Nintedanib in systemic sclerosis-associated interstitial lung disease: real-world cohort study on tolerability and discontinuation

P. Kaenmuang[1-3], N.R. Goldman[4], A. Srirangan[1,5], F. Danzo[1,6], W.-H. Yip[1,7], A. Taki[8], S. Boreland[1], B. Vitri[1], C.J.W. Stock[1,2], C.P. Denton[4], A.U. Wells[1,2], V.H. Ong[4], P. Sestini[9], E.A. Renzoni[1,2]

[1]Interstitial Lung Disease Unit, Royal Brompton Hospital, Guy's and St Thomas' National Health Service Foundation Trust, London, UK; [2]Margaret Turner Warwick Centre for Fibrosing Lung Disease, National Heart and Lung Institute, Imperial College London, UK; [3]Respiratory and Respiratory Critical Care Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand; [4]Division of Medicine, Centre for Rheumatology, University College London, UK; [5]Post Graduate Institute of Medicine, Colombo, Sri Lanka; [6]Department of Biomedical and Clinical Sciences (DIBIC), Università degli Studi di Milano, Italy; [7]Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong; [8]Department of Pharmacy, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, UK; [9]Department of Medical and Surgical Sciences and Neurosciences, University of Siena, Italy.

Abstract

Objective

Nintedanib slows progression of systemic sclerosis-associated interstitial lung disease (SSc-ILD), but its tolerability in this patient group is a potential concern.

Methods

This multicentre study evaluated tolerability and treatment-related interruptions in SSc-ILD patients receiving nintedanib. Factors associated with interruption were analysed by logistic regression, with multivariable adjustment for potential confounders. Fisher's exact test was used when complete separation precluded logistic regression. Cox regression assessed time to first interruption. Weight changes before and after treatment were compared using the Wilcoxon signed-rank test.

Results

Among 63 patients (mean age 56.5±13.8 years, 22% male), 76% received nintedanib 150 mg twice daily, the remainder 100 mg twice daily; 86% were on mycophenolate. Over a median 22.2-month follow-up (95% CI 18.1-26.2), 51% experienced nintedanib interruptions. Patient-reported reasons for treatment interruption included diarrhoea (33.3%), nausea/vomiting (20.6%), weight loss (9.5%) and reflux (1.6%). Older age ($p< 0.03$) and BMI <18.5 kg/m^2 ($p=0.024$) were independently associated with interruption. BMI <18.5 kg/m^2 was also independently linked to shorter time to interruption. Permanent discontinuation occurred in 20.6%, with no significant predictors identified. Weight loss in the 12±6 months after treatment initiation (mean 2.05 kg) was significantly greater than in the preceding 12±6 months (1.09 kg) ($p=0.001$).

Conclusion

Adverse effects frequently led to treatment interruptions in SSc-ILD patients. Older age and lower BMI were predictors of interruption, while no clear predictors of permanent discontinuation were identified. Most patients resumed treatment, highlighting the need for close monitoring and supportive care to manage side effects and maintain treatment continuity.

Key words

systemic sclerosis, interstitial lung disease, systemic sclerosis-associated interstitial lung disease, nintedanib, tolerability, discontinuation, real-world data, SSc-ILD, ILD

*Punchalee Kaenmuang, MD**
*Nina R. Goldman, MB BChir**
*Arthihai Srirangan, MD**
Fiammetta Danzo, MD
Wing-Ho Yip, FRCP
Ali Taki, MPharm, PGDipGPP
Shereen Boreland, MPharmS
Benedetta Vitri, MSN
Carmel J.W. Stock, PhD
Christopher P. Denton, PhD, FRCP
Athol U. Wells, MBChB, MD, PhD, FRACP, FRCP, FRCR
Voon H. Ong, PhD, FRCP
Piersante Sestini, MD
Elisabetta A. Renzoni, MD, PhD

**Contributed equally.*

Please address correspondence to:
Punchalee Kaenmuang
Interstitial Lung Disease Unit,
Royal Brompton Hospital,
Guy's and St Thomas' National Health Service Foundation Trust,
Sydney Street,
London, SW3 6NP, UK.
E-mail: punchalee.k@psu.ac.th

