Tolerability of nintedanib-related diarrhea in patients with idiopathic pulmonary fibrosis

（特発性肺線維症患者におけるニンテダニブ関連下痢症の忍容性）

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Abstract

Background: Nintedanib is an important drug for the treatment of idiopathic pulmonary fibrosis (IPF). However, the drug is discontinued in some patients who present with diarrhea. In this study, we aimed to assess the drug continuation rate in patients who developed diarrhea during nintedanib therapy and to evaluate if antidiarrheal drugs or nintedanib dose reductions improved clinical tolerability and efficacy.

Methods: Eighty-six patients with IPF were treated in our institution between December 2015 and March 2018. Among them, 50 patients who experienced nintedanib-related diarrhea were analyzed regarding tolerability and persistence rate.

Results: In 50 patients who experienced nintedanib-related diarrhea, 26 (n=11, without reduction and n=15, with reduction) continuously received nintedanib. Meanwhile, the drug was discontinued in 24 patients (n=13, without reduction and n=11, with reduction). In 9 of 24 patients, the drug was discontinued due to diarrhea. The annual rate of decline in forced vital capacity and the duration of nintedanib administration were not significantly different between groups with and without dosage reduction. Moreover, 23, 13, 8, and 2 patients received 1, 2, 3, and 4 agents, respectively. *Clostridium butyricum* is a probiotic bacterium most commonly used as an antidiarrheal agent. In this study, it was used in 28 of 46 patients. The total durations of nintedanib administration differed significantly according to the number of antidiarrheal drugs taken: 853 ± 221 days, more than three agents; 424 ± 365 days, without an agent ($p = 0.043$); and 460 ± 142, one agent ($p = 0.0003$).

Conclusions: When diarrhea occurs within a year after using nintedanib, the dose reduction may be acceptable without affecting pulmonary function. Moreover, treatment with multiple antidiarrheals may be a practical option to maintain the use of nintedanib therapy compared with monotherapy and no

therapy.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia (1) that has a median survival of only 3–4 years from diagnosis in the absence of treatment (2). Although its pathogenesis is not completely understood, it is thought to involve profibrotic mediators, including fibroblast growth factors (FGFs), platelet-derived growth factors (PDGFs), and transforming growth factor beta (3). Several clinical trials of medications for IPF have consistently failed to show a significant treatment effect, but more recently, the antifibrotic agents, pirfenidone and nintedanib, have shown positive effects (4-6). Nintedanib, a multiple intracellular tyrosine kinase inhibitor that targets vascular endothelial growth factors (VEGFs), PDGFs and FGFs, is currently central to IPF therapy worldwide (7, 8).

Several international trials have shown that nintedanib reduces disease progression in IPF by slowing the rate of decline in the forced vital capacity (FVC) (4, 8-10). The TOMORROW phase II trial of nintedanib revealed that the annual rate of FVC decline in patients receiving 150 mg twice daily was lower than in patients receiving placebo (8). In the multicenter, randomized, double-blind, placebo-controlled INPULSIS-1 and -2 trials of nintedanib, a similar positive effect was shown for 150 mg twice daily over 52 weeks compared with placebo (4). Moreover, in both INPULSIS trials, the risk of an acute exacerbation was reportedly decreased in the nintedanib group. The TOMORROW trial and its open-label extension, together with the INPULSIS-ON trial, also suggested that nintedanib had a manageable safety and tolerability profile, with no new safety signals beyond 4 years (9, 10).

Although nintedanib has since been confirmed to have an acceptable safety and efficacy profile in the clinical setting (11), patients with IPF sometimes need to discontinue nintedanib administration because of diarrhea. The INPULSIS trials showed that 4% of patients discontinued administration for this reason (4), whereas the

TOMORROW trial and its open-label extension showed that 4.7% discontinued for this reason (9). Moreover, the INPULSIS-ON trial revealed that 10% of newly initiated patients discontinued nintedanib administration due to diarrhea (10). Each study indicated that diarrhea was the main reason for discontinuation in the course of treatment. Prescribing data recommend dosage modifications or treatment interruptions when diarrhea occurs (12), while ensuring adequate hydration and using antidiarrheal medication (e.g., loperamide), as appropriate. After these management, drug interruption or cessation should be considered. However, since few effective medications for IPF exist, it is critical to optimize the management of nintedanib-related diarrhea.

