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Efficacy of Pirfenidone as Antifibrotic Agent in Patients with Post Covid Fibrosis

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ABSTRACT

Backkground: Due to repeated respiratory infections induced by the coronavirus, pulmonary fibrosis develops over time. Life's quality is negatively impacted. Pirfenidone may be essential in avoiding serious lung problems because it has anti-fibrotic properties.

Objective: This study aimed at prevention of the damage produced by post covid-19 fibrosis and avoiding long term complications.

Methods: This study enrolled 50 adult patients with post covid fibrosis without chest diseases history, who were randomly chosen from Chest Outpatient Clinic, Zagazig University. They were divided into 2 groups. One group received pirfenidone and prednisolone and the other received prednisolone. Demographics and laboratory parameters were evaluated. Forced vital capacity (FVC), baseline oxygen saturation (SpO_2), 6-minute walk distance test (6MWT), King's brief interstitial lung diseases (K-BILD) and CT severity score (CSS) were performed at the first visit, after one and three months.

Results: Each group included 25 patients with a mean age of 47.1 ± 8.7 and 49.3 ± 13.7 years. There were statistically non-significant differences between both groups as regards age, sex, comorbidities and period from acute infection of COVID-19. At the first visit, there were statistically non-significant differences as regards FVC, SpO_2, 6MWT, K-BILD and CSS. There were statistically significant differences as regards K-BILD and CSS and highly significant as regards 6MWT after one month of treatment. After 3 months, there were highly statistically significant differences as regards all parameters, which were all higher among pirfenidone + prednisolone group.

Conclusion: Antifibrotic medications as pirfenidone can reduce fibrotic changes and enhance patients' quality of life who have post-COVID-19 fibrosis.

Keywords: Post COVID-19, Pulmonary Fibrosis, Pirfenidone.

INTRODUCTION

The cause of the coronavirus pandemic is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV2). Because of high fatality rate and lack of a specific, effective treatment, COVID-19 pandemic has generated serious concern. Millions of people around the world have been infected by SARS-CoV2. In most seriously ill SARS-CoV-2 patients, acute respiratory distress syndrome (ARDS) develops [(1)].

About forty percent of COVID-19 cases develop ARDS according to available statistics [(2)]. Most of SARS-COV2 patients have bilateral shadows in the form of ground glass opacities (GGOs) that may be associated with or without consolidation, favoring the lower parts [(3)].

However, it is crucial to remember that after virus clearance, long-term pulmonary damage, primarily fibrotic ILD, may occur [(4)].

Over time, it becomes apparent how common fibrosis is after COVID-19. More than one-third of recovered cases, according to early investigations of patients who were discharged from the hospital, have fibrotic alterations [(5)].

There is no effective method of preventing ARDS-related lung fibrosis and damage [(6)]. Corticosteroids' potent anti-inflammatory and antifibrotic properties, especially in the latter stages, may contribute to the reduction of inflammatory changes in the lung [(7)].

Regardless of the fibrosis underlying origin, licensed drugs with anti-fibrotic capabilities may help to lessen the profibrotic pathology that related to COVID-19 [(8)]. Pirfenidone, one of anti-fibrotic drugs that has potent anti-oxidative, anti-inflammatory, and anti-fibrotic properties [(7)].

AIM OF THE STUDY

This study aimed at prevention of the damage produced by post-covid-19 fibrosis and avoiding long term complications.

PATIENTS AND METHODS

I- Technical design

The population of the study:

50 patients with post-Covid-19 fibrosis were randomly selected for this study. They were 17 females (34%) and 33 males (66%) with a mean ± SD of their age was 48.26± 11.46 years.

Inclusion Criteria:

Patients over 18 years old who had verified SARS-CoV-2 infection with residual lung fibrosis with normal or decreased oxygen saturation in patients who were free from any previous chest diseases.

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- CT imaging features of pulmonary fibrosis [9]: Broncho-vascular bundle distortion, inter-lobar septal thickening, fibrotic bands, traction bronchiectasis, and architectural distortion.

Exclusion Criteria:

Patients with previous chest diseases. Patients with contraindication to pirfenidone [10] as drug hypersensitivity, severe hepatic or renal injury (CrCl 30 ml/min or end-stage kidney illness needing dialysis) and concurrent fluvoxamine use.

