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# Evaluation of the efficacy of pirfenidone in progressive chronic hypersensitivity pneumonitis

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## Abstract

**Background:** The present data about the treatment of progressive CHP are few and largely based on observational studies and expert opinion. It is suggested that pirfenidone may slow disease progression in cases of CHP as it has some anti-inflammatory in addition to antifibrotic effects, so this study aimed to evaluate the efficacy of pirfenidone in chronic hypersensitivity pneumonitis. This study included 40 adult patients ( $\geq 18$  years) with a diagnosis of chronic progressive hypersensitivity pneumonitis. The included patients were divided into 2 groups 20 patients in each one. Group 1 received pirfenidone in addition to the conventional treatment Group 2 was maintained on conventional treatment.

Forced vital capacity (FVC), 6-min walking test (6MWT), oxygen tension in the arterial blood ( $\text{PaO}_2$ ), and St. George's Respiratory Questionnaire (SGRQ) were measured before and after 6 months of a pirfenidone treatment trial.

**Results:** The present study showed that in patients with progressive chronic hypersensitivity pneumonitis, adding pirfenidone to their conventional treatment was associated with significantly higher FVC, 6MWT,  $\text{SaO}_2$ , and  $\text{PaO}_2$ , and significant lower SGRQ score compared to patients who were maintained only on their conventional treatment at 6 months after treatment

**Conclusion:** Pirfenidone can reduce the progression of chronic hypersensitivity pneumonitis and so it can be considered a therapeutic option in its treatment.

**Trial registration:** ClinicalTrials.gov, [NCT04675619](https://clinicaltrials.gov/ct2/show/study/NCT04675619).

**Keywords:** Hypersensitivity pneumonitis, Pirfenidone, ILD

## Background

Idiopathic pulmonary fibrosis (IPF) is the most often studied fibrotic lung disease. Recent trials reported that patients with IPF who received nintedanib showed a significantly lower rate of decline in the forced vital capacity [1].

Other interstitial lung diseases (ILDs) have a fibrotic phenotype [2], and some of them may initially be inflammatory and then progress to a fibrotic phenotype, as in the case of chronic hypersensitivity pneumonitis (CHP) [3, 4]

These other fibrotic lung diseases share similar pathophysiological, clinical, radiological, and histopathological characters to IPF. The pattern of usual interstitial pneumonia (UIP) is nonspecific, as the UIP is seen in patients with IPF, CHP, connective tissue disease (CTD), and drug-induced lung disease [4–6]

Some patients thought to have IPF and studied in clinical trials may have other fibrotic lung diseases. As the diagnosis of IPF in the INPULSIS 1 and 2 trials was not ascertained by histopathology features of UIP in patients who did not have honeycombing [7]. A previous prospective study reported that nearly half of patients who were originally diagnosed with IPF based on 2011 criteria were subsequently diagnosed

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with CHP after evaluation of exposure history, imaging, and histopathology by experts in ILD [8].

It is suggested that some patients presumed to have IPF who showed a treatment response to nintedanib in the INPULSIS trials may have had non-IPF-PF. This implies that nintedanib may slow disease progression in other ILD and the same may be true for pirfenidone. Both nintedanib and pirfenidone have anti-inflammatory effects in addition to antifibrotic effects, and this supports trials for diseases thought to initially be more inflammatory [7, 9].

### Rationale

The present data about the treatment of CHP are few and largely based on observational studies and expert opinion. It is suggested that pirfenidone may slow disease progression in cases of CHP as it has some anti-inflammatory in addition to antifibrotic effects.

### Hypothesis

Pirfenidone will slow disease progression in chronic hypersensitivity pneumonitis patients.

