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ORIGINAL RESEARCH ARTICLE

Enhancing Outcomes in Chronic Fibrotic Interstitial Lung Disease Through Aggressive Management of Nintedanib-Induced Adverse Drug Reactions: A Retrospective Analysis

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Abstract

Background and Objectives Nintedanib, a tyrosine kinase inhibitor, is integral in slowing pulmonary fibrosis progression in chronic fibrotic interstitial lung disease (ILD). However, the occurrence of adverse drug reactions (ADRs) often limits its use, leading to treatment discontinuation, typically within 3–12 months. Discontinuation adversely affects patient outcomes. The study investigated whether aggressive ADR management can prolong nintedanib therapy and improve patient outcomes.

Methods This retrospective, single-center study enrolled Taiwanese patients with chronic fibrotic ILD who were treated with nintedanib from January 2016 to December 2022 in Kaohsiung Chang Gung Memorial Hospital. Patients were categorized into those who discontinued treatment within 180 days and those continuing beyond. Management of ADRs was identified through concurrent prescriptions for symptoms such as nausea, vomiting, diarrhea, or hepatic dysfunction. Baseline demographics, comorbidities, pulmonary function tests, and instances of acute exacerbation were analyzed.

Results The study enrolled 94 patients, with 71 (75.5%) experiencing ADRs. Among these, 41 (43.6%) discontinued nintedanib within 180 days. The administration of medications for managing nausea/vomiting [17 (41.5%) versus 36 (67.9%), $p = 0.0103$] and diarrhea [12 (29.3%) versus 33 (62.3%), $p = 0.0015$] was less frequent in the discontinued group compared with the continued group. Additionally, a higher incidence of acute exacerbation was observed in the discontinued group (34.1% versus 20.8%, $p = 0.016$).

Conclusion Aggressive management of ADRs may enhance patient tolerance to nintedanib, potentially prolonging treatment duration and improving outcomes in chronic fibrotic ILD.

Abbreviations

ADRs	Adverse drug reactions
BMI	Body mass index
BSA	Body surface area
DLco	Diffusing capacity of the lung for carbon monoxide
FVC	Forced vital capacity
ILDs	Interstitial lung diseases
IPF	Idiopathic pulmonary fibrosis
PF-ILD	Progressive fibrosing interstitial lung disease
SSc-ILD	Systemic sclerosis-associated ILD

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Key Points

1. Higher incidence rate of ADRs was noted in the discontinued group.
2. Medications for ADRs were significantly less frequently prescribed in the discontinued group.
3. Aggressive management of ADRs may help patients tolerate nintedanib prolonging the duration of management and improving outcomes in chronic fibrotic ILD.

1 Introduction

Interstitial lung diseases (ILDs) encompass a diverse group of diffuse parenchymal lung disorders that share similar clinical presentations and lung injury patterns. Idiopathic pulmonary fibrosis (IPF) is the predominant chronic fibrotic ILD and is a progressive disease characterized by deteriorating lung function and early mortality [1, 2]. Nintedanib is a tyrosine kinase inhibitor that targets key pathways involved in fibrotic ILDs and is approved for treating IPF [3–6], systemic sclerosis-associated ILD (SSc-ILD) [7], and progressive fibrosing interstitial lung disease (PF-ILD) [8]. Nintedanib has been shown to slow disease progression in IPF, PF-ILD, and SSc-ILD, potentially reducing the risks of lung function decline, acute exacerbations, and respiratory hospitalizations.

Adverse reactions (ADRs) to nintedanib usually involve the gastrointestinal system (e.g., nausea, vomiting, and diarrhea) or liver. Dose adjustments, temporary interruptions, and discontinuation of treatment can be necessary to eliminate these ADRs [3–8]. In the INPULSIS-ON study, nintedanib exhibited an acceptable safety and tolerability profile even over a long period (63 months), although safety concerns led to treatment discontinuation in approximately 10% of the included patients [9]. In a study involving patients with SSc-ILD, patients receiving nintedanib reported a higher incidence of common ADRs [8] than did those not receiving nintedanib.

