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Early View

Study protocol

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FITNESS: Protocol for long-term effect of pulmonary rehabilitation under nintedanib in IPF

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Take home message

FITNESS is the first randomized controlled study to evaluate the long-term effects of pulmonary rehabilitation (PR) in idiopathic pulmonary fibrosis treated with nintedanib. Effectiveness of this comprehensive therapeutic approach will be addressed.

ABSTRACT

Background: Pulmonary rehabilitation (PR) causes short-term improvement in exercise capacity, dyspnea, 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 PR is anticipated to contribute to the long-term maintenance of the PR effects. The long-term effect of PR under nintedanib treatment in IPF (FITNESS) study is a multicenter, randomized, prospective, parallel-group, open-label trial.

Methods: The study will enroll 82 patients with IPF who have been treated with nintedanib. Patients in the PR group will receive a programmed short-term induction PR program, followed by a maintenance home-based PR program, 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 endpoint of the study is to compare the change in the 6-minute walk distance from the baseline to 12-months between the PR and control groups. The main secondary endpoint is endurance exercise time, measured using a bicycle ergometer.

Discussion: FITNESS is the first randomized controlled study to evaluate the long-term effects of PR 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 PR, thus leading to a comprehensive therapeutic approach of “nintedanib and PR” in the antifibrotic era.

Keywords: antifibrotics; exercise; interstitial lung disease; rehabilitation; therapy

Background

Idiopathic pulmonary fibrosis (IPF) is defined as a specific type of chronic progressive fibrosing interstitial pneumonia of unknown cause with histopathologic and/or radiologic 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 dyspnea and decreased exercise capacity, which lead to reduced physical activity in daily living. Improving the dyspnea, 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 (PR) is a comprehensive intervention, which mainly includes structured and supervised exercise training and education that has been clearly demonstrated to reduce dyspnea, increase exercise capacity, and improve health-related quality of life in individuals with chronic obstructive pulmonary disease (COPD) [10]. The effect of PR 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, PR 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 PR in IPF.

The transient effect of PR in patients with IPF may be partly due to disease progression of IPF and acute respiratory events, including exacerbations and/or hospitalizations during and after the PR program [15]. Therefore, we hypothesized that concomitant use of nintedanib with PR contributes to the maintenance of the long-term effects of PR due to its ability to slow the disease progression and thus, prolong the time for acute exacerbation [18].

Herein, we describe the design of the Randomized 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 PR for the maintenance of the long-term effects of PR. 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. **A**ll 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 (https://www.umin.ac.jp/ctr/index.htm).

Study design

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

Eligible patients will be randomly assigned 1:1 to PR or control groups using the minimization method [19] following baseline assessment in the 4-week-screening period. Dynamic randomization 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 PR group will

receive an outpatient induction PR program for 12 weeks, followed by a maintenance home-based PR program 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 dyspnea of the modified Medical Research Council (MRC) 1 to 3 [21]

5) Without infection and/or acute exacerbation within 3 months

6) Taking nintedanib (150 mg or 100 mg bid) for at least 4 weeks before enrollment and expected to continue for 12 months thereafter

7) Able to attend outpatient PR program twice a week for 12 weeks and subsequent maintenance program once every 2–4 weeks for the following 40 weeks

8) Pulmonary function test within a month before the enrollment of FVC ≥ 50% predicted, 79% ≥ diffusion capacity of the lung for carbon monoxide (DLco) ≥ 30% predicted, and forced expiratory volume in 1 s (FEV_1)/FVC ≥70%

Exclusion criteria

1) Collagen vascular disease, neuromuscular disease, orthopedic disease, or any other disease affecting exercise capacity and/or training

2) History of PR within 12 months

3) Systemic corticosteroid administration of > 15 mg/day, 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 2-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 bid) will be continued for the study duration, with dose modification permitted at the investigator's discretion, similar to the INPULSIS trial [18].

