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The clinical, functional, and radiological effect of long-term used immunosuppressive therapy for post-COVID-19 interstitial lung disease

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Abstract. *Background and aim:* Persistent interstitial lung disease (ILD) after COVID-19 infection can lead to severe loss of respiratory function and a decrease in the quality of life. There is no consensus regarding the treatment of post-COVID-19-ILD. This study aims to investigate the effectiveness of immunosuppressive treatment for this group of patients. *Methods:* This retrospective observational study included patients diagnosed with post-COVID-19-ILD from 2021 to 2022. Patients who had pulmonary symptoms, required prolonged oxygen therapy, and/or had restrictive pulmonary function test (PFT) and/or DLCO <80%, with diffuse parenchymal involvement on high-resolution computed tomography (HRCT), were given immunosuppressive treatment with methylprednisolone and/or mycophenolate mofetil (MMF) and followed up for 6 months. *Results:* Among the 48 patients, 35 were treated. Two patients were excluded due to discontinued treatment and passed away before the study period ended. Of 33 cases, 21 (66.6%) were treated with methylprednisolone, 11 (33%) with methylprednisolone + MMF, and 1 (0.4%) with MMF alone. Comparing baseline and 6th-month data revealed significant improvement in mMRC score, saturation (SpO2), FVC, FVC%, FEV%, and DLCO% values ($p<0.005$). While regression was observed in all radiologic findings, regression in ground glass and reticulation was statistically significant ($p<0.005$). When the 1st and 6th-month data were compared, a significant increase was observed in SpO2 and DLCO% values ($p=0.016$) and there was a significant regression in reticulation radiologically ($p=0.01$). *Conclusions:* Long-term immunosuppressive therapy may be preferred in proper cases of post-COVID-19-ILD as an effective and safe treatment option that improves the quality of life, respiratory parameters, and radiologic findings.

Key words: immunosuppressive therapy, interstitial lung diseases, post-COVID-19

Introduction

While COVID-19 infection causes asymptomatic or mild disease in the majority of the population, it has resulted in severe infection or acute respiratory distress syndrome (ARDS) in some individuals requiring hospitalization in the ward and/or intensive care unit (1). Various studies have shown that many patients have prolonged symptoms and signs of lung involvement after COVID-19 infection (2–4). Post-COVID-19 symptoms can be observed in 4.7%-80% of patients and have been shown to persist even 9 months after infection (5). According to the duration of symptoms, this condition is classified as potentially infection-related-symptoms

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(when symptoms persist for 4-5 weeks), acute post-COVID symptoms (when symptoms persist for 5-12 weeks), long post-COVID symptoms (when symptoms persist for 12-24 weeks), and persistent post-COVID symptoms (when symptoms persist for more than 24 weeks) (6).

Interstitial involvement is a contributing factor to the persistence of symptoms in the post-COVID-19 period. In the study by Lerum et al., one-fourth of the patients had persistent radiological findings three months after COVID-19 hospitalization and intensive care unit (ICU) admission. (7). Touman et al. revealed that 50% of patients with COVID-19 infection had parenchymal changes 10 weeks later, and ground-glass opacities, traction bronchiectasis, parenchymal bands, and reticulations were shown as the most frequent radiologic findings (2).

There is no consensus in the literature regarding the treatment of interstitial lung disease (ILD) caused by COVID-19. There are a few studies that observed improvement in symptoms, oxygenation, and radiological findings with corticosteroid treatment (3,8,9). In this study, we aimed to investigate the efficacy of immunosuppressive treatment in patients with persistent respiratory symptoms and/or impaired oxygenation, deterioration in pulmonary function test values, and persistent signs of interstitial lung disease in the lung parenchyma in the period after COVID-19 infection.

Methods

In this retrospective observational study, patients with persistent respiratory symptoms and post-COVID-19-ILD findings on radiology after COVID-19 infection in 2021-2022 were included. Inclusion criteria were defined as being over 18 years of age, having interstitial lung disease findings on radiology after COVID-19 infection, but not advanced fibrosis findings such as honeycombing, not having any diagnosis of interstitial lung disease before COVID-19 infection, and not taking any immunosuppressive therapy. In addition, patients with a duration of 4 weeks or more from the onset of COVID-19 infection were included in the study. As diagnostic criteria for COVID-19 infection, all patients had a positive COVID-19 reverse transcription-polymerase chain reaction (RT-PCR). Ethical approval for this study was obtained from the University of Health Sciences Yedikule Chest Diseases and Thoracic Surgery Education and Research Hospital Ethics Committee (14.4.2022-216).

Patients were retrospectively assessed. Demographic information, treatments during COVID-19 infection, pulmonary symptoms, modified Medical Research Council (mMRC) values, pulmonary function tests (PFT), diffusion capacities (DLCO), 6-minute walking test (6MWT) results, high-resolution computed tomography (HRCT) findings and treatments initiated for post-COVID-19-ILD at the time of admission and the 1st, 3rd, and 6th months following admission were recorded.

