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BRIEF REPORT

# Real world experience with nintedanib in connective tissue disease-related interstitial lung disease: a retrospective cohort study

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## Abstract

Various connective tissue diseases tend to affect specific organs, lungs being the organ with the most serious repercussions and consequences. The diagnosis of interstitial lung disease makes the treatment more difficult and worsens long-term prognosis and overall survival. Positive results from the registration studies of nintedanib led to approval of the drug for the treatment of idiopathic pulmonary fibrosis and chronic fibrosing interstitial lung diseases in connective tissue diseases. After registration, real-world data on the use of nintedanib are being collected in everyday clinical practise. The objective of the study was to collect and analyse real world experience gathered after the registration of nintedanib for the treatment of CTD-ILD and to show if the positive results collected from a homogeneous and "representative" study population can be applied to everyday clinical practice. We are presenting a retrospective observational case-series study of patients treated with nintedanib from the three largest Croatian centers specialised in the treatment of connective tissue diseases with interstitial lung diseases. Stabilisation or improved of lung function tests was reported in 68% of patients when changes in predicted FVC were observed and in 72% of patients when changes in DLco were analysed. Almost all of the reported patients (98%) were treated with nintedanib as an add-on drug to immunosuppressants. The most common side-effects were gastrointestinal symptoms and abnormal liver function tests in less extent. Our real-world data confirm the tolerability, efficacy and similar side-effects of nintedanib as reported in pivotal trials.

**Key Points**

- *Interstitial lung disease is a common manifestation of several connective tissue diseases and its progressive fibrosing phenotype contributes to high mortality rate and many unmet needs regarding the treatment remain.*
- *Registration studies of nintedanib obtained sufficient data and positive results to support approval of the drug.*
- *Real-world evidence from our CTD-ILD centres confirm the clinical trial data regarding efficacy, tolerability and safety of nintedanib.*

**Keywords** Connective tissue diseases · Interstitial lung diseases · Nintedanib · Progressive pulmonary fibrosis · Real world experience

## Introduction

Various pathophysiological processes of connective tissue diseases (CTD) result in different tissue and organ damage and make the patients susceptible to diverse clinical presentations.

Interstitial lung disease (ILD) is common in CTDs but the prevalence among them varies. The diseases with the highest prevalence of ILD are systemic sclerosis, mixed connective tissue disease, rheumatoid arthritis, idiopathic inflammatory myopathies and Sjoegren's syndrome [1–5]. Progressive pulmonary fibrosis is a term used to describe a phenotype of patients with a tendency of ILD progression

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over time and is defined as a combination of clinical and/or physiological and/or radiological deteriorating criteria [6, 7]. Antifibrotics (pirfenidon and nintedanib) are the drugs used for the treatment of pulmonary fibrosis [8]. Nintedanib is an oral intracellular inhibitor of tyrosine kinase, an enzyme involved in the process of lung fibrosis, which targets vascular endothelial growth factor receptors 1, 2 and 3 (VEGF), platelet-derived growth factor (PDGF) a and b receptors, and fibroblast growth factor receptor 1, 2 and 3 (FGF) [9, 10]. Following a comprehensive clinical trial program, nintedanib has been approved for idiopathic pulmonary fibrosis [11], systemic sclerosis associated interstitial lung disease [12] and for chronic fibrosing interstitial lung diseases with a progressive phenotype [13].

## Patients and methods

This retrospective observational case-series study was performed between January 2020 and February 2023. The inclusion criteria were as follows: age ≥ 18 years; diagnosis of CTD; diagnosis of interstitial lung disease (ILD) associated with CTD (CTD-ILD); fulfilment of the criteria for the diagnosis of progressive pulmonary fibrosis; and nintedanib treatment for ≥ 3 months (without interruption). According to the inclusion criteria 25 patients were enrolled. Three patients were not included in the study because they had started the treatment with nintedanib recently and were left out of the final analysis.

