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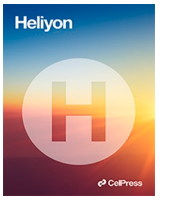

Case report

Nintedanib in chronic fibrosing interstitial lung diseases. A case series

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ABSTRACT

Progressive pulmonary fibrosis (PPF) can be fatal in non-idiopathic interstitial lung diseases. We report a descriptive series of 13 patients with PPF who received treatment with nintedanib, a multitargeted tyrosine kinase inhibitor with antifibrotic effect. Although the reduced number of patients and the observational nature of a case series prevent us from providing strong evidence, our results suggest that nintedanib could be effective in PPF of various etiologies. Nintedanib could also be useful in specific populations such as patients awaiting lung transplant and elderly patients.

1. Introduction

Non-idiopathic interstitial lung diseases (ILDs) are a group of heterogeneous chronic pulmonary disorders. They can be related to primary diseases such as sarcoidosis, environmental exposure such as pneumoconiosis due to inhalation of inorganic particles, exposure to products such as illicit drugs or irradiation, and autoimmune diseases such as rheumatoid arthritis (RA) or primary Sjögren's disease [1]. More than 30% of patients with non-idiopathic ILDs develop progressive pulmonary fibrosis (PPF), which can be fatal [2]. All ILDs share common pathogenic pathways [3,4] and have a similar clinical presentation, with PPF, worsening respiratory symptoms, and decline in pulmonary function, accompanied by loss of quality of life [3,4]. The 2022 guidelines of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Asociación Latinoamericana de Tórax (ALAT) define PPF based on up to three criteria: worsening respiratory symptoms and physiological evidence and/or radiological evidence of disease progression within the previous year. At least two criteria should be present, and there should be no other explanation for the disorder [5].

First-line treatment of fibrosis in PPF was traditionally with corticosteroids (CS) [2], although antifibrotic drugs have been used in recent years [6]. Nintedanib is the only recommended antifibrotic therapy for PPF-ILDs in the 2022 ATS/ERS/JRS/ALAT guidelines [6]. Another antifibrotic drug, pirfenidone, has been studied in PPFs [7], although evidence on its efficacy is not as consistent as for nintedanib, and more research is needed [6]. Here, we report a descriptive series of 13 patients with PPF-ILD who received treatment with nintedanib.

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Table 1
Summary of clinical records of 13 patients with non-idiopathic progressive pulmonary fibrosis treated with nintedanib.