### Research questions

1. Can pirfenidone slow disease progression in cases of CHP?
2. What about the safety of pirfenidone in cases of CHP?

*This study aimed to evaluate the efficacy of pirfenidone in chronic hypersensitivity pneumonitis.*

### Objectives

1. To compare the functional and radiological parameters between patients group who receive pirfenidone in addition to conventional treatment and the patient group who receive conventional treatment: forced vital capacity (FVC), 6 minutes walking distance, the partial pressure of oxygen in arterial blood (PaO<sub>2</sub>), pulmonary artery systolic pressure, St. George's Respiratory Questionnaire (SGRQ) score, and Quantitative ILD score (QILD), by quantitative HRCT chest
2. To compare the side effects between patients' group who receive pirfenidone treatment and the patient group who receive conventional treatment

### Methods

This study recruited 40 adult patients ( $\geq 18$  years) with a diagnosis of chronic hypersensitivity pneumonitis from the outpatient clinic of Chest Department Faculty of Medicine Zagazig University in the period from December 2019 to June 2020. Approval from the institutional board review and written informed consent from the patients were received.

### Study design

An interventional prospective randomized controlled study

### Sample size

Sample size calculated by EPI info program with power 80% and confidence level 95% based on previous finding; the minimum sample size was calculated to be 40 cases.

### Inclusion criteria

Patients  $\geq 18$  years old with a diagnosis of chronic progressive hypersensitivity pneumonitis:

- $> 10\%$  extent of fibrosis (e.g., reticulation) on high-resolution CT (HRCT) scan
- Absolute decline in FVC% predicted  $> 5\%$  within the previous 6 months despite conventional treatment [10, 11]

### Exclusion criteria

- Pregnancy or breastfeeding period
- Patients with peptic ulcer, severe hepatic disease, severe kidney disease, severe cardiac disease, and patients with other chronic pulmonary diseases
- Presence of active infection
- History of alcohol or drugs abuse
- Active smokers

The included patients were divided into 2 groups 20 patients in each one.

Group 1 received pirfenidone in addition to the conventional treatment.

Group 2 was maintained on conventional treatment.

### Outcome

#### Primary outcome

- Forced vital capacity (FVC)
- 6-min walking distance test

#### Secondary outcome

- Partial pressure of oxygen in arterial blood (PaO<sub>2</sub>)
- Pulmonary artery systolic pressure with an echocardiogram
- Radiological changes in HRCT chest
- St. George's Respiratory Questionnaire (SGRQ) score

### Methods

- Spirometry was done according to guidelines as previously described [12].
- Arterial blood gasses analysis

- 6 minutes walking distance test was performed using standard procedures [13].
- Echocardiography
- Dyspnea assessment by using the Medical Research Council (MRC) dyspnea scale [14]
- SGRQ score: Scores are calculated for three domains which are symptoms, activity, and impacts (psycho-social) psychometric; scores range from 0 to 100, with higher scores pointing to more limitations [15].
- HRCT chest: Quantitative ILD score (QILD), which is calculated by the sum of quantitative lung fibrosis + quantitative honeycomb + quantitative ground glass expressed as a percentage of total lung and individual lobar involvement

A change of 4% of QILD in a lobe of maximum involvement or 2% in the whole lung was considered significant changes according to previous studies [16, 17].

Pirfenidone administered orally in 267-mg capsules taken with food. The dose was titrated over 2 weeks from one capsule three times a day during week 1 to two capsules three times a day during week 2 then maintenance dose (three capsules three times a day week 3).

#### Statistical analysis

Data collected throughout history, basic clinical examination, laboratory investigations, and outcome measures were coded, entered, and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0). Qualitative data represented as number and percentage, and quantitative

data represented by mean  $\pm$  SD. *P*-value was set at  $< 0.05$  for significant results and  $< 0.001$  for highly significant result.

#### Results

This study included 40 adult patients ( $\geq 18$  years) with a diagnosis of chronic progressive hypersensitivity pneumonitis. The included patients were divided into 2 groups 20 patients in each one.

Group 1 received pirfenidone in addition to the conventional treatment.

Group 2 was maintained on conventional treatment.

Mean age was distributed as  $48.65 \pm 8.59$  and  $44.55 \pm 7.46$  respectively between groups with no significant difference and also there was no significant difference regarding BMI between groups. Duration since diagnosis of HP was  $1.85 \pm 0.62$  and  $1.77 \pm 0.57$  year respectively with no significant difference between groups; also, there was no significant difference between groups, as regards sex or co-morbidity as shown in Table 1.

