A comparison trial of eight weeks versus twelve weeks of exercise program in interstitial lung diseases

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Abstract. *Background:* Exercise training have been shown to be the effective approach for functional outcomes in interstitial lung diseases (ILD). In many studies, the duration of exercise programs (EPs) varies between 8-12 weeks. However, the optimal duration of EPs is still unknown. *Objective:* In our prospective non-controlled study, we aimed to compare the results of the 8th week with the results of the 12th week of the PR programs applied to the patients with ILD. *Methods:* A total of 14 patients [Age; 63(53,70) years, body mass index: 28(25,32) kg/m², disease duration; 1.5 (1,4) years] with ILD [11 idiopathic pulmonary fibrosis, 2 sarcoidosis (stage 3 and 4) and 1 nonspecific interstitial pneumonia] were included in the study. 6-minute walk test, pulmonary function test, arterial blood gas analysis, mMRC dyspnea scale, quality of life questionnaires and hospital anxiety depression scale were performed at before and 8 and 12 weeks after the program. *Results:* 6-minute walk distance, dyspnea, anxiety, depression and quality of life improved both at 8th and 12th week after EP when compared the with the initial assessment($P<0.05$). When compared with 8th week; mMRC dyspnea score, 6-minute walk distance and quality of life scores significantly improved at 12th weeks ($P=0.046$, $P=0.016$, $P<0.05$, respectively). *Conclusions:* Prolonging duration of the EPs results in more improvement in functional outcomes in patients with ILD. However, it has no effect on pulmonary functions and arterial blood gas results. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 299-307)*

Key words: exercise, interstitial lung diseases, program duration, six minute walk test, dyspnea, quality of life

Introduction

Interstitial lung diseases (ILD) are a group of diseases causing different levels of disorders in lung parenchyma characterized by an increase in elastic recoil pressure and a reduction in pulmonary volume and compliance (1,2). Although the underlying etiology of ILD changes, clinical, radiographic and pathophysiological features are similar (3).

Symptoms such as fatigue, loss of respiratory and peripheral muscle strength, dyspnea, exercise intolerance, anxiety or depression that may occur during the course of the disease result in a reduction in daily activities. As a result of physical deconditioning due to the decreased level of activity, fatigue, exercise intolerance, muscle weakness and reduction in daily activities may be observed in patients. The quality of life of the patients significantly deteriorates stuck in this negative vicious circle (4-7).

Pulmonary rehabilitation (PR) is an interdisciplinary and extensive program that consists of approaches such as individual exercise training following a patient evaluation, education and behavior change. It aims at improving the physical and emotional states of patients with chronic respiratory dis-

eases while promoting health-improving long-term and permanent behavioral changes. With the gradually increasing amount of scientific evidence, PR is now deemed as a standard care recommended for patients with chronic lung diseases (8).

Recently, PR has become an accepted treatment approach for ILD (9). While the evidence value of the exercise training that is the cornerstone of PR programs in ILD has been gradually increasing following a few randomized controlled studies, its optimal exercise prescription is yet to be known (10-15).

Studies related to the optimal duration of PR programs are often conducted on patients with Chronic Obstructive Pulmonary Disease (COPD) and at least an 8-week duration is recommended to benefit from the program as it is stated in these studies that the gains obtained from long-term programs last longer (16-19).

As for patients with ILD, there are a limited number of studies comparing the duration of different exercise programs (EPs). There is no comparative study of 8 and 12 weeks frequently used clinically. For this reason, we aim to analyze the impact of the 8- and 12-week EPs on functional results in patients with interstitial lung diseases.

Methods

Design

We conducted a prospective uncontrolled study. Prior to the study, all participating patients had been informed and their written consents had been taken. The study protocol (N: 334:7271) was approved by Izmir Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital. The study has been registered at the Clinical Trial registration website.

Setting

Pulmonary Rehabilitation Unit

Participants

Patients with ILD who were referred to the PR Unit from ILD Clinic of our hospital by a relevant specialist physician in 2014-2016 were included in this study. Sample size calculation was based on detecting a mean difference of 25 meters minimally clinically important difference on the 6- minute walk distance (6-MWD) for patients with ILD at the time of study design. The sample size of a minimum 14 patients was chosen to give a power of 90% to detect a 25 meters increase assuming an SD of 24 meter with a two-sided test at the 0.05 level.

