Protocol for long-term effect of pulmonary rehabilitation under nintedanib in idiopathic pulmonary fibrosis

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Shareable abstract (@ERSpublications)
FITNESS is the first randomised controlled study to evaluate the long-term effects of pulmonary rehabilitation in idiopathic pulmonary fibrosis treated with nintedanib. Effectiveness of this comprehensive therapeutic approach will be addressed. https://bit.ly/3zvoBTr

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Abstract

Background Pulmonary rehabilitation causes short-term improvement in exercise capacity, dyspnoea and health-related quality of life in idiopathic pulmonary fibrosis (IPF); however, long-term maintenance of the improvement is difficult. Nintedanib, an antifibrotic drug, has been shown to delay the worsening of pulmonary function in IPF. Therefore, the concomitant use of nintedanib with pulmonary rehabilitation is anticipated to contribute to the long-term maintenance of the pulmonary rehabilitation effects. The long-term effect of pulmonary rehabilitation under nintedanib treatment in IPF (FITNESS) study is a multicenter, randomised, prospective, parallel-group, open-label trial.

Methods The study will enrol 84 patients with IPF who have been treated with nintedanib. Patients in the pulmonary rehabilitation group will receive a programmed short-term induction pulmonary rehabilitation programme, followed by a maintenance home-based pulmonary rehabilitation programme, while patients in the control group will receive usual outpatient care. Patients in both groups will continue to receive nintedanib treatment throughout the study period. The primary end-point of the study is to compare the change in the 6-min walk distance from the baseline to 12 months between the pulmonary rehabilitation and control groups. The main secondary end-point is endurance exercise time, measured using a bicycle ergometer.

Discussion FITNESS is the first randomised controlled study to evaluate the long-term effects of pulmonary rehabilitation in IPF treated with nintedanib. This study will address the hypothesis that concomitant use of nintedanib contributes to the maintenance of long-term effects of pulmonary rehabilitation, thus leading to a comprehensive therapeutic approach of "nintedanib and pulmonary rehabilitation" in the antifibrotic era.

Background

Idiopathic pulmonary fibrosis (IPF) is defined as a specific type of chronic progressive fibrosing interstitial pneumonia of unknown cause with histopathological and/or radiological patterns of usual interstitial pneumonia (UIP) [1]. The prognosis is considered poor, with a median survival of 2–3 years before the development of antifibrotic agents [2]. Although the prognosis is expected to be fairly prolonged with

antifibrotics [3–6], most patients with IPF still develop dyspnoea and decreased exercise capacity, which lead to reduced physical activity in daily living. Improving the dyspnoea, exercise capacity and daily physical activity are important goals in IPF management since they are associated with health-related quality of life and longevity [7–9].

Pulmonary rehabilitation is a comprehensive intervention, which mainly includes structured and supervised exercise training and education that has been clearly demonstrated to reduce dyspnoea, increase exercise capacity and improve health-related quality of life in individuals with COPD [10]. The effect of pulmonary rehabilitation has been shown in patients with IPF [11–13]; however, these benefits are reportedly moderate and transient [14]. Although some long-term benefits have been reported [15, 16], biases such as a low number of patients and intermingling of interstitial lung disease other than IPF could not be excluded. Hence, pulmonary rehabilitation is still considered an intervention that is weakly recommended for patients with IPF [17]. There is an urgent need to develop new strategies to maintain the long-term effects of pulmonary rehabilitation in IPF.

The transient effect of pulmonary rehabilitation in patients with IPF may be partly due to disease progression of IPF and acute respiratory events, including exacerbations and/or hospitalisations during and after the pulmonary rehabilitation programme [15]. Therefore, we hypothesised that concomitant use of nintedanib with pulmonary rehabilitation contributes to the maintenance of the long-term effects of pulmonary rehabilitation owing to its ability to slow the disease progression and thus, prolong the time for acute exacerbation [18]. Herein, we describe the design of the Randomised Controlled Trial: Long-term Effect of Pulmonary Rehabilitation under Nintedanib Treatment in Idiopathic Pulmonary Fibrosis (FITNESS study).

Methods

Objectives

The objective of the FITNESS study is to provide evidence of concomitant use of nintedanib with pulmonary rehabilitation for the maintenance of the long-term effects of pulmonary rehabilitation. This study received approval from the Ethics Committee of the Nagasaki University Hospital (No.17082106) as well as from ethics committees from all institutions that participated. Informed written consent will be obtained by the investigator prior to inclusion in the study. All methods are performed in accordance with the relevant guidelines and regulations of the Declaration of Helsinki.

This trial was registered at the University Hospital Medical Information Network (UMIN000026376) 3 March 2017 (www.umin.ac.jp/ctr/index.htm).

Study design

The FITNESS study is a multicenter, randomised, prospective, parallel-group, open-label trial comparing the long-term effect of pulmonary rehabilitation to usual care in patients with IPF treated with nintedanib.

