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Antifibrotic treatment in patients with idiopathic pulmonary fibrosis: Our experience in 41 cases

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Abstract:

INTRODUCTION: It has been shown that antifibrotic agents (pirfenidone and nintedanib), used in the treatment of idiopathic pulmonary fibrosis (IPF) in recent years, decelerate the worsening of pulmonary function tests and the progression of the disease and also reduce the frequency of acute exacerbations and hospitalizations. In this study, we aimed to evaluate the results of antifibrotic treatment that we have been using since 2013 in our clinic.

MATERIALS AND METHODS: Forty-one patients diagnosed as IPF between August 1, 2013, and February 1, 2019, in the eighth clinic of our hospital were included in this study. The information of the patients was obtained from the patient files. Data were analyzed by descriptive statistical methods, Kolmogorov–Smirnov test, and Wilcoxon test.

RESULTS: Thirty-eight patients were male and three patients were female. The mean age was 65.6 ± 7.0 years. The diagnosis of 34 patients was made clinically and radiologically, and 7 patients were diagnosed pathologically. The longest usage time of antifibrotic drugs was 5.5 years in 2 patients, and the minimum usage time was 6 months in 2 patients. Thirty-four patients were using pirfenidone and seven patients were using nintedanib according to the data of their last visit. There was no significant difference between the baseline 6-min walk test results and the 6th-month, 1st-year, 2nd-year, 3rd-year, and 4th-year results. A significant decrease was determined in diffusing capacity of the lungs for carbon monoxide (DLCO) test results of the 6th month and 1st year compared to baseline (baseline: 63%, 6th month: 57%, and 1st year: 43%) ($P < 0.05$). There was no significant difference in DLCO test results of the 2nd, 3rd, and 4th year compared to baseline ($P > 0.05$). A significant decrease was determined in forced vital capacity (FVC) results of the 2nd year compared to baseline (68% and 59%, respectively) ($P < 0.05$). There was no significant difference in the FVC results of the 6th month, 1st year, 3rd year, and 4th year compared to baseline ($P > 0.05$).

CONCLUSION: Similar to the literature, we have experienced that antifibrotic drugs decelerate the progression of the disease, reduce the risk of developing exacerbations, and are more tolerable in terms of side effect profile compared to the previous treatments.

Keywords:

Antifibrotic drug, idiopathic pulmonary fibrosis, progression

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Introduction

Idiopathic pulmonary fibrosis (IPF), characterized by progressive fibrosis, is a chronic, noncurative disease with unknown etiology and has a worse prognosis than many cancers. It is mostly seen in the sixth and seventh decades, but the incidence of the disease increases with age due to decreased apoptosis and regeneration ability. It is seen rarely <50 years of age except familial cases. The prevalence and incidence of IPF are higher in men than in women.

Smoking is the most important risk factor for IPF. Chronic microaspirations related to gastroesophageal reflux (GER), viral and bacterial infections, environmental and occupational exposures, genetic mutations, hepatitis C, and family history are the other risk factors.[1] The survival time is usually 3–5 years after diagnosis. The clinical course and prognosis vary widely among individual patients with IPF.

It has been shown that antifibrotic agents (pirfenidone and nintedanib), having been used in the treatment of IPF in the recent years, prevent the progression of pulmonary fibrosis, decelerate the worsening of pulmonary function tests (PFTs) and progression of the disease, and decrease the frequency of attacks and hospitalizations. In this study, we aimed to evaluate the results of antifibrotic treatment that we have been using since 2013 in our clinic.

Materials and Methods

Forty-one patients diagnosed as IPF between August 1, 2013, and February 1, 2019, in the eighth clinic of our hospital were included in the study. The variables of the patients were obtained from patient files and hospital information system. The baseline demographic characteristics, symptoms, physical examination findings, GAP scores, PFT parameters, diffusion measurements (diffusing capacity of the lungs for carbon monoxide [DLCO]), 6-min walk test (6MWT) measurements and echocardiography (ECHO) measurements, and the functional evaluation (DLCO, PFT, 6MWT, and ECHO) results of the patients in the 6th month and annual controls during the usage of antifibrotic treatment were recorded.

Statistical methods

The data of the study were analyzed in SPSS 22.0 statistical program (IBMM/Chicago, USA). Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in descriptive statistics of the data. The distribution of variables was measured by Kolmogorov–Smirnov test. Wilcoxon test was used for the analysis of dependent quantitative data.