The majority of the patients ($n = 16$; 64%) were diagnosed with systemic sclerosis, while the rest of them had other CTDs (3 patients (12%) MCTD; 2 patients (8%) Sjoegren's syndrome; 1 patient (4%) antisynthetase syndrome; 1 patient (4%) inflammatory idiopathic myopathy and 2 patients (8%) overlapped systemic sclerosis and myositis). The most common comorbidities were arterial hypertension, osteoporosis and thyroid disorders (hypothyreosis and Hashimoto's disease). The immunosuppressants most frequently used prior to the diagnosis of progressive pulmonary fibrosis were i.v. cyclophosphamide, methotrexate (MTX) and azathioprine (AZA) in 13 (52%), 9 (36) and 7 (28%) patients, respectively. The second line of immunosuppressive therapy was mycophenolate mofetil (MMF), antimalarials, rituximab (RTX) and intravenous immunoglobulins in 6 (24%), 5 (20%), 5 (20%) and 2 (8%) patients, respectively. Following the diagnosis of progressive pulmonary fibrosis, nintedanib treatment was initiated in only two patients (8%) as monotherapy and in the rest of the patients (92%) as add-on therapy to immunosuppressants. The concomitant immunosuppressants most frequently used were MMF, RTX and a combination of MMF and RTX in 16 (64%), 6 (24%) and 3 (12%) patients, respectively. Twenty-two (88%) patients were treated with prednisone. The data for pulmonary function tests (forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLco)), High-resolution computed tomography (HRCT) pattern and clinical response to the nintedanib treatment were collected at different periods. The baseline data were collected 3 to 6 months prior to nintedanib initiation and subsequent data recorded on every other follow-up visit: 3–5, 6–11, 12–23 and > 24 months after the initiation of nintedanib treatment.

We defined clinical improvement as amelioration of respiratory symptoms (dyspnoea on exertion) reported by the patients. Taking into account PFTs, improvement in FVC was defined as increase ≥ 5% and deterioration as decrease ≥ 5% registered at the last available follow-up. Improvement in DLco was defined as increase ≥ 10% and deterioration as decrease ≥ 10%. Patients who experienced neither improvement nor deterioration were categorised as stable patients with preserved values of PFTs. Changes in percent of predicted FVC and DLco for patients treated with nintedanib are shown in Figs. 1 and 2, respectively. The baseline demographic characteristics and clinical features of the patients are included in Table 1.

## Results

The median age of the presented patients at nintedanib initiation was 61 (ranging from 26 to 73 years) and disease duration at nintedanib initiation ranged from 8 to 384 months (median 84). The median duration of nintedanib treatment was 11 months, ranging from 3 to 37 months of treatment. All 25 patients were taking nintedanib for 3–5 months, 17 patients for 6–11 months, 11 patients for 12–23 months and 7 patients for > 24 months. In nineteen patients (76%) the dosing regimen was 150 mg BID and the rest of the patients used 100 mg BID. The side-effects of nintedanib treatment were reported in 16 patients (56%), most of them mild. The most common side-effects were gastrointestinal (diarrhoea and vomiting) and abnormal liver function tests in 15 (60%) and 1 (4%), respectively. Three patients discontinued the nintedanib treatment permanently, two due to moderate gastrointestinal intolerance which did not resolve after dietary modifications and one patient died of a condition unrelated to nintedanib treatment.

The improvement was categorised and analysed for three different categories according to the definition of progressive pulmonary fibrosis. We compared the data collected 3 to 6 months prior to the initiation of nintedanib (baseline data) and at the last available follow-up for each patient.

Clinical improvement was detected in 11 (44%) patients. According to FVC, physiological improvement was detected

