CASE REPORT AND LITERATURE REVIEW

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ADDING NINTEDANIB TO IMMUNOSUPPRESSIVE THERAPY IN CONNECTIVE TISSUE RELATED INTERSTITIAL LUNG DISEASES; CASE SERIES BASED ON REAL-LIFE DATA FROM A SINGLE CENTRE

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Abstract

Connective tissue-related interstitial lung disease (CTD-ILD) is a severe process that progresses in approximately 30% of patients. These patients may need aggressive treatment. Therefore, new treatment strategies are being developed. Anti-fibrotic agents used in idiopathic pulmonary fibrosis are now being used in patients with a diagnosis of CTD-ILD. In the systemic sclerosis safety and efficacy study, the use of nintedanib in systemic sclerosis-related interstitial lung disease was shown to slow the loss of forced vital capacity (FVC). It has been shown to slow the loss of FVC. We retrospectively analyzed four patients diagnosed with CTD-ILD who used nintedanib for one year. The first two cases were diagnosed with systemic sclerosis, the third case with primary Sjögren's disease, and the fourth case with anti-synthetase syndrome. FVC, carbon monoxide diffusion capacity, 6-minute walking test, and echocardiography data of the cases were obtained. High-resolution computerized tomography records available in the system were re-evaluated with semi-quantitative and quantitative methods (artificial intelligence). We added nintedanib to mycophenolate mofetil treatment in our first, second and fourth cases. In our third case, we added nintedanib to the rituximab treatment. No severe side effects were encountered due to the combined treatment. In our third case, the treatment was terminated due to progressive severe weight loss. Except for the third case, all patients showed improvement in the modified borg dyspnea indices. In our second case, both semi-quantitative and quantitative interstitial lung disease scores were regressed. CTD-ILD is a complex pathology that requires patient-specific evaluation and personalized treatment. Immunosuppressive therapy was modified in all our patients. Immunosuppressive therapy is vital in the treatment of CTD-ILD. Patients with progressive pulmonary fibrosis should receive adequate and effective doses of immunosuppressive therapy. Despite this, treatment should be modified in patients with progression. The addition of nintedanib may contribute to the treatment of these patients.

Keywords: Connetive tissue disease, interstitial lung disease, nintedanib

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INTRODUCTION

Interstitial lung disease (ILD) may develop during connective tissue diseases (CTD). Most of these patients do not show any severe progression. However, about 30% of patients show a progressive and fatal course (1). Such patients may need aggressive and new treatment strategies. Nintedanib, which has anti-fibrotic properties, is one of these drugs. One of the causes of mortality in patients with CTD is ILD. Pulmonary function test [forced vital capacity (FVC)], carbon monoxide diffusion test (DLCO), and 6-minute walk test (6MWT) are important clinical parameters in the follow-up of patients with ILD (2).

Nintedanib is multiple tyrosine kinase inhibitor. Platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor show their effect by activating the receptor signaling cascade (3). It inhibits fibroblast proliferation and migration. TheSafety and Efficacy of Nintedanib in Systemic Sclerosis (SENCSIS) study consisted of patients diagnosed with Ssc-ILD. The INBUILD (Nintedanib in patients with progressive fibrosing ILD) study consisted of patients diagnosed with non-idiopathic pulmonary fibrosis (IPF) progressive pulmonary fibrosis. The FVC measurement in these patients has been shown to that nintedanib slows its loss (5,6). The INBUILD study identified other disease groups with progressive pulmonary fibrosis, such as hypersensitivity pneumonitis (26.1%), autoimmune disease-related ILDs (25.6%), idiopathic non-specific interstitial pneumonia (NSIP) (18.9%), and unclassifiable idiopathic interstitial pneumonia (17.2%). The INBUILD study showed a slowdown in FVC decline in ILDs with non-IPF pulmonary fibrosis, independent of groups (6).

Nintedanib has been shown to act as an anti-inflammatory and anti-fibrotic agent for scleroderma-related ILD and other CTD characterized by progressive pulmonary fibrosis ((7). Therefore, it has been used both in scleroderma-related ILD and in other CTD-ILD patients with progressive pulmonary fibrosis. In a study with 663 , those using nintedanib were divided into two groups, mycophenolate mofetil (MMF) and non- MMF treatment, and compared. In both groups, FVC decline was statistically significantly slower than that in the placebo group. Although the FVC decline was less in the group receiving MMF, it was statistically insignificant. However, it was concluded that this result may be due to the small number of patients (8).

