ISSN: 03875547
Volume 44, Issue 06, December, 2021

THE ADVANTAGES OF USING PIRFENIDONE WITH COVID-19 PATIENTS

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Keywords:
pirfenidone, COVID-19, pulmonary fibrosis

ABSTRACT

The COVID 19 pandemic of 2020 has killed an extra 1,800,000 people around the planet. Shortness of breath and fibrosis of the lungs are common side effects for people who recover with Covid-19, but others require a long time to recover. *Idiopathic pulmonary fibrosis* is a disease that can be treated with the medicine pirfenidone. Pirfenidone has been shown to reverse pulmonary fibrotic damage. There are five cases here where this medicine was added and showed a significant improvement in both symptoms and radiological results, which we discuss. This novel condition necessitates a thorough examination of the fraction of patients who develop chronic lung disease as a result of fibrosis following recovery from COVID-19. Pirfenidone should be studied further in people with pulmonary fibrosis due to Covid-19 infection to see if it helps. Methods verified COVID-19 patients admitted to al-Hindia general hospital between February 1, 2020, and August 1, 2020, were examined retrospectively for around six months. Pirfenidone was used to treat 13 incidences of lung fibrosis in 19 of the 107 patients who presented with covid symptoms. Idiopathic pulmonary fibrosis (IPF) was licensed as an anti-fibrotic drug in China in December 2013. Impairment of TGF-, CTGF, PDGF, and TNF- in inflammatory disorders is critical to the anti-fibrotic effect of pirfenidone. A severe hazard to the long-term prognosis of problems, pulmonary fibrosis, should also be considered. In the treatment of pulmonary fibrosis, pirfenidone may be the most successful medication COVID-19, pirfenidone, and Pulmonary fibrosis are all relevant terms.

1. INTRODUCTION

SARS-CoV-2 and Lung FibrosisA new coronavirus, SARS-CoV-2, surfaced in Wuhan, China, in December 2019, causing a severe acute respiratory sickness (COVID-19). Interstitial fibrosis causes pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), excessive collagen and extracellular matrix accumulation by fibroblasts matrix, as well as normal pulmonary function to build something [1], [2], [6]. Pulmonary fibrosis progresses, resulting in death and an inability to breathe due to a deterioration in lung function capillary alveoli exchange oxygen [7]. Pulmonary embolism Age, smoking, and virus infections all contribute to inflammation; oxidative stress is one of the pathogenic processes [8] an overproduction of reactive oxygen species due to stress and anxiety (ROS) TGF-b, FGF, and PDGF all have a role in the formation of ROS (of fibrosis. Inflammation that is out of control, such as in COVID-19's most severe

stages. The cytokine storm is likely to be the primary source of infection and a major contributor to the development of severe and long-term lung damage. Some lung lesions can be lethal. According to the available evidence, the majority of severe instances of COVID-19 are marked by a high concentration of the virus fibrotic tissue in the lungs, and studies have shown that serum concentrations of growth factors and cytokines are responsible for causing the Patients mentioned above with a history of pulmonary fibrosis to have a much higher risk of developing the condition In the COVID-19. These include mediators including TGF-, VEGF, IGF-1, and Il-6TNF- vascular dysfunctions can contribute to the course of the disease; as shown in this study, fibrosis IPF and pulmonary fibrosis share several pathological similarities Infection with the COVID-19 virus implies similar pathogenesis to that of HIV thus, the pulmonary fibrosis mechanism in these two illnesses medicines that can be used to treat cancer are thought to exist patients with COVID-19 may also benefit from IPF influenza is at its most dangerous in these stages.

The sudden and overwhelming release of proinflammatory cytokines characterizes lung injury is caused by mediators, which rapidly develop respiratory distress syndrome (RDS). Bilateral interstitial pneumonia is linked to [3]infected by COVID-19, which is named for its ability to attack the brain tissue that covers the lung alveoli is linked to caused by an excess of collagen (fibrosis) in the body hyper inflammation of the pulmonary crevice A pharmaceutical strategy can be used in this direction such as antifibrotic drugs, to minimize or prevent fibrotic state A diagnosis of idiopathic pulmonary fibrosis [4] can be a helpful tool in preventing major or deadly consequences from COVID-19in those who are still infected or have already recovered with lingering fibrotic lung scarring mechanism of COVID-19-induced lung fibrosisAlmost all chronic inflammatory disorders resulted in fibrosis, which was the last stage (The heart, liver, lungs and kidneys are no exception) [18].

