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ORIGINAL ARTICLE

Assessing prognostic factors correlating with response to nintedanib for connective tissue disease-associated interstitial lung disease: A real-world single-center study

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Abstract

Objective: For patients with connective tissue disease-associated interstitial lung disease (CTD-ILD), early medical intervention would be desirable. This study analyzed the real-world, single-center use of nintedanib for CTD-ILD patients.

Methods: Patients with CTD who received nintedanib from January 2020 to July 2022 were enrolled. Medical records review and stratified analyses of the collected data were conducted.

Results: Reduction in the percentage of predicted forced vital capacity (%FVC) was seen in the elderly group (>70 years; $P = .210$), males ($P = .027$), the late group who started nintedanib >80 months after confirmation of an ILD disease activity ($P = .03$), the severe %DLco (diffusing capacity for carbon monoxide as a percentage of predicted) group (<40%; $P = .20$), the group who had extensive pulmonary fibrosis at the beginning of nintedanib (pulmonary fibrosis score >35%), and the low-dose group (nintedanib 50-100 mg/d; $P = .40$). %FVC did not decrease by >5% in the young group (<55 years), the early group who started nintedanib within 10 months after confirmation of an ILD disease activity, and the group whose pulmonary fibrosis score at the beginning of nintedanib was <35%.

Conclusion: It is important to diagnose ILD early and start antifibrotic drugs with proper timing for cases in need. It is better to start nintedanib early, especially for patients at risk (>70 years old, male, <40% DLco, and >35% areas of pulmonary fibrosis).

KEYWORDS
connective tissue disease, drug use results survey, interstitial lung disease, nintedanib

1 | INTRODUCTION

1.1 | Background

Connective tissue disease-associated interstitial lung disease (CTD-ILD) is one of the most essential causes of morbidity in patients with systemic sclerosis (SSc), dermatomyositis (DM), and rheumatoid arthritis (RA). Nintedanib is a potent small molecule inhibitor of the receptor tyrosine kinases platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor.[1] In vitro data showed that nintedanib blocks lung fibrosis by releasing proinflammatory and profibrotic mediators, the migration and

differentiation of fibrocytes induced by growth factors, and vascular cell proliferation. In animal models with features of ILD, nintedanib has an antifibrotic effect despite the trigger for lung pathology.[2] In Japan, nintedanib was approved for idiopathic pulmonary fibrosis (IPF) in July 2015, SSc-associated ILD in December 2019, and progressive fibrosing ILD (PF-ILD) in May 2020. The annual rate of decline in forced vital capacity (FVC) was lower with nintedanib than with placebo for IPF,[3] SSc-ILD,[4] and PF-ILD.[5] Although there are some real-world studies about IPF,[6] there are few real-world studies on CTD-ILD, which is a challenging area with diverse entities and variable outcomes.[7] For patients with CTD-ILD, early medical intervention is desirable because pulmonary fibrosis can often be irreversible.

1.2 | Objectives

A real-world single-center use of nintedanib for CTD-ILD patients who started nintedanib from January 2020 to July 2022 was analyzed, with early and late intervention groups depending on the approval date of nintedanib. Through assessing factors correlating with response to nintedanib, we searched for what kind of patients need early medical intervention of nintedanib.

2 | PATIENTS AND METHODS

2.1 | Patients

This study enrolled all of the patients with CTD who visited the Department of Dermatology, Japan Community Healthcare Organization Chukyo Hospital, and received nintedanib for CTD-ILD from January 2020 to July 2022. Nintedanib was administered to patients with SSc, DM, and RA who had ILD disease activity. Corticosteroids were administered to all patients, and combined administration with mycophenolate mofetil (MMF, 1000-2000 mg/d) was given to most SSc patients, with cyclophosphamide pulse or tacrolimus to most DM patients, and with tacrolimus or tocilizumab to RA patients. All patients had no history of other antifibrotic agents, such as pirfenidone.

