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Efficacy and tolerability of antifibrotic agents in idiopathic pulmonary fibrosis: An experience from Turkey

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Abstract:

INTRODUCTION: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease associated with poor prognosis. Antifibrotic drugs have come into use in the treatment of IPF, for which no effective therapeutic option existed until recently. This study makes an evaluation of IPF patients receiving pirfenidone or nintedanib as treatment.

MATERIALS AND METHODS: This retrospective study included IPF patients who received antifibrotic therapy in our outpatient clinic between 2017 and 2020. The demographics, clinical symptoms, spirometric results, modified Medical Research Council (mMRC) and Leicester Cough Questionnaire (LCQ) scores, drug-related side effects, and treatment responses (at 6 months) were recorded.

RESULTS: There were 52 patients (32:male-61.5% and 20:female-38.5%) with mean age of 70.65 ± 9.18. The most common presenting symptoms were dyspnea (86.5%) and cough (61.5%). The patients received pirfenidone (n = 31) and nintedanib (n = 21) therapies. The rate of side effects was 53.1%. At the 6-month control examination, 66% of the patients reported symptom relief. No significant difference was found in clinical symptoms, mMRC, respiratory parameters, or occurrence of side effects between the two treatment groups (P = 0.936, 0.393, 0.124, and 0.962, respectively). There was a stastistically significant improvement at LCQ score in patients treated with pirfenidone (P < 0.01). At the 6th month of the treatment process, there was a statistically significant improvement in the mMRC, LCQ scores, and forced vital capacity level (P < 0.01 all).

CONCLUSION: The outcomes of antifibrotic therapy in IPF are particularly promising in terms of relieving clinical symptoms and the preservation of lung capacity. IPF patients receiving pirfenidone as a treatment seems to have a significant improvement in cough-related health quality.

Keywords:

Evaluation of response, idiopathic pulmonary fibrosis, nintedanib, pirfenidone

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease that is associated with poor prognosis. Prognosis is poor particularly in the types of a disease characterized by rapid progression and acute exacerbations, with a 5-year survival rate of 20%–40%.[1]

IPF is characterized by a histopathological and radiological appearance that is consistent with usual interstitial pneumonia (UIP), particularly in patients older than 50 years.[2] The diagnosis is based on the exclusion of other possible causes and the demonstration

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of a UIP pattern. In patients exhibiting the clinical features of IPF, the presence of a typical UIP on a high-resolution computed tomography (HRCT) (reticular opacities that are more intense in the lower zones and peripheral, subpleural localizations, honeycombing, and the presence of traction bronchiectasis) and the absence of risk factors that lead to fibrosis (asbestos exposure, hypersensitivity pneumonia, and rheumatic diseases) are the diagnostic criteria.[3] The diagnostic importance of radiological and clinical features was emphasized in a report published by the American Thoracic Society in 2018.[4]

Although immunosuppressive drugs, antioxidants, and agents such as interferon gamma and etanercept are used from time–to-time in the treatment of IPF, these options have been circumvented due to the lack of sufficient efficacy, their extensive side-effect profile, and the frequency of infections and hospitalizations.[5] In recent years, antifibrotic drugs have come into use in the treatment of IPF, for which no effective therapeutic option has been discovered until recently. The preservation of lung function, a reduction in disease progression, improvement in the quality of life, and the favorable effects on survival can be expected from an early diagnosis of IPF and the institution of antifibrotic therapy.

The present study aims to evaluate the outcomes of patients with IPF who received antifibrotic therapy either with pirfenidone or nintedanib in our clinic.

Materials and Methods

The data of the patients with IPF who were placed on antifibrotic therapy upon a decision of a multidisciplinary council at İzmir Katip Çelebi University Atatürk Training and Research Hospital between 2017 and 2020 were retrieved from the hospital records. The patients' charts and medical histories recorded on the computer were reviewed retrospectively.

The demographic characteristics of the patients, clinical symptoms, pulmonary function test (PFT) results, drug-related side effects, and treatment responses (at 6 months) were recorded.

The presence of dyspnea, cough, and sputum were investigated at every visit. The modified Medical Research Council (mMRC) Dyspnea Scale was used to make an objective assessment of dyspnea.