The inclusion criteria for the study were determined as being over 18, medically stable, describing dyspnea on exertion despite standard medical treatment, being ambulated and cooperative. The exclusion criteria were determined as history of syncope, severe orthopedic or neurologic deficits that would prevent participation in the tests and exercises, unstable cardiac disease, having participated in a EP within the last 12 months, presence of mixed lung diseases, history of lobectomy or pneumonectomy, lack of motivation, poor compliance or having financial problems (8,11,20). Patients were not informed about the research hypothesis, although they were informed about the evaluations and exercise program.

Outcome measures

Demographic information (age, gender, body mass index), diagnose, disease duration, smoking history, medications, long-term oxygen treatment (LTOT), comorbidities, the number of visits to the emergency departments and hospitalization of the patients within a year had been recorded before the study. All measurements were repeated at the 8th and 12th week before and after the program by the same clinician.

6-MWD, which is the primary result measure of our study, was performed in a 30-meter long corridor in accordance with American Thoracic Society criteria (21). Changes in heart rate and peripheral oxygen saturation pre and post-tests were calculated. Modified BORG scale (0=no dyspnea, 10=very severe dyspnea) was used for exertional dyspnea perception (22). Walking distance was recorded after the test. By using values of age, gender, height and weight expected walking distance was calculated based on the recommended formula (23). The test was applied with oxygen support for the patients receiving LTOT.

Lung functions were evaluated by measuring body plethysmography (Zan 500, Germany), carbon

monoxide diffusing capacity (DLCO) test (Zan 300) and blood gas analysis (24).

Modified Medical Research Council (mMRC) Dyspnea Scale which is valid for ILD was used for dyspnea that patients felt during their daily activities. Patients were required to mark the most suitable phrase in the scale (1-5) for themselves (25).

St. George Respiratory Questionnaire (SGRQ), which is a disease-specific quality of life scale, and Short Form 36 (SF-36) Health Survey which assesses the quality of life related to health were used for patients with the respiratory disease to assess their quality of life. SGRQ (min: 0, max: 100) consists of four parts which are; symptom, activity, impact and total score and the lowest score show the highest quality of life in this scale (26). SF-36 Health Survey (min:0, max:100) consists of eight subtitles (physical function, social function, role physical, role emotional, general health, mental health, bodily pain, vitality) and high scores show the high quality of life in this survey (27).

Hospital Anxiety and Depression (HAD) Inventory was used for assessment of anxiety and depression. Scores of anxiety and depression are calculated separately. The maximum score for both is 21 and high scores correspond to high degree anxiety and depression. Cut-off scores for anxiety and depression were determined as 10/11 and 7/8 respectively (28).

Intervention

For 2 days a week, all patients participated in a supervised EP individually programmed for each patient. Breathing control, pursed-lip breathing, diaphragmatic and thoracic breathing, aerobic and strengthening training were applied in approximately 60-90 minute sessions. The patients were informed to apply for the training program at least once at home (8).

The aerobic training consisted of stationary cycling and walking on the treadmill for 15 minutes each. The initial walking intensity was set at a speed that was 80% of the peak speed (km/hr) achieved on the 6-MWD. The initial intensity of the stationary cycling prescribed at 70% of their maximum work rate calculated from their 6-MWD. When the patients achieved 15 minutes of continuous cycling or walking, the workload was increased within symptom tolerance (8,29).

Resistance training applied according to American College of Sports Medicine recommendations with 10-15 repetitions for upper and lower extremities using free weights and elastic bands. First, patients started training against gravity and then progressed as patient tolerance increased (30). It is adjusted to obtain a score of perceived exertion and dyspnea of 4-6 on the modified Borg scale. During exercise, pulse oximetry was used for supervision and oxygen supplementation was provided for patients receiving LTOT and if the SpO_2 dropped below 85% (8,10).

Statistical Analysis

The statistical analysis of the data obtained from the study was done via the statistics program 'Statistical Package for Social Science for Windows version 17'. The data distribution normality was checked with Shapiro Wilk analysis. Continuous variables were stated as median [interquartile range (IQR)] and the categorical variables were stated as percentages (%). Wilcoxon Signed Ranks test was used in the comparison of the pre- and post-treatment values of the same group. The test results were interpreted according to the 0.05 significance level of the p-value.