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ORCID iD:
P. Kaenmuang: 0000-0001-7877-0468
N.R. Goldman: 0000-0002-6800-4230
A. Srirangan: 0000-0002-4905-6393
F. Danzo: 0000-0001-8833-3675
W.-H. Yip: 0000-0002-7688-379X
C.J.W. Stock: 0000-0003-4090-8761
C.P. Denton: 0000-0003-3975-8938
A.U. Wells: 0000-0003-2108-6248
V.H. Ong: 0000-0001-5474-0053
P. Sestini: 0000-0002-8195-0811
E.A. Renzoni: 0000-0002-1118-797X

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Introduction

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is the leading cause of death in SSc (1). The SENSCIS trial demonstrated that nintedanib, a tyrosine kinase inhibitor, reduces the rate of SSc-ILD progression (2). However, discontinuation rates due to adverse effects were higher with nintedanib than placebo. Common side-effects are gastrointestinal (GI), including diarrhoea, nausea, vomiting, abdominal pain, and weight loss. Pre-existing gastrointestinal (GI) complications are often seen in SSc-ILD patients (3) and the concurrent use of disease-modifying antirheumatic drugs (DMARDs) such as mycophenolate, itself associated with GI side effects, raises concerns about the tolerability of nintedanib in real-world settings. Therefore, we conducted a retrospective study to evaluate the tolerability of nintedanib and identify factors associated with nintedanib interruption in a real-world setting. We also assessed changes in body weight.

Materials and methods

Study population

Patients with SSc-ILD initiated on nintedanib at the Royal Brompton and Royal Free Hospitals (London, UK) were retrospectively reviewed. Clinical data, pulmonary function parameters, laboratory results and medication use, including corticosteroids and immunosuppressive agents at baseline, were collected from electronic medical records. Body weight at each visit, patient-reported GI side effects, and reasons for interruption following nintedanib initiation were also recorded. All patients were followed for at least six months, except for two who died within a month of initiation, one from sudden death and the other from SSc-related multiorgan failure. The study received institutional approval (IRAS ID 279682; 007272). Participant consent was not required for institutional approval due to the retrospective nature of the study.

Nintedanib interruption

Nintedanib interruption was defined as any temporary or permanent discontinuation of nintedanib specifically due to treatment-related side effects, irrespective of the number or duration of episodes per patient. All cases of interrupted treatment were related to side effects, except for one instance where Nintedanib was temporarily paused due to a chest infection. This case was not classified as an interruption in the analysis. Patients who discontinued nintedanib were counselled on side effect management. If patients agreed, once symptoms had subsided, they restarted nintedanib, either at the standard dose 150 mg twice daily (bd) or at the reduced dose 100 mg bd. Permanent discontinuation refers to patients who permanently stopped treatment due to treatment-related side effects (Supplementary Fig. S1).

Statistical analyses

Factors associated with nintedanib interruption were assessed using logistic regression, with multivariable analyses adjusting for potential confounders, including age at nintedanib initiation, sex, ethnicity, smoking status, and one of the following confounders in separate models: forced vital capacity (FVC) %predicted, diffusing capacity of the lungs for carbon monoxide (DLCO %predicted), or the composite physiologic index (CPI) (4). Fisher's exact test was used when complete separation precluded logistic regression. Time to first treatment interruption was analysed by Cox proportional hazards analysis. Changes in body weight over the 12±6 months before and after nintedanib initiation, adjusted for follow-up duration in months, were assessed using the Wilcoxon signed-rank test. Statistical analyses were performed using Stata version 18 for Windows, StataCorp, College Station, TX.