It is possible for myofibroblasts from different sources (including mesenchymal cells, circulatory fibroblasts) to initiate wound healing in response to tissue injury by modifying the extracellular environment in order to restore tissue integrity and encourage the replacement of parenchymal cells. When tissue heals, this pro-fibrosis pathway is usually shut off. It is possible, however, for repeated damage and repair (severe COVID-19) to lead to this process becoming imbalanced and resulting in excessive pathological ECM protein deposition, accompanied by an increase in myofibroblast activity, which leads to an environment of macrophage and immune cell infiltration. Pro-inflammatory and pro-fibrotic cytokines were generated in this cellular milieu, which activated fibrosis-related pathways. TGF- signaling, WNT signaling, and the YAP/TAZ signaling pathways were all major components [19].

1.1 A pirfenidone-based treatment for pulmonary fibrosis

An entirely new class of pyridone, pirfenidone, had potent anti-inflammatory and antifibrotic properties. Pirfenidone's mechanism of action was not understood. It has been shown that pirfenidone can reduce inflammation, the growth of fibroblasts, and the buildup of ECM-extracellular matrix proteins in the tissues.

For the first week of treatment, the dose was 267mg three times a day; for the second week, it was 534mg three times a day; and for the third and subsequent weeks, it was 801mg three times a day (taking it after a meal or with meal). Nausea, rash, dizziness, abdominal pain, diarrhea, and exhaustion are some of the most prevalent side effects [20]. Non-severe and severe cases of drug-induced liver injury (DILI), including severe liver injury and death, have been observed, according to the drug instructions for pirfenidone. In three phase 3 trials, patients consuming 2403 mg of pirfenidone per day had a greater incidence of elevated ALT or AST than individuals taking placebo (3.7 per cent and 0.8 percent, respectively). When initiating treatment with pirfenidone, the liver should be examined before and every three months after that [15]. Pirfenidone's potential for drug interactions, particularly in the elderly, who are more likely to take

ISSN: 03875547
Volume 44, Issue 06, December, 2021

numerous medications, merited our consideration. Pirfenidone with fluvoxamine (a potent inhibitor of CYP1A2) can cause an evident pharmacological interaction and considerably reduce the clearance rate. Pirfenidone should not be taken in combination with moderate (e.g., ciprofloxacin) or strong CYP1A2 inhibitors (e.g., fluvoxamine