Studies have shown the efficacy of nintedanib in patients with CTD-ILD. In addition, no serious side effects have been reported with immunosuppressive agents such as MMF. Therefore, we added nintedanib to the treatment of our patients, due to the progression of their existing pulmonary fibrosis.

In this article, we presented a total of four cases, two of whom were diagnosed with Ssc-ILD, one with primary Sjögren's disease-associated ILD, and one with the diagnosis of anti-synthetase syndrome-associated ILD (ASS-ILD), for whom nintedanib was initiated due to their progression despite adequate treatment. In our case series, all patients were under immunosuppressive therapy before nintedanib. MMF was added to the treatment of three patients, and nintedanib was added to the rituximab (RTX) treatment of one patient.

METHODOLOGY

Inclusion/Exclusion Criteria

Patients with progression of existing pulmonary fibrosis despite adequate duration and dose of immunosuppressive therapy were included. Patients who did not sign informed consent and did not want to share their data were excluded.

Clinical Analysis

Patients with a diagnosis of CTD-ILD who regularly used nintedanib for one year were retrospectively analyzed. For this purpose, physical examination findings, routine laboratory parameters, FVC, DLCO, 6MWT, and echocardiography were obtained at three-month follow-ups.

High Resolution Computerized Tomography (HRCT) Analysis

High resolution computerized tomography was done if the clinician considered it necessary based on clinical and laboratory findings that suggested disease progression, and HRCT data were screened and retrieved retrospectively. Images were obtained in the supine position at full inspiration without intravenous contrast material using a multi-detector computed tomography (CT) system (Aquilion ONE ViSION edition; Canon Medical Systems Corporation, Otawara, Japan) through helical scanning from the apex to the base of the lungs. Acquisition parameters were as follows: detector width, 80x0.5 mm; tube voltage (120 kV): tube current 250-300 mAs; slice thickness, 3 mm; slice interval, 1,5 mm; rotation duration, 0.35; pitch factor (PF) 1.388; and FOV variable, between 35-45 cm (e.g., 40*40 cm). A phantom with a 32-cm diameter representing the body of an adult was used, and mean CDTIvol and DLP values were 4.8 mGy and 182.7 mGycm, respectively.

Semiquantitative HRCT Analysis

All HRCT images were examined by two observers blinded to the clinical findings, pulmonary function test results, and quantitative measurements of the patients, and decisions were made by consensus. Differences between observers could not be evaluated due to the very limited number of patients.

Examinations were done with the lung window setting (window center, 500-600 HU; window width, 1600 HU), and evaluations were made using the ILD staging system described by Goh et al. (9) CT images were scored at five levels: origin of large vessels, carina, pulmonary venous junction, middle of the third and fifth segments, and just above the right hemidiaphragm. Disease involvement was estimated for each level in the nearest 5% of total area and multiples of 5% (Figures 1 and 2). Patients were assigned to two groups based on semiquantitative image analysis: patients with limited (<20%) and diffuse (>20%) ILD.

Quantitative HRCT Analysis

All images were analyzed using a workstation (Vitrea; Canon Medical Systems Corporation, Otawara, Japan) and software called "lung density analysis" by a single trained radiology resident. Owing to the nature of quantitative measurements, inter-observer agreement was not examined. Minimal user intervention was allowed when necessary to exclude pulmonary vessels, esophagus, trachea, and main bronchus. With threshold values previously used in patients with systemic sclerosis, the ratio of ILD volume to the total lung volume was calculated. The device calculated ILD volume and total lung volume in milliliters using voxels between -200 and -700 HU and voxels between -200 and -950 HU, respectively (10). An example of the measurements is shown in Figures 1 and 2 (Case 3).

CASE REPORTS

Case 1

A 59-year-old female was admitted to our clinic with Raynaud's phenomenon, sclerodactyly, esophageal dilatation in 2016. Antinuclear antibody (ANA) test findings were as follows: granular pattern positive and anti-Sc170 positive. The patient was diagnosed with SSc. HRCT findings were consistent with fibrotic NSIP. Treatment with nine courses of cyclophosphamide (CYC) 1000 mg/month was initiated, and MMF 2 g/day was used as the maintenance treatment. In February 2021, the following findings were considered ILD progression: progression on HRCT; FVC, 66% (1670 mL); diffusing capacity of lung for DLCO, 75% (5.47 mmol/kPa/min); and 6MWT, 140 m (<440m). Nintedanib 300 mg/day was added to the ongoing treatment. FVC was 95% (2400 ml) at the third month of nintedanib treatment, and at the sixth month FVC and DLCO were 83% (2030 ml) and 91% (6.58 mmol/kPa/min), respectively. Due to radiological progression on HRCT and a 10% decline in FVC, MMF 1 g/day and RTX 2 g/6-months were added, and the patient was followed with MMF, RTX, and nintedanib treatment. During the 6-month follow-up period, FVC decline stopped, the Modified Borg Dyspnea Index (MBDI) score decreased to 3 from 5, the 6MWT increased from 140 m to 280 m, and no desaturation was evident during the test procedure. During a 13-month follow-up, a transient elevation of transaminases (less than two times normal) was seen within the first three months, and they spontaneously returned to normal. The patient lost 6 kg during the first three months (less than 10% of total body weight), but weight loss stopped spontaneously. She had diarrhea (not more than three times a day) during the first three months, which was controlled with loperamide. The combination treatment with MMF, RTX, and nintedanib was well-tolerated without any side effects. The patient is still receiving the treatment and follow-up data is given in Tables 1 and 2. Semiquantitative measurements were not consistent with progression; however, quantitative measurements identified 5% progression of parenchymal involvement at one year.