To date, there has been no detailed assessment of the tolerability of nintedanib-related diarrhea in patients with IPF, including the role of antidiarrheal drugs. Therefore, we aimed to identify the drug persistent rate in patients developing diarrhea due to nintedanib and to evaluate whether dose reduction and antidiarrheal therapy correlated with its tolerability and efficacy in clinical practice.

2. Methods

2.1 Ethical approval

All study procedures involving human participants were approved by the Human Ethics Committee of the Graduate School of Medicine, Chiba University (no. 3481). This study was designed and conducted in accordance with the ethical principles of 1964 Helsinki Declaration and subsequent amendments. We obtained informed consents by all patients.

2.2 Study design

This was single-center retrospective study of consecutive patients with IPF who started taking nintedanib between December 2015 and March 2018 at Chiba University

Hospital. Patients who had no IPF, had lung cancer at the start of therapy, and who did not have diarrhea in the course of treatment were excluded. IPF was diagnosed based on the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association IPF guidelines of 2018 (1).

2.3 Nintedanib administration

The criteria for starting nintedanib was a %FVC decline >10% and/or radiological worsening. Nintedanib was administrated as continuous oral treatment at a starting dose of 150 mg twice daily. Dose reduction of 150 mg twice daily to 100 mg twice daily was allowed for the management of adverse events. An experienced attending doctor determined whether to continue, reduce, or stop nintedanib, or whether to add an antidiarrheal, when adverse reactions occurred. Adverse events were assessed by medical records review for all patients who received at least one dose of nintedanib.

2.4 Diarrhea

Diarrhea and other adverse events were defined using the Common Terminology Criteria for Adverse Events, version 4.0. Diarrhea implied an increase in the frequency of bowel movements and/or the presence of loose or watery stools. Any increase of 4–6 stools/day over baseline was considered the need for a reduced drug dosage.

2.5 Statistical analysis

Clinical data are expressed as means ± standard deviations. Fisher's exact test was used for categorical data and the Mann–Whitney *U* test was used for continuous data. Drug continuation rates were tested by the log-rank test. All analyzes were performed by JMP® pro 13.2.0 (SAS Institute Inc. Cary, NC, USA). A p-value < 0.05 was considered statistically significant for all analyzes.

3. Results

3.1 Participants

We identified 86 consecutive patients with IPF during the study period. After applying the exclusion criteria, 50 of them were enrolled (**Figure 1**).

3.2 Characteristics of the participants

In 50 patients who experienced nintedanib-related diarrhea, 26 (n=11, without reduction and n=15, with reduction) continuously received nintedanib. Meanwhile, the drug was discontinued in 24 patients (n=13, without reduction and n = 11, with reduction). The leading causes of discontinuation were progression of IPF (n = 12 [50%]), diarrhea (n =9 [38%]), and anorexia (n = 3 [12%]). One patient required a gradual dose reduction to 50 mg twice daily. The mean annual rate of decline in FVC from baseline to 1 year was 84 mL. The continuation rate at 1 year and in overall period were 84% and 52 %. Eight patients died during the observation period. The characteristics of the participants are shown in **Table 1**.

3.3 Efficacy and tolerability of nintedanib

The comparison between those who continued and discontinued nintedanib administration due to diarrhea are shown in **Table 2**. The BMI (p = 0.036) and serum albumin levels (p = 0.018) were significantly lower in the group who discontinued the treatment due to diarrhea. During the administration period (p = 0.014), the persistence rate at 3 months and 1 year after starting treatment with nintedanib (p = 0.012) significantly differed. Based on the logistic regression analysis of serum albumin level, BMI, and FVC at baseline in patients who discontinued the treatment due to diarrhea, only serum albumin level significantly differed (p = 0.034, odds ratio = 0.04, 95% confidence interval: 0.0016–1.20).