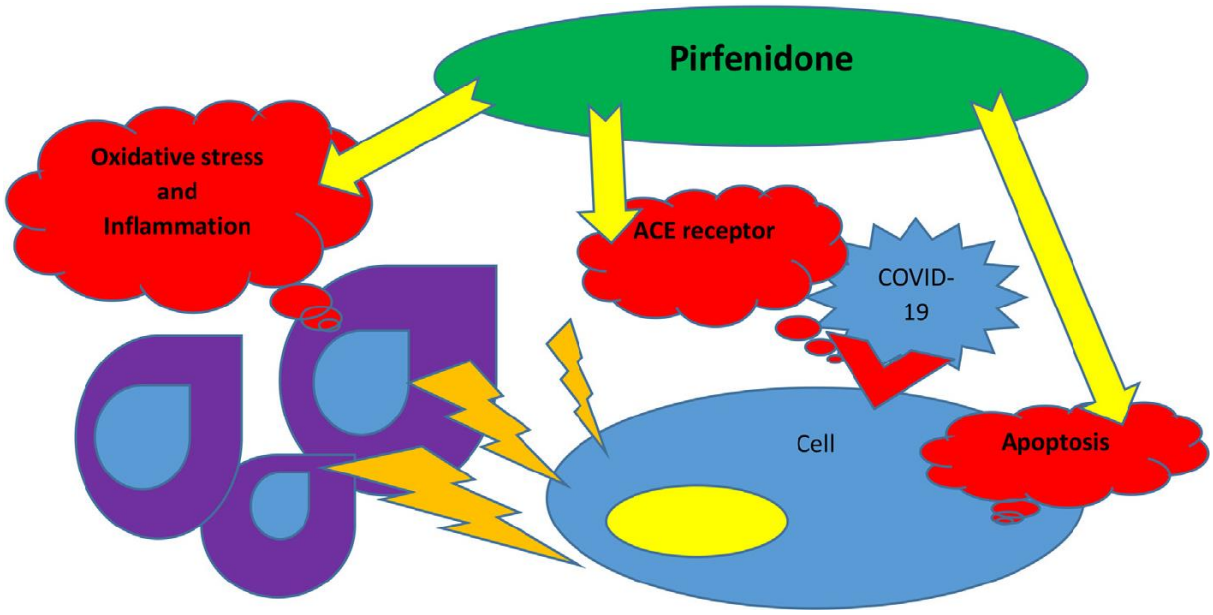

Fig. 1. Pirfenidone could inhibit apoptosis, downregulate ACE receptors expression, decrease inflammation by several mechanisms, ameliorate oxidative stress, and protect pneumocytes and other cells from the COVID-19 invasion and cytokine storm simultaneously.

1.2 Risk factor

Smoking, previous infection of COVID-19, and virus strain are predisposing factors for lung fibrosis, also a second risk factor hypertension, diabetes, and other comorbidities labs results such as lymphopenia and coronary artery disease [12] leukocytosis and a high lactate dehydrogenase activity (LDH) [7]. As a marker of illness, serum LDH levels have been utilized for how bad things get after an acute lung injury. It is a sign of pulmonary dysfunction tissue deterioration linked to an increased risk of death mortality. Eighty percent of the world's population is at risk, according to the WHO. 14% of SARS-CoV patients acquire severe symptoms from 2 infections, whereas the remaining 80% are minor, and 6% of those will be critically unwell. The third risk factor is a long stay in the ICU and an extended stay in the hospital. Ventilation using mechanical means. Concerning the degree of illness, the duration of time in the ICU is a factor in mechanical ventilation's risk of lung harm from using a ventilator (VILI); this is due to abnormal pressure or volume setting the release of proinflammatory modulators after an injury higher mortality or pulmonary emphysema from worsening acute lung damage in survivors, fibrosis is also common. Tobacco use is associated with a 1.4-fold increased risk of severe symptoms COVID-19 with a 2.4-fold increased risk of in-patient care being admitted and receiving mechanical ventilation or dying in smokers [14], [15]. The National Institutes of Health (NIH) and the world have released a release from the National Institute on Alcohol Abuse and Alcoholism Warnings to individuals not overboard with their alcohol consumption. COVID-19 susceptibility may be increased by drinking, according to the statement severity. Having a drinking problem raises the likelihood of complications of the COVID-19 [16].

1.3 A clinical training program

How many of the 19 covid 19 patients had lung fibrosis at the time of the study? Doubtful and should not be

taken for granted as a suitable examination of the future. However, we can extract information from the epidemic of SARS and MERS. [17] investigated 71 cases of SARS at the start of the study; the researchers found 9.4 percent of the patients, 4.6 percent of one-year-olds, and 3.2 percent of 15-year-olds had lung disease, respectively CT scans show the presence of tumors. In addition to MERS, In the case of 36 MERS patients, a follow-up for pulmonary fibrosis developed in an average of 43 days. Many patients in recovery were found to be dangerous elderly individuals who had been hospitalized for a long time in ICU patients with life-threatening illnesses18. For the time being, we do not have much information on pulmonary fibrosis following covid use. In one of the studies19, a chest CT was performed two days before discharge; the patient had a CT scan post-discharge for between two and four weeks. Compared to the last time. Prior to release, a CT scan was performed to look for any abnormalities (such as focused or diffuse) numerous GGOs, consolidation, and thickening of the interlobular septum in the lungs, subpleural lines and uneven lines in the first and second post-discharge follow-ups64.7 percent of the patients released had entirely cleared lung lesions was completely absorbed four weeks later. COVID-19's damage to lung tissue may be reversible in the majority of cases. Other findings indicated a worsening prognosis. Fortunately the prognosis for non-severe patients and clinical intervention effectively avoids common COVID-related issues, a total of 19 patients ranging from deteriorating to critical between April 2020 and March 2021. Therefore, a second study will be placed in Italy. Persistent symptoms in 143 patients will be evaluated in May 2020 after recovering from COVID; they were released from the hospital. At a mean of 60.3 days after the onset of symptoms, 19 patients were evaluated preliminary findings from an examination of COVID-19 symptom onset COVID-19 related symptoms were found in only 18 (or 12.6 per cent) of the patients 32 percent experienced one or two symptoms, while 55 percent had three or more.

