

# Pulmonary Rehabilitation in Patients with Interstitial Lung Disease. Experience in a Specialized Hospital in Argentina

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## Abstract

**Introduction:** Interstitial lung diseases generate in patients exercise intolerance, dyspnea, and a decrease in health-related quality of life. Pulmonary Rehabilitation plays an important role in the treatment of these patients.

**Materials and Methods:** We conducted a retrospective study in a cohort of patients with interstitial lung disease (DILD) who underwent Pulmonary Rehabilitation (PR) between 2012 and 2015. Patients completed a 4-month treatment program including aerobic, core, and upper and lower limbs strength training and health education. Quality of life was measured with the St. George's Respiratory Questionnaire (SGRQ), and exercise tolerance with the 6-minute walk test (6MWT) pre- and post-PR. Results were compared among patients with idiopathic pulmonary fibrosis (IPF) and other ILDs.

**Results:** 93 patients were included (46 male); 42 (44.09%) completed the program. After the PR, the SGRQ mean score decreased by 8.7 (95% CI [confidence interval]: 2.85-14.42), with no differences between the IPF and other diagnoses. The results of the 6MWT showed mean improvement of 14.07 m, not reaching statistical significance ( $p = 0.132$ ). The subgroup of patients who walked less than 400 m ( $n = 18$ ) showed clinical and statistically significant improvement (40.8 m;  $p = 0.025$ ). We didn't find differences in this test in terms of diagnosis.

**Conclusions:** PR in this cohort of patients with ILD showed improvement in quality of life and exercise tolerance, with no differences regarding the specific diagnosis.

**Key words:** Diffuse interstitial lung disease, Pulmonary rehabilitation, Quality of life, Exercise tolerance

## Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of conditions with certain clinical, functional and radiologic common characteristics. Though they are considered as rare diseases, in the pulmonology practice they represent up to 15% of consultations<sup>1</sup>.

Recently published international guidelines analyze the existing evidence and make recommendations regarding the diagnosis and treatment of these diseases, especially the idiopathic pulmonary disease (IPF), the most prevalent of the group<sup>2, 3</sup>.

Regardless of their differences, ILDs as a group generate in patients exercise intolerance, dyspnea and a decrease in health-related quality of life (HRQOL)<sup>4</sup>. The tools used to quantify these aspects are the same as those used in other respiratory diseases, such as the 6-minute walk test (6MWT) to evaluate exercise tolerance, and the Saint George Respiratory Questionnaire (SGRQ) to measure quality of life<sup>5</sup>.

A review of this questionnaire administered to patients with IPF has recently been published, showing its internal consistency and good correlation with prognosis and severity variables of the disease<sup>6</sup>.

Pulmonary Rehabilitation (PR) plays an important role in the treatment of patients with ILD, though the available degree of evidence is lower than that of patients with COPD (chronic obstructive pulmonary disease)<sup>5</sup>. This difference may be due to the lower prevalence of DILDs. There is an increasing amount of studies that show the benefits of PR as regards quality of life and exercise tolerance in these patients, with more evidence in favor of this intervention<sup>7</sup>. However, the sole report about this intervention in our country is a series of cases of two patients in the waiting list for lung transplant<sup>8</sup>. For that reason, we proposed conducting a study with the main objective of evaluating the impact of PR on quality of life and exercise tolerance in patients with ILD referred to the PR program of the Respiratory Rehabilitation Hospital María Ferrer. As a secondary objective, we analyzed the difference between patients with IPF and individuals with other diagnoses taking into account the result variables previously mentioned.

## Materials and Methods

We analyzed a retrospective cohort of patients with ILD referred to RR in a hospital specialized in respiratory diseases, from January 2012 to December 2015. We included all the patients with diagnosis of ILD made by their primary care physician (in all the cases a chest physician, member of the group practice office specialized in ILD of that institution).

The following was confirmed: demographic data (age and sex), the specific ILD diagnosis and data from initial respiratory functional tests: Forced Vital Capacity (FVC), in liters, and percentage of a theoretical value. The specific diagnosis of each case of ILD was made according to reference criteria.<sup>1,2</sup> Respiratory function tests were conducted according to the criteria suggested by the ATS (American Thoracic Society)/ERS (European Respiratory Society)<sup>9</sup>.

The following parameters were evaluated before and after the PR program: quality of life with the SGRQ and exercise tolerance with the 6MWT. These were the analyzed result variables.

The SGRQ is a self-administered questionnaire divided in different areas: symptoms (S), activities (A), impact (I) and total value (T). The result is a numerical value expressed as continuous variable, where patients with higher values have worse quality of life<sup>10</sup>. A change of more than 4 points after an intervention was considered as the Minimal Clinically Important Difference (MCID)<sup>11</sup>.