Results

Figure 1 shows a flow diagram of patient recruitment and follow – up through the study. In this study, 14 patients, 9 of which were women [Age; 63(53,70) years, body mass index: 28(25,32) kg/m², disease duration; 1.5 (1,4) years, Table 1] were enrolled. 11 of the patients (78.6 %) were followed with idiopathic pulmonary fibrosis (IPF), 2 (14.3%) were followed with sarcoidosis (stage 3 and 4) and 1 (7.1%) was followed with nonspecific interstitial pneumonia.

There were no active smokers among the patients. 4 of the patients (28.6 %) were ex-smokers and their cigarette consumption was 22 (20.29) p*years (Table 1). Within the past year; the number of emergency service visits was 0(0.1), and hospitalization was 0(0.0) (Table 1). When the comorbidities of the patients were inquired it was observed that 7 patients (50.0%) had hypertension, 2 patients (14.3%) had type 2 diabetes, 2 patients (14.3%) had heart failure,
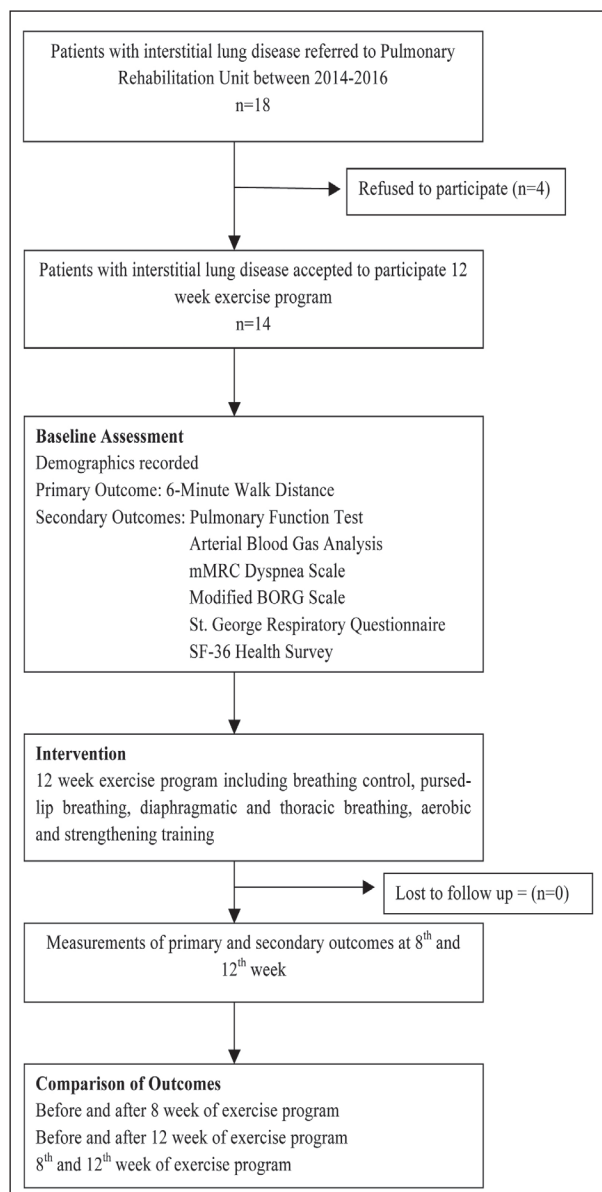
Fig. 1. Flow diagram of the study

1 patient (7.1%) had goiter and 1 patient (7.1%) had Behcet's disease.

There were 3 patients (21.4%) who received LTOT. There were 2 patients (14.3%) who received oral corticosteroid treatments and 7 patients (50.0%) who took inhaled corticosteroids.

When the results were compared to the initial values, no significant change was observed in pulmonary function test and arterial blood gas parameters in week 8 or 12 ($P > 0.05$, Table 2). Significant improvement was observed in 6 MWD and dyspnea perception in the 8th week with ($P = 0.001$, $P = 0.003$, respectively; Table 3) and this improvement significantly increased in the 12th week ($P = 0.016$, $P = 0.046$, respectively; Table 3). While exertional dyspnea after 6 MWT decreased in the 8th week ($P = 0.005$, Table 3), no change was observed at the 12th week compared to the 8th ($P = 0.739$, Table 3).