Results

Between 1st September 2017 and 30th September 2024, 63 patients with SSc-ILD who started on nintedanib were identified. Mean age was 56.5±13.8 years, 22.2% male and 55.6% ever smokers, 48 (76.2%) received nintedanib 150 mg twice daily, the remainder 100 mg twice daily. Autoantibody testing showed positivity for anti-topoisomerase 1 antibody in 35 patients (55.6%), anti-RNA polymerase 3 anti-

body in 8 patients (12.7%), anti-Ro52 antibody in 8 patients (12.7%), anti-PM-Scl antibody in 5 patients (7.9%), anti-SSA in 5 patients (7.9%), anti-centromere antibody in 4 patients (6.4%). Concomitant use of mycophenolate mofetil (MMF) was observed in 54 patients (85.7%). At baseline, gastrointestinal (GI) symptoms were reported by 54 patients (85.7%), including reflux in 51 patients (81.0%), nausea/vomiting in 20 patients (31.8%), and diarrhoea in 9 patients (14.3%). Disease duration before starting nintedanib was 8.4 years (interquartile range (IQR): 5.1–15.6 years). Median follow up was 22.2 months (95% CI 18.1–26.2).

Following the initiation of nintedanib, 37 patients (58.7%) reported worsening GI symptoms with diarrhoea, and 26 patients (41.3%) required loperamide. Worsening reflux was reported in 30 patients (47.6%), and nausea or vomiting in 21 patients (33.3%). At least one interruption was experienced by 32 out of 63 patients (50.8%) (Supplementary Fig. S1), with the first interruption occurring after a median of five months (IQR: 1.9–7.3). Patient-reported reasons for treatment interruption (patients could report more than one) included diarrhoea in 21 cases (33.3%), nausea or vomiting in 13 (20.6%), reflux in 1 (1.6%), weight loss in 6 (9.5%). Abnormal liver function tests were the reason for treatment interruption in 3 patients (4.7%) (Supplementary Table S1).

All six patients with low BMI (<18.5) experienced an interruption (p=0.024, Fisher's exact). The proportion of patients remaining on uninterrupted treatment over time was significantly lower among those with BMI<18.5 (Fig. 1), even after adjustment for age at nintedanib initiation, sex, ethnicity, smoking status, and FVC %predicted [HR: 4.4 (95% C.I. 1.7–11.7, p=0.003) or in alternative models adjusting for DLCO [HR: 3.6 (95% C.I. 1.4–9.6), p=0.009], or CPI [HR: 4.9 (95% C.I. 1.8–13.7), p=0.002). On logistic regression analysis, older age (whether assessed as a continuous variable or as >65 years), was significantly associated with interruption on univariable and multivariable analyses adjusted for sex, ethnicity, smoking status, and FVC %predicted (Table I). Similar results were observed when CPI was used in place of FVC % in multivariable models, except that Caucasian ethnicity was significantly associated in this model (Table I). Nintedanib interruption was experienced by a significantly higher number of patients on a starting Nintedanib dose of 150 mg bd [29/48 (60.4%)] compared to 3/15 (20%) of those on the 100 mg bd dose (p=0.011); this association remained significant on multivariable analyses. Baseline GI symptoms and concurrent DMARD use were not associated with treatment interruption (Table I). Most patients who experienced interruption were able to restart treatment, either at reduced or full dose (Suppl. Fig. S1). Permanent discontinuation occurred in 13 patients (20.6%) after a median of 6.3 months (QR: 1.6–16.5) However, no factor was significantly associated with permanent discontinuation.

