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Comparison of methotrexate and methylprednisolone as addition to antifibrotic therapy in progressive pulmonary fibrosis due to COVID-19

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Abstract. *Background:* Post-covid pulmonary fibrosis (PCPF) is an essential cause of hypoxic respiratory failure, especially in patients with severe COVID-19 infection. In our study, we aimed to compare the effectiveness of methylprednisolone and methotrexate treatments in patients diagnosed with PCPF and in whom progression was observed despite nintedanib treatment. *Methods:* Forty-eight patients diagnosed with PCPF between April 2022 and February 2023 were followed up in our study. Progressive pulmonary fibrosis was observed in 18 of these patients despite nintedanib treatment. Nintedanib + methylprednisolone treatment was started in Group 1 patients, and nintedanib + methotrexate treatment was started in Group 2 patients, and after three months, a respiratory function test (PFT), 6-minute walk test (6MWT), saturation, pulse, and side effect levels were compared. *Results:* In comparing the groups at the end of the third month, the change in PFT parameters was higher in Group 2 patients than in Group 1 patients. However, there was no statistically significant difference. However, the increase in fingertip saturation, 6MWT levels, and decrease in pulse levels were statistically significantly different in Group 2 patients compared to Group 1 patients (p=0.001 for all). It was observed that complaints of muscle and joint pain, weight gain, and atrophy in peripheral extremities in Group 1 patients were statistically significantly higher than in Group 2 patients (p=0.001, 0.002, 0.001, respectively). *Conclusion:* Methotrexate can be used as an alternative to methylprednisolone in PCPF due to its low side effect profile and its effectiveness in PFT, 6MWT, and saturation levels.

Key words: post-covid fibrosis, pulmonary function test, 6MWT

Introduction

The COVID-19 infection caused by SARS-CoV-2 has continued to exist until today, decreasing in severity after emerging in 2019. In some of the patients who were followed up in the ward and intensive care unit due to COVID-19 infection, the findings in the lung parenchyma were aggressive and caused the development of acute respiratory distress (1,2).

The most common respiratory symptoms of COVID-19 have been a significant decrease in diffusion capacity in the lungs (DLCO) and associated pulmonary interstitial damage (3). One year after moderate COVID-19, the incidence of impaired DLCO and permanent lung injury ranges from 28% to 52%, with one-third of patients presenting with severe DLCO impairment and fibrotic lung injury (4). Many reasons have been blamed for the formation of this condition, defined as post-COVID pulmonary fibrosis (PCPF). Among these, the most accepted reason is abnormal tissue repair

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and pro-inflammatory cytokine discharge that will increase the release of pro-fibrotic agents. Alveolar epithelial cells (AEC) are divided into two groups (5,6). AEC1 surrounds the alveoli and forms the squamous epithelial layer, which is the gas exchange area, while AEC2 produces the surfactant substance that reduces surface tension. In case of excessive AEC1 damage, AEC2 cells also serve as AEC1 differentiating progenitor cells. Abnormal damage to AEC cells due to viral infection causes an increase in TGF-β levels, defective repair, and pulmonary fibrosis. In addition, after COVID-19 infection, IL-4, 5, and 13 synthesized from cytotoxic T lymphocytes increase the polarization of macrophages into M2 macrophages. This situation causes an increase in cytokine discharge, increasing the transformation of fibroblasts into myofibroblasts (5,7).

The physiopathology of PCPF formation has led to the conclusion that anti-inflammatory treatments may benefit these patients (8). However, despite methylprednisolone treatment being used as an anti-inflammatory agent, anti-fibrotic therapies have also been tried, and successful results have been obtained in order to prevent progressive fibrosis (4,9). However, when to stop these treatments and how to use them is still a more critical problem. Comorbidities caused by the anti-inflammatory agents used in patients may lead to discontinuation of the drugs. After treatment is stopped, the progressive course may increase again with only antifibrotic treatment. In our study, we aimed to compare the effectiveness of methotrexate treatment with methylprednisolone treatment in patients who do not want to use steroid treatment or are contraindicated due to developing comorbidities.

Material and Method

Study design

Between April 2022 and February 2023, patients with shortness of breath, cough, low saturation, and exertional dyspnea at least 12 weeks after COVID-19 infection (Chronic COVID-19) were evaluated at Atatürk University Chest Diseases Polyclinic. It was learned that all of these patients were followed for a while due to macrophage activation syndrome due to COVID-19. It was learned that the patients received methylprednisolone treatment for a while after COVID-19 when they applied to our polyclinic, and then their treatment was discontinued by the physician they were following. After radiological evaluations, it was observed that PCPF developed in 48 patients. Approval was received from Erzurum Atatürk University Faculty of Medicine Ethics Committee to conduct the research. Before starting the research, the patients who would participate in the study were informed about the purpose of the research, its method, and the time they were asked to allocate for the research. It was explained to the patients that participating in the study did not carry any risks, that participation was completely voluntary, and that they could withdraw from the study at any time.