Results

Thirty-eight patients were male and three patients were female. The mean age was 65.6 ± 7.0 years. Thirty-four patients were diagnosed clinically and radiologically, and seven of them were diagnosed pathologically. Twenty-nine patients were still alive. The general characteristics of the patients are shown in Table 1. The mean pulmonary arterial pressure

Table 1: The general characteristics of the patients

	n (%)
Gender	
Female	3 (7.3)
Male	38 (92.7)
Symptoms	
Cough	23 (56.1)
Dyspnea	25 (61.0)
Sputum	2 (4.9)
Clubbing	17 (41.5)
Family history	
(−)	39 (95.1)
(+)	2 (4.9)
Diagnosis	
Pathologically	7 (17.1)
Radiologically	34 (82.9)
Lung cancer	
(−)	40 (97.6)
(+)	1 (2.4)
OSAS	
(−)	32 (78.0)
(+)	9 (22.0)
GER	
(−)	24 (58.5)
(+)	17 (41.5)
Respiratory failure	
(−)	23 (56.1)
(+)	18 (43.9)
Smoking status	
Never	7 (17.1)
Ex-smoker	29 (70.7)
Smoker	5 (12.2)
Side effect	
(−)	16 (39.0)
(+)	25 (61.0)
The reason of changing treatment	
Photosensitivity	3 (7.3)
Elevation of liver function test	2 (4.9)
Progression	2 (4.9)
New drug	
Nintedanib	7 (17.1)
Attack	
(−)	40 (97.6)
(+)	1 (2.4)
Life status	
Alive	12 (29.3)
Exitus	29 (70.7)

GER: Gastroesophageal reflux, OSAS: Obstructive sleep apnea syndrome

and ejection fraction were 33.8 ± 10.4 and 57.6 ± 4.1, respectively.

During the following up, lung cancer developed in one patient, nine patients were diagnosed with obstructive sleep apnea syndrome, and IPF acute exacerbation developed in one patient. History of hospitalization was 1 time for 5 patients, 2 times for 2 patients, and 3 times for 1 patient. Totally 41 patients had been using antifibrotic treatment for at least 6 months, 39 patients for 1 year, 20 patients for 2 years, 12 patients for 3 years, 7 patients for 4 years, and 2 patients for 5.5 years.

The longest usage time of antifibrotic treatment was 5.5 years in 2 patients, and the minimum usage time was 6 months in 2 patients. Totally 34 patients were using pirfenidone and 7 patients were using nintedanib according to their last visit. Twenty-five patients had some side effects during treatment [Table 2]. Drug alteration was made due to liver dysfunction in two patients, due to photosensitivity in three patients, and due to the progression of the disease in two patients.

There was no significant difference between in all 6th-month, 1st-year, 2nd-year, 3rd-year, and 4th-year results of 6MWT compared to baseline (P > 0.05). There was a significant decrease in the DLCO results of the 6th month and 1st year compared to baseline (baseline: 63%, 6th month: 57%, and 1st year: 43%) (P = 0.048 and P = 0.002, respectively). There was no significant difference in DLCO results of the 2nd year, 3rd year, and 4th year compared to baseline (P > 0.05). A significant decrease was determined in the forced vital capacity (FVC) results of the 2nd year compared to baseline (68% and 59%, respectively) (P = 0.046). There was no significant difference in the FVC results of the 6th month, 1st year, 3rd year, and 4th year compared to baseline (P > 0.05) [Figure 1]. Any significant difference was demonstrated in desaturation rate of the 6th month, 1st year, 2nd year, 3rd year, and 4th year compared to baseline (P > 0.05). PFT, SPO_2, and 6MWT results in the 6th month and 1st year compared to the beginning of the IPF treatment in patients under antifibrotic treatment are shown in Tables 3 and 4.

Table 2: Main adverse events during the antifibrotic treatment

Adverse events	Pirfenidone (n=24), n (%)	Nintedanib (n=1)
Dyspepsia	10 (41.6)	-
Dizziness	2 (8.3)	-
Fatigue	2 (8.3)	-
Sexual dysfunction	2 (8.3)	-
Photosensitivity	6 (25)	-
İmpaired liver function	6 (25)	-
Diarrhea (%)	-	1 (14)

Table 3: Baseline and after 6-month treatment pulmonary function test results

Parameters	Baseline (mean±SD)	After the 6th month (under treatment)	P
FVC (pred.%)	66.2±15.7	64.1±15.5	0.344
FEV_1/FVC (pred.%)	85.1±6.8	84.2±5.9	0.725
DLCO (pred.%)	57.2±18.6	51.4±19.7	0.048
DLCO/VA (pred.%)	85.5±25.4	79.9±27.4	0.048
6MWT (m)	401.6±119.7	402.3±102.0	0.429
SPO_2 (at rest), %	92.3±6.9	93.0±3.9	0.592

