



EFFICIENCY EVALUATION OF PIRFENIDONE IN EGYPTIAN IDIOPATHIC PULMONARY FIBROSIS PATIENTS

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a complicated disease in which histopathological abnormalities in the form of, proliferation of mesenchymal cell, fibrosis, overproduction and disorganization of collagen deposition, extra cellular matrix changes with distortion of pulmonary structure and the appearance of subpleural cysts, with accumulation of both myofibroblast and fibroblast. Pirfenidone has been available in Japan since 2008. In 2011, the approval by the European Medicine Agency (EMA) was indicated by the efficacy of pirfenidone in decreasing lung function deterioration in IPF patients.

Aim of the Study: The aim of the study is to study the efficiency and safety of Pirfenidone in a group of IPF Patients.

Ethical aspects: The thesis protocol was approved by IRB committee, Faculty of Medicine, Zagazig University.

Subjects and Methods: This study was carried on 40 adult patients with IPF. Patients were divided into:

- Group (A): 20 patients accepted to be treated with pirfenidone.
- Group (B): also 20 patients they have been treated with conventional treatment for IPF

Results: Mean change in distance walked during 6MWD test was 0.05 ± 56.24 for group (A) and -12.65 ± 67.86 for group (B). Mean decline in predicted FVC was $-0.89 \% \pm 14.55$ for group (A) and $-5.48 \% \pm 10.89$ for group (B) there were progression of the disease according to HRCT in 60% in group (A) and 70% in group (B), while only 10% in group (A) showed regression of the disease with statistical significant differences between two groups.

Conclusion: Pirfenidone didn't improve health related quality of life in IPF patients, Pirfenidone did not affect oxygenation in treatment group after 3 months therapy, Pirfenidone has good impact on radiological presentation of IPF patients. Pirfenidone not only slow loss in FVC but also improved it in one third of treated patients, GIT upset is the main adverse effects of pirfenidone which are mild.

Key words: Idiopathic pulmonary fibrosis, Pirfenidone, steroids

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is non-predictable, irreversible, debilitating and finally it is a fatal chronic fibrotic lung disease associated with dyspnea and a progressive reduction in lung function. From all forms of idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis is considered the most frequent and fatal form, although the clinical course varies, prognosis is poor

with a median survival from the onset of symptoms of only 2.8-4.2 years (1).

Early, IPF was considered to be an inflammation-driven disorder so initial treatment aimed to defeat and suppress the inflammatory process (e.g. corticosteroids and immunomodulatory agents). However, there is a new clue that inflammation is not a major histopathological finding in UIP and that fibroblast foci develop early in UIP (2)

Pirfenidone was the first approved anti-fibrotic agent for the treatment of IPF. It was approved in 2008 and gave the hope for IPF patients and physicians for a new era in the treatment of IPF (3). The pirfenidone antifibrotic effect caused suppression of inflammatory cytokines, as indicated in a mouse model of bleomycin-induced pulmonary fibrosis. Pirfenidone inhibits transforming growth factor- β (TGF- β) and has antifibrotic, anti-inflammatory, and antioxidant effects (4).

- **Technical design:**

- **Site of the study:**

This study was carried out at Chest Department, Zagazig University Hospitals across one year period starting from January 2017.

- **Patients:**

This study was conducted on 40 IPF patients, randomly selected from the Chest Outpatients Clinic attendants according to the inclusion criteria. All patients were clinico-radiologically diagnosed as IPF prior to inclusion in the study.

Patients were divided into:

- Group (A): This group included twenty patients who accepted to start pirfenidone treatment according to the advice of their prescribing physicians. They were 13 females and 7 males. Their age was 57.1 ± 8.19 years.
- Group (B): This group included 20 sex (13 females and 7 males) and age (57.25 ± 8.05 years) matched patients starting conventional treatment for IPF (systemic steroids and azathioprine) according to their prescribing physicians.