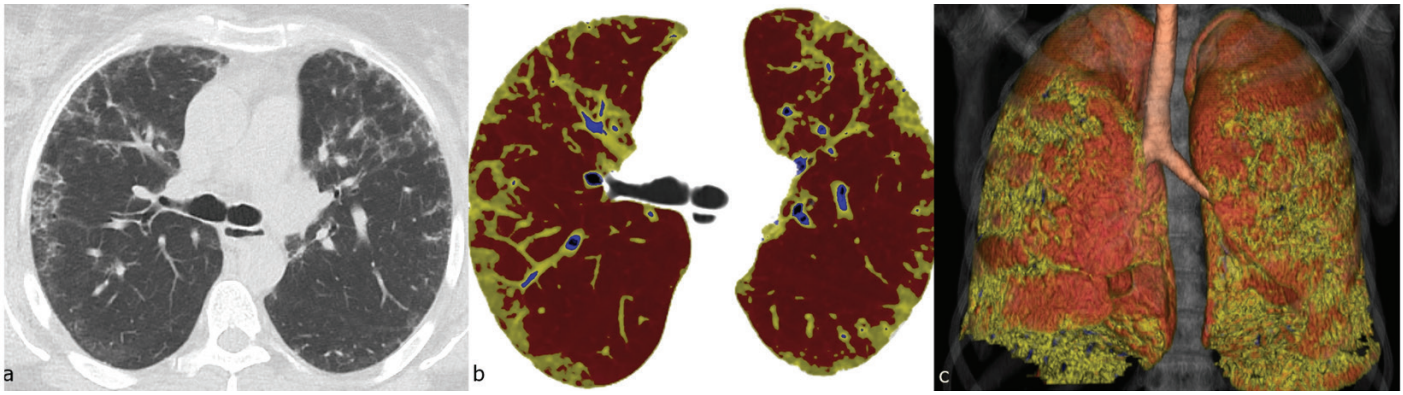

Figure 1. Involvement with peripherally located patchy fine reticulations is seen after treatment on axial HRCT section from carina level (Case 3) (a). In the quantitative analysis of the same section, threshold values corresponding to -200 to -700 HU are represented in yellow (b). Three-dimensional and color quantitative analysis of the same patient (c)