2.2 | Study design

Medical records of 14 patients administered with nintedanib were examined. Each capsule included 100 mg or 150 mg nintedanib ethane sulfonate. The nintedanib dosage was started from 100 mg once daily to 300 mg divided into 2, without specific criteria. The follow-up period was from January 2020 to July 2022. Data included age, gender, body weight, smoking history, primary diseases (SSc/DM/RA), onset time, subjective symptoms (dyspnea/cough), other treatment histories, nintedanib dosage, adverse events, blood test (Krebs von den Lungen-6 [KL-6], liver enzymes) results, chest high-resolution computed tomography scan, and respiratory function test (%VC: vital capacity as a percentage of predicted, %FVC: FVC as a percentage of predicted, and %DLco: diffusing capacity for carbon monoxide as a percentage of predicted). The pulmonary fibrosis score was calculated as the average sum of reticulation and honeycombing across 5 zones: (A) arch of aorta; (B) bifurcation of the trachea; (C) confluence of pulmonary veins; (D) intermediate point between (C) and (E); and (E) right upper diaphragm.[8] ILD disease activity was defined for patients with a ≥10% or 5% to 10% relative decrease of %FVC with a ≥15% relative decrease of %DLco compared to the first visit.[9] Adverse events of nintedanib were attributed if they did not have any other plausible causes for the events, even if they did not need a reduction of nintedanib. To analyze the results, patients were divided into groups by age (young: <55 years, middle: 55-70 years, and old: >70 years), gender, delay until nintedanib initiation from confirmation date of ILD disease activity (early: within 10 months, middle: 10-80 months, and late: >80 months), %DLco at the beginning of nintedanib (mild: >40% and severe: <40%), pulmonary fibrosis score at the beginning of nintedanib (</>35%), maintenance dose of nintedanib (low: 50-100 mg, middle: 200-300 mg, high: 150 mg, $P = .40$), smoking history (yes/no), primary disease (SSc/DM/RA), nintedanib treatment duration (</>18 months), and dosing history of MMF (yes/no). A >5% decrease of %FVC was defined as an event for Kaplan–Meier analysis. This study was approved by the Japan Community Healthcare Organization Chukyo Hospital Research Ethics Committee on September 15, 2022 (reference no. 2022032). Patient consent was obtained through an opt-out methodology.

2.3 | Statistical analysis

This study collected case data (summarizing average ± standard deviation) and performed univariate analysis on sociodemographic data (age, gender, smoking history), primary diseases, initial treatment delay including corticosteroids and immunosuppressants, respiratory function test and serum KL-6 assessed at nintedanib initiation, pulmonary fibrosis score at nintedanib initiation, delay until nintedanib initiation from confirmation date of ILD disease activity, treatment duration of nintedanib and MMF. Statistical analysis was performed using the Mann–Whitney *U* test, Spearman's rank correlation coefficient, and Kruskal–Wallis test, Kaplan–Meier analysis, log-rank test, and log-rank trend test.

3 | RESULTS

3.1 | Patient characteristics, changes in subjective symptoms, and adverse events

A total of 14 patients were enrolled (4 males and 10 females, ages 29-83 years; Table 1). Six patients were former smokers, and 8 patients were never smokers. Their body weight was 54.6 ± 14.1 kg. They had

