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THE ROLES OF ANTIFIBROTIC THERAPIES IN POST-SARS-CoV-2 INFECTION

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Abstract

Coronavirus Disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has affected over hundred million people worldwide. Other than acute symptoms after infection, the patients are also suffering with long-term health complications associated with COVID-19 called long COVID or post-COVID conditions by which pulmonary fibrosis (PF) was observed in one-third of the patients. Since post-COVID-19-associated PF (PCPF) shares similar symptoms with idiopathic pulmonary fibrosis (IPF), the ongoing studies focuses on the potential use of therapeutic approaches for IPF in PCPF patients. Hence, this study summarises the potential roles of these therapies to treat the PCPF include antifibrotic drugs, mesenchymal stem cell (MSC) therapy and inhaled curcumin nanoformulations by assessing their efficacies for the PCPF treatment.

INTRODUCTION

In late 2019, it was reported that a new pathogenic human virus has been identified and characterised as a novel coronavirus (nCoV-2019), initially discovered in their natural carrier hosts, bats [1-3]. Emerging from Wuhan, China, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) was recognised to be the cause of a pandemic outbreak known as Coronavirus Disease 19 (COVID-19), which infected nearly 546.4 million and killed over 6 million people globally as reported by the World Health Organisation (WHO) (as of 3rd July 2022) [2, 4]. A study involving 1,099 COVID-19 patients found that the most severely affected demographics by the virus were that of elderly men and patients with a history of smoking (57.8%), high blood pressure (23.7%), diabetes mellitus (16.2%), and coronary artery disease (5.8%) [5]. After the development and utilisation of COVID-19 vaccines, the fatality rate amongst the infected overall seemed to decline over a 7-month period (Table 1) [4].

The Centres for Disease Control and Prevention (CDC) has reported that some COVID-19 patients may experience prolonged effects of the infection even after recovery. This condition is commonly known as long COVID or post-COVID conditions (PCC). Patients with PCC may experience complications such as multiorgan dysfunction (brain, heart, lungs, kidneys, and skin) and autoimmune disorders with symptoms that lasts up to weeks or months, especially those suffering from severe COVID-19 [6]. Another possible outcome associated with SARS-CoV-2 infection, as seen in approximately one-third of COVID-19 patients, is pulmonary fibrosis (PF). This may be due to the emergence of acute respiratory distress syndrome (ARDS) leading to the scarring of lung tissues [3, 7].

Table 1. Monthly reports by WHO regarding the decrease in fatality rate percentage of Coronavirus Disease 2019 (COVID-19) patients [4]

Date	Confirmed Cases	No. of Deaths	Fatality (%)
30 January 2022	370,572,213	5,649,390	1.52
28 February 2022	434,154,739	5,944,342	1.37
29 March 2022	481,756,671	6,127,981	1.27
24 April 2022	507,184,387	6,219,657	1.23
22 May 2022	522,970,476	6,277,407	1.20
26 June 2022	541,313,815	6,327,547	1.17
24 July 2022	567,312,625	6,378,748	1.12

PULMONARY FIBROSIS ASSOCIATED WITH SARS, MERS, AND COVID-19

PF refers to the thickening of damaged lung tissues due to repeated epithelial cell injury, fibroblast persistence, increased collagen synthesis and other extracellular matrix (ECM) components, along with the breakdown of the normal lung architecture [1, 2]. The thickening of the lung tissues can affect the elasticity of alveoli, disrupt lung function and cause dyspnoea [8-10].

As of now, research on the pathophysiology of PF is still ongoing because of its complexity – there are many contributing factors causing various primary mechanisms, which lead to the fibrotic outcome. These factors include ARDS, viral infections, tobacco smoke and chronic exposure to irritants such as silica and asbestos, which in turn activate alveolar epithelial cells to mount an immune defence for the removal of irritants from the lungs. The longer the irritants stay in the lungs, the lower the probability of removing them completely, causing distress and surge of myofibroblasts [11].

Other than the activation of alveolar macrophages, cytokine storms are also the cause of inflammatory response in the lungs, thus causing an imbalance in the deposition of extracellular matrix. This in turn will lead to the apoptosis of pneumocytes. When the inflammatory response diminishes, the aggregation of fibroblasts which are differentiated from myofibroblasts, as well as synthesis of collagen fibres, collectively result in an obstructed airway and compromised lung function. Figure 1 summarises the pathogenesis of PF [11].

