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Original Article

The Effect of Pirfenidone on Idiopathic Pulmonary Fibrosis Patients of Masih Daneshvari Hospital in Tehran, Iran

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Abstract

Background: Idiopathic Pulmonary Fibrosis (IPF) is the most common form of lung fibrosis. This chronic and lethal disease is characterized by the gradual progression of fibrosis in the lung and decreased lung oxygen exchange capacity. This study aimed to evaluate the effect of pirfenidone on pulmonary parameters such as TLC, FVC, DLCO, 6-Minute Walk Distance (6MWD), and SPO_2 has been done.

Methods: In this study, 40 patients with IPF participated in two groups. Pulmonary indicators such as TLC, FVC, VC, and DLCO by wind box and the SPO^2 index were calculated by pulse oximetry. The variable of 6MWD is the distance traveled in *meters* in 6 *min*. Variables such as age, sex, height, weight, and hospitalization were obtained through interviews with patients. The indicators were reviewed in both groups at 3 and 6 months.

Results: Data analysis showed that there was no significant difference ($p>0.05$) between the two groups. The mean reduction in these indexes was lower in the pirfenidone group and the decrease was significant over time. Also, the mean increase in the percentage of distance traveled in the 6MWD in the group of patients receiving pirfenidone was 53.53 and in the placebo group, it was 20.3%, which had a significant difference between the group receiving the drug and placebo was observed.

Conclusion: The results of this study demonstrated that pirfenidone is considered as a preferred drug in all phases of the treatment of IPF disease and it has more therapeutic effects than other medicines.

Keywords: Clinical trial, Idiopathic pulmonary fibrosis, Pirfenidone, Placebo

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Introduction

Pulmonary fibrosis is a lung disease in which the walls of the airways and air sacs become thick and hardened and the ability of the lungs to expand and fill with air is reduced, making it difficult to breathe (1). Complications of lung fibrosis include increased blood pressure in the lungs (pulmonary hypertension), right heart failure, respiratory failure, and lung cancer. Idiopathic pulmonary fibrosis is a specific form of chronic and progressive interstitial fibrous pneumonia which has an unknown cause.

Idiopathic Pulmonary Fibrosis (IPF) is a disease in which the lungs become sore and breathing becomes increasingly difficult. It is not clear what causes the disease, but people between the ages of 70 and 75 usually have the condition, and patients rarely have it under the age of 50 (2). The disease is characterized by a gradual onset of shortness of breath and a dry cough and progresses to the point of disabling the patient. The average survival time of a patient after diagnosis with or without treatment is 2-3 years (3). In general, important symptoms of IPF consist of persistent cough, fatigue, unexplained weight loss, coughing up blood, and increased red blood cells (erythrocytosis), Dyspnea, hypoxemia, chest pain, and loss of appetite (4). Experts believe that factors such as exposure to certain types of dust, such as metal or wood dust, viral infections, family history, gastroesophageal reflux disease, tobacco use, genetic factors, and cancer treatment are important in IPF (5). The IPF can be a bit difficult to diagnose since its symptoms are similar to other lung diseases, such as Chronic Obstructive Pulmonary Disease (COPD) (6). Today, the use of High-Resolution CT scanning (HRCT) has made it possible to accurately diagnose IPF and in most cases, it has ruled out biopsy (7). There is currently no definitive cure for IPF, and the main goal of treatment is to relieve symptoms as much as possible and slow their progression (8). Previous standard IPF treatments based on the hypothesis that the disease was inflammatory include corticosteroids (pirfenidone), cytotoxic drugs such as azathioprine, cyclophosphamide (which reduces the activity of the immune system), and N-acetyl cysteine (a mucolytic drug that has antioxidant properties) (9).

There are more than 120,000 people in the United States with IPF, most of who are currently receiving anti-fibrotic medication. In previous treatments for IPF, the goal was to use N-acetyl cysteine in combination with prednisolone and triple therapy to repair the imbalance between oxidants and antioxidants in lung tissue (10). The new treatment for IPF, two of the anti-fibrotic drugs called pirfenidone in 2014 and nintedanib in 2015 have been approved by the FDA America. These drugs do not cure patients with IPF, but they do slow down the progression of the disease and scarring, correct Vital Capacity (VC) and Forced Vital Capacity (FVC), and extend the patient's lifespan (11).