HRCT: High resolution computerized tomography

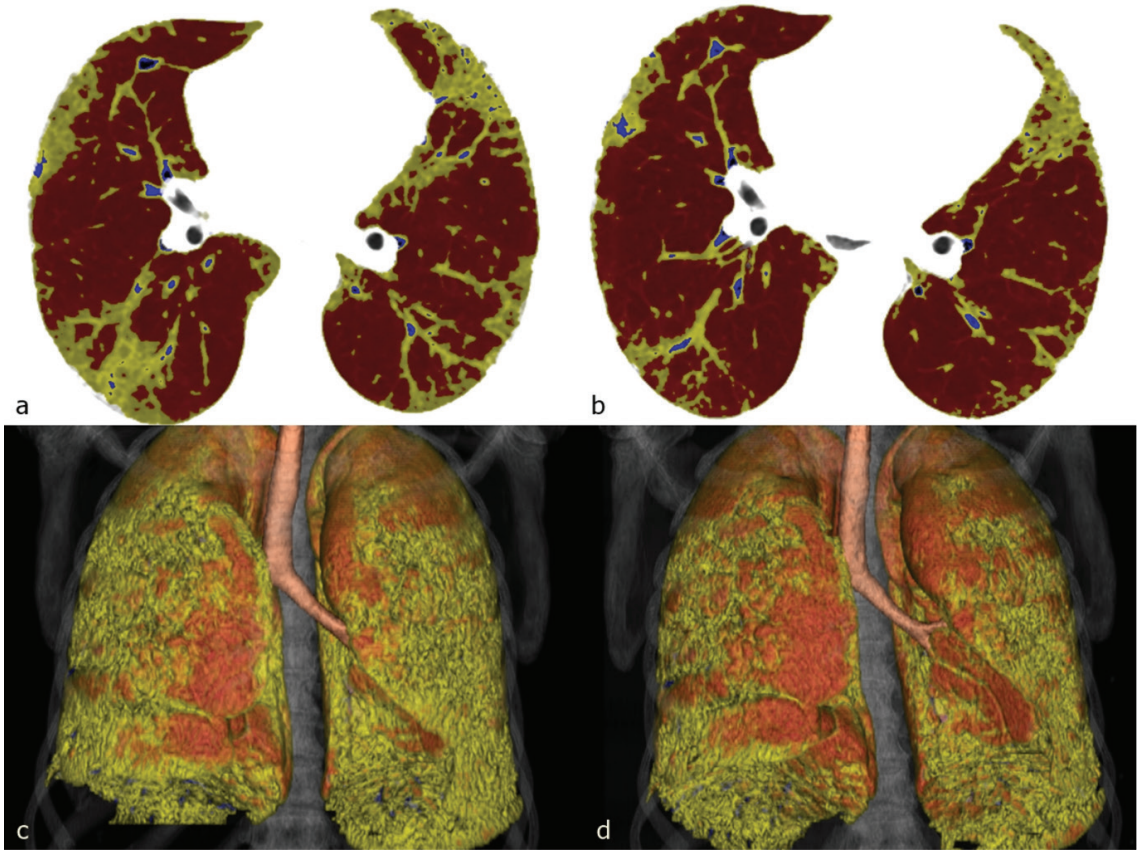

Figure 2. A visual reduction in the involvement after treatment is evident in the following images of Case 3: pre-treatment color axial section (a) and three-dimensional image (b), post-treatment axial section (c), and three-dimensional image (d). Threshold values between -200 and -700 HU corresponding to the involved regions are represented in yellow

Case 2

A 45-year-old female was admitted to our clinic in 2018 with Raynaud syndrome and digital swelling in both hands. She was diagnosed with Ssc and treatment was initiated based on the following findings: ANA homogenous (+), anti-Scl-70 (+), dilated capillaries and microhemorrhage on capillaroscopy, skin thickening beyond metacarpophalangeal joints, sclerodactyly, and Raynaud phenomenon. At that time, DLCO and FVC were 74% and 81%, respectively. On HRCT, >20% involvement was present, and findings were consistent with fibrotic NSIP. Twelve courses of CYC 1000 mg/month treatment were followed by MMF 2 g/day maintenance treatment. In February 2021, MBDI was 5 and the patient was evaluated for progression. DLCO, FVC, and 6MWT were 59% (5.02 mmol/kPa/min), 65% (2.06 L), and 300 m, respectively. HRCT revealed bilateral regions of ground glass appearance, primarily in the lower lung lobes, and increased reticular density in 32% of the lung. Based on these findings, the condition of the patient was considered progression and the treatment was continued with MMF 3 g/day and nintedanib 300 mg/day. At 6, 9, and 12 months, FVC was 75% (2360 mL), 75% (2390 mL), and 70% (2190 mL), respectively. DLCO was 82% (6.90 mmol/kPa/min) and 96% (7.99 mmol/kPa/min) at 6 and 12 months, respectively (Table 2). 6MWT increased but no desaturation was observed. In addition, the MBS dyspnea index score regressed (Table 1). On HRCT, both semiquantitative, (from 32% to 23%) and quantitative measurements (from 32.4% to 26%) demonstrated regression. No side effects were seen during the 12-month follow-up. The patient is continuing treatment with MMF 3 g/day and nintedanib 300 mg/day.

Case 3

A 43-year-old man was admitted to our clinic with non-productive cough, dyspnea on effort, sclerodactyly of the hands, and Raynaud phenomenon in 2010. He was diagnosed with primary Sjögren's disease-associated ILD based on the following findings: ANA (+), Anti-dsDNA (+), Anti-SSA (+), and usual interstitial pneumonia (UIP) pattern on HRCT. FVC and DLCO were 62%, (2420 mL) and 47%, respectively. Anti-Scl-70 and Jo-1 were negative. The patient received methylprednisolone 1 g/day for

