07/05/2026 01:25

Nintedanib in rheumatoid arthritis related interstitial lung disease: real-world safety profile and risk of side effects and discontinuation

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Key Indexing Terms: rheumatoid arthritis, interstitial lung disease, nintedanib, safety
The source(s) of support in the form of grants or industrial support: the study received no financial support

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Conflict of interest: MS and AM received fees for consultancy from Boehringer-Ingheleim

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Statement of ethics and consent: the study was submitted to the local ethical committee and the authors gave their consent for the publication of the paper

Abstract

Objectives. Some concerns remain about the safety of nintedanib in patients with interstitial lung disease (ILD) related to rheumatoid arthritis (RA-ILD), such as in presence of comorbidities or in combination with biologic, targeted synthetic and/or conventional synthetic disease modifying antirheumatic drugs (DMARDs).

In this multicentre study, we retrospectively evaluated the safety of nintedanib in a real-world population of RA-ILD patients from Italian GISEA registry and the possible role of comorbidities and DMARDs on drug safety and withdrawal. Secondary aim was to investigate the causes of nintedanib discontinuation.

Methods. Sixty-five patients treated with nintedanib according to the current therapeutic indications were enrolled in the study. Nintedanib was prescribed in combination with DMARDs and/or steroids in 62 patients (95.4%).

Results. Twelve-month retention rate of nintedanib was 76.7% and the drug was effective on about 80% of patients with at least 6 months of follow-up. Adverse events were recorded in 36 subjects (55.3%), mainly gastroenteric. Thirty-one subjects required a reduction of the nintedanib dose; among them, a transient or permanent reduction of the daily dose of nintedanib allowed to continue the treatment in 22, while 15 (23.1%) withdrew the drug, in all cases for treatment-related adverse events. Comorbidities were significantly associated to side effects at multivariate analysis, while adverse events of nintedanib were the main cause of discontinuation.

Conclusion. Combination therapy with DMARDs didn't reduce safety and effectiveness of nintedanib, while adverse events were the main cause of drug withdrawal or reduction of the dose of drug, mainly due to comorbidities.

Word count: 2375

Keywords: rheumatoid arthritis, interstitial lung disease, nintedanib, pulmonary progressive fibrosis, safety, combination therapy, comorbidity

Key messages

- A combination therapy with DMARDs does not affect safety and effectiveness of nintedanib on rheumatoid arthritis patients
- Comorbidities are associated to an increased frequency of side effects in rheumatoid arthritis patients treated with nintedanib
- Side effects are the main cause of discontinuation of nintedanib in patients with rheumatoid arthritis related interstitial lung disease

Introduction

Interstitial lung disease (ILD) is a severe extra-articular manifestation of rheumatoid arthritis (RA), significantly compromising quality of life and survival (1). A pulmonary progressive fibrosis (PPF) (2) has been described in about a third of RA-ILD patients (3) and it has been associated to a worse prognosis and survival (4). In these patients, nintedanib demonstrated to be effective on reducing the progression of lung damage in a randomized controlled trial including more than 650 patients (5, 6), including 89 with a diagnosis of RA (7). Nevertheless, some concerns remain about the safety of nintedanib in real-life (8, 9), when the drug is prescribed in patients with comorbidities or in combination with biologic (b-), targeted synthetic (ts-) and/or conventional synthetic (cs) disease modifying antirheumatic drugs (DMARDs). The only available study, investigating safety and retention rate of antifibrotic drugs, namely nintedanib and pirfenidone, reported adverse events in 55% of patients, mainly referred to the gastroenteric tract (8,10). In this study, the initial antifibrotic drug was discontinued in 46% of patients (11).

Aim of this multicentre Italian study was to evaluate the safety of nintedanib in a real-world population of RA-ILD patients. Secondary aim was to investigate the possible role of comorbidities and concurrent therapies in the occurrence of adverse events and drug discontinuation.

Patients and methods

The GISEA registry (12) enrols patients affected by RA according to the 1987 or 2010 American College of Rheumatology (ACR) classification criteria (13). Data evaluated for the study included age, gender, disease duration, clinical and laboratory parameters, extra-articular RA manifestations, and use of oral corticosteroids, conventional synthetic (namely methotrexate, leflunomide, and sulfasalazine; hydroxychloroquine was not collected), biologic, and targeted synthetic-DMARDs.