Study groups

It was observed that 18 of the patients followed for PCPF had progression despite antifibrotic treatment (Figure 1). Methylprednisolone treatment was started in 12 of these patients in addition to antifibrotic treatment (Group 1). Methotrexate treatment was started in addition to antifibrotic treatment in 6 patients who had previously received methylprednisolone treatment and developed complications due to this (Group 2).

Inclusion criteria

In our study, patients who were diagnosed with COVID-19 by real-time PCR from nasopharyngeal swab at least 3 months ago and whose chronic COVID-19 symptoms continued

1. Patients older than 18 years of age
2. Patients who developed fibrosis secondary to COVID-19 with radiological sampling
3. Those with a fibrosis rate over 5% and a 5% absolute decrease in FVC and DLCO levels during follow-up
4. Worsening of respiratory symptoms
5. With or without comorbid conditions
6. Patients who did not need intubation and mechanical ventilation
7. Patients who agreed to come for follow-ups within the 12-week period declared in our study were included.

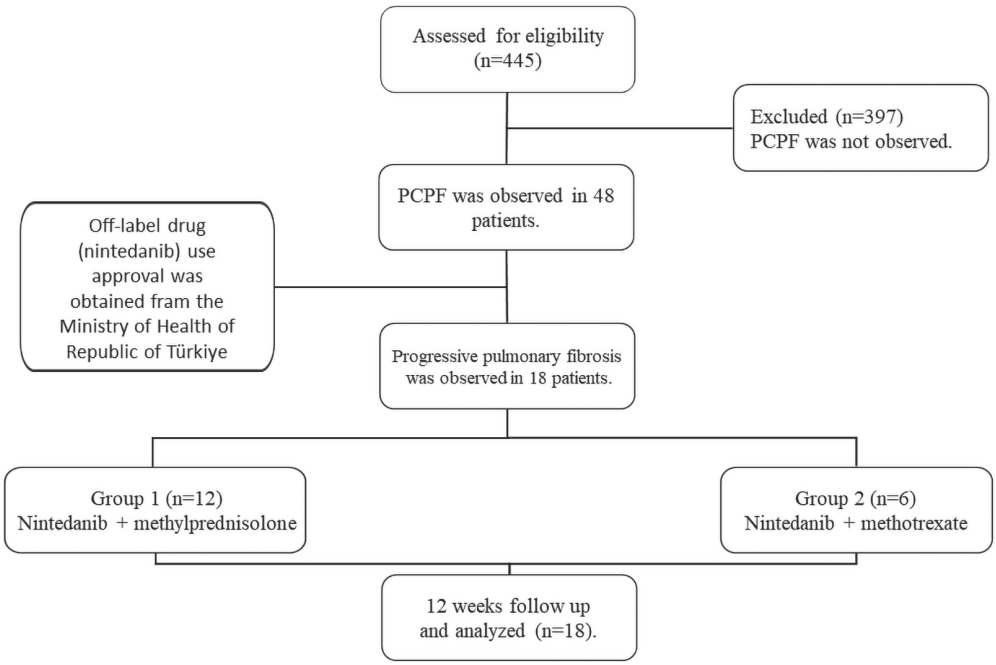

Figure 1. Study design.

Exclusion criteria

As well as patients who did not meet the inclusion criteria

1. Conditions that may contraindicate the application of pulmonary function test (recently MI, pulmonary embolism, cerebral aneurysm, active hemoptysis, pneumothorax, nausea, vomiting, 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 were excluded from the study.

PFT application

The rules that patients should follow before spirometry were announced to the patients in line with the ATS/ERS 2019 guideline. The movement to be performed was explained to the patient by the technician. The patient was performed 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 (10). 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.

6-Minute walk test (6MWT) and fingertip oxygen saturation measurement

The patients rested for at least 15 min at the beginning of the 30-m track, and their oxygen saturation, heart rate was measured using a fingertip pulse oximeter and recorded. Under the supervision of a physician, patients were instructed to walk along the level corridor as fast as they could for 6 min. In the event of any symptoms such as excessive fatigue, dyspnea, or palpitations during the test, it was ended early to avoid endangering the patient. At the end of the test, the patient rested while the distance walked was recorded in meters.

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 CT examinations were performed using. All images were transferred to a commercial workstation (Singo via. Workstation, Siemens, Erlangen, Germany). The images were assessed by a radiologist who were blinded to the patients' identities. The reader had 18 years of experience in thoracic radiology of experience in radiology.