Persistence rate was not significantly different between those required a dose reduction due to diarrhea within one year and those not required a reduction (p = 0.14) (**Figure 2**). Similarly, the annual rate of decline in FVC was not different between two groups (107.8 ± 59.3 in those required a dose reduction vs. 62.3 ± 56.4 in those not

required) (p = 0.58) (**Figure 3**). Pulmonary function was examined in 40 patients (non-reduction n = 21, reduction n = 19) at one year after starting administration of nintedanib.

3.4 Antidiarrheal drugs

Details of the antidiarrheal treatment are shown in **Figures 4a - c.** All drugs are approved for antidiarrheal therapy in Japan. Hangeshashinto is a traditional herbal medicine used in East Asia, and it is composed of seven crude herbs in fixed proportions. This agent has been used empirically for the treatment of various gastrointestinal disorders, such as dyspepsia, nervous gastritis, and stomatitis. Overall, 46 patients received at least one agent: 23 (50%) received only one agent and 13 (28%) received two agents. *Clostridium butyricum* was the most frequently prescribed antidiarrheal agent, which was used in 28/46 patients, followed by loperamide hydrochloride in 25/46, codeine phosphate in 9/46, Hangeshashinto in 8/46, albumin tannate in 4/46, and berberine chloride hydrate in 2/46 patients.

The administration periods of nintedanib significantly differed according to the number of antidiarrheal drugs used (853 ± 221 days, more than three drugs; 460 ± 142 days, a single agent [p = 0.0003]; and 424 ± 365 days, without therapy [p = 0.043]) (**Figure 5**). The length of nintedanib administration was significantly differ between the group treated with dose reduction (718 ± 90 days) and the group treated with adding an antidiarrheal agent (406 ± 50) (p < 0.01) (**Figure 6**). The groups were classified into three according to the initial decision when the patients presented with diarrhea: 1) reduction of nintedanib dosage, 2) use of full-dose nintedanib plus antidiarrheal agent, and 3) both reduction of nintedanib dosage and use of antidiarrheal drug at the same time (bilateral group). The dose reduction group included patients who reduced nintedanib dosage due to diarrhea after one year of administration.

4. Discussion

Three major findings were indicated in this study. First, a lower serum albumin level was associated with a significantly higher incidence of discontinuation due to diarrhea. Second, nintedanib dose reduction, even beyond one year of administration, resulted in longer nintedanib use compared with adding an antidiarrheal drug. Third, the use of multiple antidiarrheal drugs prolonged the use of nintedanib when compared with monotherapy. To our knowledge, no other study has reported on the association between dose reduction and antidiarrheal therapy in terms of their effect on nintedanib continuation.

Although our results did not show how serum albumin affected the tolerability of nintedanib, we speculate that hypoalbuminemia has an important role affecting its pharmacokinetics (e.g., absorption, distribution, and metabolism). Indeed, albumin has various important physiologic effects, acting as an antioxidant and as an inhibitor of endothelial cell apoptosis (13). Malnutrition is considered a leading cause of hypoalbuminemia, yet albumin levels remain unchanged until starvation is terminal (14). Albumin levels are also decreased by protein loss in the nephrotic syndrome and by reduced synthesis in liver disease. In the present study, no patient had liver disease or nephrotic syndrome. Despite having a poor understanding of the mechanism, malnutrition may play any role in the presence of hypoalbuminemia (15). From another perspective, idiopathic interstitial pneumonia with low serum albumin has been associated with increased mortality, serving as a marker of inflammation and fibroblast activity (16). In addition, in the acute exacerbation of IPF, a low serum albumin level was considered a poor prognostic factor of inflammation (17). In our study, patients with IPF who had a low albumin level could have had malnutrition, chronic inflammation, or higher fibroblastic activity, with each of these potentially contributing to the discontinuation of nintedanib.