All consecutive RA-ILD patients enrolled in the GISEA registry and treated with nintedanib for a PPF, according to the current therapeutic indications, were included in the study. For each patient, demographic, clinical, serological, and therapeutic parameters were retrospectively collected at the

moment of nintedanib initiation, every six months and at the last follow-up (last available data or when nintedanib was discontinued). According to the Charlson Comorbidity Index, comorbidities were also recorded, focusing on cardiovascular diseases, previous major acute cardiovascular events, and diabetes (14). Adverse events occurred during the follow-up were carefully reported, namely nausea, vomiting, diarrhoea, abdominal pain, liver disfunction, cardiovascular events.

Lung function tests (LFTs), namely percentage of predicted forced vital capacity (FVC) and percentage of predicted single breath diffusion lung of carbon monoxide (DLCO), were recorded every six months. Finally, baseline images of high-resolution computed tomography (HRCT) were centrally re-evaluated for each patient. According to the Fleischner Society White Paper (15) the HRCT pattern of disease was recorded as definite, probable usual interstitial pneumonia (UIP), or indeterminate for UIP. If an indeterminate pattern for UIP was noted, it was furtherly classified as nonspecific interstitial pneumonia (NSIP), or other patterns (2,16).

According to the inclusion criteria of the INBUILD trial and current prescription criteria for nintedanib, patients were defined as having a progressive ILD in presence of a relative decline in FVC≥10% or a relative decline in FVC≥5%, associated to an increased extent of fibrotic changes in chest imaging over a 24-month period or a worsening of respiratory symptoms, namely cough or dyspnoea, associated to an increased extent of fibrotic changes at HRCT or a relative decline in FVC≥5%.

The study was approved by the local ethical committee and all participants provided written informed consent.

Continuous variables were reported as median and interquartile range (IQR), while categorical variables were reported as absolute numbers and percentages. Categorical variables were analysed via Fisher's exact test, and differences between the medians were determined using Mann–Whitney test for unpaired samples. Clinical features were reported as dichotomic or ordinal parameters. Drug retention was explored by Kaplan-Meier analysis. Then, a Cox multivariate analysis was performed to analyse the effect of features at patient baseline regarding drug discontinuation or the appearance

of side effects. Analyses were made using the Statistic for Data Analysis software (IBM SPSS statistic, version 29, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant (17).

Results

Sixty-five patients were enrolled in this multicentre Italian study and followed for a median time of 35.7 weeks (IQR 26.1-72.3). Males were 50.8%, and the median age was 71 years (IQR 66-75) at the enrolment. Median RA duration was 7 years (IQR 6-17), while median ILD duration was 3 years (IQR 1-12). Anti-citrullinated protein antibodies (ACPA) and rheumatoid factor were detected in 75.4% and 78.5%, respectively; positivity of both ACPA and rheumatoid factor was recorded in 64.6% of cases, while patients with a seronegative RA were seven (10.8%). Antinuclear antibodies were positive in 41.5% of cases. Cardiovascular comorbidities, including diabetes and previous deep venous thrombosis, were reported in 75.4% of cases; smokers were 43%. Finally, more than 90% of patients showed respiratory symptoms, namely exertional or rest dyspnoea in 90.8% and cough in 47.7%.

A probable or definite UIP pattern were described in 80% of cases, a fibrotic NSIP in 16.9%, while the radiologic ILD pattern was not classifiable in 3.1% of subjects.

Nintedanib was prescribed at the standard dose of 150 mg twice daily in all patients. The drug was prescribed in combination with a b- or ts-DMARD in 38 patients (58.5%), namely abatacept in 21 (32.3%), rituximab in 7 (10.8%), Janus kinases inhibitors in 5 (7.7%), IL-6 antagonists in 3 (4.6%), and tumour necrosis factor inhibitors in 2 (3.1%). Methotrexate was prescribed in 23 patients, in 11 of them in combination with a b-/ts-DMARD, while leflunomide was administered in only 3 cases. Fifty-two subjects (80%) were taking corticosteroids, that were the only treatment in 11 patients (except for combination therapy with hydroxychloroquine, not collected in our study). Finally, nintedanib was not associated to any DMARD in 3 subjects.

Adverse events related to the therapy were recorded in 36/65 subjects (55.3%), and in 33/36 they appeared in the first six months of treatment. Among them, diarrhoea was reported in 61.1% of cases, nausea and/or epigastric pain in 30.5%, liver function abnormalities in 11.1%, and other side effects in 13.9% of cases. Some patients experienced more than one side-effect. Globally, a reduction in the dose of nintedanib (100 mg twice daily) was requested in 31 subjects (44.6%); among them, a transient or permanent reduction of the daily dose of nintedanib allowed to continue the treatment in 22 (33.8%). As consequence of this reduction in some patients, the daily mean dose of nintedanib was 259.2±56.5 mg after six month and 236.7±61.5 mg after twelve months of treatment.