In the SGRQ; improvement was recorded in all sub-parameters in the 8th week ($P < 0.05$, Table 4) and it was observed that these improvements significantly increased in the 12th week ($P < 0.05$, Table 4). In the SF-36 survey; while significant improvement was recorded in physical function, general health, mental health and vitality parameters ($P = 0.006$, $P = 0.005$, $P = 0.036$, $P = 0.005$, respectively; Table 4); in the 12th week, no significant change was observed in these parameters or the parameters that showed no improvement in the 8th week ($P > 0.005$, Table 4). Anxiety and depression scores improved in the 8th week ($P = 0.038$, $P = 0.008$, respectively; Table 4). Prolonging the program to 12 weeks did not change the improvement of anxiety and depression scores ($P > 0.05$, Table 4).

All functional measurement changes in the 8th and 12th weeks compared to the initial values are listed in table 5. It is observed that the gain in the 6-MWD, our primary result measurement, reached 50 meters in the 8th week and 60 meters in the 12th week.

Table 1. Demographic and clinical features of patients

Variables (n=14)	Median (IQR)	Minimum	Maximum
Age (years)	63 (53,70)	50	82
Disease duration (years)	1.5 (1,4)	0.5	15
Body mass index (kg/m2)	28 (25,32)	23	40
Smoking consumption (pack*year)	22 (20,29)	20	30
Emergency admission (n/last year)	0 (0,1)	0	10
Hospital stay (n/last year)	0 (0,0)	0	1

IQR: Interquartile range

Table 2. Comparison of pulmonary function tests and arter blood gase analyses before and after 8 and 12 weeks of pulmonary rehabilitation

Variables	BPR	APR (8th week)	APR (12th week)	P*	P**	P***
FEV_1 (% predicted)	78(69,83)	79 (71,82)	78 (66,83)	0.972	0.900	0.609
FVC (% predicted)	74 (67,78)	76 (66,80)	78 (58,81)	0.428	0.575	0.806
FEV_1/FVC	85 (81,87)	85 (81,90)	89 (82,107)	0.779	0.278	0.100
VC (% predicted)	79 (64,88)	79 (55,89)	85 (78,91)	0.674	0.499	0.395
IC (% predicted)	63 (59,87)	59 (42,95)	95 (70,109)	0.917	0.091	0.091
RV (% predicted)	90 (63,317)	71 (51,87)	82 (66,103)	0.068	0.109	0.285
DLCO (% predicted)	40 (19,45)	43 (23,50)	43 (26,51)	0.069	0.406	0.074
PaO_2 (mmHg)	80 (78,91)	85 (75,89)	88 (74,97)	0.396	0.116	0.136
$PaCO_2$ (mmHg)	37 (35,40)	39 (36,41)	38 (37,41)	0.328	0.388	0.583
SaO_2 (%)	96 (95,98)	97 (95,98)	97 (95,98)	0.470	0.382	0.722

Wilcoxon Signed Rank Test, Data are expressed as median (interquartile range), BPR: Before pulmonary rehabilitation, APR: After pulmonary rehabilitation, FEV_1: Forced expiratory volume in the 1s, FVC: Forced vital capacity, VC: Vital capacity, IC: Inspiratory capacity, RAW: Airways resistance, RV: Residuel Volume, DL_{CO}: Carbon monoxide diffusing capacity. PaO_2: Partial arterial oxygen pressure, $PaCO_2$: Partial arterial oxygen pressure. SaO_2: Arterial oxygen saturation
*for comparison of outcomes before and 8 weeks after PR
** for comparison of outcomes before and 12 weeks after PR
***for comparison of outcomes of 8 and 12 weeks of PR

Table 3. Comparison of dyspnea and exercise capacity before and after 8 and 12 weeks of pulmonary rehabilitation

Variables	BPR	APR (8th week)	APR (12th week)	P*	P**	P***
MMRC	3 (2,4)	2 (1,3)	2 (1, 2)	0.003	0.002	0.046
6MWD (meter)	355 (261,412)	390 (357,442)	420 (380, 442)	0.001	0.001	0.016
6MWD (% predicted)	70 (53,79)	74 (72,88)	78 (76,90)	0.001	0.001	0.028
ΔHeart rate (beats/minute)	19 (9,28)	19 (8,31)	18 (8,29)	0.889	0.116	0.327
ΔMB (dyspnea)	1.5 (1,3)	1 (0,2)	0 (0,2)	0.005	0.018	0.739
$ΔSpO_2$	2 (0,3)	1 (1,5)	2 (1,4)	0.123	0.270	0.552