Table 2 shows that there was no significant difference at pretreatment regarding FVC, 6-min walking test (6MWT), or SGRQ score while at 6 months after treatment group 1 was significantly higher at FVC (Fig. 1), 6MWT (Fig. 2), and significantly lower SGRQ score (Fig. 3).

In this study, as shown in Table 3, there were no significant changes at FVC, 6MWT, PaO<sub>2</sub>, PAP, and SGRQ score in group 1, but group 2 significantly deteriorated at all of these parameters.

In this study side, effects related to pirfenidone therapy during the 6 months of treatment were mild to

**Table 1** Basic demographic and clinical data distribution of the studied patients

			Group 1	Group 2	<i>t</i> / $\chi^2$	<i>P</i>
Age(year)			48.65 $\pm$ 8.59	44.55 $\pm$ 7.46	1.611	0.115
BMI (kg/m <sup>2</sup> )			28.98 $\pm$ 4.85	29.13 $\pm$ 3.99	0.784	0.485
Duration (year)			1.85 $\pm$ 0.62	1.77 $\pm$ 0.57	- 0.851	0.412
Sex	Female	<i>N</i>	6	7		
		%	30.0	35.0		
	Male	<i>N</i>	14	13	0.114	0.73
		%	70.0	65.0		
Comorbid	No	<i>N</i>	15	17		
		%	75.0	85.0		
	DM	<i>N</i>	2	2	1.12	0.57
		%	10.0	10.0		
	HTN	<i>N</i>	3	1		
		%	15.0	5.0		
Total	<i>N</i>	20	20			
	%	100.0%	100.0%			

BMI body mass index, DM diabetes mellitus, HTN hypertension

**Table 2** Comparison between groups regards pulmonary function, SGRQ score, and 6MWT at pretreatment and 6 months post-treatment

	Group 1	Group 2	t	P
FVC (ml)	1287.6 ± 106.79	1276.0 ± 106.74	0.344	0.733
FVC% predicted	55.75 ± 4.26	57.45 ± 6.16	0.200	0.842
6MWT (m)	287.5 ± 33.06	290.0 ± 28.383	- 0.255	0.800
PaO <sub>2</sub> at rest(mmHg)	64.75 ± 2.31	62.85 ± 4.24	- 1.892	0.121
SaO <sub>2</sub>	93.5 ± 2.48	92.5 ± 2.63	- 1.792	0.142
Estimated PAP	35.0 ± 5.36	33.25 ± 7.74	1.795	0.081
SGRQ SCORE	37.2 ± 1.43	37.85 ± 2.42	- 0.995	0.326
FVC (ml) 6 M	1265.55 ± 215.15	1100.5 ± 109.46	4.031	0.00**
FVC% predicted 6 M	48.85 ± 6.42	44.5 ± 4.53	3.231	0.002*
6MWT 6 M	310.0 ± 74.09	267.0 ± 37.98	2.356	0.028*
PAP 6 M	33.0 ± 6.56	36.8 ± 5.95	- 2.186	0.037*
SaO <sub>2</sub> 6 M	94.15 ± 3.52	87.0 ± 3.07	2.745	0.017*
PaO <sub>2</sub> 6 M	66.05 ± 2.81	54.9 ± 3.53	10.113	0.00**
SGRQ SCORE 6M	38.25 ± 2.35	44.5 ± 4.52	6.789	0.00**

\*Significant difference

\*\*refer to highly significant results

FVC forced vital capacity, 6MWT 6-min walking test, PaO<sub>2</sub> partial pressure of oxygen in arterial blood, SaO<sub>2</sub> oxygen saturation in arterial blood, PAP pulmonary artery pressure, SGRQ St. George's Respiratory Questionnaire

moderate and so did not indicate stoppage of pirfenidone, and they were in the form of gastrointestinal reaction in 3 patients (15%) and elevations of a hepatic enzyme in 5 patients (25%).