Modified medical research council (mMRC), pulmonary function testing and 6-minute walking test

The mMRC dyspnoea scale with a range of 0 to 4 was used (10). During all follow-ups, PFT and DLCO were conducted in our hospital's pulmonary function test laboratory. PFT and DLCO are performed in our laboratory by the same technician and with the same spirometry device (Minibox+ PFT, Pulmone, USA) under the ATS/ERS 2019 guidelines (11).

6 MWT is performed by a physician in our center. Patients rested for at least 15 minutes before the walking test. Using pulse oximetry, oxygen saturation, and pulse rate were measured before and after the procedure. In patients whose dyspnea became evident during the test, who were unable to walk due to weakness or palpitations, or who had chest discomfort, the test was terminated early.

Radiological evaluation

Experienced thoracic radiologists independently reviewed all images without knowledge of the clinical history of the participants. For thorax non-contrast enhanced HRCT examinations, patients were positioned supine and instructed to retain their breath after inspiration (Philips, Ingenuity elite-2016). Patients were imaged utilizing a 128-slice section multidetector CT scanner with 10 and 0.75 mm collimation.

HRCT findings of the patients at admission and 1st, 3rd, and 6th months were evaluated. Utilizing the studies of Wei J. et al. and Demirciolu O. et al., we developed a scoring system to define all HRCT findings according to their severity and prevalence and to determine their alterations with treatment in the present study (12,13). The radiologist who performed the evaluation classified the extent of COVID-19 infection in the lung parenchyma numerically (as 0,1,2,3, and 4) to characterize the pulmonary involvement. The HRCT evaluation of the disease's involvement was as follows: no involvement: 0, involvement of less than one segment (≤25%): 1, involvement of more than one segment (25%-50%): 2, involvement of 3 or more segments (51%-75%): 3, involvement of all segments bilaterally (76%-100%): 4. The same numerical classification was used to measure the variations in ground glass opacities, reticulation and fibrotic bands with corticosteroid treatment. The numerical classification of these radiologic findings was as follows:

- Ground glass opacity, absent: 0, slight: 1, marked but not diffuse: 2, marked and diffuse: 3
- Consolidation, absent: 0, mild: 1, marked but not extensive: 2 if marked and extensive: 3
- Reticulation, absent: 0, the inter-intralobular septal thickening is indistinct: 1, the inter-intralobular septal thickening is evident but not extensive: 2, the inter-intralobular septal thickening is evident and extensive: 3
- Parenchymal bands, absent: 0, slight and sporadic thin bands: 1, marked thickenings and thick bands but not diffuse involvement: 2, marked thickenings and diffuse thick bands: 3
- Traction bronchiectasis, absent: 0, mild: 1, marked but not extensive: 2, extensive: 3
- Bulla-blep-cystic areas, absent: 0, mild: 1, marked but not extensive: 2, marked and extensive: 3.

Treatment

Treatment was initiated with methylprednisolone 0,5 mg/kg/day in consenting patients with respiratory symptoms, need for long-term oxygen therapy (LTOT) and/or restriction on PFT and/or DLCO <80%, and diffuse parenchymal involvement. After one month of an initial treatment dose, the dose was reduced by 4 mg per week and maintained at 4 mg per day. When patients were reviewed in 1st month, Mycophenolate mofetil (MMF) was added to the treatment of patients who had active pulmonary symptoms and desaturation with effort, needed to reduce steroid dose quickly because of steroid side effects and no adequate improvement in radiological findings. For patients who could tolerate the medication, MMF was administered at an initial dose of 1 g daily, which was then followed by a maintenance dose of 2 g per day (taken twice daily). Prophylaxis with a salt-free diet, proton pump inhibitor, calcium replacement, and trimethoprim-sulfamethoxazole was given for the prolonged immunosuppressive therapy.

Statistical analysis

Data analysis was done using the IBM SPSS 25 package program. Frequency and percentage values for qualitative variables, and arithmetic mean and standard deviation values for quantitative variables are presented. Changes in respiratory parameters according to months were examined with repeated measures ANOVA. Changes in radiology and mMRC scores at the first and last measurements were compared using the McNemar test. Type I error rate was taken as 0.05 in the study.

Results

Immunosuppressive treatment was initiated in 35 of 48 patients diagnosed with post-COVID-19-ILD. Thirteen patients with no or minimal respiratory symptoms with low mMRC scores preserved PFT and DLCO values and were not allowed treatment, followed up without medication. Two patients were excluded from the evaluation in the treated group because one discontinued treatment in the fourth month and the other passed away in the fifth month. Of the remaining 33 patients, 21 (66.6%) received methylprednisolone, 11 (33%) received methylprednisolone and mycophenolate mofetil, and 1 (0.4%) received mycophenolate mofetil alone (Figure 1). Table 1 summarizes the demographic information, treatment status during COVID-19 infection, respiratory symptoms, mMRC scores, PFT, DLCO, and 6MWT values of patients at the time of admission. The untreated group had higher pulmonary function parameters, DLCO, and a numerical value of 6MWT compared to the treated group. We did not perform a statistical comparison between the two groups because of the small number of patients in this group. The most frequent HRCT findings in the treated and untreated groups were ground-glass opacity, reticulation, and reticulation