Eligible patients will be randomly assigned 1:1 to pulmonary rehabilitation or control groups using the minimisation method [19] following baseline assessment in the 4-week screening period. Dynamic randomisation adjustment factors will be the 6-min walk distance (6MWD) (cut-off: 350 m), institution and forced vital capacity (FVC) (cut-off: 70% predicted). The pulmonary rehabilitation group will receive an outpatient induction pulmonary rehabilitation programme for 12 weeks, followed by a maintenance home-based pulmonary rehabilitation programme for 40 weeks, while the control group will receive only usual outpatient care. Patients in both groups will continue to receive nintedanib treatment throughout the study period. The study design is illustrated in figure 1 [20].

Eligibility criteria

Patients who meet all the following criteria will be eligible:

1) Age range 40 to 80 years at the time of consent
2) Diagnosis of IPF confirmed at each institution by the 2011 guidelines [17]
3) 600 m > 6MWD ⩾200 m
4) Exertional dyspnoea of the modified Medical Research Council (mMRC) 1 to 3 [21]
5) Without infection and/or acute exacerbation within 3 months
6) Taking nintedanib (150 mg or 100 mg twice daily) for at least 4 weeks before enrolment and expected to continue for 12 months thereafter
7) Able to attend outpatient pulmonary rehabilitation programme twice a week for 12 weeks and subsequent maintenance programme once every 2–4 weeks for the following 40 weeks

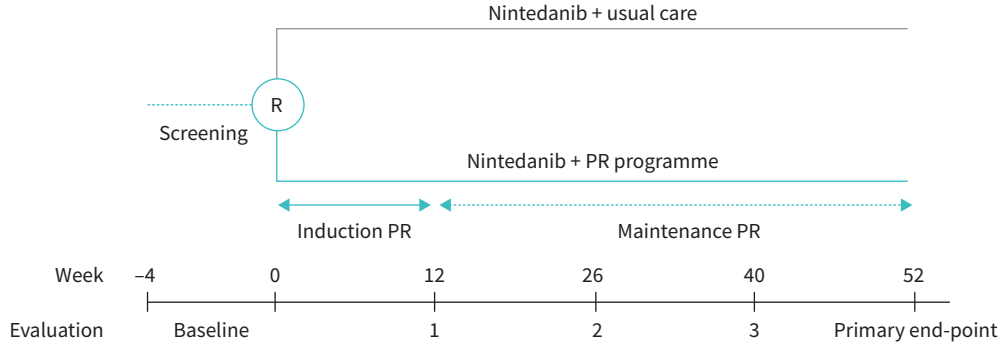

FIGURE 1 Study overview. After written consent is obtained, patients undergo baseline evaluation during the screening period (−4 to 0 weeks). After the randomisation (0 week), the control group will receive usual outpatient care (0 to 52 weeks). The pulmonary rehabilitation group will receive outpatient induction pulmonary rehabilitation twice a week (24 sessions) under the supervision of the physical therapists. After the induction pulmonary rehabilitation, the patients will continue to undergo a combination of pulmonary rehabilitation at home by themselves at least 4 times a week and outpatient pulmonary rehabilitation at least once every 4 weeks as maintenance pulmonary rehabilitation (13–52 weeks). The status of home pulmonary rehabilitation will be evaluated with a diary that the patients will record by themselves. In both groups, the number of steps taken each day will also be evaluated with a pedometer. In both groups, nintedanib (150 mg or 100 mg twice daily) will be continued if possible for the duration of the study. PR: pulmonary rehabilitation; R: randomisation.

8) Pulmonary function test within a month before the enrolment of FVC ⩾50% predicted, 79% ⩾ diffusing capacity of the lung for carbon monoxide (D_{LCO}) ⩾30% predicted and forced expiratory volume in 1 s (FEV_1)/FVC ⩾70%

Exclusion criteria

1) Collagen vascular disease, neuromuscular disease, orthopaedic disease or any other disease affecting exercise capacity and/or training
2) History of pulmonary rehabilitation within 12 months
3) Systemic corticosteroid administration of >15 mg·day^{-1}, prednisolone equivalent and/or immunosuppressive drugs within 3 months
4) Pirfenidone administration within 3 months
5) Cardiac complications (unstable angina, myocardial infarction, percutaneous coronary angioplasty, coronary artery bypass grafting, arrhythmia requiring treatment) within 1 month and/or cerebrovascular disease within 6 months
6) Clinically severe pulmonary hypertension
7) Abnormal laboratory parameters (liver transaminases or bilirubin above two-fold upper limit of normal)
8) Full-dose anticoagulant therapy or high-dose antiplatelet therapy
9) Malignancies that are not confirmed recurrence-free for at least 3 years
10) Inability to perform full pulmonary function test

Nintedanib

In both groups, nintedanib (150 mg or 100 mg twice daily) will be continued for the study duration, with dose modification permitted at the investigator's discretion, similar to the INPULSIS trial [18].