PR program

In this study, physical therapists at each institute will perform the exercise assessment and PR program. A written procedure was developed before the start of the study to ensure uniformity of the assessment and PR. 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 randomization, patients will receive outpatient induction PR twice a week (24 sessions) under the supervision of the physical therapists in the outpatient clinic. Induction PR 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 PR group, the patients will continue to undergo a combination program of PR at home by themselves at least 4 times a week and outpatient PR at least once every 4 weeks as maintenance PR (13–52 weeks). The status of home PR 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 centers (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 endpoint is to compare the change in 6MWD from baseline to 12-month between the two groups.

Secondary outcomes

The main secondary endpoint is to compare the change in the endurance time measured by a bicycle ergometer from baseline to 12-month between the two groups. Additional secondary endpoints are as follows: comparing the change in patient-centered outcomes from baseline to 12-month between the two groups, comparing the relative change in 6MWD, comparing the

change in steps on a pedometer, comparing the change in FVC, DLco, and oxygen saturation (SpO_2) at rest and after the 6-min walk, comparing the frequency of unscheduled hospitalization and mortality rate, compliance with planned long-term rehabilitation (ratio: actual/plan) in the PR group and change in 6 MWD in patients with good compliance (≥ 70%). Patient-centered outcomes include scores in the St. George's Respiratory Questionnaire (SGRQ) [22], the COPD Assessment Test (CAT) [23, 24], the Transitional Dyspnea Index (TDI) [25], Dyspnea-12 [26], and Hospital Anxiety and Depression Scale (HADS) [27].

Statistical Analysis

Sample size

There is little reference data from previous studies to estimate the magnitude of increase in the 6MWD when PR 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 PR programs may support their walking distance. Therefore, we hypothesized that the change in 6MWD following long-term PR in patients with IPF treated with nintedanib is similar to that following short-term PR. We calculated the standard deviation (SD) for changes in 6MWD to be 55 m based on previous studies of short-term PR in IPF [28]. The difference in the 6MWD one year following the registration between the groups with and without PR 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 endpoint 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 endpoint, 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 randomized patients who had undergone baseline assessment and at least one evaluation point following randomization. Sensitivity analyses will be performed using per-protocol set (PPS). PPS was defined as all the patients who met the pre-specified criteria. Data handling was defined for each endpoint. 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% interval will be calculated using a linear mixed-effect model including treatment group, 6 MWD 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 be also compared using the mixed effect model for repeated measures. Other secondary endpoints (steps, health-related quality of life (SGRQ and CAT scores), dyspnea (TDI and dyspnea-12 scores), FVC, DL_{CO}, 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 analyzed using Student's t-test and Fisher’s exact test, respectively. As serious cardiac complications, the number of patients who developed ischemic cardiac disease and arrhythmias requiring treatment will be tabulated and compared between treatment groups using Fisher's exact test. Other adverse events will be summarized 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 PR in patients with IPF undergoing antifibrotic treatment in a randomized controlled fashion. Demonstrating the long-term benefit of PR under nintedanib treatment will revolutionize the management of IPF in clinical practice. The findings would suggest the importance of PR and promote rehabilitation therapy in patients with IPF. Although most patients with IPF develop disabling dyspnea over time, which leads to reduced exercise capacity and lowered physical activity, the combination of PR and nintedanib treatment might change this dismal course.

Previous studies on PR in patients with IPF demonstrated a short-term effect on exercise capacity, dyspnea, and health-related quality of life [28]. However, few studies have evaluated the long-term effects of PR with inconsistent results [13-16]. Disease progression of IPF and acute respiratory events during and after PR might interfere with the long-term effect of PR [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 PR benefit, is reasonable. Moreover, in this era of antifibrotic agents [3, 4], the effect of PR 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 dyspnea and short walk distance experience little improvement after short-term PR [31], we defined the inclusion criteria as 6MWD of 200 to 600m. We also chose cycle endurance time as the main secondary endpoint 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 hospitalization, and mortality. Considering the physical activity level to be significantly associated with mortality [9], the combination strategy of PR 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 PR protocol specific to IPF, although the protocol will be carried out based on the PR protocol for COPD [10]. 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 PR and nintedanib. Third, the 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 PR.