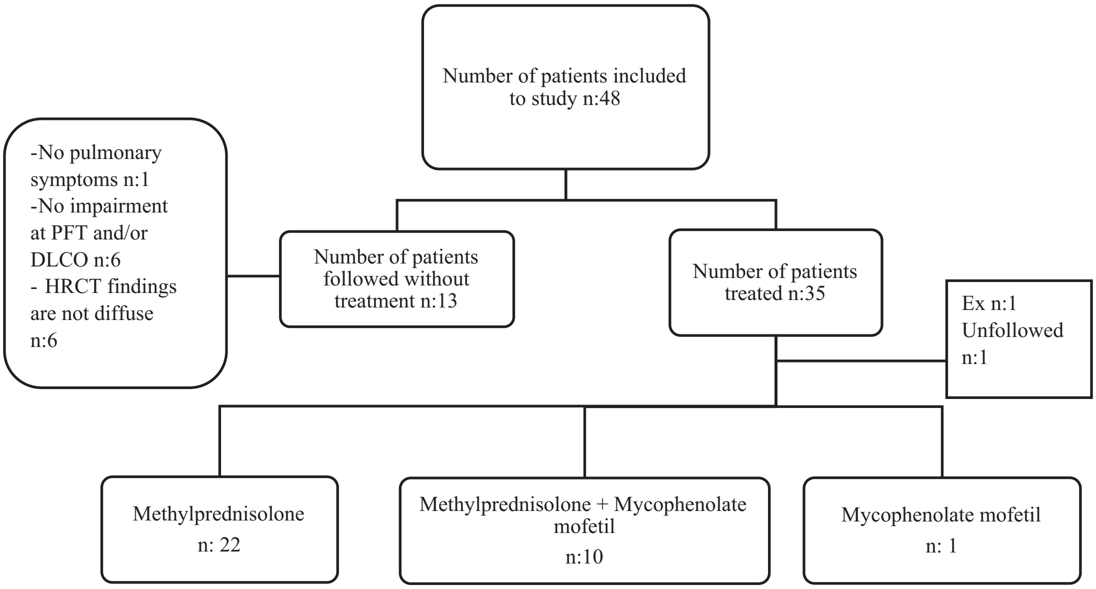

Figure 1. Flowchart of the patients' Abbreviations: PFT: pulmonary function test; DLCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography.

+ traction bronchiectasis + parenchymal band, respectively (Table 1).

When the patients were evaluated at the end of the sixth month, dyspnea had completely regressed in three (9%) patients compared to the initial evaluation. Comparing the mMRC levels revealed a statistically significant decrease; whereas the mMRC level was 4 in 16 patients at baseline, it was 4 in 1 patient at month 6 ($p<0.001$) (Table 2). 17 patients required LTOT at baseline, however, 15 patients (88.2%) did not require oxygen support by the end of the sixth month. Fingertip saturation of room air (SpO2), FEV1, FVC, DLCO, and 6MWT results at baseline, 1, 3, and 6 months are displayed in Table 3. At the end of the sixth month, SpO2, FVC, FVC%, FEV1%, and DLCO% values displayed statistically significant improvement compared to baseline. There was a quantitative improvement in 6MWT results, nevertheless, it was not statistically significant. Figure 2 represents the progression of these values throughout treatment. Since we provided our patients with long-term medical treatment, we compared their data after the first and sixth months of treatment. SpO2 and DLCO% values increased statistically significantly between the first and sixth months ($p=0.016$). Although not statistically significant, FVC% and 6MWT values also increased significantly.

In the radiologic assessment, when the HRCT findings at admission and 6th month were compared, a numerical regression was observed in all radiologic changes, whereas the improvement in ground glass opacity and reticulation was statistically significant ($p<0.005$) Although statistical analysis could not be performed, a significant quantitative decrease in the grade of involvement was observed (Table 4). Figure 3 and Figure 4 represent HRCT images of our patients whose radiologic findings improved significantly. At the end of the sixth month, HRCT results for five (15.2%) patients were normal. Comparing the thorax imaging findings of 32 patients at 1 month to those at 6 months revealed a statistically significant decrease in reticulation ($p=0.01$).

The treatment was well-tolerated by all patients, with no significant adverse effects that required discontinuation. It is worth noting that some patients did report minor side effects, including a Cushingoid appearance (20%), muscle weakness (14%), skin lesions like petechiae or local bruising (8%), increased appetite (2.8%), and anemia (2.8%).

Discussion

This study demonstrated the efficacy and safety of immunosuppressive therapy in post-COVID-19-ILD patients who are symptomatic, require

Table 1. Demographic data, pulmonary function test, and radiological findings of patients who received and did not receive immunosuppressive therapy at the time of admission.

