European Review for Medical and Pharmacological Sciences 2021; 25: 6326-6332

Feasibility and safety of treatment switch from Pirfenidone to Nintedanib in patients with idiopathic pulmonary fibrosis: a real-world observational study

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Abstract. – OBJECTIVE: Idiopathic Pulmonary Fibrosis is a disease characterized by a devastating fibrosing process. Two anti-fibrotic agents, pirfenidone and nintedanib, have been found to alter the disease progression. In this study, we sought to determine whether switching treatment to nintedanib is feasible and safe in patients that had to discontinue treatment with pirfenidone due to side effects.

PATIENTS AND METHODS: We analyzed patients that had to discontinue pirfenidone due to side effects. Patients were prospectively enrolled for treatment with nintedanib between March 2015 and June 2019. Side effects and Pulmonary Function Tests were recorded.

RESULTS: 12 patients received nintedanib after discontinuing treatment with pirfenidone. Side-effects that led to discontinuation were diarrhea (33.3%), nausea (16.6%), photosensitivity (33.3%) and difficulty adhering to pirfenidone's dosage scheme (16.6%). After the initiation of nintedanib, diarrhea was the most common side effect (66.6%). Four patients of these patients could not tolerate the full dose of 300 mg daily and had to reduce it to 200 mg daily. No patient has had experienced liver damage. During the last twelve months of treatment with pirfenidone, mean ΔFCV was +2.47 ± 3.69%, mean ΔDLco was -0.36 ± 2.64% and mean difference of the distance walked during the 6MWT was 5 ± 56.48 meters. During the first year of treatment with nintedanib, mean ΔFCV was -1.32 ± 1.12% (p=0.68), mean ΔDLco was -1.59 ± 3.45% (p=0.54) and mean difference of the distance walked during the 6MWT was 14.17 ± 59 meters (p=0.078). 50% of patients had stable disease under pirfenidone (6-month FVC decline < 5% and/or 6-month DLco decline < 10%) *vs*. 50% under nintedanib, 33.3% had marginal 6-month decline (5% ≤ 6-month FVC ≤ 10% and/or (≤ 10% 6- month DLco decline ≤15%) under pirfenidone *vs*. 33.3% under nintedanib and 16.6% had disease progression (6-month FVC decline > 10% and/or 6-month DLco decline > 15%) under pirfenidone *vs*. 16.6% under nintedanib.

CONCLUSIONS: These results suggest that nintedanib is a safe option for the treatment of patients that had to discontinue pirfenidone due to adverse reactions. Further studies with greater patient numbers are needed for accurate results concerning efficacy.

Key Words:
Idiopathic pulmonary fibrosis, Nintedanib, Pirfenidone, Adverse.

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is characterized by a devastating fibrosing process driven by epithelial-to-mesenchymal transition (EMT). This ultimately results in lung scarring and loss of normal parenchymal architecture, leading to impairment of gas-exchange capability and respiratory failure[1,2]. IPF incidence is increasing, however, the absence of disease-specific clinical features and the short survival time (median 2-3 years, if left untreated), the prompt diagnosis and optimal management still represents a major challenge[3].

Despite the dismal prognosis, two anti-fibrotic agents, pirfenidone and nintedanib, have been found[4-11] to alter the disease natural history and prolong survival. These agents have essentially different mechanism of action but exert similar benefits for the patient, although a randomized study directly comparing them is lacking in current literature.

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Pirfenidone has anti-fibrotic, anti-inflammatory and antioxidant effects and was the first drug approved for IPF treatment[12]. The mechanism of action, although not completely understood, is thought to include the inhibition of known fibrogenic pathways, especially those regulated by Transforming Growth Factor – beta1 (TGFβ1) and Fibroblast Growth Factor (FGF)[13]. Pirfenidone has been shown to inhibit *in vitro* collagen production by downregulating collagen V in IPF fibroblasts and direct interaction with triple-helical collagen[14]. Approval was granted on the ground of abating the Forced Vital Capacity (FVC) decline rate and reducing the risk of death at one year in patients with mild to moderate disease[4,5]. Importantly, post-approval, real-life reports suggest similar benefits for patients with severe IPF and improvement of survival[10,15].

Nintedanib was also approved after demonstrating a reduction of the FVC decline rate complimented by a decrease of the frequency of acute exacerbations[16-18]. Post-marketing, observational studies[19] have also confirmed a beneficial effect on survival. Nintedanib exerts its antitumor, anti-angiogenic and anti-fibrotic effects by inhibition of multiple tyrosine kinases, including Vascular Endothelial Growth Factor (VEGF), Platelet-derived Growth Factor (PDGF), FGF and, possibly, by the activation of the Src homology – region 2 – domain containing phosphatase-1 (SHP-1)[20-22]. In particular, nintedanib has been shown[14,23] to inhibit *in vitro* fibroblast proliferation and differentiation to myofibroblast as well as myofibroblast collagen production.