TABLE 1 Patient characteristics at baseline and at end of follow-up

Case	Age/gender	Primary disease/autoantibody	Types of ILD	Treatment history	Delay until nintedanib initiation (mo)	Adverse event of nintedanib	At the beginning of nintedanib/at the last visit							
							%FVC (%)	%DLco (%)	KL-6 (U/mL)	Pulmonary fibrosis score (%)	Dyspnea	Cough	Dose of nintedanib (mg)	Duration (mo)
1	50/F	SSc/Anti-Scl-70 antibody	NSIP	PSL, MMF	7	–	60.2/56.8	56/44.5	2289/1216	62/57	–/–	–/–	300/300	29
2	65/F	SSc/Anti-Scl-70 antibody	fNSIP	PSL, IVCY, TAC, AZA, MMF, TCZ	95	Diarrhea	81.5/68.1	81.1/62	1925/1261	54/55	On exertion/On exertion	+/+	300/100	19
3	66/F	DM/Anti-PL-7 antibody	UIP	mPSL, PSL, CyA, TAC, IVIG	107	–	104.9/77.7	66/45.9	1134/1059	38/32	–/–	+/–	200/300	20
4	61/F	SSc/Anti-Scl-70 antibody	UIP	PSL, IVCY, AZA, MMF	53	Diarrhea	78/70.6	36.4/26.6	4670/1706	88/86	On exertion/On exertion	–/–	200/200	21
5	34/F	SSc/Anti-Scl-70 antibody	UIP	PSL, IVCY, AZA, MMF	21	Elevated liver enzyme	69/-	46.9/–	1424/–	–/–	–/–	–/–	200/0	0.5 (excluded)
6	78/F	SSc/Anti-Scl-70 antibody	UIP	PSL, mPSL, MMF	40	Diarrhea	63.9/73.9	84.3/57.8	1179/552	24/21	On exertion/-	–/–	150/150	23
7	73/M	SSc/Anti-Scl-70 antibody	UIP	PSL, MMF	16	–	62.2/56.4	29.3/14.1	3066/2172	85/94	At rest/on exertion	+/+	150/150	24
8	63/F	DM/Anti-Jo-1 antibody	OP	PSL, MMF, TAC	0	–	56.3/72.6	72.1/68.2	653/706	16/18	On exertion/–	+/–	200/200	17
9	55/M	SSc/Anti-Scl-70 antibody	UIP	PSL, IVCY, MMF	115	–	74.2/71.8	71/84.1	4379/3359	39/42	On exertion/-	+/–	100/200	7
10	64/F	DM/Anti-Jo-1 antibody	NSIP	mPSL, PSL, TAC, CyA, IVIG, MMF	48	Diarrhea	75/67.2	53/41.8	1176/1507	32/40	On exertion/-	–/–	150/100	15
11	83/M	RA/Rheumatoid factor	UIP	MTX, PSL, TAC	10	Stomach pain	68.8/77.8	68.5/74.6	1519/1736	65/66	–/on exertion	–/–	100/50	5
12	72/M	RA/Rheumatoid factor	UIP	MTX, PSL, IFX, TCZ	82	Abdominal bloating	58.9/49.5	–/–	395/513	67/72	On exertion/On exertion	+/+	150/100	3
13	30/F	DM/Anti-Jo-1 antibody	NSIP	mPSL, TAC, IGU, SASP	55	Nausea, elevated liver enzyme (mild)	58.8/71.2	55.0/69.6	357/359	23/21	–/–	–/–	200/50	7
14	65/F	SSc/Anti-Scl-70 antibody	NSIP	PSL, IVCY, AZA, TAC	80	Diarrhea	80.5/88.4	52.2/56.2	857/811	19/15	–/on exertion	+/+	100/150	6

Abbreviations: AZA, azathioprine; CyA, cyclosporin A; DM, dermatomyositis; %DLco, diffusing capacity for carbon monoxide as percent of predicted; fNSIP, fibrotic non-specific interstitial pneumonia; %FVC, Forced vital capacity; IFX, infliximab; IGU, iguratimod; ILD, interstitial lung disease; IVCY, intravenous cyclophosphamide; MMF, mycophenolate mofetil; mPSL, methylprednisolone; MTX, methotrexate; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PL-7, precipitin line-7; PSL, prednisolone; SASP, salazosulfapyridine; Scl-70, scleroderma-70; SSc, systemic sclerosis; TAC, tacrolimus; TCZ, tocilizumab; UIP, usual interstitial pneumonia; RA, rheumatoid arthritis; RF, rheumatoid factor.

