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Weight loss in nintedanib-treated patients with idiopathic pulmonary fibrosis

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ABSTRACT

Nintedanib is approved for the treatment of idiopathic pulmonary fibrosis (IPF). Weight loss is recognized as an adverse event during nintedanib treatment, and is a common complication exploitable as a prognostic indicator of IPF. Here, we report a single-center, retrospective cohort study to assess body weight changes during nintedanib therapy in patients with IPF. Sixty-one patients treated with nintedanib for >6 months were included (45 males, mean age ± standard deviation 73.1 ± 7.4 years). Baseline body weight and body mass index were 60.1 ± 12.0 kg and 23.2 ± 3.5 kg/m^2, respectively. Mean weight loss during the first 6 months of nintedanib treatment was significant (−3.2 ± 3.4 kg, $p < 0.0001$) with Common Terminology Criteria for Adverse Events (CTCAE) grades 0,1,2 or 3 of 30, 17, 13 and 1, respectively. Pulmonary function test records 6 months before nintedanib administration were available in a subset of patients (n = 40). Significant differences in weight change over the 6 months before-vs-after nintedanib administration were also observed in these patients [mean differences −2.5 ± 3.4 kg, 95% confidence interval (CI) −3.6, −1.4, $p < 0.0001$]. Multivariate analysis showed that only baseline body weight was significantly associated with weight loss of CTCAE grade ≧2 (odds ratio 0.921, 95% CI 0.854, 0.994). Median follow-up from starting nintedanib was 34.8 months. There was a significant difference in overall survival between patients with CTCAE grade ≧2-vs-grade<2 (median survival of 25.5 months and 55.2 months, $p = 0.014$). In the model adjusting for age, sex and lung function, weight loss CTCAE grade ≧2 was an independent predictor for all-cause mortality (hazard ratio 2.448, 95% CI 1.080–5.551). In conclusion, weight loss is an important issue for the management of patients with IPF treated with nintedanib.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a type of chronic, progressive, fibrosing interstitial pneumonia of unknown cause [1]. It is mostly seen in older adults and is the most common form of idiopathic interstitial lung disease (ILD) for which there are unmet clinical needs. IPF therapy was radically changed in 2014 following the results of two phase III clinical trials documenting that treatment with either of the antifibrotics pirfenidone or nintedanib ameliorated declining lung function [2,3]. These results strongly suggested that clinical outcomes of IPF patients would be improved by the application of these drugs. In fact, not only modelling and extrapolation of survival data from clinical trials [4,5], but also large real-world data registries [6,7] consistently indicate that antifibrotics increase the life expectancy of IPF patients. A progressive fibrosing phenotype may also develop in certain patients with other fibrosing ILDs, with symptoms including decline in lung function and early mortality, similar to what is seen in IPF, despite standard-of-care treatment [8,9]. Nintedanib has also proven effective for such patients [10].

Many studies on the safety and tolerability of approved antifibrotics have revealed that intolerance due to adverse events is common, resulting in dose reduction or even discontinuation [2,3]. Most of the adverse events associated with either drug are gastrointestinal, including loss of appetite, nausea and lethargy as most common for

Abbreviations: ATS, American Thoracic Society; BID, bis in die; BMI, body mass index; CTCAE, Common Terminology Criteria for Adverse Events; CI, confidence interval; DLco, diffusing capacity for lung carbon monoxide; ERS, European Respiratory Society; FVC, forced vital capacity; GAP, Gender-Age-Physiology; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; JRS, Japanese Respiratory Society; ALAT, Latin American Thoracic Society; MRC, Medical Research Council; OR, odds ratio; SD, standard deviation; CCI, Charlson comorbidity index; KL-6, Krebs von den Lungen-6; SP-D, Surfactant protein-D.

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pirfenidone, and diarrhea, nausea and reduced appetite for nintedanib. In addition to these common gastrointestinal-associated events, skin-associated adverse events are specific to pirfenidone and weight loss is more common with nintedanib [11].