Research Design: This research was randomized controlled trial conducted in the Chest Department's Outpatient Clinic, Zagazig University Hospitals in the period from August 2021 to August 2022.

II-operational design:

The study was described obviously to the patients. The following were done for all patients:

- The patients' demographic characteristics and complete medical histories were noted.
- Full laboratory tests.
- Pulmonary function tests: FVC was measured at the beginning of the study, then after 1 month and 3 months by using spirometer device (Spirotube, IDEGEN TECHNOLOGY, Hungary).
- Six-minute walking test: It was carried out in a 35 m long hallway at the beginning of the study and after 1 month and 3 months. Patients were encouraged to move with the greatest pace they could. The distance walked and oxygen saturation, before and after the test, were notified.
- The questionnaire (King's Brief Interstitial Lung Disease) was evaluated for all patients. K-BILD evaluates the health problems that caused by ILD. There are 15 questions in this survey which categorised into 3 groups; psychological effect, dyspnea and activity, and respiratory complaints by a Likert Scale with 7 points. The overall score is from 0 to 100, where greater values represent a healthier state of affairs [11].
- HRCT chest was done at the beginning of the study and after 1 month and 3 months. For all patients, based on how each of the 5 lung regions involved, CSS was evaluated (0 point indicated no affection; 1 point, with less than 5% affection; 2 points, affection of 5-25%; 3 points, affection of 26-50%; 4 points, affection of 51-75%; and 5 points, affection of more than 75%). Finally, the scores, which varied from zero to 25, were added to determine the overall CSS [12].
- Our patients were randomly divided into 2 distinct groups:

First group (25 patients) received pirfenidone beginning in the first week at a dose of 267 mg tds and progressively increasing to a maximum of 2400 mg in weekly dose additions after that [13] in combination with 20 mg/day corticosteroids (prednisolone).

Second group (25 patients) received 20 mg/day corticosteroids (prednisolone) [14].

Approval for the Ethics and Participation:

Zagazig University's Institutional Review Board gave their approval to this project (ZU-IRB#7084/8-8-2021). Patients enrolled in this study provided signed informed consents. The Helsinki Declaration, the Code of Ethics of the World Medical Association, was followed when conducting this research on human being.

Statistical analysis

All results were collected, tabulated, & statistically analyzed using SPSS version 19. To describe categorical qualitative variables, absolute frequencies (number) and relative frequencies (%) were utilized, whereas the mean, median (range), and standard deviation were used to represent continuous quantitative variables.

The normality of continuous data was examined using the Kolmogorov-Smirnov test. The distinct samples; 2 sets of quantitative statistics that were both normally and not normally distributed were analyzed using the Student's t-test and Mann-Whitney test respectively. To analyze categorical results, the Chi-square test was employed. The Friedman test was used to compare repeated measurements. All tests were two-sided and the following thresholds were used to conclude degree of significance (p-value): statistical significance (S) was defined as ≤ 0.05., < 0.001 was considered highly significant (HS), and > 0.05 was considered statistically non-significant (NS).

RESULTS

This study included 50 adult patients who were divided into two groups. First group included 25 patients with a mean age of 47.1 ± 8.7 years. They were 8 (32%) females and 17 (68%) males.

The second group included 25 patients with a mean age of 49.3 ± 13.7 years. They were 9 (36%) females and 16 (64%) males. The duration from acute phase of COVID-19 infection and the first visit to our clinic was from 3 to 7 weeks with a median of 1st group was 5 weeks and 2nd group was 4 weeks. Regarding age, sex, comorbidities and the duration from the acute phase of COVID-19 infection. There were statistically non-significant differences between both groups (Table 1).