TABLE 2 Stratified analysis of the results of 13 patients

	Case		At the beginning of nintedanib					Treatment duration	
	Age	Gender (male/female)	%FVC (%)	Serum KL-6 (U/mL)	Delay until nintedanib initiation (mo)	%DLco (%)	Pulmonary fibrosis score (%)	Nintedanib (mo)	MMF (mo)
Total	63.2±13.4	4/9	68.2±12.6	1815.0±1423.0	54.5±39.2	60.4±16.7	47.1±24.7	15.1±8.5	9.7±13.1
Case									
Age									
<55	44.3±13.4	1/2	66.4±11.3	2341.7±2011.5	59.0±54.1	60.7±9.0	41.3±19.6	14.3±12.7	15.3±18.6
55-70	63.7±1.9	0/6	73.8±11.5	1735.8±1501.0	63.8±38.8	60.1±16.1	41.2±26.7	16.3±5.5	9.3±12.6
>70	76.5±5.1	3/1	61.2±13.9	1539.8±1121.1	37.0±32.7	60.7±28.3	60.3±25.8	13.8±11.3	6.0±12.0
P value	–	.05	.54	.94	.65	.94	.38	.95	.57
Gender									
Male	70.5±12.1	4/0	62.7±15.2	2339.8±1745.6	55.8±51.2	56.3±23.4	64.0±18.9	9.8±9.6	8.5±11.4
Female	59.9±13.6	0/9	70.7±11.3	1582.2±1302.4	53.9±36.3	61.8±15.4	53.9±36.3	17.4±7.4	10.2±14.5
P value	.16	–	.76	.44	.76	.78	.06	.19	.99
At the beginning of nintedanib									
Delay until nintedanib initiation (mo)									
<10	65.0±16.7	1/2	65.5±8.5	1487.0±818.5	5.7±5.1	65.5±8.5	47.7±27.5	17.0±12.0	12.0±20.8
10-80	61.7±17.2	1/5	69.7±9.2	2355.3±1712.9	48.7±20.9	51.7±19.0	45.2±32.3	16.0±8.0	8.5±11.1
>80	64.0±7.5	2/2	68.9±21.3	1958.3±1730.5	99.8±14.4	72.7±7.7	49.5±13.8	12.3±8.5	9.8±13.8
P value	.99	.56	.93	.99	–	.15	.83	.69	.98
%DLco (%)									
>40	61.5±15.0	2/8	72.3±10.1	1546.8±1147.4	55.7±42.4	65.9±11.6	37.2±17.8	14.8±8.3	8.1±13.4
<40	68.7±6.7	2/1	54.8±11.6	2710.3±2159.6	50.3±33.1	32.9±5.0	80.0±11.4	16.0±11.4	15.0±13.1
P value	.5	.14	.03	.4	.99	–	.01	.74	.46
Pulmonary fibrosis score (%)									
<35	59.6±18.2	0/5	72.4±5.2	844.4±352.2	44.6±29.1	63.3±14.3	22.8±6.1	13.6±7.1	1.2±2.7
>35	65.4±10.7	4/4	65.6±15.3	2422.1±1518.7	60.6±45.1	58.3±19.0	62.3±18.5	16.0±9.7	15.0±14.4
P value	.55	.07	.28	.02	.45	.81	–	.62	.03
Maintenance dose of nintedanib (mg/d)									
50-100	62.4±20.2	2/3	64.7±13.2	1074.4±690.6	58.0±33.0	64.4±13.1	48.2±19.8	9.8±6.9	7.0±12.6
150	72.0±6.6	1/2	70.6±9.8	1700.7±1193.3	45.3±32.3	55.3±27.6	42.7±36.7	17.7±10.1	8.0±13.9
200-300	58.6±6.5	1/4	70.3±15.0	2625.0±1836.0	56.4±53.9	60.3±14.8	48.6±27.4	18.8±7.9	13.4±15.3
P value	.13	.8	.96	.38	.85	.81	.67	.07	.04

Abbreviations: %DLco, diffusing capacity for carbon monoxide as percent of predicted; %FVC, forced vital capacity as percent of predicted; KL-6, Krebs von den Lungen; MMF, mycophenolate mofetil.