three days, which was followed by 13 courses of CYC 1 g/month. Then, maintenance treatment was given with MMF 2 g/day. In 2014, the treatment was changed to RTX 2 g every 6 months since FVC was 74% (2780 ml) and DLCO was 47%, in addition to progression findings on HRCT. In 2020, maintenance treatment with MMF 2 g/day was re-initiated. Routine investigation findings in 2021, were suggestive of disease progression: progression of parenchymal involvement on HRCT; MBDI score, 6; FVC, 58% (2170 mL); DLCO, 46% (5.05 mmol/kPa/min) with desaturation on effort, and 46% parenchymal involvement on semiquantitative HRCT measurements. Nintedanib 300 mg/day was added, and the patient received it in combination with MMF for the first six months. The 6MWT could not be measured due to the oxygen need. During the first 6-month follow-up (Tables 1 and 2), no improvement was seen in dyspnea score, and oxygen need, although FVC was stable. Although semiquantitative measurements did not indicate significant parenchymal progression, quantitative measurements showed an increase in involvement. MMF treatment was changed to RTX treatment (1 g/6-month), due to clinical worsening. The patient lost weight during this period. Tables 1 and 2 show the 10-month follow-up data. No significant progression was seen in FVC. However, dyspnea and oxygen need increased. The patient lost 8 kg in 10 months (more than 10% of body weight). This continued. Nintedanib treatment was discontinued at the end of 10 months due to side effects. At that time, FVC and DLCO were 58% (2.21 L) and 32% (3.08 mmol/kPa/min), respectively. The patient started to gain weight after discontinuation of nintedanib, but symptoms persisted.

Case 4

A 29-year-old female was admitted to our clinic in 2014 with dyspnea on effort, Raynaud phenomenon, arthritis of both wrists, sclerodactyly, subcutaneous calcinosis at left elbow, and bibasilar velcro-type crackles. The patient was diagnosed with antisynthetase syndrome (ASS)-associated ILD based on the following findings: rheumatoid factor positivity, ANA (++) centromere pattern, anti dsDNA (++), anti-SSA (+), anti-Jo1

Table 1. Patient data

	Case 1	Case 2	Case 3	Case 4
Gender	Female	Female	Male	Female
Age	64	49	53	37
Additional disease	None	None	None	None
Diagnosis	SSc	SSc	Primary SjD	ASS
Antibodies	ANA ++ Anti-Scl-70 +	ANA +++ (Homogeneus) Anti-Scl-70 +	ANA ++ Anti-dsDNA + Anti-SSA +	ANA ++ (Centromer) Anti-dsDNA++ Anti-SSA: +++ Anti Jo1>100 (Normal value: <12 AU/mL)
Disease duration	6 (year)	4 (year)	12 (year)	8 (year)
Skin involvement	Diffuse	Limited	None	None
Interstitial lung involvement pattern	Fibrotic NSIP	Fibrotic NSIP	UIP	UIP
Previous immunosuppressive therapies	CYP RTX MMF	CYP MMF	CYP RTX MMF	CYP AZA Abatacept MMF
Current immunosuppressive therapy	MMF (2 g/day)	MMF (3 g/day)	RTX (1000 mg/6 months)	MMF (2 g/day)
Nintedanib duration (months)	13 months (300 mg/day)	12 months (300 mg/day)	10 months (300 mg/day)	12 months (300 mg/day)
Nintedanib continue	Yes	Yes	No	Yes

SSc: Systemic sclerosis, SjD: Sjögren's disease, ASS: Antisynthetase syndrome, ANA: Antinuclear antibody, Anti-Scl-70: Anti-topoisomerase I antibody, Anti-dsDNA: Anti-double stranded DNA antibody, Anti-SSA: Anti-Sjogren's-syndrome-relaeted antigen A, Anti-Jo1: Anti-histidyl-tRNA synthetase antibody, AU: Arbitrary unit, NSIP: Non-spesific intertisiel pneumonia, UIP: Usual intertisial pneumonia, CYP: Cyclophosphamide, RTX: Rituximab, MMF: Mycophenolate mofetil, AZA: Azathioprine, Anti-Sm: Anti-smith