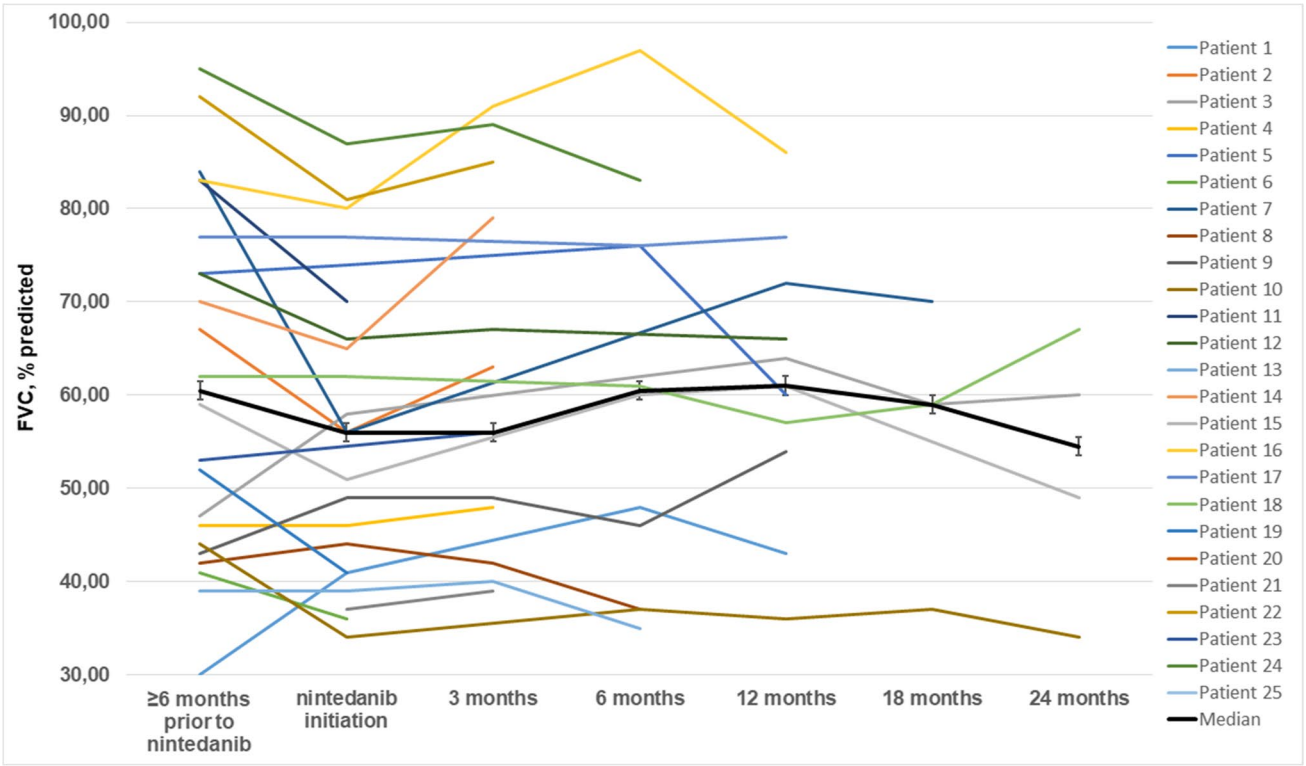


**Fig. 1** Changes in percent of predicted FVC for patients treated with nintedanib. The black time represents the mean ± standard error for all patients. Color version available online