Weight loss is recognized as a common complication of IPF [12], with recent studies showing that changes in weight or body mass index (BMI) might act as prognostic indicators for IPF [13–15] and fibrosing ILDs including IPF [16,17]. Furthermore, weight loss is recognized as an important domain of frailty defined as a clinical condition of decreased resilience in the face of endogenous and exogenous stressors [18]. Many fibrosing ILDs, including IPF, increase in incidence with age [19] and frailty is highly prevalent in older populations. Weight loss is of special importance in such frail patients [20]. Indeed, frailty is common in ILD patients and has reported to be an independent predictor of increased mortality [21]. Taken together, available data suggest that weight loss during nintedanib treatment is important in the context of adverse events and disease prognosis. To date, however, few clinical studies have specifically investigated weight loss in IPF patients treated with nintedanib. Accordingly, we carried out a retrospective study addressing this issue with the objective of assessing body weight change and determining its prognostic impact.

2. Materials and methods

2.1. Study design and patients

A single-center, retrospective cohort study of patients with IPF treated with nintedanib between September 2015 and May 2022 was conducted. IPF diagnosis followed the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) clinical practice guidelines [1,22]. Only patients continuing nintedanib for >6 months were included in the study, and those with a history of cancer over one year prior to starting nintedanib treatment were excluded. According to our experience in earlier studies [23,24], we often started nintedanib at the low dose of 100 mg bis in die (BID) for patients with small physiques, despite Japanese guidelines recommending starting at 150 mg BID and then decreasing and/or interrupting it depending on adverse events. Chronic comorbid conditions were reported using the updated Charlson comorbidity index [25,26]. Clinical and laboratory data, concomitant therapy and adverse events were retrieved from medical records. Data on patients' weight and height were obtained from the pulmonary function test record. Data collected included before 6 months (±one month) if available, at the initiation, and every 6 months (±one month) subsequently following the start of nintedanib administration for as long as the drug was continued. When pulmonary function tests were not performed, data on patients' weight were obtained from the routine clinical practice medical records in outpatient clinics. The Gender-Age-Physiology (GAP) index, the most widely validated prognostic tool for patients with IPF [27] was used to divide patients into stages of disease severity.

Subsequently, we dichotomized the patients according to weight loss stratification by the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [28] grade ≧ 2 or grade <2 during the first 6 months of nintedanib administration. Weight loss CTCAE grade 2 was defined as a decrease of 10–20% from baseline, meaning that nutritional support was indicated. The rate of weight change was calculated using the following formula: {% weight change = 100 × (weight at 6 months follow-up weight - weight at the initiation of nintedanib)/weight at the initiation of nintedanib}. We compared the baseline data, nintedanib treatment status, adverse events other than weight loss, changes in laboratory and pulmonary function data and survival between the two groups.

2.2. Statistics

All statistical analyses were performed using JMP software package version 13 (SAS Institute Inc., Cary, NC, USA). Descriptive measures for baseline characteristics and for the clinical course were reported as means ± standard deviation (SD), medians (interquartile ranges) and as percentages. Categorical variables were compared using Chi-square and Fisher's exact tests. Continuous variables were compared using unpaired t and Mann-Whitney U tests.

Baseline clinical characteristics were compared between patients who had weight loss CTCAE grade ≧2 versus those who had grade <2 during the first 6 months of nintedanib administration. A multiple logistic regression analysis was applied to identify independent predictors of weight loss at CTCAE grade ≧2 and to estimate odds ratios (ORs). The latter were adjusted for possible confounding factors identified by univariate analysis ($p < 0.10$). The 95% confidence interval (CI) for each OR was calculated, and the statistical significance was determined from the 95% CI, not including 1.00 for the logistic analyses.

Log-rank testing was used to evaluate the Kaplan-Meier curves for the time to cessation of nintedanib and survival. The primary outcome measure was all-cause mortality with survival times calculated from the date of first nintedanib administration to death or the time of last follow-up. All data were censored at November 2022. Time-to-event models were constructed using the Cox proportional hazards approach, adjusting for the GAP index stage. Adjusted hazard ratios and 95% CI were determined and statistical significance was accepted at $p < 0.05$.