Wilcoxon Signed Rank Test, Data are expressed as median (interquartile range), Δ values show changes between pre and post test, BPR: Before pulmonary rehabilitation, APR: After pulmonary rehabilitation, MMRC: Medical Research Council Dyspnea Scale 6MWD: Six minutes walk distance, MB: Modify Borg Scale, SpO_2: Peripheral oxygen saturation
*for comparison of outcomes before and 8 weeks after PR
** for comparison of outcomes before and 12 weeks after PR
***for comparison of outcomes of 8 and 12 weeks of PR

Discussion

In our study, where we compared different EP durations in patients with ILD, we observed that prolonging the 8-week program to 12 weeks was more effective in terms of exercise capacity, dyspnea and disease-related quality of life parameters.

Under clinical conditions, the duration of exercise training programs is usually planned according to the routine operation of the health center or the availability of the patients (31). In studies with ILD patients, usually 8-12 week programs for 2 to 3 times a week were carried out (11-13,20). In a study by Salhi et al. it was stated that prolonging the 12-week program to 24 weeks in a mixed group of chest wall diseases and patients with ILD was extra beneficial in terms of exercise capacity and dyspnea (32). Simi-

lar to our study, this study also revealed no change in pulmonary function parameters. Although the 24-week program applied in this study provided significant benefits, it is longer than the routine clinical applications and thus might not be practical for every patient. However, most clinicians find it difficult to decide whether to go with 8 weeks or 12 weeks, the durations we compare in our study. The effects of such a short-term change had not been analyzed in previous studies. Although the result of our study supports the argument that is longer programs are more effective especially in COPD patients (16), it would also provide insight for clinicians working on patients with ILD while creating exercise plans. It was observed that even an extension of 4 weeks in the program was effective in exercise capacity, dyspnea and quality of life.

Table 4. Comparison of quality of life and anxiety and depression before and after 8 and 12 weeks of pulmonary rehabilitation

Variables	BPR	APR (8th week)	APR (12th week)	P*	P**	P***
SGRQ						
Symptom	56 (37,72)	33 (22,57)	30 (21,53)	0.006	0.004	0.005
Activity	56 (48,83)	53 (43,68)	50 (40,72)	0.015	0.016	0.023
Impact	49 (22,62)	37 (9,47)	34 (9,42)	0.046	0.016	0.009
Total	57 (30,69)	47 (23,52)	45 (21,50)	0.005	0.002	0.001
SF-36						
Physical Function	65 (20,80)	75 (40,86)	75 (45,81)	0.006	0.016	0.512
Social Function	75 (50,94)	87 (59,87)	84 (64,88)	0.319	0.423	0.572
Role Physical	25 (25,100)	50 (25,81)	50 (25,75)	0.571	0.317	0.374
Role Emotional	33 (0,100)	50 (31,100)	58 (46,90)	0.389	0.278	0.285
General Health	40 (17,66)	58 (39,69)	60 (40,69)	0.005	0.007	0.687
Mental Health	72 (38,80)	66 (58,81)	68 (72,82)	0.036	0.033	0.444
Bodily pain	62 (51,84)	76 (49,90)	75 (60,90)	0.423	0.366	0.766
Vitality	50 (27,80)	73 (54,86)	66 (59,88)	0.005	0.003	0.779
HAD						
Anxiety	6 (5,10)	5 (2,8)	5 (2,6)	0.038	0.013	0.096
Depression	4 (1,10)	3 (0,6)	3 (0,5)	0.008	0.009	0.334

Wilcoxon Signed Rank Test, Data are expressed as median (interquartile range), BPR: Before pulmonary rehabilitation, APR: After pulmonary rehabilitation, SGRQ: St. George Respiratory Questionnaire, SF-36: Short-Form Health Survey, HAD: Hospital Anxiety and Depression Scale
*for comparison of outcomes before and 8 weeks after PR
** for comparison of outcomes before and 12 weeks after PR
***for comparison of outcomes of 8 and 12 weeks of PR

Table 5. Changes in outcomes between initial and 8th and 12th week of pulmonary rehabilitation