	Not received therapy n (%)	Received therapy n (%)
Sex		
Male	8 (61,5)	19 (57,6)
Female	5 (38,5)	14 (42,4)
Age	59,62±5,56	56,91±9,39
Smoking		
Yes	7 (53,8)	9 (27,3)
Comorbidities		
DM	4 (30,8)	15 (45,5)
HT	6 (46,2)	12 (36,4)
CCF	3 (23)	2 (6,1)
COPD	1 (7,7)	3 (9,1)
Asthma	2 (15,4)	3 (8,6)
Post tuberculosis	0 (0)	2 (6,1)
Other	10 (76,9)	14 (42,4)
COVID-19 treatment at		
home	0 (0)	2 (6,1)
the hospital	13 (100)	28 (84,8)
ICU	5 (38,5)	19 (57,6)
Length of stay in hospital (day)	25,69±16,04	37,81±21,79
Oxygen treatment		
Nasal oxygen	6 (46,2)	17 (51,5)
Oxygen with a reservoir	7 (53,8)	16 (48,5)
HFO	4 (30,8)	17 (51,5)
NIMV	4 (30,8)	16 (48,5)
IMV	0 (0)	1 (3)
Day from diagnosis to admission	167,69±142,67	176,06±144,58
Symptoms at admission		
Dyspnea	11 (84,6)	30 (90,9)
Cough	3 (23,1)	5 (15,2)
Chest pain	0 (0)	2 (6,1)
Fatigue	0 (0)	5 (15,2)
Other	1 (7,7)	2 (6,1)
mMRC median (min-max)	1 (0-3)	3 (1-4)
Oxygen requirement at admission	0 (0)	17 (51,5)
Velcro ral on auscultation	5 (38,5)	19 (57,6)
Clubbing	1 (7,7)	5 (15,2)
SpO2 %	97,23±1,36	93,64±3,91
FVC (L)	3,3±0,85	2,43±0,98
FVC%	92,92±19,61	68,06±19,09
FEV1 (L)	2,85±0,7	2,17±0,81
FEV1%	97,38±22,9	73,81±19,37
FEV1/FVC	85,84±6,02	91,38±13,05
DLCO	9,98±6,96	8,46±7,17
DLCO%	62,98±27,39	45,1±18,7
6MWT (meter)	416,38±145,52	368,11±153,49
6MWT Pre SpO2 %	95,77±3,11	94,32±2,71
6MWT Post SpO2 %	94,85±2,51	89,18±7,07
HRCT findings		
Ground glass	13 (100)	33 (100)
Reticulation	8 (61,5)	31 (93,9)
Consolidation	1 (7,7)	4 (12,1)
Bul-blep-cyst	3 (23,1)	4 (12,1)
-emphysema	10 (76,9)	30 (90,9)
Reticulation+traction bronchiectasis +parenchymal band		

Abbreviations: DM: diabetes mellitus; HT: hypertension; CCF: congestive cardiac failure; COPD: chronic obstructive pulmonary disease; TBC: tuberculosis; ICU: intensive care unit; HFO: high flow oxygenation; NIMV: non-invasive mechanical ventilation; SpO2: oxygen saturation as measured by pulse oximetry; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-minute walk test; HRCT: high-resolution computed tomography. Data are presented as mean±standard deviation unless otherwise stated.

long-term oxygen therapy, have impaired functional capacity, and have diffuse parenchymal involvement. The results showed significant improvement in mMRC and saturation values, FVC, FVC%, FEV1%, and DLCO%. There was a significant decrease in radiologic findings of involvement, particularly in ground glass opacity and reticulation at a statistically significant level.

There is currently no consensus regarding the definition and treatment of ILD after COVID-19. It is recommended that patients with symptoms persisting for at least three months and parenchymal changes of greater than 10% on thoracic CT be closely monitored (14). In the study of Martino et al., in which they followed up patients for up to 12 months after COVID-19, it was shown that 18.7% of the patients continued to have shortness of breath for 12 months, and low DLCO was observed in approximately half of the patients (15). In a study conducted in China involving a large number of patients evaluated in the post-COVID-19 period, 68% of patients had at least one post-COVID-19 symptom by the sixth month, while this rate decreased to 48% by the twelfth month. The incidence of dyspnea was 26% in the sixth month and 30% in the twelfth month. 6MWT was lower than normal at 14% after 6 months and 12% after 12 months. While pulmonary function tests improved almost entirely at 12 months, DLCO was found to be 53% lower, particularly in the group hospitalized in an intensive care unit and receiving high flow oxygen (HFO) or non-invasive

Table 2. Comparison of Modified Medical Research Council (mMRC) scores before the treatment and after 6 months of treatment.

		mMRC score after 6 months						
		0	**1**	**2**	**3**	**4**	**Total**	**p**
mMRC score at admission	0	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	**<0,001**
	1	5 (62,5)	3 (37,5)	0 (0)	0 (0)	0 (0)	8 (100)	
	2	5 (33,3)	8 (53,3)	2 (13,3)	0 (0)	0 (0)	15 (100)	
	3	0 (0)	4 (66,7)	1 (16,7)	1 (16,7)	0 (0)	6 (100)	
	4	0 (0)	4 (25)	8 (50)	3 (18,8)	1 (6,3)	16 (100)	

Table 3. Comparison of pulmonary function test, DLCO, and 6MWT results before the treatment, at 1st and 6th months of treatment in patients receiving immunosuppressive therapy.