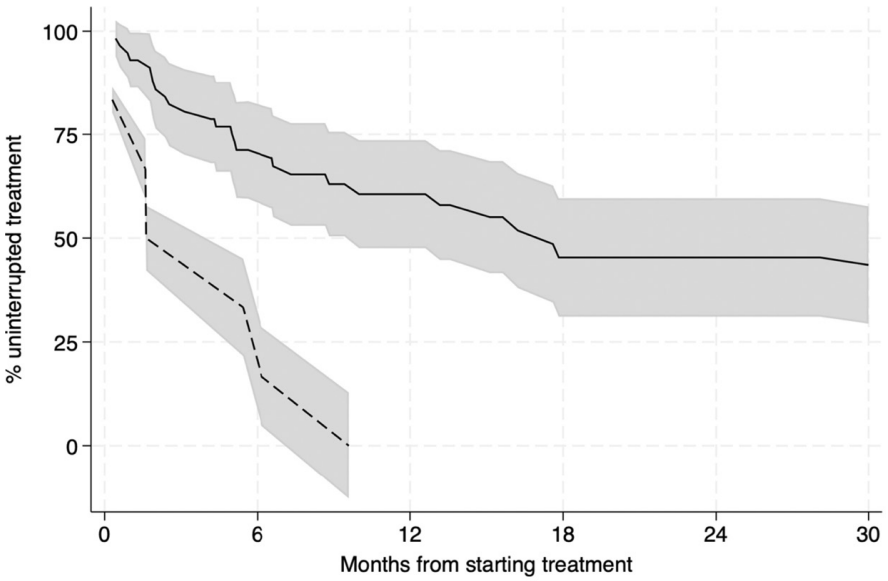

Fig. 1. Smoothed representation of the Kaplan-Meier survival curve showing the proportion of patients remaining on uninterrupted treatment over time, stratified by body mass index (BMI) (<18.5 *vs*. ≥18.5 kg/m²). The dashed line represents patients with BMI<18.5 kg/m²; the solid line represents patients with ≥18.5 kg/m². Shaded areas represent the 95% Confidence Interval (C.I.)

Regarding body weight changes, the mean weight loss over 12 (±6) months after nintedanib initiation was greater than the weight loss observed in the 12±6 months before treatment initiation (2.05 kg (95% C.I. 0.75–3.36) *versus* 1.09 kg (95% C.I. 0.08-2.10), p=0.001). When assessing the monthly rate of weight loss adjusted for individual observation time, the increased rate remained statistically significant (p=0.002), suggesting that nintedanib contributed to an accelerated rate of weight loss.

Discussion

In this study, approximately 50% of patients with SSc-ILD receiving nintedanib experienced at least one interruption, with the majority subsequently able to resume therapy. However, 20.6% permanently discontinued nintedanib due to intolerable side effects. This appears to be in keeping with the rate reported in the SENSCIS trial (16%) and in real world studies in different fibrotic lung diseases, with discontinuation rates ranging from 10-39% (5-7). The higher rates observed in some real-world studies may result from differences in study populations, increased comorbidities and/or or reduced support compared to controlled clinical trials.

Real-world data regarding risk factors for treatment discontinuation in SSc-ILD remain limited. Post-hoc analyses from the SENSCIS trial did not identify a difference in side effects leading to discontinuation according to baseline BMI (8), while our findings suggest that a low baseline BMI increases the risk of treatment interruption. A real-world study from Portugal on fibrotic ILD found that patients with a lower

Table I. Baseline characteristics according to nintedanib interruption.

