DOI: 10.4149/BLL_2022_105

Bratisl Med J 2022; 123 (9)
653 – 658

CLINICAL STUDY

When and how important is anti-fibrotic therapy in the post-COVID-19 period?

KERGET Bugra[1], CIL Gizem[1], ARAZ Omer[1], ALPER Fatih[2], AKGUN Metin[1]

Department of Pulmonary Diseases, Ataturk University School of Medicine, Yakutiye, Erzurum, Turkey. **bjkerget1903@gmail.com**

ABSTRACT

PURPOSE: In addition to the highly variable clinical presentation of acute COVID-19 infection, it can also cause various post-acute signs and symptoms. In our study, we aimed to examine the efficacy of anti-fibrotic therapy in patients who developed pulmonary fibrosis after COVID-19.

METHODS: In total, 15 patients who applied to the Post-Covid Outpatient Clinic between May 2021 and August 2021 and were diagnosed with COVID-19 pneumonia, and whose cough, dyspnea, exertional dyspnea and low saturation continued to be present at least 12 weeks after the diagnosis, were included in the study. Off-label pirfenidone treatment was started according to the radiological findings, pulmonary function test parameters (PFT) and 6-minute walking test (6MWT) results. The patients were followed up for 12 weeks.

RESULTS: While all of the FVC, FVC%, FEV1, FEV1%, DLCO%, DLCO/VA%, 6MWT, and room air saturation levels were observed to increase statistically significantly in the patients at the 12th week, it was determined that there was a statistically significant decrease in the pulse level in room air (p = 0.01, 0.01, 0.01, 0.01, 0.004, 0.001, 0.002, 0.001, and 0.002, respectively). In regression analysis based on radiological scoring, it was observed that the DLCO and room air saturation levels at the 12th week of the treatment were statistically significantly higher in patients with lower scores at the beginning (p = 0.04, 0.03). In addition, it was observed that anti-fibrotic treatment, which was started in the earliest period, i.e., 12 weeks after the diagnosis, resulted in an improvement in radiological, PFT and 6MWT parameters.

CONCLUSION: Patients who still had dyspnea and low saturation 12 weeks after the diagnosis, defined as chronic COVID-19, should be evaluated for anti-fibrotic therapy after the necessary radiological and PFT evaluation. Early treatment commencement brings about, besides radiological improvement, a better response obtained in PFT and 6MWT *(Tab. 2, Fig. 2, Ref. 21)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, pirfenidone, radiological score.

Introduction

At the end of 2019, a highly infectious infection began to spread rapidly around the world. It was soon discovered that the disease was caused by a new coronavirus called SARS-CoV-2, hence the name of the disease was abbreviated to COVID-19 (COVID). The global medical community has directed its efforts not only to find effective treatments against the deadly pathogen, but also to combat the accompanying complications.

The most common respiratory symptoms of COVID were a significant reduction in diffusing capacity (DLCO) of the lungs and associated pulmonary interstitial damage. One year after moderate COVID-19, the incidence of impaired DLCO and permanent lung injury still exceeds 30 %, with one-third of patients presenting with severe DLCO impairment and fibrotic lung injury (1). Permanent respiratory complications can cause morbidity, loss of work force, and even death due to progression of lung fibrosis in patients who go through the disease (2). The incidence of COVID-induced pulmonary fibrosis can be estimated based on a 15-year observational study of post-SARS lung pathology (3).

Most SARS patients with fibrotic lung injury recovered within the first year and remained healthy thereafter; however, a significant fibrosis progression was found within 5–10 years in 20 % of cases. Based on these data, the incidence rate of post-COVID pulmonary fibrosis can be estimated to be 2–6 % after moderate disease (4). It is even worse that fibrosis may be one of the major long-term complications of COVID in asymptomatic individuals (5). Despite all the efforts of the global medical community, there is no current treatment for COVID-induced pulmonary fibrosis.