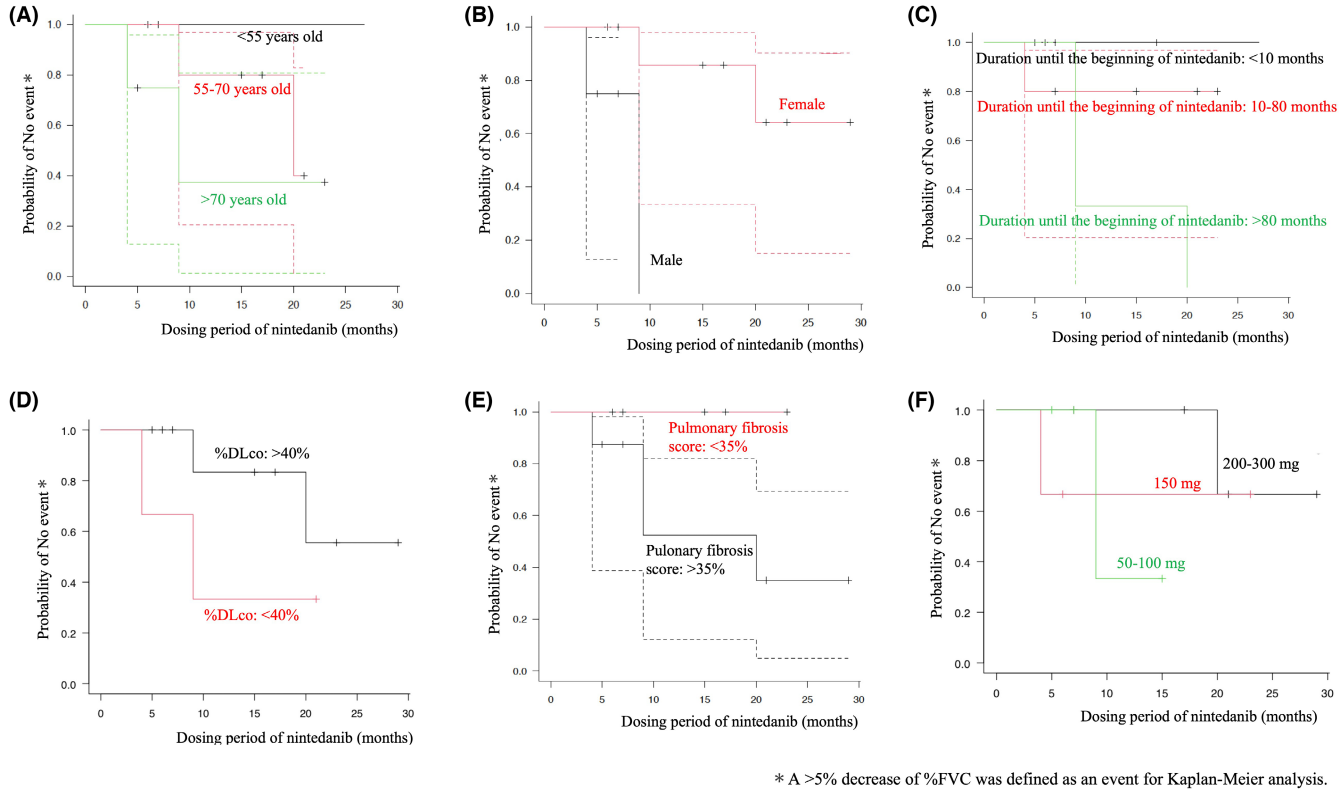

FIGURE 1 A-F, A >5% decrease of percentage of predicted forced vital capacity (%FVC) was defined as an event, and Kaplan–Meier analysis, log-rank test, and log-rank trend test were performed. A, In the elderly group, %FVC decreased more (black: <55 years, red: 55-70 years, green: >70 years, $P = .210$). B, Males lost %FVC significantly more (red line: female, black line: male, $P = .027$). C, %FVC did not decrease in the early group who started within 10 mo after confirmation of an ILD disease activity (black: <10 mo, red: 10-80 mo, green: >80 mo). D, FVC decreased more in the severe %DLco (diffusing capacity for carbon monoxide as a percentage of predicted) group (black: >40%, red: <40%, $P = .20$). E, %FVC did not decrease in the group whose pulmonary fibrosis score at the beginning of nintedanib was <35% (black: <35%, red: >35%, $P = .128$). F, %FVC decreased more in the low-dose group (black: 200-300 mg, red: 150 mg, green: 50-100 mg, $P = .40$)

been diagnosed definitively with anti-Scl-70 antibody-positive SSc (8 patients), anti-aminoacyl tRNA synthetase (ARS) antibody-positive DM (4 patients), and RA (2 patients with rheumatoid factor). Their ILD types included usual interstitial pneumonia, non-specific interstitial pneumonia, and organizing pneumonia patterns. Adverse events occurred in 9 cases (64.3%). Adverse events included diarrhea (5 patients, 35.7%), elevated liver enzymes (2 patients, 14.3%), nausea (1 patient), abdominal bloating (1 patient), and stomach pain (1 patient). After 2 weeks, 1 female patient discontinued nintedanib due to elevated liver enzymes and was excluded from the analysis of the results. The initial nintedanib dosage was 100 to 300 mg (176.92 ± 66.51 mg), and the final nintedanib dosage was 0 to 300 mg (150 ± 91.29 mg).

3.2 | Results of 13 patients who continued nintedanib

Table 2 summarizes the results of %FVC at nintedanib initiation (63.4 ± 21.9%), serum KL-6 at nintedanib initiation (1787.3 ± 1371.2 U/mL), pulmonary fibrosis score at nintedanib initiation (47.1 ± 24.7%), the duration between onset and initial treatment (15.1 ± 17.2 months), delay until nintedanib initiation from confirmation date of ILD disease activity (52.1 ± 38.7 months), nintedanib treatment duration (14.0 ± 9.1 months), maintenance dose of nintedanib (157.7 ± 146.8 mg/day), and MMF treatment duration (9.0 ± 12.9 months). On average, FVC decreased by ~40 mL in ~15 months.

3.3 | A stratified analysis

Regarding pulmonary function, %FVC decreased more in the elderly group (>70 vs 55-70 vs <55 years; Figure 1A; $P = .210$), in males (Figure 1B; $P = .027$), in the late group who started nintedanib >80 months after confirmation of ILD disease activity (Figure 1C; $P = .03$), the severe %DLco group (>40% vs <40%; Figure 1D; $P = .14$), the group whose pulmonary fibrosis score at the beginning of nintedanib was >35% (Figure 1E), and the low-dose group (50-100 mg/d; Figure 1F; $P = .40$). In contrast, %FVC did not decrease in the young group (<55 years; Figure 1A), the early group who started within 10 months (Figure 1C), and the group whose pulmonary fibrosis score at the beginning of nintedanib was <35% (Figure 1E).

