



# Pirfenidone: A novel hypothetical treatment for COVID-19

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## ABSTRACT

Cytokine storm, multiorgan failure, and particularly acute respiratory distress syndrome (ARDS) is the leading cause of mortality and morbidity in patients with COVID-19. A fulminant ARDS kills the majority of COVID-19 victims.

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone), is a novel anti-fibrotic agent with trivial adverse effects. Pirfenidone is approved for the treatment of Idiopathic Pulmonary Fibrosis (IPF) for patients with mild to moderate disease. Pirfenidone could inhibit apoptosis, downregulate ACE receptors expression, decrease inflammation by several mechanisms and ameliorate oxidative stress and hence protect pneumocytes and other cells from COVID-19 invasion and cytokine storm simultaneously. Based on the pirfenidone mechanism of action and the known pathophysiology of COVID-19, I believe that pirfenidone has the potential for the treatment of COVID-19 patients.

## Introduction

### COVID-19

Every minute, an American dies of COVID-19. Cytokine storm, multiorgan failure and particularly acute respiratory distress syndrome (ARDS) are the leading causes of mortality and morbidity in patients with COVID-19. A fulminant ARDS kills the majority of COVID-19 victims [1]. Also, there are whispers that some of the survivors might develop pulmonary sequels. Further investigations and follow-ups are warranted in this case [2,3]. A large number of suggested treatments such as ivermectin, hydroxychloroquine, and azithromycin are currently under investigation. Among them, hydroxychloroquine, azithromycin, and recently remdesivir showed acceptable results in clinical trials, as of June 2020 [4–10]. Nevertheless, the results of these interventions are not completely satisfactory and studies for other medications are still warranted.

### Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone), is a novel anti-fibrotic agent with trivial adverse effects [11–13]. Pirfenidone is

approved for the treatment of Idiopathic Pulmonary Fibrosis (IPF) in humans for patients with mild to moderate disease [14,15].

Diverse action mechanisms have been suggested for pirfenidone, among them are downregulating effects on a series of cytokines, including transforming growth factor (TGF)- $\beta$ 1, connective tissue growth factor (CTGF), platelet-derived growth factors (PDGF), and tumor necrosis factor (TNF)- $\alpha$  [16–20]. Additionally, pirfenidone is a reactive oxygen species (ROS) scavenger, and last but not the list, pirfenidone downregulates the expression of ACE receptor, the major cellular receptor for COVID-19 [21–23]. Additionally, some other characteristics of pirfenidone makes it an appropriate treatment for COVID-19, among them are anti-apoptotic and anti-fibrotic effects of pirfenidone. The details of the hypothesis have been discussed below. Based on known pirfenidone mechanism of action and the pathophysiology of COVID-19, I believe that pirfenidone has the potential for the treatment of COVID-19 patients.

### The Hypothesis/theory

Cytokine storm, severe inflammation, oxidative stress, and reactive oxygen species damage and increased permeability of vascular bed are responsible for the development of ARDS and multi-organ damage in

**Abbreviations:** COVID-19, Coronavirus Disease 2019; COVID-19-SARS, Coronavirus Disease 2019 – Severe Acute Respiratory Syndrome; ARDS, Acute respiratory distress syndrome; IPF, Idiopathic Pulmonary Fibrosis; TGF- $\beta$ 1, Transforming growth factor  $\beta$ 1; TGF, Connective tissue growth factor; PDGF, Platelet-derived growth factors; TNF- $\alpha$ , Tumor necrosis factor- $\alpha$ ; ADP, Adenosin Diphosphate; ACE, Angiotensin Converting Enzyme; NADPH, Nicotinamide adenine dinucleotide phosphate; ECM, Extracellular matrix; FDA, US Food and Drug Administration

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patients with COVID-19 [24,25]. Elderly patients, particularly those with comorbidities such as DM, cardiovascular disorder, and cancer are at increased risk of severe manifestation of COVID-19 [26,27]. Pathologic manifestation of COVID-19 under microscope includes the presence of exudate, vascular congestion, inflammatory clusters with fibrinoid material and multinucleated giant cell. Reactive alveolar hyperplasia and fibroblastic proliferation have been shown in alive patients with COVID-19 who underwent a lung biopsy due to cancer before the diagnosis of COVID-19 [28,29].

Almost all of the current promising treatments have anti-inflammatory characteristics, beyond their antibiotic effects. For example, both azithromycin and hydroxychloroquine possess anti-inflammatory effects [4].

Pirfenidone, a novel anti-fibrotic agent is known to have several anti-fibrotic, anti-inflammatory, oxygen radical scavenger/antioxidant effects [11,22,23,30,31].