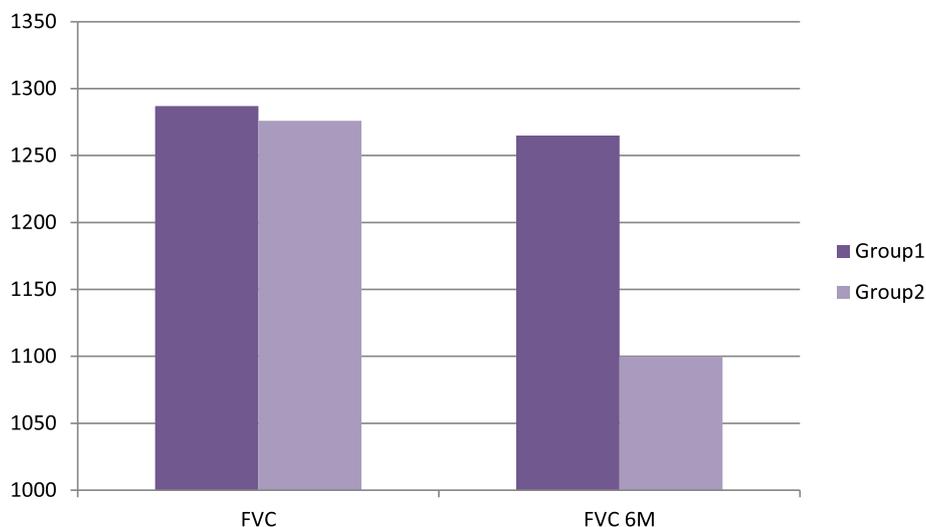
## Discussion

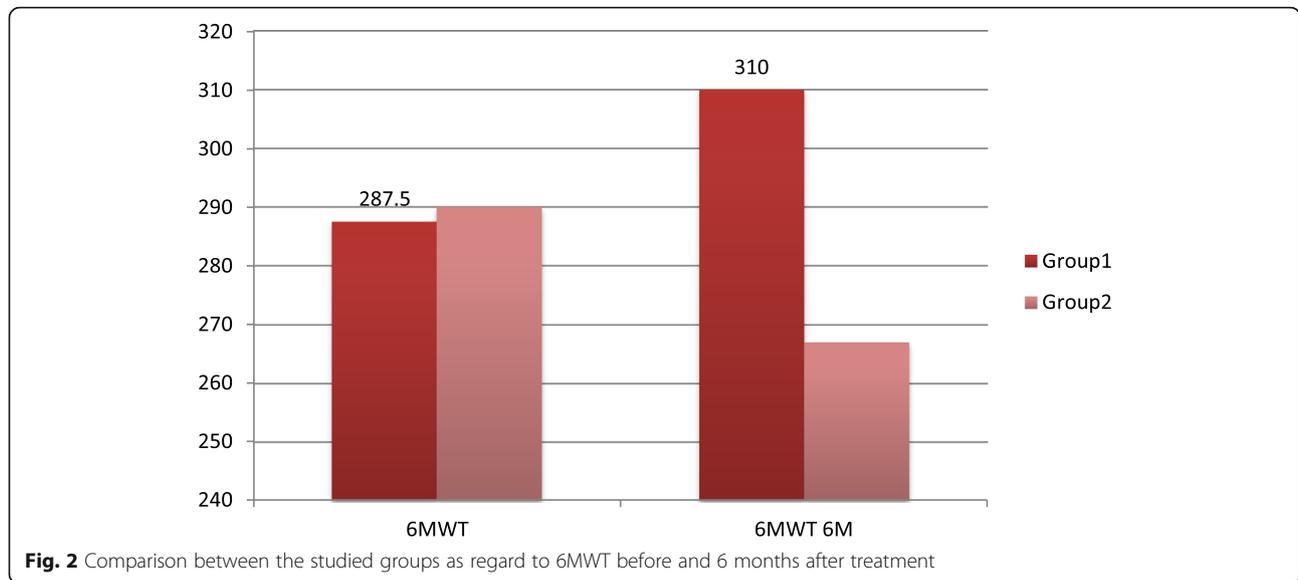
The present study showed that in patients with progressive chronic hypersensitivity pneumonitis, adding pirfenidone to their conventional treatment was associated with significantly higher FVC, 6MWT, and PaO<sub>2</sub> and

lower SGRQ score compared to patients who were maintained only on their conventional treatment at 6 months after treatment.