Aside from the COVID-19 outbreak, pulmonary complications may also be dated back to the last two epidemics caused by other coronaviruses (CoV), such as the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). All three CoVs predominantly target the respiratory and vascular systems [1-3]. Similar to SARS- and MERS-CoV, SARS-CoV-2 enters their human host by binding to the angiotensin-converting-enzyme 2 (ACE2) receptor, which functions as a dominant host receptor for SARS-CoV. The entry mechanism of SARS-CoV-2 relies on the cellular transmembrane protease serine 2 (TMPRSS2), which is essential for CoV to infect lung cells [12, 13].

In the pathogenesis of SARS, the lungs present with different morphological lesions. PF develops during the healing process in three phases, namely acute exudative inflammation, proliferation of myofibroblasts and fibroblasts, and synthesis of type I and IV collagen fibres leading to the final fibrotic stage. It often occurs among older generations and patients with severe pulmonary diseases. A study involving 80 SARS patients in a 15-year follow-up reported that initially, 9.4% of patients had visible pulmonary lesions as shown in a CT scan. One year after the infection, CT scans showed that 3.2% ± 4.78% had visible lesions, and those percentage increased to 4.60% ± 6.37% after 15 years. Results of a study on MERS patients reported to be similar, however, there are variations between the lesions found in SARS and in MERS due to different cytokines released during infections [3]. Due to the similarities between the complications and symptoms of SARS and COVID-19, it is evident that patients that suffer from COVID-19 also sustain a high risk of developing PF after infection. It is important to consider the information and knowledge gained from the infection and post-infection of SARS can be useful in identifying and preventing the initial proliferation of SARS-CoV-2 before it progresses into PF.

The SARS-CoV-2 virus causes alveolar cell damage and activates immune system. Immunes cells such as neutrophils, macrophages and natural killer (NK) cells secrete various pro-inflammatory cytokines including interferon (IFN)-gamma, interleukins (IL)-6, IL-8, IL-2 and tumour necrosis factor (TNF)-alpha. In addition, growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF) are released, and this causes fibroblast proliferation and myofibroblast transformation. ECM proteins deposition together with other factors such as transforming growth factor (TGF)-β, D-dimer, ferritin and C-reactive protein contribute to the development of post-COVID-19-associated PF (PCPF) [14].