2.3. Ethical issues

This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kobe City Medical Center West Hospital (approval number 22–002, approval date 24, May 2022.). The requirement for informed consent was waived because of the retrospective nature of the study and the anonymity of the patients.

3. Results

3.1. Study population

We identified 81 patients with IPF treated with nintedanib at our hospital during the study period. Of these, 9 with malignancy (7 lung cancers, one liver cancer, one gastric cancer), 10 who discontinued nintedanib within 6 months and one patient without follow-up were excluded. Reasons for the discontinuation of nintedanib included death due to IPF progression (n = 2), acute exacerbation of IPF (n = 2), and adverse events (n = 6). The latter consisted of elevated transaminases (n = 3), diarrhea (n = 1), nausea (n = 1) and pulmonary hypertension (n = 1). Finally, 61 patients (45 males and 16 females, at a mean age of 73.1 ± 7.4 years) were included in the study (Table 1). The mean percent predicted forced vital capacity (%FVC) and percent predicted diffusing capacity for lung carbon monoxide (%DLco) at baseline was 67.0 ± 19.9% and 52.2 ± 18.8%, respectively, and the GAP index stageI/II/III were 20/24/17. Before starting treatment with nintedanib, one patient had been receiving treatment with pirfenidone.

3.2. Changes in body weight

The baseline body weight and BMI were 60.1 ± 12.0 kg and 23.2 ± 3.5 kg/m^2, respectively. Changes in body weight subsequent to nintedanib administration are shown in Fig. 1 a). Mean weight loss during the first 6 months of nintedanib treatment was −3.2 ± 3.4 kg, a significant change from baseline ($p < 0.0001$). Weight loss continued thereafter (−4.1 ± 4.4 kg at 12 months, −5.0 ± 5.3 kg at 18 months, −5.7 ± 6.2 kg at 24 months) and no recovery was observed. The rate of weight loss was maximum during the first 6 months of nintedanib administration.

Table 1
Study cohort baseline characteristics and comparison between patients with weight loss CTCAE grade ≧2-vs-grade <2 during the first 6 months of nintedanib administration.

	Total (n = 61)	Weight loss CTCAE grade		
		grade≧2(n = 14)	grade < 2(n = 47)	P value
Male gender	45(73.8)	9(64.3)	36(76.6)	0.369
Age, y	73.1 ± 7.4	74.5 ± 10.3	72.7 ± 6.5	0.425
Never smoked	17(28.3)	7(50.0)	10(21.7)	0.087
Updated CCI	1(1–1)	1(1–1.5)	1(1–1)	0.566
Diabetes mellitus	18(29.5)	5(35.7)	13(27.7)	0.739
mMRC grade	2(1–3)	3(1–3)	1(1–2)	0.020
Home oxygen therapy	13(21.3)	7(50.0)	6(12.8)	0.006
Total protein, g/dL	7.6 ± 0.7	7.8 ± 0.9	7.6 ± 0.6	0.399
Albumin, g/dL	4.1 ± 0.3 (n = 59)	4.0 ± 0.4	4.1 ± 0.3 (n = 45)	0.103
KL-6, U/mL	1229.7 ± 718.0	1445.8 ± 947.7	1165.3 ± 632.6	0.202
SP-D, ng/mL	312.5 ± 198.4 (n = 59)	338.2 ± 199.1	304.5 ± 199.7 (n = 45)	0.583
Body weight, kg	60.1 ± 12.0	52.4 ± 7.7	62.5 ± 12.2	0.005
Body mass index, kg/m^2	23.2 ± 3.5	20.9 ± 2.4	23.8 ± 3.5	0.005
FVC %predicted, %	67.0 ± 19.9	56.3 ± 15.6	69.9 ± 20.0	0.027
DLco % predicted, %	52.2 ± 18.8 (n = 50)	48.7 ± 16.6 (n = 10)	53.1 ± 19.4 (n = 40)	0.518
GAP index stage I/II/III	20/24/17	2/6/6	18/18/11	0.161

Categorical data are given as a number (%); continuous data as means ± standard deviation or medians (interquartile ranges).
Abbreviations.
CCI: Charlson comorbidity index.
CTCAE: Common Terminology Criteria for Adverse Events.
DLco: diffusion capacity for carbon monoxide.
FVC: forced vital capacity.
GAP: gender, age and lung physiology.
KL-6: Krebs von den Lungen-6.
mMRC: modified Medical Research Council.
SP-D: Surfactant protein-D.