The prescribing information for nintedanib includes recommendations for the management and monitoring of ADRs, which may include symptom treatment, dose adjustment, or discontinuation of treatment [10]. Given the limited availability of effective ILD treatments, discontinuing nintedanib could lead to rapid disease progression and reduced quality of life. Therefore, aggressively managing ADRs is warranted to prolong the duration of nintedanib use. However, this assumption lacks evidence and requires further investigation.

2 Methods

2.1 Study Design, Population, and Group Classifications

This study is a retrospective analysis conducted in a single center- Kaohsiung Chang Gung Memorial Hospital. Taiwanese patients aged ≥ 18 years with chronic fibrotic ILD who underwent nintedanib treatment between January 2016 and December 2022 were included. Diagnoses were reassessed in multidisciplinary discussions, and patients who were deemed to in fact not have chronic fibrotic ILD were excluded. Patients were excluded if they had a diagnosis of liver cirrhosis, chronic hepatitis, liver function impairment, or an active gastrointestinal tract disorder before receiving nintedanib or if they received any other antifibrotic agents.

Demographic characteristics, body surface area (BSA), body mass index (BMI), smoking history, comorbidities, fibrosis severity, results of pulmonary function tests, high-resolution computed tomography (HRCT) patterns, and instances of acute exacerbation for each patient were obtained from electronic medical records. Acute exacerbations were defined based on the consensus [11, 12].

Information regarding the prescription, interruption, or permanent discontinuation of nintedanib and the management of ADRs, such as the use of domperidone, mosapride, loperamide, silymarin, or ursodeoxycholic acid, was obtained from the database of hospital pharmacy attached to the medical center. Patients were divided into discontinued and continued groups depending on whether they discontinued nintedanib within 180 days.

Ethical approval for this study was obtained from the Institutional Review Board of Chang Gung Medical Foundation (IRB no.: 202201260B0 and 202201284B0). The study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

2.2 Statistical Analysis

Data are expressed as mean ± standard deviation unless otherwise stated. Categorical variables were analyzed using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test. The multiple logistic regression analysis with stepwise model selection was used to identify potential risk factors associated with nintedanib discontinuation. The regression model included the following variables:

age in 10-year increments, gender, BSA (< 1.58 or ≥ 1.58 m^2), GAP stage, smoking history, underlying fibrotic ILD (IPF or SSc-ILD), advanced ILD, chronic respiratory disease, and the requirement for additional medication to manage ADRs (nausea/vomiting and diarrhea). Stepwise regression was performed and covariates with a 0.1 significance level entered the model, while a 0.05 significant level was required to stay in the model.. Data analysis was performed using IBM SPSS software version 21.0. A two-sided *p* value of < 0.05 was considered statistically significant.

3 Results

In this study, 97 patients undergoing nintedanib therapy were identified from the database of hospital pharmacy. Following multidisciplinary discussions, three patients were excluded, leaving a total of 94 patients, comprising 78 with IPF and 16 with SSC-ILD (Fig. 1).

Patient baseline characteristics are presented in Table 1. The mean age was 70.7 years, with 34 (36.2%) of the patients being older than 75 years. Most patients ($n = 67$, 71.3%) were men, and 57 (60.6%) patients had a history of smoking. The most common radiological finding on HRCT was a usual interstitial pneumonia pattern (88.3%). Patients were categorized into gender, age, and physiology (GAP) stages, with 27 (28.7%), 45 (47.9%), and 22 (23.4%) patients being categorized into stages I, II, and III, respectively. Advanced ILD [defined as diffusing capacity of the lung for carbon monoxide (DLco) ≤ 35% or forced vital capacity (FVC) ≤ 50%] was present in 22 (23.4%) patients, and