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

Abbreviations

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DLco: diffusion capacity of the lung for carbon monoxide; $FEV_{1:}$ forced expiratory volume in one second; FVC: forced vital capacity; HADS: Hospital Anxiety and Depression Scale; IPF: idiopathic pulmonary fibrosis; MRC: Medical Research Council; PPS: per-protocol set; PR: pulmonary rehabilitation; SD: standard deviation; 6MWD: 6-min walk distance; SpO_2: oxygen saturation; SGRQ: St. George's Respiratory Questionnaire; TDI: Transitional Dyspnea Index; UIP: usual interstitial pneumonia

Availability of data and materials

The datasets will be available from the corresponding author upon reasonable request.

Competing Interests

Dr. Nishiyama, Dr. Kataoka, and Dr. Ogura received honoraria for lectures from Nippon Boehringer Ingelheim Co., Ltd.. Dr. Kondoh received consulting fee and honoraria for lectures from Nippon Boehringer Ingelheim Co., Ltd..

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Authors' contributions

Study design and protocol: O.N., K.K., S.A., Y.M., K.N., T.Ogawa, A.S., F.W., R.K., T.Ogura, and Y.K. Statistical analysis and interpretation of data: M.A. Manuscript draft and/or editing: O.N. and K.K. Technical support, critical feedback, and revisions of the final manuscript: R.K., T.Ogura, and Y.K.

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Figure Legends

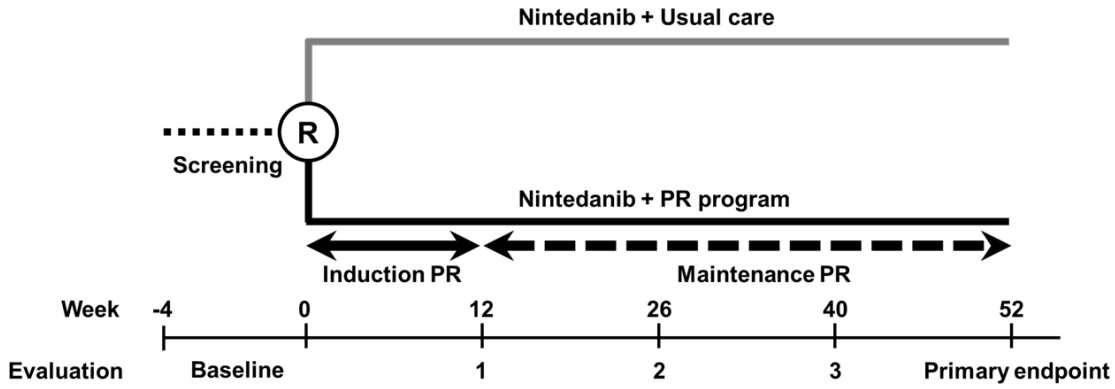

FIGURE 1. Study overview. After a written consent is obtained, patients undergo baseline evaluation during the screening period (-4 to 0 weeks). After the randomization (0 week), the control group will receive usual outpatient care (0 to 52 weeks). The PR group will receive outpatient induction PR twice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

PR; pulmonary rehabilitation, R; randomization

Item \ Time	Baseline	12-week	26-week	40-week	52-week
Informed consent	X				
Patient characteristics	X				
SpO_2	X	X	X	X	X
6-minutes walk test	X	X	X	X	X
Endurance time	X	X	X		X
SGRQ, CAT	X		X		X
Dyspnea-12	X	X	X		X
HADS	X	X	X		X
Pedometer	X	X	X		X
Pulmonary function test	X	X	X	X	X
ECG	X	X	X	X	X
Nintedanib medication diary	X	during the study period			
Adverse events		during the study period			

FIGURE 2. Schedule of visits and assessments.

CAT, COPD Assessment Test; ECG, electrocardiogram; HADS, Hospital Anxiety and Depression Scale; SGRQ, St. George's Respiratory Questionnaire; SpO_2, arterial oxygen saturation measured by pulse oximetry