Inclusion Criteria:

- Patients who fulfilled investigations according the study protocol.
- Patients who kept on follow up for the entire study.
- All patients fulfilling the clinical and radiological criteria of IPF. According the IPF guidelines of the American Thoracic Society/European Respiratory

Society /JRS/ Latin-American Thoracic Association (ALAT). (5).

- Clinically stable IPF patients.
- Patients who signed informed consent.

Exclusion criteria:

- Clinical and radiological features of idiopathic interstitial pneumonias other than IPF.
- IPF patients with neuromuscular disease, chronic renal failure, HCV infection, evidence of coexisting respiratory infection, lung cancer and other concomitant pulmonary diseases.
- History of pirfenidone therapy to avoid previous effect of pirfenidone.

Study design

Controlled Clinical Study
(Interventional Drug Study)

- **Methods:**

The following parameters were fulfilled for all the patients

- 1- **Medical history and clinical examination;**
- 2- **Complete clinical examination:** Full clinical examination has been done.
- 3- **Laboratory investigations (before and at end of treatment or, moreover, if recommended):**
- 4- **Arterial blood gases analysis (ABGs).**
- 5- **Spirometric Pulmonary Function Testing (PFT)**
- 6- **Plain chest X-ray (postero-anterior and lateral views).**
- 7- **HRCT of Chest**

HRCT of Chest was performed to all patients in this study, before and after recruitment. Findings of HRCT are fundamental in the diagnosis of IPF, Diagnosis of IPF is possible without surgical lung biopsy when HRCT demonstrates a typical IPF pattern and causes of interstitial pneumonia remain unknown. treatment (Group B) was evaluated for three months

Treatment

In this study the effectiveness of pirfenidone therapy (Group A) vs. conventional period. Follow up the studied cases was carried out through; symptoms score, HRCT of the chest, arterial blood gases, 6 minutes' walk test

and spirometric pulmonary function test pre- and post- recruitment. Possible treatment side effects were monitored

DOSAGE AND ADMINISTRATION

Testing prior to pirfenidone Administration

Conduct liver function tests prior to initiating treatment with pirfenidone

Recommended Dosage The recommended daily maintenance dosage of pirfenidone is 801 mg (three 267 mg tablets) three times a day with food for a total of 2403 mg/day. Doses should be taken at the same time each day.

Dosage Titration for pirfenidone in Patients with IPF (6).

Pirfenidone therapy is started with a 14-day titration regimen of 801 mg/day (one capsule,

three times per day) on days 1–7 of 1,602 mg/day (two capsules, three times per day) on days 8–14. The daily dose from day 15 onwards is pirfenidone 2,403 mg/day (three capsules, three times per day)

STATISTICAL ANALYSES

All statistical analyses were carried out using the SPSS (statistical package for the social science software) statistical package version 20.0 (SPSS Inc., Chicago, IL, USA) for Windows. Quantitative data were expressed as mean and standard deviation (X + SD) and analyzed by applying student t-test for comparison of two groups of normally distributed variables. The results of the "t"-value is then checked on student's "t"-table to find out the significance level (p-value) according to the degree of freedom.

RESULTS

Table 1 Socio-demographic data of studied patients

			Group		Total	X ²	P
			Group A	Group B			
Sex	F	N	13	13	26	0.00	1.00
		%	65.0%	65.0%	65.0%		
	M	N	7	7	14		
		%	35.0%	35.0%	35.0%		
	EX Smoker	N	4	6	10		
		%	20.0%	30.0%	25.0%		
	Non Smoker	N	10	5	15		
		%	50.0%	25.0%	37.5%		
passive smoker	N	1	5	6			
	%	5.0%	25.0%	15.0%			
Comorbidities	DM	N	3	7	10	8.2	0.004*
		%	15%	35%	25%		
	HTN	N	4	7	11		
		%	20%	35	27.5%		
Total	N	20	20	40			
	%	100.0%	100.0%	100.0%			