Table (1): Basic criteria of the groups under study

Variable	(1st group) Pirfenidone + prednisolone (n=25)	(2nd group) Prednisolone (n=25)	Test	P value
Age: (years) Mean ± SD	47.1 ± 8.7	49.3 ± 13.7	-0.674#	0.503
Duration from acute phase (weak): Median Range	5 3 - 7	4 3 - 7	-0.229$	0.819
Sex: Female: Male:	8 (32%) 17 (68%)	9 (36%) 16 (64%)	0.089^	0.765
Comorbidities: No: Cardiac: Cardiac and hypertension: Diabetic: Hypertension:	16 (64%) 3 (12%) 0 0%) 2 (8%) 4 (16%)	13 (52%) 1 (4%) 1 (4%) 3 (12%) 1 (4%)	15.31^	0.053

1. # Independent t-test, $ Mann-Whitney test, ^ Chi-square test, *SD* standard deviation
2. *NS* non-significant difference (p>0.05).

Table (2) showed that there were statistically insignificant differences as regards baseline FVC, 6MWD, SpO_2 at rest, K-BILD questionnaire and CSS between both groups.

Table (2): Clinical parameters of the studied groups at the first visit

Variable	1st group (Pirfenidone + prednisolone) (n=25)	2nd group Prednisolone (n=25)	Test	P value
FVC: Mean ± SD Range	1177.2 ± 60.2 1090 - 1300	1178.4 ± 65.8 1080 - 1310	-0.067#	0.947 (NS)
6MWT: Median Range	200 180 - 250	200 180 - 230	-0.228$	0.820 (NS)
SpO_2 at rest: Mean ± SD Range	81.6 ± 2.7 77 - 88	81.8 ± 2.3 77 - 86	-0.166#	0.689 (NS)
K-BILD questionnaire: Mean ± SD Range	34.4 ± 5.8 25 - 45	34.8 ± 4.6 27 - 43	-0.268#	0.790 (NS)
CT severity score: Mean ± SD Range	17.9 ± 3.1 12 - 24	17.7 ± 2.3 13 - 22	-0.306#	0.761 (NS)

1. # Independent t-test, $ Mann-Whitney test, SD standard deviation.
2. *NS* non-significant difference (p>0.05).

Table (3) showed the comparison between both groups after 1 month as regards the previous clinical parameters. In terms of 6MWT one month following therapy, significant difference was statistically high between the tested groups. Also, there were statistically significant differences between them as regards K-BILD questionnaire and CSS as shown in Figure (1). When compared to the other group, the first group scored significantly higher on the 6MWT and K-BILD questionnaire. However, in comparison with the other group, CSS was discovered to be significantly lower in the first group.

Table (3): Clinical parameters of the studied groups after one month of the treatment

Variable	1st group Pirfenidone + prednisolone (n=25)	2nd group Prednisolone (n=25)	Test	P value
FVC: Median Range	1300 1180 - 1500	1250 1150 - 1500	-1.075*$*	0.282 (*NS*)
6MWT: Median Range	300 240 - 350	250 220 - 300	**-3.831*$***	**<0.001** **(*HS*)**
SpO_2 at rest: Median Range	86 81 - 90	84 81 - 90	-0.889*$*	0.374 (*NS*)
K-BILD questionnaire: Mean ± SD Range	47.3 ± 5.3 39 - 57	42.7 ± 5.6 32 - 55	**2.976#**	**0.005** **(*S*)**
CT severity score: Mean ± SD Range	12.2 ±2.3 8 - 17	14.08 ± 2.8 9 - 20	**-2.536#**	**0.01** **(*S*)**

1. *#*: Independent t-test, *$* Mann-Whitney test, *SD* standard deviation.
2. *NS* (p>0.05): non-significant difference, *S* (p<0.05): significant, *HS* (p<0.001): highly significant.