The 6MWT was conducted according to the criteria suggested by the ATS<sup>12</sup>. The test was carried out without supplemental oxygen and the distance traveled expressed in meters was recorded. A MCID of 28 meters after the intervention was considered an improvement<sup>13</sup>.

The intervention included 4 months of PR based on aerobic training and muscle strengthening of limbs and core. The patients had one and a half-hour sessions of PR 3 times a week (total of 48 sessions). No specific active follow-up method was applied. Patients who didn't complete at least 70% of the program (32 visits) were excluded.

For aerobic training we used the Variable Continuous Method (VCM), whose intensities varied systematically between 50% and 90% of the maximum speed reached in an incremental test limited by symptoms in a treadmill, starting with 3 minutes at 50% and 3 minutes at 90% with a density of 1:1, until reaching in each session 30-35 minutes of stimuli, with loading phase times progressing at 90% (densities 2:1; 3:1; 4:1; 5:1). Patients who did not tolerate this type of treatment were trained with an intermittent high-intensity method with a stimulus of 30 seconds at 90% intensity of the incremental test, followed by 30 seconds of passive pause, until reaching 30 minutes of total volume. For patients who developed desaturation with exercise, we used supplemental oxygen in order to reach and maintain more than 90% saturation.

For muscle strength training, we planned general routines with exercises for UL (upper limb), LL (lower limb) and core, starting with 2 series of 10 repetitions at 70% of the estimation of a maximum repetition with the Brzycki<sup>14</sup> (1RM) formula, increasing the number of repetitions up to 12, then increasing the number of series (3) and subsequently the intensity (80% of 1 RM). Once the mentioned

objective was attained, we reevaluated the strength so as to establish new objectives.

As part of the PR program, patients participated in 8 educational meetings about disease-related issues, such as: promotion of physical activity, oxygen therapy, symptom recognition, etc. and they participated also in one weekly psychological support meeting, arranged by hospital specialists. The study was approved by the Ethics Committee of the Respiratory Rehabilitation Hospital María Ferrer in Buenos Aires, Argentina.

### Statistical Analysis

For categorical variables, we calculated the relative frequency as percentage, for continuous variables with normal distribution, we calculated the mean and standard deviation (SD), and for variables with another distribution, we estimated the median and interquartile range (25-75%)

We analyzed the difference between mean values before and after the intervention with the Student Test for paired samples. A p value of 0.05 or less was considered as significant. The analysis was carried out with the PASW Statistics 18<sup>®</sup> software. Since it is a retrospective study, we worked with a fixed sample size.

## Results

### Cohort Characteristics

A total of 93 patients (49.5% male) were included in the program. 42 (44.09%) completed the minimum established amount of sessions. The other patients were excluded from the analysis. When comparing functional, exercise tolerance and HRQOL data among patients who adhered to the program and those who were excluded, we found that excluded patients showed worse quality of life in all the areas of the SGRQ and the total value with statistically significant differences (**Table 1**).

Distribution according to diagnosis: IPF 36%, non-specific interstitial pneumonia 13.98%, hypersen-

**TABLE 1.** Basal characteristics of patients with ILD referred to pulmonary rehabilitation during the 2012-2015 period. Comparison between patients who completed and those who didn't complete the pulmonary rehabilitation program

	Total n = 93	Completed the PR program (n = 42)	Didn't complete the PR program (n = 51)	P value
Age	59.2 (14.6)	57.8 (10.9)	58.8 (12.6)	0.70
FVC (%)	62.7 (19.4)	66.4 (16.2)	61.88 (19.8)	0.39
6MWT (m)	416.5 (70.1)	429.6 (69.4)	405 (68.1)	0.11
Minimum SO <sub>2</sub>	84.7 (7.2)	83.7 (7.4)	85.5 (6.8)	0.25
SGRQ (S)	49.6 (19.6)	43.5 (18.4)	53.1 (19.4)	0.02
SGRQ (A)	66.9 (22.3)	54.9 (24.2)	74.0 (17.4)	0.01
SGRQ (I)	37.2 (18.3)	29.9 (16.8)	41.5 (17.7)	0.01
SGRQ (T)	48.3 (17.1)	39.6 (17.7)	53.4 (14.7)	0.01

Values expressed in mean and standard deviation; FVC (%): Forced Vital Capacity in percentage of a theoretical value; SGRQ: Saint George Questionnaire; SGRQ A: Saint George Questionnaire, "Activities" component; SGRQ I: Saint George Questionnaire, "Impact" component; SGRQ S: Saint George Questionnaire, "Symptoms" component; SGRQ T: Saint George Questionnaire, Total Value; 6MWT: Six Minute Walk Test; PR: Pulmonary Rehabilitation Program; minimum SO<sub>2</sub>: minimum saturation percentage.

sitivity pneumonitis 11.83%, histiocytosis X 3.23%, other 16.13% and unclassifiable interstitial disease 16.13%. When comparing basal characteristics according to admitting diagnosis (IPF versus other diagnoses) we only found a statistically significant difference in minimum saturation during the walk test, with lower values for patients with IPF (**Table 2**).