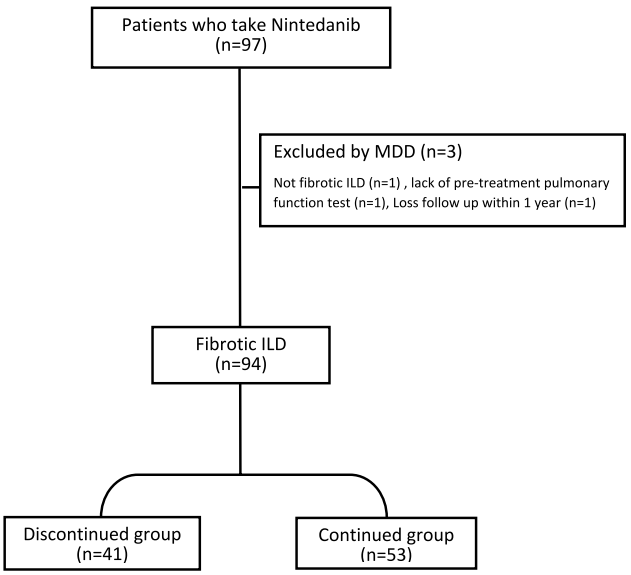

Fig. 1 Study flow chart. *MMD* Multidisciplinary discussions, *ILD* Interstitial lung disease

39 (41.5%) patients had chronic respiratory disease. Inhaled medications, including long-acting bronchodilators (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids, were prescribed for 67 (71.3%) patients, and 46(48.9%) patients undergoing oral corticosteroid therapy at baseline. Nintedanib was initiated at a low starting dose in 5 (5.3%) patients. Acute exacerbation within 12 months occurred in 25 (26.6%) patients.

Baseline characteristics between the discontinued and continued groups displayed no significant differences, except in the incidence of acute exacerbations (34.1% versus 20.8%, $p = 0.0160$) and GAP index ($p = 0.0408$; Table 1). FVC (% of predicted value) and DLco (% of predicted value) remained stable within the first 180 days and exhibited no significant differences between the two groups (Table 2).

ADRs were experienced by 71 (75.5%) patients, with a higher incidence in the discontinued group (82.9% versus 69.8%, $p = 0.0132$; Table 3). Five patients in the discontinued group died, with their deaths suspected to be due to ADR-related sepsis. ADR-related dose reductions occurred in 14 (14.9%) patients, and 24 (25.5%) needed to discontinue nintedanib. Most discontinuations (23.4%) were temporary, but two patients in the discontinued group permanently stopped treatment. Medical therapy for ADRs, such as nausea/vomiting, diarrhea, and hepatitis, was prescribed in both groups. Medications specifically for nausea/vomiting, and diarrhea were significantly less frequently prescribed in the discontinued group compared with the continued group. The figures were 17 (41.5%) and 12 (29.3%) in the discontinued group versus 36 (67.9%) and 33 (62.3%) in the continued group for nausea/vomiting and diarrhea, respectively ($p =$ 0.0103 and 0.0015, respectively; Table 3).

Multivariable analysis considered potential factors influencing discontinuation (each 10-year age increase, BSA < 1.58 m^2, GAP index, and medications for ADRs; Table 4). Older age (in 10-year increments) and low BSA (< 1.58 m^2) were independently associated with discontinuation. A lower GAP index (stage II versus III) and aggressive medication management for ADRs were associated with less discontinuation (Table 4).

4 Discussion

This study highlights the importance of aggressive management ADRs in enhancing patient tolerance to nintedanib, prolonging the duration of management, and improving outcomes for those with chronic fibrotic ILD.

Our findings align with relevant clinical trials and real-world studies that show a high incidence of ADRs [3–,10,13–15]. Notably, Asian patients appear to experience ADRs at a higher rate compared with their counterparts in Europe and the USA [16–24]; the reasons for this

Table 1 Basic characteristics of the study population.