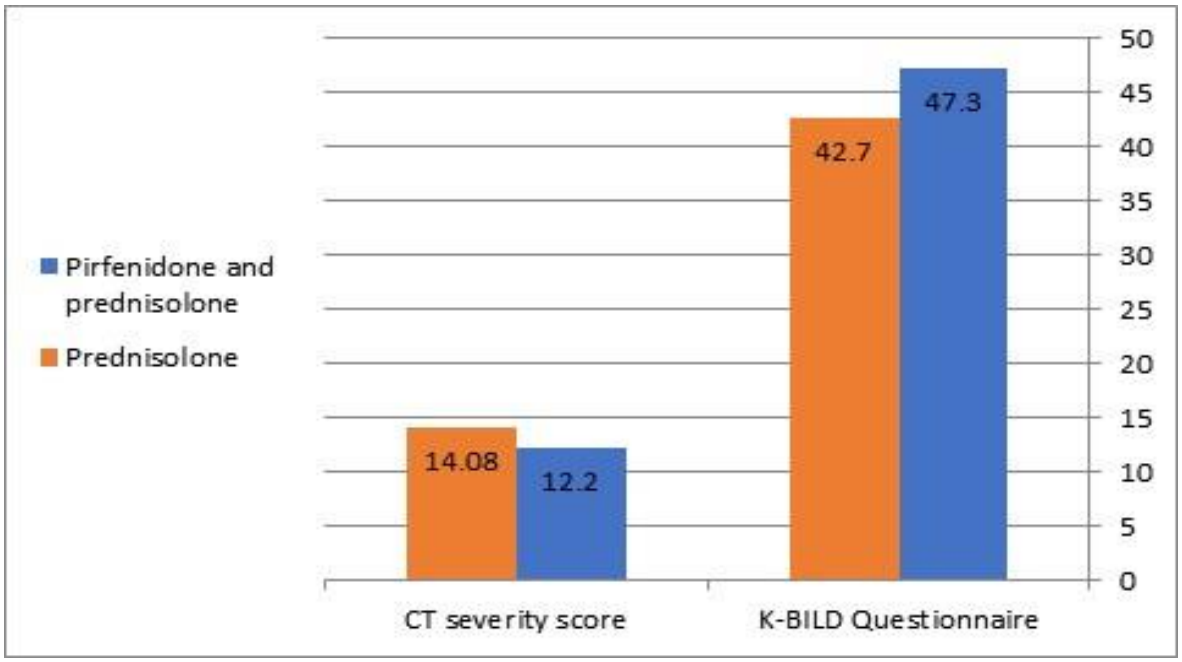

Figure (1): Comparison of K-BILD questionnaire and CT severity score among the studied groups.

After 3 months, the comparison between both groups as regards the same parameters was shown in table (4). This table showed that there were highly statistically significant differences between the studied groups as regards all clinical parameters after 3 months of treatment which all appeared to be significantly better among group of pirfenidone + prednisolone versus the other except for CSS which was significantly lower as shown in (Fig. 2).

Table (4): Clinical parameters of the studied groups after three months of the treatment

Variable	1st group Pirfenidone+ Prednisolone (n=25)	2nd group Prednisolone Only (n=25)	Test	P
FVC:				
Median	1700	1400	-	**<0.001**
Range	1400 - 1950	1200 - 1500	**5.785$**	**(HS)**
6MWT:				
Median	450	300	-	**<0.001**
Range	350 - 500	220 - 450	**5.818$**	**(HS)**
SpO_2 at rest:				
Mean ± SD	91.9 ± 2.1	87.8 ± 3.3	**5.183#**	**<0.001**
Range	88 - 95	80 - 94		**(HS)**
K-BILD questionnaire:				
Median	79	67	**-5.173$**	**<0.001**
Range	69 - 90	39 - 75		**(HS)**
CSS:				
Mean ± SD	5.9 ± 2.7	11.4 ± 3.5	-	**<0.001**
Range	2 - 11	4 - 18	**6.197#**	***(HS)***

1. # Independent t-test, *$* Mann-Whitney test, *SD* Standard deviation. 2. *HS* (p<0.001): highly significant.