**TABLE 2.** Basal characteristics of patients with ILD referred to pulmonary rehabilitation during the 2012-2015 period. Comparison according to admitting diagnosis

	IPF n = 32	Another ILD (n = 61)	P value
Age	63.4 (7.3)	58.8 (12.1)	0.25
FVC (%)	58.1 (17.5)	66.2 (19.4)	0.14
6MWT (m)	417.9 (73.2)	431.1 (73.4)	0.32
Minimum SO <sub>2</sub>	79.3 (6.24)	85.7 (7.32)	0.01
SGRQ (S)	44.9 (16.5)	42.7 (20.1)	0.85
SGRQ (A)	61.2 (11.1)	51.2 (29.3)	0.72
SGRQ (I)	32.8 (16.1)	28.3 (17.8)	0.69
SGRQ (T)	43.2 (11.4)	37.6 (20.0)	1

Values expressed in mean and standard deviation; FVC (%): Forced Vital Capacity in percentage of a theoretical value; ILD: diffuse interstitial lung disease; IPF: idiopathic pulmonary fibrosis; SGRQ: Saint George Questionnaire; SGRQ A: Saint George Questionnaire, "Activities" component; SGRQ I: Saint George Questionnaire, "Impact" component; SGRQ S: Saint George Questionnaire, "Symptoms" component; SGRQ T: Saint George Questionnaire, Total Value; 6MWT: Six Minute Walk Test; RR: Respiratory Rehabilitation Program; minimum SO<sub>2</sub>: minimum saturation percentage.

### Effect of the Pulmonary Rehabilitation Program

**Quality of Life:** After the PR we observed statistically significant improvement in the 4 areas of the SGRQ, beyond the MCID, within the total population (**Table 3**). The IPF group showed worse HRQOL at the beginning of the program, though it wasn't statistically significant. We evaluated the difference between pre- and post-PR SGRQ, comparing IPF with other diagnoses, and didn't find statistically significant differences between IPF and other ILDs in the various areas of the questionnaire: symptoms (-9.6 vs. -11.1), activities (-9.2 vs. -11.6), impact (-9.1 vs. -6.5) and total (-8.8 vs. -8.6), respectively.

**TABLE 3.** Differences in Saint George Questionnaire between patients with ILD before and after the pulmonary rehabilitation program during the 2012-2015 period

	Pre PR	Post PR	Difference	P value	95% CI
Symptoms	43.6 (18.4)	33 (19.25)	- 10.6	0.02	4.12-16.99
Activities	54.9 (24.2)	44.2 (28.34)	- 10.7	0.02	1.27-20.17
Impact	29.9 (16.8)	22.5 (17.39)	- 7.5	0.01	1.83-13.06
Total	39.7 (17.7)	31 (18.71)	- 8.7	0.25	2.85-14.42

Values expressed in mean and standard deviation. SGRQ: Saint George Questionnaire; Pre-PR: before the Pulmonary Rehabilitation Program; Post-PR: after the Pulmonary Rehabilitation Program.

**Exercise Tolerance:** In the 6MWT, we compared the distance traveled in meters before and after the PR program, and didn't find statistical or clinically significant differences (pre-PR  $429.60 \pm 69.46$  m vs. post-PR  $443.67 \pm 69.25$ ;  $p = 0.12$ ;  $\Delta 14.7$  m). We conducted a subgroup analysis, discriminating between patients who walked less than 400 m ( $n = 18$ ) and those who walked more than 400 m ( $n = 24$ ) in the initial evaluation. We observed in the first group a statistically significant and clinically important difference in meters walked after the PR program (pre-PR  $361.17 \pm 34.69$  vs. post-PR  $402.00 \pm 59.64$ ;  $p = 0.025$ ;  $\Delta 40.8$  m), whereas the second group didn't get such difference (pre-PR  $480.90 \pm 38.1$  vs. post-PR  $474.90 \pm 59.90$ ;  $p = 0.471$ ;  $\Delta -6$  m). When we differentiated groups according to diagnosis, we didn't find statistically significant changes in meters walked or in MCID or IPF (pre-PR 417.93 m vs. post-PR 426 m;  $p = 0.624$ ;  $\Delta 8.07$  m). There weren't any statistically significant differences, either, in the group with another diagnosis (pre-PR: 431.18 m vs. 454 m;  $p = 0.389$ ;  $\Delta 22.82$  m).