Characteristics	All ($n = 94$)	Discontinued group ($n = 41$)	Continued group ($n = 53$)	p-value
Age, years	70.7 ± 9.9	72.3 ± 9.9	69.5 ± 9.9	0.1759
< 75 years	60 (63.9)	25 (61.0)	35 (66.0)	0.6125
≥ 75 years	34 (36.2)	16 (39.0)	18 (34.0)	
Sex				
Female	27 (28.7)	15 (36.6)	12 (22.6)	0.1384
Male	67 (71.3)	26 (63.4)	41 (77.4)	
BMI (kg/m^2)	23.1 ± 3.9	23.0 ± 3.1	23.1 ± 4.4	0.8988
BSA (m^2)	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.0852
< 1.58	66 (70.2)	22 (53.7)	44 (83.0)	0.0842
≥ 1.58	28 (29.8)	19 (46.3)	9 (17.0)	
Smoking history				
Never	38 (40.4)	17 (41.5)	31 (58.5)	0.1015
Current/former	56 (59.65)	24 (58.54	22 (41.5)	
Fibrotic ILD				
IPF	78 (83.0)	33 (80.5)	45 (84.9)	0.5719
SSC-ILD	16 (17.0)	8 (19.5)	8 (15.1)	
HRCT pattern				
UIP	83 (88.3)	34 (82.9)	49 (92.5)	0.1542
Others	11 (11.7)	7 (17.1)	4 (7.5)	
GAP index				0.0408
Stage I (0–3)	27 (28.7)	12 (29.3)	13 (24.5)	
Stage II (4–5)	45 (47.9)	15 (36.5)	32 (60.4)	
Stage III (6–8)	22 (23.4)	14 (34.2)	8 (15.1)	
Advanced ILD[a]	22 (23.4)	7 (17.1)	15 (28.3)	0.2023
Chronic respiratory disease[b]	39 (41.5)	14 (34.2)	25 (47.2)	0.2038
Inhaled medicine	67 (71.3)	29 (70.7)	38 (71.7)	0.3642
LAMA alone	6 (6.4)	4 (9.8)	2 (3.8)	
LABA + LAMA	38 (40.4)	14 (34.2)	24 (45.3)	
LABA + ICS	12 (12.8)	4 (9.8)	8 (15.1)	
LABA + LAMA + ICS	11 (11.7)	7 (17.1)	4 (7.6)	
Oral corticosteroid[c]	51 (54.3)	19 (46.3)	32 (60.4)	0.1942
Starting dose of nintedanib, *n* (%)				
300 mg/day	89 (94.7)	39 (95.1)	50 (94.3)	0.8669
< 300 mg/day	5 (5.3)	2 (4.9)	3 (5.7)	
Acute exacerbation during follow-up, *n* (%)	25 (26.6)	14 (34.1)	11 (20.8)	0.0160

Values are displayed as number (%), mean ± standard deviation

BMI body mass index, *BSA* body surface area, *DLco* diffusion capacity of carbon monoxide, *FVC* forced vital capacity, *GAP* gender–age–physiology, *ICS* inhaled corticosteroid, *ILD* interstitial lung disease, *LABA* long-acting β_2 agonist, *LAMA* long-acting muscarinic antagonist

[a]DLco pred ≤ 35% or FVC pred ≤ 50%

[b]Chronic obstructive pulmonary disease or asthma

[c]Baseline using oral steroid before nintedanib management

discrepancy are unclear. Efforts to reduce ADRs are crucial for enhancing drug tolerability and maximizing long-term benefits for patients receiving nintedanib. Early intervention is key to reducing drug discontinuation. Although our study did not find an association between baseline or 24-week FVC and DLco levels and nintedanib discontinuation (Table 2), a deterioration in FVC was observed in a Japanese study [15] when nintadanib was discontinued within 3 months. This aligns with several studies indicating that early discontinuation of nintedanib is associated with a higher risk of acute exacerbation [3–8], a finding also supported by our study

Table 2 Pulmonary function test at baseline, 24 weeks and difference between 0 and 24 weeks