At univariate analysis, side effects of nintedanib were significantly associated to the presence of one or more comorbidities (table 1). On the contrary, the presence of ACPA and/or rheumatoid factor and a concurrent treatment with a b-/ts-DMARD, regardless of methotrexate, reduced the appearance of adverse events. Finally, the value of DLCO was directly correlated with appearance of side effects. Multivariate Cox regression analysis confirmed that seropositivity for both ACPA and rheumatoid factor and comorbidities, mainly cardiovascular and diabetes, were associated to adverse events, with an odds ratio of 0.19 (95%CI 0.43-0.84; p=0.03) and 10.54 (95%CI 1.65-67.47; p=0.01), respectively; a slight association was confirmed also for DLCO, with an odds ratio of 1.09 (95%CI 1.02-1.16; p=0.02) (table 1).

Twelve-month retention rate of nintedanib was 76.7% (standard error 6.5%) (figure 1). Overall, discontinuation of nintedanib was reported in 15/65 patients (23.1%); ten of them withdrew the drug during the first six months, other two within the first year, and 3/15 discontinued the drug late during the follow-up, after one year of treatment. In all cases, discontinuation was due to adverse events related to the treatment, mainly diarrhoea. Neither deaths nor acute exacerbations were reported during the follow-up.

Many parameters were associated to the drug discontinuation (table 2). In particular, the appearance of side effects within 6 months of treatment significantly increased the risk of drug discontinuation (OR 18.36, CI95% 2.40-140.22, p< 0.01). Moreover, the risk to withdraw nintedanib increased

according to the age of ILD diagnosis (OR 1.09, CI95% 1.01-1.17; p=0.02) and the age of first nintedanib administration (OR 1.09, CI95% 1.01-1.18; p=0.03). On the contrary, an ongoing treatment with a b- or ts-DMARD, regardless a combination therapy with cs-DMARDs or steroids, was a protective factor for nintedanib discontinuation (OR 0.54, 95% CI 0.30-0.96; p=0.04), as well as a previous or concurrent treatment with abatacept (OR 0.15, CI95% 0.03-0.70; p=0.01). Finally, the baseline value of DLCO was associated to nintedanib discontinuation (OR 1.07, CI95% 1.02-1.12; p<0.01).

At multivariate Cox regression analysis, in a model including DLCO at baseline, 6-month side effects, combination therapy with a b- or ts-DMARD, and the age at ILD diagnosis and at beginning of the treatment with nintedanib, only the presence of 6-month side effects was confirmed to be significantly associated to the drug discontinuation (OR 11.17; CI95% 1.24-100.31; p= 0.03).

Finally, the effect on lung function was available for 51 patients maintaining the treatment with nintedanib for at least 6 months (among them, 30 patients had an evaluation after 12 months, too). Lung function was stable in 30 subjects, improved in 11 (relative improvement of FVC ≥10% or relative improvement of FVC ≥ 5% and improvement of symptoms) and worsened in 10 cases.

Discussion

The INBUILD trial demonstrated the efficacy of nintedanib in the treatment of PPF (5), but this study didn't allow to answer to some issues, frequently observed in clinical practice. In fact, safety issues related to comorbidities and a combination therapy with b- or ts-, and/or cs-DMARDs, were poorly addressed in the INBUILD trial (5). In this study, only 21.3% of RA patients were taking b-DMARDs and 53.9% cs-DMARDs, mainly hydroxychloroquine, a relatively small percentage when compared with clinical practice (5,7). In our study, almost 60% of subjects were treated with a b- or ts-DMARD (combined to a cs-DMARD in 34.2% of cases) and only 3/65 patients received monotherapy with nintedanib. In patients with RA-ILD, the possibility of a combination therapy with DMARDs and nintedanib would be crucial for a holistic therapeutic approach to the disease (18). Our data suggest

