Safety and tolerability of nintedanib in patients with interstitial lung diseases in subgroups by sex: a post-hoc analysis of pooled data from four randomised controlled trials

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Summary

Background Nintedanib is a tyrosine kinase inhibitor used in the treatment of progressive fibrosing interstitial lung diseases (ILDs). We assessed the safety and tolerability of nintedanib in patients with autoimmune disease-related ILDs and with other ILDs in subgroups by sex.

Methods In this post-hoc analysis, we pooled data from the two INPULSIS trials in patients with idiopathic pulmonary fibrosis (IPF), the SENSCIS trial in patients with fibrosing ILDs associated with systemic sclerosis, and the INBUILD trial in patients with progressive fibrosing ILDs other than IPF. In each trial, patients were randomly assigned to receive oral nintedanib 150 mg twice daily or matched placebo. We assessed adverse events reported over 52 weeks in patients with autoimmune disease-related ILDs and other ILDs in subgroups by sex.

Findings In these analyses, we included 746 patients with autoimmune disease-related ILDs (523 [70%] were female, 223 [30%] were male; 615 [82%] had systemic sclerosis), of whom 370 (50%) received nintedanib (268 [72%] female and 102 [28%] male patients) and 376 (50%) received placebo (255 [68%] female and 121 [32%] male patients); and 1554 patients with other ILDs (437 [28%] female, 1117 [72%] male; 1061 [68%] with IPF), of whom 888 (57%) received nintedanib (237 [27%] female and 651 [73%] male patients) and 666 (43%) received placebo (200 [30%] female and 466 [70%] male patients). Of 102 male and 268 female patients with autoimmune disease-related ILDs treated with nintedanib, nausea was reported in 21 (21%) male and 92 (34%) female patients, vomiting in 12 (12%) male and 73 (27%) female patients, alanine aminotransferase increase in four (4%) male and 31 (12%) female patients, aspartate aminotransferase increase in three (3%) male and 23 (9%) female patients, and adverse events leading to dose reduction in 18 (18%) male and 101 (38%) female patients; 28 (27%) male and 107 (40%) female patients had at least one treatment interruption. Of 651 male and 237 female nintedanib-treated patients with other ILDs, nausea was reported in 135 (21%) male and 95 (40%) female patients, vomiting in 51 (8%) male and 70 (30%) female patients, alanine aminotransferase increase in 19 (3%) male and 31 (13%) female patients, aspartate aminotransferase increase in 17 (3%) male and 26 (11%) female patients, and adverse events leading to dose reduction in 106 (16%) male and 84 (35%) female patients; 155 (24%) male and 82 (35%) female patients had at least one treatment interruption. The proportions of patients with adverse events leading to discontinuation of nintedanib were similar between female and male patients with autoimmune disease-related ILDs (44 [16%] of 268 *vs* 17 [17%] of 102), but were greater among female than male patients with other ILDs (62 [26%] of 237 *vs* 112 [17%] of 651). Across subgroups by diagnosis and sex, diarrhoea was the most frequent adverse event associated with nintedanib (autoimmune-related ILDs: 198 [74%] of 268 female and 73 [72%] of 102 male patients; other ILDs: 155 [65%] of 237 female and 408 [63%] of 651 male patients), and was the event that most frequently led to treatment discontinuation (autoimmune-related ILDs: 20 [7%] female and five [5%] male patients; other ILDs: 16 [7%] female and 27 [4%] male patients).

Interpretation The adverse event profile of nintedanib was generally similar between male and female patients with autoimmune disease-related ILDs, and between male and female patients with other ILDs, but nausea, vomiting, liver enzyme elevations, dose reductions, and treatment interruptions were more frequent in female patients than in male patients. Sex should be considered in the monitoring and management of adverse events that might be associated with nintedanib.

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Introduction

Interstitial lung disease (ILD) can develop as a manifestation of systemic autoimmune diseases including systemic sclerosis,[1] rheumatoid arthritis,[2] idiopathic inflammatory myositis,[3] and mixed connective tissue disease.[4] Although autoimmune diseases are more common in women than men, ILD has been shown to be more common in male than female patients with

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Research in context

Evidence before this study

Before this study, data on the safety and tolerability of nintedanib versus placebo in patients with interstitial lung diseases (ILDs) were available from individual clinical trials, but the adverse event profile of nintedanib in subgroups by sex had not been analysed.

