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Antifibrotic therapy in idiopathic pulmonary fibrosis candidates for lung transplantation undergoing pulmonary rehabilitation

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ABSTRACT

Objective: To investigate the impact of pulmonary rehabilitation (PR) on functional outcomes and health-related quality of life (HRQoL) in idiopathic pulmonary fibrosis (IPF) patients placed on a lung transplant waitlist and receiving antifibrotic therapy (AFT). **Methods:** This was a retrospective observational study of consecutive IPF patients receiving AFT with either pirfenidone or nintedanib (the AFT group) and undergoing PR between January of 2018 and March of 2020. The AFT group and the control group (i.e., IPF patients not receiving AFT) participated in a 12-week PR program consisting of 36 sessions. After having completed the program, the study participants were evaluated for the six-minute walk distance (6MWD) and HRQoL. Pre- and post-PR 6MWD and HRQoL were compared within groups and between groups. **Results:** There was no significant difference between the AFT and control groups regarding baseline characteristics, including age, airflow limitation, comorbidities, and oxygen requirement. The AFT group had a significant increase in the 6MWD after 12 weeks of PR (effect size, 0.77; $p < 0.05$), this increase being significant in the between-group comparison as well (effect size, 0.55; $p < 0.05$). The AFT group showed a significant improvement in the physical component of HRQoL at 12 weeks (effect size, 0.30; $p < 0.05$). **Conclusions:** Among IPF patients undergoing PR, those receiving AFT appear to have greater improvements in the 6MWD and the physical component of HRQoL than do those not receiving AFT.

Keywords: Idiopathic pulmonary fibrosis; Lung transplantation; Rehabilitation.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and irreversible lung disease that is currently the second most common indication for lung transplantation worldwide.[1] The prognosis of IPF is poor, with a mean life expectancy of 2-5 years after the diagnosis has been made. The course of IPF is irreversible, and most patients experience episodes of acute pulmonary exacerbation, with recurrent hospitalizations being required for respiratory support and symptom control in many cases.[2] Additionally, progressive hypoxia and impaired exercise tolerance lead to reduced health-related quality of life (HRQoL).[3]

There are currently two antifibrotic therapies (AFTs) that have been shown to slow the progression of IPF, reduce the decline in FVC, and decrease all-cause mortality: pirfenidone and nintedanib.[4,5] However, these AFTs do not improve dyspnea, exercise tolerance, or HRQoL.[6] On the other hand, pulmonary rehabilitation (PR) has been shown to improve these functional outcomes (and HRQoL) significantly, and therefore remains a central component in the management of IPF.[7-9] Although most studies have found that AFT does not have a significant impact on functional outcomes, whether or not patients receiving AFT have a better functional response to PR than do those not receiving AFT has yet to be extensively investigated, particularly in Brazil.

The objective of the present study was to investigate the impact of PR on functional outcomes and HRQoL in IPF patients placed on a lung transplant waitlist and receiving AFT.

METHODS

This was a retrospective observational study performed at a referral center for lung transplantation in the city of Porto Alegre, Brazil. Consecutive patients diagnosed with IPF and undergoing PR between January of 2018 and March of 2020 while on a waiting list for lung transplantation were included in the study. Cases were defined as those using either pirfenidone or nintedanib prior to starting PR, and controls were defined as those who were not on any AFT before starting PR. A multidisciplinary team of pulmonologists, radiologists, pathologists, and generalists discussed imaging and histopathological findings in order to rule out secondary causes of fibrotic lung disease.

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Selected cases underwent surgical lung biopsy. IPF was diagnosed on the basis of HRCT findings and surgical lung biopsy findings in selected patients, in accordance with the 2011 or 2018 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/*Asociación Latinoamericana de Tórax* guidelines, with the latter being used for patients with a more recent diagnosis.[10,11] During PR, demographic, histopathological, clinical, and functional data were obtained.

Patients with clinically significant resting hypoxemia (resting SpO_2 ≤ 88%) were prescribed long-term oxygen therapy. Data were retrospectively reviewed from patient medical records, including pre- and post-PR data (when available). Completion of a PR program was defined as participation in at least 36 sessions[12] and all post-PR evaluations, including a six-minute walk test (6MWT) and an HRQoL questionnaire.[13,14] This study was approved by the local institutional review board (Protocol n. 04453412.7.0000.5335) with waiver of consent.