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a new anti-fibrotic agent with a low side-effect profile. Pirfenidone can inhibit apoptosis, downregulate the expression of ACE receptors, reduce inflammation by various mechanisms, and ameliorate oxidative stress (6). Pirfenidone is approved for the treatment of idiopathic pulmonary fibrosis (IPF) in patients with mild to moderate disease. In the long-term follow-up of IPF patients, it was

[1]Department of Pulmonary Diseases, Ataturk University School of Medicine, Yakutiye, Erzurum, Turkey, and [2]Department of Radiology, Ataturk University School of Medicine, Yakutiye, Erzurum, Turkey

Address for correspondence: Bugra KERGET, MD, Yakutiye Medical Research Center, Chest Disease Department, 25240, Yakutiye, Erzurum, Turkey
Phone: +904423447446, Fax: +904423446528

observed that pirfenidone also slowed the progression of profibrotic foci (7, 8).

In our study, we aimed to observe the effectiveness of pirfenidone treatment in pulmonary function test (PFT), 6-minute walk test (6MWT), and clinical and radiological improvement in patients with persistent respiratory symptoms after 12 weeks, defined as chronic COVID-19, and in whom progression to fibrosis was observed in thorax computed tomography.

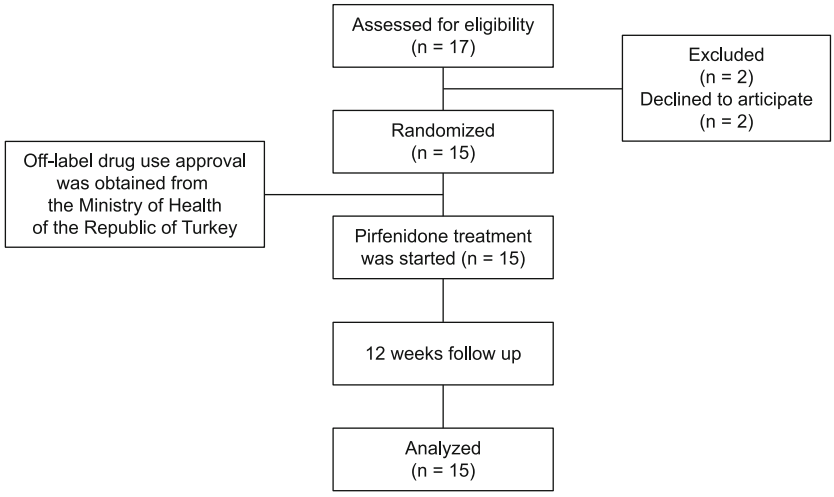

Fig. 1. CONSORT diagram.

Material and method

Our research is a prospective study conducted in Atatürk University Medical Faculty Hospital Chest Diseases Post-Covid polyclinic. In this study, 15 patients who applied to the Atatürk University Medical Faculty Hospital Post-Covid Outpatient Clinic between May 2021 and August 2021 and were diagnosed with COVID-19 pneumonia and whose cough, dyspnea, exertional dyspnea and low saturation continued to be present at least 12 weeks after the diagnosis were included (Fig. 1). The aim of the study was to carry out clinical laboratory and radiological follow-ups of these patients for three months and to evaluate the results. In order to conduct the study, an approval was obtained from the Ethics Committee of Erzurum Atatürk University Faculty of Medicine. Before starting the study, the patients who were to participate in the study were informed about the purpose, method of the study and time they were asked to allocate for the research. It was explained to the patients that participating in the study does not carry any risk, the participation is completely voluntary, and that they could leave the study at any time.

Inclusion criteria

In our study, patients who were diagnosed with COVID-19 by real-time PCR from nasopharyngeal swab at least three months ago, and whose chronic COVID-19 symptoms continued to be present were included in the study under inclusion criteria as follows:

1. Patients older than 18 years of age
2. Patients who developed fibrosis secondary to COVID-19 with radiological sampling
3. Patients with or without comorbid conditions
4. Patients who did not need intubation and mechanical ventilation
5. Patients who agreed to come for follow-ups within the 12-week period declared in our study

Exclusion criteria

The conditions excluded from the study were as follows:

1. Conditions that may contraindicate the application of pulmonary function test (recent MI, pulmonary embolism, cerebral aneurysm, active hemoptysis, pneumothorax, nausea, vomiting, and recent thoracic, abdominal and eye surgery) were determined in patients before the pulmonary function test and these patients were excluded from the study.
2. Mentally retarded or uncooperative patients
3. Patients with previously known or detected lung pathology during follow-up