Variables	Interruption n=32	No interruption n=31	*p*-value univariable	*p*-value multivariable[#]	*p*-value multivariable[†]
Female sex	28 (88%, 70-95)	21 (68%, 49-82)	0.067	0.083	0.025
BMI categories					
<18.5 kg/m^2	6 (19%, 8-37)	0 (0%, 0-12)	0.024*	-	-
18.5-24.9 kg/m^2	11 (34%, 20-53)	16 (52%, 34-69)	-	-	-
25-29.9 kg/m^2	8 (25%, 13-43)	11 (35%, 20-54)	0.926	0.734	0.247
≥30 kg/m^2	7 (22%, 10-40)	4 (13%, 5-31)	0.206	0.528	0.384
Age at nintedanib initiation	60.4 (55.6-65.2)	52.4 (48.0-56.8)	0.025	0.024	0.027
Age at nintedanib initiation ≥65 years	13 (41%, 25-59)	4 (13%, 5-31)	0.018	0.015	0.025
Caucasian	19 (59%, 41-75)	12 (39%, 23-57)	0.103	0.091	0.029
Ever smoker	16 (50%, 33-67)	19 (61%, 43-77)	0.368	0.949	0.499
FVC %predicted	69.2 (62.5-75.9)	69.8 (63.6-76.0)	0.837	0.069	0.480
FVC %predicted <70	17 (53%, 65-70)	14 (45%, 28-63)	0.528	0.110	0.355
DLCO %predicted	40.8 (36.6-45.0)	42.5 (37.6-47.4)	0.566	0.793	0.992
CPI score	50.7 (46.9-54.4)	50.0 (45.8-54.1)	0.810	0.608	0.608
Disease duration	8.4 (5.4-14.8)	8.0 (4.2-19.0)	0.961	0.269	0.260
Anti-topoisomerase 1 antibody	16 (50%, 32-68)	19 (61%, 44-79)	0.368	0.937	0.888
DMARD use	29 (91%, 73-97)	28 (90%, 73-97)	0.967	0.798	0.542
prednisolone	18 (56%, 38-73)	18 (58%, 40-74)	0.884	0.644	0.367
mycophenolate mofetil	29 (91%, 74-97)	25 (81%, 62-91)	0.267	0.341	0.466
azathioprine	0 (0%, 0-11)	2 (6%, 2-23)	0.238*	-	-
rituximab	4 (13%, 5-30)	7 (23%, 11-41)	0.298	0.879	0.423
tocilizumab	3 (9%, 3-26)	5 (16%, 7-34)	0.426	0.752	0.312
hydroxychloroquine	9 (28%, 15-47)	10 (32%, 18-51)	0.721	0.953	0.312
Any baseline GI symptom	27 (84%, 67-94)	27 (87%, 69-95)	0.758	0.618	0.361
Reflux	25 (78%, 60-90)	27 (87%, 69-95)	0.353	0.361	0.177
PPI usage	25 (78%, 60-90)	26 (84%, 66-93)	0.563	0.425	0.145
Oesophageal dysmotility	18 (56%, 38-73)	19 (61%, 43-77)	0.685	0.398	0.163
Diarrhoea	4 (13%, 5-30)	5 (16%, 7-34)	0.681	0.442	0.177
Constipation	1 (3%, 0.4-20)	5 (16%, 7-34)	0.113	0.078	0.057
Faecal incontinence	1 (3%,0.4-20)	2 (6%, 2-23)	0.544	0.437	0.360
SIBO	4 (13%, 5-30)	4 (13%, 5-31)	0.962	0.876	0.836
GAVE	3 (9%, 3-26)	1 (3%, 0.4-21)	0.339	0.753	0.832
Promotility drug use	13 (41%, 25-59)	13 (42%, 26-60)	0.916	0.435	0.300
Starting dose of nintedanib					
150 mg BD	29 (91%, 74-97)	19 (62%, 43-77)	-	-	-
100 mg BD	3 (9%, 3-26)	12 (39%, 23-57)	0.011	0.010	0.026

Data are presented as mean (95% confidence interval (CI)) for age, FVC %predicted, and DLCO %predicted; all other data are presented as number (%, 95% CI). Nintedanib interruption included any patients who had one or more interruptions, whether temporary or permanent.

*Fisher's exact test.

[#]Adjusted for age at nintedanib initiation, sex, ethnicity, smoking, and FVC %predicted.

[†]Adjusted for age at nintedanib initiation, sex, ethnicity, smoking, and CPI.

BD: twice daily; BMI: body mass index; CPI: composite physiologic index; DLCO: diffusing capacity for carbon monoxide; DMARD: disease-modifying anti-rheumatic drug; FVC: forced vital capacity; GI: gastrointestinal GAVE: gastric antral vascular ectasia; OR: odds ratio; PPI: proton pump inhibitors; SIBO: small intestinal bacterial overgrowth.

BMI were at increased risk of requiring dose reduction or discontinuation on univariable analysis, although this was not confirmed on multivariable analysis (9). We observed that treatment interruption was less frequent when the starting dose of nintedanib was 100 mg bd rather than 150 mg bd. Further studies are needed to assess whether a protocol of gradual up titration, starting with 100 mg bd before increasing to the full dose of 150 mg bd would lead to greater treatment continuity in patients with SSc-ILD.