Pulmonary function test records and body weights 6 months before nintedanib administration were available in 40 patients. In these patients changes in body weight before 6 months, and every 6 months subsequent to nintedanib administration are shown in Fig. 1 b). Mean weight loss during the 6 months before nintedanib administration was −0.7 ± 2.2 kg (not significant, p = 0.055). In contrast, mean weight loss during the first 6 months of nintedanib administration was −3.2 ± 3.7 kg (p < 0.0001). Differences in weight change comparing that observed during 6 months before and after nintedanib administration were significant (mean differences −2.5 ± 3.4 kg, 95%CI -3.6, −1.4, p < 0.0001).

3.3. Factors associated with weight loss

We then focused on weight loss during the first 6 months of nintedanib administration. During that period, numbers of patients experiencing weight loss CTCAE grade 0,1,2,3 were 30, 17, 13, 1, respectively. Comparisons of baseline characteristics between patients who had weight loss CTCAE grade ≧2 (n = 14) and grade <2 (n = 47) during that period are shown in Table 1. In the CTCAE grade ≧2 group, significantly more patients used home oxygen (p = 0.006) with significantly worse modified Medical Research Council (mMRC) grade (p = 0.020) compared with the CTCAE grade <2 group. The two groups exhibited significant differences in body weight (p = 0.005), BMI (p = 0.005), and

Table 2
Multivariate analysis of the baseline characteristics: patients who had weight loss CTCAE grade ≧2 versus those who had weight loss CTCAE grade <2 during the first 6 months of nintedanib administration.

Variable	Odds ratio	95% confidence interval	P value
Never smoked	4.613	0.807, 26.383	0.086
mMRC grade	2.100	0.727, 6.064	0.159
Home oxygen therapy	1.863	0.280, 12.402	0.520
Body weight	0.921	0.854, 0.994	0.022
FVC %predicted	0.961	0.918, 1.006	0.073

Abbreviations.
CTCAE: Common Terminology Criteria for Adverse Events.
FVC: forced vital capacity.
mMRC: modified Medical Research Council.