Nevertheless, these two anti-fibrotic agents may share efficacy results, but also share their most common adverse reactions, although frequency may differ[9,11]. Nausea, diarrhea, abdominal discomfort, and vomiting are the most common adverse effects of both compounds, while photosensitivity rash is specific to pirfenidone and increase of liver enzymes levels is attributed mostly to nintedanib[9-11,24]. This is important because it is not rare for a patient to discontinue treatment with either pirfenidone or nintedanib, due to the onset of side effects, just to initiate therapy with the alternative drug with similar adverse reactions that had led to treatment interruption.

Taking into consideration the above, we sought to determine whether switching treatment to nintedanib is feasible and safe in patients who had to discontinue treatment with pirfenidone, due to its side effects.

Patients and Methods

Patients were prospectively enrolled from the Department of Pneumonology of our institution between March 2015 and June 2019.The present observational study protocol was carried out in accordance with the Helsinki Declaration of Human Rights (as revised in 2013) after being approved by the Local Ethics Committee of the University Hospital of Alexandroupolis.

All participants fulfilled the diagnostic criteria of IPF according to the ATS/ERS/JRS/ALAT guidelines and had completed at least one year of treatment with pirfenidone[25]. All participants had to have low probability of death within 1 year from recruitment and were not referred for lung transplantation. In addition, they had to be native Greek speakers and able to communicate well with the investigators. Discontinuation of pirfenidone was due to side effects not otherwise treated, and the decision was made by the attending physician after thorough clinical evaluation and discussion with the patient. Patients were informed about the side-effects of the new medication along with management options, and those that did not agree to receive the proposed treatment were excluded from the study and received standard of care and regular follow up. Patients were also excluded if they had active infection at the time of enrollment, history of malignancy within the past 5 years or increased liver enzymes (>3 times Upper Limit of Normal – ULN).

The included patients initially received 150 mg of nintedanib twice daily and dosage was reduced to 100 mg twice daily in case of persistent adverse effects that could not be managed differently. Follow up of patients was regular in 3 to 6 months intervals and included pulmonary function tests (PFTs) with diffusion capacity for carbon monoxide (DLco) and 6-minute walk test (6MWT). Results were recorded and stored in an encrypted, password-protected database. Information regarding adherence to treatment and possible side effects was also registered. Liver function tests were performed monthly until the third month of treatment and trimonthly afterwards. Adverse reactions developed during treatment with pirfenidone, along with PFTs and 6MWT were retrospectively recorded for all participants. Disease status was determined using FVC and DLco changes and was categorized as follows: stable (ΔFVC < 5% and/or ΔDLco <10%), marginal decline (5% $\leq$ ΔFVC <10% and/or 10% $\leq$ ΔDLco < 15%) or disease progres-

Table I. Patients' demographic and disease-related clinical data at the time of treatment switch (study initiation).

Age (years)	75.4 ± 6.53
Gender (male/female)	10/2
Smoking status (previous/current/never)	10/0/2
Patients who underwent VATS biopsy	8 (66.6%)
HRCT pattern (definite UIP/probable UIP/indeterminate for UIP)	5/7/0
Mean time (months) between discontinuation of pirfenidone and initiation of nintedanib	4
Patients with mild/medium disease	12
Patients with severe disease	0
Patients with PH	5 (41.67%)

VATS: Video-assisted Thoracic Surgery; HRCT: High-resolution Computed Tomography; UIP: Usual Interstitial Pattern; PH: Pulmonary Hypertension. Mild/medium disease: Forced Vital Capacity >50% and DLco >35%; Severe disease: Forced Vital Capacity ≤ 50% and/or DLco ≤ 35%.

sion (ΔFVC ≥ 10% and/or ΔDLco ≥ 15%)[26,27]. Due to the prescription model for anti-fibrotics in Greece (patient files should be first examined by an expert committee for approval), usually 3 to 5 weeks could pass until initiation of the new treatment.

All statistical analyses were carried out using the IBM Statistical Package for Social Sciences version 17.01 (IBM SPSS, Armonk, NY, USA). Normality of distribution was tested with the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± SD, while data with skewed distribution were reported as median (range). Comparison for changes in lung function during therapy with pirfenidone *vs.* nidentanib were assessed by the paired Student's *t*-test, while pair comparison for categorical values was performed by chi-squared test.

