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**Review Article**

# Efficacy and Safety of Nintedanib in Patients with Interstitial Lung Disease with or without Systemic Sclerosis: A Meta-Analysis

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**Abstract**

**Background:** Nintedanib is a potent intracellular inhibitor of tyrosine kinases and modulates the pathways involved in the development of fibrosis. We assessed nintedanib efficacy and safety in interstitial lung disease (ILD) patients.

**Methods:** We searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Register to identify available articles (up to April 2022). We conducted a meta-analysis of randomized controlled trials (RCTs) examining nintedanib efficacy and safety in patients with ILD with or without systemic sclerosis (SSc).

**Results:** Meta-analysis of five RCTs including 2,470 patients with ILD (1,343 nintedanib group and 1,127 controls) revealed that the annual rate of change in forced vital capacity (FVC) was significantly lower in the ILD group than in the control group (standardized mean difference [SMD] = 0.336; 95% confidence interval (CI) = 0.256–0.416, $P$<0.001). Stratification by disease type showed a low annual rate of change in FVC in patients with and without SSc (SMD = 0.389, 95% CI=0.294–0.478, $P$<0.001; SMD=0.177, 95% CI=0.013–0.340, $P$<0.00). The incidence of serious adverse events did not differ between the nintedanib and placebo groups; however, adverse events (AEs) and withdrawals due to AEs were significantly higher in the nintedanib group than in the placebo group (SMD =2.365, 95% CI=1.673-3.343, $P$<0.001; SMD =1.740, 95% CI= 1.385-2.185, $P$<0.001).

**Conclusion:** Nintedanib is effective for ILD with or without SSc. However, it increased the incidence of AEs and withdrawals due to AEs.

**Keywords:** Nintedanib; Efficacy; Safety; Interstitial lung disease

## Introduction

Interstitial lung diseases (ILDs) are a type of diffuse parenchymal lung disease that is marked by interstitial involvement induced by inflammation and fibrosis (1,2). Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of idiopathic interstitial pneumonia that has no recognized etiology. It is a progressive disease that causes growing dyspnea and gradual decline of lung function, leading to substantial morbidity and mortality (3). A reduction in forced vital capacity (FVC) is linked to the onset of illness and is predictive of a limited survival time. ILD is

widespread in patients with connective tissue diseases (1), and lung involvement is common in patients with systemic sclerosis (SSc) and is linked with a poor outcome (4,5).

Several signaling pathways regulated by tyrosine kinase receptors have been linked to pulmonary fibrosis (6). The activation of cell-signaling pathways by tyrosine kinases, involving receptor kinases such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), has been connected to the pathophysiology of ILD (7). Nintedanib is a potent intracellular inhibitor of these tyrosine kinases (8). As a result, nintedanib may modulate the pathways involved in the development of fibrosis.

Several clinical trials have been conducted to evaluate the effectiveness and safety of nintedanib in patients with ILD (9-12). The usage of nintedanib (150 mg twice day) slows the pace of FVC reduction, which slows disease progression. However, there has yet to be a well-researched meta-analysis of nitedanib's effectiveness and safety in individuals with ILD with or without connective tissue diseases.

The purpose of this meta-analysis was to evaluate the effectiveness and safety of nintedanib in patients with ILD with or without SS, utilizing data from randomized controlled trials (RCTs).

## Methods

### *Identification of eligible studies and data extraction*

We performed an exhaustive search for studies that examined the efficacy and safety of nintedanib in patients with ILD. Literature searches were performed using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register to identify available articles (up to April 2022). The following keywords and subject terms were used in the searches: 'nintedanib' and 'interstitial lung disease'. All references in the studies were reviewed to identify additional studies not indexed by electronic databases.

RCTs were included if they met the following criteria: 1) the study compared nintedanib with placebo for ILD, 2) the study provided endpoints for the clinical efficacy and safety of nintedanib, and 3) the study included patients diagnosed with ILD based on clinical classification. The exclusion criteria were as follows: 1) the study compared nintedanib with other drugs for ILD and 2) the study included duplicate data or did not contain adequate data for inclusion.

The efficacy outcome was the annual rate of change in FVC over a 52-wk period. The safety outcomes were the number of patients with adverse events (AEs) or serious adverse events (SAEs) and the number of withdrawals due to AEs. The following information was extracted from each study: first author, publication year, nintedanib dose, follow-up duration, and efficacy and safety outcomes. Data extraction and quality control of the meta-analysis methods and results were performed by two independent reviewers. The quality of the RCTs was carried out using the RoB 2.0 version of the Cochrane risk-of-bias tool, which included 5 domains that refer to randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results (13). Every domain could be classified as low risk of bias, high risk of bias or unclear risk of bias according to the judgment criteria. Any disagreements in the quality evaluation were resolved by discussion and consensus. We performed the meta-analysis in compliance with the guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (14).