Patient #	**1**			**2**		
Age, y/sex	61/F			42/M		
Diagnosis	Seropositive RA (2005) + PPF			Fibrotic pattern, indeterminate for UIP		
Chest HRCT pattern	UIP with exuberant honeycombing progression			Fibrotic NSIP with progression of reticulation, traction bronchiectasis, and signs of acute exacerbation		
Previous treatments	RTX + CYC (12 cycles), then TCL			CS + RTX		
Ongoing therapy	–			CS and RTX		
Antifibrotic treatment	NTD			NTD as bridge therapy to lung transplant		
Lung function	*12 months before initiation*	*At initiation*	*After initiation*[d]	*12 months before initiation*	*At initiation*	*After initiation*[d]
FVC % predicted	68	68	80	42	48	50
FVC (ml)	1550	1530	1760	1710	1930	2020
FEV1 % predicted	57	62	78	44	49	50
FEV1 (ml)	1080	1160	1400	1480	1660	1690
FEV1/FVC	70	76	79	87	85	84
D_{LCO} %[a]	29	21	30	30	24	29
Adverse events[b]	No			No		
Outcome and current status	Clinical and radiological improvement before dying of COVID-19 in January 2021			Bilateral transplant in June 2019 owing to progressive worsening. Alive, no NTD.		
Patient #	**3**			**4**		
Age, y/sex	48/M			82/F		
Diagnosis	Unclassifiable			Exacerbated hypersensitivity pneumonitis		
Chest HRCT pattern	Vast reticulation with traction bronchiectasis predominantly in upper lobes and unclassifiable septal thickening			Suspicion of hypersensitivity pneumonitis with fibrosis progression, signs of acute exacerbation and progressive air entrapment		
Previous treatments	CS			CS		
Ongoing therapy	–			CS boluses		
Antifibrotic treatment	NTD			NTD		
Lung function	*12 months before initiation*	*At initiation*	*After initiation*[d]	*12 months before initiation*	*At initiation*[c]	*After initiation*[d]
FVC % predicted	49	51	50	80	–	82
FVC (ml)	1850	2040	1940	1130	–	1230
FEV1 % predicted	57	52	50	95	–	96
FEV1 (ml)	2210	1690	1620	1040	–	1041
FEV1/FVC	84	83	100	92	–	112
D_{LCO} %[a]	44	30	30	40	–	31
Adverse events[b]	No			No		
Outcome and current status	Bilateral transplant in June 2022 owing to progressive worsening. Alive, no NTD.			Died of COVID-19 pneumonia.		
Patient #	**5**			**6**		
Age, y/sex	62/M			72/F		
Diagnosis	Fibrotic NSIP in progression			Sarcoidosis		
Chest HRCT pattern	Fibrotic NSIP			Bilateral and diffuse lung involvement predominantly in upper lobes, with reticulation and areas of ground-glass opacity, air entrapment, and traction bronchiectasis, suggestive of sarcoidosis		
Previous treatments	CS + CYC			CS - MTX		
Ongoing therapy	–			–		
Antifibrotic treatment	Bilateral transplant in June 2020 owing to progressive worsening. Alive, no NTD.			NTD		
Lung function	*12 months before initiation*	*At initiation*	*After initiation*[d]	*12 months before initiation*	*At initiation*	*After initiation*[d]
FVC % predicted	57	44	50	67	79	78
FVC (ml)	2350	1770	2000	1580	1880	2030
FEV1 % predicted	60	47	52	60	66	69
FEV1 (ml)	1940	1460	1500	1170	1290	1370
FEV1/FVC	82	83	75	74	69	67
D_{LCO} %[a]	45	30	–	46	40	42
Adverse events[b]	No			No		
Outcome and current status	Alive, no NTD after lung transplant.			Treated with NTD and stable.		
Patient #	**7**			**8**		
Age, y/sex	75/F			84/F		
Diagnosis	Seropositive RA + PPF			Sarcoidosis		
Chest HRCT pattern	UIP in a patient with RA			Suggestive of sarcoidosis in fibrotic stage		
Previous treatments	TCZ + low-dose CS			CS		
Ongoing therapy	–			–		
Antifibrotic treatment	NTD			NTD		
Lung function	*12 months before initiation*	*At initiation*[c]	*After initiation*[d]	*12 months before initiation*	*At initiation*	*After initiation*[d]
FVC % predicted	81	–	82	75	55	70

(*continued on next page*)

Table 1 (*continued*)

Patient #	**7**			**8**		
FVC (ml)	1550	–	1700	990	940	900
FEV1 % predicted	92	–	90	94	54	92
FEV1 (ml)	1430	–	1500	800	710	750
FEV1/FVC	92	–	88	80	75	83
D_{LCO} %[a]	69	–	70	23	–	20
Adverse events[b]	Diarrhea			Diarrhea		
Outcome and current status	NTD dose was reduced to 100 mg/12 h and diarrhea was controlled. Patient weight 49 kg. Currently stable, treated with NTD 100 mg/12 h.			NTD dose was reduced to 100 mg/12 h and diarrhea was controlled. Patient height 1.50 m and weight 45 kg. Currently stable, treated with NTD 100 mg/12 h.		
Patient #	**9**			**10**		
Age, y/sex	80/M			79/F		
Diagnosis	Antisynthetase syndrome with anti-Jo-1			Sarcoidosis		
Chest HRCT pattern	Fibrotic NSIP			Sarcoidosis		
Previous treatments	CS + RTX			CS + MTX		
Ongoing therapy	RTX + immunoglobulins			–		
Antifibrotic treatment	NTD			NTD		
Lung function	*12 months before initiation*	*At initiation*[c]	*After initiation*[d]	*12 months initiation*	*At initiation*	*After initiation*[d]
FVC % predicted	71	–	95	79	63	55
FVC (ml)	2150	–	2780	1280	1020	880
FEV1 % predicted	71	–	95	80	66	53
FEV1 (ml)	1510	–	2040	1020	840	660
FEV1/FVC	70	–	74	80	83	76
D_{LCO} %[a]	49	–	61	41	45	33
Adverse events[b]	No			Liver toxicity		
Outcome and current status	Treated with NTD, with clinical and radiological improvement and radiological stability.			NTD was discontinued after 3 months of therapy because of severe liver toxicity. Antifibrotic therapy was rejected by the patient; clinical, functional, and radiological progression with CS + MMF therapy.		
Patient #	**11**			**12**		
Age, y/sex	69/F			68/F		
Diagnosis	IPAF with fibrotic NSIP			Idiopathic NSIP		
Chest HRCT pattern	Fibrotic NSIP			Fibrotic NSIP		
Previous treatments	CS + MMF			CS + CYC		
Ongoing therapy	–			–		
Antifibrotic treatment	NTD			NTD		
Lung function	*12 months before initiation*	*At initiation*	*After initiation*[d]	*12 months before initiation*	*At initiation*[c]	*After initiation*[d]
FVC % predicted	67	44	44	41	–	41
FVC (ml)	1620	1210	1470	790	–	810
FEV1 % predicted	74	70	61	37	–	42
FEV1 (ml)	1470	1300	1310	590	–	680
FEV1/FVC	92	105	89	74	–	85
D_{LCO} %	37	30	35	28	–	30
Adverse events[b]	No			Liver toxicity		
Outcome and current status	Treated with NTD and stable.			NTD was suspended because of liver toxicity. Then, after normalization of liver function, NTD was initiated at 100 mg/12 h. Pending new follow-up to assess NTD dose increase.		