Added value of this study

Our findings add to the understanding of the safety and tolerability of nintedanib in male and female patients with autoimmune disease-related ILDs and with other ILDs. In both diagnostic groups, similar types of adverse event were reported in patients of both sexes, but nausea, vomiting, hepatic adverse events, and dose reductions and treatment interruptions used to manage adverse events, were more frequent in female patients than in male patients, while serious adverse events were more common in male patients than in female patients.

Implications of all the available evidence

Sex should be considered in patient education and in the monitoring and management of adverse events that might be associated with nintedanib.

systemic sclerosis or rheumatoid arthritis.[5,6] The most common ILD, idiopathic pulmonary fibrosis (IPF), is more common in men than women.[7] Studies in patients with various ILDs have found male sex to be associated with more severe ILDs than female sex, as indicated by increased lung function impairment and increased risk of mortality.[7,8]

Nintedanib is a tyrosine kinase inhibitor that inhibits processes fundamental to the progression of pulmonary fibrosis.[9] Nintedanib has been licensed for the treatment of fibrosing systemic sclerosis-associated ILD, IPF, and other chronic fibrosing ILDs with a progressive phenotype. Randomised placebo-controlled trials have found that nintedanib reduced the rate of decline in forced vital capacity (FVC) in patients with these ILDs, with no evidence of heterogeneity in its treatment effect across diagnostic groups.[10–15] Across trials, the adverse event profile of nintedanib in patients with ILDs was characterised mainly by gastrointestinal adverse events, particularly diarrhoea.[10–12,16–18]

In patients with autoimmune-related lung disease, sex might affect pathobiological processes, clinical manifestations, and responses to therapy.[19] The safety profile of a drug might show important differences between the sexes because of factors such as a smaller body size and differences in hormonal milieu.[20] Clinical trials provide an excellent opportunity to investigate differences in the adverse event profile of a drug between the sexes because a standardised methodology is used for data collection. We used pooled data from clinical trials to assess the safety and tolerability of nintedanib in patients with autoimmune disease-related ILDs and in patients with other ILDs in subgroups by sex.

Methods

Study design and participants

In this post-hoc analysis, we pooled data from the two INPULSIS trials in patients with IPF,[10] the SENSCIS trial in patients with fibrosing systemic sclerosis-associated ILD,[11] and the INBUILD trial in patients with progressive fibrosing ILDs other than IPF.[12] The pooled data from patients with autoimmune disease-related ILDs comprised data from all patients in the SENSCIS trial and from the subgroup of patients with autoimmune disease-related ILDs in the INBUILD trial. The pooled data from patients with ILDs not related to autoimmune disease came from all patients in the INPULSIS trials and patients with ILDs other than those related to autoimmune diseases in the INBUILD trial. The designs of these trials have been described and the protocols are publicly available.[10–12] All studies were randomised placebo-controlled phase 3 trials.

All the trials were conducted in accordance with their protocols, the principles of the Declaration of Helsinki, and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation and received ethical approval by local authorities. Written informed consent was obtained from all participants before study entry.

Procedures

In all the trials, patients were randomly assigned (3:2 in the INPULSIS trials and 1:1 in the SENSCIS and INBUILD trials) to receive nintedanib or placebo. All trials were of double-blind design, such that patients and investigators were masked to participant treatment assignment. The success of masking was not assessed.

Participants were randomised to receive either oral nintedanib 150 mg twice daily or matched placebo for at least 52 weeks. Treatment interruptions (for ≤4 weeks for adverse events considered related to trial medication or ≤8 weeks for other adverse events) and dose reductions to 100 mg twice daily were recommended to manage adverse events. After resolution of the adverse event, nintedanib could be reintroduced or the dose increased back to 150 mg twice daily. Specific recommendations were provided to the investigators for the management of diarrhoea and hepatic enzyme elevations.[16–18] Adverse events were reported throughout the trials by the investigators irrespective of cause and coded according to preferred terms in the Medical Dictionary for Regulatory Activities (version 23.0). The severity of diarrhoea was graded using the Common Terminology Criteria for Adverse Events (version 4).

Outcomes

In this post-hoc analysis, we assessed adverse events reported over 52 weeks in patients with autoimmune disease-related ILDs and in patients with non-autoimmune disease-related ILDs (hereafter referred to as other ILDs) in subgroups by sex. Data on sex were collected in case report forms; data on gender were not collected.

Statistical analyses

Analyses were descriptive and based on patients who received at least one dose of trial drug. The INPULSIS trials are registered with ClinicalTrials.gov, NCT01335464 and NCT01335477, the SENSCIS trial is registered with ClinicalTrials.gov, NCT02597933, and the INBUILD trial is registered with ClinicalTrials.gov, NCT02999178.