Variables	Δ1	Δ2	Δ3
MMRC	-1 (-1.5,-1)	-1 (-2,-1)	0 (-0.5,0)
6MWD (meter)	50 (20,86)	60 (35,109)	10 (0,22)
SGRQ			
Symptom	-17 (-27,-4)	-18 (-31,-4)	-2 (-4,0)
Activity	-6 (-24,0)	-10 (-27,-4)	-3 (-5,0)
Impact	-10 (28,5)	-10 (-29,2)	-2 (-4,0)
Total	-10 (-26,-1)	-11 (-27,-6)	-2 (-4,-1)
SF-36			
Physical Function	10 (3,23)	10 (-2,28)	1 (0,5)
Social Function	13 (-13,25)	10 (-13,28)	0 (-1,3)
Role Physical	13 (-13,56)	25 (-31,56)	0 (0,6)
Role Emotional	0 (0,33)	17 (-13,50)	0 (-1,19)
General Health	22 (9,25)	20 (5,31)	-1 (-2,-1)
Mental Health	8 (0,18)	5 (-1,22)	0 (-2,5)
Bodily pain	1 (-6,13)	4 (-8,15)	0 (-2,2)
Vitality	15 (3,30)	15 (5,33)	0 (-2,6)
HAD			
Anxiety	-3 (-4,0)	-3 (-5,-1)	0 (-1,0)
Depression	-2 (-4,-1)	-2 (-5,-1)	0 (-1,0)

Data are expressed as median (interquartile range), MMRC: Medical Research Council Dyspnea Scale 6MWD: Six minutes walk distance, SGRQ: St. George Respiratory Questionnaire, SF-36: Short-Form Health Survey, HAD: Hospital Anxiety and Depression Scale
Δ1: Changes of outcomes before and 8 weeks after PR
Δ2: Changes of outcomes before and 12 weeks after PR
Δ3: Changes of outcomes 8 and 12 weeks after PR

The exercise limitation in ILD patients is related to various factors including deterioration in respiratory mechanics, gas changes, circulatory reasons, peripheral muscle dysfunction, hypoxia, tiredness and physical inactivity (33-36).In addition to cardiopulmonary exercise testing, 6-minute walk test (6MWT) has been extensively used in determining the exercise capacity in the studies conducted on these patients (37,38). The 6-MWT is becoming increasingly important in determining the prognosis in patients with IPF (5,39). Similarly, a relation has been found between the level of desaturation during the 6-MWT and mortality (40). Thus, the importance of PR, a non-pharmacological approach, and exercise in these patients has been gradually increasing (8). The median of 6-MWD of the patients included in our study was 355 meters. This was determined to be approximately 70% of the expected value according to age and gender. This result is consistent with the literature. In addition, in the studies conducted by Ryerson et al. on ILD patients, the patients were observed to have walked 70% of the expected walk distance (14). Similar to our study, the pre-exercise distance in the study by Holland et al. is 375 meters (11). The minimum clinically important difference value of the gain in the 6-MWD in patients with ILD is approximately 25 meters (11,41). While the gain in the exercise capacity in our study is 50 meters in the 8th week, this gain increased to 60 meters in the 12th week. This gain is a little more than the amounts in other studies in the literature. This might be due to the fact that ILD describes a heterogenic disease group and thus, the disease progressions might vary.

Although it is well known in the literature that patients with ILD have a slow response to exercise, lack of occurrence of significant symptoms during PR and being medically stable may increase their response to exercise. According to the feedback received from the patients, we think that another reason behind the high gain in the walking distance may be their compliance with home programs. However, patient compliance could not be assessed with exercise diaries.

In our study, the lack of any change in the medical treatment, LTOT, etc. of patients during the 12-week suggests that the gains are largely related to the prolongation of the exercise program. All gains may be related to each other. We observed that the prolongation of the program duration had a significant impact on the recovery of dyspnea. We believe that this might be due to the increased exercise capacity. Moreover the increase in compliance with dyspnea reduction strategies and learning to cope with dyspnea by experiencing repeated dyspnea during the patient's exercise program might be a reason for these gains. Decreased dyspnea may be a cause of the reduction in symptom score in disease-related quality of life assessment. Patients may be more active due to decreased dyspnea. At the same time, participating in the group exercise program might have made them feel better socially. The longer the duration of the program, the more likely it is that changes in compliance with care and lifestyle changes are expected. In addition, the increase in 6-MWD walk distance can be attributed to the increase in muscle strength that is one of the most important factors affecting the exercise capacity in ILD patients (32). However, since muscle strength measurement is not carried out in our study, it is not possible to make a definite comment on this issue.