Patient #	**13**		
Age, y/sex	70/F		
Diagnosis	Seropositive RA		
Chest HRCT pattern	UIP		
Previous treatments	CS		
Ongoing therapy	MTX + RTX		
Antifibrotic treatment	NTD		
Lung function	*12 months before initiation*	*At initiation*[c]	*After initiation*[d]
FVC % predicted	79	–	80
FVC (ml)	2000	–	2020
FEV1 % predicted	80	–	82
FEV1 (ml)	1500	–	1600
FEV1/FVC	75	–	79
D_{LCO} %[a]	50	–	48
Adverse events[b]	8 kg weight loss		
Outcome and current status	NTD dose was reduced to 100 mg/12 h. Pending new control to assess NTD dose increase.		

CS, corticosteroids; CYC, cyclophosphamide; D_{LCO}, diffusing capacity of the lungs for carbon monoxide; F, female; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; h, hour; HRCT, high-resolution computed tomography; IPAF, interstitial pneumonia with autoimmune features; M, male; MMF, mycophenolate mofetil; MTX, methotrexate; NSIP, non-specific interstitial pneumonia; NTD, nintedanib; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; RTX, rituximab; TCL, tacrolimus; TCZ, tocilizumab; UIP, usual interstitial pneumonia.

[a] Some D_{LCO}% data not available.
[b] Only nintedanib-related adverse events as per physician's criteria.
[c] Lung function tests not performed.
[d] 12 months after initiation. For patients #2, 3, 5, 10, and 12, lung function tests were performed at 4, 8, 5, 4, and 9 months, respectively. For patient #9, these tests were performed after almost 13 months of nintedanib therapy.

2. Case presentations

The case series include nine women and four men aged between 45 and 86 years from a single center. All medical procedures were performed in accordance with the Declaration of Helsinki. The diagnoses were sarcoidosis (n = 3), seropositive RA (n = 3), idiopathic non-specific interstitial pneumonia (NSIP) (n = 2), interstitial pneumonia with autoimmune features (n = 1), fibrotic pattern indeterminate for usual interstitial pneumonia (UIP) (n = 1), hypersensitivity pneumonitis (n = 1), unclassifiable disease (n = 1), and antisynthetase syndrome (n = 1). Some patients had two or more autoimmune diseases, including patient #8, who had psoriasis, primary biliary cirrhosis, and hypothyroidism, in addition to advanced sarcoidosis, and patient #9, who presented with myasthenia gravis and was subsequently diagnosed with antisynthetase syndrome with anti-Jo-1 and hypogammaglobinemia.

All PPFs were consistent with the criteria specified in the 2022 ATS/ERS/JRS/ALAT guidelines [6]. A well-established multidisciplinary committee comprising pulmonologists, radiologists, rheumatologists, pathologists, and pharmacists assessed the underlying diseases causing PPF.