	Admission	**1st month**	**6th month**	**F**	**p**	**difference**
SpO2 %	90,09±5,22	94,1±3,13	95,88±2	22,285	**<0,001**	Pre<1<6
FVC (L)	2,43±0,98	2,85±1	2,75±1,01	5,795	**0,006**	Pre<1,6
FVC %	68,06±19,09	73,95±16,76	77,48±18,11	12,262	**0,001**	Pre<1<6
FEV1 (L)	2,17±0,81	2,48±0,88	2,36±0,89	3,356	0,045	-
FEV1 %	73,81±19,37	79,5±20,56	81,16±20,62	6,024	**0,005**	Pre<1,6
FEV1/FVC	91,38±13,05	89,23±9,35	87,39±11,2	0,081	0,922	-
DLCO	8,46±7,17	9,23±5,13	11,53±6,25	1,947	0,172	-
DLCO %	45,1±18,7	47,95±16,3	54,87±23,46	5,123	**0,011**	Pre<1,6
6MWT (meter)	368,11±153,49	416,91±160,44	435,32±153,22	2,964	0,086	-
6MWT Pre SpO2 %	94,32±2,71	94,91±3,07	95,41±3,31	0,172	0,765	-
6MWT Post SpO2 %	89,18±7,07	89,87±8,38	90,67±8,91	0,244	0,785	-

Abbreviations: SpO2: oxygen saturation as measured by pulse oximetry; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-minute walk test. Data are presented as mean±standard deviation unless otherwise stated.

mechanical ventilation and invasive mechanical ventilation therapy (16). In neither study was it specified whether the patients required oxygen at the time they were enrolled. In addition, there is no information regarding whether they received treatment after COVID-19 infection. In our study, the mean time to presentation after COVID-19 infection was 176 days, and all patients presented with symptoms, with dyspnea being the most prevalent. Significant improvement in mMRC scores was observed at the end of treatment. While 57.6% of our patients received treatment in the ICU, approximately half of them received HFO or non-invasive and/or invasive mechanical ventilation. Similar to other studies, especially DLCO value of our patients was significantly low, and a significant increase was observed after immunosuppressive therapy. At the time of admission, 51.5% of patients used LTOT, and 88.2% of these patients did not require oxygen after treatment.

Post-COVID-19-ILD radiology usually shows ground-glass opacity, consolidation, reticulation, interlobular septal thickening, parenchymal bands, and traction bronchiectasis. Progressive honeycombing is rare. A study revealed that 63% of patients still had radiologic findings even after their post-COVID-19 symptoms decreased in intensity at the 12-month mark. (15). A different study showed that radiologic changes persisted in 87% at 12 months post-COVID-19 (16). Organized pneumonia pattern and fibrosis-like findings are the most common terms used in the literature to describe radiological findings. Due to these radiologic findings, it was deemed appropriate to prioritize steroid treatment (8,17). In our study, grounded glass opacity, reticulation, traction bronchiectasis, and parenchymal bands were the most common radiologic findings, and therefore steroid treatment was considered appropriate. At the end of the treatment, significant improvement was observed in ground glass opacity and reticulation.