The PR program consisted of medical appointments with the PR team every two months and included psychiatric evaluation, nutritional counseling, social assistance, and monthly educational lectures.[12] The physical training component of the program was administered by two physical therapists, with three sessions per week for a total of 36 sessions. During physical training, patients performed an initial warm-up, followed by muscle strengthening and aerobic exercises. The warm-up consisted of breathing exercises (respiratory cycle) and arm raising. Muscle strengthening was based on arm and leg exercises performed with an initial load of 30% of a one-repetition maximum test, with a set of ten repetitions per exercise. The load was increased by 0.5 kg every seven sessions depending on exercise tolerance.[12] Aerobic exercises were performed on a treadmill at 70% of the speed achieved on the 6MWT, the speed being progressively increased every 6 min for a total of 30 min of exercise. The speed was increased by 0.3 km/h every seven sessions. The exercises were interrupted if patients reported dyspnea or leg fatigue, as assessed by a modified Borg scale score > 4, or if SpO_2 reached 92%. When patients presented with an SpO_2 of < 92%, exercise intensity was reduced and oxygen flow was increased in an attempt to sustain exercise effort and encourage patients to tolerate dyspnea. At the end of each session, patients performed stretching exercises for all of the major muscle groups involved. During PR, all patients received continuous oxygen therapy as prescribed and were constantly monitored by pulse oximetry so that SpO_2 was maintained at ≥ 92%. The modified Borg scale was used in order to assess dyspnea and leg discomfort.

Patient medical records were reviewed for treatment with pirfenidone or nintedanib before PR, and those patients who were using either drug before PR were included in the AFT group. The minimum dose was 267 mg (2 tablets) three times per day for pirfenidone and 100 mg twice per day for nintedanib. Patients in whom AFT had been discontinued 12 weeks before PR were included in the control group.[15]

Pulmonary function tests were performed in accordance with the American Thoracic Society/European Respiratory Society technical procedures and acceptability and reproducibility criteria.[16,17] All pulmonary function tests were performed in our pulmonary function laboratory, which is certified by the Brazilian Thoracic Association. In addition to administering the pulmonary function tests, the same physical therapists administered the 6MWT, in accordance with the American Thoracic Society recommendations,[13] and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36),[14] in order to evaluate HRQoL.

Our primary outcome was to evaluate the impact of PR on functional outcomes and HRQoL using the 6MWT and SF-36, respectively. Pre- and post-PR six-minute walk distance (6MWD) and HRQoL were compared within groups and between groups, with post-PR 6MWD and HRQoL being compared between AFT and control group patients. Data were presented as absolute and relative frequencies, mean ± standard deviation (95% confidence interval), or median (interquartile range). The normal distribution of the data was evaluated with the Shapiro-Wilk test. Comparisons of proportions were made with the chi-square test for categorical variables and the Student's t-test for continuous variables. For within-group differences, the effect size was calculated in accordance with Cohen,[18] by dividing the difference between the mean values at baseline and at follow-up by the pooled standard deviation of both values. For between-group differences, the effect size was calculated in accordance with Carlson & Smith,[19] by using the pooled pretest standard deviation for weighting the differences of the pre-post-means.[20] Effect sizes were classified as small (0.2), medium (0.5), or large (0.8). A two-sided p-value of 0.05 was considered statistically significant. All analyses were performed with the Stata statistical software package, version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 32 patients with IPF were included in the present study. Of those, 16 were in the AFT group and 16 were in the control group. Most of the patients were male, were 60 years of age or older, had a history of smoking (26-30 years of smoking), and were on long-term oxygen therapy (Table 1). There were no differences between the AFT group and the control group regarding FEV_1, FVC, or the FEV_1/FVC ratio (Table 1). There was no significant difference in the 6MWD between the AFT and control groups at study entry.

Tables 2 and 3 summarize the effects of PR on the 6MWD and HRQoL in the AFT and control groups. Although there was no significant change in the 6MWD after 12 weeks in the control group, there was an increase in the 6MWD in the AFT group (effect size,

0.77; p < 0.05). There was a significant difference in the pre- and post-PR 6MWD between the two groups, with an effect size of 0.554 (p < 0.05). The other parameters measured during the 6MWT (heart rate, oxygen saturation, dyspnea, and leg discomfort) were not significantly different at 12 weeks when they were compared either within groups or between groups.