Role of the funding source

The funder participated in the study design, data collection, data analysis, data interpretation, writing of the report, and decision to submit for publication.

Results

In the INPULSIS trials, 841 (79%) of 1061 treated patients were male and 220 (21%) were female, of whom 180 (21%) male patients and 56 (25%) female patients discontinued trial medication before week 52. In the SENSCIS trial, 143 (25%) of 576 treated patients were male and 433 (75%) were female, of whom 17 (12%) male patients and 70 (16%) female patients discontinued trial medication before week 52. And in the INBUILD trial, 356 (54%) of 663 treated patients were male and 307 (46%) were female, of whom 69 (19%) male patients and 60 (20%) female patients discontinued trial medication before week 52.

The pooled dataset of patients with autoimmune disease-related ILDs comprised 746 patients, of whom 523 (70%) were female and 223 (30%) were male (table 1). 615 (82%) patients in this group had systemic sclerosis-associated ILD (appendix p 2). In this group, female patients had a lower mean bodyweight, lower FVC (mL), and greater % predicted mean diffusing capacity of the lungs for carbon monoxide (DLCO), and a smaller proportion were taking corticosteroids than male patients in the diagnostic group (table 1). The pooled dataset of patients with other ILDs comprised 1554 patients, of whom 437 (28%) were female and 1117 (72%) were male (table 1). 1061 (68%) patients in this group had IPF (appendix p 2). Female patients in this group had a lower mean bodyweight and lower FVC (mL) than did male patients, and a higher proportion were taking corticosteroids (table 1). The patients with autoimmune disease-related ILDs were generally younger, had lower BMI, lower % predicted FVC, higher % predicted DLCO (in female patients), and were more likely to be taking corticosteroids (in male patients) than the patients with other ILDs (table 1).

Among the patients with autoimmune disease-related ILDs, median exposure to trial drug was 12·2 months (minimum–maximum: 0·0–12·2) in the nintedanib group and 12·2 months (0·4–12·2) in the placebo group in male patients and 12·2 months (0·0–12·2) in the nintedanib group and 12·2 months (0·3, 12·2) in the placebo group in female patients (regardless of whether the dose of nintedanib was reduced or not). Among the patients with

	Autoimmune disease-related ILDs				Non-autoimmune disease-related ILDs			
	Female		Male		Female		Male	
	Nintedanib (n=268)	Placebo (n=255)	Nintedanib (n=102)	Placebo (n=121)	Nintedanib (n=237)	Placebo (n=200)	Nintedanib (n=651)	Placebo (n=466)
Age, years	55·9 (12·1)	54·5 (13·2)	58·0 (11·6)	59·6 (12·5)	66·0 (8·5)	66·5 (8·9)	66·6 (8·6)	67·0 (8·2)
Bodyweight, kg	66·3 (14·2)	67·5 (15·8)	79·0 (16·9)	78·7 (14·9)	71·7 (15·8)	69·2 (16·5)	81·8 (15·9)	82·3 (16·2)
BMI, kg/m²	26·0 (5·0)	26·4 (5·6)	26·5 (4·6)	26·1 (4·3)	28·8 (5·5)	28·0 (6·1)	28·0 (4·3)	28·0 (4·5)
Race								
White	178 (66%)	163 (64%)	76 (75%)	85 (70%)	155 (65%)	141 (71%)	394 (61%)	291 (62%)
Asian	66 (25%)	73 (29%)	21 (21%)	33 (27%)	68 (29%)	46 (23%)	184 (28%)	137 (29%)
Black or African-American	20 (7%)	16 (6%)	3 (3%)	1 (1%)	1 (<1%)	4 (2%)	3 (<1%)	0
Other*	3 (1%)	3 (1%)	1 (1%)	0	0	0	0	0
Missing	0	0	0	0	13 (5%)	9 (5%)	69 (11%)	38 (8%)
Time since diagnosis of ILD, years	3·1 (2·8)	2·8 (2·3)	2·8 (2·2)	3·1 (2·9)	2·7 (3·1)	3·1 (3·2)	1·9 (1·9)	2·1 (2·4)
FVC, mL	2190 (560)	2241 (605)	3030 (793)	3046 (851)	1901 (472)	1859 (484)	2872 (691)	2880 (728)
FVC, % predicted	72·0 (16·6)	73·6 (16·5)	71·2 (16·2)	70·4 (15·2)	76·7 (20·0)	74·5 (19·7)	76·5 (17·2)	75·6 (17·2)
DLCO, % predicted†	52·9 (15·5)	54·7 (14·9)	46·4 (12·8)	48·4 (15·3)	46·2 (14·8)	47·5 (15·8)	46·6 (12·3)	46·7 (12·8)
Taking corticosteroids‡	149 (56%)	122 (48%)	64 (63%)	80 (66%)	133 (56%)	99 (50%)	231 (35%)	173 (37%)