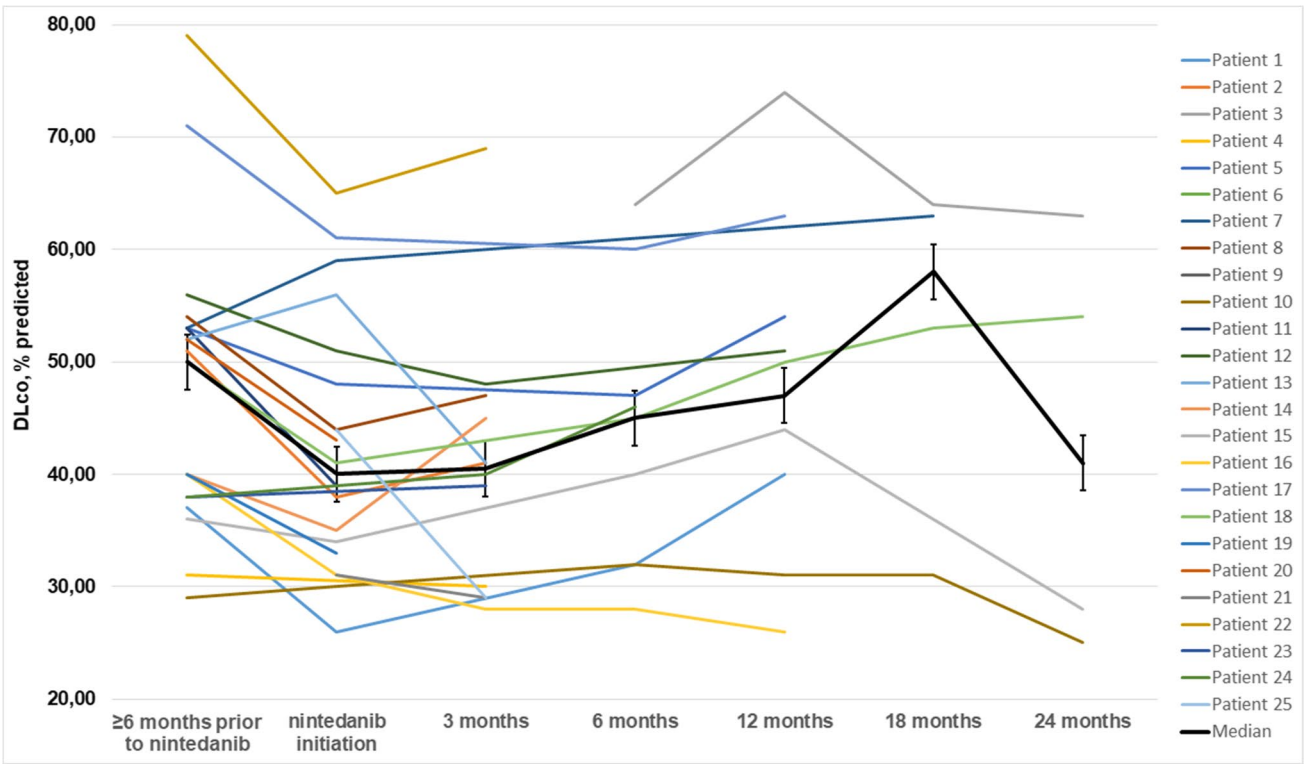


**Fig. 2** Changes in percent of predicted DLco for patients treated with nintedanib. The black time represents the mean ± standard error for all patients. Color version available online

**Table 1** Baseline demographic characteristics, clinical features and treatment of the patients ($n=25$) prior to nintedanib treatment

| Variable | | Value |
|---|---|---|
| Gender | Male, n (%) | 2 (8) |
| | Female, n (%) | 23 (92) |
| Diagnosis | Systemic sclerosis, n (%) | 16 (64) |
| | MCTD*, n (%) | 3 (12) |
| | Sjoegren's syndrome, n (%) | 2 (8) |
| | Systemic sclerosis + myositis, n (%) | 2 (8) |
| | IIM**, n (%) | 1 (4) |
| | Antisynthetase syndrome, n (%) | 1 (4) |
| Age at diagnosis, median (IQR) (years) | | 55 (16–69) |
| Comorbidities | Arterial hypertension, n (%) | 6 (2) |
| | Osteoporosis, n (%) | 5 (20) |
| | Thyroid disorder***, n (%) | 4 (16) |
| | Atrial fibrillation, n (%) | 2 (8) |
| | Cancer history****, n (%) | 2 (8) |
| | No comorbidities, n (%) | 5 (20) |
| Age at nintedanib initiation, median (IQR) (years) | | 61 (26–73) |
| Disease duration at nintedanib initiation, median (IQR) (months) | | 84 (8–384) |
| Concomitant prednisone use, n (%) | | 22 (88) |
| Previous immunosuppressant | Cyclophosphamide i.v., n (%) | 13 (52) |
| | Methotrexate, n (%) | 9 (36) |
| | Azathioprine, n (%) | 7 (28) |
| | Mycophenolate mofetil, n (%) | 6 (24) |
| | Chloroquine / hydroxychloroquine, n (%) | 5 (20) |
| | Rituximab, n (%) | 5 (20) |
| | Intravenous immunoglobulins, n (%) | 2 (8) |
| Ongoing immunosuppressant | None, n (%) | 2 (8) |
| | Mycophenolate mofetil, n (%) | 16 (64) |
| | Rituximab, n (%) | 6 (24) |
| | Methotrexate, n (%) | 2 (8) |
| | Cyclophosphamide i.v., n (%) | 1 (4) |
| | Azathioprine, n (%) | 1 (4) |
| | Rituximab + Mycophenolate mofetil, n (%) | 3 (12) |
| HRCT pattern | NSIP, n (%) | 18 (72) |
| | non-NSIP, n (%) | 7 (28) |