Nintedanib was initiated after failure of CS and immunosuppressants (see Table 1 for details). Chest high-resolution computed tomography (HRCT) suggested NSIP (n = 5), UIP (n = 3), sarcoidosis (n = 3), and hypersensitivity pneumonitis (n = 1). HRCT findings in patient #3 were unclassifiable. Five patients (#1, 2, 3, 4 and 5) had signs of radiological progression, and two patients (#2 and 4) showed signs of acute exacerbation before treatment with nintedanib. Patients underwent lung function tests before or at initiation of nintedanib. Five of the 13 patients underwent further lung function tests after a variable period of treatment with nintedanib, and eight patients underwent these tests at 12 months. Furthermore, all patients except three performed the 6-min walk test (6-MWT), with or without supplementary oxygen, either before or at initiation of nintedanib. All but one experienced oxygen desaturation. Four patients underwent a second 6-MWT after treatment with nintedanib and were found to have lower oxygen desaturation. As some patients were elderly, biopsy was not considered because of the risk-benefit balance of this test in older individuals.

All patients initially received nintedanib 150 mg/12 h. Thirteen patients had previously received CS, and six patients had been treated with immunosuppressants. Patient #9 had previously been treated with CS and pyridostigmine, as well as with rituximab and immunoglobulins (Table 1).

Nintedanib was generally safe and well tolerated. Two patients had diarrhea, and their nintedanib dose was reduced to 100 mg/12 h. In a further two patients (#10 and #12), nintedanib was discontinued because of severe liver toxicity, with AST and ALT $>5 \times$ ULN. Patient #10 recovered normal liver function, but she refused antifibrotic therapy and experienced clinical, functional, and radiological progression. After 1 month, liver function values returned to normal in patient #12, and nintedanib was reintroduced at 100 mg/12 h. Finally, patient #13 lost 8 kg of weight unexpectedly during the first six months of nintedanib treatment, and the dose was also reduced to 100 mg/12 h.

At the end of follow up, eight patients were still being treated with nintedanib. One was on a waiting list for lung transplant and the other seven patients were clinically, functionally, and/or radiologically stable. In a further two patients, who were also alive, nintedanib was administered as bridge therapy to lung transplant and was discontinued after surgery. In the patient with severe liver toxicity who did not re-initiate nintedanib, clinical status worsened. Two patients died of COVID-19 complications.

Table 1 shows detailed data on each of the 13 patients.

3. Discussion

This case series shows the heterogeneity of PPFs, as well as the potential benefit of nintedanib as antifibrotic therapy. While the 13 patients we report had PPF of different causes, sarcoidosis and RA were the most common. However, we were unable to report cases from patients with PPF associated with occupational, therapeutic, or recreative exposures or patients with ILD with cysts and/or airspace filling according to the 2022 guidelines [5]. Almost all patients had impaired lung function before receiving nintedanib. While patient #9 showed previous improved FVC, he experienced clinical and radiological worsening in the previous year that was consistent with PPF. Radiological progression after initiation of nintedanib was not assessed.

Nintedanib usually stabilized lung function. In addition, the improvement in patients #1 and #8 was better than expected in PPFs, even with antifibrotic therapy. We could speculate that this improvement was due to the previous anti-inflammatory treatment with CS, although this effect was not observed in other patients who had also received CS. Moreover, CS were the recommended first-line therapy for PPFs before the arrival of antifibrotics.

The tolerability and safety of nintedanib were acceptable. Adverse events were reported in five patients (39%), with most being mild and reversible. The dose of nintedanib was reduced to 100 mg/12 h in four patients because of adverse events, namely, diarrhea, significant weight loss, and severe liver toxicity. All four patients continue to receive nintedanib at a reduced dose. The only case of discontinuation involved a patient who developed severe liver toxicity and rejected further antifibrotic therapy.