Medical treatment applied during follow-up

Thorax CT was performed on patients who presented to our outpatient clinic with chronic COVID-19 symptoms and did not respond despite symptomatic treatment. An application was made to the Ministry of Health of the Republic of Türkiye for off-label antifibrotic nintedanib treatment for patients with PCPF detected on thorax imaging and FVC and DLCO levels below 80% in respiratory function test parameters. In 18 of the 48 patients whose treatment was started after the application was accepted (Nintedanib 300 mg/day), it was observed that there was a 5% absolute decrease in FVC and DLCO and a worsening of respiratory symptoms in the third month of follow-up despite the treatment. Methylprednisolone treatment was started in 12 of 18 patients at a dose of 0.5 mg/kg/day. On the 15th day of follow-up, this dose was reduced to 0.25 mg kg/day. It was learned that six patients developed sugar dysregulation, cushingoid appearance, and avascular necrosis of the femoral head due to previous methylprednisolone treatment. In these patients, in addition to antifibrotic treatment, methotrexate treatment was started once a week at a dose of 5 mg/week, and after 15 days, the dose was increased to 7.5 mg/week. For the five days when he/she did not receive treatment, folic acid treatment was administered at a dose of 5 mg/day. Eighteen patients receiving anti-inflammatory treatment were followed monthly for three months.

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. P values < 0,05 were considered statistically significant.

Results

The average age of the patients in our study was 62.4 ± 4.5 years. The mean age of Group 1 patients was 61.6 ± 5.3 years, while that of Group 2 patients was 60.9 ± 3.7 years. While 75% of Group 1 patients were male, 50% of Group 2 patients were male. While there was no statistically significant difference between the average ages of the groups, a significant difference was observed between genders ($p = 0.78$, $p = 0.03$, respectively).

When PFT, 6MWT, fingertip saturation, and pulse values of the patients were compared at the beginning of the treatment and in the third month of the treatment, it was observed that PFT, 6MWT, and fingertip saturation values did not show statistically significant differences between the two groups at the beginning of the treatment and in the third month of the treatment. ($p > 0.05$ for all). However, the pulse value, which was at a similar level at the beginning of the treatment, was statistically lower in Group 2 patients compared to Group 1 in the third month of the treatment ($p = 0.01$). A comparison of the changes in PFT, 6MWT, fingertip saturation, and pulse levels of the groups after three months of treatment is shown in Table 1. Accordingly, the change in PFT parameters was higher in Group 2 patients than in Group 1 patients. However, there was no statistically significant difference. However, the increase in fingertip saturation, 6MWT levels, and decrease in pulse levels were statistically significantly different in Group 2 patients compared to Group 1 patients ($p = 0.001$ for all).

Side effects observed during the treatment in patients receiving methylprednisolone or methotrexate

Table 1. Comparison of changes in PFT, fingertip saturation, 6MWT, and pulse levels between groups in the 3rd month of treatment.

	Group 1 (n=12) Mean ± SD	Group 2 (n=6) Mean ± SD	p
ΔFVC (Lt)	0.1 ± 0.1	0.2 ± 0.1	0.33
ΔFEV1 (Lt)	0.1 ± 0.2	0.1 ± 0.1	0.38
ΔDLCO (%)	2.4 ± 4.7	3.8 ± 3.2	0.55
ΔDLCO/Va (%)	1.4 ± 5.8	1.8 ± 2.9	0.9
ΔFinger SO2 value (%)	1.3 ± 2.3	8.5 ± 4.8	0.001
Δ6MWT (meter)	6.9 ± 8.2	54 ± 27.8	<0.001
ΔPulse (BPM)	-4.1 ± 4	-14 ± 6.5	<0.001

Abbreviations: FVC: Forced vital capacity, FEV1: forced expiratory volume in 1 second, DLCO/VA: Diffusing capacity divided by the alveolar volume, 6MWT: 6 minutes walking test, SO2: Fingertip saturation in room air

Table 2. Comparison of side effect profiles between groups.

	Group 1 (n=12) n (%)	Group 2 (n=6) n (%)	p
Diarrhea	8 (%67)	4 (%67)	1,00
Stomach ache	10 (%83)	5 (%83)	1,00
Muscle-joint pain	6 (%50)	1 (%16)	0.001
Weight gain	5 (%42)	1 (%16)	0.002
Atrophy in peripheral limbs	6 (%50)	1 (%16)	0.001
Tiredness	10 (%83)	5 (%83)	1,00
Mood disorder	2 (%16)	-	N/A

treatment in addition to antifibrotic therapy are shown in Table 2. Accordingly, the most common side effects in both groups were diarrhea and abdominal pain. It was observed that complaints of muscle and joint pain, weight gain, and atrophy in peripheral extremities in Group 1 patients were statistically significantly higher than in Group 2 patients (p = 0.001, 0.002, 0.001, respectively).

