











Original research

# Long-term effect of pulmonary rehabilitation in idiopathic pulmonary fibrosis: a randomised controlled trial

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## ABSTRACT

**Background** Idiopathic pulmonary fibrosis (IPF) is characterised by worsening dyspnoea and exercise intolerance.

**Research question** Does a long-term pulmonary rehabilitation improve exercise tolerance in patients with IPF treated with standard antifibrotic drugs, which are expected to reduce disease progression?

**Methods** This open-label randomised controlled trial was performed at 19 institutions. Stable patients receiving nintedanib were randomised into pulmonary rehabilitation and control groups (1:1). The pulmonary rehabilitation group underwent initial rehabilitation which included twice-weekly sessions of monitored exercise training for 12 weeks, followed by an at-home rehabilitation programme for 40 weeks. The control group received usual care only, without pulmonary rehabilitation. Both groups continued to receive nintedanib. The primary and main secondary outcomes were change in 6 min walking distance (6MWD) and change in endurance time (using cycle ergometry) at week 52.

**Results** Eighty-eight patients were randomised into pulmonary rehabilitation (n=45) and control (n=43) groups. Changes in 6MWD were −33 m (95% CI −65 to −1) and −53 m (95% CI −86 to −21) in the pulmonary rehabilitation and control groups, respectively, with no statistically significant difference (mean difference, 21 m (95% CI −25 to 66), p=0.38). Changes in endurance time were significantly better in the pulmonary rehabilitation (64 s, 95% CI −42.3 to 171) than in the control (−123 s (95% CI −232 to −13)) group (mean difference, 187 s (95% CI 34 to 153), p=0.019).

**Interpretation** Although pulmonary rehabilitation in patients taking nintedanib did not improve 6MWD in the long term, it led to prolonged improvement in endurance time.

**Trial registration number** UMIN000026376.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Maintaining long-term exercise tolerance is an unmet medical need for patients with idiopathic pulmonary fibrosis (IPF). Most studies examining the efficacy of pulmonary rehabilitation for IPF have used short-term efficacy as the outcome, and no study has been performed on pulmonary rehabilitation in combination with antifibrotic drugs, which is currently the standard of care.

## WHAT THIS STUDY ADDS

⇒ The FITNESS study was the first randomised controlled trial to evaluate the effects of long-term pulmonary rehabilitation in patients taking antifibrotic drugs. The pulmonary rehabilitation group underwent induction rehabilitation for 12 weeks, followed by at-home maintenance rehabilitation programme for 40 weeks, while the control group received only usual care only, without pulmonary rehabilitation. Both groups continued to receive nintedanib. The findings suggested no significant difference between the two groups in terms of changes in 6 min walking distance (6MWD) between baseline and week 52 (the primary outcome). Endurance time measured using cycle ergometry (main secondary outcome), was significantly better in the pulmonary rehabilitation group than in the control group.

## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an intractable disease characterised by chronic, irreversible progression of fibrosis.<sup>1</sup> The natural history of IPF includes worsening of pulmonary function, dyspnoea on exertion, exercise intolerance, reduced physical activity and quality of life impairment.<sup>2–5</sup> Patients with IPF have needs for prolonged

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The combination of nintedanib and pulmonary rehabilitation in patients with IPF resulted no difference in 6MWD compared with usual care with nintedanib, but a greater improvement in endurance time. Thus, pulmonary rehabilitation with nintedanib may be effective in improving long-term exercise capacity, although further studies with strategies such as the inclusion of a sophisticated long-term maintenance programme are needed before it can be recognised as a robust care protocol for patients with IPF.

improvement in these impairments, but optimal management for meeting those needs has not been established.

Pulmonary rehabilitation is expected to be effective in improving dyspnoea and exercise tolerance in patients with chronic respiratory disorders,<sup>6</sup> and several studies have reported the benefits of pulmonary rehabilitation in interstitial lung disease,<sup>7,8</sup> including the effects of pulmonary rehabilitation on IPF.<sup>7,9,10</sup> A majority of the previous studies showed short-term benefits of pulmonary rehabilitation on IPF. A few studies evaluated the long-term effects at 6 months or longer; but failed to demonstrate any long-term positive effects of pulmonary rehabilitation on exercise tolerance.<sup>10–12</sup> The findings, therefore, suggest that conventional pulmonary rehabilitation alone may not lead to prolonged improvement in exercise tolerance,<sup>13</sup> which could be attributed to the relatively rapid progression of disease in IPF.

Past studies have demonstrated that the benefits of a few months of pulmonary rehabilitation wane in patients with IPF after 6 months; therefore, we believe it is necessary to develop an effective way to maintain long-term effectiveness. Programmed maintenance rehabilitation in addition to a regular rehabilitation programme would seem to be a promising approach, but there are no studies of outpatient induction rehabilitation, followed by maintenance rehabilitation.