Nintedanib is a multitargeted tyrosine kinase inhibitor that acts on key pathways leading to pulmonary fibrosis and inhibits key fibrotic processes [3,8]. Initially approved for the treatment of idiopathic pulmonary fibrosis (IPF), nintedanib was also subsequently approved by the United States Food and Drug Administration and the European Medicines Agency for the treatment of chronic

fibrosing ILDs other than IPF. Its use in PPFs was supported by the results of the phase-3 INBUILD clinical trial, an international, double-blind placebo-controlled clinical trial analyzing 663 patients with UIP or other chronic fibrosing ILDs. After 52 weeks, the rate of decline in forced vital capacity was significantly lower among the 332 patients treated with nintedanib (−80.8 mL/year) than in the 331 patients who received placebo (−187.8 mL/year). The difference of 107 mL/year in forced vital capacity was statistically significant ($p < 0.001$) [4]. After two years, nintedanib reduced the risk of events related to progression of ILD, with fewer patients whose ILD progressed and who died ($p = 0.0003$ compared with placebo) and fewer patients who experienced acute exacerbation and died ($p = 0.04$ compared with placebo) [9].

Given the strict inclusion and exclusion criteria in the INBUILD trial, patients such as those in this case series were poorly represented. Additionally, some of the patients had D_{LCO} or FVC levels below the threshold established in the clinical trial. Therefore, we provide new data on the use of nintedanib in a real-world population. Moreover, nintedanib was also used as a bridge to lung transplant in some cases, despite the absence of previous evidence, because patients who had 'Planned major surgical procedures' were excluded from the clinical trial. Finally, nintedanib was combined with other treatments, thus making it possible to obtain data not only on effectiveness, but also on safety.

More data will be provided by the INREAL (NCT04702893) and INCHANGE (NCT05151640) studies, two ongoing real-world evaluations of nintedanib in patients with PPF.

Our results are consistent with clinical trial data [9] and other real-world experiences in PPF associated with RA [10] or systemic sclerosis [11]. Nintedanib generally attenuated the progression of pulmonary fibrosis in patients with non-IPF and advanced lung function impairment, including patients awaiting lung transplant and elderly patients.

4. Conclusions

- Although the reduced number of patients and the observational nature of a case series preclude us from providing robust evidence, our results suggest that nintedanib could be effective in PPF of different etiologies in real-world clinical practice.
- Nintedanib could also be useful in special populations such as patients awaiting lung transplant and elderly patients.

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Ethical declaration and informed consent

This case series report was conducted in accordance with the principles contained in the Declaration of Helsinki and was approved by the Research Ethics Committee of Hospital General Universitario de Alicante (Ref. CEIm: 2023-053). The procedure for obtaining the informed consent and the plan for recruiting patients were appropriate according to the Ethics Committee.