Data are mean (SD) or n (%) of patients. Not all patients provided data for all variables. DLCO=diffusing capacity of the lungs for carbon monoxide. FVC=forced vital capacity. ILD=interstitial lung disease. *Includes American Indian, Alaska Native, Native Hawaiian, and other Pacific Islander; in the INPULSIS trials, patients who were American Indian or Alaska Native were considered to be Asian. †Corrected for haemoglobin. ‡WHO standardised drug grouping.

Table 1: **Baseline characteristics in subgroups by sex**

other ILDs, median exposure to trial drug (regardless of whether the dose of nintedanib was reduced or not) was 11·9 months (minimum–maximum: 0·0–12·5) in the nintedanib group and 11·9 months (0·0–13·1) in the placebo group in male patients and 11·9 months (0·0–12·7) in the nintedanib group and 12·1 months (0·2–12·8) in the placebo group in female patients.

Among the patients with autoimmune disease-related ILDs, the adverse event profile of nintedanib was generally similar between male and female patients, but nausea, vomiting, and liver enzyme elevations were more frequent in female than male patients (table 2). Similar observations were made in the patients with other ILDs (table 2). The adverse event profile of nintedanib was generally similar between patients with autoimmune disease-related ILDs and other ILDs, but diarrhoea and skin ulcers were more common in patients with autoimmune disease-related ILDs than in those with other ILDs (both in the nintedanib and placebo groups and in both sexes). In both sexes, approximately half of the patients with autoimmune disease-related ILDs who had diarrhoea reported their first event within 31 days (inclusive) after starting treatment (appendix pp 3–4). In this patient group, only a small proportion of the diarrhoea adverse events were reported to be of severe intensity (appendix pp 3–4).

Among the patients with autoimmune disease-related ILDs, serious adverse events were more frequent in male than in female patients in both the nintedanib and placebo groups (table 2). This difference was not observed among the patients with other ILDs (table 2). The most frequent serious adverse events were related to respiratory events or infections (appendix p 5).