An important finding of this study is that pre-existing GI symptoms did not predict nintedanib interruption. This is particularly significant, as patients with SSc commonly experience GI symptoms that may accrue over time and coincide with the late stage of disease where nintedanib may be considered for progressive ILD (10, 11). Baseline use of mycophenolate and other immunosuppressive agents was not associated with treatment interruption, in keeping with the subgroup analysis of the SENSCIS trial, which found that GI symptoms were not increased in SSc-ILD patients receiving nintedanib and mycophenolate at baseline compared to those on mycophenolate and placebo (12). These findings support the safety of combining nintedanib with mycophenolate in patients with SSc-ILD in a real-world clinical setting. As the number of patients on immunosuppressants other than mycophenolate was small we cannot reach a conclusion on alternative immunosuppressants.

We did not identify a significant association between baseline lung function parameters and discontinuation of nintedanib. Conversely, Fletcher *et al*. reported that patients with idiopathic pulmonary fibrosis and lower baseline FVC were more likely to discontinue nintedanib (13). In contrast, patients

with rheumatoid arthritis-associated ILD with higher baseline DLCO reported more side effects and were more likely to discontinue treatment, although the underlying reasons for this association remain unclear (14). Patients with more severe disease may have a lower tolerance to medication due to higher symptom burden and lower physiologic reserve. The lack of association between disease severity and nintedanib interruption in our cohort may reflect other factors, such as patient perception, treatment expectations, individual coping mechanisms, or physician management strategies. In our cohort, Caucasian ethnicity was associated with a higher likelihood of nintedanib interruption, but only in the multivariable model adjusted for CPI. This association was not observed in the univariable analysis and should therefore be interpreted cautiously. Given the limited representation of non-Caucasian patients and limited evidence in prior studies, further studies with larger, ethnically diverse populations are needed to confirm its validity and to elucidate potential contributing factors. Data on differences in nintedanib discontinuation across ethnicities remain limited. A discontinuation rate of 25.9% was reported among Japanese patients with connective tissue disease-associated ILD, of whom 55% had SSc-ILD(15), markedly higher than a cohort from Italy where permanent nintedanib discontinuation was documented in 10% of patients (5). Further studies involving ethnically diverse populations are needed to better understand this potential association.

The observed weight loss following nintedanib initiation may have clinical implications. Even modest weight loss can contribute to reduced muscle mass, decreased exercise tolerance, exacerbate frailty, increased risk of treatment discontinuation, impact quality of life, and importantly adversely affect survival in patients with progressive fibrosis (16, 17). These findings highlight the importance of monitoring body weight and nutritional status during therapy, as early interventions such as dietary counselling may help mitigate the potential negative effects of weight loss on patient outcomes (18).

This study has some limitations. First, as a retrospective analysis with a relatively small sample size, the statistical power of the analyses and generalisability of the findings may be limited. Nonetheless, the data reflect real-world clinical practice from specialist referral centres managing patients with SSc-ILD. Second, treatment-related adverse effects were identified through chart reviews, which may be subject to individual interpretation and reporting bias. Finally, the retrospective design precludes control over possible confounding variables which may not have been measured, potentially influencing the results.

Our findings confirm that patients with SSc-ILD frequently experience adverse effects during nintedanib therapy, leading to treatment interruptions or permanent discontinuation. Lower BMI and older age were associated with discontinuation, highlighting the need for closer monitoring of these patients during treatment initiation. The fact that all six patients with low BMI experienced interruption, together with the accelerated rate of weight loss after nintedanib initiation, suggest that early dietician support with nintedanib treatment initiation needs to be evaluated by prospective studies, particularly in patients with low BMI or with a history of weight loss. Pre-existing GI symptoms and the use of mycophenolate and/or other immunosuppressive agents were not associated with treatment discontinuation. In this cohort, no single factor was identified as significantly associated with permanent discontinuation. The observation that most patients who interrupted treatment were able to resume nintedanib, often at a reduced dose or with side effect management, highlights the importance of close monitoring and clinical support in facilitating treatment continuation.

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