PFT application

The personnel who were to perform the pulmonary function test were taken to the negative pressure room with protective equipment to prevent possible contamination. Age, height and weight of patients were measured before the pulmonary function test. Before the test, attention was paid to the fact that prior to the pulmonary function test, the patients had not been smoking for 24 hours, had not been drinking alcohol for 4 hours, had not done hard exercise for 30 minutes, were not wearing clothes restricting the chest and abdomen movements, and had not eaten heavy meals for 2 hours. BTPS correction was performed according to room air and barometric pressure. The movement to be performed was explained to the patient by a technician. The patient underwent 3 acceptable spirograms. Tests complying with the pulmonary function test reproducibility and acceptability criteria published by ATS/ERS in 2019 were included in the study (9). The lower limit of normal parameters determined for the healthy population are presented by calculating on a spirometry device in accordance with the criteria in this declaration. Spirometry was performed by the same technician with Plusmed MIR SpiroLab III device.

Radiological assessment

All patients underwent contrast-enhanced CT scans of the chest on a second-generation Somatom Definition Flash 256-slice dual-source multidetector CT scanner (Siemens Healthcare, Forchheim, Germany). CT examinations were performed with breath holding during deep inspiration. All images were transferred to a commercial workstation (Singo via. Workstation, Siemens, Erlangen, Germany). The images were assessed by a radiologist who

was blinded to the patients' identities. The reader had 18 years of experience in thoracic radiology.

Whichever of the following radiological appearances exceeded 50% in the evaluated lobe, its score was taken as the basis.

Consolidation or ground glass dominance: 1 point

Reticulation and intralobular septal thickening: 2 points

Linear opacity, traction bronchiectasis: 3 points

Band formation: 4 points

Fibrosis in a degree to cause volume loss: 5 points

The 5 lobes of the bilateral lung were evaluated separately. A new scoring method that had never been used by the reader before was used for scoring. According to this scoring method, a total score between 5 and 25 points was achieved.

Medical treatment applied during follow-ups

All the patients who applied to our outpatient clinic due to chronic COVID-19 used oxygen concentrators at home due to low saturation. It was observed that all patients continued methylprednisolone treatment for at least 8 weeks after discharge. PFT, 6MWT and high-resolution computed tomography (HRCT) examinations were performed at the time of admission. The consent for initiating the anti-fibrotic therapy (pirfenidone) was obtained from patients with a restrictive pattern in PFT, DLCO level < 80 %, and profibrotic areas in HRCT as well as > 5 % fibrosis. The current analyses and tomography images of the patients were sent to the Ministry of Health of the Republic of Turkey for off-label drug application. It was planned to approve the drug application for a period of 3 months for all patients and to extend it according to the clinical course. The patients were started on pirfenidone at 600 mg in the first week, 1,200 mg in the second week, and 1,800 mg starting from the third week. Steroid treatments of the patients receiving methylprednisolone treatment were tapered off within 2 weeks.

Statistical analysis

Analyses were performed using IBM SPSS, version 20.0 software (IBM Corp, Armonk, NY). Data were presented as mean, standard deviation, number, and percentage. Shapiro-Wilk test and Kolmogorov-Smirnov test were used to determine whether continuous variables were normally distributed. Continuous variables were compared between more than two dependent groups using analysis of variance Wilcoxon test if normally distributed. Post-hoc tests after ANOVA were performed using Tukey's test when variances were homogeneous and Tamhane's T2 test when variances were not homogeneous. Post-hoc analysis after Kruskal-Wallis test was performed using the Kruskal-Wallis one-way ANOVA (k samples) test. Relationships between two quantitative variables were examined using Pearson correlation analysis if normally distributed and Spearman correlation analysis if non-normally distributed. p values < 0.05 were considered statistically significant.

Results

The mean age of the patients included in our study was 62.6 ± 8.1. Nine of the patients (60 %) were female. While the mean age of female patients was 62.6 ± 8.1, it was 62.6 ± 8.9 for males. No statistically significant difference was observed in the age distribution of the patients by gender.

Tab. 1. Comparison of PFT, 6MWT, room air saturation and pulse levels of the patients before and at the 12th week of treatment.