Pulmonary rehabilitation programme

In this study, physical therapists at each institute will perform the exercise assessment and pulmonary rehabilitation programme. A written procedure was developed before the start of the study to ensure uniformity of the assessment and pulmonary rehabilitation. Furthermore, a joint practice session with the physical therapists in each facility was conducted to ensure uniformity in the methods.

For 12 weeks following the randomisation, patients will receive outpatient induction pulmonary rehabilitation twice a week (24 sessions) under the supervision of the physical therapists in the outpatient

clinic. Induction pulmonary rehabilitation consists of the following elements: endurance training on a bicycle ergometer aiming for 80% of the patient's maximum load, resistance training for the upper and lower extremities with an increase in the load as much as possible, endurance training by walking, and resistance training by squatting and standing calf raise. After the induction pulmonary rehabilitation group, the patients will continue to undergo a combination programme of pulmonary rehabilitation at home by themselves at least four times a week and outpatient pulmonary rehabilitation at least once every 4 weeks as maintenance pulmonary rehabilitation (13–52 weeks). The status of home pulmonary rehabilitation will be evaluated using the diaries recorded by the patients. The number of steps taken each day will be evaluated using a pedometer that will be uniform among the centres (FB-732, TANITA Corporation, Tokyo, Japan). The target of the number of steps a day will be increased by 10% every month unless it exceeds 6000 steps.

Study outcomes

Primary outcome

The primary end-point is to compare the change in 6MWD from baseline to 12 months between the two groups.

Secondary outcomes

The main secondary end-point is to compare the change in the endurance time measured by a bicycle ergometer from baseline to 12 months between the two groups. Additional secondary end-points are as follows: comparing the change in patient-centred outcomes from baseline to 12 months between the two groups, comparing the relative change in 6MWD, comparing the change in steps on a pedometer, comparing the change in FVC, D_{LCO} and oxygen saturation measured by pulse oximetry (SpO_2) at rest and after the 6-min walk, comparing the frequency of unscheduled hospitalisation and mortality rate, compliance with planned long-term rehabilitation (ratio: actual/plan) in the pulmonary rehabilitation group and change in 6MWD in patients with good compliance (⩾70%). Patient-centred outcomes include scores in the St. George's Respiratory Questionnaire (SGRQ) [22], the COPD Assessment Test (CAT) [23, 24], the Transitional Dyspnoea Index (TDI) [25], Dyspnoea-12 [26], and Hospital Anxiety and Depression Scale (HADS) [27]. The schedule of visits and assessments is summarised in table 1.

Statistical analysis

Sample size

There is little reference data from previous studies to estimate the magnitude of increase in the 6MWD when pulmonary rehabilitation is combined with nintedanib treatment. For patients treated with nintedanib, the gradient of serial decrease in 6MWD will be considered small, although the actual amount is unknown. In addition, the maintenance pulmonary rehabilitation programmes may support their walking distance. Therefore, we hypothesised that the change in 6MWD following long-term pulmonary rehabilitation in patients with IPF treated with nintedanib is similar to that following short-term pulmonary rehabilitation. We calculated the standard deviation (SD) for changes in 6MWD to be 55 m based on previous studies of short-term pulmonary rehabilitation in IPF [28]. The difference in the 6MWD 1 year following the registration between the groups with and without pulmonary rehabilitation was expected to be 36 m. Therefore, a sample of 74 patients in total provides a significant level of 5% (two-sided) and >80% power for the primary end-point in this long-term comparative rehabilitation study. Assuming some inestimable patients, the sample size of this study will be a total of 84 patients. This sample size was similar to that of the HOPE IPF study [29]. Considering the main secondary end-point, based on a previous study, the difference in pre/post bicycle ergometer endurance time between the two groups was estimated to be 10 min with a maximum SD of 10 min [30]. Therefore, the difference between the two groups can be detected with a significance level of 5% (two-sided) and a power of >90% by accumulating 84 patients.