Pirfenidone, a new anti-inflammatory, and anti-fibrosis drug is a small, low-molecular-weight, non-peptide molecule with the chemical name 5-Methyl-1-phenyl pyridine-2-one (12). Pirfenidone in mice has destroyed pulmonary fibrosis caused by bleomycin and cyclophosphamide. In phases 2 and 3 of its trial, this drug has shown its beneficial effects in studies and no dangerous side effects have been reported (13). The results of a study by Nathan *et al* showed that after 52 weeks, the relative mortality risk for patients treated with pirfenidone was significantly lower than in the placebo group (14). In a study by Celine *et al*, the results demonstrated that 57 and 34% of IPF patients in Europe and the United States recovered after treatment with pirfenidone, respectively (15). Pirfenidone reduces hydroxyproline, inflammatory cells, and TGB-B in BAL fluid. Pirfenidone also reduces the number of fibrocytes and their migration in lung fibrosis caused by bleomycin in animal models. Recently, these results have also been confirmed in human lung fibroblast cell culture media and have shown that pirfenidone reduces fibroblast proliferation. In the hamster, Pirfenidone blocks the pulmonary fibrosis caused by bleomycin by inhibiting collagen synthesis. In this study, we studied patients with pulmonary threat such as pulmonary fibrosis, which was the most important variable of FVC or total lung capacity, and FEV1, which represents the air outlet with pressure in the first second, is more applicable to patients with pulmonary obstruction. Therefore, due to the fact that patients were treated for pulmonary fibrosis, more attention was paid to the total pulmonary capacity of FVC and there was no need to evaluate FEV1. Thus, this study aimed to investigate the effect of pirfenidone

on the progression of IPF in IPF patients referred to the lung disease clinics of Masih Daneshvari Hospital in Tehran.

Materials and Methods

The present study is a randomized controlled clinical trial that was performed on 40 patients with idiopathic pulmonary fibrosis. Among all patients, 20 were randomly assigned to receive the drug Pirfenidone and 20 were randomly assigned to the placebo group. Criteria for entering the study for patients include the desire to enter the study, having lung biopsy, which indicates IPF. Also, having a UIP view in HRCT of the lung is due to the uncertainty that corresponds to the IPF based on the ATS-ERS criteria. Exclusion criteria were having connective tissue diseases, having occupational exposure to substances that cause lung fibrosis, and contact with animals. In this study, the variables of age, sex, weight, height, and acute exacerbation were obtained using a demographic questionnaire. The variables of TLC, FVC, VC, and DLCO were calculated by a body box device. The amount of SPO_2 was calculated by a pulse oximetry and the variable of 6-Minute Walk Distance (6MWD) is the amount of distance traveled in 6 minutes.

Initially, patients underwent liver function testing as a baseline and underwent wind box tests, DLCO; PFT; 6MWD placed. Patients were discontinued if they were treated with immunosuppressive drugs and were given a daily dose of 10 *mg* if they received corticosteroids. Patients were then randomly divided into two groups. The first group received a placebo in addition to previous drugs, and the other group received 200 *mg* of pirfenidone, a brand name of pirfenidone, at a dose of 1,200 *mg* per day. The drug was initially started three times a day and gradually increased to 400 *mg* three times a day for two weeks. All patients were given antacids such as potassium hydrogen pump blockers and all patients used sunscreen with SPF>=50. Drug side effects were explained to patients and the telephone number of the project implementer was provided to patients to report. Patients were visited monthly and their side effects were evaluated and liver function tests were performed. The initial tests were repeated after three months and, then, six months.

Data analysis

In this study, data were analyzed using statistical tests. The obtained data were analyzed using software version 22 and statistical tests of independent t-test, chi-square and paired t-test and one-way variance and the significance level was considered 0.05.