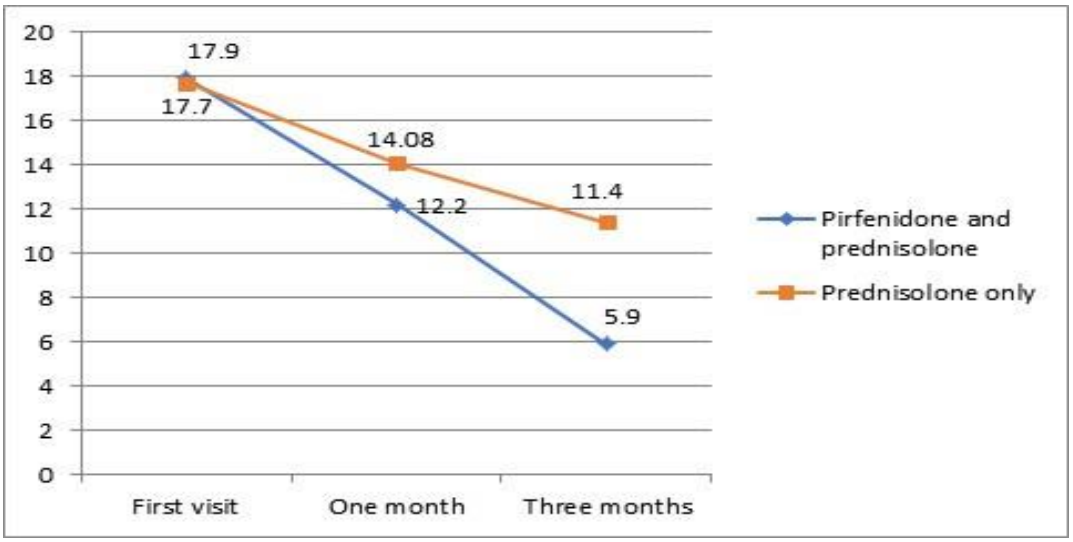

Figure (2): Comparison of CSS at different timings among the studied groups.

DISCUSSION

After developing a worldwide disaster for approximately 2 years, there are now indications that the COVID-19 pandemic is decreasing. But the number of patients with ongoing post-COVID-19 lung problems is still significant and growing. Pulmonary fibrosis, among the most serious long-lasting effects of COVID-19, is a worrying new development. Because of variable degrees of fibrotic alteration in the lungs, about 10 to 15% of moderate to severe, non-critically ill, COVID-19 cases are referred [(15)]. The cause of this is the recruitment and persistence of pro-fibroblastic cells (such as fibroblasts, platelet derived growth factor (PDGF), transforming growth factor-beta (TGF-β) & fibroblast growth factor) with upregulation of pro-inflammatory cytokines (like interleukins and tumor necrosis factor-alpha) [(16)]. Considering these evidences, clinicians all over the world are confused whether antifibrotics administered for other PF-ILDs would assist COVID-19 patients with lung fibrosis [(15)].

A brand-new antifibrotic with low adverse effects, pirfenidone is also identified as 5-methyl-1 phenyl-2-[1H] pyridone. For Idiopathic pulmonary fibrosis (IPF) cases with mild to severe severity, pirfenidone has been licensed for its management [(17)]. Pirfenidone is also a scavenger of reactive oxygen species (ROS). Lastly, but not on the list, it also prevents the angiotensin converting enzyme (ACE) receptor, which is COVID-19's main cellular receptor, from being expressed. It also has certain additional qualities that make it a successful COVID-19 management; include its anti-fibrotic and anti-apoptotic activities [(17)]. The inflammatory cells' recruitment due to different stimuli has been shown to be reduced by pirfenidone. It reduces fibroblast proliferation, protein and cytokine production. Additionally, it reduces the increase in extracellular matrix production and accumulation that

is triggered by growth factors like TGF-β and PDGF [18].

From the Outpatient Clinic, 50 patients with post-COVID-19 fibrosis were randomly selected for this research. They were 17 females (34%) and 33 males (66%) with a mean age of 48.26 ± 11.46 years. Our patients were randomly separated into 2 groups. First group (25 cases) got pirfenidone in a dose of 267 mg tds at 1st week, which was further raised in weekly dosage increments to a maximum of 2400 mg [13], in addition to 20 mg/day corticosteroids (prednisolone). Second group (25 cases) received 20 mg /day corticosteroids (prednisolone) [14]. There were no considerable variations between the two groups concerning demographics, K-BILD questionnaire results, clinical values, comorbidities, or CT scores at the time of admission. There were 66 % males. There were no significant differences as regards all clinical parameters at the first visit of patients.