### *Evaluation of statistical associations*

We calculated odds ratios (ORs) for dichotomous data, standardized mean differences (SMDs) for continuous data, and corresponding 95% confidence intervals (CIs). SMDs were calculated by dividing the mean difference between the two groups by the pooled SD and were used when different scales were integrated to measure the same concept. This measure compares the case and control arms in terms of standardized scores.

The magnitude of SMD was regarded as follows: 0.2–0.5, small effect; 0.5–0.8, medium effect; and ≥ 0.8, large effect (15). We assessed within- and between-study variations and heterogeneities using Cochran's Q-statistics (16). The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When a significant Q-statistic ($P$<0.10) indicated heterogeneity across studies, the random effects model was used for the meta-analysis; if not, the fixed effects model was used. The fixed effect model considers only within-study variation and assumes that all studies estimate the same underlying effect. We quantified the effect of heterogeneity using $I^2 = 100\% \times (Q-df)/Q$ (17), where $I^2$ measures the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than chance. $I^2$ ranges between 0% and 100%; $I^2$ values of 25%, 50%, or 75% are referred to as low, moderate, and high estimates, respectively. Statistical analyses were performed using the Comprehensive Meta-Analysis software program (Biostat, Englewood, NJ, USA).

### *Evaluation of publication bias*

Funnel plots are normally used to detect the publication bias. However, because funnel plots require a range of studies with different sizes and subjective judgments, we evaluated publication bias using Egger's linear regression test, which measures funnel plot asymmetry using a natural logarithm scale (18). An ethics statement is not applicable because this study is based exclusively on published literature.

## Results

### *Studies included in the meta-analysis*

Seven hundred and eighty-seven studies were identified by electronic or manual searches, with ten of these selected for full-text review based on title/abstract (Fig. 1).

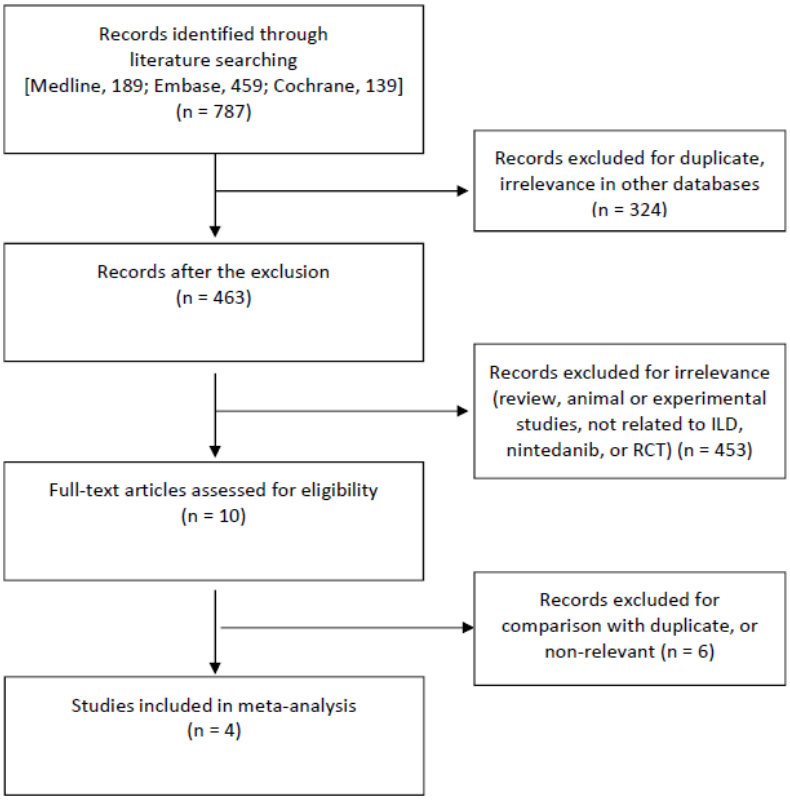


**Fig. 1:** Flow chart of study selection

However, six of the ten studies were excluded as they contained duplicate data or did not contain adequate data for inclusion. Thus, four studies met the inclusion criteria (9-12). One of the eligible studies contained data on two different groups that were treated independently (11). Therefore, five comparisons were considered in the meta-analysis, which included a total of 2,470 patients with ILD (1,343 nintedanib group and 1,127 controls) (Table 1).