Results

Overall, 12 patients (10 males and 2 females) received nintedanib after discontinuing treatment with pirfenidone and were filled the inclusion criteria. Mean age was 75.4 ± 6.5 years. Diagnosis of IPF was made by video-assisted thoracoscopic surgery in 8 (66.6%) patients. High resolution computed tomography criteria were fulfilled in 5 (41.7%) patients for definite and in 7 (58.3%) patients for probable usual interstitial pneumonia pattern. All participants exhibited mild/moderate disease severity[28]. Patients' demographic and clinical data are displayed in Table I. Mean duration of treatment with pirfenidone was 14.5 months. Side-effects that led to discontinuation of treatment were the following: diarrhea (4 patients, 33.3%), nausea (2 patients, 16.6%), photosensitivity (4 patients, 33.3%) and failure to adhere to pirfenidone's dosage scheme (2 patients, 16.6%). After the initiation of nintedanib, diarrhea, mostly manageable with dietary changes and/or loperamide, was the most common side effect (8 patients, 66.6%). In 4 of them, the dose of nintedanib had to be reduced to 200 mg daily. No patient experienced liver damage, as assessed by the regular liver function tests. Side effects frequency is demonstrated in Table II.

Compared with the 12-month period therapy with pirfenidone, treatment with nintedanib of the same duration had no statistically significant effect in terms of FVC (mean ΔFCV: 2.47 ± 3.69% *vs.* -1.32 ± 1.12% respectively, $p = 0.680$), DLco (mean ΔDLco: -0.36 ± 2.64% *vs.* -1.59 ± 3.45% respectively, $p = 0.590$) and distance walked during the 6MWT (mean difference of distance: 5 ± 56.48 *vs* 14.17 ± 59 meters respectively, $p = 0.078$). Differences in FVC and DL_{CO} for each patient over 6-month intervals are illustrated in Figure 1. FVC and DL_{CO} variations during treatment with pirfenidone and nintedanib are demonstrated in Figure 2. Comparisons of pulmonary function, distance walked in the 6MWT and disease status during treatment with pirfenidone and nintedanib are presented in Table III.

Further subgroup analysis revealed no statistically significant differences regarding disease progression during the period of each treatment.

Table II. Adverse reactions and frequency for Pirfenidone and Nintedanib.

AE	Pirfenidone	Nintedanib
Photosensitivity rash	33.3%, n = 4	0
Diarrhea	33.3%, n = 4	66.6%, n = 8
Nausea	16.6%, n = 2	0
Difficulty to follow dosage plan	16.6%, n = 2	0
Liver toxicity	0	0

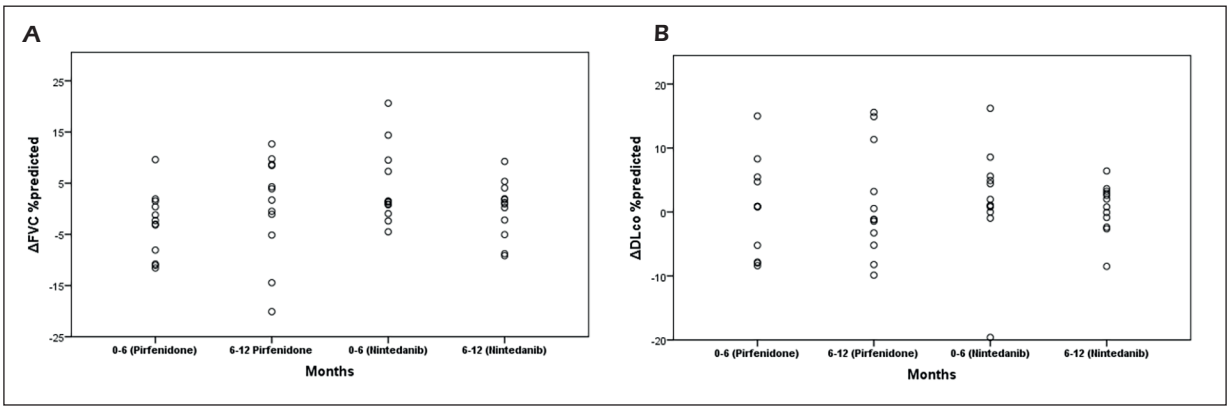

Figure 1. A, Forced Vital Capacity (ΔFVC) during treatment with pirfenidone and nintedanib for each individual patient. **B,** Diffusion Capacity for Carbon Monoxide differences (ΔDLco) during treatment with pirfenidone and nintedanib for each individual patient.