With regard to the SF-36, almost all physical and mental components improved between the groups and within the AFT group before and after PR. A within-group improvement in the physical component was observed after PR in the AFT group (effect size, 0.30; p < 0.05), although not in the control group. However, the between-group difference in the physical component was not significant.

DISCUSSION

This study sought to evaluate the impact of PR on functional outcomes and HRQoL in IPF patients placed on a lung transplant waitlist and receiving AFT in comparison with those not receiving AFT. We found that those who were receiving AFT had significant within- and between-group improvements in the 6MWD after 36 sessions (12 weeks) of PR, along with a significant within-group improvement in physical functioning, as assessed by the SF-36.

A PR program includes training to improve muscle strength, aerobic training to improve endurance, and patient education, involving a multidisciplinary team of generalists, physical therapists, nutritionists, and psychologists.[7,21] The effects of PR include improved exercise tolerance, decreased dyspnea, increased exercise duration, increased 6MWD, and, consequently, improved HRQoL.[9,12,22] PR is safe and has a low risk of adverse events in patients with IPF, with a recommended duration of 12 weeks at specialized centers.[23]

Dyspnea is one of the predominant symptoms in patients with IPF and worsens HRQoL when associated with muscle weakness, thus contributing to the development of depression.[24] Hypoxemic patients with advanced disease can have high exertional oxygen requirements to participate in aerobic training, and oxygen therapy at rest or during exercise is essential to improve dyspnea, which can be minimized by means of PR.[25,26] In this study, although there was no significant change in SaO_2 or in dyspnea as assessed by the modified Borg scale, the study participants reported a significant improvement in the physical component of HRQoL as assessed by the SF-36, which is a surrogate for better physical performance at the end of 36 sessions of PR.

Despite the positive effects of AFT on lung function and survival, AFTs are not known to improve HRQoL or dyspnea. For this reason, PR has become an important adjuvant in the management of patients with IPF, particularly those on a lung transplant waitlist. However, there is a lack of studies investigating whether AFT can have an adjuvant effect on functional parameters and, consequently, HRQoL when associated with PR, given that AFT and PR both slow disease progression. Thus, our findings suggest that the use of AFT can increase the beneficial effects of PR on functional outcomes in these patients. One explanation for this is that patients who are not on AFT have a more rapid

Table 1. Baseline characteristics of the study participants.[a]

Variable	Group		p
	Control (n = 16)	AFT (n = 16)	
Male sex	13 (81.3)	12 (75.0)	1.000
Age, years	60 ± 9	63 ± 5	0.373
BMI, kg/m^2	25.9 ± 1.42	27.8 ± 4.54	0.113
FEV_1, L	1.70 ± 0.46	1.68 ± 0.40	0.919
FEV_1, % predicted	55 ± 13	55 ± 14	0.953
FVC, L	1.98 ± 0.64	1.93 ± 0.54	0.818
FVC, % predicted	51 ± 14	49 ± 14	0.694
FEV_1/FVC ratio	0.87 ± 0.08	0.88 ± 0.08	0.785
DL_{CO}, % predicted	39 ± 11	37 ± 5	0.591
PASP, mmHg	45.5 ± 11.5	45.0 ± 14.9	0.919
6MWD, m	429 ± 104	358 ± 100	0.164
Hypertension	7 (43.8)	4 (25.0)	0.458
Diabetes mellitus	2 (12.5)	2 (12.5)	1.000
Osteopenia	4 (25.0)	1 (6.3)	0.333
Ischemic heart disease	5 (31.3)	3 (18.8)	0.685
Former smoker	11 (68.8)	8 (50.0)	0.473
Smoking, years	26 [18-31]	30 [5-37]	0.817
Long-term oxygen therapy	12 (85.7)	13 (81.3)	1.000
Oxygen flow rate, L/min	5.00 ± 1.96	4.81 ± 1.42	0.765

[a]Data presented as n (%), mean ± SD, or median [IQR]. AFT: antifibrotic therapy; PASP: pulmonary artery systolic pressure; and 6MWD: six-minute walk distance.