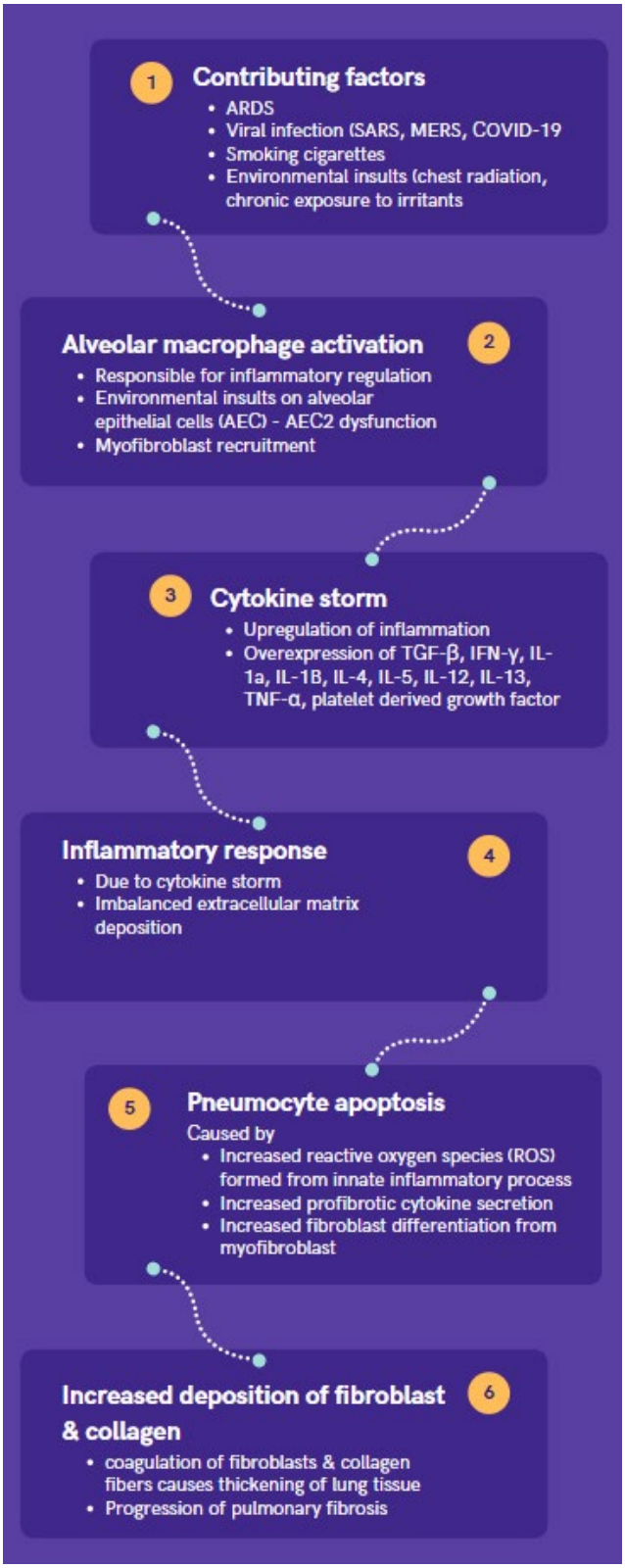

Figure 1. Pathogenesis of Pulmonary Fibrosis (PF).

POTENTIAL THERAPIES OF POST-COVID-19-ASSOCIATED PULMONARY FIBROSIS

Following the spread of SARS-CoV-2 infection, the burden of fibrotic lung disease will likely grow given the scope of the pandemic. Although it is not a direct outcome of post-SARS-CoV-2 infection, idiopathic pulmonary fibrosis (IPF) shares similar symptoms and risk factors, suggesting that treatments of IPF have a potential use in treatment of PCPF. The management goal is to slow disease progression as there are still no definite treatment [2]. Several studies had reported the potential use of anti-fibrotic drugs in PCPF [14-16]. Pirfenidone and nintedanib are two common antifibrotic drugs approved worldwide by the Food and Drug Administration (FDA) for treatment of IPF [2, 17-20]. Despite both drugs having different modes of actions, based on results proven from previous case studies, both drugs are efficacious in reducing the rate of pulmonary function decline, and has become the basis of IPF therapy to improve life expectancy in patients [18,19]. Besides the drugs, other therapies such as mesenchymal stem cell (MSC) therapy and inhaled curcumin nanoformulations have shown potential in becoming novel treatments for treating PCPF. Table 2 shows the summary of the ongoing clinical trials for pulmonary fibrosis therapies [3].

Table 2. Evaluation of the ongoing clinical trials of post-COVID-19-associated pulmonary fibrosis therapy

Therapeutic agents	Clinical trial ID	Phase	Participants	Compared to
Pirfenidone	NCT04282902	III	294	Standard treatment
Nintedanib	NCT04338802	II	96	Placebo
Mesenchymal stem cells	NCT04288102	II	90	Placebo

ROLE OF PIRFENIDONE AS AN ANTI-FIBROTIC DRUG

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally administered anti-fibrotic drug used in the treatment of patients with mild to moderate symptoms of IPF [7, 20]. Several studies have proven that pirfenidone has anti-fibrotic and anti-inflammatory properties as it significantly inhibiting TGF-β-1-induced fibronectin synthesis and downregulating the expression of profibrotic genes, including alpha-smooth muscle actin (α-SMA) and N-cadherin, and the secretion of collagens [7, 20]. Furthermore, pirfenidone affects PDGF, connective tissue growth factor (CTGF) and TNF-α associated with PF [7, 20].

Pirfenidone also improves the regulation of regulator of G-protein signalling 2 (RGS2), which is suggested to be a new mechanism to improve healing from pulmonary fibrosis. Other than that, pirfenidone is known as a reactive oxygen species (ROS) scavenger, thus it is able to inhibit cell apoptosis and downregulate the expression of ACE2 receptors, as well as decrease oxidative stress and inflammation in the lungs. This in turn protects the pneumocytes and other cells from being invaded by the SARS-CoV-2 and cytokine storm simultaneously [20].

Phase III clinical trials of pirfenidone on IPF patients showed that the drug is effective in significantly alleviating the vital capacity decline of patients with lung fibrosis. In the initial study, a reduction of 56.3% in vital capacity decline is reported. In the following trials, where the effect of pirfenidone was compared to a placebo over 52 weeks, the positive treatment group showed encouraging results as the patients' forced vital capacity decline was significantly lower than placebo group. In an accumulative analysis involving 1,247 IPF patients from another phase III trial of pirfenidone treatment, the number of patients who died due to IPF was reported to be fewer than those of placebo group. The hazard ratio (HR) of pirfenidone was recorded at 0.52, 95% Cl with p value of 0.01 [21].