Antifibrotic agents are currently a conditional recommended treatment for IPF to slow disease progression and suppress the decline of exercise capacity, and to prevent acute exacerbation.<sup>1,13–17</sup> They are also expected to sustain the effects of pulmonary rehabilitation. Therefore, in the current antifibrotic era, pulmonary rehabilitation may be expected to take place concurrently with the administration of antifibrotic agents, but in the three previous studies that evaluated the effect of long-term pulmonary rehabilitation for IPF,<sup>10–12</sup> only a small percentage (0%–9.4%) of patients received antifibrotic agents.

In this study, we hypothesised that a long-term rehabilitation programme (induction rehabilitation followed by maintenance rehabilitation) would have a long-term effect on maintaining or slowing the decline in exercise capacity in patients with IPF receiving a standard drug therapy of nintedanib.

**METHODS****Study design and participants**

The FITNESS (Long-term effect of pulmonary rehabilitation under nintedanib in idiopathic pulmonary fibrosis) study was a multicentre, randomised, prospective, parallel-group, unblinded, controlled trial performed at 19 institutions in Japan (online supplemental e-Table 1). The pulmonary rehabilitation group underwent initial rehabilitation that included twice-weekly sessions of monitored exercise training for 12 weeks,

followed by an at-home rehabilitation programme for 40 weeks. The control group received usual care only, without pulmonary rehabilitation. Both groups continued to receive nintedanib. The purpose, design and methods of the study, which were previously reported<sup>18</sup> and the final protocol, are available in online supplemental appendix.

The main inclusion criteria were as follows: (1) age between 40 and 79 years at the time of consent, (2) diagnosis of IPF based on the 2011 guideline criteria,<sup>19</sup> (3) previous 6 min walking distance (6MWD) of 200 m or more and less than 600 m, (4) dyspnoea on exertion (modified Medical Research Council (mMRC) grade scale 1–3),<sup>20</sup> (5) stable disease without infection or acute exacerbation within 3 months prior to enrolment and (6) receiving nintedanib (150 mg or 100 mg two times per day) for at least for 4 weeks and able to receive the drug for more than 12 months after registration.

**Randomisation**

Eligible patients were randomised into the pulmonary rehabilitation and control groups in a 1:1 ratio with a minimisation method using a web-based system. The dynamic randomisation factors were baseline 6MWD during the screening period ( $\geq 350$  m or  $< 350$  m), institutions and forced vital capacity (FVC) at registration (the cut-off value was calculated as 70% of the predictive value). Study group allocation was performed via an electronic data capture system using computer-generated random numbers. Study physicians and patients were aware of the allocated study group.

**Pulmonary rehabilitation programme**

In this study, physical function assessment and the pulmonary rehabilitation programme were performed by a cardiorespiratory physiotherapist at each institution. To equalise the evaluation methods for exercise tolerance and the pulmonary rehabilitation programmes, a detailed protocol was developed prior to the study. In addition, physical therapists in each participating institution were required to participate in joint practical training.

The detailed rehabilitation programme is described in a previous report<sup>18</sup> and will be briefly introduced. During the first 12 weeks after the start of the pulmonary rehabilitation programme, induction pulmonary rehabilitation was performed during two outpatient visits per week (24 sessions) under the supervision of a cardiorespiratory physiotherapist. In addition to the outpatient visits, participants were instructed to perform self-rehabilitation at home at least twice a week in the induction pulmonary rehabilitation phase (online supplemental appendix, page 25). The initial pulmonary rehabilitation included 30 min of endurance training using a cycle ergometer and walking, and resistance training. Endurance training intensity in cycling targeted 80% of the peak work rate, and the initial intensity for cycling was 80% of the walking speed achieved on the baseline 6 min walk test. Depending on the improvement in maximum exercise tolerance, resistance training of the upper and lower limbs was performed using free weights or the patient's own body weight, with gradually increasing load. A home exercise programme was also prescribed during the pulmonary rehabilitation programme; squatting and standing calf raises were used for resistance training. The initial pulmonary rehabilitation programme was followed by the 40-week maintenance programme, consisting of self-training at home and outpatient pulmonary rehabilitation supervised by a cardiorespiratory physiotherapist (more than once every 4 weeks). The patients

were required to record the status of self-training and the daily number of steps in a diary.

## Study outcomes

### Primary outcome

The primary outcome was the results of a comparison between the two groups in terms of changes in 6MWD between baseline and week 52.

### Secondary outcomes

The main secondary outcome was the result of comparison of changes in endurance time between baseline and week 52 in the two groups, as measured using cycle ergometry<sup>21</sup> (see online supplemental appendix).