Table 2. Effects of pulmonary rehabilitation on parameters measured during the six-minute walk test.[a]

Outcome	PR	Mean ± SD		Within-group comparison between pre- and post-PR values	Between-group comparison between pre- and post-PR values
		Pre-PR	Post-PR	Mean difference (95% CI); Effect size[18] *	Mean difference (95% CI); Effect size[19,20] *
Six-minute walk test					
6MWD, m	CG	429 ± 104	448 ± 107	18 (−17 to 55); 0.18	59 (11 to 105); 0.554**
	AFT	358 ± 100	435 ± 99	77 (43 to 111); 0.77**	
Post-PR HR, bpm	CG	120 ± 26	132 ± 22	12 (1 to 24); 0.49	2 (−16 to 18); 0.087
	AFT	115 ± 18	129 ± 21	14 (1 to 27); 0.71	
Post-PR SpO_2, %	CG	76 ± 6	76 ± 8	0 (−2.0 to 0.4); 0.00	−1.0 (−7.3 to 5.6); 0.110
	AFT	81 ± 11	80 ± 7	−1.0 (−2.7 to 1.1); 0.10	
Post-PR dyspnea, modified Borg scale score	CG	5 ± 3	4 ± 2	−1.0 (−2.0 to 2.8); 0.32	0.0 (−2.0 to 2.5); 0.000
	AFT	5 ± 3	4 ± 1	-1.0 (−2.7 to 1.0); 0.44	
Post-PR leg discomfort, modified Borg scale score	CG	2 ± 2	2 ± 2	0.0 (0.0 to 0.0); 0.00	0.0 (0.0 to 0.0); 0.000
	AFT	2 ± 2	2 ± 2	0.0 (0.0 to 0.0); 0.00	

[a]Data presented as mean ± SD or mean difference (95% CI). PR: pulmonary rehabilitation; CG: control group; and AFT: antifibrotic therapy group. *For within-group differences, the effect size was calculated in accordance with Cohen,[18] by dividing the difference between the mean values at baseline and at follow-up by the pooled standard deviation of both values. For between-group differences, the effect size was calculated in accordance with Carlson & Smith,[19] by using the pooled pretest standard deviation for weighting the differences of the pre-post-means.[20] **p < 0.05.

Table 3. Effects of pulmonary rehabilitation on health-related quality of life.[a]

Outcome	PR	Mean ± SD		Within-group comparison between pre- and post-PR values	Between-group comparison between pre- and post-PR values
		Pre-PR	Post-PR	Mean difference (95% CI); Effect size[18] *	Mean difference (95% CI); Effect size[19,20] *
SF-36					
Physical component summary	CG	33 ± 14	36 ± 17	3 (−5 to 10); 0.19	3 (−6 to 12); 0.134
	AFT	36 ± 15	41 ± 18	6 (0 to 12); 0.30**	
Mental component summary	CG	54 ± 18	61 ± 19	7(−3 to 18); 0.37	−4 (−19 to 10); 0.154
	AFT	56 ± 20	60 ± 27	3 (−8 to 15); 0.16	

[a]Data are presented as mean ± SD or mean difference (95% CI). PR: pulmonary rehabilitation; CG, control group; AFT: antifibrotic therapy group; and SF-36: Medical Outcomes Study 36-item Short-Form Health Survey. *For within-group differences, the effect size was calculated in accordance with Cohen,[18] by dividing the difference between the mean values at baseline and at follow-up by the pooled standard deviation of both values. For between-group differences, the effect size was calculated in accordance with Carlson & Smith,[19] by using the pooled pretest standard deviation for weighting the differences of the pre-post-means.[20] **p < 0.05.

decline in pulmonary function and therefore benefit less from PR than do those who are receiving AFT.

Our study has limitations. First, this was a single-center study involving a small sample of patients. This limits the generalization of our results and might have influenced some of the differences that we found between the groups. Second, this was a retrospective observational study rather than an interventional placebo-controlled trial, and it has all of the limitations inherent to this design. Therefore, potential confounding variables, including the placebo effect, could have contributed to the improvement observed herein, although there was no statistically significant difference in baseline demographics between the groups. Furthermore, our data pragmatically reflect real-world clinical practice and should be interpreted as such.

In this retrospective observational study conducted in a referral center for lung transplantation in Brazil, exploratory findings suggest that AFT is associated with improvements in the 6MWD after 36 sessions of PR. In addition, the group of patients receiving AFT while undergoing PR reported a positive within-group change in the physical component of HRQoL at the end of 12 weeks of PR.

AUTHOR CONTRIBUTIONS

MMPP, GB, SA, and GW: conceptualization; methodology; investigation; data curation; and drafting of the manuscript. JF, DZN, ASR, GMH, FBN, and IR: investigation; data curation; drafting of the manuscript; and reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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