**Table 1:** Characteristics of individual studies included in the meta-analysis

| *Author* | *Study name* | *Disease* | *Number of patients* | | *Age, years* | |
|---|---|---|---|---|---|---|
| | | | Nintedanib | Placebo | Nintedanib | Placebo |
| Distler, 2019 (9) | SENSCIS | SSc-ILD | 288 | 288 | 54.6±11.8 | 53.4±12.6 |
| Flaherty, 2019 (10) | INBUILD | ILD | 332 | 331 | 65.2±9.7 | 66.3±9.8 |
| Richeldi, 2014 (11) | INPULSIS-1 | ILD | 309 | 204 | 66.9±8.4 | 66.9±8.2 |
| Richeldi, 2014 (11) | INPULSIS-2 | ILD | 329 | 219 | 66.4±7.9 | 67.1±7.5 |
| Richeldi, 2011 (12) | TOMORROW | ILD | 85 | 85 | 65.4±7.8 | 64.8±8.6 |

Plus–minus values are means ± standard deviation. SSc: Systemic sclerosis, ILD: Interstitial lung disease

The characteristics of the studies included in this meta-analysis are listed in Table 1. In all studies, the patients received nintedanib 150 mg twice daily; ILD was not associated with connective tissue disorders, except in one study where ILD was associated with SSc (9). The follow-up period was 52 wk. The risk of bias evaluated showed an overall low risk of bias for all trials included.

### *Meta-analysis of the efficacy of nintedanib for interstitial lung disease*

Meta-analysis revealed that the annual rate of change in FVC was significantly lower in the ILD group than in the control group (SMD =0.336, 95% CI=0.256–0.416, $P<0.001$) (Table 2, Fig. 2).

**Table 2:** Meta-analysis of randomized controlled trials of nintedanib in interstitial lung disease

| *Study type* | *Outcome* | *No. of Studies* | *Test of association* | | | Test of heterogeneity | | |
|---|---|---|---|---|---|---|---|---|
| | | | SMD* or OR | 95% CI | *P*-value | Model | *P*-value | $I^2$ |
| Efficacy: Annual rate of decline FVC, ml/yr | All | 5 | 0.336 | 0.256-0.416 | < 0.001 | F | 0.133 | 43.3 |
| | ILD | 4 | 0.389 | 0.294-0.478 | < 0.001 | F | 0.520 | 0 |
| | SSc-ILD | 1 | 0.177 | 0.013-0.340 | 0.034 | NA | NA | NA |
| Safety | AE | 5 | 2.365 | 1.673-3.343 | < 0.001 | F | 0.744 | 0 |
| | SAE | 5 | 1.010 | 0.847-1.205 | 0.911 | F | 0.665 | 0 |
| | Withdrawals due to AE | 5 | 1.740 | 1.385-2.185 | < 0.001 | F | 0.277 | 21.5 |

SMD: Standard mean difference, OR: Odds ratio, CI: Confidence Interval, ILD: Interstitial lung disease, SSc: Systemic sclerosis, FVC: Forced vital capacity, AE: Adverse event, SAE: Serious adverse event, F: Fixed effects model, NA: Not available, *: Magnitude of Cohen's d effect size (SMD): 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥ 0.8, large effect