Other outcomes were the results of a comparison of changes in parameters between baseline and week 52 in the two groups. These parameters included the total score on the St. George's Respiratory Questionnaire (SGRQ),<sup>22</sup> the rate of changes (%) from baseline evaluation of 6MWD, number of daily steps, each SGRQ component score, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT),<sup>23–25</sup> dyspnoea (Transition Dyspnoea Index (TDI),<sup>26</sup> Dyspnoea-12),<sup>27</sup> Hospital Anxiety and Depression Scale (HADS),<sup>28</sup> changes from baseline in FVC, diffusing capacity for carbon monoxide (DLCO), saturation of percutaneous oxygen (at rest and immediately after the 6 min walk test), results of a comparison of mortality before final evaluation, and the incidence of adverse events observed during the study period. In addition, this study compared changes between the baseline and week 26 in primary and secondary outcomes between the two groups. For the pulmonary rehabilitation group, compliance until the time of evaluation (week 52) (the percentage of the number of pulmonary rehabilitation sessions performed divided by the number of scheduled pulmonary rehabilitation sessions), percentage of patients with high pulmonary rehabilitation compliance ( $\geq 70\%$ ) and compliance with the long-term pulmonary rehabilitation programme until the time of evaluation (week 52) were compared. Changes in 6MWD between baseline and week 52 were also compared between the high and low pulmonary rehabilitation compliance ( $\geq 70\%$  and  $< 70\%$ , respectively) subgroups. One review reported rates of adherence to home exercise programmes, with mean percentage rate of adherence across studies of 67%.<sup>29</sup> We preliminarily defined the 'good compliance group' as those who performed the pulmonary rehabilitation at least five times a week (approximately 70%).

## Statistical analysis

### Sample size

There are limited data from previous studies estimating the magnitude of increase in 6MWD after rehabilitation in combination with nintedanib treatment. For patients treated with nintedanib, the decreasing gradient in 6MWD was considered low, although the actual value was unknown. As the maintenance pulmonary rehabilitation programme could facilitate long-term maintenance of the previously reported effects of short-term pulmonary rehabilitation programmes, we hypothesised that the effects of the combination of programmed long-term pulmonary rehabilitation and nintedanib may be equivalent to those of short-term pulmonary rehabilitation. Based on the four previous short-term pulmonary rehabilitation studies for IPF described in the review reported,<sup>13</sup> the SD of the 6MWD predifference and postdifference was calculated to be 55 m. In this study, the expected value of the difference in the pre/post

6MWD between the nintedanib with and without long-term rehabilitation group was set at 36 m. Based on the above, we calculated that the sample size required to show a significant difference at the primary endpoint with 80% power in a two-tailed test (5% level of significance) was 37 patients in each group, for a total of 74 patients. In anticipation of drop-outs, we set a target of 42 patients per group for a total of 84 patients. As for the main secondary endpoint, based on previous studies,<sup>13</sup> the difference between prerenal and postrehabilitation endurance time, as measured using a cycle ergometer, was estimated to be 10 min. For the achieved target sample size of 84 patients, a statistical power of  $\geq 90\%$  (at  $p < 0.05$ ) was calculated to be sufficient for detecting a statistically significant difference between the treatment groups.<sup>18</sup> The sample size for this study was similar to that of the previous HOPE IPF study.<sup>30</sup>

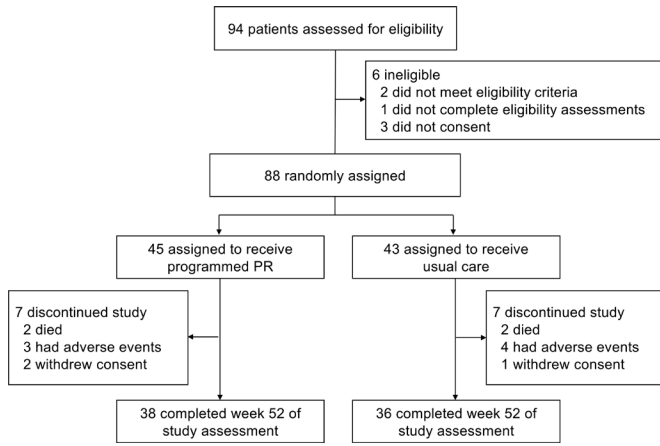
### Outcome analysis

Efficacy analysis was performed on intention-to-treat basis, using a full analysis set consisting of all randomised patients having undergone baseline evaluation and at least one postbaseline evaluation. Data handling was defined for each outcome, and safety analysis was performed in patients who received nintedanib at least once after registration. Comparisons of changes in 6MWD from baseline were performed between the treatment groups considering  $p < 0.05$  (two tailed) as significant, using a mixed-effect model for repeated measures. Least squares mean and 95% CIs were calculated using a linear mixed-effect model for repeated measures with each treatment group, 6MWD at baseline (randomisation), time of evaluation and the interaction term for each treatment group and time of evaluation as fixed effects. Changes in endurance time from baseline, as measured with a cycle ergometer, were also compared between the two groups using a mixed-effect model for repeated measures. Other secondary outcomes (the number of steps, health status (SGRQ and CAT scores), dyspnoea (TDI and Dyspnoea-12 scores), FVC, DLCO, modified MRC grade and the minimum saturation of percutaneous oxygen after the 6 min walk test) were also evaluated using the same method. For severe cardiac complications, the number of patients with ischaemic heart disease or arrhythmia requiring treatment was calculated and compared between the treatment groups using Fisher's exact test. Other adverse events were also calculated and compared between the two groups using Fisher's exact test. In all analyses, a  $p < 0.05$  was considered statistically significant. This study was registered with UMIN-CTR (number: UMIN000026376).