	FVC (lt)	FVC%	FEV1 (lt)	FEV1%	DLCO%	DLCO/VA%	6MWT	SO_2	Pulse
Before treatment Mean±SD	1.84±0.5	67.2±13.9	1.6±0.5	68.9±13.2	53.3±10.1	60.9±9.1	210.1±110.4	77.8±10.1	111.4±9.9
At 12th week of treatment Mean±SD	2.04±0.8	74.4±19.6	1.7±0.7	76.3±18.6	62.2±14.3	69.4±12.5	239.9±121.4	83.3±10.5	98.4±12.3
P	0.01	0.01	0.01	0.01	0.004	0.001	0.002	0.001	0.002

FVC – forced vital capacity, FEV1 – forced expiratory volume in 1 second, DLCO/VA – diffusing capacity divided by the alveolar volume, 6MWT – 6-minute walking test. SO_2 – fingertip saturation in room air

Tab. 2. Linear regression analysis of patients' 12-week PFT, 6MWT and room air saturation and pulse values according to baseline radiological score.

Coefficients[a]							
	Unstandardized coefficients		Standardized coefficients	t	p	95,0% Confidence Interval for B	
	B	std. error	Beta			Lower Bound	Upper Bound
(Constant)	17.111	.914		18,718	0,000	14,761	19,461
ΔFVC	-6.014	7.059	-.745	-.852	0.433	-24.159	12.132
ΔFVC%	.245	.235	1.179	1.045	0.344	-.358	.849
ΔFEV1	-17.472	8.438	-1.834	-2.071	0.093	-39.163	4.219
ΔFEV1%	.423	.221	1.858	1.917	0.113	-.144	.991
ΔDLCO%	-.553	.192	-2.030	-2.881	0.035	-1.046	-.059
ΔDLCO/VA%	.107	.190	.274	.563	0.597	-.381	.596
Δ6MWT	.078	.050	.757	1.566	0.178	-.050	.206
ΔSO2	-.674	.232	-1.147	-2.900	0.034	-1.272	-.077
ΔPulse	-.160	.114	-.655	-1.404	0.219	-.452	.133

a. Dependent variable – radiological score

The PFT, 6MWT, room air saturation and heart rate levels of the patients at the beginning of the treatment and at the 12th week after the treatment are shown in Table 1. According to this, while all parameters of FVC, FVC%, FEV1, FEV1%, DLCO%, DLCO/VA%, 6MWT, and room air saturation were observed to be increased statistically significantly in the patients at the 12th week, it was determined that there was a statistically significant decrease in the pulse level in room air (p = 0.01, 0.01, 0.01, 0.01, 0.004, 0.001, 0.002, 0.001, 0.002, respectively). Pre-treatment radiological scores of the patients were 14.1 ± 2.8. The radiological scores at the 12th week of the treatment were 9 ± 4.6. It was observed that there was a statistically significant difference between the radiological scores of the patients at the beginning and at the 12th week of the treatment (p = 0.001).

Table 2 shows the logistic regression analyses between PFT parameters, 6MWT, saturation in room air and heart rate in room air according to the radiological scores of the patients at the beginning of the treatment. Accordingly, it was observed that DLCO and room air saturation levels at the 12th week of the treatment were statistically significantly higher in patients with lower radiological scores at the beginning (p = 0.04, 0.03).

In the correlation analysis of the radiological scoring at the beginning and at the 12th week of the treatment as well as of changes in the saturation and pulse levels in PFT, 6MWT and room air; it was observed that FVC%, DLCO%, DLCO/VA%, and 6MWT parameters increased in positive correlation with the increase in radiological improvement (r = 0.52, p = 0.05, r = 0.884, p = 0.01, r = 0.6, p = 0.05, r = 0.675, p = 0.05, respectively) (Fig. 2).