Outcome analysis

The analyses for efficacy will be performed in the full analysis set comprising all the randomised patients who had undergone baseline assessment and at least one evaluation point following randomisation. Sensitivity analyses will be performed using a per-protocol set (PPS). PPS was defined as all the patients who met the pre-specified criteria. Data handling was defined for each end-point. Safety analysis will be performed in patients who received at least one dose of nintedanib. A mixed-effect model for repeated measures will be applied to the comparison of the change in 6MWD from baseline between treatment groups with a significance level of 5% (two-sided). The least-squares mean and 95% confidence interval will be calculated using a linear mixed-effect model including treatment group, 6MWD at baseline, evaluation time point, and an interaction term of the treatment group and evaluation time point as fixed effects. No imputation is performed. The change in endurance time measured by a bicycle ergometer from baseline will also be compared using the mixed-effect model for repeated measures. Other secondary

end-points (steps, health-related quality of life (SGRQ and CAT scores), dyspnoea (TDI and dyspnoea-12 scores), FVC, D_{LCO}, arterial partial pressure of oxygen, mMRC and the lowest SpO_2 after the 6-min walk test) will be evaluated in the same manner. As for demographic and clinical characteristics, continuous and categorical variables will be analysed using t-test and Fisher's exact test, respectively. As serious cardiac complications, the number of patients who developed ischaemic cardiac disease and arrhythmias requiring treatment will be tabulated and compared between treatment groups using Fisher's exact test. Other adverse events will be summarised and compared using Fisher's exact test. For all the statistical analyses, a significance is set at 0.05.

Discussion

The FITNESS study will be the first to evaluate the long-term effect of pulmonary rehabilitation in patients with IPF undergoing antifibrotic treatment in a randomised controlled fashion. Demonstrating the long-term benefit of pulmonary rehabilitation under nintedanib treatment will revolutionise the management of IPF in clinical practice. The findings would suggest the importance of pulmonary rehabilitation and promote rehabilitation therapy in patients with IPF. Although most patients with IPF develop disabling dyspnoea over time, which leads to reduced exercise capacity and lowered physical activity, the combination of pulmonary rehabilitation and nintedanib treatment might change this dismal course.

Previous studies on pulmonary rehabilitation in patients with IPF demonstrated a short-term effect on exercise capacity, dyspnoea and health-related quality of life [28]. However, few studies have evaluated the long-term effects of pulmonary rehabilitation with inconsistent results [13–16]. Disease progression of IPF and acute respiratory events during and after pulmonary rehabilitation might interfere with the long-term effect of pulmonary rehabilitation [15]. Therefore, the hypothesis that nintedanib would delay the loss of lung function and decrease the frequency of acute exacerbations, thereby providing an additive long-term pulmonary rehabilitation benefit, is reasonable. Moreover, in this era of antifibrotic agents [3, 4], the effect of pulmonary rehabilitation should be re-evaluated.

In this study, we selected the 6MWD as the primary outcome because it has been commonly used to assess exercise capacity in patients with IPF. Given previous evidence that patients with severe dyspnoea and short walk distance experience little improvement after short-term pulmonary rehabilitation [31], we defined the inclusion criteria as 6MWD of 200 to 600 m. We also chose cycle endurance time as the main secondary end-point because it is reportedly the most responsive exercise outcome [30]. Other secondary outcomes include patient-centered outcomes, walk steps assessed using a pedometer as a surrogate for physical activity, frequency of unscheduled hospitalisation and mortality. Considering the physical activity level to be significantly associated with mortality [9], the combination strategy of pulmonary rehabilitation and nintedanib might improve and maintain increased physical activity resulting in prolonged longevity in patients with IPF.

This study has several limitations. First, there is no established pulmonary rehabilitation protocol specific to IPF, although the protocol will be carried out based on the pulmonary rehabilitation protocol for COPD [10].

TABLE 1 Schedule of visits and assessments

Item	Time				
	Baseline	12 weeks	26 weeks	40 weeks	52 weeks
Informed consent	•				
Patient characteristics	•				
S_{pO_2}	•	•	•	•	•
6-min walk test	•	•	•	•	•
Endurance time	•	•	•		•
SGRQ and CAT	•	•	•		•
Dyspnoea-12	•	•	•		•
HADS	•	•	•		•
Pedometer	•	•	•		•
Pulmonary function test	•	•	•	•	•
ECG	•	•	•	•	•
Nintedanib medication diary	•	During the study period			
Adverse events		During the study period			

S_{pO_2}: oxygen saturation measured by pulse oximetry; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; HADS: Hospital Anxiety and Depression Scale.

Second, a group with patients who will not receive nintedanib has not been included. However, considering that withholding nintedanib for a year is not permitted for ethical reasons, the current design is the most optimal for evaluating the effect of the combination strategy of pulmonary rehabilitation and nintedanib. Third, the coronavirus disease 2019 (COVID-19) pandemic transpired following the start of the study. Hence, we were unable to predict the impact of COVID-19 on the effects of pulmonary rehabilitation.

In conclusion, the FITNESS study will address the hypothesis that concomitant use of nintedanib with pulmonary rehabilitation contributes towards the maintenance of long-term effects of pulmonary rehabilitation in IPF, thus leading to a comprehensive therapeutic approach of "nintedanib and pulmonary rehabilitation" in the anti-fibrotic era.

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This study is registered at https://www.umin.ac.jp/ctr/ with identifier number UMIN000026376. The datasets will be available from the corresponding author upon reasonable request.

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