The participants were provided with a Leicester Cough Questionnaire (LCQ) to assess cough-related life quality at the visits to our pulmonology clinic.[6] This questionnaire includes three subscales measuring physical, psychological, and social impacts of cough. The total score, which ranges from 0 to 21, is the sum of these three subscales. The results of the LCQ were also recorded. Kurhan *et al*. published the validity and reliability of the Turkish Version of LCQ.[7]

For the radiological examination, the HRCT reports recorded in the hospital's database were taken as the reference. The HRCT results of the patients were reviewed by the physicians taking a part in the present study independently from the issued report, and the accuracy of the HRCT reports was confirmed. An opinion from the department of radiodiagnostics was requested should suspicion arise regarding a particular patient.

The parameters of the pulmonary function test, including forced vital capacity (FVC), forced expiratory volume at 1 s (FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), and FEV1/FVC ratio were recorded. All spirometric procedures were carried out in the pulmonary function testing laboratory of our hospital and by the same nurse trained in pulmonary function testing.

Rheumatological markers are routinely tested in our clinic for patients who undergo investigations for interstitial lung disease. Patients with positive or suspected test results had a consultation with a rheumatologist. It was confirmed that rheumatological diseases were ruled by consultation with a rheumatologist in all IPF patients included in the present study.

Ethics committee approval for the study was obtained from the noninterventional Trials Ethics Committee of the İzmir Katip Çelebi University Atatürk Training and Research Hospital.

The study was performed in accordance with the Declaration of Helsinki's Good Clinical Practice guidelines.

Results

There were 52 patients; 32 male (61.5%) and 20 females (38.5%) with a mean age of 70.46 ± 8.92 in the study. Of the patients, 67.3% had at least one comorbid condition. The most common comorbidities were hypertension (34.8%) and coronary artery disease (21.7%). There were 25 nonsmokers (48.1%), 23 ex-smokers (44.2%), and 17 current smokers (7.7%) with IPF.

Cardinal presenting symptoms of the patients were dyspnea (86.5%) and cough (61.5%). Velcro-type crackles were present in 32 (61.5%) and clubbing in 5 (9.6%) patients at physical examinations. The demographic

data and characteristics of the patients are presented in Table 1.

The most common radiological findings at the time of diagnosis were reticular opacities (78%) and honeycombing (68%); 91.1% of the patients had peripheral involvement and 56.8% had lower lobe predominance. Of the patients who were diagnosed with IPF based on clinical and radiological findings, 80% had a definitive and 20% had a probable UIP pattern.

According to the results of the FVC levels, 36.2% of the patients had mild, 23.1% had moderate and 7.7% had a severe restrictive impairment. Nearly one-third of the participants had no restrictive lung diseases. DLCO was found decreased in 89.7% of the patients (lower than 80%) due to the carbon monoxide diffusion test. Mean respiratory parameters, MRC, and LCQ scores were in Table 1.

Forty-seven of 52 patients (90.4%) joined the visit at the 6th month of treatment. According to this visit, nearly two-thirds of the patients reported symptom relief (65.7% in cough and 51.2% in dyspnea). The pulmonary reserve (FVC) had been preserved in 68% of the patients.

IPF patients in the study received pirfenidone (n = 31, 59.6%) or nintedanib (n = 21, 40.4%) as pharmacological therapy. The rate of side effects was 53.1% (55.5% for nintedanib and 51.7% for pirfenidone). The most common side effect was nausea with pirfenidone therapy and diarrhea with nintedanib therapy [Figure 1]. Of the total, six patients required dose reduction, six required drug discontinuation, and four required drug change during their treatment process. The reasons for dose reduction, drug discontinuation, and drug change are presented in Table 2.

Table 1: Demographic data and characteristics of patients with idiopathic pulmonary fibrosis

Patient characteristics	*n* (%)/number or mean
Age (mean)	70.65±9.18
Gender, *n* (%)	
Male	32 (61.5)
Female	20 (39.5)
Symptoms, *n* (%)	
Shortness of breath	45 (86.5)
Cough	32 (61.5)
Physical examination findings, *n* (%)	
Rales < Velcro-type >	32 (61.5)
Clubbing	5 (9.6)
Presence of comorbidity, *n* (%)	35 (67.3)
mMRC dyspnea scale (mean)	1.34±0.76
FEV1 (%) (mean)	83.57±21.45
FVC (%) (mean)	74.61±18.45
FEV1/FVC (%) (mean)	84.30±10.08
DLCO (%) (mean)	52.13±16.57
LCQ total score (mean)	12.14±2.60

mMRC: Modified medical research council, FEV1: Forced expiratory volume at one second, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, LCQ: Leicester cough questionnaire

No significant difference was found in clinical symptoms, mMRC, respiratory parameters, or occurrence of side effects between the two treatment groups (P = 0.936, 0.393, 0.124, and 0.962, respectively). There was a statistically significant improvement at LCQ score in patients treated with pirfenidone (P < 0.01) [Table 3].