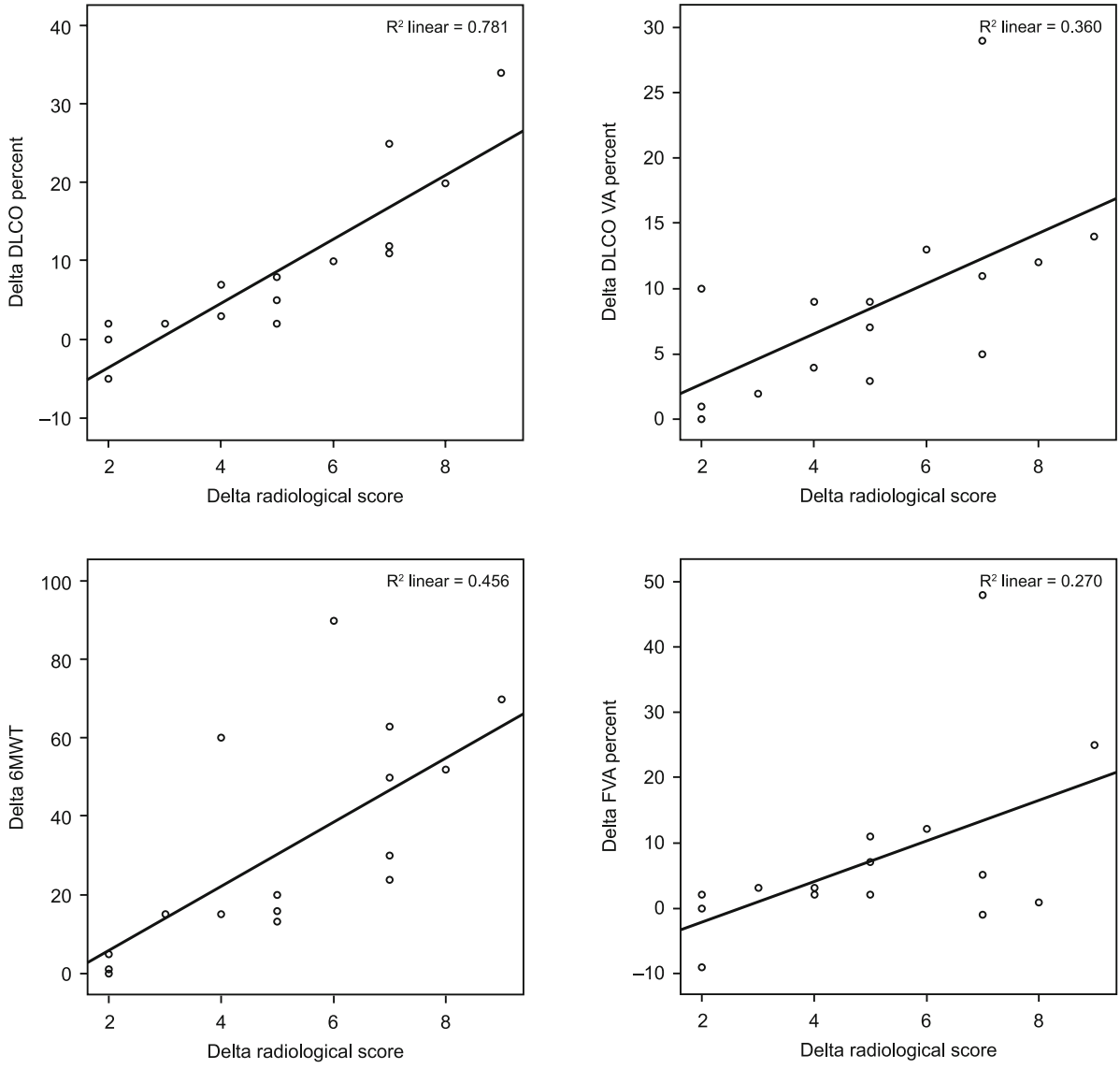

Fig. 2. Correlation analysis between the radiological score, which changed during the 12-week period with treatment; PFT and 6MWT.

The time from the diagnosis of COVID-19 pneumonia to the initiation of our treatment was 4.3 ± 1.2 months. In the correlation analysis performed between time and change in PFT, 6MWT and radiological score, it was observed that there was a statistically significant negative correlation between the change in DLCO, 6MWT and radiological score (r= -0.649, p= 0.01, r= -0.75, p= 0.01, r= -0.846, p= 0.01).

Discussion

In our study, it was observed that patients who were followed up with pirfenidone, antifibrotic agent, for 12 weeks had an increase in both PFT parameters and 6MWT and saturation levels. It was observed that this increase was at a better level in the patient group with low radiological scores as compared to HRCT taken at the beginning of the treatment. In addition, it was observed that the change in radiological score for12 weeks and the increase in PFT, 6MWT and room air saturation level increased in correlation. In addition, PFT, 6MWT and radiological improvement were observed to decrease as the time got longer at the start of treatment.