	Autoimmune disease-related ILDs				Non-autoimmune disease-related ILDs			
	Female		Male		Female		Male	
	Nintedanib (n=268)	Placebo (n=255)	Nintedanib (n=102)	Placebo (n=121)	Nintedanib (n=237)	Placebo (n=200)	Nintedanib (n=651)	Placebo (n=466)
Any adverse event	264 (99%)	240 (94%)	98 (96%)	115 (95%)	229 (97%)	180 (90%)	618 (95%)	416 (89%)
Most frequent adverse events*								
Diarrhoea	198 (74%)	77 (30%)	73 (72%)	38 (31%)	155 (65%)	48 (24%)	408 (63%)	85 (18%)
Nausea	92 (34%)	35 (14%)	21 (21%)	14 (12%)	95 (40%)	20 (10%)	135 (21%)	29 (6%)
Nasopharyngitis	34 (13%)	41 (16%)	12 (12%)	21 (17%)	26 (11%)	19 (10%)	96 (15%)	76 (16%)
Cough	23 (9%)	39 (15%)	13 (13%)	19 (16%)	33 (14%)	35 (18%)	83 (13%)	60 (13%)
Vomiting	73 (27%)	22 (9%)	12 (12%)	14 (12%)	70 (30%)	8 (4%)	51 (8%)	13 (3%)
Bronchitis	18 (7%)	28 (11%)	11 (11%)	9 (7%)	28 (12%)	32 (16%)	68 (10%)	47 (10%)
Dyspnoea	14 (5%)	20 (8%)	13 (13%)	16 (13%)	16 (7%)	30 (15%)	63 (10%)	52 (11%)
Upper respiratory tract infection	30 (11%)	31 (12%)	9 (9%)	8 (7%)	15 (6%)	16 (8%)	61 (9%)	41 (9%)
Decreased appetite	29 (11%)	9 (4%)	13 (13%)	4 (3%)	34 (14%)	7 (4%)	67 (10%)	33 (7%)
Bodyweight decreased	34 (13%)	8 (3%)	10 (10%)	6 (5%)	27 (11%)	10 (5%)	69 (11%)	15 (3%)
Fatigue	27 (10%)	15 (6%)	9 (9%)	8 (7%)	22 (9%)	19 (10%)	46 (7%)	31 (7%)
Headache	30 (11%)	21 (8%)	4 (4%)	7 (6%)	27 (11%)	20 (10%)	43 (7%)	19 (4%)
Abdominal pain	32 (12%)	18 (7%)	8 (8%)	5 (4%)	28 (12%)	5 (3%)	55 (8%)	11 (2%)
Back pain	18 (7%)	10 (4%)	2 (2%)	5 (4%)	20 (8%)	21 (11%)	32 (5%)	23 (5%)
Progression of IPF†	0	0	0	0	12 (5%)	12 (6%)	52 (8%)	49 (11%)
Abdominal pain upper	25 (9%)	12 (5%)	5 (5%)	3 (2%)	26 (11%)	8 (4%)	35 (5%)	11 (2%)
Urinary tract infection	31 (12%)	25 (10%)	2 (2%)	0	21 (9%)	17 (9%)	11 (2%)	10 (2%)
Skin ulcer	42 (16%)	37 (15%)	12 (12%)	13 (11%)	1 (<1%)	0	2 (<1%)	1 (<1%)
Arthralgia	18 (7%)	12 (5%)	5 (5%)	13 (11%)	5 (2%)	12 (6%)	13 (2%)	23 (5%)
ALT increased	31 (12%)	6 (2%)	4 (4%)	0	31 (13%)	4 (2%)	19 (3%)	6 (1%)
AST increased	23 (9%)	4 (2%)	3 (3%)	1 (1%)	26 (11%)	3 (2%)	17 (3%)	6 (1%)
Hepatic adverse events‡	49 (18%)	11 (4%)	13 (13%)	6 (5%)	63 (27%)	8 (4%)	91 (14%)	18 (4%)
Elevation in ALT or AST, or both, of ≥3 × ULN	20 (7%)	1 (<1%)	2 (2%)	1 (1%)	34 (14%)	5 (3%)	26 (4%)	4 (1%)
Serious adverse events§	57 (21%)	53 (21%)	40 (39%)	37 (31%)	75 (32%)	63 (32%)	199 (31%)	147 (32%)
Fatal adverse events	3 (1%)	3 (1%)	5 (5%)	5 (4%)	10 (4%)	8 (4%)	35 (5%)	37 (8%)

Data are n (%) of patients with at least one such event reported over 52 weeks. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis. MedDRA=Medical Dictionary for Regulatory Activities. ULN=upper limit of the normal range. *Adverse events reported in >10% of female or male patients in the nintedanib or placebo groups of patients with autoimmune or non-autoimmune disease-related ILDs based on preferred terms in the MedDRA (version 23.0). †Based on the MedDRA (version 23.0) preferred term "idiopathic pulmonary fibrosis". ‡Based on the standardised MedDRA (version 23.0) query "liver related investigations, signs and symptoms" (broad definition). §Event that resulted in death, was life-threatening, resulted in hospitalisation or prolonged hospitalisation, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed serious for any other reason.

Table 2: **Adverse events and elevations in hepatic enzymes over 52 weeks, in subgroups by sex**

Adverse events led to reduction of the dose of nintedanib more frequently in female than male patients, both in those with autoimmune disease-related ILDs and in those with other ILDs (table 3). Nintedanib treatment interruptions were also more common in female than male patients in both diagnostic groups (table 4). The proportion of patients with adverse events leading to permanent discontinuation of nintedanib was similar between male and female patients with autoimmune disease-related ILDs, but greater in female than male patients with other ILDs (table 5). Diarrhoea was the adverse event that most frequently led to dose reduction and permanent discontinuation of nintedanib in both sexes and both diagnostic groups (tables 3, 5). Diarrhoea led to permanent discontinuation of nintedanib in 20 (7%) of 268 female patients and five (5%) of 102 male patients with autoimmune disease-related ILDs and 16 (7%) of 237 female patients and 27 (4%) of 651 male patients with other ILDs.

In both patients with autoimmune disease-related ILDs and patients with other ILDs, hepatic adverse events associated with nintedanib therapy, including elevations in alanine aminotransferase or aspartate aminotransferase, or both, of at least 3 times the upper limit of the normal range, were more common in female than male patients (table 2).

Among the patients with autoimmune disease-related ILDs, bleeding adverse events were more frequent in male than in female patients in both treatment groups, but these events were more common in female than in male patients in patients with other ILDs (appendix p 6).