ROLE OF NINTEDANIB AS AN ANTI-FIBROTIC DRUG

Nintedanib (6-methoxycarbonyl-substituted indolinone) is an active small molecule tyrosine kinase inhibitor that acts as an oral therapeutic drug for IPF treatment. Its efficacy has been evaluated in clinical trials as recorded in previous studies as it selectively targets the receptors of the profibrotic mediators, including PDGF, VEGF, and FGF [17, 18, 22]. Nintedanib has been associated with the inhibition of the downstream signalling pathways involving the proliferation, migration and maturation of lung fibroblasts by inhibiting the pro-fibrotic mediators [17, 23, 24].

In a phase II trial of nintedanib on IPF patients, a dose-dependent trend shows the reduction in the decline of lung function and acute exacerbation incidence. While in phase III trials, two subsequent trials were carried out comparing the effects of nintedanib with placebo. Over the course of 52 weeks, the results show that in nintedanib treated patients, the relative decline in forced vital capacity was lower, at 47.9% and 55.1% compared to placebo group. A pooled data analysis recorded that the HR of nintedanib was 0.32, 95% Cl with a p value of 0.001 [21].

MESENCHYMAL STEM CELL-BASED THERAPY

Mesenchymal stem cell (MSC)-based therapy has been gaining attention in regenerative medicine due to its potential in tissue regeneration for repair, growth, and wound healing.

Thus, it can be used as an optimal source for lung scaffold re-cellularisation [25, 26]. Amniotic fluid MSCs (AF-MSCs) have been known to have anti-inflammatory and antifibrotic factors, a higher regenerative ability and a doubling time of 36 hours, while placenta-derived MSCs (P-MSCs) have also shown to be an effective treatment in improving lung functions and reducing PF in *in vivo* animal models [3, 26].

Clinical studies suggest that MSCs show potential as a form of therapy for PC PF in high doses. MSCs have been proven safe and well-tolerated by IPF patients with rapid decline in lung functions. In a study, MSCs ($2x10^6$ cells) were administered to a group of IPF patients every three months for 12 months and compared to the placebo group. No adverse effects were experienced by patients after MSC administration, and additionally, compared to the placebo group, the MSCs group showed significant improvements in the 6-minute walking distance after 13 weeks, lung diffusion for carbon monoxide (DLCO) in 26 weeks and forced vital capacity after 39 weeks of treatment [27, 28].

INHALED CURCUMIN NANOFORMULATION IN POST-COVID-19 FIBROSIS TREATMENT

Curcumin is a plant-derived bioactive compound that has been proven to be useful in respiratory illnesses such as asthma and acute lung injury. Curcumin may harbour potential for PF treatment as it acts as an anti-inflammatory agent to control cytokine expression, and as a TGF-β signalling-targeting antifibrotic agent in post-COVID-19. The use of inhaled curcumin nanoformulations has been approved by the United States FDA as it is proven to be safe and cost-effective [29, 30].

Preliminary trials showed that curcumin nanoformulations should be administered in high doses for it to effectively exert its therapeutic effects, but not high enough to be counterproductive as a dose exceeding 7,5000 mg/day could instead assist the SARS-CoV-2 entry into the lungs as it increases regulation of ACE2 expression. Therefore, not only this treatment is cost-effective, but it may also potentially become a new antifibrotic treatment for PCPF. However, it may be too early to claim that curcumin nanoformulations are better than the conventional drugs as further studies are needed to validate their long-term effects, safety and efficacy. Furthermore, optimum doses and timing for the curcumin aerosol delivery should be determined [29].

CONCLUSION

In conclusion, SARS-CoV-2 infection demonstrates similar pulmonary complications and pathophysiological mechanisms compared with previous coronavirus outbreaks, SARS and MERS. Based on evidence from past epidemics, it is crucial that prevention of viral proliferation and elimination of the causative agents are done in the earlier phases of PF development for a more effective treatment. However, this is a challenge to clinicians as there are still no definite treatments for PCPF. Nonetheless, with the promising antifibrotic effects of pirfenidone and nintedanib, the drugs have shown breakthrough findings and their utilisation would be considerably beneficial in high-risk patients. The ongoing clinical studies for MSC therapy and inhaled curcumin nanoformulations carried out at different phases and its evaluations show great potential and can be advantageous as novel treatments for preventing and treating PCPF.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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