## RESULTS

Ninety-four patients underwent evaluation for eligibility between 30 October 2017 and 23 January 2020. During the screening period, six patients were excluded as they were ineligible, and the remaining 88 patients were allocated into the pulmonary rehabilitation ( $n = 45$ ) and control ( $n = 43$ ) groups (figure 1). The mean age was 70.7 years (SD 3.0). The duration of IPF was 27.7 months (SD 13.1), and the mean duration of nintedanib treatment was 293 days (SD 177); the mean FVC was 2435 mL (SD 400), which was 73.9% of the predictive value (SD 7.9%). There was no significant difference in patient characteristics at randomisation between the two groups (table 1).

During the study, there were seven drop-outs in each group; 38 (84%) and 36 (84%) patients in the pulmonary rehabilitation and control groups, respectively, completed the evaluation at week 52.



**Figure 1** Flow chart of patient selection. PR, pulmonary rehabilitation.

In the pulmonary rehabilitation group, the 6MWD decreased from 447 m at baseline (95% CI 423 to 472) to 415 m at week 52 (95% CI 376 to 455). In the control group, the 6MWD decreased from 459 m at baseline (95% CI 435 to 484) to 406 m at week 52 (95% CI 365 to 446). Changes between baseline and week 52 6MWD (primary outcome) were  $-33$  m (95% CI  $-65$  to  $-1$ ) in the pulmonary rehabilitation group and  $-53$  m (95% CI  $-86$  to  $-21$ ) in the control group; there was no statistically significant difference between the two groups (mean difference, 21 m (95% CI  $-25$  to 66),  $p=0.38$ ). Changes between baseline and week 12 6MWD were 18 m (95% CI 4 to 32) in the pulmonary rehabilitation group and  $-5$  m (95% CI  $-19$  to 9) in the control group ( $p=0.029$ ). Likewise, changes between baseline and week 26 6MWD in the pulmonary rehabilitation and control groups were 15 m (95% CI  $-2$  to 33) and  $-16$  m (95% CI  $-34$  to  $-1$ ), respectively ( $p=0.013$ ) (figure 2).

In the pulmonary rehabilitation group, the endurance time measured using a cycle ergometer increased from 372 s at baseline (95% CI 298 to 445) to 441 s at week 52 (95% CI 325 to 557). In the control group, the endurance time measured using a cycle ergometer decreased from 396 s at baseline (95% CI 320 to 472) to 275 s at week 52 (95% CI 155 to 395). Changes between the baseline and week 52 endurance times (main secondary outcome) were significantly better in the pulmonary rehabilitation group (64 s (95% CI  $-42.3$ –171)) than in the control group ( $-123$  s (95% CI  $-232$  to  $-13$ )) (mean difference, 187 s (95% CI 34 to 153),  $p=0.019$ ). Likewise, changes between baseline and week 12 and week 26 endurance times were significantly better in the pulmonary rehabilitation group than in the control group ( $p<0.0001$  and  $p=0.0007$ , respectively) (figure 3). For the other secondary outcomes, the p values for the difference between the two groups in terms of change from baseline to each evaluation point are shown in table 2.

A mixed-effect model for repeated measures was used to compare the pulmonary rehabilitation and control groups for changes between baseline and each evaluation point.

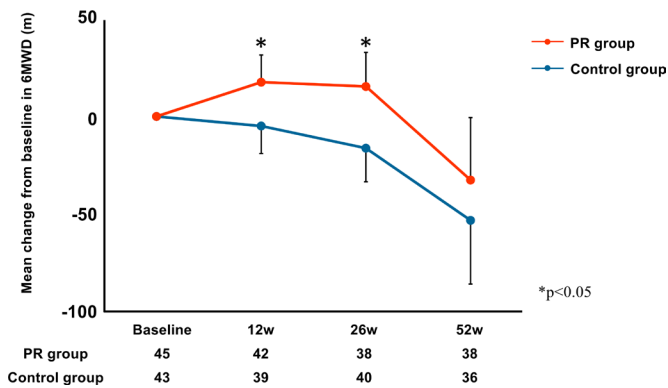
As with comparisons of absolute values, comparisons of the percentage of change in 6MWD from baseline showed a significant difference at weeks 12 and 26, but not at week 52. The TDI at all evaluation points was significantly higher in the pulmonary rehabilitation than in the control group (online supplemental e-Figure 1). In the pulmonary rehabilitation group, the FVC changed from 72.8% at baseline (95% CI 68.7% to 76.8%) to 68.1% at week 52 (95% CI 63.4% to 72.8%). In the control group, the FVC changed from 75.0% at baseline (95% CI 70.9% to 79.1%) to 72.0% at week 52 (95% CI 67.1% to 76.9%).