	Autoimmune disease-related ILDs				Non-autoimmune disease-related ILDs			
	Female		Male		Female		Male	
	Nintedanib (n=268)	Placebo (n=255)	Nintedanib (n=102)	Placebo (n=121)	Nintedanib (n=237)	Placebo (n=200)	Nintedanib (n=651)	Placebo (n=466)
Any adverse event leading to dose reduction	101 (38%)	9 (4%)	18 (18%)	3 (2%)	84 (35%)	9 (5%)	106 (16%)	5 (1%)
Most frequent adverse events leading to dose reduction*								
Diarrhoea	59 (22%)	3 (1%)	11 (11%)	0	42 (18%)	1 (1%)	73 (11%)	2 (<1%)
Nausea	8 (3%)	1 (<1%)	1 (1%)	0	14 (6%)	0	5 (1%)	1 (<1%)
ALT increased	9 (3%)	0	1 (1%)	0	10 (4%)	2 (1%)	3 (<1%)	0
Vomiting	7 (3%)	0	0	0	13 (5%)	2 (1%)	1 (<1%)	1 (<1%)
AST increased	5 (2%)	0	1 (1%)	0	6 (3%)	1 (1%)	4 (1%)	0
Decreased appetite	3 (1%)	0	2 (2%)	1 (1%)	3 (1%)	1 (1%)	5 (1%)	1 (<1%)
Bodyweight decreased	4 (1%)	0	1 (1%)	0	3 (1%)	1 (1%)	5 (1%)	1 (<1%)
Abdominal pain upper	2 (1%)	1 (<1%)	0	0	4 (2%)	0	0	0
Hepatic enzyme increased	3 (1%)	0	0	1 (1%)	1 (<1%)	0	1 (<1%)	0
GGT increased	2 (1%)	0	0	0	3 (1%)	0	1 (<1%)	0

Data are n (%) of patients with at least one such event reported over 52 weeks. Only permanent dose reductions were considered for the SENSCIS and INPULSIS trials; all dose reductions were considered for the INBUILD trial. ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=gamma-glutamyltransferase. ILD=interstitial lung disease. MedDRA= Medical Dictionary for Regulatory Activities. *Adverse events leading to dose reduction in >1% of female or male patients in the nintedanib or placebo groups of patients with autoimmune or non-autoimmune disease-related ILDs based on preferred terms in the MedDRA (version 23.0).

Table 3. **Adverse events leading to dose reduction over 52 weeks in subgroups by sex**

	Autoimmune disease-related ILDs				Non-autoimmune disease-related ILDs			
	Female		Male		Female		Male	
	Nintedanib (n=268)	Placebo (n=255)	Nintedanib (n=102)	Placebo (n=121)	Nintedanib (n=237)	Placebo (n=200)	Nintedanib (n=651)	Placebo (n=466)
Patients with ≥1 treatment interruption	107 (40%)	28 (11%)	28 (27%)	14 (12%)	82 (35%)	18 (9%)	155 (24%)	47 (10%)
Number of treatment interruptions per patient								
1	73 (27%)	18 (7%)	20 (20%)	14 (12%)	53 (22%)	13 (7%)	114 (18%)	44 (9%)
2	21 (8%)	3 (1%)	6 (6%)	0	24 (10%)	5 (3%)	31 (5%)	3 (1%)
>2	13 (5%)	7 (3%)	2 (2%)	0	5 (2%)	0	10 (2%)	0
Total duration of treatment interruptions, days	23·5 (17·6)	21·2 (21·1)	19·1 (13·8)	16·4 (16·8)	24·4 (18·3)	23·6 (14·1)	24·6 (18·8)	22·6 (15·3)

Data are n (%) of patients or mean (SD). ILD=interstitial lung disease.