Vascular endothelial growth factor (VEGF) inhibition may have a role in the development of diarrhea during treatment with nintedanib (18). It is known that VEGF receptors (VEGFRs) are highly expressed in the intestines (19), and that VEGFR inhibitors can dramatically reduce the capillary network of intestinal villi (20) and can

change blood flow in the intestinal mucosa to cause metabolic changes consistent with hypoxia (21). Given that epithelial hypoxia has been associated with diarrhea in clinical settings (22), it may be that VEGF inhibition changes the mucosal conditions in the intestines. In patients with renal cell cancer receiving VEGF tyrosine kinase inhibitors, such as sunitinib, diarrhea is associated with *Bacteroides* spp. in the stool (23). Notably, targeting these organisms with antibiotics in a duration-dependent manner can improve progression free-survival rates (24). Further investigation is needed to determine whether the stool microbiome is affected in cases of nintedanib-related diarrhea.

After the onset of diarrhea, dose reduction (even if administration is over 1 year) was associated with significantly longer nintedanib use in our cohort when compared with adding antidiarrheal agents (**Figure 6**). Our data clearly show that adding antidiarrheals alone is insufficient to ensure drug continuation. However, despite dose reduction being the most effective approach, it raises valid concerns about the potential for reduced efficacy. Countering these concerns, the INPULSIS-ON revealed no difference in annual decline in FVC between groups with and without dose reductions. We also showed no significant difference in the annual decline of FVC between comparable groups over 1 year (Figure 3). Therefore, it could be that dose reduction within 1 year of commencing treatment has only a minimal impact on the efficacy of nintedanib in patients who developed drug-induced diarrhea.

In addition to the relationship between dose reduction and antidiarrheal drugs, there have been no reports about the types or optimal number of antidiarrheal agents that should be used to treat nintedanib-related diarrhea effectively. On the assumption that it is preferable to maintain the therapeutic dose of nintedanib, we showed that the use of multiple antidiarrheal agents was associated with significantly longer nintedanib continuation when compared with monotherapy and no therapy (**Figure 5**). These findings may also suggest that the mechanism of diarrhea does not involve a single

pathway.

Finally, it should be noted that our study was limited by being conducted retrospectively, in a single center, and with a small sample size in each group. Further large-scale studies must be conducted to confirm the findings of the current study. Thus, it would be necessary to demonstrate the relationship among administration period, dose reduction, and antidiarrheal drug use in a large-scale, nationwide, prospective study of patients with nintedanib-related diarrhea.

5. Conclusion

In conclusion, a lower serum albumin level is associated with a higher incidence of nintedanib discontinuation among patients with IPF who develop diarrhea. Moreover, dose reduction within a one-year period has no apparent major impact on the annual decline of FVC, while dose reduction is associated with longer nintedanib use than full dose of nintedanib plus adding an antidiarrheal drug after the onset of diarrhea. When necessary, combined antidiarrheal therapy prolongs the tolerable duration of administration compared with monotherapy and no therapy.

Conflicts of interest

MA, KTs and KTa reports receipt of lecture fees from Boehringer Ingelheim Japan.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contributions

YH, MA, JT, MS, KS, KY, KTs and KTa contributed to the study concept and design. YH and MA examined the enrolled patients in the hospital. YH and JT performed the statistical analyses. All authors have read and approved the final manuscript.

Acknowledgements

The authors would like to thank Enago (www.enago.jp) for the English language review.