This table shows Socio-demographic data of both patients' groups Most of patients were females (26 patients) with percentage of 65%, 13 in group (A) and 13 in group (B), none of the patients was current smoker , 15 patients were nonsmokers with percentage of 37.5%, 10 in group (A) and 5 in group (B), 10 patients were Ex-smokers with percentage of 25%, 4 in group (A) and 6 in group (B), 10 patients had DM with percentage of 25%, 3 in group (A) and 7 in group (B), while 11 patients had hypertension with percentage of 27.5%, 3 in group (A) and 7 in group (B), no statistical significant differences regarding sex, special habits and (P>0.05) but there was significant statistical difference between patients' groups according to comorbidities (P<0.05).

Table 2 Six minutes walk test and Oxygen saturation before and after treatment in both groups.

		Group	N	Mean	Std. Deviation	t/ Mann Whitney	P
Before Treatment	Distance	Group A	20	318.15	50.92851	.927	.360
		Group B	20	301.90	59.62153		
	O2_saturation pre test	Group A	20	93.95	1.90498	1.76	0.086
		Group B	20	92.85	2.03328		
	O2_saturation post test	Group A	20	88.35	3.73145	0.41	0.68
		Group B	20	87.80	4.65211		
After Treatment	Distance	Group A	20	318.20	56.24346	1.469	.150
		Group B	20	289.25	67.86509		
	O2_saturation pre test	Group A	20	93.45	2.35025	1.980	0.055
		Group B	20	91.55	3.59056		
	O2_saturation post test	Group A	20	87.40	5.35478	1.702	0.097
		Group B	20	84.15	6.65128		

This table shows that there is no change in distance of the six minutes walk test in pirfenidone group after treatment but there is loss in distance of the six minutes walk test in other group after treatment with no statistical significant differences between two groups (P>0.05) .

For Oxygen saturation the table shows loss in both groups after treatment but the loss in pirfenidone group was less than other group with no statistical significant differences between two groups (P>0.05)

Table 3 Dyspnea severity before and after treatment among studied groups

			Group		Total	X ²	P			
			Group A	Group B						
Before Treatment	Gr 0	N	0	0	0	2.46	0.48			
		%	0%	0%	0%					
	Gr 1	N	3	4	7					
		%	15.0%	20.0%	17.5%					
	Gr 2	N	12	13	25					
		%	60.0%	65.0%	62.5%					
	Gr 3	N	5	2	7					
		%	25.0%	10.0%	17.5%					
Gr 4	N	0	1	1						
	%	0.0%	5.0%	2.5%						
After Treatment	Gr 0	N	0	0	0	1.23	0.74			
		%	0%	0%	0%					
	Gr 1	N	6	5	11					
		%	30.0%	25.0%	27.5%					
	Gr 2	N	7	8	15					
		%	35.0%	40.0%	37.5%					
	Gr 3	N	7	6	13					
		%	35.0%	30.0%	32.5%					
	Gr 4	N	0	1	1					
		%	0.0%	5.0%	2.5%					
	Total		N	20	20			40		
			%	100.0%	100.0%			100.0%		

This table show grades of Dyspnea according to mMRC before and after treatment among studied groups with no statistical significant differences between two groups neither before nor after treatment (P>0.05).

Table 4 Changes of distance in 6 min walk test before and after treatment in Group (A)

	Mean	N	Std. Deviation	Paired t	P
Distance before treatment	318.15	20	50.92851	-.017-	.986
Distance after treatment	318.20	20	56.24346		

This table shows mean Distance in 6 Min Walk test before and after treatment 318.15 ± 50.92 , 318.2 ± 56.24 respectively in group (A) the distance is almost the same before and after treatment with no statistical significant improvement ($P > 0.05$).