In patients with non-fibrotic HP, corticosteroids combined with exposure avoidance may be enough to stop and even reverse the disease process. But treatment is more difficult in fibrotic progressive HP phenotype [3, 4].

Pirfenidone is an antifibrotic drug that showed efficacy in the treatment of IPF as this drug decreases migration, differentiation, and activation of fibroblasts, which are

**Fig. 1** Comparison between the studied groups as regard to FVC before and 6 months after treatment



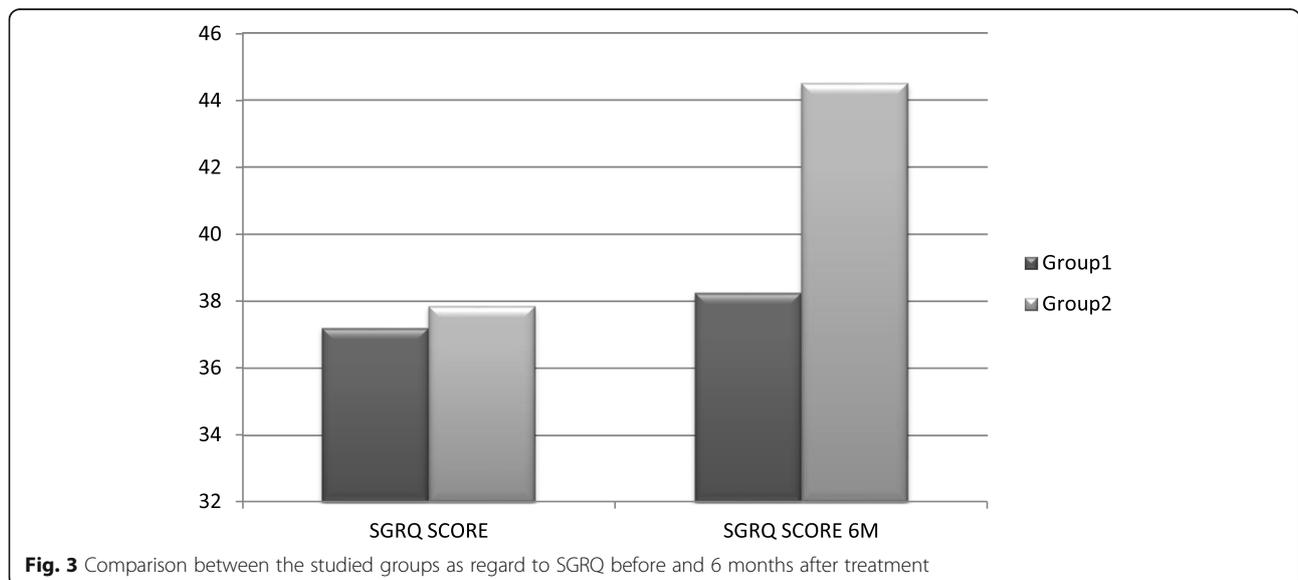
the main cells that leads to development and progression of pulmonary fibrosis [18, 19]. Recently, studies have investigated the efficacy of antifibrotic drugs like nintedanib and pirfenidone in patients with non-IPF PF-ILDs. And these studies have suggested that pirfenidone may be an effective treatment for fibrotic interstitial lung diseases other than IPF, such as scleroderma [20, 21]. But up to now, very little is known about the efficacy of pirfenidone in patients with chronic progressive HP. So our study aimed to evaluate the efficacy of pirfenidone in chronic progressive hypersensitivity pneumonitis.

In our study, after 6 months from the beginning, the mean FVC (ml) in the studied patients who maintained on their conventional treatment significantly decreased

from 1276.0 to 1100.5 while in patients who received pirfenidone in addition to their treatment there was no significant decline of the mean FVC (ml) as it decreased from 1287.6 to 1265.5 ( $p = 0.3125$ ).

A similar finding was reported in a previous retrospective study in patients with chronic hypersensitivity pneumonitis in which the change of VC was  $- 292 \pm 77.8$  ml over the 6 months before the start of pirfenidone and  $- 152 \pm 56.1$  ml over the 6 months after the beginning of therapy with significant difference [22].