Table 4: **Treatment interruptions over 52 weeks, in subgroups by sex**

	Autoimmune disease-related ILDs				Non-autoimmune disease-related ILDs			
	Female		Male		Female		Male	
	Nintedanib (n=268)	Placebo (n=255)	Nintedanib (n=102)	Placebo (n=121)	Nintedanib (n=237)	Placebo (n=200)	Nintedanib (n=651)	Placebo (n=466)
Any adverse event leading to treatment discontinuation	44 (16%)	21 (8%)	17 (17%)	13 (11%)	62 (26%)	23 (12%)	112 (17%)	57 (12%)
Most frequent adverse events leading to treatment discontinuation*								
Diarrhoea	20 (7%)	1 (<1%)	5 (5%)	1 (1%)	16 (7%)	1 (1%)	27 (4%)	0
Progression of IPF†	0	0	0	0	1 (<1%)	4 (2%)	12 (2%)	17 (4%)
Nausea	6 (2%)	0	0	1 (1%)	8 (3%)	0	6 (1%)	0
Progression of ILD‡	3 (1%)	1 (<1%)	0	2 (2%)	0	6 (3%)	2 (<1%)	4 (1%)
Vomiting	4 (1%)	0	0	1 (1%)	6 (3%)	0	2 (<1%)	0
ALT increased	4 (1%)	0	1 (1%)	0	4 (2%)	0	3 (<1%)	1 (<1%)
Decreased appetite	0	0	0	0	2 (1%)	0	8 (1%)	2 (<1%)
Bodyweight decreased	1 (<1%)	0	0	0	4 (2%)	0	3 (<1%)	2 (<1%)
Abdominal pain upper	3 (1%)	1 (<1%)	0	0	1 (<1%)	1 (1%)	2 (<1%)	1 (<1%)
Abdominal pain	0	0	0	1 (1%)	5 (2%)	0	1 (<1%)	1 (<1%)
Drug-induced liver injury	1 (<1%)	1 (<1%)	0	0	3 (1%)	0	3 (<1%)	0
AST increased	1 (<1%)	0	1 (1%)	0	4 (2%)	0	1 (<1%)	1 (<1%)
Liver injury	1 (<1%)	0	0	0	4 (2%)	1 (1%)	0	0
Dyspnoea	0	0	0	2 (2%)	0	0	0	1 (<1%)

Data are n (%) of patients with at least one such event reported over 52 weeks. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis. MedDRA=Medical Dictionary for Regulatory Activities. *Adverse events leading to treatment discontinuation in >1% of female or male patients in the nintedanib or placebo groups of patients with autoimmune or non-autoimmune disease-related ILDs based on preferred terms in the MedDRA (version 23.0). †Based on the MedDRA (version 23.0) preferred term "idiopathic pulmonary fibrosis". ‡Based on the MedDRA (version 23.0) preferred term "interstitial lung disease".

Table 5: **Adverse events leading to treatment discontinuation over 52 weeks, in subgroups by sex**

The proportion of patients with cardiovascular adverse events was low and appeared to be similar between the sexes (appendix p 7).

Discussion

This post-hoc analysis of data from 2300 patients with ILDs treated with nintedanib or placebo for approximately 1 year enabled us to compare the safety and tolerability profile of nintedanib in male and female patients in the context of a clinical trial. Diarrhoea, the most common adverse event associated with nintedanib, was reported in similar proportions of male and female patients, and was infrequently severe, but was the main reason for discontinuation of nintedanib in both sexes. Nausea, vomiting, and liver enzyme elevations were more frequent in female than in male patients, but infrequently led to discontinuation of treatment. Dose reductions and treatment interruptions were more common in female than in male patients. Interestingly, permanent discontinuations of nintedanib occurred in similar proportions of male and female patients with autoimmune disease-related ILDs, but in a greater proportion of female than male patients with other ILDs. Previous studies have found adherence to other treatments to be lower in female than in male patients with autoimmune diseases[21,22] and that female patients with IPF are more likely than male patients to discontinue antifibrotic treatment.[23,24] We found serious adverse events were more frequent in male than female patients with autoimmune disease-related ILDs in both the nintedanib and placebo groups. Previous studies have also found a worse course of disease in male patients than female patients with ILDs.[1,7,8]

Based on pharmacokinetic studies in patients with IPF, age, bodyweight, smoking, and Asian race influence nintedanib exposure, within the range of interpatient variability.[25,26] Further analyses of data from patients with various ILDs showed a positive association between nintedanib exposure and the risk of liver enzyme elevations.[27] Female sex was also an exposure-independent risk factor for increases in liver enzyme concentrations (after correcting for covariates including bodyweight).[27] Consistent with these observations, and with the lower bodyweight of female patients than male patients in our dataset, hepatic adverse events were more frequent in female patients than in male patients treated with nintedanib. Previous analyses of data from the SENSCIS and INBUILD trials found that increased hepatic enzyme concentrations were more common in Asian patients than in White patients,[17,18] suggesting that the highest risk might occur in female Asian patients of low bodyweight. Liver function tests should be done before initiation of nintedanib, regularly during the first 3 months of treatment, and periodically thereafter, and the nintedanib dose reduced, interrupted, or discontinued if needed.[17,18]

Although some patient characteristics are associated with an increased risk of some adverse events associated with nintedanib, prediction of which patients will experience adverse events, or the severity of these events if they do occur, is not possible. Analyses of the rate of decline in FVC in patients who did and did not reduce dose or interrupt treatment with nintedanib in clinical trials suggest that the dose adjustments used to manage adverse events did not have a meaningful effect on the efficacy of nintedanib.[17,18] However, this observation should not be misinterpreted as indicating that patients should be started or maintained on a lower dose than 150 mg twice daily. A phase 2 dose-finding study found that 150 mg twice daily is the optimal dose of nintedanib for reducing the rate of decline in FVC,[28] and no other starting doses were investigated in phase 3 trials. Thus, other than in patients with mild hepatic impairment, nintedanib should be initiated at 150 twice daily.