Data availability statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, the authors grant all external authors access to clinical study data pertinent to the development of their publications. The datasets and analysis are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Raquel García Sevila: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Juan José Arenas Jiménez:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Paloma Vela Casasempere:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ester Nofuentes Pérez:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ignacio Gayá García-Manso:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] M. Wijsenbeek, V. Cottin, Spectrum of fibrotic lung diseases, N. Engl. J. Med. 383 (2020) 958–968, https://doi.org/10.1056/nejmra2005230.
[2] M. Wijsenbeek, M. Kreuter, A. Olson, A. Fischer, E. Bendstrup, C.D. Wells, C.P. Denton, B. Mounir, L. Zouad-Lejour, M. Quaresma, V. Cottin, Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management, Curr. Med. Res. Opin. 35 (2019) 2015–2024, https://doi.org/10.1080/03007995.2019.1647040/SUPPL_FILE/ICMO_A_1647040_SM2480.DOCX.
[3] L. Wollin, J.H.W. Distler, E.F. Redente, D.W.H. Riches, S. Stowasser, R. Schlenker-Herceg, T.M. Maher, M. Kolb, Potential of nintedanib in treatment of progressive fibrosing interstitial lung diseases, Eur. Respir. J. 54 (2019) 1900161, https://doi.org/10.1183/13993003.00161-2019.
[4] K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, K.K. Brown, Nintedanib in progressive fibrosing interstitial lung diseases, N. Engl. J. Med. 381 (2019) 1718–1727, https://doi.org/10.1056/NEJMOA1908681.
[5] G. Raghu, M. Remy-Jardin, L. Richeldi, C.C. Thomson, K.M. Antoniou, B.D. Bissell, D. Bouros, I. Buendia-Roldan, F. Caro, B. Crestani, T. Ewing, M. Ghazipura, D. D. Herman, L. Ho, S.M. Hon, T. Hossain, Y. Inoue, T. Johkoh, S. Jones, F. Kheir, Y.H. Khor, S.L. Knight, M. Kreuter, D.A. Lynch, M. Macrea, T.M. Maher, M. J. Mammen, F.J. Martinez, M. Molina-Molina, J. Morisset, J.L. Myers, A.G. Nicholson, A.L. Olson, A. Podolanczuk, V. Poletti, C.J. Ryerson, M. Selman, M. E. Strek, L.K. Troy, M. Wijsenbeek, K.C. Wilson, Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an Official ATS/ERS/JRS/ALAT clinical practice guideline, Am. J. Respir. Crit. Care Med. 205 (2022) E18–E47, https://doi.org/10.1164/rccm.202202-0399ST.
[6] C. Albera, G. Verri, F. Sciarrone, E. Sitia, M. Mangiapia, P. Solidoro, Progressive fibrosing interstitial lung diseases: a current perspective, Biomedicines 9 (2021) 1237, https://doi.org/10.3390/biomedicines9091237.
[7] J. Behr, A. Prasse, M. Kreuter, J. Johow, K.F. Rabe, F. Bonella, R. Bonnet, C. Grohe, M. Held, H. Wilkens, P. Hammerl, D. Koschel, S. Blaas, H. Wirtz, J.H. Ficker, W. Neumeister, N. Schönfeld, M. Claussen, N. Kneidinger, M. Frankenberger, S. Hummler, N. Kahn, S. Tello, J. Freise, T. Welte, P. Neuser, A. Günther, N. Schönfeld, C. Schade-Brittinger, B. Aminossadati, C. Nasemann, S. Yahiaoui, C. Dupuy Backofen, M. Hahmann, M. Wittenberg, F. Drakopanagiotakis, D. von der Beck, S. Ghofrani, S. Heinemann, E. Krauss, H. Rethorn, A. Koch, G. Leuschner, S. Matthes, C. Neurohr, T. Veit, K. Milger-Kneidinger, F. Herth, J. Benstz, T. Bahmer, H. Biller, B. Waschki, R.M. Apel, U. Costabel, E. Börner, T. Wessendorf, M. Arnrich, L. Ilie, A. Wald, H.J. Seyfarth, C. Reinhardt, A. Cinar, M. Vogler, S.M. Huhn, J. Richter, U. Neff, T.G. Blum, S. Vesenbeckh, C. Boch, H. Semper, A. Wilke, M. Pfeifer, A. Schweda, A. Krill, C. Lensch, F. Joa, B. Schröder, A. Plaßmeier, S. Baron, K.P. Froehling, Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial, Lancet Respir. Med. 9 (2021) 476–486, https://doi.org/10.1016/S2213-2600(20)30554-3.
[8] L. Wollin, E. Wex, A. Pautsch, G. Schnapp, K.E. Hostettler, S. Stowasser, M. Kolb, Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis, Eur. Respir. J. 45 (2015) 1434–1445, https://doi.org/10.1183/09031936.00174914.
[9] K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, Y. Inoue, L. Richeldi, S.L.F. Walsh, M. Kolb, D. Koschel, T. Moua, S. Stowasser, R.-G. Goeldner, R. Schlenker-Herceg, K.K. Brown, Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial, Eur. Respir. J. 59 (2021) 2004538, https://doi.org/10.1183/13993003.04538-2020.
[10] J. Narváez, V. Vicens-Zygmunt, J.J. Alegre, S. Herrera-Lara, J.M. Nolla, M. Molina-Molina, Nintedanib for the treatment of refractory progressive rheumatoid arthritis-related interstitial lung disease: a real-life case series, Rheumatology 59 (2020) 3983–3986, https://doi.org/10.1093/RHEUMATOLOGY/KEAA503.
[11] J. Bordas-Martinez, A.B. Llanos-González, R. Jodar-Masanes, V. Vicens-Zygmunt, G. Bermudo, P. Luburich, J. Dorca, M. Molina-Molina, G. Suarez-Cuartin, Experience with nintedanib in severe pulmonary fibrosis associated with systemic sclerosis: a case series, Open Respir. Arch 3 (2021) 100080, https://doi.org/10.1016/J.OPRESP.2020.100080.