**Table 1** Baseline patient characteristics

	Pulmonary rehabilitation group (n=45)	Control group (n=43)
Age, year	71.2 (4.9)	70.4 (5.5)
Sex		
Male	36 (80%)	33 (77%)
Female	9 (20%)	10 (23%)
Smoking status		
Current smoker	4 (9%)	1 (2%)
Former smoker	33 (73%)	33 (77%)
Never smoker	8 (18%)	9 (21%)
Body mass index, kg/m <sup>2</sup>	23.4 (3.5)	23.7 (2.8)
Honeycombing on HRCT	30 (67%)	32 (74%)
Diagnosis of IPF, months	28.0 (26.3)	27.4 (33.8)
Modified MRC grade		
0	1 (2%)	0 (0%)
1	23 (51%)	25 (58%)
2	19 (42%)	16 (37%)
3	2 (4%)	2 (5%)
Lung function		
FVC, % predicted value	72.8 (14.5)	75.0 (12.9)
DLCO, % predicted value	49.4 (12.5)	46.3 (11.1)
PaO <sub>2</sub> , mmHg	83.5 (14.0)	80.7 (9.9)
6 min walk test		
Distance, m	447 (89)	459 (74)
SpO <sub>2</sub> before starting, %	96.0 (1.6)	96.2 (1.6)
Lowest SpO <sub>2</sub> , %	86.0 (6.5)	83.2 (8.9)
Baseline Dyspnoea Index	7.6 (2.3)	6.8 (2.8)
Dyspnoea-12	2.9 (4.4)	3.1 (3.7)
SGRQ total	35.6 (16.4)	36.5 (15.0)
COPD assessment test	14.3 (7.4)	14.0 (7.2)
HADS		
Depression	5.1 (3.9)	5.1 (3.6)
Anxiety	3.5 (3.7)	3.4 (3.1)
Pedometer, steps	4528 (2,893)	4568 (2,364)
Nintedanib dosing period, days	306 (276)	280 (406)
Nintedanib dose		
150 mg × 2/day	27 (60%)	26 (61%)
100 mg × 2/day	18 (40%)	17 (40%)
Systematic corticosteroid therapy	1 (2%)	3 (7%)
Oxygen therapy	1 (2%)	2 (5%)

Data are presented as mean with SD and n (%). DLCO, diffusion capacity for carbon monoxide; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; MRC, Medical Research Council; PaO<sub>2</sub>, partial pressure of arterial oxygen; SGRQ, St. George's Respiratory Questionnaire; SpO<sub>2</sub>, saturation of percutaneous oxygen.

There was no significant difference between the two groups ( $p=0.37$ ). There was no significant difference between the two groups in terms of SGRQ, CAT, Dyspnoea-12 and HADS scores, number of steps measured by a pedometer, oxygen saturation and FVC at any evaluation point.



**Figure 2** Mean change in 6 min walking distance between baseline and week 52. Error bars indicate the SE.

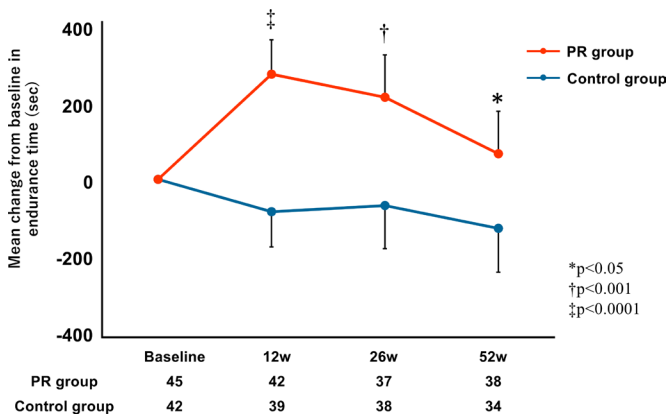
After excluding two patients (who did not keep a diary) from the 45 patients in the pulmonary rehabilitation group, there were 21 and 22 patients in the high and low compliance groups, respectively. In these groups, compliance with the pulmonary rehabilitation programme was found to be 93.5% (95% CI 90.2% to 96.8%) and 46.9% (95% CI 42.1% to 51.7%), respectively. Changes between baseline and week 52 6MWD were significantly smaller in the high compliance group (−8 m (95% CI −47 to 31)) than in the low compliance group (−106 m (95% CI −172 to −40)) (p=0.017) (online supplemental e-Figure 2).

The incidence of adverse events was equivalent between the two groups (table 3). The incidence of diarrhoea was 74% and 79% in the pulmonary rehabilitation and control groups, respectively; the incidence of diarrhoea of grade 3 or above was 7% in both groups. Acute exacerbation of IPF during the study period was observed in 5 (11%) and 4 (9%) patients, respectively. There were two deaths in each group; the cause of death in all cases was acute exacerbation of IPF.

Nintedanib compliance in the pulmonary rehabilitation and control groups was found to be 94% (95% CI 89.1% to 98.8%) and 96% (95% CI 92.9% to 99.1%), respectively.