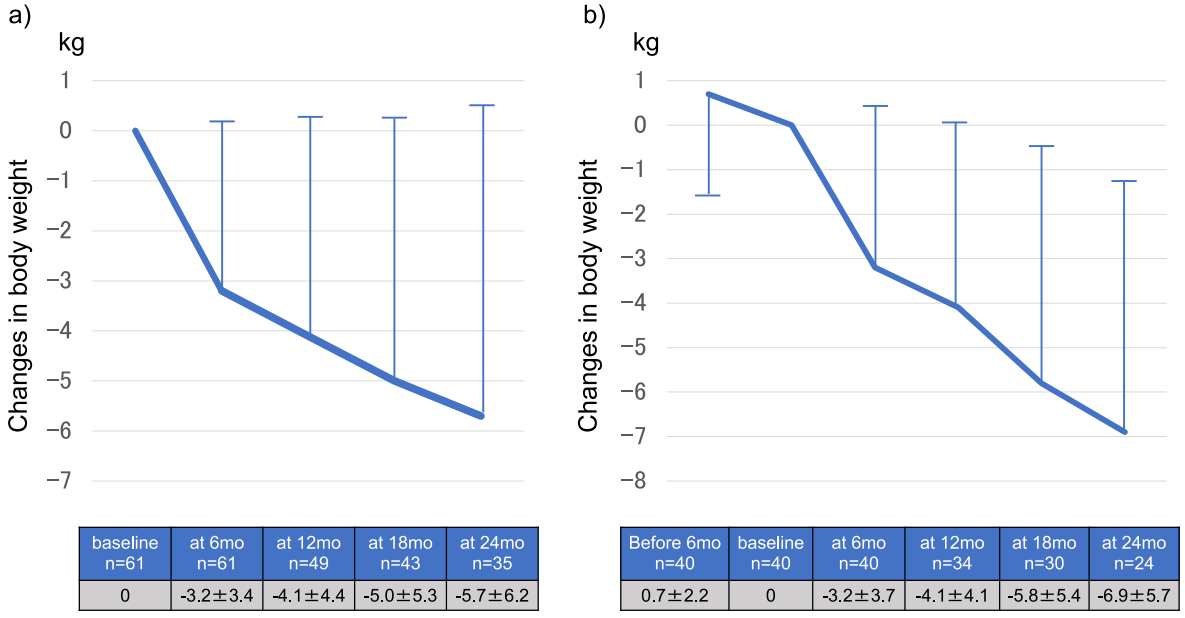

Fig. 1. Changes in body weight
a) Changes in body weight subsequent to nintedanib administration Bar shows mean + standard deviation, b) Changes in body weight before 6 months and every 6 months subsequent to nintedanib administration Bar shows mean − or + standard deviation.

%FVC (p = 0.027) at baseline. Table 2 shows the results of the multivariate analysis. We selected body weight instead of BMI for this. Only baseline body weight (OR 0.921, 95% CI: 0.854, 0.994) had a significant association with weight loss of CTCAE grade ≧2 during the first 6 months of nintedanib administration (p = 0.022).

Table 3 shows a comparison of the clinical courses of patients who had weight loss CTCAE grade ≧2 or grade <2 during the first 6 months of nintedanib administration. With regard to adverse events other than weight loss, anorexia and pneumothorax were reported more frequently in the former (p = 0.029, p = 0.0497, respectively), but there were no significant differences for diarrhea. The two groups displayed significant differences in changes in Krebs von den Lungen-6 (KL-6) (p = 0.009). While pulmonary function tests were not performed due to pneumothorax or poor condition in 5 patients in the group with weight loss CTCAE grade ≧2, the two groups displayed significant differences in changes in %FVC (p = 0.043).

3.4. Impact of weight loss on nintedanib termination and prognosis

Median follow-up from starting nintedanib treatment was 34.8 (16.1, 49.4) months and median duration of treatment was 29.7 (11.6, 44.6) months. There had been 27 deaths in the cohort by the end of follow-up, 9 of which were in the weight loss CTCAE grade ≧2 group and 18 in the CTCAE grade <2 group. No patients received a lung transplant. Fig. 2 a) shows Kaplan–Meier curves for termination of nintedanib comparing the two groups. A significant difference in treatment duration between the two groups is seen (median duration of treatment of 21.0 months and 47.6 months, p = 0.007 by log-rank testing). There were no patients who switched to pirfenidone after nintedanib termination during follow-up. Fig. 2 b) depicts all-cause mortality in the two groups, which just reached significance (median survival of 25.5 months and 55.2 months, p = 0.014 by log-rank testing). In the model adjusted for age, sex, and lung function using the GAP index stage, weight loss CTCAE grade ≧2 was an independent predictor for all-cause mortality (adjusted hazard ratio 2.448, 95% CI 1.080–5.551) (Table 4).

Table 3
Comparison of clinical course between patients who had weight loss CTCAE grade ≧2 and grade <2 during the first 6 months of nintedanib administration.

	Weight loss CTCAE grade		
	grade≧2(n = 14)	grade < 2(n = 47)	P value
Nintedanib treatment status			
Starting dosage			
100 mg bis in die	4(28.6)	13(27.7)	1.000
150 mg bis in die	10(71.4)	34(72.3)	
Required dose reduction	4(28.6)	6(13.0)	0.222
Concomitant therapy other than nintedanib			
Corticosteroid	0	4(8.5)	0.565
Immunosuppressive therapy	0	2(4.3)	1.000
Adverse events other than weight loss			
Anorexia	10(71.4)	16(34.0)	0.029
Diarrhea	9(64.3)	34(72.3)	0.739
Elevated transaminases	5(35.7)	9(19.2)	0.277
Pneumothorax	2(14.3)	0	0.0497
Changes in laboratory and pulmonary function data			
ΔTotal protein, g/dL	−0.29 ± 0.60	−0.08 ± 0.51	0.183
ΔAlbumin, g/dL	−0.33 ± 0.35	−0.13 ± 0.37 (n = 44)	0.075
ΔKL-6, U/mL	−497.1 ± 766.9	−44.3 ± 470.6	0.009
ΔSP-D, ng/mL	−71.4 ± 102.1 (n = 12)	−48.1 ± 108.8 (n = 45)	0.508
ΔFVC %predicted, %	−6.4 ± 10.7 (n = 9)	0.04 ± 8.0	0.043