* Mixed connective tissue disease

** Inflammatory idiopathic myopathies

*** Hypothyreosis; Hashimoto's disease

**** Thyroid and colonic cancer

in 6 (24%) patients and 11 (44%) continued to have stable values of FVC. Three (12%) patients improved DLco and 15 (60%) experienced stable DLco at the last available follow-up. None of the patients improved HRCT finding, the pattern remained the same.

Although 11 patients experienced clinical improvement, their underlying medications (immunosuppressants) were left unchanged. The dose of prednisone was tapered if the inflammatory component of the CTD allowed that. The results are summarized in Table 2.

## Discussion

Patients diagnosed with CTD-ILD (especially systemic sclerosis patients) and progressive pulmonary fibrosis phenotype are the most difficult patients to treat, with lung function deterioration contributing to high mortality rate [14, 15]. Many important unmet therapeutic needs regarding this clinical manifestation still exist [16] and the encouraging results of antifibrotic treatment according to SENSCIS and INBUILD studies [12, 13] raise hope for better treatment outcomes.

**Table 2** Characteristics of patients treated by nintedanib for ≥ 3 months ($n = 25$)

| Variable | | | Value |
|---|---|---|---|
| Duration of nintedanib treatment, median (IQR) (months) | | | 11 (3–37) |
| Nintedanib treatment duration, months /Number of patients, n (%) | | | 3–5/25 |
| | | | 6–11/17 |
| | | | 12–23/11 |
| | | | > 24/7 |
| Nintedanib dosing | 150 mg BID, n (%) | | 19 (76) |
| | 100 mg BID, n (%) | | 6 (24) |
| Side-effects of nintedanib treatment | Overall, n (%) | | 16 (56) |
| | Mild, n (%) | | 14 (64) |
| | Moderate, n (%) | | 2 (8) |
| | Diarrhea and vomiting, n (%) | | 15 (60) |
| | Abnormal LFT*, n (%) | | 1 (4) |
| Nintedanib treatment termination, n (%) | | | 3 (12) |
| Reasons for stopping nintedanib | Gastrointestinal intolerance, n (%) | | 2 (8) |
| | Death**, n (%) | | 1 (4) |
| Improvement*** | Clinical, n (%) | | 11 (44) |
| | Physiological | Increased FVC, n (%) | 6 (24) |
| | | Stable FVC, n (%) | 11 (44) |
| | | Increased DLco, n (%) | 3 (12) |
| | | Stable DLco, n (%) | 15 (60) |
| | Radiological, n (%) | | 0 |

* Liver function tests

** Not related to nintedanib treatment

*** According to the data collected at a last available follow-up

A large proportion of Croatian patients with CTDs and CTD-ILDs are being diagnosed, treated and followed-up in specialized University Hospital Centers in Croatia. For this study, we analysed the data from the three largest Croatian centers where, to our knowledge, the majority of CTD-ILD patients are being treated. The CTD-ILD patients were diagnosed according to the international [17] and recently published Croatian Delphi-based expert consensus [18] for ILD screening. All patients had progressive pulmonary fibrosis (PPF) which was diagnosed by fulfilling at least two out of three criteria (consisting of clinical and/or physiological and/or radiological criteria) [7] and discussed by Multidisciplinary teams (rheumatologists / clinical immunologists, pulmonologists and radiologists ± pathologists and cytologists) of the three recruiting centers. The majority of the CTD-ILD patients (mostly systemic sclerosis) are patients with severe and progressive disease already treated with different immunosuppressive treatment. The disease duration prior to nintedanib treatment in our cohort ranged from only 8 to 384 months (median 84). Several patients had long-lasting illnesses with a high burden of disease (especially systemic sclerosis patients), in whom several treatment modalities were used unsuccessfully over the course of the disease. On the other hand, the patient taking nintedanib the longest (37 months) is the patient with systemic sclerosis who was started on nintedanib 8 months after she had been diagnosed with systemic sclerosis and progressive pulmonary fibrosis.