Table 5 Weight of studied patients before and after treatment in Kgs

	Group	N	Mean	Std. Deviation	t	P
Before treatment	Group A	20	88.20	15.83667	.837	.408
	Group B	20	84.25	13.96565		
After treatment	Group A	20	85.95	15.62884	-.450-	.655
	Group B	20	88.10	14.57431		

This table shows the mean weight of two groups before and after which found 88.2 ± 15.83 KG for group (A) and 84.25 ± 13.96 for group (B) before treatment and 85.95 ± 15.62 KG for group (A) and 88.1 ± 14.57 for group (B) after treatment there is a weight gain in patients of group (B) and weight loss in patients of group (A) with no statistical significant differences between two groups after treatment ($P > 0.05$).

DISCUSSION

Idiopathic pulmonary fibrosis (IPF) is a specific form of fibrosed interstitial pneumonia which is progressive, chronic and its cause isn't known. It is limited to the lungs, occurs mainly in older adults and is associated with histological and/or radiological characteristics of usual interstitial pneumonia (UIP) (7)

Although the disease has been considered rare, it occurs with same rate of stomach, brain, and testicular cancers (8).

After the explanation of the nature of the disease that appears to be related to inflammation and fibrosis, this gives us the idea to begin the "anti-fibrotic" era (9).

These are in agreement with **Suraj et al., (2015) (10)**. In this Indian study of 23 IPF patients who were followed up for one year, female patients were 54%. Patients had DM (12.5%) and hypertension (12.5%). **Salih et al., (2016) (11)** reported that none of their IPF patients were current smokers.

In contrary, **King et al., (2014) (12)** reported that most of their patients were males with percentage of 79.9% for pirfenidone group and 76.9 for placebo group. **Albera et al., (2016) (13)** reported that Ex-smokers were percentage of 64.4%. **Tzouvelekis et al., (2017) (14)** reported that current smokers at the time of their study constituted 21.3%

The minimum clinically important difference in 6 minutes' walk distance test (6MWD) distance in patients with idiopathic pulmonary fibrosis has been reported as 24–45 meter. (15).

This was in accordance with **Noble et al., (2011) (16)** who found no significant differences in mean change in distance walked during 6MWD test ($P > 0.05$) which was $-45.1\% \pm 32$ in patients received pirfenidone and

$-76.9\% \pm 60.4$ in patients of placebo group, respectively in CAPACITY 006. When comparing the distance lost on follow up in current study and their study, their patients lost more distance. This obviously attributed to the fact their study duration was 72 weeks

while in current study it was about 12 weeks only.

In contrary **King et al., (2014) (12)** and **Albera et al., (2016) (13)** found that patients who received pirfenidone had significant differences in mean change in distance walked during 6MWD test compared with placebo. While **Hosein et al., (2016) (17)** found slight improvement in 6MWD test distance in patients who received pirfenidone. This is in agreement with **Noble et al., (2011) (16)** and **King et al., (2014) (12)** who found that no significant difference was noted in worst SpO₂ during 6MWD test between both pirfenidone and placebo groups.

A compelling support to these results was given by **Noble et al., (2011) (16)** and **King et al., (2014) (12)** who found no significant difference in dyspnea between pirfenidone and control groups.

This result is contraindicated by **Albera et al., (2016) (13)** who found significant difference between the pirfenidone and placebo groups in dyspnea (P<0.05). This may be attributed to the longer duration of their study; 12 months compared to 3 months in the current study

These results are matching **Harari et al., (2015) (18)** who found no statistical significant improvement in distance walked during 6MWD test.

On the other hand; the results of this study were in contrast with the results of **Suraj et al., (2015) (10)** who found significant improvement in distance walked during 6MWD test in pifenidone group.

The explanation of previous results was that the sample size of current study was small compared to the other, the duration of current study was only 3 months and patient were proved only according to definite pattern of UIP on HRCT.

The main side effect of steroids is increasing of weight

Weight loss is a side effect of pirfenidone. This was reported in previous studies **Noble et al., (2011) (16)** (8%), **King et al., (2014) (12)** (12.6%) and **Salih et al., (2016) (11)** (23%)

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