At the 6th month of the treatment process, there was a significant improvement in the mMRC, LCQ scores, and FVC levels (P < 0.01 all) [Table 4]. HRCT scans, which were performed in 17 patients at the 6th month, demonstrated progression of fibrosis in 23.5% of them. Radiological findings of IPF were stable in 76.5% of these patients.

Discussion

IPF often has a progressive and rapid disease course for which no curable therapy has been identified to date. As the 5-year survival rate is lower than that of many cancer types, slowing disease progression is an important criterion in achieving survival benefits. The present study reports on the outcomes of patients with IPF who were treated in our clinic with pirfenidone and nintedanib.

No significant difference was found in clinical symptoms, mMRC, or respiratory parameters between the two treatment groups in our study. There has been no head-to-head randomized and controlled trial comparing pirfenidone and nintedanib in literature. In a review comparing the two drugs, favorable effects on survival independent from progression, and reduction in hospitalization due to respiratory causes were observed in patients receiving pirfenidone, whereas a decrease in acute exacerbations and the favorable effects on survival were more predominant with nintedanib therapy.[8] The lack of any significant difference in terms of clinical symptoms and respiratory parameters between the

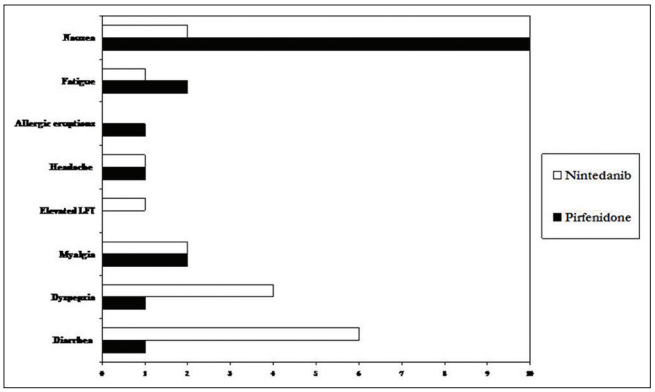

Figure 1: Side effects with pirfenidone and nintedanib therapy

Table 2: Conditions arising in patients with idiopathic pulmonary fibrosis and patient management

Condition	Patients management	Final decision
Headache	Dose reduction	Continuing nintedanib therapy at a lower dose
Allergic eruptions	Dose reduction	Continuing pirfenidone therapy at a lower dose
Diarrhea and abdominal pain	Dose reduction, symptomatic therapy (loperamide)	Continuing with optimum nintedanib dose after symptom relief
Headache, blurred vision, nausea, and vomiting	Dose reduction	Continuing pirfenidone therapy at a lower dose
Nausea and dyspepsia	Dose reduction and titration	Continuing with optimum pirfenidone dose after titration
Episodes under therapy	Drug discontinuation	No new therapy initiated due to poor general condition
Patient incompliance with the therapy	Drug discontinuation	Patient placed in follow-up without treatment
Recent kCO at 6 months meets reporting criteria	Drug discontinuation	Patient placed in follow-up without treatment
Persistent fatigue*	Drug change	Switching from pirfenidone to nintedanib
Nausea with nintedanib*	Dose reduction	Follow-up with low-dose nintedanib therapy
Unresponsiveness to therapy (pirfenidone)**	Drug change	Switching from pirfenidone to nintedanib
While under nintedanib*	Dose reduction	Drug discontinuation due to persisting elevation in LFTs
Elevated LFTs**		

*,**Complications occurring in the same patient. kCO: CO transfer coefficient, LFT: Liver function test

Table 3: Comparison of two treatment agents of idiopathic pulmonary fibrosis

Parameters	Pirfenidone arm (*n*=29)	Nintedanib arm (*n*=18)	*P*
Improvement in pulmonary symptoms (yes/no)	19/10	12/6	0.936
Preserved pulmonary reserves < FVC > (yes/no)	8/8	6/2	0.124
Improvement in MRC score (yes/no)	12/14	9/6	0.393
Improvement in LCQ score (yes/no)	22/4	4/9	<0.01*
Presence of side effects (yes/no)	15/14	10/8	0.962

*Statistically significant. FVC: Forced vital capacity, mMRC: Modified medical research council, LCQ: Leicester cough questionnaire

Table 4: Parameters before and at 6 months after therapy

Parameters	Mean (SD)		*P*
	Pretreatment	Posttreatment	
FVC (%)	74.61 (18.45)	77.61 (22.32)	<0.01*
DLCO (%)	52.13 (16.57)	49.17 (14.95)	0.063
mMRC score	1. 34 (0.76)	0.96 (0.81)	<0.01*
LCQ score	12.14 (2.60)	12.57 (3.52)	<0.01*

*Statistically significant. FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, mMRC: Modified medical research council, LCQ: Leicester cough questionnaire, SD: Standard deviation

two drugs in our study may indicate that the drugs are comparable in terms of efficacy.

