (15). Pirfenidone and Nintedanib are are two antifibrotic medications that have been approved by the FDA. Despite the fact that they have diverse modalities of action, both are beneficial in slowing the rate of deterioration of lung function and are largely thought to increase life expectancy (6). Based on scientific evidence and demographic findings, Pirfenidone and Nintedanib, used alone or in combination with anti-inflammatory agents and this combination is effective in pre-venting serious complications during COVID-19 infection. The same strategy can be efficacious as post-infection therapy in individuals with persistent lung fibrotic injury. This study showed enormous use of antifibrotic therapy in SARS-CoV-2 infection, which is very officious in minimizing and avoiding fibrotic damage induced by inflammatory/immune dysfunction. Evidently pirfeniodne has shown its pleiotropic effectivity to decrease the inflammation and oxidative reactive shock associated with fibrosis (16).

A clinical investigation evaluating the safety and efficacy of pirfenidone in new coronavirus patients >18 years old began in February 2020. Using chest CT images, oxygenation, changes in blood gas content, and the King's Brief Interstitial Lung Disease (K-BILD). questionnaire, the authors analysed the dynamics of damaged lung areas during the four-day study. The researchers also looked at the death rate, clinical manifestation dynamics (dyspnea and coughing)., and blood parameters like lymphocyte counts, viral nucleic acid, and inflammatory markers in the blood. The researchers also looked at the death rate, clinical manifestation dynamics (dyspnea and coughing)., and blood parameters like lymphocyte counts, viral nucleic acid, and inflammatory markers in the blood. In August 2020, a new pirfenidone clinical trial was initiated in patients with fibrotic alterations after COVID. The goal of this trial was to see how pirfenidone affected COVID-induced fibrotic changes, lung FVC, exercise tolerance during the 6-minute walking test (6MWT)., requests for hospitalization (general and associated with respiratory disease)., requests for emergency or outpatient care due to respiratory diseases, lung transplants, and mortality (15). Pirfenidone slows fibrosis by blocking pro-fibrotic and pro-inflammatory cytokine pathways, such as TGF-β signaling, which is important in the pathophysiology of IPF. Pirfenidone inhibits TGF- β stimulated collagen synthesis. Pirfenidone inhibited the synthesis of tumour necrosis factor (TNF-α)., interferon gamma (INF-g)., interleukin-1beta (IL-1β)., and interleukin-6 (IL- 6)., resulting in an anti-inflammatory action. Depending on the concentration, pirfenidone has been demonstrated to have antioxidant capabilities (15). It also functions as an antipyretic, non- narcotic analgesic, and non-steroidal anti-inflammatory medication (11).

Nintedanib is an orally active small molecule tyrosine kinase inhibitor that has been studied for the treatment of IPF in large clinical studies (11). In April 2020, nintedanib began its first clinical trial. The efficacy and safety of nintedanib for the treatment of lung fibrosis in patients with moderate and severe COVID symptoms were studied in a single-center, randomised, placebo-controlled trial. Patients in the study ranged in age from 18 to 70 years old and had developed fibrosis in both lungs after recovering from COVID. The FVC measurement after eight weeks of therapy was the primary effectiveness outcome, with DLCO levels, 6MWT parameters, and HRCT eight weeks later as supplementary goals. In October 2020, a phase III trial of nintedanib began. The primary goal was to evaluate the efficacy of nintedanib to placebo in preventing lung fibrosis advancement in COVID survivors expressed as FVC levels after 12 months. The third clinical trial of nintedanib (phase IV; ongoing since November 2020). aims to see if it can slow down lung fibrosis in patients over 18 years old who have infiltrates or progressive lung damage on chest X-rays orCTs not more than 4 weeks after the onset of the first symptoms and an FVC ratio of less than 80% or DLCO of less than 50% of normal values (15). In Phase III trials, the INPULSIS studies (INPULSIS 1, INPULSIS 2). looked at the efficacy and safety of nintedanib 150 mg twice daily against placebo in patients with IPF. In these investigations, nintedanib slowed the fall in FVC in patients with IPF, which is consistent with a slowing of disease progression (17). Nintedanib has an inhibitory action on pro-fibrotic mediators such as platelet-derived growth factor (PDGF). and fibroblast growth factor (FGF)., transforming growth factor beta (TGF-)., and vascular endothelial growth factor (VEGF). Nintedanib binds to the targeted receptors' intracellular ATP pockets, inhibiting pro-fibrotic signalling and reducing fibroblast proliferation, migration, and differentiation, as well as secretion of extracellular matrix components (15). Patients who were already taking antifibrotic therapy saw a reductionin the number of acute exacerbations of IPF (11).

Combination therapy with nintedanib and pirfenidone is gaining popularity, especially because the mechanisms of antifibrotic effect are different between the two medications. There are no major randomised controlled trials comparing the efficacy of combination therapy versus treatment with a single antifibrotic. Although there was a trend toward reduced exposure to nintedanib in the presence of pirfenidone in early investigations, pharmacokinetically, nintedanib does not seem to influence pirfenidone bioavailability (18).

4. Conclusion

Till now antifibrotics such as nintedanib and pirfenidone are used to treat IPF patients demonstrating that patients with IPF who were given either drug had a slower rate of deterioration in FVC over time. In this review we provide a brief description of antifibrotic drugs and their use in post covid 19 lung fibrosis, However, more studies are required for usage of antifibrotic in non-IPF patients.

Compliance with ethical standards

Acknowledgments

We would like to thank our Principal Sir, our guide and friends for supporting us in writing this review article, institute's library, and non-teaching staff for their support.

Disclosure of conflict of interest

No conflict of interest existed between authors.

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