Regarding the 6MWT one month after treatment, there was a highly statistically significant difference between groups of the study. Also, there were significant differences between them as regards K-BILD questionnaire and CSS. When compared to the other group, the pirfenidone + prednisolone group performed much better on the 6MWT and K-BILD questionnaire. After one month of treatment, however, it was discovered that the first group's CSS was much lower than that of the other group. This is in agreement with **Acat *et al.*** [13] that found variation in CT scores at time of diagnosis, the scores in the group of methylprednisolone & pirfenidone were statistically significantly diminished. However **Zhang *et al.*** [19] stated that after treatment, The K-BILD survey results did not differ statistically from one another, when compared to the patients allocated to the standard treatment group. A pattern of an increase from baseline was observed in patients who received pirfenidone for a period of four weeks. Likewise, after 4 weeks of treatment, there was no discernible difference between the 2 studied groups in terms of CT imaging. However, there were some variations in scores, such as consolidation, the GGO and the reticulation between-groups. This may be due to features, demographics and different sample size of the patients.

In our research, all clinical parameters FVC, 6MWT, SpO2, K-BILD questionnaire and CSS showed substantially statistically difference between the analysed groups after 3 months of treatment with the exception of CSS that was considerably greater in the pirfenidone + prednisolone group compared to the other group. This is consistent with **Acat *et al.*** [13] who discovered that patients' second-month pulmonary function tests of the methylprednisolone + pirfenidone group had significantly higher FEV_1, FVC% and FEV_1% / FVC values than the methylprednisolone group. Also, **Güler *et al.*** [20] compared to the methylprednisolone group, the pirfenidone + methylprednisolone group had significantly higher FEV_1, FVC%. Also, **Momen *et al.*** [21] reported that after covid-19, patients with pulmonary fibrosis who received standard medications were not able to recover, necessitating the use of an anti-fibrotic such as pirfenidone, which led to a considerable improvement in both the radiological results and the patient's symptoms. However, **Zhang *et al.*** [19] reported that neither the K-BILD nor the CT scores showed a statistically significant difference between the two groups. This may be because of the lesser sample size and short observation period (four weeks). **Chaudhary *et al.*** [22] claimed that current antifibrotics, which are used to treat chronic disorders, are not effective for stopping fibrosis or curing it. They claimed that the positive outcome and reduced prevalence of extensive scarring among survivors make the use of antifibrotic drugs unjustified scientifically. In contrast, **Ferrara *et al.*** [18] demonstrated that pirfenidone, an anti-fibrotic medicine, is effective in preventing significant COVID-19 infection-related outcomes whether administered as monotherapy or in combination with anti-inflammatory drugs (acting early, at the optimal doses, and at the appropriate time). Patients who still have pulmonary fibrotic damage may benefit from the same strategy as a post-infection treatment.

The phrase "post-COVID-19 pulmonary fibrosis" has been criticised by an expert working committee because it implies a "permanent" nature, which the majority of people with fibrotic lung disease after COVID-19 do not have. ILD post-COVID-19 is a better expression to use [23]. It is not known for sure how long antifibrotic medications should be taken. About one-third of specialists said they would take antifibrotic medications for eight to twelve weeks. 60% of them stated that they would utilize it for up to 6 months [23]. The small number of patients in our study was one of its limitations. The control group consisted only of prednisolone-treated individuals. There was no untreated placebo group.

CONCLUSIONS

Fibrosis of the lungs after COVID-19 is anticipated to be challenging for many physicians. Pirfenidone is an antifibrotic drug that can help patients who have recovered from COVID-19 infection but still have fibrotic lung lesions by reducing fibrotic alterations and improving quality of life. Also, it can aid in shortening the period of steroid therapy and avoiding its negative side effects.

ABBREVIATIONS

6MWT: Six-minute walking test;
ACE: angiotensin converting enzyme;
ARDS: acute respiratory distress syndrome; **COVID-19:** coronavirus disease-19;
CSS: CT severity score;
FEV_1: forced expiratory volume at 1st second,
FVC: forced vital capacity;
GGO: ground glass opacity;
HRCT: High resolution computed tomography;
IPF: Idiopathic Pulmonary Fibrosis;

KBILD: The King's Brief Interstitial Lung Disease;
PDGF: platelet-derived growth factor;
PF-ILDs: progressive fibrosing-interstitial lung disease;
ROS: reactive oxygen species;
SARS-CoV2: severe acute respiratory syndrome coronavirus 2;
TGF-β: transformative growth factor beta.

DECLARATIONS

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