Not a single one of the patients was experiencing any fever or other symptoms of severe sickness. However, the quality of life was found to have deteriorated in over half (46.1%). They also discovered that the most common cause of death was a heart attack, tiredness was a symptom that lingered after treatment was completed (53.1 percent), 43.4 percent of people reported dyspnea, 27.3 percent reported joint pain, and 43.4 percent reported chest pain (21.7 percent). An additional follow-up study [20] focused on the lungs COVID-19's function and associated physiological properties 55 patients were registered by survivors three months following their recovery and identified radiological abnormalities in 39 patients. At the time of admission, the blood urea nitrogen concentration was linked to a high rate of abnormalities on a CT scan. Research shows that the most prevalent abnormality is a congenital heart defect lung function in COVID-19 survivors who have been discharged is diffusion capacity impairment. Restrictive the severity of a patient's breathing problems, the ailment 11,20 KCO and decreased alveolar volume are both possible outcomes that contribute to the deterioration of diffusion capacity 13 3-months post-discharge, there were still anomalies in the patient's body pulmonary function was found in 25.55% of the study participants when the impaired pulmonary function was less severe thanAs soon as possible after being released from COVID-19Ten anomalies in lung function measured in 14 of the 55 individuals screened D-dimer levels may be helpful to in admission prediction of a defective diffusion flaw.

All verified COVID-19 patients admitted to al-Hindia general hospital between February 1, 2020, and August 1, 2020, were evaluated in a six-month retrospective study. Patients with pulmonary fibrosis accounted for 13 of the 107 COVID-19 patients admitted to the hospital. Perfinadon has been utilized for more than six months.

2. METHODS

2.1 Choosing a Patient

All patients admitted with covid.19 infections confirmed by polymerase chain reaction (PCR) testing of a swab specimen were included. There was a review of mortality status for all patients till the first of October 2020. Patients who had been given the order to "Do Not Resuscitate" were not included in this study. From the electronic medical records, demographic data such as age, gender, and ethnicity were retrieved (EMR).

2.2 The study of statistics

The SPSS version 19 was used to do the statistical analysis. The t-test was used to evaluate continuous variables, and the means and standard deviations were expressed. In order to investigate categorical parameters, Pearson's Chi-square test was utilized. Logistic regression was used to investigate the link between gastrointestinal bleeding and mortality and other univariate analyses.

2.3 AIM

Perfinadon has been utilized to treat lung fibrosis following covid 19, prevent pulmonary fibrosis, and decrease our patients' mortality at the hospital.

3. RESULTS

TABLE 1 Demographic and baseline characteristics of study

Patients number	107 total
lung fibrosis	13
lung fibrosis used Perfinadon	9
time presentation after covid 19	3 to 6 months
Age years	40 to80
spo2	70 to 79
male	60
female	47
Weight kg	50 to 95
bacco use	83
forced vital capacity % pred mean±SE	
Historical value closest to 6 months prior to screening¶	72.6±1.7
At baseline	71.8±1.7
Patients categorised by baseline FVC % pred	
<65%	32 (36)
65–<80%	31 (35)
diffusing capacity of the lung for carbon monoxide.	
Historical value closest to 6 months prior to screening	50.0±1.4
At baseline	48.4±1.3
side effect of Perfinadon	
Diarrhoea	3
Nausea	5
Fatigue	7
Weight decreased	6
Deep vein thrombosis	3
Hepatic function	
GGT increased	8