## Discussion

Our study shows that a 4-month PR program improves quality of life evaluated with SGRQ. It also improves the distance walked in meters in the 6MWT within the subgroup of patients who walked less than 400 meters before starting the test. In the comparison of patients according to diagnosis (IPF vs. other diagnoses), we didn't find significant differences between pre- and post-PR.

This study has some limitations. In the first place, there was an important amount of patients who couldn't complete the PR program and were excluded from the analysis. This group of patients had worse values in all SGRQ areas at baseline, allowing us to suggest that individuals with worse basal quality of life have some kind of barrier (physical, psychological or resource-related) that keeps them from carrying out a pulmonary rehabilitation program. In the second place, our work doesn't have a control group, thus representing an obstacle difficult to overcome when it comes to evaluating the effect of an intervention.

Pulmonary rehabilitation is part of the integral treatment of chronic obstructive pulmonary disease (COPD), providing benefits in terms of quality of life, dyspnea and exercise tolerance and also reducing exacerbations and health-related costs<sup>15</sup>. In the group of interstitial diseases, published results suggest that this intervention provides benefits mainly regarding improvement in quality of life and exercise tolerance, even though there is a low degree of evidence about it<sup>16</sup>. This happens mainly because less studies have been conducted and the fact that most are retrospective and uncontrolled<sup>17</sup>.

The results of our study agree with those of other groups. There are two studies that could be used as a parameter due to the quality of their design<sup>18-19</sup> which showed improvement in quality of life measured by the Chronic Respiratory Questionnaire (CRQ) and the SGRQ. Thus, the Nishiyama group used the SGRQ to evaluate 13 patients with IPF after a 10-week PR program and found a change of -2.9 points ( $50.2 \pm 16.3$  vs.  $47.3 \pm 17.4$ ). Recently, Vainshelboim et al<sup>7</sup> published a study that evaluated 15 patients with IPF subject to 12 weeks of PR. They studied, among other variables, the change in the SGRQ<sup>11</sup> pre- and post-PR and found a difference of -9.7 points (95% CI -13 to -6). In our work we found results similar to this last report with a difference of -8.7 points. It is important to emphasize that patients from the Vainshelboim study showed better quality of life than our population at the beginning of the program, represented by a total SGRQ value of  $20.6 \pm 6.7$  vs.  $39.7 \pm 17.1$  respectively.

As regards exercise tolerance, most studies have used the 6MWT as an evaluation tool<sup>20</sup>. In our work we didn't find a significant change regarding distance walked in the 6MWT within the total population or the subgroups according to diagnosis (IPF and other diagnoses). When making a sub-analysis differentiating patients who walked more or less than 400 m at baseline, patients who initially walked less than 400 m did reach the MCID. This result agrees with the description of Huppmann et al, who showed that patients who walk less at baseline have greater improvement potential than those who walk more<sup>21</sup>.

At last, as already mentioned, the only report of this intervention in our country is a series of cases of two male patients in the waiting list for lung transplant, one of 36 years of age, diagnosed with silicosis, with a traveled distance of 307 meters in the 6MWT and 69 points in the total SRGQ, and another one of 61 years of age, diagnosed with IPF and mild pulmonary hypertension, who traveled 270 meters in the 6MWT and with 46 points in the total SRGQ, both subject to 12-month duration PR<sup>8</sup>. In the 6MWT they observed, in the first case, a 6 meter increase in the first 6 months plus an 8 meter increase at 12 months ( $\Delta 14$ m). In the second case, there was a 150 meters increase at 6 months plus 136 meters increase at 12 months ( $\Delta 286$  m). The HRQOL improved in both cases, evidenced by a decrease in the total SGRQ score of 6 and 39 points, respectively. Given the broad gap of results obtained in these two patients, we are not able to compare with our results, yet we can mention that in both cases the PR shows improvement. On the other hand, we must say that 36% of our population were patients with IPF, many of them in the waiting list or candidates to be evaluated for lung transplant.

In view of what has been mentioned previously, we believe that our work is the first in our country to report PR results in patients with ILD from a broad group. Also, the results agree with information published up to now by researchers of other countries and provides evidence about the usefulness of pulmonary rehabilitation in patients with interstitial lung diseases. There are still some questions to ask about this: In what instance of clinical evolution must rehabilitation begin? Which is the most effective training method? Do patients with IPF respond to treatment in the same way than other patients of the group?

It is apparent that still more prospective, randomized and controlled studies must be conducted in order definitely establish the role of this intervention within this group of diseases.

## Conclusion

In this cohort of patients with ILD, PR showed improvement in quality of life and exercise tolerance.

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