#### *Anti-inflammatory effects of pirfenidone*

The anti-inflammatory effects of pirfenidone have been shown in several experimental studies. It has been shown that pirfenidone inhibits TNF- $\alpha$  secretion and decrease a large number of other inflammatory cytokines as well [20,32–34]. Additionally, Li et al. in a recent study shown that pirfenidone ameliorates lipopolysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation [35,36].

#### *Anti-fibrotic effects of pirfenidone*

It has been shown in several studies that pirfenidone significantly inhibits TGF- $\beta$  1-induced fibronectin synthesis [17,18]. Down-regulating of profibrotic gene expression and collagen secretion has been shown in humans and animal models treated with pirfenidone [37–39]. Reduction of overexpression of TGF- $\beta$  in inflammatory conditions plays a key role in the antifibrotic activity of pirfenidone [38,40].

Pirfenidone inhibits collagen I fibril formation and causes a reduction in collagen fibril bundles [39,41,42]. It has been shown that pirfenidone has pleiotropic actions on both the immune system and extracellular matrix (ECM), such as hyaluronan, a major component of the ECM that regulates tissue injury and repair [43]. Recently, the upregulation of RGS2 has been suggested as a novel mechanism of amelioration of pulmonary fibrosis with pirfenidone treatment [44].

#### *Protection against oxidative stress and lipid peroxidation*

The followings are probable endpoints of an overactive inflammatory response and WBC free radical formation in Microsome (via microsomal NADPH cytochrome c reductase) and Mitochondria (NADH-quinone oxidoreductase of the inner/outer membranes): excitotoxicity, damage to lipids and proteins, apoptosis, ADP-ribosylation, injury to mitochondrial DNA, and impaired NO activity [11,22,45]. Cytoskeletal damage and lipid peroxidation are the other destructive effects of inflammation and severe oxidative stress due to cytokine storm [23,45,46]. Hence, the antioxidant character of pirfenidone makes it potent for the treatment of hyperimmune response [11,22,23,30,31].

Lipid peroxidation, which is initiated by generated superoxide in the cyclic reduction-oxidation is one of the mechanisms of cytokine storm-inflammation-oxidative stress end-organ-damage and pulmonary toxicity [11]. It has been shown that pirfenidone could inhibit NADPH dependent lipid peroxidation [22,45].

#### *Anti-apoptotic effects of pirfenidone*

It has been shown that Fas-dependent alveolar apoptosis that results in inflammatory reaction and finally interstitial fibrosis is responsible

for the battle against viruses and also responsible for sequels of infections such as Poxvirus, bacterial LPS, etc [35,47]. On the other hand, it has been shown that pirfenidone could decrease apoptosis [19,48–51].

#### *Down regulation of ACE receptor expression*

ACE receptors are the major COVID-19-SARS virus receptor in humans. Trials that targeted the inhibition of these receptors with antibodies are under investigation [52]. Surprisingly, it has been shown that pirfenidone inhibits the AT1R/p38 MAPK pathway, decreased angiotensin-converting enzyme (ACE), angiotensin II, and angiotensin II type 1 receptor expression, and strongly enhanced liver X receptor- $\alpha$  expression [21]. This will not only protect cells from developing fibrosis (LXR- $\alpha$ ) also by decreasing the ACE receptor expression decrease entrance of the COVID-19-SARS virus into cells.

With respect to the known characteristics of pirfenidone (anti-inflammatory, anti-fibrotic, antioxidant) and our current understanding of severe COVID-19 pathophysiology (cytokine storm, inflammation, probable fibrosis, hyper-immunity and as a result oxidative stress, it is rational to suggest pirfenidone application in the treatment of patients with moderate to severe COVID-19-SARS.

#### *Evaluation of the hypothesis*

Uncontrolled overreaction of the immune system to the virus leads to the release of numerous inflammatory cytokines, further superoxide production, ARDS development and subsequently matrix remodeling and overproduction of collagen and other matrix components that may cause fibrosis in survivors [25,53,54]. Cytokine storm, an uncontrolled immune reaction is responsible for the development of multi-organ damage and ARDS in patients with COVID-19-SARS [53].