In our study, we used mMRC dyspnea scale, which is a valid measurement in the assessment of shortness of breath and symptom severity in patients with ILD (11,42). The dyspnea levels of the patients were found to be more severe than that of the patient group in the study by Downman et al. and moderate in the study by Holland et al. similar to our study. Moreover, in the study by Holland et al. improvement was observed in dyspnea in the 8th week following the training program similar to ours. The minimum clinical significance value of the MMRC dyspnea scale for COPD patients is 1; however, there is no value determined for ILD (43). In our study, we obtained the value that applies to COPD patients in the 8th week.

It was revealed that one-third of the ILD patients, especially the ones with severe dyspnea, had anxiety and 25%, especially the ones with a high number of comorbidity, had depression (44). However, there are only a few number of studies conducted on these patients that evaluate anxiety and depression (12,14,45). The HAD questionnaire we used is also used in the study by Naji et al. and after an 8-week training performed twice a week, the only difference from our study was a significant improvement in the depression score (12). In our study, the improvement was observed in both anxiety and

depression scores; however, the prolongation of the program did not lead to an increased gain. We believe that the reason behind this is the fact that the anxiety and depression scores of our patients were very low prior to the program.

SF-36 and SGRQ are the most frequently used questionnaires in the evaluation of the quality of life in patients with ILD. Longitudinal data utilizing the SGRQ-original in a group of patients with IPF indicates that the SGRQ is an independent predictor of disease progression (46). In previous studies, 5-8 unit changes for SGRQ and 2-4 unit changes for SF-36 were given as the minimum clinically important difference values in patients with IPF (47). In our study, which comprises mainly of patients with IPF, the gains in the scores of both questionnaires are above these values.

In studies about PR programs conducted on patients with ILD, the exercise training was most frequently utilized and it was revealed that the exercise training improved the exercise tolerance, dyspnea perception and quality of life in these patients. However, the optimal program in the programs applied on patients with ILD is not clearly set. In previous studies, EPs applied on patients with COPD were tried out and were found safe (8-10). In our study, we also applied the EP prescribed in ILD studies and observed no adverse effects.

It is noticed that in studies conducted on a mixed group of patients with ILD, the majority of the patient group usually consists of patients with IPF (11,13,14,32,42). In these patients, the exercise-induced gas change anomalies are more frequent than the other ILDs. Similarly, the majority of the patient group in our study comprises of patients with IPF. However, we could not compare the data of IPF with other patients because of our small sample size.

There were some limitations to our study. The first limitation was that the extremity and respiratory muscle strength of the patients could not be evaluated due to lack of technical equipment. Another limitation of our study was that the patients in either group could not be evaluated in the long-term. It is stated that in some studies conducted on these patients, the gains from the program usually disappear after 6 months. Although we believe that the effects of longer programs last longer, we could not prove that with a long-term follow-up evaluation. As the study group was a rather small group, no subgroup analysis was performed on the patients that take corticosteroids or receive oxygen support.

The purpose of our study was to show whether prolonging the exercise programs from 8 weeks to 12 weeks were achieving gains in clinics of patients. However, it is difficult to say that the 12 weeks is optimal. If we prolonged the duration of the program a little longer (e.g. 16 weeks or more), the gains would have been more. Therefore, our recommendation to clinicians is to prolong the duration of the program if factors such as working conditions of health centers and patient participation are available in patients with ILD.

Conclusion

While prolonging the duration of the program from 8 weeks to 12 did not cause any change in parameters that had not changed within 8 weeks, such as pulmonary function test or arterial blood gas results, it had positive effects on the exercise capacity, dyspnea perception and quality of life in patients with ILD. We believe that with suitable clinical conditions and patient compliance, prolonging the duration of the program will benefit these patients.