ALT increased	5
AST increased	4

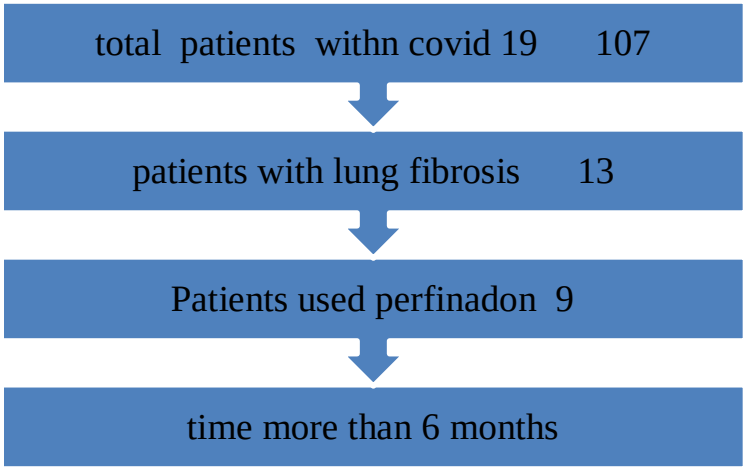

FIGURE 2 Patient disposition

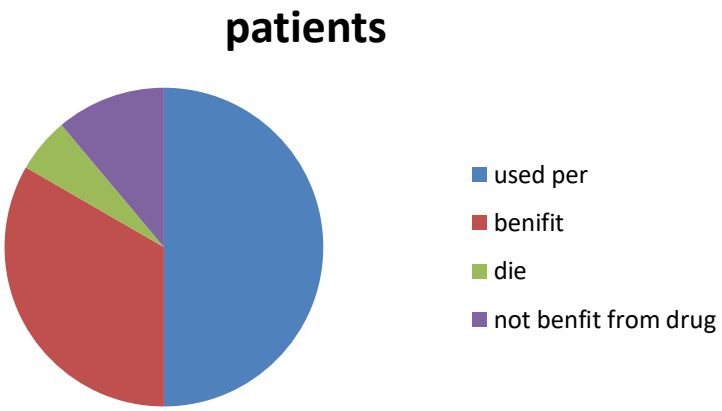

Table and figure 2 show the response to treatment

Table 3. Clinical trials of drugs for the treatment of post-COVID lung fibrosis.

Treatment	NCT Number	Phase	Number Enrolled	Study Design
Nintedanib	NCT04338802 [34]	II	96	Single-center,randomized,placebo-controlled 150mg POBID for 8 Weeks.
	NCT04541680 [35]	III	250	Single-center,randomized,placebo-controlled 150mg POBID for 12 months.
	NCT04619680 [36]	IV	120	Multicenter, randomized, Placebo-controlled 150 mg POBID for 180 days
Pirfenidone	NCT04282902 [37]	III	294	Single-center,randomized,placebo-controlled 2.267 mg POTID for 4 weeks

	NCT04607928 [38]	II	148	Multicenter, randomized, Placebo-controlled 2.267 mg POTID , 7 days after 4.267 mg TID for 24 weeks.
Treamid	NCT04527354 [39]	II	60	Multicenter, randomized, Placebo-controlled study 50 mg daily PO for 4 weeks.
LYT-100	NCT04652518 [40]	II	168	Multicenter, randomized, Placebo-controlled PO BID for 91 days.
Collagen-polyvinylpyrrolidone	NCT04517162 [41]	I	90	Single-center,randomized,placebo-controlled 1.5 ml 1M BID for 3 days, then 1.5 ml QD for 4 days.
Prednisone	NCT04551781 [42]	-	450	Single-center,randomized,placebo-controlled 20 mg daily for 14 IM
Bovhyaluronidase azoximer	NCT04645368 [43]	-	160	Multicenter, randomized, Placebo-controlled 3000 ME IM once in 5 days for 15 IM
BIO 300(genistein)	NCT04482595 [44]	II	66	Single-center,randomized,placebo-controlled 1500 mg daily PO for 12 weeks.
Tetrandrine	NCT04308317 [45]	IV	60	Single-center,randomized, compared to standard therapy 60 mg daily PO for a week.
Fuzheng Huayu tablet	NCT04279197 [46]	II	160	Single-center,randomized,placebo-controlled 1.6 g TID PO for 24 weeks.
Anluohuaxian	NCT04334265 [47]	-	750	Multicenter, randomized, compared to standard therapy 6 g BIDPO for 3 months
Stromal Vascular Fraction	NCT04326036 [48]	I	10	Single-center,randomized,placebo-controlled IV for 6 months , NO data for injection frequency
IN01 Vaccine	NCT04537130 [49]	Ib	40	On first stage , IN01 is injected on days 1 ,14,28 , 42 , and 56 On support stage , vaccination is carried out every 2 months with the same dosage and regimen as during introduction , compared to the patients receiving standard therapy