	All ($n = 94$)	Discontinued group ($n = 41$)	Continued group ($n = 53$)	p-value
FVC, % of predicted value, baseline	69.2 ± 19.9	69.3 ± 17.3	69.2 ± (15.1)	0.9893
Category, *n* (%)				
< 70%	46 (48.9)	22 (53.7)	25 (47.2)	0.5327
≥ 70%	48 (51.1)	19 (46.3)	28 (52.8)	
< 50%	9 (9.6)	5 (12.2)	4 (7.5)	0.4476
≥ 50%	85 (90.4)	36 (87.8)	49 (92.5)	
< 50%	9 (9.6)	5 (12.2)	4 (7.6)	0.4725
≥ 50% and < 80%	64 (68.1)	29 (70.7)	35 (66.0)	
≥ 80%	21 (22.3)	7 (17.1)	14 (26.4)	
FVC, % of predicted value, at 24 weeks	66.7 ± 16.3	65.4 ± 14.9	67.5 ± 17.0	0.6539
Change FVC between 0 and 24 weeks	− 1.7 ± 8.6	− 1.3 ± 1.5	− 0.1 ± 1.0	0.5076
FEV1,% of predicted value, at baseline	76.1 ± 17.1	78.3 ± 18.0	74.5 ± 16.3	0.2900
FEV1,% of predicted value, at 24 weeks	73.4 ± 17.8	74.5 ± 16.7	73.0 ± 18.4	0.7824
DLco, % of predicted value, at baseline	48.0 ± 15.5	51.3 ± 14.4	46.0 ± 15.9	0.1711
DLco, % of predicted value, at 24 weeks	44.3 ± 15.9	42.0 ± 32.1	45.1 ± 39.0	0.5866
Change DLco between 0 and 24 weeks	− 0.7 ± 9.2	− 4.0 ± 6.4	0.47 ± 9.8	0.1724

Values are displayed as number (%), mean ± standard deviation

DLco diffusion capacity of carbon monoxide, *FEV1* forced expiratory volume in one second, *FVC* forced vital capacity

Table 3 Adverse drug reactions and the medication for ADRs in the study groups

	All ($n = 94$)	Discontinued group ($n = 41$)	Continued group ($n = 53$)	p-value
Any ADRs	71 (75.5)	34 (82.9)	37 (69.8)	0.0132
ADRs leading to:				
Death	5 (5.3)	5 (12.2)	0	< 0.0001
Lost follow-up	8 (8.5)	4 (9.8)	4 (7.6)	0.6715
Dose reduction	14 (14.9)	5 (12.2)	9 (17.0)	0.6864
Discontinuation	24 (25.5)	17 (41.5)	7 (13.2)	< 0.0001
Temporary	22 (23.4)	15 (36.6)	7 (13.2)	< 0.0001
Permanent	2 (2.1)	2 (4.9)	0 (0)	0.0453
Medication for ADRs:				
For nausea/vomiting	53 (56.4)	17 (41.5)	36 (67.9)	0.0103
For diarrhea	45 (47.9)	12 (29.3)	33 (62.3)	0.0015
For hepatic dysfunction	21 (22.3)	8 (19.5)	13 (24.5)	0.5626

Values are displayed as number (%)

ADR adverse drug reactions

(Table 1). Patients discontinuing nintedanib within 180 days had a higher risk of acute exacerbations.

The primary ADRs associated with nintedanib include nausea, vomiting, diarrhea, and hepatic dysfunction [3–10, 13–15], each of which can negatively affect the nutritional status of patients. Japanese real-world data [15] indicated that a BSA of less than 1.58 m^2 was associated with early discontinuation of nintedanib within 3 months. Our study corroborates these findings, indicating the necessity for strategies to counteract the nutritional effects. These gastrointestinal ADRs also reduce the willingness of patients to continue nintedanib, thereby influencing their compliance and adherence. Although our study associated ADR management with continued nintedanib use, direct evidence linking aggressive ADR management to enhanced drug toleration and patient compliance remains limited and requires further investigation. Notably, this association applies to all ADRs except for those related to hepatic dysfunction. This study is among the first to explore this concept, although further prospective