Results

The demographic characteristics of the study population are shown in table 1. As shown in table 1, 4 females and 16 males participated in the placebo group and 5 females and 15 males participated in the pirfenidone group, and the result of the Chi-square test showed that among the participants in the two groups, there was no statistical difference in groups. The mean age in the placebo group was 64.05±6.23 years and in the pirfenidone group 64.21±7.96 years. The mean height in the placebo group was 171.5±6.73 *cm* and in the pirfenidone group 169.6±7.12 *cm*. Also, the mean weight was 68.3±6.87 *kg* in the placebo group and 67.4±6.51 *kg* in the pirfenidone group. The results

Table 1. Demographic characteristics of the subjects (N=40)

Demographic characteristics		Placebo (n=20) Mean ± SD	Pirfenidone (n=20) Mean ± SD	p-value
Sex	Female number (%)	4 (20%)	5 (25.3%)	0.714
	Male number (%)	16 (80%)	15 (74.7%)	
Age		64.05±6.23	64.21±7.96	0.412
Height (*cm*)		171.5±6.73	169.6±7.12	0.682
Weight (*kg*)		68.3±6.87	67.4±6.51	0.941

of the independent t-test indicated that there was no statistical difference between the studied individuals in terms of the mentioned variables (p>0.05).

As shown in table 2, there is no difference between the mean of TLC index based on the statistical test at different periods in the two groups receiving the drug and placebo. However, the mean TLC index decreased over time in both groups and this decrease was significantly based on the Repeated Measure test (p<0.001).

According to the information in table 3, the mean FVC index at different time points is not different between the two groups receiving medication and placebo, but the mean FVC index has decreased over time in both groups and this decrease is significantly based on the Repeated Measure test (p<0.01). The Effect of pirfenidone on the value of SPO_2 at rest in IPF patients is shown in table 3. As can be seen in table 3, based on statistical analyzes at different periods, there is no significant difference in the value of SPO_2 at rest between the two groups receiving medication and placebo. However, the mean resting SPO_2 index

Table 2. The effect of Pirfenidone on TLC in IPF patients

Study groups	TLC Mean ± SD	TLC after 3 months Mean ± SD	TLC after 6 months Mean ± SD	p-value*
Pirfenidone	60.68±10.65	58.32±10.8	58±10.41	<0.001
Placebo	63±6.94	60.2±6.92	58.1±7.18	0.001
p**	0.423	0.512	0.971	

*Repeated measure.**Independent sample T-test.

Table 3. The effect of Pirfenidone on TLC, O2 at rest, O_2 in operation, DLCO, 6-minute walk test in IPF patients

Variable	Study groups	Mean ± SD	After 3 months Mean ± SD	After 6 months Mean ± SD	p-value*
FVC	Pirfenidone	55.53±8.84	53.26±10.01	53.53±10.96	0.001
	Placebo	57.7±7.34	54±7.13	52.3±7.54	<0.001
	p**	0.408	0.79	0.68	
O_2 at rest	Pirfenidone	90.11±3.01	88.42±2.54	88.68±2.45	<0.001
	Placebo	90.45±2.18	88.5±2.16	87.9±2.26	<0.001
	p**	0.68	0.91	0.3	
O_2 in operation	Pirfenidone	84.74±2.9	82.9±3.89	82.9±3.39	0.001
	Placebo	85.8±3.44	83.6±3.54	82.8±2.47	<0.001
	p**	0.305	0.55	0.91	
DLCO	Pirfenidone	53.11±13.9	51.37±14.27	49.7±16.4	0.001
	Placebo	54.4±10.34	52.1±10.69	51.2±10.7	<0.001
	p**	0.74	0.85	0.74	
6-minute walk test	Pirfenidone	361.74±80.01	381.26±81.49	415.3±84.1	<0.001
	Placebo	342.5±69.7	347.1±78.4	362.8±76.7	<0.001
	p**	0.422	0.191	0.155	

* Repeated measure, ** Independent sample T-test.

decreased over time in both groups, and this decrease was significantly based on the Repeated Measure test ($p<0.001$). The effect of pirfenidone on the value of SPO_2 in operation in IPF patients is shown in table 3. As can be seen in table 3, according to the Independent Sample T-test, there is no difference between the two groups receiving medication and placebo at different time points.

However, the average SPO_2 in operation, over time has decreased in both groups and this decrease was significantly based on the Repeated Measure test. According to statistical analyzes at different periods, there was no difference between the two groups receiving the drug and placebo in terms of a 6-minute walking test over time. However, the average distance traveled in the 6-minute walk test increased over time in both groups, and this increase was statistically significant ($p<0.001$).