Data are presented as a number (%) or mean ± standard deviation.
Abbreviations.
CTCAE: Common Terminology Criteria for Adverse Events.
FVC: forced vital capacity.
KL-6: Krebs von den Lungen-6.
SP-D: Surfactant protein-D.

4. Discussion

This retrospective single-center study assessed body weight changes during nintedanib therapy in patients with IPF and determined its prognostic significance. Significant weight loss subsequent to nintedanib administration was observed and weight loss CTCAE grade ≧2 during the first 6 months was related to nintedanib treatment duration over 6 months and was an independent predictor of all-cause mortality. To date, there are few clinical studies focused on weight change in patients treated with nintedanib. To our knowledge, this study is the first to explore the clinical implications of weight loss amongst nintedanib-treated patients with IPF.

Although the mechanisms associated with weight loss in IPF have not been explored, several factors such as chronic inflammation, oxidative stress, and adipose tissue metabolism have been causally implicated in pathological weight loss in other chronic diseases [29–31]. Weight loss is a clearly recognized adverse event associated with the use of antifibrotics, especially nintedanib [11]. Data from 1690 patients with IPF from 5 clinical trials indicated weight loss as a critical adverse event in nintedanib-treated patients relative to placebo at baseline both in those aged <75 years (7.9% vs 1.9%) and ≥75 years (14.6% vs 3.4%) [32]. Also in the INBUILD trial [10] of nintedanib in 663 patients with progressive fibrosing ILD, weight loss was again more frequent than in the placebo group (12.3% vs 3.3%). In the present study, mean weight loss during the first 6 months of nintedanib administration was −3.2 ± 3.4 kg and CTCAE grade ≧1 was observed in 50.8% (31 of 61 patients), suggesting a higher incidence. The reason for this may be the real-world setting investigated here, complicated by patient characteristics such as older age, severity of the disease, comorbidities or concomitant medications.

According to other real-world data, the reported frequency of weight loss ranges from to 7.8% (5 of 64 patients) [33] to 50.0% (31 of 62 patients) [34]. In a Japanese study using CTCAE grading as we did here, weight loss CTCAE grade ≧2 was observed in 13.4% IPF patients (19 of 142) [24]. However, that study included patients who discontinued nintedanib within 6 months. Due to this high early discontinuation rate (51 of 142, 35.9%), the results of our study, which was limited to patients who continued nintedanib for >6 months, may be consistent with that report. Furthermore, we showed significant differences in weight change between that occurring during 6 months before and after nintedanib administration among patients in whom pulmonary function test records and body weight 6 months before nintedanib administration were available. To the best of our knowledge, this is the first study to reveal significant changes in body weight before as well as after nintedanib administration. We should be aware that although weight loss is recognized as a common complication of IPF [12], nintedanib may accelerate it as an adverse event, suggesting a specific medication effect. Although the exact mechanisms of weight loss during nintedanib therapy are unknown, weight loss may be related to reduction of food intake due to nausea or malabsorption due to diarrhea. In fact, in the present study, anorexia was reported more frequently in the group with weight loss CTCAE grade ≧2 than grade <2. On the other hand, data from in vitro experiments indicate that tyrosine kinase inhibitors can reduce lipogenesis by isolated adipocytes, implying that a fat storage defect may be at least partly responsible for weight loss [35].

In the present study we investigated factors associated with weight loss. Multivariate analysis showed that only baseline body weight was significantly associated with weight loss CTCAE grade ≧2 during the first 6 months of nintedanib administration. A previous study [14], which included IPF patients with and without antifibrotics therapy, concluded that not baseline BMI, but the annual rate of FVC change, having diabetes mellitus, the amount of total protein, and never having smoked all had a significant association with weight loss. Since the present study included only IPF patients treated with nintedanib, recognition of baseline body weight, that is small physiques, is important to predict weight loss during nintedanib therapy.