P<0.05 was considered statistically significant. DLCO: Diffusing capacity of the lungs for carbon monoxide (hemoglobin corrected), 6MWT: 6-min walk test, FVC: Forced vital capacity, VA: Alveolar volume, SPO_2: O_2 saturation, SD: Standard deviation

Table 4: Baseline and after 1-year treatment pulmonary function test results

Parameters	Baseline (mean±SD)	After the 1st year (under treatment)	P
FVC (pred.%)	66.2±15.7	63.8±16.4	0.931
FEV_1/FVC (pred.%)	85.1±6.8	85.2±9.2	0.365
DLCO (pred.%)	57.2±18.6	43.8±18.3	0.002
DLCO/VA (pred.%)	85.5±25.4	76.2±22.2	0.049
6MWT (m)	401.6±119.7	364.3±224.6	0.933
SPO_2 (at rest), %	92.3±6.9	91.0±6.6	0.304

P<0.05 was considered statistically significant. DLCO: Diffusing capacity of the lungs for carbon monoxide (hemoglobin corrected), 6MWT: 6-min walk test, FVC: forced vital capacity, VA: Alveolar volume, SPO_2: O_2 saturation, SD: Standard deviation

Discussion

The approaches of the treatment in IPF have changed dramatically in the last decade. Historically, corticosteroids and immunosuppressive agents have represented the standard of care for patients with IPF based on the prevailing hypothesis that chronic inflammation may precede and progresses to pulmonary fibrosis. Correspondingly, recent clinical trials have evaluated the efficacy of compounds targeting the wound healing cascade and fibrogenesis. More recently, two compounds pleiotropic in their mechanisms of action pirfenidone and nintedanib have been approved for the treatment of IPF based on their ability to slow down the pace of functional decline and disease progression in Phase 3 clinical trials.[2,3] In this article, we summarized and discussed the results of antifibrotic treatment, having been used since 2013 in our clinic.

In this study, a vast majority of patients (85.3%) with IPF showed a stable FVC over a 6-month period of antifibrotic treatment. The rest of the patients (14.7%) were accepted as having progression of the disease defined as at least a 10% decline of FVC when compared to the basal value. The results of our real-life study were compatible with the results of CAPACITY,[4] ASCEND,[2] and INPULSIS[3] studies about the protective role of pirfenidone and nintedanib treatment, respectively, in terms of disease progression.

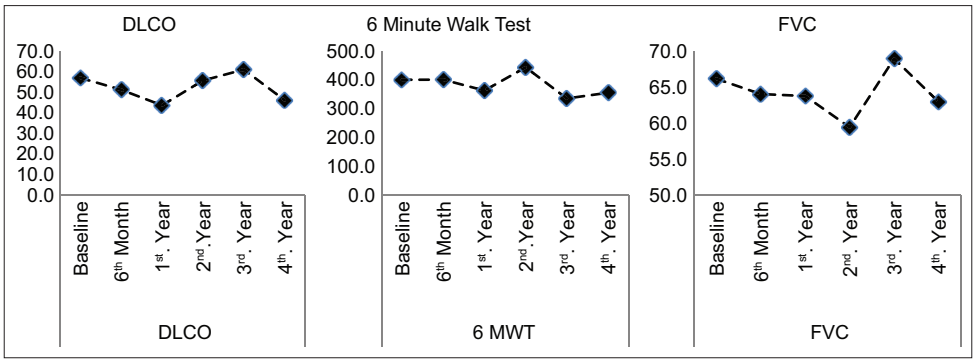

Figure 1: The evaluation of the functional status of ipf patients. DLCO: Diffusing capacity of the Lung for carbon monoxid, (hemoglobin corrected), 6MWT: 6 Minute Walk Test, FVC: Forced Vital Capacity

Dyspnea and cough are the early symptoms of the disease, whereas fatigue, lack of appetite, and weight loss are typically seen in advanced stages of the disease. Dyspnea is very insidious and progressive and usually in the form of exertional dyspnea. Cough is another common symptom that deteriorates the quality of life, present in up to 80% of patients with IPF, although the proportion of patients with a troublesome cough is likely to be less than this.[5] In our study, patients also presented with the most frequent complaints of dyspnea and cough. Fine basal "velcro-like" inspiratory crackles are characteristically heard in IPF (>90% cases) and clubbing often accompanies.[6,7]