Discussion

In this study, the effects of using pirfenidone on 20 patients with IPF were studied. The mean reduction in TLC index in both groups of patients, the recipients of pirfenidone and the placebo group were 2.68 and 4.9, respectively. However, there was no significant difference in the percentage of TLC in people with pirfenidone and placebo. IPF is a rare disease with unknown causes with advanced and irreversible fibrosis in the lung tissue. The results of a study by Iwasawa *et al* showed that the mean TLC index in pirfenidone and drug recipients were 68.1±11.5 and 72.3±15, respectively. The average TLC index in the Iwasawa study was roughly consistent with the results of this study, but the mean was different in the placebo group (16). In this study, pirfenidone as a new and effective drug treatment for IPF patients showed a good performance. The drug has been approved by European and American pharmaceutical companies for the treatment of IPF. Pirfenidone is an anti-fibrotic drug with an inhibitory mechanism in the GLI transcription factor but the answer to the question of whether this deterrence is related to the anticonvulsant and cough effects is unclear. Also, the mean reduction in the FVC index in pirfenidone and drug recipients was 2 and 5.4, respectively. As can be seen, the reduction in FVC was lower in the pirfenidone receiving group, but there was no significant difference in the percentage of FVC in people exposed to pirfenidone and pharmacodynamics ($p=0.48$).

Various studies have shown that pirfenidone significantly reduces the risk of death in people with IPF (15). Phase 3 experiments in Japan have shown that pirfenidone causes a major reduction in VC reduction and a significant improvement in life expectancy. Various studies have proven the antioxidant effects of pirfenidone in laboratory models (16). Cortes *et al* in 2014 reported that the mean FVC index in patients was 71±18, which is different from the results of this study (17). The difference in sample size was probably due to the difference in the average FVC index. The results of a study by Oltmanns *et al* showed that pirfenidone had a significant effect on reducing FVC loss over 12 months among 3874 patients (18). The mean reduction in SPO2 index for both groups of pirfenidone and placebo were 1.79 and 2.95, respectively. As can be seen, the reduction rate in the pirfenidone receiving group is lower. However, the true mechanism of performance of pirfenidone in the treatment of IPF patients is still unclear. However, anti-inflammatory effects result from inhibition and suppression of Tumor Necrosis Factor (TNF-), Interleukin-6 (IL), IL-12, IL-8, while the anti-fibrotic effects as a result of inhibition in expression are a factor in the conversion of beta growth factor. The average decrease in the percentage of DLCO index in the group of patients who received pirfenidone was 2.37 and in the group who received placebo was 3.2. As can be seen, the reduction rate in the pirfenidone receiving group is lower.

The results of this study indicate that pirfenidone is considered as a preferred drug in all stages of IPF treatment and has more effects than other drugs. This could be because the drug was used in Europe at the time of the study, and European physicians were less inclined to use nintedanib to treat IPF patients (18). The results of a study by Azuma *et al* in 2005 showed that the mean DLCO index was 57.6±17.2 in the pirfenidone receiving group and 57.73±13.8 in the drug group (19). The mean increase distance index in the 6-*min* walking test for both gropes patients receiving pirfenidone and placebo were 53.53 and 20.3, respectively. As can be seen, the increase was less in the pirfenidone receptor group.

In a review study by Noble *et al*, pirfenidone at a concentration of 2403 (*mg/day*) demonstrated a significant decrease in the distance traveled in the 6-minute walking test in IPF patients over 72 *hr* (6). Pirfenidone is a safe and generally usable drug, and despite being prescribed three times a day, it is an ongoing and tolerable treatment for IPF patients (16). The side effects of pirfenidone are mild to moderate and in rare cases, lead to treatment failure. A lower overall mortality rate associated with IPF treatment with pirfenidone has been demonstrated against the control group. Recommendations for ATS/ERS/JRS/ALAT in 2011 include recommendations for the use of pirfenidone for selected patients, and it is one of the few drugs which has potential therapeutic benefits in the treatment of IPF.

Conclusion

In this study, the effects of using pirfenidone on 20 patients with IPF were investigated. Data analysis showed that there was no statistically significant difference between the two groups receiving the drug and placebo. However, the decrease in the mean of the mentioned indices in the group of recipients of pirfenidone was less and this decrease was significant over time. The average FVC index decreased over time in both groups, and this decrease was significantly based on statistical analysis.

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Conflict of Interest

All authors declare that there is no conflict of interest in this study.

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