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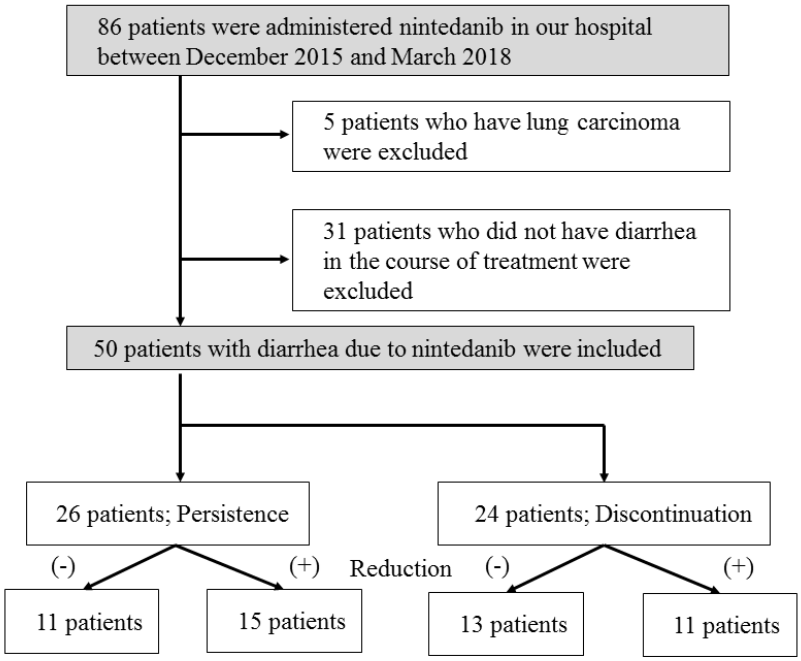


Figure 1: Study flow chart

Of the 86 patients with IPF who received nintedanib during the study period, we excluded 55, leaving a final sample of 50. The drug was continuously administered in 26 of 50 patients who experienced nintedanib-related diarrhea (n=11, without reduction and n=15, with reduction). Meanwhile, it was discontinued in 24 patients (n=13, without reduction and n=11, with reduction).

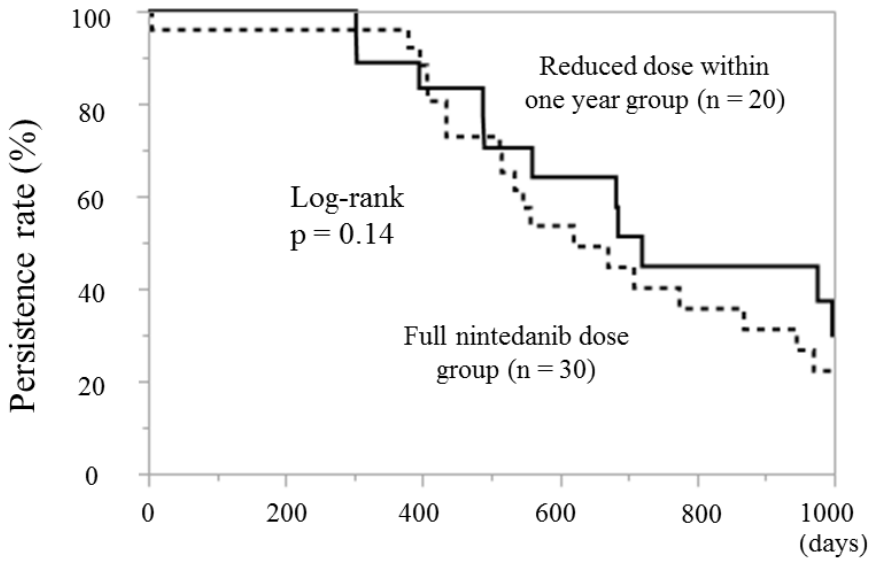


Figure 2: Persistence rates in patients on full and those on reduced dose of nintedanib within 1 year