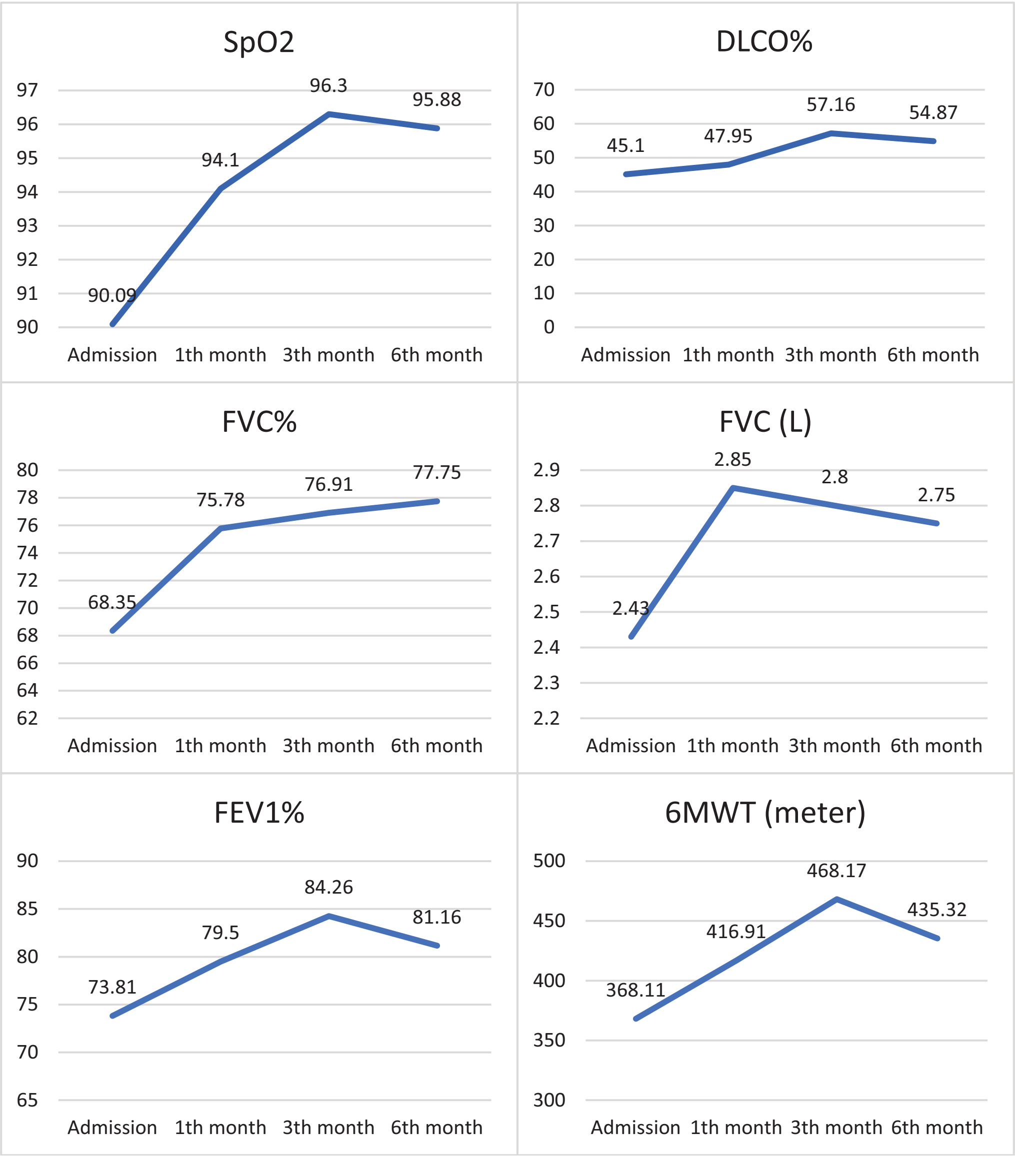

Figure 2. Saturation, pulmonary function test, DLCO, and 6-minute walk test data of patients receiving immunosuppressive therapy at admission and the 1st, 3rd, and 6th months of treatment. Abbreviations: SpO2: oxygen saturation as measured by pulse oximetry; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-minute walk test.

There are limited studies investigating the use of immunosuppressive therapy in patients with symptomatic and loss of function in the treatment of post-COVID-19-ILD. A guideline published in Switzerland recommended that patients should be evaluated in experienced centers for corticosteroid treatment in this group of patients (18). In the study by Segala et al., intravenous methylprednisolone was started at a dose of 1mg/kg for 2 weeks in 10 patients who continued to have respiratory failure at post-COVID-19 week 3 and the dose was reduced and discontinued every three days, and a significant improvement in oxygenation was observed (9). Based on the fact that this particular group of patients is in the initial 5-week period and displays broad ground glass areas, there remains a possibility that they are still experiencing acute radiological symptoms of COVID-19 infection. When Günay et al. evaluated the patients they followed for 3 months after hospitalization with severe pneumonia due to COVID-19,

Table 4. Comparison of high-resolution computed tomography (HRCT) findings at admission and at the 6th month of treatment.

HRCT findings and numeric scores	At admission n (%)	6th month n (%)	p
Involvement			
0	0	5 (15,2)	-
1	2 (6,1)	21 (63,6)	
2	8 (24,2)	6 (18,2)	
3	14 (42,4)	1 (3)	
4	9 (27,3)	0	
Ground-glass			
0	0	11 (33,3)	**<0,001**
1	3 (9,1)	16 (48,5)	
2	10 (30,3)	5 (15,2)	
3	18 (54,5)	1 (3)	
4	2 (6,1)	0	
Reticulation			
0	2 (6,1)	8 (24,2)	**0,001**
1	5 (15,2)	17 (51,5)	
2	11 (33,3)	6 (18,2)	
3	15 (45,5)	2 (6,1)	
Consolidation			
0	29 (88)	29 (88)	1,000
1	2 (6)	2 (6)	
2	2 (6)	2 (6)	
Bul-blep-cyst-emphysema			
0	29 (87,9)	28 (84,8)	0,506
1	1 (3)	2 (6,1)	
2	2 (6,1)	1 (3)	
3	1 (3)	2 (6,1)	
Reticulation+traction bronchiectasis +parenchymal band			
0	4 (12,1)	9 (27,3)	0,125
1	18 (54,5)	17 (51,5)	
2	7 (21,2)	5 (15,2)	
3	4 (12,1)	2 (6,1)	