The physical examination findings of our patients were consistent with the literature. IPF occurs primarily an age typically older than 60 years. It is mostly seen in elder patients beyond 60 years of age and appears to be limited to the lung. It is defined by the histopathologic and/or radiologic pattern of UIP. Patients with IPF who are younger than 50 years old are rare; such patients may subsequently manifest features of an underlying CTD that was subclinical at the time IPF was diagnosed[8] or may have familial IPF.[9] More men have been reported with IPF than women. The prevalence and incidence are higher in men than in women, and the majority of patients have a history of past cigarette smoking.[10] The mean age of the patients was 66 years at diagnosis, and 92.7% of the patients were male. Two patients with family history were under 60 years of age. 82.9% of the patients had a history of smoking.

GER occurs in a high proportion of patients with IPF, and chronic microaspiration secondary to GER is believed to play a role in the pathogenesis and progression of the disease.[11,12] GER was present in 41% of our patients. The most common side effects of pirfenidone are related to the skin (skin eruption: 26.2% and photosensitivity: 9.3%) and the gastrointestinal tract (16%–32%; dyspepsia, anorexia, nausea, vomiting, and diarrhea). Weakness, liver toxicity, and neurological symptoms such as headache and dizziness are the other side effects of pirfenidone.[13] We determined most frequently dyspepsia and photosensitivity due to pirfenidone. The other side effects detected in our patients were dizziness, fatigue, impaired liver enzymes, and sexual dysfunction, which are not in the literature. There was an increase in liver function tests three times or more than the upper limit of normal in 4% of our patients.[14] All liver function test disorders were improved by dose reduction or interruption of treatment. Elevations in Alanine transaminase (ALT) and/or Aspartate transaminase (AST) may require dose reduction or interruption of treatment. The liver function tests did not improve although the drug dose was reduced in 3 patients, so drug modification was performed for them.

Photosensitivity can be treated with drug dose reduction, topical therapies, and systemic steroid therapy. If there is no response, the drug should be discontinued or changed. We have changed the medications in 3 patients because of the photosensitivity findings that did not improve despite treatment. Taking the drugs during meals can alleviate gastrointestinal side effects.[15]

All patients were advised to take the drugs with meals, and proton-pump inhibitors except omeprazole were given to the patients who developed dyspepsia.

The side effects of nintedanib most frequently leading to discontinuation were diarrhea, nausea, vomiting, and elevated liver enzyme levels.[16] Diarrhea developed in 1 patient in our study. According to clinical trials, diarrhea leads to dose reduction in 11% of the patients and leads to discontinue the medication in 5% of the patients and it is treated with hydration and antidiarrheal drug (e.g., loperamide). It is recommended to reduce the drug to 100 mg twice daily in some cases.[17] We treated diarrhea with antidiarrheal medication in our study.

It has been reached as a result that pirfenidone, decelerates the decrease of FVC and the progression of the disease, increases the exercise tolerance, and prolongs the progression free survival (2). Pirfenidon licensed in our country since August 2016 and reimbursed since December 2016.[2] As in the retrospective real-life study of Hanta *et al*.,[18] pirfenidone also had tolerable and relatively acceptable side effects in our study too. It has been found that it reduces 1-year mortality by 48% and IPF-induced mortality by 68%.[4]

It was found that nintedanib, licensed in our country since 2017, reduced the annual decrease of FVC by 50% and the acute exacerbations by 68%; however, no significant effect of the drug on survival was shown.[3] It has been shown that it improves the quality of life and prevents acute exacerbations.[16] We have determined deceleration in decline of FVC, DLCO, and 6MWT in all patients using antifibrotic users. Hospitalization and frequency of attacks were detected significantly low.

During the follow-up of IPF patients, acute exacerbation occurs in 5%–10% of the patients, and those who received pirfenidone treatment were found to have less acute exacerbations than placebo.[19] Acute exacerbation is more frequent in IPF patients with functionally advanced disease, and nintedanib may decrease the risk of emerging an acute exacerbation in these patients.[20] Acute exacerbation was developed in one patient (0.2%) with IPF in our study similar to the literature.

Conclusion

Similar to the literature, we have observed that antifibrotic drugs decelerate the progression of the disease, reduce the risk of developing attacks, and are safer in terms of side effect profile than previous treatments as a result.

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Conflicts of interest
There are no conflicts of interest.

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