Our patients were slightly older than in the study by Liang et al. [19] who analysed the efficacy of nintedanib in patients with inflammatory myopathies, but the mean duration of nintedanib administration was similar. An important question that remains unanswered concerns the timing of antifibrotic initiation in the treatment of CTD-ILD and we lack the tools for the detection of an early progression.

The ILD-RISC score is a recently developed score for the presence of SSc-ILD, developed with the aim to guide physicians in ordering both baseline and follow-up HRCTs for the detection and progression of ILD [20].

Despite an unknown timing of nintedanib initiation, a large proportion of our patients achieved clinical and physiological improvement. Although improving PFTs is the goal of any treatment modality, we are very often satisfied with stable values of PFTs, bearing in mind patients with CTD-ILD are difficult to treat and have a progressive disease course in spite of the immunosupressants. In 17 (68%) patients stable or improved values of FVC were observed and 18 (72%) had stable or improved values of DLco. Improvement in both FVC and DLco was observed in only 2 patients (8%). As expected,

none of the patients improved the HRCT pattern. As it was reported, 98% of the patients from our everyday clinical practice were treated with nintedanib as an add-on drug to one or more immunosuppressants (mostly MMF and RTX).

The patients on nintedanib who did not show improvement or stabilization of LFTs nor improvement in clinical presentation, were declared non-responders. The large majority of the non-responders were females with the diagnosis of systemic sclerosis with the long disease duration at nintedanib initiation (median 155 months) who were treated with several immunosuppressants prior to the initiation of antifibrotic. Presumably, the non-response could be attributed to the damage acquired during the progressive course of the disease and the timing of the initiation of immunosuppressive drugs and antifibrotics.

Taking our cohort into account, we are in favour of using a combination of an antifibrotic and an immunosuppressant in the treatment of CTD-ILD. Published data from SENSCIS trial report similar adverse event profile of a combination of nintedanib and MMF compared to the nintedanib monotherapy group [21]. Our patients tolerated nintedanib well, with gastrointestinal intolerance being the most prominent side-effect, especially among systemic sclerosis patients (similar to the data gathered from the SENSCIS study). Similar side-effects were reported in the aforementioned study by Liang et al. [19].

In our cohort, gastrointestinal intolerance was reported in patients with long-lasting systemic sclerosis with involvement of the gastrointestinal tract, most likely due to malabsorption. One reported death was not related to the nintedanib treatment, but was caused by sepsis in a patient with a severe form of systemic sclerosis. Surprisingly, although ILD is common in RA, until now there have been no RA patients among our treated patients. Although approximately up to 10% of the patients with RA-ILD have progressive pulmonary fibrosis, in our daily clinical practice they are not dominant and are not candidates for nintedanib.

The limitations of this report include the retrospective nature of the study, a short period of treatment with nintedanib in some of the patients and a relatively small number of patients included. Although, considering the number of all the Croatian CTD-ILD patients and particularly CTD-ILD patients with progressive pulmonary fibrosis, the majority of eligible patients were included and analysed in our report.

In conclusion, although treatment options improved over time, many unmet needs among patients with CTD-ILDs remain. Antifibrotics are drugs intended to reduce fibrotic processes in the lungs of the patients with CTD-ILDs and nintedanib is a drug approved for the treatment of idiopathic pulmonary fibrosis, systemic sclerosis associated interstitial lung disease and other CTD-ILDs. Our real-world data confirm previous findings regarding the tolerability and efficacy reported in pivotal nintedanib trials.

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**Data availability** The data from this study are available from the corresponding author upon reasonable request.

## Declarations

**Conflict of interest** We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We have no conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome. As the corresponding author, I confirm that the manuscript has been read and approved for submission by all named authors with subsequent modifications. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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