symptoms and persistent parenchymal findings were observed more frequently in elderly and male patients. Corticosteroid treatment was found to be effective in the improvement of radiological and functional parameters in this group of patients (19). In the study by Myall et al., patients hospitalized due to COVID-19 infection were reached by phone four weeks after discharge, and those with persistent symptoms were invited for evaluation six weeks later. Moderate dose methylprednisolone treatment was given to 30 patients with radiologically organized pneumonia patterns and significant improvement was observed in symptoms, pulmonary function test, and DLCO values in the evaluation 6 weeks later. Although there was a noticeable improvement in the radiological results, no statistical data could be provided as there was no scoring available (8). In the study by Dhooria et al., low dose (10mg/day) and high dose (beginning with 40mg/day and weekly dose reduction) steroid treatment was administered to two groups of symptomatic patients with impaired oxygenation and especially parenchymal involvement compatible with organized pneumonia 6 weeks after the onset of COVID-19 infection and approximately 2 weeks after discharge. After the 6-week treatment period, both groups demonstrated significant clinical-radiologic improvement (3). Kostorz-Nosal and colleagues found that post-COVID-19 patients, especially those with an organizing pneumonia pattern, experienced a significant functional and radiological improvement when they started high-dose steroid treatment and gradually reduced the dose over two months. The importance of long-term steroid treatment was highlighted, as it is recommended to undergo steroid therapy for up to six months to treat organizing pneumonia. (20). Similar to this study, we found it appropriate to give long-term treatment during patient follow-up to ensure the continuity of the improvement we saw in the patients.

Unlike other studies, mycophenolate mofetil was added to the treatment to rapidly reduce the steroid dose in patients who did not achieve adequate clinical and functional response in the first month of treatment. Mycophenolate mofetil is an immunosuppressive agent that we use in our center for patients with hypersensitivity pneumonia (HP) who cannot stop or reduce the dose of steroid treatment. In studies using MMF to reduce the dose of steroids in the treatment of HP, both a successful dose reduction and a significant increase in DLCO were observed. (21,22). In addition, in several reviews including treatment algorithms in interstitial lung diseases, the use of MMF in the HP treatment algorithm has been suggested (23,24). In studies, it has been mentioned that MMF is effective in the treatment of HP as it inhibits T cell proliferation and suppresses inflammation (21). Case-based publications are showing that MMF can be used in steroid-resistant organizing pneumonia and post-COVID-19 interstitial lung disease (25,26). In our study, we preferred to use MMF in suitable patients, since the radiological involvement was similar to HP and we had previous experience with this immunosuppressive agent. MMF was well tolerated by patients and no serious drug-specific side effects were observed.

In many studies, the treatment initiation period is between 2 and 6 weeks after discharge;

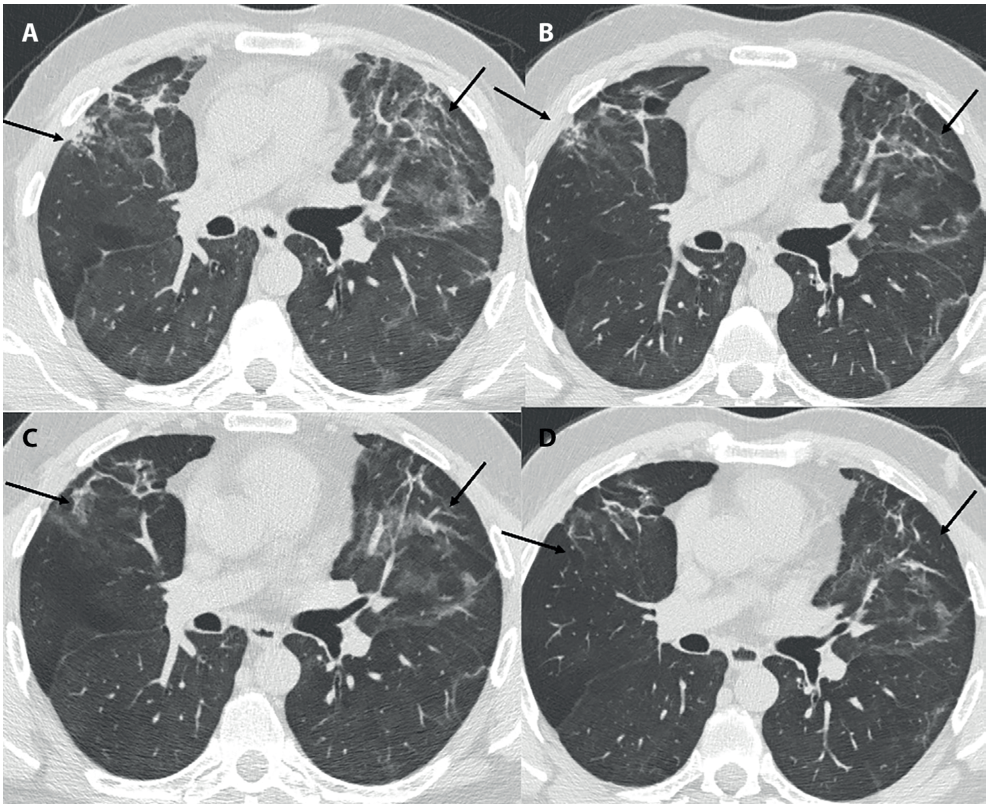

Figure 3. High-resolution computed tomography images passing through the subcarinal level of a 66-year-old male patient. A: before treatment, B: 1 month after immunosuppressive therapy, C: 3rd month, and D:6th month. It is observed that reticulations gradually decrease with treatment (black arrows).