**DISCUSSION**

Currently, antifibrotic drugs are the standard therapy for IPF. The FITNESS study was the first randomised controlled trial to evaluate the effects of long-term pulmonary rehabilitation combining induction rehabilitation with subsequent maintenance rehabilitation in patients taking antifibrotic drugs. This is also the largest study to evaluate the effects of pulmonary



**Figure 3** Mean change in endurance time, as measured by a cycle ergometer between baseline and week 52. Error bars indicate the SE.

rehabilitation in 88 patients with IPF alone. The findings showed no significant difference between the two groups in terms of changes in 6MWD between baseline and week 52 (the primary outcome). However, the change in endurance time using cycle ergometry (main secondary outcome), was significantly better in the pulmonary rehabilitation group than in the control group. The mean reduction in FVC at week 52 was 116 mL; this was similar to that of previous studies on the effects of nintedanib.<sup>15</sup>

Although the intervention in this study did not lead to a significant difference in 6MWD between the two groups, significantly positive effects were observed in terms of endurance time. This could be due to the difference in responsiveness to evaluation. As numerous studies have used 6MWD as the primary outcome measure to evaluate the effects of pulmonary rehabilitation on interstitial lung diseases,<sup>7-9 11 12</sup> this study used changes in 6MWD as the primary outcome measure to evaluate the impact of combined therapy in patients with IPF. Endurance time was used as the main secondary outcome measure, because one of our previous studies demonstrated that endurance time was the most sensitive measure of the positive effects of rehabilitation in IPF.<sup>21</sup> Recent reports indicate that constant load tests of submaximal exercise performance, similar to those of daily activities, reflect the severity of shortness of breath better than tests of peak exercise performance (such as the 6 min walk test).<sup>30</sup> Indeed, some studies have recently used changes in endurance time during cycling exercise tests at a constant work rate as the primary outcome measure.<sup>31</sup>

In IPF, no study evaluating differences between baseline and week 26 6MWD has ever found a significant difference between the pulmonary rehabilitation and usual care groups.<sup>13</sup> The FITNESS study is the first to demonstrate a significant improvement in week 26 6MWD among patients with IPF. The findings suggest that the combination of initial 12-week rehabilitation with nintedanib and subsequent maintenance of pulmonary rehabilitation facilitates maintenance of the beneficial effects until week 26. Some reports suggest that maintenance rehabilitation programmes can improve exercise capacity in COPD over the long term<sup>32</sup>; however, a systematic review concluded that the effects remained uncertain as of that time.<sup>33</sup> The results of this study clearly indicate that the effect of pulmonary rehabilitation is lost after 26 weeks; one possible reason for this is the presence of patients with low compliance to rehabilitation. In fact, the low compliance group showed a significant worsening of 6MWD, while the high compliance group maintained an improvement in 6MWD (online supplemental e-Figure 2). Improving compliance with rehabilitation is likely to be an important issue in maintaining the effectiveness of long-term rehabilitation. Another possible reason is that the effect of rehabilitation may have been negated by a decrease in exercise capacity due to disease progression. In terms of the safety of pulmonary rehabilitation, there was no significant difference in suspected pulmonary rehabilitation-related cardiovascular or orthopaedic adverse events between the two groups. Our present findings on nintedanib-related and IPF-related adverse events are consistent with those of previous studies.<sup>15</sup>

This study has some limitations. First, the pulmonary rehabilitation group was not blinded to the treatment, nor were they blinded to the assessors. This could have affected the results. To minimise the impact of unblinding in this study, fixed procedures were prepared to objectively assess outcomes and assessors were pretrained to be equal across sites. Second, the subjects were required to record the status of self-training at home in a diary, as a means to maintain the exercise load intensity of the maintenance pulmonary rehabilitation programme following induction