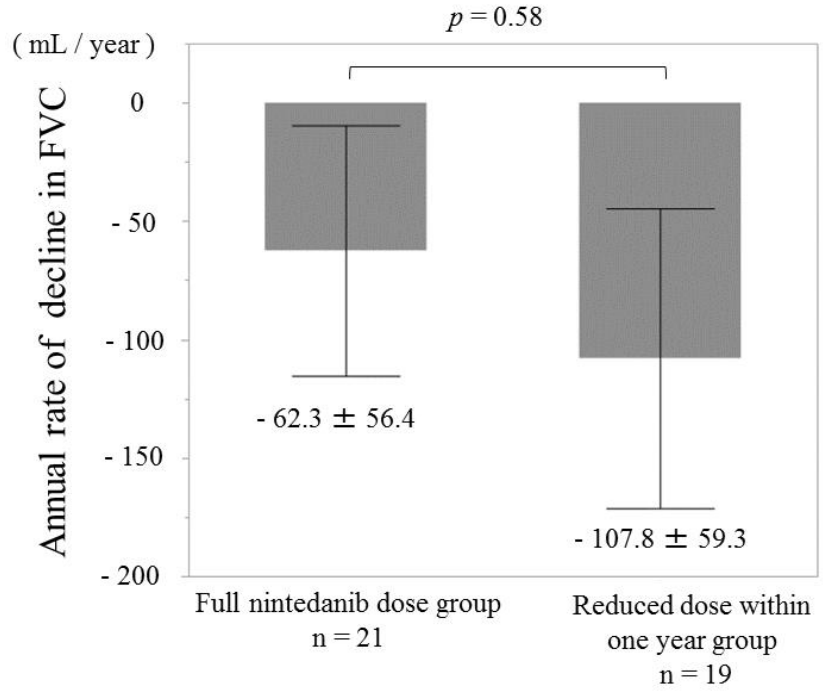
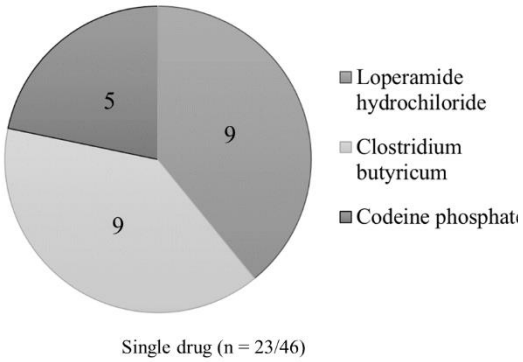


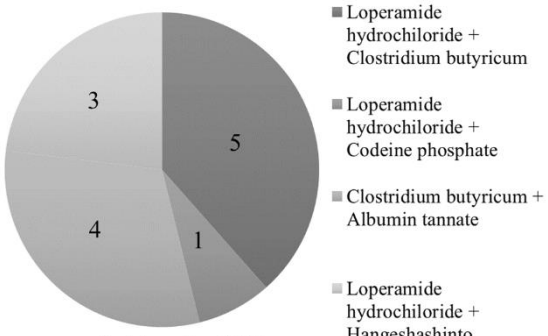
Figure 3: Annual rate of decline in FVC in patients on full and reduced dose of nintedanib within 1 year



Single drug (n = 23/46)

Lope + Clos + Berb	2
Lope + Clos + Hang	2
Lope + Clos + Code	1
Lope + Clos + Albu	1
Clos + Albu + Hang	1
Clos + Code + Hang	1

Triple drugs (n = 8/46)



Dual drugs (n = 13/46)

Lope + Clos + Code + Hang	1
Lope + Clos + Albu + Hang	1

Quadruple drugs (n = 2/46)

Figure 4-a (left upper): Number of patients treated with the specific combinations of antidiarrheal drugs (single drug)

Figure 4-b (left lower): Number of patients treated with the specific combinations of antidiarrheal drugs (dual drugs)

Figure 4-c (right): Number of patients treated with the specific combinations of antidiarrheal drugs (triple and quadruple drugs)

Abbreviations: Albu, Albumin tannate; Berb, Berberine chloride hydrate; Clos, *Clostridium butyricum*; Code, Codeine phosphate; Hang, Hangeshashinto; Lope, Loperamide hydrochloride