however, in our study, the earliest presentation occurred at 4 weeks, and the mean duration was 6 months. Contrary to other studies, treatment was also administered to patients who presented at a later stage, and similar to other studies, treatment was administered to symptomatic patients with impaired oxygenation, respiratory dysfunction, and diffuse parenchymal involvement. In addition, contrary to previous investigations, the duration of immunosuppressive treatment was extended to a total of six months. Significant clinical (mMRC) and functional (SpO2, FVC, FVC%, FEV%, and DLCO%) improvement and regression of radiologic findings were observed in the treated group. According to the results of our data, prolonged immunosuppressive therapy should be considered in post-COVID-ILD treatment.

The most significant limitations of our study are that it was retrospective, did not include patients who did not receive immunosuppressive treatment, and was a single-center study. Because of the retrospective design, randomization could not be performed. The other limitation is the inability to make a comparison between the untreated group and the treatment groups due to the insufficient number of patients. Although radiological images were evaluated by an experienced radiologist, the fact that only one radiologist made the evaluation can be considered as another limitation.

In conclusion, long-term immunosuppressive therapy may be preferred as an effective and safe treatment option for symptomatic patients with post-COVID-19-ILD, as it improves the quality of life, respiratory parameters, and radiologic findings. In suitable patients, treatment can be started even after a long period of infection. Randomized controlled trials are required to establish immunosuppressive treatment protocols for this patient population.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article

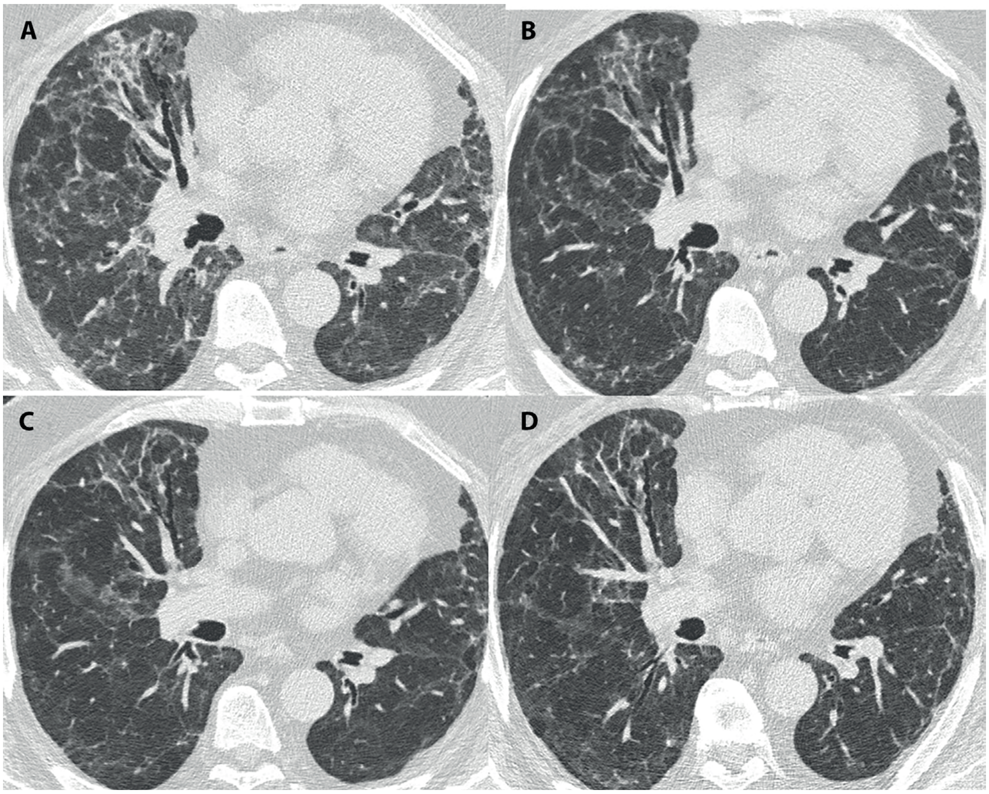

Figure 4. Follow-up high-resolution computed tomography images of a 67-year-old male patient who applied in the 2nd month of COVID-19 infection. Approximately similar HRCT sections passing through the basal level: A: before treatment, B: 1 month after immunosuppressive therapy, C: 3rd month, and D:6th month. There is a marked decrease in diffuse reticular areas accompanying the ground glass areas and a decrease in bronchiectasis density in areas with traction bronchiectasis.

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