The safety profile of nintedanib in patients with autoimmune disease-related ILDs was generally similar to that observed in patients with ILDs of other causes. However, in both the nintedanib and placebo groups and in both sexes, diarrhoea was more common in patients with autoimmune disease-related ILDs than other ILDs. This was expected because autoimmune diseases such as systemic sclerosis are commonly associated with gastrointestinal problems, including diarrhoea,[29] and some other treatments for autoimmune diseases have gastrointestinal side-effects.[30] In the SENSCIS trial in patients with systemic sclerosis-associated ILD, the adverse event profile of nintedanib, including the proportion of patients with diarrhoea, was similar between patients who were and were not taking mycophenolate at baseline, with no increase in treatment discontinuations in patients taking both drugs.[31] We found that skin ulcers were more common in patients with autoimmune disease-related ILDs than in patients with other ILDs. This was as expected because 615 (82%) of 746 patients with autoimmune disease-related ILDs had systemic sclerosis, which is frequently associated with skin ulcers.[1]

Strengths of our analyses include the large dataset, obtained from 2300 patients with rare diseases, and the standardisation of data collection in the settings of four clinical trials. Our analyses also have several limitations. The group of patients with autoimmune disease-related ILDs was dominated by patients with systemic sclerosis-associated ILD, whereas most patients with other ILDs had IPF; thus, these populations cannot be considered representative of patients with autoimmune disease-related ILDs and non-autoimmune disease-related ILDs. The analyses were based on data from only 1 year of treatment and the trials differed in the co-medications that were allowed and used. Among patients with non-autoimmune disease-related ILDs in our dataset, corticosteroid use was less frequent in male patients than in female patients, reflecting lower use of corticosteroids in patients with IPF (a male-dominated group) than in patients with other ILDs. The use of anti-diarrhoeal and anti-emetic medications in the subgroups by sex and diagnosis has not been analysed, and these medications might have had an effect on the observed adverse events, dose adjustments, and discontinuations. In our analyses, we did not adjust for differences in bodyweight between male and female patients, which might have had an effect on the results. The small number of patients who had individual diagnoses, or who were taking specific concomitant therapies, did not permit these subgroups to be analysed separately. Differences based on small numbers of events should be interpreted with caution.

Education of patients about the adverse events that might be associated with nintedanib, and the effective management of adverse events when they occur, using symptomatic therapy, dose adjustment, and treatment interruption, is important to minimise the effect of adverse events and help patients remain on treatment. Patient education and monitoring should be part of care for all patients prescribed nintedanib, but these data suggest that particular attention should be given to patients who are female or of low bodyweight, or both. Previous analyses of data from clinical trials in patients with IPF suggest that particular attention should also be given to patients aged 75 years and older, who are more likely to discontinue nintedanib therapy.[32] Qualitative research has indicated that patients are able to make trade-offs between attributes of treatments for ILD, including the risk of particular types of adverse events, highlighting the importance of keeping patients informed and involved in discussions about their treatment.[33]

In summary, both in patients with autoimmune-disease related ILDs and with other ILDs, the safety and tolerability profile of nintedanib was similar between male and female patients, but nausea, vomiting, and hepatic adverse events, and dose reductions and treatment interruptions, were more frequent in female patients than in male patients, whereas serious adverse events were more common in male patients. Sex should be considered in patient education and in the monitoring and management of adverse events that might be associated with nintedanib.

Contributors

A-MH-V, MK, and OD contributed to conceptualisation of the analysis. IT contributed to data curation and analysis. All authors contributed to interpretation of the data and in the writing and critical review of the manuscript. A-MH-V, IT, LL, and OD had access to and verified the underlying study data. All authors had access to data and final responsibility for the decision to submit for publication. The authors did not receive payment for the development of this Article. The authors were not precluded from accessing data and accept responsibility for submission for publication.

Declaration of interests

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Data sharing

Information on data sharing is provided in the appendix (p 8).

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