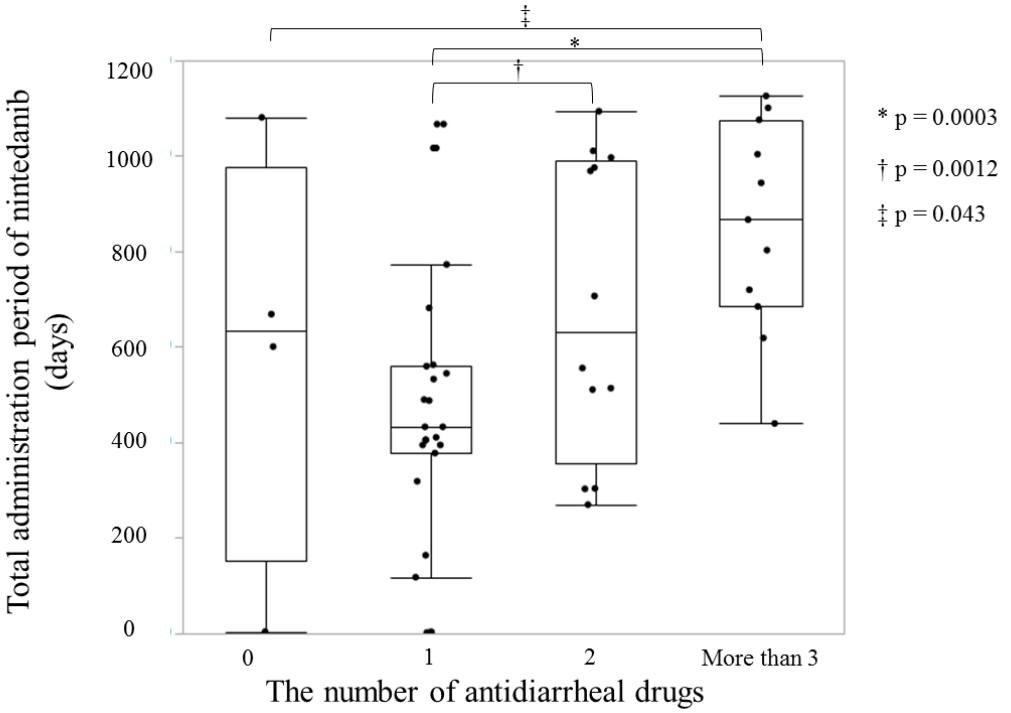


Figure 5: Total administration period of nintedanib according to the number of antidiarrheal drugs used

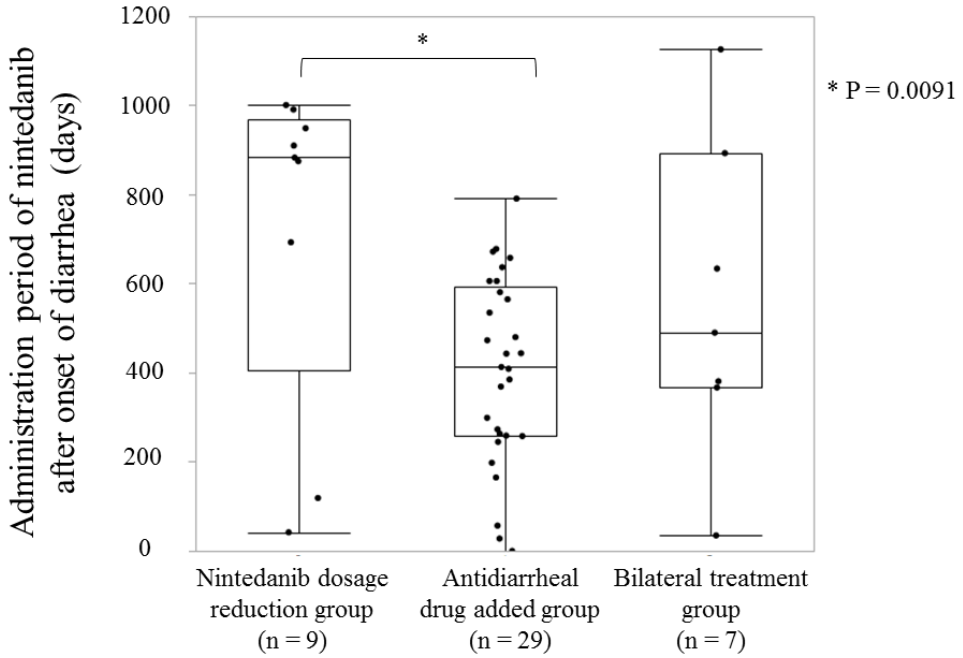


Figure 6: Administration period of nintedanib after the onset of diarrhea

Table 1. Characteristics of the participants (n=50).