Fibrosis is the end result of almost all chronic inflammatory diseases (heart, liver, lungs and kidneys are no exception) (10). In response to tissue injury, myofibroblasts from multiple sources (resident fibroblasts, mesenchymal cells, circulating fibroblasts, and other cell types) can initiate wound healing by remodeling the extracellular environment to restore tissue integrity and support the replacement of parenchymal cells. Usually, this pro-fibrosis process is closed once the tissue has healed. However, repeated damage and repair (in patients with severe COVID-19) will lead to instability of this process and result in excessive pathological accumulation of extracellular matrix (ECM) protein. Down-regulation of myofibroblast activity in this region causes immune cells, primarily macrophages, to come to the environment and the chronic inflammatory process is activated. In this cellular environment, massive proinflammatory and profibrotic cytokines are released and they activate fibrosis-related pathways. These pathways mainly include the TGF-β signaling pathway, the WNT signaling pathway, and the YAP/TAZ signaling pathway (11).

While COVID-19 infection manifests itself with a mild to moderate clinical course in most patients, it may show a more aggressive course in some patients. This aggressive course is manifested by macrophage activation syndrome and acute respiratory distress in COVID-19 patients. During the cytokine storm, IL-6, TNF-alpha, TGF-beta, PDGF and VEGF, which are released at an intense level, cause intense fibroblast and myofibroblast activity in the extracellular matrix (12–14). This process, which is beneficial for tissue repair in the initial period, may result in fibrosis in the lung parenchyma after intense cytokine discharge and cumulative accumulation. Systemic corticosteroid treatments and anti-cytokine treatments administered to prevent this cytokine discharge in the acute period have yielded successful results. However, in the follow-up of some patients, it was observed that this process continued increasingly despite the systemic steroid treatment given as maintenance (15, 16). The condition with symptoms and signs of COVID-19 persisting for more than 12 weeks is defined as chronic COVID-19. In the evaluations performed, diffusion restriction, desaturation and insufficient effort capacity were observed in the PFTs of these patients (2, 17).

Pirfenidone is a new type of pyridone with a broad-spectrum of anti-inflammatory and anti-fibrotic effects. The mechanism of action of pirfenidone is not fully clear. The results show that pirfenidone can reduce the accumulation of inflammatory cells, proliferation of fibroblasts and deposition of ECM (18, 19). Pirfenidone plays a role in the anti-inflammatory effect by suppressing the production of IL-6, TNF-alpha, PDGF and TGF-beta. The decrease in the synthesis of these cytokines also prevents the proliferation of fibroblasts and myofibroblasts in the extracellular matrix and reduces the progression of pulmonary fibrosis (20). This agent, which was first used to prevent idiopathic pulmonary fibrosis progression, has been brought to attention as to whether it can be used in the treatment of COVID-19, with the observation that the same process as that in IPF causes pulmonary fibrosis. However, after pirfenidone use, anti-inflammatory response can be clearly observed within 4 weeks at the earliest (21). Therefore, its use for acute effects in patients with cytokine storm due to COVID-19 does not seem very appropriate for now.

In our study, it was determined that PFT, 6MWT and saturation levels increased in the 12th week of treatment as compared to the level before the start of pirfenidone treatment. In addition, it was observed that the radiological score also regressed with the treatment. In the regression analysis, it was determined that DLCO and saturation levels were increased more in patients with low radiological scores. It was observed that profibrotic radiological findings were more common in patients who did not respond adequately to systemic steroid treatment at the 12th week, which is the beginning of the chronic COVID-19 period. When this situation is evaluated together with the results we found in the follow-ups, it was shown that the sooner the anti-fibrotic treatment was started after the 12th week, the more effective was the response. With the advancing periods, the progression of profibrotic radiological findings towards the fibrotic period caused a decrease in the effectiveness of the treatment. In the correlation analysis of PFT, the 6MWT and saturation level of the 12-week radiological score change with the treatment, while the best correlation was observed with DLCO and 6MWT. It can be evaluated that this situation is related to the decrease in extracellular matrix components that cause diffusion restriction. The increased diffusion rate may have caused an increase in 6MWT, which is an objective indicator of the effort in patients.