>100 (<12 AU/mL), UIP pattern on HRCT. FVC and DLCO were 86% (2670 mL) and 73%, respectively. A ten-course of CYC (1 g/month) treatment was initiated and this was followed by azathioprine (AZT) 150 mg/day maintenance treatment. Due to the emergence of AZT-associated cytopenia during follow-up, the AZT dose was decreased to 100 mg/day, and abatacept 750 mg/month was added. However, a satisfactory response could not be achieved, and the maintenance treatment was changed to MMF 2 g/day. The condition of the patient was stable until the year 2021. In 2021, the following findings were suggestive of disease progression: FVC, 74% (2380 mL); DLCO, 59% (5.00 mmol/kPa/min); 6MWT, 280 m; and 15% increase in parenchymal involvement on semiquantitative HRCT measurements. Nintedanib 300 mg/day was added to the treatment. All follow-up data are given in Tables 1-3. At 6 months, a decrease in FVC and DLCO was evident, and the patient was diagnosed with pneumonia. Complaints improved following treatment; however, the treatment was changed as follows due to ground-glass appearance on HRCT: MMF 3 g/day, prednisolone 5 mg/day, and nintedanib 300 mg/day. At 9 months, FVC and DLCO improved (Table 2); no saturation was evident on the 6MWT test, but the distance was slightly reduced. The reduction in distance was attributed to bilateral knee osteoarthritis. Findings at 9 months were also maintained at 12 months, and a significant improvement of 6MWT was evident. A similar improvement was also seen in MBDI. No progression of parenchymal involvement was seen on semiquantitative HRCT measurements. However, quantitative measurements showed a 3% increase (Table 3) These findings were considered to be disease remission. No side effects were seen after the initiation of nintedanib except for

Table 2. Patient follow-up data

Case		FVC [% predicted (L)]	DLCO [% predicted (mmol/kPa/min.)]	6 min. walking test (meter)	Modified Borg Dyspnea Index	EKO (EF%-sPAB) (mmHg)
Case 1	Before nintedanib	66 [1.67]	75 [5.47]	140	5	65 - 15
	3rd month	95 [2.40]	None	None	None	None
	6th month	83 [2.03]	91 [6.58]	None	None	None
	9th month	84 [2.13]	None	280	None	None
	12th month	82 [2.05]	81 [5.79]	280	3	65-15
Case 2	Before nintedanib	65 [2.06]	64 [5.43]	300	5	65-20
	3rd month	None	None	None	None	None
	6th month	75 [2.36]	82 [6.90]	360	2	None
	9th month	75 [2.39]	None	None	None	None
	12th month	70 [2.19]	96 [7.99]	360	1	65-20
Case 3	Before nintedanib	56 [2.12]	46 [5.05]	None**	5	65-20
	3rd month	61 [2.33]	None	None	None	None
	6th month	58 [2.21]	None	None	5	None
	9th month	57 [2.16]	32 [3.08]	None	6	65-30
	12th month	58 [2.17]*	None	None	6	60-30
Case 4	Before nintedanib	74 [2.38]	59 [5.00]	280	4	65-25
	3rd month	74 [2.39]	40 [3.45]	310	4	None
	6th month	66 [2.13]	46 [3.94]	None	None	65-25
	9th month	70 [2.25]	54 [4.55]	280	3	None
	12th month	68 [2.22]	58 [4.87]	340	2	None

*Measurement after nintedanib was discontinued. **The walking test could not be performed in the patient who used continuous oxygen. FVC: Forced vital capacity, DLCO: Diffusing capacity of the lung for carbon monoxide, min.: Minute, EKO: Echocardiography, EF: Ejection fraction, sPAB: Systolic pulmonary artery pressure

Table 3. High resolution computed tomography measurements

Case	Before treatment		After treatment	
	Semiquantitative ILD score (%)	Quantitative ILD score (%)	Semiquantitative ILD score (%)	Quantitative ILD score (%)
Case 1	23%	17.30%	23% →	22.4% ↑
Case 2	32%	32.40%	23% ↓	26.0% ↓
Case 3	46%	37.10%	46% →	43.3% ↑
Case 4	15%	17.60%	15% →	20.1% ↑

ILD: Interstitial lung disease

mild diarrhea after one month and 4 kg weight loss during the first 6 months (less than 10% of body weight). Subsequently, weight loss stopped spontaneously. The patient is still receiving the same treatment with stable FVC and DLCO levels and without any serious side effects.

DISCUSSION

FVC, DLCO, 6MWT, and HRCT have important roles in ILD for long-term follow-up and predicting progression (11). In previous studies, limiting FVC decline has been shown to affect mortality directly (12). An annual FVC decline >10% and DLCO decline >15% are associated with a significant increase in mortality (13,14). The SENSCIS study used FVC decline in mL as a primary endpoint (5). In the present study, ILD diagnosis was made using clinical findings, serological tests, and HRCT findings in all patients. None of the patients required biopsies.