Table 4 Multivariate analysis of factors associated with discontinuation of nintedanib

Variables	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age in years, 10-year increments	1.851 (1.049–3.013)	0.0365	1.562 (1.011–3.262)	0.0449
Gender (F versus M)	2.172 (0.960–5.019)	0.0650		
BSA, ($< 1.58\ m^2$ versus $\geq 1.58\ m^2$)	2.172 (1.160–6.019)	0.0253	2.660 (1.198–7.205)	0.0343
GAP stage, (I versus III)	0.581 (0.179–1.834)	0.8727		
GAP stage, (II versus III)	0.289 (0.102–0.781)	0.0188	0.203 (0.059–0.622)	0.0072
Smoking history (never versus current/former)	0.503 (0.219–1.135)	0.1006		
Fibrotic ILD (IPF versus SSc-ILD)	1.671 (0.743–3.814)	0.2171		
Advanced ILD (N versus Y)	1.186 (0.528–2.677)	0.6802		
Chronic respiratory disease (without versus with)	1.533 (0.682–3.487)	0.3033		
Medication for ADRs:				
For nausea/vomiting	0.321 (0.136–0.735)	0.0081	0.302 (0.110–0.779)	0.0154
For diarrhea	0.266 (0.111–0.615)	0.0024	0.226 (0.082–0.582)	0.0028

ADR adverse drug reactions, *BSA* body surface area, *GAP* gender–age–physiology.

investigations are warranted to confirm these findings and provide stronger evidence.

The INPULSIS-ON study [9] revealed that patients who continued nintedanib beyond 52 weeks rarely discontinued it due to diarrhea, suggesting that longer treatment durations may enhance tolerance to ADRs and improve patient outcomes. Our data, alongside the INPULSIS-ON study results, reinforce the necessity of optimal care for patients on nintedanib. Aggressive management of ADRs contributes to the continued use of nintedanib and superior patient outcomes.

4.1 Limitations

Our study demonstrates the advantages of early intervention in managing ADRs, which aids in maintaining the continuity of nintedanib treatment. However, acknowledging the study's limitations is crucial. These include the study being retrospective, conducted at a single center, involving a relatively small patient cohort, and lacking detailed data on the incidence and severity of nausea, vomiting, diarrhea, and hepatic dysfunction. Additionally, the study lacks information on the severity of acute exacerbations and the incidence rate of acute exacerbation is notably high although similar results were observed [25, 26].

5 Conclusions

Our study underscores the significance of aggressive management of ADRs in helping patients tolerate nintedanib, thereby prolonging the duration of management and improving outcomes in chronic fibrotic ILD. The findings suggest that further prospective studies are necessary to validate these observations and to provide more comprehensive insights into this area of treatment.

Declarations

Funding This study did not receive financial support from any public, commercial, or nonprofit funding agencies.

Conflict of Interest The authors have no conflicts of interest to declare.

Ethics Approval Ethical approval for this study was obtained from the Institutional Review Board of Chang Gung Medical Foundation (IRB no.: 202201260B0 and 202201284B0). The study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

Consent to Participate We anonymized the data retrospectively. Taiwan medical ethics guidelines do not require informed consent be obtained for this type of research.

Consent for Publication Not applicable.

Data Availability Data will be made available on reasonable request.

Code Availability Not applicable.

Author Contributions Yu-Wen Chang: Data collection, Statistic analysis and Manuscription. Meng-Yun Tsai: Data collection, Statistic analysis and Manuscription. Yu-Ping Chang: Data collection. Chien-Chang Liao: Data collection, multidisciplinary discussions. Yu-Ting Lin: Data collection, multidisciplinary discussions. Chien-Hao Lai: Data collection, multidisciplinary discussions. Meng-Chih Lin: Study design and consultation, multidisciplinary discussions. Kuo-Tung Huang: Study design and consultation, multidisciplinary discussions, and Corresponding author.

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