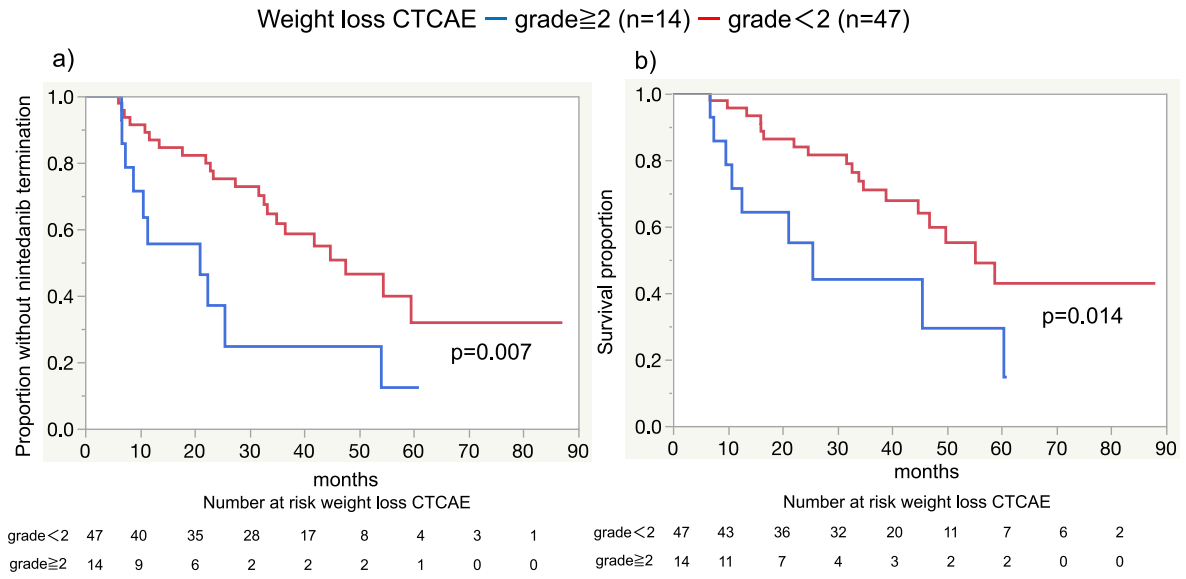

Fig. 2. Kaplan–Meier curves
a) Kaplan–Meier curves for termination of nintedanib comparing weight loss CTCAE grade ≧2 vs grade <2 during the first 6 months of nintedanib administration, b) Kaplan–Meier curves for all-cause mortality comparing weight loss CTCAE grade ≧2 vs grade <2 during the first 6 months of nintedanib administration.

Table 4
Weight loss during the first 6 months of nintedanib administration and risk of all-cause mortality.

	Unadjusted analysis		Adjusted analysis	
	hazard ratios (95% CI)	P value	hazard ratios (95% CI)	P value
GAP index				
stageI	Reference		Reference	
stageII	4.893 (1.415, 16.918)	0.012	4.599 (1.327, 15.933)	0.016
stageIII	6.029 (1.612, 22.553)	0.008	5.847 (1.553, 22.015)	0.009
CTCAE				
grade <2	Reference		Reference	
grade ≧2	2.666 (1.186, 5.989)	0.018	2.448 (1.080, 5.551)	0.032

Abbreviations.
CI: confidence interval.
CTCAE: Common Terminology Criteria for Adverse Events.
GAP: gender, age and lung physiology.

The present study reports the clinical course stratified by weight change during the first 6 months of nintedanib administration. With regard to adverse events other than weight loss, anorexia was reported more frequently in the group with CTCAE grade ≧2 than grade <2, as mentioned above. As with previous studies [14,36], weight loss was significantly associated with decrease in %FVC. The present study also showed significant changes in KL-6 between patients in the two groups. Sekine et al. [37] reported that among ILD patients with obesity, following nutritional education, the level of KL-6 tended to decrease as well as a significant improvement in FVC after weight loss. Because our study population with a baseline BMI of 23.2 ± 3.5 kg/m^2 was not obese and weight loss was significantly associated with decreased %FVC, the reason for this remains unclear.