Age, (years)	72.4 ± 5.1
Male, no. (%)	37 (74)
BMI (kg/m^2)	24.1 ± 4.2
BMI after 1 year of administration n=34	23.8 ± 4.0
BSA (m^2)	1.65 ± 0.21
Pulmonary function tests	
FVC (mL)	2217 ± 804
FVC after 1 year of administration (mL) n=40	2203 ± 913
%FVC (%)	69 ± 17
%FVC after 1 year of administration (%) n=40	69 ± 20
$\%D_{LCO}$ (%)	59 ± 21
$\%D_{LCO}$ (%) after of 1 year of administration n=34	56 ± 16
Observation period (days)	680 ± 279
Administration period (days)	610 ± 316
Annual rate of decline in FVC (mL)	84 ± 40
Time to diarrhea from the start of administration (days)	163 ± 146
Time until the drug dose reduction (days)	238 ± 46
Time until the drug discontinuation (days)	412 ± 221
Persistence without dose reduction, no (%)	11/50 (22)
Persistence with dose reduction, no (%)	15/50 (30)
Discontinuation without dose reduction, no (%)	13/50 (26)
Discontinuation with dose reduction, no (%)	11/50 (22)
Reasons for permanent drug discontinuation, no (%)	24/50 (48)
Progression of IPF, no (%)	12/24 (50)
Diarrhea, no (%)	9/24 (38)
Anorexia, no (%)	3/24 (12)
Persistence rate at 3 months, no (%)	46/50 (92)
Persistence rate at 1 year, no (%)	42/50 (84)
Persistence rate in overall period, no (%)	26/50 (52)

Data are expressed as mean ± standard deviation.

BMI; body mass index, BSA; body surface area, FVC; forced vital capacity, D_{LCO}; diffusing capacity of the lungs for carbon monoxide, IPF; idiopathic pulmonary fibrosis

Table2. Comparison between groups by whether they continued despite diarrhea.

	Continued despite diarrhea (n=26)	Discontinued due to diarrhea (n=9)	*p* - value
Age (years)	72 ± 4.9	74 ± 1.6	0.32
Male, no (%)	20 (76)	5 (62)	0.39
BMI (kg/m^2)	24 ± 4.6	21 ± 1.3	**0.036**
BSA (m^2)	1.68 ± 0.22	1.54 ± 0.07	0.11
Pulmonary function tests			
FVC (mL)	2454 ± 819	1941 ± 267	0.09
%FVC (%)	76 ± 18	67 ± 5	0.15
$\%D_{LCO}$ (%)	58 ± 3	67 ± 7	0.65
Annual rate of decline in FVC (mL)	51 ± 47 (n = 24)	217 ± 95 (n = 3)	0.11
White blood cell count (/μL)	7769 ± 2432	9444 ± 884	0.44
Total protein (g/dL)	7.4 ± 0.5	7.2 ± 0.1	0.25
Albumin (g/dL)	4.0 ± 0.3	3.7 ± 0.1	**0.018**
Full dose of nintedanib, no (%)	11 (42)	4 (44)	0.91
Administration period (days)	810 ± 256	345 ± 286	**0.0014**
Persistence rate at 3 months, no (%)	26 (100)	6 (66)	**0.012**
Persistence rate at 1 year, no (%)	26 (100)	6 (66)	**0.012**

Data are expressed as mean ± standard deviation.

BMI; body mass index, BSA; body surface area, FVC; forced vital capacity, D_{LCO}; diffusing capacity of the lungs for carbon monoxide

Pulmonary Pharmacology & Therapeutics. Vol 62, No.101917

2020 年　3 月　20 日 公表済み

DOI: 10.1016/j.pupt.2020.101917.