not only that a combination therapy with a DMARD doesn't reduce the safety of nintedanib, but it might improve the retention rate of this antifibrotic drug. It remains unclear if this result derives from a synergistic effect of the drugs on lung involvement or from a better control of RA-related joint disease. In the last years, some DMARDs, mainly abatacept and JAK inhibitors, have been showed to be potentially effective on RA-related lung disease, even in UIP pattern of ILD (19-21), but no specific studies investigated the effect of combination therapies, including DMARDs and nintedanib, compared to nintedanib alone, on the progression of lung disease. The tolerability of nintedanib is quite low, mainly due to the gastrointestinal side effects of the drug (22), reported by more than 40% of patients. Physician should provide a careful information about these possible adverse events together with nutritional support to all the patients before the beginning of the treatment, in the attempt of improving the awareness of these possible symptoms. In the INBUILD study (5), about a third of patients reduced the dose of nintedanib leading to a permanent dose reduction of the drug, and 19.6% discontinued the drug for adverse events, mainly gastroenteric (11); in the subgroup of RA patients, just 23.8% of subjects discontinued nintedanib, a percentage very close to that observed in our real-life Italian cohort (7). In fact, during the all-follow-up period, 23.1% of patients withdrew nintedanib for side effects or scarce tolerance to the drug and 44.6% of the whole cohort reduced the dose of the drug, in many cases being able to reintroduce the full dosage in a second moment. Of interest, a transient increase of liver enzymes was observed in only 4 patients during the follow-up, without the need to discontinue the treatment (both nintedanib and DMARD) in any case. Moreover, our data confirmed that in many cases the reduction of the dose of nintedanib could allow to continue the treatment; sometimes, the full dose could be recovered without a reiteration of side effects.

In our study, comorbidities represent the main factor associated to side effects with an odd ratio of 10.54, despite they didn't directly affect the risk of drug withdrawal. Therefore, in patients with comorbidities, including patients with polytherapy, a careful monitoring should be ensured to reduce the risk of adverse events.

Finally, a slight increase of side effects has been associated to DLCO at baseline, therefore patients with a better DLCO reported side effects more frequently. This apparent paradox is not fully explainable; we can only suppose that compromised patients were less prone to report side effects. On the other hand, considering also the retrospective design of the study, in this group of patients the physicians might have been less careful in asking about side effects. Only larger studies could confirm and better explain this possible association.

Although the evaluation of effectiveness was not an aim of this study, the drug allowed a good satisfactory clinical response, being effective on about 80% of patients with a 12 month-retention rate of 76.7%.

In our population, 16.9% of the whole cohort were treated with corticosteroids alone (or in combination with hydroxychloroquine), reflecting the difficulty, in a real-life setting, in the treatment of RA-ILD patients, also in consideration of the lack of dedicated therapeutic recommendations (1,18,19). In one study, abatacept in combination with methotrexate provided a greater glucocorticoid-sparing effect compared with abatacept monotherapy in RA-ILD patients (23). In our population, only few patients were treated with a combination therapy including abatacept and methotrexate, therefore we cannot evaluate a role of this combination therapy as corticosteroid-sparing. However, our study demonstrates that b- and ts-DMARDs don't affect safety and persistency in therapy of nintedanib, allowing a more effective treatment also in RA-ILD patients, possibly reducing the use of corticosteroids and their long-term side effects.

In conclusion, in this multicentre Italian study, nintedanib confirmed, in a real-world setting, a safety profile very similar to that observed in the INBUILD trial (2). In particular, a combination therapy with DMARDs was safe and didn't affect the long-term retention rate of the drug. An adequate control of comorbidities and the prevention of diarrhoea and gastrointestinal side effects with dietary supplementation and anti-diarrhoeic could reduce adverse events and improve the retention rate of the drug.

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Conflict of interest statement: no authors report conflicts of interest

Data availability statement: data are available if requested from the authors

Table 1. Association between demographic, clinical and serological parameters and adverse events in RA-ILD patients treated with nintedanib

Patients showing adverse events: 36 (44.6%)

	Univariate analysis			Multivariate analysis		
Parameter	**OR**	**95%IC**	**p**	**OR**	**95%IC**	**p**
Male sex	1.36	0.51-3.61	0.54			
Smoke	1.67	0.60-4.60	0.3			
ACPA	0.19	0.48-0.74	**0.02**	0.49	0.09-2.53	0.39
Rheumatoid factor	0.14	0.28-0.67	**0.01**	0.19	0.26-1.35	0.09
ACPA+rheumatoid factor	0.13	0.04-0.45	**<0.01**	0.19	0.04-0.84	**0.03**
Antinuclear antibodies	1.12	0.42-3.03	0.82			
Bone erosions	0.46	0.17-1.26	0.46			
DAS28 at baseline	0.90	0.63-1.27	0.55			
Ever abatacept	0.39	0.14-1.07	0.68			
Ever methotrexate	0.41	0.14-1.19	0.10			
Ever TNFi	0.41	0.13-1.32	0.14			
Ever IL6i	0.68	0.20-2.30	0.53			
Ever rituximab	0.47	0.10-2.15	0.33			
Ever JAKi	0.26	0.61-1.08	0.06			
ILD preceding RA	0.92	0.47-1.80	0.81			
FVC baseline	1.02	0.99-1.06	0.15			
DLCO baseline	1.05	1.00-1.11	**0.04**	1.09	1.01-1.16	**0.02**
Dyspnoea	0.21	0.02-1.88	0.16			
Cough	1.08	0.41-2.87	0.88			
Ongoing methotrexate	1.56	0.55-4.37	0.40			
Ongoing steroids	0.67	0.19-2.34	0.53			
Age RA diagnosis	1.03	0.98-1.09	0.24			
Age ILD diagnosis	1.06	0.99-1.14	0.08			
DMARDs*±methotrexate	0.31	0.11-0.87	**0.03**	0.26	0.58-1.14	0.07
Age at nintedanib start	1.06	0.98-1.14	0.17			
Radiologic UIP pattern	2.25	0.61-8.23	0.22			
Comorbidities	3.47	1.04-11.57	**0.04**	10.54	1.65-67.47	**0.01**