**Table 2** Comparison of changes between baseline and each evaluation point in the two groups

	12 weeks		26 weeks		52 weeks	
	Difference† (SE)	P value	Difference† (SE)	P value	Difference† (SE)	P value
6 min walking distance	22.5 (10.1)	0.029	31.7 (12.5)	0.013	20.7 (23.4)	0.38
Endurance time	344.1 (62.9)	<0.0001	271.0 (77.2)	0.0007	186.8 (77.9)	0.019
6 min walking distance, percentage of change	0.07 (0.02)	0.0068	0.08 (0.03)	0.0055	0.06 (0.05)	0.28
SGRQ total	-1.03 (2.34)	0.66	1.25 (2.74)	0.65	-0.20 (3.72)	0.96
SGRQ symptoms	-1.12 (3.43)	0.75	-0.71 (3.74)	0.85	-5.48 (4.34)	0.21
SGRQ activity	-1.86 (2.96)	0.53	0 (3.19)	1.00	0.52 (4.17)	0.90
SGRQ impact	-0.89 (2.8)	0.75	1.96 (3.33)	0.56	0.66 (4.31)	0.88
COPD assessment test	-1.36 (1.24)	0.28	-0.15 (1.54)	0.92	-0.97 (1.64)	0.55
Pedometer, step	274 (401)	0.50	546 (394)	0.17	540 (480)	0.26
Transitional Dyspnoea Index	2.32 (0.66)	0.0005	1.97 (0.66)	0.0035‡	1.46 (0.67)	0.032
Dyspnoea-12	-0.48 (1.01)	0.63	0.58 (1.16)	0.62	1.35 (1.51)	0.37
Hospital Anxiety and Depression Scale, Depression	0.03 (0.61)	0.96	-0.16 (0.60)	0.79	0.31 (0.65)	0.64
Hospital Anxiety and Depression Scale, Anxiety	0.41 (0.60)	0.50	-0.2 (0.67)	0.76	0.56 (0.74)	0.45
Saturation of percutaneous oxygen (SpO <sub>2</sub> ), stable	0.44 (0.30)	0.15	0.42 (0.34)	0.22	0.55 (0.47)	0.24
SpO <sub>2</sub> , lowest	-0.64 (1.12)	0.57	-0.44 (1.07)	0.69	0.07 (1.20)	0.95
FVC	0.69 (1.64)	0.68	1.08 (1.65)	0.51	-1.61 (1.80)	0.37
DLCO	NA		NA		-1.09 (3.79)	0.77

Positive value indicates that the pulmonary rehabilitation group is better.

DLCO, diffuse capacity for carbon monoxide; FVC, forced vital capacity; NA, not applicable; SGRQ, St. George's Respiratory Questionnaire.

pulmonary rehabilitation. However, it was difficult to quantify the load actually being applied. To monitor the exercise intensity of the maintenance pulmonary rehabilitation programme, a remote monitoring system may be employed in the future. Third, the pulmonary rehabilitation programme used was originally developed for patients with COPD; a programme needs to be developed specifically for IPF. Future studies are needed to

determine whether patients with IPF, a restrictive disorder and COPD, an obstructive disorder, may be rehabilitated using the same programme and load configuration. Fourth, it is unclear whether the same results would be obtained for patients who do not meet the eligibility criteria (6MWD, mMRC grade and pulmonary function, among others) adopted in this study, for example, those with FVC less than 50%, mMRC grade 4, etc.

**Table 3** Adverse events observed during the study period

	Pulmonary rehabilitation group (n=45)		Control group (n=43)		P value
	Grades 1–2	Grades 3–5	Grades 1–2	Grades 3–5	
Diarrhoea	30 (67%)	3 (7%)	31 (72%)	3 (7%)	0.62
Nausea	9 (20%)	0	4 (9%)	1 (2%)	0.38
Abdominal pain	5 (11%)	0	1 (2%)	2 (5%)	0.71
Liver enzyme elevation	12 (27%)	0	9 (21%)	0	0.62
Vomiting	2 (4%)	0	0	0	0.49
Anorexia	11 (24%)	0	7 (16%)	1 (2%)	0.61
Weight loss	1 (2%)	0	1 (2%)	1 (2%)	0.61
Bleeding	0	2 (4%)	2 (5%)	0	1.00
Acute coronary syndrome	0	0	0	0	1.00
Stroke	0	0	0	0	1.00
Arrhythmia	0	0	0	0	1.00
Heart failure	0	0	1 (2%)	0	0.49
Deep vein thrombosis	0	1 (2%)	0	0	1.00
Pulmonary infection	2 (4%)	3 (7%)	1 (2%)	2 (5%)	0.71
Progression of IPF	2 (4%)	1 (2%)	0	3 (7%)	1.00
Acute exacerbation of IPF	0	5 (11%)	0	4 (9%)	1.00
Death		2 (4%)		2 (5%)	1.00

Data indicate n (%) of the patients. P values were calculated for the difference between the pulmonary rehabilitation and control groups for the number of events of all grades. IPF, idiopathic pulmonary fibrosis.

Future studies are needed to identify patients who may benefit from this treatment strategy. Fifth, considering the decline in exercise capacity shown at week 52 in the pulmonary rehabilitation group, a larger sample size will be needed to detect the long-term effect. Finally, because of the mandatory use of nintedanib in this study, the results may not be applicable to patients for whom nintedanib is not used or in countries with restrictions on the use of nintedanib. However, in a long-term study of IPF, it would be difficult not to administer antifibrotic agents, which is the recommended treatment.

In conclusion, the combination of nintedanib and pulmonary rehabilitation in patients with IPF resulted in no difference in 6MWD compared with usual care with nintedanib, but a better outcome for endurance time. Further studies with strategies such as sophisticated long-term maintenance programmes are needed before pulmonary rehabilitation with nintedanib can be recognised as a robust care protocol for patients with IPF.