There were no significant differences in %FVC changes by smoking history ($P = .28$), serum KL-6 ($P = .824$), primary diseases (SSc vs DM vs RA; $P = .49$), nintedanib dose ($P = .470$), IP subtypes (usual interstitial pneumonia [UIP]: −4.33% vs non-UIP: 1.82%; $P = .48$), and treatment history of MMF. MMF is often administered to SSc patients, especially those with significantly high serum KL-6 at the beginning of nintedanib (with MMF: 2917.5 ± 1388.7 vs without MMF: 870.6 ± 432.5; $P < .05$). Serum KL-6 improved in SSc patients (SSc vs DM vs RA; $P = .013$), the MMF-administered group ($P = .12$), and the long-term group administered with nintedanib for >18 months ($P = .08$).

4 | DISCUSSION

4.1 | Effects of long-term and early treatment with nintedanib

Previous studies proved that the annual rate of decline in FVC was lower with nintedanib than with placebo.[3–5] The degree of FVC reduction observed in our study (by ~40 mL in ~15 months) is in agreement with a previous study for PF-ILD.[10] %FVC decreased in the late group, and early treatment with nintedanib could reduce the decline of %FVC (Figure 1C,I). Although the number of cases is small, the proper timing of nintedanib might be important to exploit the maximum effect. Of course, earlier is not always better, and there might be some patients who did not need nintedanib as a result. Thus, determining the proper timing is necessary. Serum KL-6 decreased especially in the long-term group (Table 1). However, without comparing to placebo there is a possibility that serum KL-6 might decrease after an acute phase of ILD.

4.2 | Factors associated with responsiveness to nintedanib

Patients with a high pulmonary fibrosis score at the beginning of nintedanib would have widespread inflammation in the lungs. Patients with higher fibrosis extension and lower %DLco may show accentuated decrease in FVC over time, irrespective of nintedanib treatment. %FVC would decrease more for the severe group than the mild group, with less inflammation in the lungs. Treatment with nintedanib for the severe group should be continued because previous studies showed effects for severe patients.[11] This study demonstrated the benefits of starting nintedanib early, with potential benefits for the groups with worse outcomes (>70 years old, male, <40 %DLco, and >35% area of pulmonary fibrosis). A global phase III study of nintedanib for IPF (INPULSI-1) reported a higher body weight (82.0 ± 16.8 kg; males: 81.2%)[3] than this study (53.3 ± 7.8 kg; males: 28.6%). CTD patients, especially SSc patients, had a higher percentage of females. Based on this study, 150 mg nintedanib might be a good dose for small patients who worry about adverse effects, such as diarrhea.

4.3 | Other treatments

Other studies suggested that the combination of MMF and nintedanib is a safe treatment option for SSc-ILD.[12] There are other antifibrotic drugs, including pirfenidone. Evidence of the efficacy of pirfenidone in CTD-ILD is not equally compelling.[13] Pamrevlumab, a recombinant human antibody that binds to connective tissue growth factor, is a potential therapy for IPF.[14] Respiratory rehabilitation is also helpful for severe ILD patients.[15]

4.4 | Limitations

First, this study did not include a placebo, and it could not distinguish the effect of nintedanib from the natural course and the effects of other treatments. Although it is very important to control ILD disease activity with corticosteroid and immunosuppressants, we consider that how to use nintedanib also affects prognosis of ILD patients. Second, the sample size was small. It was difficult to strictly detect the effects of the complicating factors from the results because 15 patients per a factor were needed to perform a multiple regression analysis. Third, there were inconsistencies in the nintedanib dose, observation period, and other treatments, as this was a real-world single-center use of nintedanib. Fourth, this study lacked ethnic diversity.

5 | CONCLUSION

There are more and more choices to treat ILD, and it is important to diagnose ILD early and start antifibrotic drugs with proper timing for cases in need. We demonstrated the benefits of starting nintedanib early, with potential benefits for the groups with worse outcomes (>70 years old, male, <40 %DLco, and >35% area of pulmonary fibrosis). Further investigations and multicenter studies are desired to evaluate the effects of nintedanib.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest declared.

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