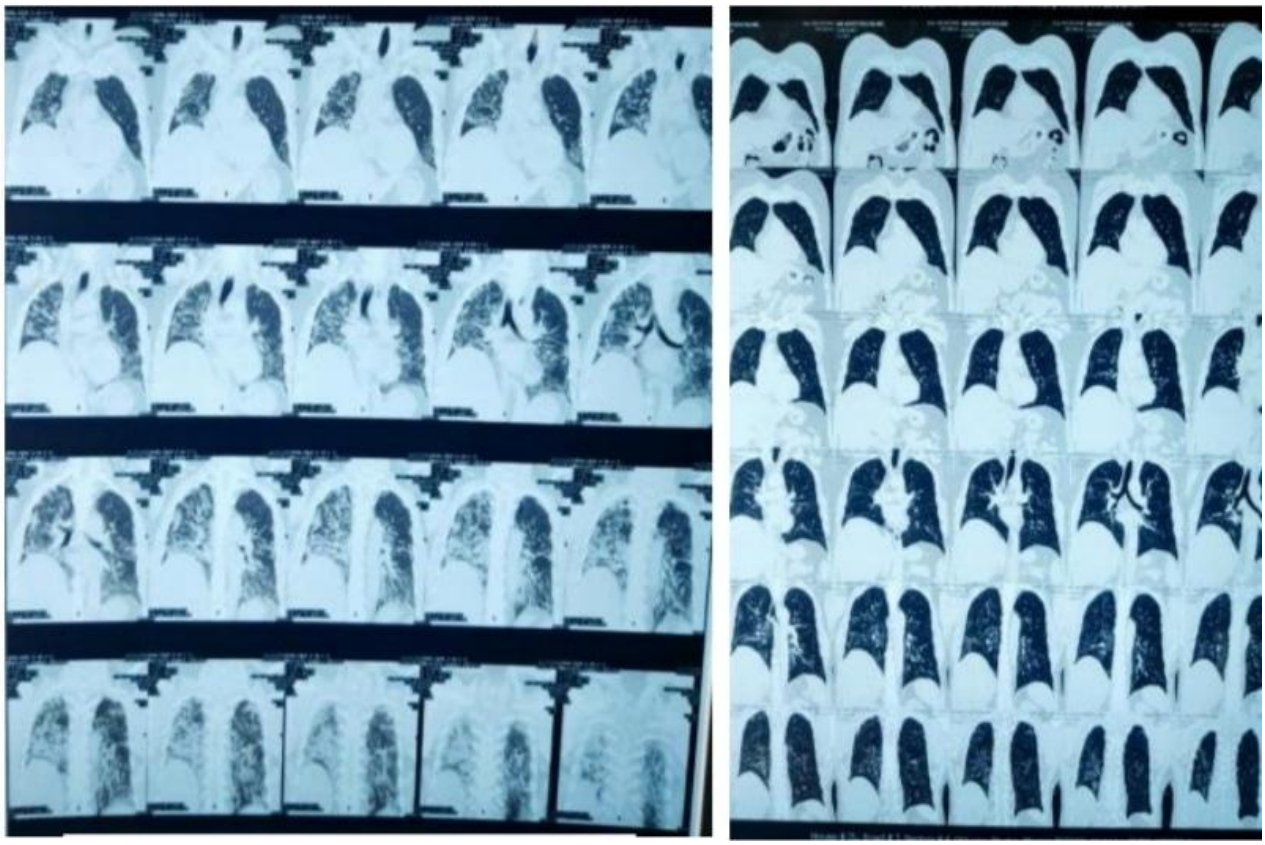

Fig. 4 Patient 3, before anti-fibrotic. Patient 3, after anti-fibrotic.