In our study, anti-fibrotic treatment was started 12 weeks (at the earliest) after the diagnosis in all patients, and our most important limitation was that we could not show how an earlier anti-fibrotic treatment could have affect the patients. However, due to the high cost of anti-fibrotic treatment, the development of fibrosis > 5 % despite systemic steroids was required for the admission of off-label applications by our ministry. This situation limited our ability to predict the results of treatment in earlier periods.

In conclusion, all patients presenting with dyspnea in the chronic COVID-19 period should be evaluated for anti-fibrotic

therapy. In patients whose dyspnea complaint did not regress despite long-term steroid therapy, steroid-induced comorbidities and atrophy arisen firstly in the extremities and respiratory muscles can lead to a vicious circle. For this reason, in accordance with the criteria determined by our ministry, anti-fibrotic treatment that is started early in patients with fibrosis > 5 % despite anti-inflammatory treatment may provide positive results in both in PFTs and quality of life of individuals.

References

1. Bazdyrev E, Rusina P, Panova M, Novikov F, Grishagin I, Nebolsin V. Lung Fibrosis after COVID-19: treatment prospects. Pharmaceuticals 2021; 14 (8): 807.

2. Kerget B, Çelik E, Kerget F, Aksakal A, Uçar EY, Araz Ö et al. Evaluation of 3-month follow-up of patients with post-acute COVID-19 syndrome. J Med Virol 2022.

3. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nature Rev Microbiol 2009; 7 (6): 439–450.

4. Rai DK, Sharma P, Kumar R. Post covid 19 pulmonary fibrosis. Is it real threat? Indian J Tuberculosis 2021; 68 (3): 330–333.

5. Ambardar SR, Hightower SL, Huprikar NA, Chung KK, Singhal A, Collen JF. Post-COVID-19 pulmonary fibrosis: novel sequelae of the current pandemic. J Clin Med 2021; 10 (11): 2452.

6. Seifirad S. Pirfenidone: A novel hypothetical treatment for COVID-19. Med Hypotheses 2020; 144: 110005.

7. Margaritopoulos GA, Trachalaki A, Wells AU, Vasarmidi E, Bibaki E, Papastratigakis G et al. Pirfenidone improves survival in IPF: results from a real-life study. BMC Pulm Med 2018; 18 (1): 1–7.

8. Zurkova M, Kriegova E, Kolek V, Lostakova V, Sterclova M, Bartos V et al. Effect of pirfenidone on lung function decline and survival: 5-yr experience from a real-life IPF cohort from the Czech EMPIRE registry. Respir Res 2019; 20 (1): 1–11.

9. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Amer J Respir Crit Care Med 2019; 200 (8): e70–e88.

10. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nature Med 2012; 18 (7): 1028–1040.

11. Piersma B, Bank RA, Boersema M. Signaling in fibrosis: TGF-β, WNT, and YAP/TAZ converge. Frontiers Med 2015; 2: 59.

12. Kerget B, Kerget F, Koçak AO, Kızıltunç A, Araz Ö, Uçar EY et al. Are serum interleukin 6 and surfactant protein D levels associated with the clinical course of COVID-19? Lung 2020; 198 (5): 777–784.

13. Kong Y, Han J, Wu X, Zeng H, Liu J, Zhang H. VEGF-D: a novel biomarker for detection of COVID-19 progression. Crit Care 2020; 24 (1): 1–4.

14. Chen W. A potential treatment of COVID-19 with TGF-β blockade. Internat J Biol Sci 2020; 16 (11): 1954.

15. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol 2021; 93 (1): 250–256.

16. Udwadia ZF, Pokhariyal PK, Tripathi AKR, Kohli A. Fibrotic interstitial lung disease occurring as sequelae of COVID-19 pneumonia despite concomitant steroids. Lung India: Official Organ of Indian Chest Society 2021; 38 (Suppl 1): S61.

17. Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. J Med Virol 2021.

18. Selvaggio AS, Noble PW. Pirfenidone initiates a new era in the treatment of idiopathic pulmonary fibrosis. Ann Rev Med 2016; 67: 487–495.

19. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. New Engl J Med 2018; 378 (19): 1811–1823.

20. Richeldi L, Du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New Engl J Med 2014; 370 (22): 2071–2082.

21. van Manen MJ, Birring SS, Vancheri C, Vindigni V, Renzoni E, Russell AM et al. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. Eur Resp J 2017; 50 (4).

Received March 22, 2022.
Accepted April 21, 2022.