Also, previous studies showed that pirfenidone in IPF showed about a 50% reduction in the rate of FVC decline and showed reduced decline in 6MWD in the treated patients compared to placebo [19, 23].



**Table 3** change assessment at each group

Group		Mean	Std. Deviation	Paired t	P
Group1	FVC (ml)	1287.6000	106.79760	- 0.990	0.3125
	FVC (ml) 6M	1265.5530	215.15587		
	FVC%predicted	55.7500	4.26584	0.340	0.814
	FVC%predicted 6M	53.8500	6.42589		
	6MWT (m)	287.5000	33.06692	1.785	0.0674
	6MWT (m) 6M	310.0000	74.09809		
	PaO <sub>2</sub> at rest	64.7500	2.31414	- 1.653	0.0881
	PaO <sub>2</sub> at rest 6M	66.0500	2.81864		
	SaO <sub>2</sub>	93.5000	2.48151	1.245	0.124
	SaO <sub>2</sub> 6M	94.1500	3.52846		
	PAP	35.0000	7.36278	1.085	0.231
	PAP 6M	33.0000	6.56947		
	SGRQ SCORE	37.2000	1.43637	1.106	0.224
	SGRQ SCORE 6M	38.2500	2.35123		
Group2	FVC (ml)	1276.0000	106.74120	4.745	0.00**
	FVC (ml) 6M	1100.5000	109.46160		
	FVC%predicted	57.4500	6.16542	1.879	0.052
	FVC%predicted 6M	48.5000	4.53640		
	6MWT	290.0000	28.83711	4.314	0.00**
	6MWT 6M	267.0000	37.98892		
	PaO <sub>2</sub> at rest	62.8500	4.24605	3.088	0.002*
	PaO <sub>2</sub> at rest 6M	54.9000	3.53777		
	SaO <sub>2</sub>	92.5000	2.65370	- 5.139	0.00**
	SaO <sub>2</sub> 6M	87.0000	3.07794		
	PAP	33.2500	5.74800	- 2.019	0.048*
	PAP 6M	36.8000	5.95686		
	SGRQ SCORE	37.8500	2.42441	- 3.795	0.00**
	SGRQ SCORE 6M	44.5000	2.35627		

\*refer to significant results

\*\*refer to highly significant results

FVC forced vital capacity, 6MWT 6 minutes walking test, PaO<sub>2</sub> partial pressure of oxygen in arterial blood, SaO<sub>2</sub> oxygen saturation in arterial blood, PAP pulmonary artery pressure, SGRQ St. George's Respiratory Questionnaire

In this study, side effects related to pirfenidone therapy in the 6 months of treatment were mild to moderate and so did not indicate stoppage of pirfenidone and they were in the form of gastrointestinal reaction in 3 patients (15%) and elevations of the hepatic enzyme in 5 patients (25%). This finding agrees with that of previous studies [19, 23] in which pirfenidone therapy was well tolerated in their studied patients.

*Limitations* of our study include the small sample size and being a single-center study. So, further multicenter studies including more patients and for a longer follow up period are recommended.

## Conclusion

Pirfenidone can reduce the progression of chronic progressive hypersensitivity pneumonitis and so it can be considered a therapeutic option in its treatment.

## Abbreviations

HP: Hypersensitivity pneumonitis; IPF: Idiopathic pulmonary fibrosis; FVC: Forced vital capacity; 6MWT: 6-min walking test; PaO<sub>2</sub>: Partial pressure of oxygen in arterial blood; SaO<sub>2</sub>: Oxygen saturation in arterial blood; PAP: Pulmonary artery pressure; SGRQ: St. George's Respiratory Questionnaire

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**Authors' contributions**

ES and TH chose the title of this research and patient collection. ES and HA shared in methods and paper writing. All authors have read and approved the manuscript.

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**Availability of data and materials**

Not applicable

**Declarations****Ethics approval and consent to participate**

Written informed consent was received from the patients, and the IRB of Faculty of Medicine Zagazig University approved this study. The committee reference number is 5889.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that there are no competing interests.

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