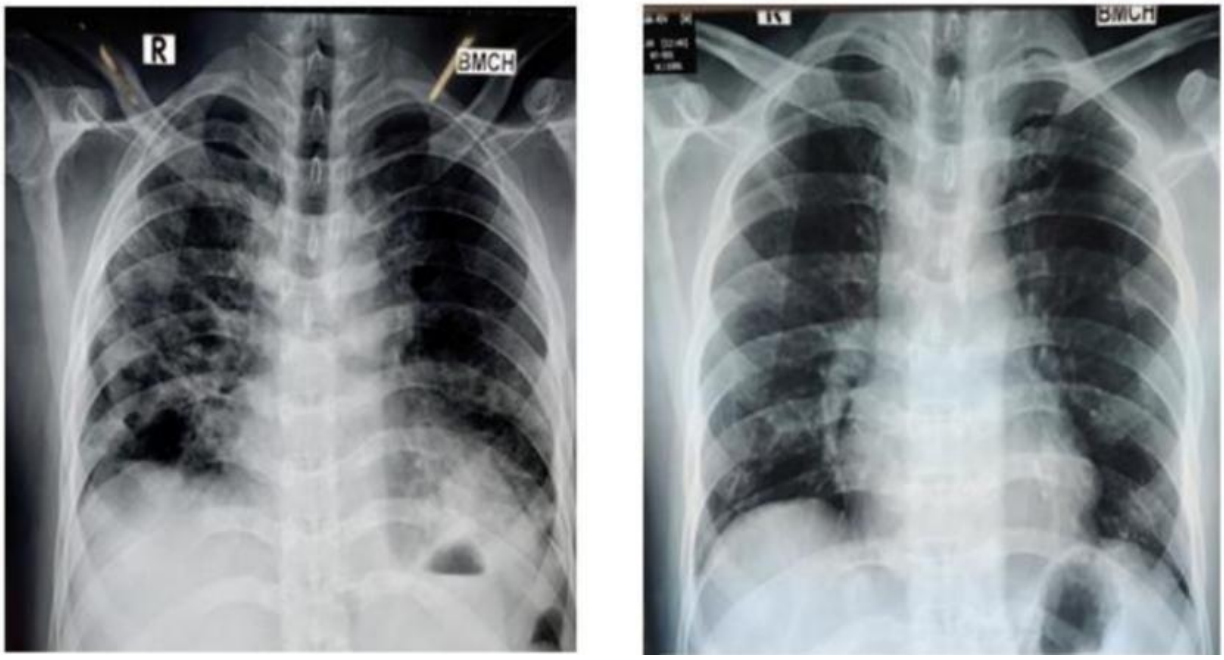

Fig. 4 Patient 3, before anti-fibrotic, Patient 3, after anti-fibrotic.

4. DISCUSSION

Idiopathic pulmonary fibrosis (IPF) was licensed as an anti-fibrotic drug in China in December 2013 [5]. The anti-fibrotic effect of pirfenidone relies on reducing TGF-, CTGF, PDGF and TNF- overexpression in

inflammatory disorders [6- 10]. Pirfenidone, commonly used to treat post-covid-19 fibrosis, was required by all five patients who acquired pulmonary fibrosis following covid-19, as was the case with many other patients. Both the patient's symptoms and the patient's radiological findings improved significantly after adding this. According to a few studies, the pandemic of COVID-19 is likely to increase the worldwide weight of lung fibrosis, which is expected to be substantial given the pandemic's extent. In addition, pirfenidone and nintedanib were also indicated as anti-fibrotic treatments [7]. According to another study, pirfenidone, an anti-fibrotic medicine, can be used as monotherapy or in combination with anti-inflammatory drugs to prevent severe consequences during viral infection. Even in patients with post-infection fibrotic damage, the same strategy can be successful [8]. Pirfenidone may reduce lung injury since it has been shown to reduce Lipopolysaccharide-induced lung injury and subsequent fibrosis by reducing NLRP3 inflammatory reaction. According to the case report of three young males (aged 40 to 59) with post-H1N1 ARDS pulmonary fibrosis, there is evidence that pirfenidone, azithromycin, and prednisolone may be useful in the treatment of this condition [21- 23].

5. CONCLUSION

A severe hazard to the long-term prognosis of problems, pulmonary fibrosis, should also be considered. In the treatment of pulmonary fibrosis, pirfenidone may be the most successful medication COVID-19, pirfenidone, and Pulmonary Fibrosis are all relevant terms.

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