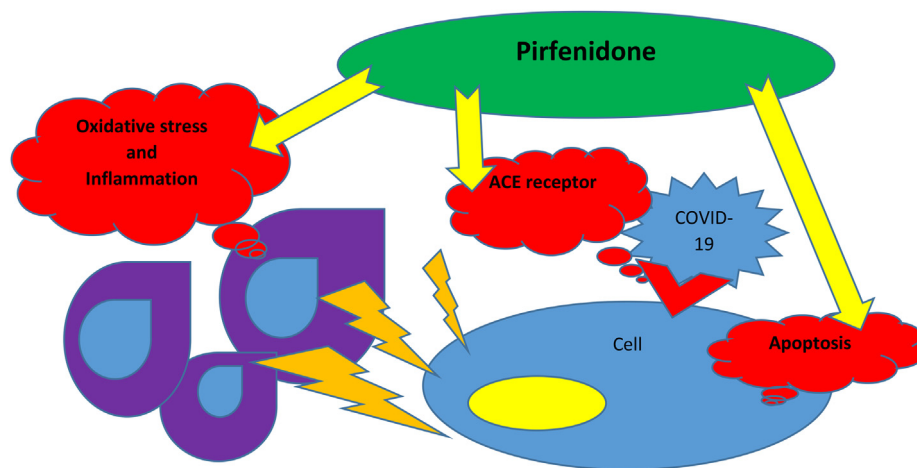
Anti-inflammatory effects of pirfenidone have been shown in several animal studies and clinical trials. The antioxidant activity of pirfenidone has been verified in several experimental studies [20,24,25,32–34,54]. Furthermore, the anti-fibrotic effects of pirfenidone have been shown in several clinical trials and tend to FDA approval of this drug for the treatment of patients with IPF [14,22,55–58].

Based on pirfenidone characteristics and therapeutic effects, I have previously suggested the treatment of paraquat poisoning with pirfenidone which is gradually opened its space in the treatment protocols of patients with paraquat poisoning [11,59–62]. Previously, Saha et al. successfully treated the patients with post H1N1 ARDS pulmonary fibrosis with combined pirfenidone, azithromycin, and prednisolone [63]. To the best of my knowledge, the mechanisms of post H1N1 ARDS fibrosis and paraquat poisoning and COVID-19 share similarities. Additionally, pirfenidone successfully improved treatment of post-H1N1 ARDS fibrosis, hence it seems equitable to evaluate the potential of pirfenidone in the treatment of COVID-19 [63]. Also, pirfenidone has been suggested and tried successfully in the treatment of ARDS due to white smoke-induced ARDS [11]. As another example, Zinc Chloride smoke (white smoke) inhalation induced severe ARDS has been successfully treated with a combination of pirfenidone and corticosteroids [35,64].

#### *Verification of the hypothesis*

Pirfenidone has been approved by the FDA for the treatment of patients with IPF. It has been tolerated very well with trivial side effects [15,65,66].

The current situation enforced clinicians and agencies to relax strict preclinical approval and extensive experimentation before starting human experimental treatment and clinical trials. The fact that our hands are empty in the battle against COVID-19, and an urgent need for treatment, enforced us to try any possible probably safe treatment, and those approved medications with low side effects are among the suggested and tried medications. Actually, our current standard of care is



**Fig. 1.** Pirfenidone could inhibit apoptosis, downregulate ACE receptors expression, decrease inflammation by several mechanisms and ameliorate oxidative stress and hence protect pneumocytes and other cells from the COVID-19 invasion and cytokine storm simultaneously.

based on these experiments.

Nevertheless, a limited number of labs have access to animal models of COVID-19-SARS and can conduct experimental studies parallel or before human trials. We have no time to wait for animal modeling, and animal models do not necessarily provide valid shreds of evidence in this case in terms of toxicity or efficacy of treatments, because mortality of this virus is almost always due to interaction of the virus with human immune system and animals are not appropriate surrogate models here [67].

At the end of the day, only a well-designed double-blind randomized controlled clinical trial is the accepted method to appropriately analyze this hypothesis.

### Consequences of the hypothesis and conclusion

In a limited number of patients, COVID-19 present as a fulminant cytokine storm, ARDS, and end-organ damage. But the death toll of this limited number of patients surpassed a one and a half million recently. This is a human tragedy that calls for immediate intervention.

New therapeutic strategies are considered in the treatment of COVID-19. However, to the best of my knowledge, pirfenidone has not been tried yet. As discussed above, I believe that pirfenidone could be a safe add on to the current protocols of COVID-19 treatment, with trivial side effects and plenty of potential benefits.

During the reviewing process of this article, some other studies proposed similar point of view [68–70]. For example, parallel to what I discussed here, George et al., also pointed to the shared risk factors of COVID-19 and IPF, and mentioned that the burden of lung fibrosis following COVID-19 is likely to be high; they concluded that given the scale of the pandemic, the global burden of fibrotic lung disease will probably increase considerably.

They also suggested a therapeutic rationale for application of approved antifibrotic therapy in acute exacerbations of IPF. Pirfenidone and nintedanib are among them.

In conclusion, pirfenidone could inhibit apoptosis, downregulate ACE receptors expression, decrease inflammation by several mechanisms and ameliorate oxidative stress and hence protect pneumocytes and other cells from COVID-19 invasion and cytokine storm simultaneously (Fig. 1).

### Declaration of Competing Interest

The author declares that he have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110005>.

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