Clinical Trial Number: NCT03302702

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Supplementary Table S1:

Full ROC Analysis

%DLCO	%FVC	Sensitivity (%)	Specificity (%)	Sum	PPV (%)	NPV (%)
<30%	<30%	7	100	107	100	75
<30%	<40%	10	99	109	80	75
<30%	<50%	14	94	108	46	75
<30%	<60%	26	92	118	55	77
<30%	<70%	26	91	117	52	77
<30%	<80%	25	90	115	54	72
<40%	<30%	7	99	106	75	74
<40%	<40%	14	98	112	75	76
<40%	<50%	36	93	129	65	80
<40%	<60%	52	88	140	61	83
<40%	<70%	55	83	138	55	83
<40%	<80%	59	79	138	51	84
<50%	<30%	7	99	106	75	74
<50%	<40%	14	97	111	67	76
<50%	<50%	38	90	128	59	80
<50%	<60%	62	82	144	55	85
<50%	<70%	67	71	138	46	85
<50%	<80%	74	64	138	43	87
<60%	<30%	7	99	106	75	74
<60%	<40%	14	97	111	67	76
<60%	<50%	38	89	127	57	80
<60%	<60%	62	81	143	54	85
<60%	<70%	69	67	136	43	85
<60%	<80%	83	49	132	38	89

Abbreviations: ROC = receiver operating curve, %DLCO = percent predicted of diffusion capacity for carbon monoxide, %FVC = percent predicted of forced vital capacity, PPV = positive predictive value, NPV = negative predictive value

Supplementary Table S2:

Baseline Characteristics of Patients with Echocardiographic PH by Scadding Stage

Variable	Scadding 0/1 (n = 18) Med/F (IQR/%)	Scadding 2 (n = 8) Med/F (IRQ/%)	Scadding 3 (n = 5) Med/F (IRQ/%)	Scadding 4 (n = 9) Med/F (IQR/%)	p-value
Race (%AA)	18 (100%)	8 (100%)	5 (100%)	8 (89%)	0.550
Gender (%F)	13 (72%)	6 (75%)	3 (60%)	5 (56%)	0.751
Age (years)	55 (46-64)	46 (44-55)	56 (44-57	57 (54-61)	0.277
BMI (kg/m^2)	27.8 (22.7-36.0)	30.6 (28.4-31.8)	29.4 (27.8-31.9)	30.4 (28.6-32.3)	0.844
%FVC	54 (46-66)	47 (40-57)	52 (41-53)	69 (52-72)	0.186
%FEV$_1$	53 (45-61)	46 (39-49)	40 (37-52)	55 (51-74)	0.143
FEV$_1$/FVC	78 (74-84)	79 (72-84)	79 (77-86)	79 (73-82)	0.971
%FEF$_{25-75}$	47 (41-70)	34 (28-52)	36 (33-48)	62 (52-80)	0.347
%TLC	61 (52-72)	67 (51-79)	57 (47-68)	70 (61-78)	0.401
%RV	65 (57-84)	82 (61-121)	83 (57-112)	75 (66-85)	0.577
%FRC	60 (50-73)	69 (51-81)	70 (49-90)	61 (58-82)	0.795
%ERV	50 (39-62)	29 (19-48)	56 (42-62)	53 (29-60)	0.323
%DLCO	36 (28-40)	29 (23-39)	42 (31-47)	48 (34-74)	0.305
%DLCO/%VA	66 (53-85)	72 (68-83)	87 (75-103)	74 (60-100)	0.291

Abbreviations: AA = African-American, F=female, BMI = body-mass index, %FVC = percent-predicted of forced vital capacity, %FEV$_1$ = percent-predicted of forced expiratory volume in one second, %FEF$_{25-75}$ = percent-predicted of forced expiratory flow at 25-75% of the pulmonary volume, %TLC = percent-predicted of total lung capacity, %RV = percent-predicted of residual volume, %FRC = percent-predicted of functional residual capacity, %ERV = percent-predicted of expiratory reserve volume, %DLCO = percent-predicted of diffusion capacity for carbon monoxide, %DLCO/VA = percent-predicted of DLCO when corrected for alveolar volume, Scadding Stage 0 = No evidence of parenchymal disease or adenopathy on chest imaging, PH= pulmonary hypertension
P-value: Kruskall-Wallis Test or Fisher's Exact Test for continuous or categorical data respectively

Med/F = Median or Frequency (for continuous or categorical variables respectively)
IQR/% = Interquartile range or percentage (for continuous or categorical variables respectively)