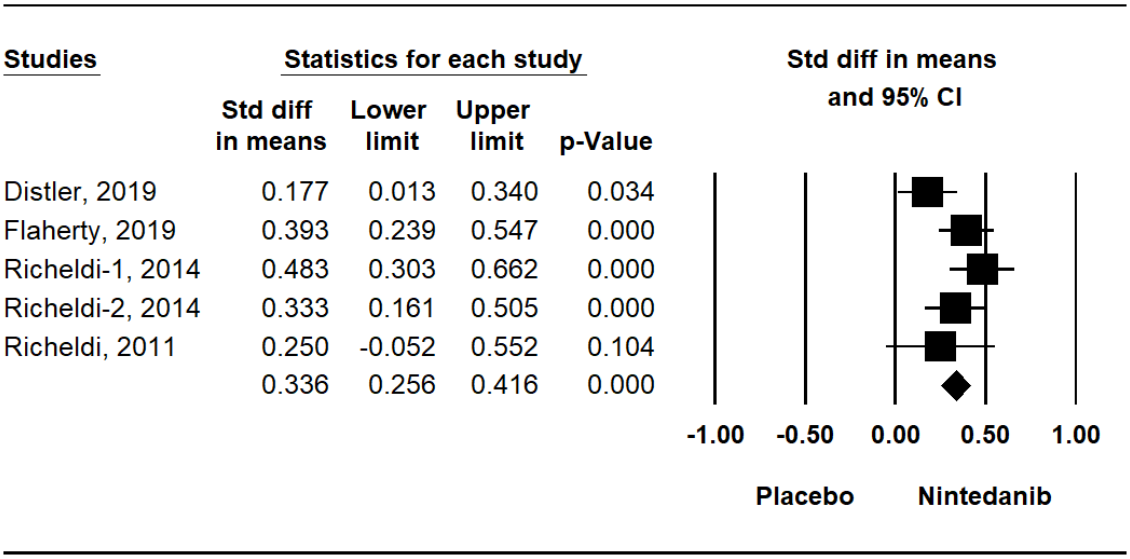


**Fig.2:** Meta-analysis of the effectiveness of nintedanib in patients with interstitial lung disease

Stratification by disease type showed a low annual rate of change in FVC in patients with SSc and those without SSc (SMD=0.389, 95% CI=0.294–0.478, *P*<0.001; SMD=0.177, 95% CI=0.013–0.340, *P*<0.00).

### *Meta-analysis of the safety of nintedanib for interstitial lung disease*

The incidence of SAEs was not different between the nintedanib and placebo groups (OR=1.010, 95% CI=0.847–1.205, *P*=0.911) (Table 2). However, AEs and withdrawals due to AEs were significantly higher in the nintedanib group than in the placebo group (SMD=2.365, 95% CI=1.673–3.343, *P*<0.001; SMD=1.740, 95% CI=1.385–2.185, *P*<0.00) (Table 2).

### *Heterogeneity and publication bias*

Between-study heterogeneity was not found in the meta-analysis (Table 2). It was difficult to correlate the funnel plot, as the number of studies included in the analysis was small. However, no evidence of publication bias was found (Egger's regression test, *P*>0.1).

## Discussion

We conducted a systematic evaluation of the clinical efficacy and safety profile of nintedanib in patients with ILD with or without SSc. The pooled findings showed that nintedanib therapy substantially slowed the decrease in FVC, which is consistent with a delay in disease progression. Regarding the safety profile, the incidence of AEs was increased in the nintedanib group; however, the frequency of SAEs in the nintedanib group was comparable to that seen in the placebo group.

The yearly rate of decrease in FVC was substantially lower in patients with ILD with or without SSc who received nintedanib than in those who received placebo. Occurrence of immune dysregulation, microvascular damage, and organ fibrosis characterizes SSc as a heterogeneous autoimmune disease (4). ILD is a frequent symptom of SSc and a main cause of mortality in patients with SSc (4). The rate of decrease in FVC was lower with nintedanib than with placebo in patients with ILD with SSc. In patients with ILD with SSc, the nintedanib treatment group significantly outperformed the placebo therapy group in terms of improvement in the yearly rate of decrease in FVC. However, there is only one study involving the SSc-ILD group. Nintedanib, independent of connective tissue disorders, may be helpful in reducing FVC decrease in patients with ILD. This assumption, however, should be validated

by RCT trials in various connective tissue disorders.

The current research has several limitations that should be examined. First, the number of included RCTs was restricted. Furthermore, the trials were not intended to assess the long-term efficacy and safety of nintedanib; the trial observation period was brief. Hence, the long-term safety and mortality effects of nintedanib are unknown. Therefore, further follow-up studies are required. Second, because there was only one study on patients with SSc-ILD, the findings of this meta-analysis may not reflect the clinical efficacy of nintedanib in patients with other connective tissue disorders (such as ILD). Nonetheless, the strength of the present study is that it is the first meta-analysis to include studies of patients with ILD and SSc-ILD. It provides additional insights into the efficacy and safety profile of nintedanib in patients with ILD (19-21). To minimize potential confounding variables, we only included high-quality placebo-controlled RCTs.

## Conclusion

Nintedanib treatment was effective in reducing the rate of decrease in FVC in patients with ILD, regardless of SSc. However, compared with the placebo, nintedanib increased the incidence of AEs and withdrawals due to AEs, despite being safe without causing any SAEs. Long-term efficacy and safety have yet to be proven. Nonetheless, nintedanib provides therapeutic advantages for patients with ILD with or without SSc. Long-term studies are required to properly evaluate the efficacy and safety of nintedanibin in patients with ILD having connective tissue disorders.

## Journalism Ethical considerations

The authors have wholly observed ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.)

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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