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#### REFERENCES

- Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–68.
- Nishiyama O, Taniguchi H, Kondoh Y, *et al.* Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? *Respir Med* 2005;99:408–14.
- Nishiyama O, Yamazaki R, Sano H, *et al.* Physical activity in daily life in patients with idiopathic pulmonary fibrosis. *Respir Investig* 2018;56:57–63.
- Nishiyama O, Taniguchi H, Kondoh Y, *et al.* A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;36:1067–72.
- Nishiyama O, Taniguchi H, Kondoh Y, *et al.* Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. *Chest* 2005;127:2028–33.
- Bolton CE, Bevan-Smith EF, Blakey JD, *et al.* British thoracic society guideline on pulmonary rehabilitation in adults. *Thorax* 2013;68 Suppl 2:ii1–30.
- Nishiyama O, Kondoh Y, Kimura T, *et al.* Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. *Respirology* 2008;13:394–9.
- Perez-Bogerd S, Wuyts W, Barbier V, *et al.* Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. *Respir Res* 2018;19:182.

- 9 Jarosch I, Schneeberger T, Gloeckl R, *et al.* Short-Term effects of comprehensive pulmonary rehabilitation and its maintenance in patients with idiopathic pulmonary fibrosis: a randomized controlled trial. *J Clin Med* 2020;9:1567.
- 10 Vainshelboim B, Oliveira J, Fox BD, *et al.* Long-term effects of a 12-week exercise training program on clinical outcomes in idiopathic pulmonary fibrosis. *Lung* 2015;193:345–54.
- 11 Holland AE, Hill CJ, Conron M, *et al.* Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. *Thorax* 2008;63:549–54.
- 12 Dowman LM, McDonald CF, Hill CJ, *et al.* The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. *Thorax* 2017;72:610–9.
- 13 Dowman L, Hill CJ, May A, *et al.* Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* 2021;2:CD006322.
- 14 Richeldi L, Baldi F, Pasciuto G, *et al.* Current and future idiopathic pulmonary fibrosis therapy. *Am J Med Sci* 2019;357:370–3.
- 15 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–82.
- 16 Canestaro WJ, Forrester SH, Raghu G, *et al.* Drug treatment of idiopathic pulmonary fibrosis: systematic review and network meta-analysis. *Chest* 2016;149:756–66.
- 17 King TE Jr, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–92.
- 18 Nishiyama O, Kataoka K, Ando M, *et al.* Protocol for long-term effect of pulmonary rehabilitation under nintedanib in idiopathic pulmonary fibrosis. *ERJ Open Res* 2021;7:00321-2021.
- 19 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
- 20 Mahler DA, Rosiello RA, Harver A, *et al.* Comparison of clinical dyspnea ratings and psychophysical measurements of respiratory sensation in obstructive airway disease. *Am Rev Respir Dis* 1987;135:1229–33.
- 21 Arizono S, Taniguchi H, Sakamoto K, *et al.* Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. *Respir Care* 2014;59:1108–15.
- 22 Jones PW, Quirk FH, Baveystock CM, *et al.* A self-complete measure of health status for chronic airflow limitation. the st. george's respiratory questionnaire. *Am Rev Respir Dis* 1992;145:1321–7.
- 23 Jones PW, Harding G, Berry P, *et al.* Development and first validation of the COPD assessment test. *Eur Respir J* 2009;34:648–54.
- 24 Matsuda T, Taniguchi H, Ando M, *et al.* Copd assessment test for measurement of health status in patients with idiopathic pulmonary fibrosis: a cross-sectional study. *Respirology* 2017;22:721–7.
- 25 Nagata K, Tomii K, Otsuka K, *et al.* Evaluation of the chronic obstructive pulmonary disease assessment test for measurement of health-related quality of life in patients with interstitial lung disease. *Respirology* 2012;17:506–12.
- 26 Mahler DA, Weinberg DH, Wells CK, *et al.* The measurement of dyspnea. contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;85:751–8.
- 27 Yorke J, Moosavi SH, Shuldham C, *et al.* Quantification of dyspnoea using descriptors: development and initial testing of the dyspnoea-12. *Thorax* 2010;65:21–6.
- 28 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
- 29 Peek K, Sanson-Fisher R, Mackenzie L, *et al.* Interventions to aid patient adherence to physiotherapist prescribed self-management strategies: a systematic review. *Physiotherapy* 2016;102:127–35.
- 30 Ryerson CJ, Camp PG, Eves ND, *et al.* High oxygen delivery to preserve exercise capacity in patients with idiopathic pulmonary fibrosis treated with nintedanib. methodology of the HOPE-IPF study. *Ann Am Thorac Soc* 2016;13:1640–7.
- 31 Schaeffer MR, Ryerson CJ, Ramsook AH, *et al.* Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *Eur Respir J* 2017;49:1602494.
- 32 Steele BG, Belza B, Cain KC, *et al.* A randomized clinical trial of an activity and exercise adherence intervention in chronic pulmonary disease. *Arch Phys Med Rehabil* 2008;89:404–12.
- 33 Malaguti C, Dal Corso S, Janjua S, *et al.* Supervised maintenance programmes following pulmonary rehabilitation compared to usual care for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2021;8:CD013569.