CTD-associated fibrosing ILD may respond well to immunosuppressive agents in the initial phase of treatment. As reported in the study by Tolle et al., disease progression may occur later despite an initial good response to treatment (15). Fibrosing-type ILD patients have a higher risk for progression and mortality (16). Disease progression is regulated by autoimmune, vascular, and fibrosing components in Ssc (17). That study did not report on the effects of MMF on remodeling and fibrosis (18). In another study, outcomes of five Ssc-ILD patients receiving RTX were as follows at one year: two patients, >10% regression; two patients, stable disease; and one patient, >10% progression (14). Nintedanib is a multiple tyrosine kinase inhibitor and prevents contraction of fibroblasts as well as their migration to the lungs. It prevents differentiation and migration of profibrotic fibrocytes. In addition, it reduces the transformation of fibroblasts to myofibroblasts in the lungs (19). Inhibition of inflammatory processes through T and B lymphocytes by MMF, through B lymphocytes by RTX, and the effect of nintedanib on fibrosis processes suggest that the combined use of these agents may act on the three components of disease progression in Ssc. In the present study, nintedanib was used in combination with immunosuppressive agents in all patients. Our study used the MMF/nintedanib combination in two patients (Cases 2 and 4). One patient received MMF/RTX/nintedanib (Case 1), and the other patient received MMF/nintedanib for the first 6 months, followed by 4 months of RTX/nintedanib (Case 3). In the SENSCIS study, no secondary parameter other than FVC improved. FVC was taken as the primary endpoint. In our cases, in addition to FVC, parameters such as DLCO, MBDI, and the 6MWT were also monitored. Close follow-up is essential in patients with the progression of pulmonary fibrosis and should not be limited to a single parameter. The cases we studied showed progression in pulmonary fibrosis, and we modified the immunosuppressive treatment of these patients. We tried to evaluate the progression with all the indicators without depending on a single parameter. In the SENSCIS study, patients with 10% pulmonary involvement were included (4). However, our cases have 15-46% pulmonary involvement, and their progression is expected to be much worse. Therefore, our cases may have different responses to treatment. In all our cases, even with the addition of nintedanib, immunosuppressive treatment was modified to prevent or slow progression. Therefore, the results obtained can never be attributed to nintedanib treatment alone.

In the Anti-Scl-70 (+) Ssc-ILD patient (Case 2), both semiquantitative and quantitative ILD scores regressed (Table 4). Lung parenchyma involvement was radiologically consistent with fibrotic NSIP. This patient showed up to a 5% improvement in FVC and a >10% improvement in DLCO. In addition, 6MWT and MBDI showed improvements. To the best of our knowledge, only one case has been reported to have improvement in parenchyma following nintedanib treatment. The 73-year-old female patient reported by Nishino et al. showed regression of parenchymal involvement after 8 months of nintedanib treatment. The patient was positive for anti-centromere, and HRCT images had prominent ground glass opacities radiologically consistent with NSIP (20). In our patient, there was more fibrotic involvement than ground glass areas, which differentiates it from other cases in the literature. However, it

is doubtful that this outcome directly resulted from nintedanib treatment. Case 2 received a higher MMF dose (3 g/day) than the other patients. Again the diagnosis of ILD associated with systemic sclerosis may have influenced this outcome. A more severe immunosuppression may also have led to this result. Further studies are needed in this respect. On the other hand, the combination of 3 g/day MMF treatment with nintedanib did not cause any serious side effects in our patient.

In our second Anti-Scl-70 (+) Ssc-ILD patient (Case 1), MMF/nintedanib treatment provided encouraging results up to the first 6 months. However, the MMF dose was reduced and RTX was added due to the development of radiological progression at 6 months. MMF/RTX/nintedanib halted progression and resulted in clinical improvement. Semiquantitative ILD score on HRCT remained stable, whereas quantitative ILD score showed 5% progression. However, the case showed >10% and >5% improvement in FVC and DLCO, respectively. In addition, MBDI and 6MWT showed significant improvements. No severe side effects developed in the 12-month treatment period. This result appears to support the pathophysiologic process contributing to disease progression. In the study by Cutolo et al., nintedanib was shown to inhibit profibrotic activities of fibroblasts more effectively in Anti-Scl-70-positive ILD patients when compared to Anti-Scl-70-negative ILD patients (13). Increased αSMA and S100A4 gene and protein expressions were detected in fibrocytes of Anti-Scl-70-positive patients with ILD, but expressions were statistically less in Anti-Scl-70-negative patients. After nintedanib treatment, the expression of these genes and proteins was suppressed more in Anti-Scl-70-positive patients than in Anti-Scl-70-negative patients. This result suggested that nintedanib may be more effective in Anti-Scl-70-positive patients. The results of Case 2 can be explained by this mechanism. However, further studies with more patients are needed.