RA: rheumatoid arthritis; ILD: interstitial lung disease; OR: odds ratio; 95%CI: 95% confidence interval; ACPA: anti-citrullinated protein antibodies; DAS28: disease activity index on 28 joints; TNFi: tumour necrosis factor inhibitors; IL6i: interleukin 6 inhibitors; JAKi: Janus kinases inhibitors; FVC: forced vital capacity; DLCO: diffusion lung on carbon monoxide; DMARD: disease modifying antirheumatic drugs; UIP: usual interstitial pneumonia; * including biologic and targeted synthetic DMARDs

Table 2. Association between demographic, clinical and serological parameters and discontinuation in RA-ILD patients treated with nintedanib

Patients discontinuing nintedanib: 15 (23.1%)

	Univariate			Multivariate		
Parameter	**OR**	**95%IC**	**p**	**OR**	**95%IC**	**p**
Male sex	1.29	0.46-3.64	0.63			
Smoke	0.92	0.33-2.56	0.87			
ACPA	0.40	0.14-1.14	0.08			
Rheumatoid factor	0.64	0.20-2.03	0.45			
ACPA+rheumatoid factor	0.69	0.41-1.15	0.16			
Antinuclear antibodies	0.48	0.15-1.52	0.21			
DAS28 at baseline	0.97	0.67-1.41	0.88			
Ever abatacept	0.15	0.03-0.70	0.01			
Ever methotrexate	1.26	0.41-3.80	0.69			
Ever TNFi	0.57	0.13-2.56	0.46			
Ever IL6i	0.58	0.13-2.61	0.48			
Ever rituximab	0.38	0.05-2.91	0.35			
Ever JAKi	0.26	0.03-1.99	0.19			
ILD preceding RA	0.43	0.16-1.7	0.10			
FVC baseline	1.01	0.98-1.05	0.40			
DLCO baseline	1.07	1.02-1.12	**<0.01**	1.05	0.99-1.10	0.08
Dyspnoea	2.24	0.29-17.35	0.44			
Cough	0.80	0.28-2.26	0.68			
Ongoing methotrexate	2.19	0.74-6.48	0.16			
Ongoing steroids	0.57	0.20-1.69	0.31			
Side effects 6 months	18.36	2.40-140.22	**<0.01**	11.17	1.24-100.31	**0.03**
Age RA diagnosis	1.03	0.98-1.10	0.25			
Age ILD diagnosis	1.09	1.01-1.17	**0.02**	0.99	0.80-1.21	0.90
DMARDs*±methotrexate	0.54	0.30-0.96	**0.04**	0.55	0.14-2.21	0.40
Age at nintedanib start	1.09	1.01-1.18	**0.03**	1.09	0.90-1.32	0.38
Radiologic UIP pattern	1.56	0.43-5.68	0.50			
Comorbidities	1.53	0.43-5.44	0.51			

RA: rheumatoid arthritis; ILD: interstitial lung disease; OR: odds ratio; 95%CI: 95% confidence interval; ACPA: anti-citrullinated protein antibodies; DAS28: disease activity index on 28 joints; TNFi: tumour necrosis factor inhibitors; IL6i: interleukin 6 inhibitors; JAKi: Janus kinases inhibitors; FVC: forced vital capacity; DLCO: diffusion lung on carbon monoxide; DMARD: biologic disease modifying antirheumatic drugs; UIP: usual interstitial pneumonia; * including biologic and targeted synthetic DMARDs

Figure 1. Retention rate of nintedanib in RA-ILD patients