IPF patients receiving pirfenidone as treatment had a significant improvement in their total LCQ score when compared to the ones in the nintedanib arm according to our results. LCQ is one of the most widely used cough-specific health status questionnaires for patients having chronic cough.[6] There are only a few studies assessing the effects of antifibrotic agents on cough-related quality of life. Holtze *et al*. revealed that no significant difference between these two groups about improvement in LCQ.[9] van Manen *et al*. had two studies about this patient. According to one, pirfenidone reduces objective 24-h cough counts and improves subjective measures of cough in IPF patients.[10] The other study revealed no effect of nintedanib on cough and related quality of life.[11] Our results support the idea that pirfenidone is superior to nintedanib in cough-related quality of life.

We demonstrated no significant difference in the rate of side effects in groups receiving pirfenidone or nintedanib. Our results also revealed that there was a more frequent occurrence of nausea with pirfenidone therapy and diarrhea with nintedanib therapy. Barratt *et al*. specified that nausea, gastrointestinal side effects, and photosensitivity are predominant side effects of pirfenidone therapy, whereas diarrhea is more commonly observed with nintedanib therapy.[12] It shows that our results about the side effects of these two drugs are similar to other studies. Besides, the occurrence of treatment-related side effects in more than half of the patients in the present study indicates a need for close and careful patient follow-up.

Reducing the frequency of symptoms is another target in IPF treatment. Dyspnea and cough are the two cardinal symptoms seen in patients with IPF.[13] Cough in IPF is one of the most important and restrictive symptoms and is an independent indicator of disease progression.[10] Dyspnea is the most common, and for the majority of IPF patients, the most debilitating symptom.[13] The present study revealed that approximately two-thirds of IPF patients reported symptom relief at the 6-month control visit. In addition, as an objective parameter, the mean mMRC score significantly decreased compared to the baseline mean before therapy. These results indicate the efficacy of antifibrotic agents in IPF treatment.

The study data revealed that lung reserves were preserved in approximately 60% of the patients at the end of 6 months. Pharmacological treatment of IPF, especially including pirfenidone or nintedanib seems to be critical to preserving patients' lung function.[14] Previous studies have also shown a significant decrease in FVC decline with antifibrotic agents in IPF patients.[15] As in our study, the lack of any significant deterioration in respiratory parameters over a 6-month period indicate that pulmonary reserves have been preserved with antifibrotic therapy.

In the follow-up of the patients, the drug dose was reduced or the drug was changed in some patients. It is known that the drug dose can be reduced to the levels as to maintain drug efficacy should side effects occur, or if the patient proves to be unable to tolerate the recommended doses. Studies have shown that dose arrangement allows more patients to continue and fewer patients to discontinue their therapies.[16] Switching between pirfenidone and nintedanib may also be appropriate if drug-related side effects occur, and this allows taking the chance of having antifibrotic efficacy of the other drug.[17]

This study has some limitations. Primarily, the small sample size in the study led to very few patients being allocated to the subgroups for subgroup analysis. Another limitation is that only 6-month evaluations of the patients were included in the study. A study involving at least a 1-year follow-up period would produce more accurate results and would lead to a more refined evaluation of the patient follow-ups and treatment outcomes. Besides, as it is a retrospective study, there are some lacks of some parameters at the 6th-month visit. There is a need for prospective, randomized, and controlled studies involving larger numbers of patients in each treatment arm to make an ideal comparison.

Previous studies and recent consensus reports have increased the popularity of the use of antifibrotic drugs in the treatment of IPF. There is a lack of data in the limited number of studies conducted in Turkey, and so data on the outcomes of cases treated with antifibrotic agents would be significant in identifying the success of such drugs in patients with IPF in our country.

Conclusion

The outcomes of antifibrotic therapy in IPF are particularly promising in terms of relieving clinical symptoms and the preservation of lung capacity. IPF patients receiving pirfenidone as a treatment seems to have a significant improvement in cough-related health quality.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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