Our primary Sögren's disease-associated ILD patient (Case 3) exhibited a UIP pattern on radiological examination. MMF/nintedanib could not be continued for the first 6 months due to gastrointestinal side effects. RTX/nintedanib combination was administered for thenext four months. This was the patient with the highest ILD involvement score. No FVC decline was seen at the end of 10 months. However, a decline greater than 10% was evident in DLCO. In addition, MBDI increased (Table 2). During this period, the patient lost 8 kg (more than 10% of body weight). During follow-up, no progression was observed in the semiquantitative ILD score for parenchymal involvement; however, the quantitative score, showed approximately 6% progression (Table 3). Considering the case reported by Tuğsal et al. (14) with progression following RTX treatment higher ILD involvement scores may result in a worse treatment response, suggesting that adding antifibrotic agents when ILD involvement score is still low may lead to a more pronounced treatment benefit. Considering the above-mentioned pathophysiologic mechanisms, as well as the absence of improvement, support that nintedanib is more effective in Anti-Scl-70 (+) patients. Nevertheless, progression in lung parenchymal involvement slowed down, indicating treatment benefit. Despite the disappearance of weight loss following discontinuation of nintedanib, oxygen requirement continued at the same level.

Radiologically, the patient with Anti-Scl-70- ASS-ILD (Case 4) had UIP pattern involvement. The MMF/nintedanib combination was very well tolerated. The semiquantitative ILD score remained stable during the one-year follow-up, whereas a 2.5% increase was evident in the quantitative ILD score (Table 3). This was not considered progression. The patient developed pneumonia once in one-year follow-up; however, this was unlikely to be associated with nintedanib. It is well known that patients receiving a full dose of immunosuppressive treatment face a relatively high pneumonia risk. Despite a transient FVC decline after pneumonia, baseline FVC, and DLCO values could be achieved after increasing MMF dose and adding a steroid to the treatment. An improvement in MBDI was evident (Table 2). This ASS patient represents the first reported case in the literature of an ASS patient treated with the MMF-nintedanib combination.

The most common side effect in our patients was weight loss. Especially in case 3, there was a significant weight loss compared to other cases. This case had the highest semiquantitative and quantitative lung scores. The FVC value at the nintedanib baseline was the lowest. The weight loss in this particular case may have been due to relatively advanced pulmonary fibrosis, the combination of RTX and nintedanib, or the low baseline FVC while on nintedanib. This issue needs to be investigated by further studies.

In cases 1, 3, and 4, there are discrepancies between semiquantitative and quantitative measurements. In all three cases, semiquantitative measurements had no clear progression, whereas quantitative measurements showed a slight progression. Semiquantitative measurement requires an experienced radiological evaluation. By its very nature, it is a measurement technique that requires human experience. This causes variability in interpersonal scores. To address this issue, a study with more patients must clearly demonstrate the distinctions between quantitative and semiquantitative measurements.

No significant changes were seen in the modified Rodnan scores of the patients during the one-year follow-up. None of the patients developed digital ulcers, and no new cases of pulmonary or systemic hypertension were observed.

Diarrhea was the most common side effect with 75.7% incidence in the nintedanib arm of the SENSCIS safety and tolerability study, necessitating treatment discontinuation in 6.9% of the cases (21). Weight loss was seen in 11.8% of the patients in the nintedanib arm (5). Two of our patients developed diarrhea, and weight loss was the most important side effect in our series. Three out of four patients had significant weight loss, which stopped spontaneously in two of them (Case 1, Case 4). However, one patient lost 8 kg, and the loss continued gradually.

CONCLUCION

In conclusion, CTD-ILD is a complex condition requiring a multidisciplinary, patient-oriented, and individualized treatment approach. The management of immunosuppressive therapy in patients with CTD-ILD is complex and crucial. In patients with progression, nintedanib may be considered in addition to immunosuppressive treatment.

Ethics

Informed Consent: Patients who did not sign informed consent and did not want to share their data were excluded.

Footnotes

Authorship Contributions

Surgical and Medical Practicez: B.O., N.A., G.Y.Ç., M.C.K., B.K., B.T., E.S.Ö., F.Y., Concept: B.O., G.Y.Ç., B.T., F.Y., Design: B.O., N.A., G.Y.Ç., F.Y., Data Collection or Processing: B.O., N.A., G.Y.Ç., M.C.K., B.K., B.T., E.S.Ö., F.Y., Analysis or Interpretation: N.A., G.Y.Ç., E.S.Ö., F.Y., Literature Search: B.O., G.Y.Ç., E.S.Ö., F.Y., Writing: B.O., G.Y.Ç., F.Y.

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