Discussion

In our study, when evaluating the effectiveness of methotrexate and methylprednisolone treatments on PFT parameters in PCPF patients, it was observed that both treatment protocols caused significant improvement in all PFT parameters. No significant difference was observed when comparing the changes in PFT parameters of the treatments over three months. However, the increase in saturation in patients treated with methotrexate was higher at 3-month follow-up than in those treated with methylprednisolone. In addition, it was observed that patients receiving methotrexate treatment had fewer side effects compared to methylprednisolone treatment.

The mechanism of the development of pulmonary fibrosis after COVID-19 has not yet been fully elucidated; however, it is thought to be multifactorial. Whatever the cause, fibrosis is believed to be due to abnormal healing of injured lung parenchyma (11). PCPF can cause significant morbidity and mortality by worsening underlying lung disease, especially in the elderly (12). Additionally, elderly patients requiring intensive care unit (ICU) management and invasive mechanical ventilation are at high risk for developing lung fibrosis (13). COVID-19 infection can cause a cytokine storm characterized by abnormal cytokine discharge, especially in patients with comorbidities or the elderly. During this period, which can be accompanied by acute respiratory distress, many cytokines are synthesized, especially TNF-α, IL-1, IL-6, and MMP-7 (3,14). Breaking

this cytokine discharge with steroids or anti-cytokine treatment in the early period can reduce the development of cytokine storms in individuals (15). The results of the meta-analysis revealed that there may be a significant PCPF development rate of 44.9%. However, radiological findings resolve over time in a substantial portion of these patients (16). In a much lower proportion, additional treatments are needed to prevent PCPF.

To prevent the progressive course in patients who develop PCPF, pirfenidone and nintedanib treatments, which have previously been proven to be effective in idiopathic pulmonary fibrosis (IPF), have been tried. Both treatments have been shown to improve both PFT parameters and 6MWT distance (4,17). In addition, another study in which steroid treatment was used alone and in addition to antifibrotic treatments showed that the application of steroid treatment together with nintedanib treatment gave better results than application alone or with pirfenidone (18). PCPF does not follow the same course in every patient. In some patients, there is a shift towards uncontrolled cellular proliferation with accumulation of fibroblasts and myofibroblasts and excessive deposition of collagen and other extracellular matrix components (19). This picture is similar to IPF, and antifibrotic treatments may be sufficient in these patients. In some patients, even during the chronic COVID-19 period, proinflammatory cytokine discharge continues, and the fibrotic-profibrotic period occurs together. These patients need anti-inflammatory treatment in addition to anti-fibrotic therapy. In this treatment, methylprednisolone is the first choice that comes to mind (18,20).

In our study, pulmonary function test parameters, 6MWT distance, fingertip oxygen saturation, and pulse levels did not show a statistically significant difference at the beginning of treatment in the groups in which methylprednisolone and methotrexate were started in PCPF patients who developed progressive pulmonary fibrosis despite anti-fibrotic treatment. However, it was observed that the pulse level was lower in the group using methotrexate in the 3rd month of treatment. In addition, the changes in 6MWT, fingertip saturation, and pulse levels over the three months were improved in the methotrexate group. Although no statistical difference was observed between the groups, the increase in DLCO level in the methotrexate group was better than in the methylprednisolone group. This may have caused further improvement in patients' oxygen saturation, 6MWT distance, and pulse levels. In addition, the higher levels of muscle atrophy, weight gain, and muscle and joint pain in the methylprednisolone group than in the methotrexate group may have caused a lesser increase in both 6MWT and oxygen saturation. The symptoms of abdominal pain, diarrhea, and fatigue observed in both groups may have developed due to nintedanib rather than to the treatment applied in addition to anti-fibrotic therapy.

Our study included our three-month observations, but long-term studies in which the number of patients will be increased are needed for long-term results and side effect profiles. However, today, when the devastating effects of COVID-19 have diminished, current patient numbers can also be guiding.

As a result, methotrexate has been an agent used in interstitial lung diseases and rheumatological diseases that will lead to pulmonary fibrosis for many years. This agent, which blocks profibrotic cytokine discharge from cytotoxic T lymphocytes, may be easier to use than methylprednisolone. It is also safe regarding lung toxicity and side effect profile when administered in low doses. Therefore, we think that PCPF can be used in patients with a progressive course in addition to anti-fibrotic treatment.

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Data Availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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