Finally, the present study documented that weight loss was related to nintedanib treatment duration and was a prognostic indicator. Although previous studies have shown that weight or BMI changes over time could be prognostic indicators for IPF [13–15], such studies included patients not treated with antifibrotics. Thus, in patients with IPF treated with nintedanib, the present study highlights the importance of body weight follow-up and supportive care, including nutritional interventions when required and encouraging patients not to be physically inactive with associated loss of muscle mass. Especially, because we have shown that the degree of weight loss was maximum during the first 6 months of nintedanib administration, we should pay attention to body weight change trajectories over that period. Delphi consensus recommendations on management of weight loss have been formulated as follows: non-pharmacologic interventions including increasing caloric intake and dietary supplementation, eating 3 meals per day with small snacks between meals, and use of high-protein nutritional drinks, as well as considering treatment interruption or dose reduction for persistent weight loss [38]. Of course, other gastrointestinal side effects such as anorexia, nausea, or diarrhea should be managed adequately, as they may interfere with nutrient intake and absorption and thus can result in weight loss. Moreover, although the impact of pulmonary rehabilitation on long-term outcomes in ILD is not yet clear, exercise training programs could increase physical activity, facilitate weight gain, improve muscle strength and increase functional capacity [39].

In the present retrospective study, some patients were started on nintedanib at a low dose of 100 mg BID. According to the clinical course stratified by weight change during the first 6 months of nintedanib administration, the starting dose of 150 mg or 100 mg BID was not related to the severity of weight loss. Uchida et al. [40] compared adverse events based on the initial nintedanib dose in older adults with IPF, and reported that the incidence of gastrointestinal adverse events and weight loss was not significantly different. In an exposure-efficacy analysis, a 150 mg BID dose of nintedanib resulted in effective plasma levels approximating the maximum drug effect regardless of baseline characteristics, including whether the patients were Asian, and had different body weights and ages [41].

The limitations of this study are that it is both retrospective and a single center study on a small number of patients, and because clinical data were captured from the patients' medical records, missing data may have altered the perceived incidence of adverse events other than weight loss. Also, only Japanese patients were included in this study, so it is conceivable that differences in the frequency of adverse events across different ethnicities may be seen. Additionally, although a few patients in our cohort were referred to clinical nutritionists for a dedicated management, an assessment of whether nutritional interventions in patients experiencing ongoing weight loss modulated disease course was not done. Considering nutritional interventions, additional studies, including multicenter studies with larger populations, are quired to determine the general applicability of our findings.

5. Conclusions

Weight loss is common and significant subsequent to nintedanib administration to patients with IPF. Weight loss during the first 6 months of nintedanib was an independent prognostic predictor and baseline body weight was significantly associated with weight loss during the first 6 months of nintedanib administration. Baseline body weight, that is small physiques, should be considered in the choice of antifibrotic medication. Follow-up of body weight, an easily measurable way to alert the physician to prognosis in daily practice, and management of weight loss, is important during nintedanib therapy.

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Declaration of competing interest

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Availability of data and materials

The datasets used can be available from the corresponding author on reasonable request.

Author statement

The contents of this manuscript have not been copyrighted or published previously, and are not now under consideration for publication elsewhere.

All authors of this research paper have directly participated in the study. All authors also have read this paper, agree with its contents, and agree to its submission to your journal.

CRediT author statement

HT was involved in the design of the study and data analysis. MI, MY, RH and HA were involved in data acquisition. All authors were involved in the interpretation of the data and in the writing and critical review of the manuscript. All authors approved the final version.

The attached paper entitled “Weight loss in nintedanib-treated patients with idiopathic pulmonary fibrosis” has been carefully reviewed by an experienced medical editor whose first language is English and who specializes in editing papers written by physicians and scientists whose native language is not English.

Data availability

Data will be made available on request.

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