Specifically, six patients who received pirfenidone and six patients who received nintedanib remained stable, four patients who received pirfenidone and four patients who received nintedanib presented marginal decline and two patients that received pirfenidone and two patients that received nintedanib had significant disease progression. Comparisons of Pulmonary Function Tests under pirfenidone and nintedanib treatment are presented in Table III and Figure 1.

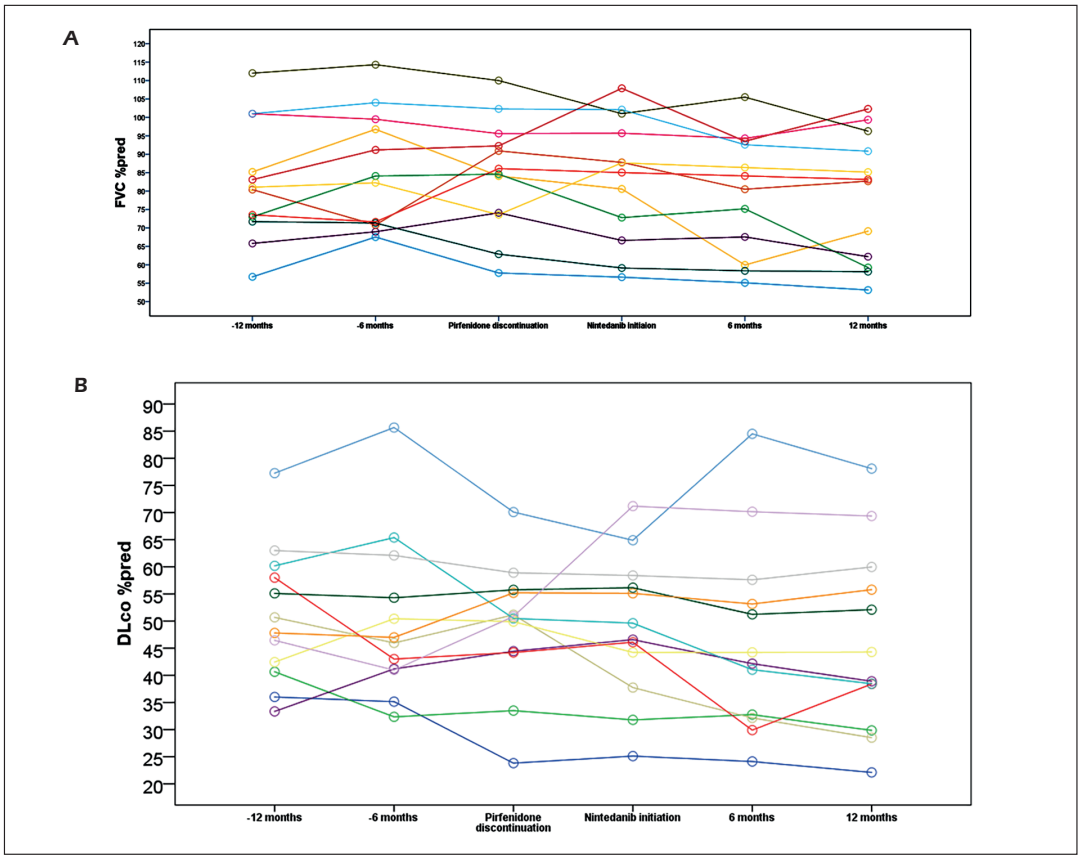

Figure 2. A, Forced Vital Capacity (FVC) course over time for each individual patient. **B,** Diffusion Capacity for Carbon Monoxide (DLco) course over time for each individual patient.

Table III. Comparison of pulmonary function, distance walked in the 6MWT and disease course during treatment with pirfenidone and nintedanib.

	Pirfenidone	Nintedanib	p
ΔFVC%	2.47 ± 3.69	-1.32 ± 1.12	0.68
ΔDLco%	-0.36 ± 2.64	-1.59 ± 3.45	0.59
6MWT (m)	5 ± 56.48	14.17 ± 59	0.078
Stable disease	6	6	
Marginal decline	4	4	
Disease progression	2	2	

Discussion

In this study, we sought to elucidate the tolerability and safety profile of nintedanib, administered after discontinuation of pirfenidone due to side effects. Despite the availability of two pharmaceutical compounds for the treatment of IPF, common clinical dilemmas remain without answer. This study aims in adding to the accumulating real-world evidence regarding the treatment of IPF and specifically the feasibility of treatment switch from one compound to another, since this issue has not been studied extensively and only real-world, retrospective, observational studies are available[29-31].

Pirfenidone and nintedanib are currently the only available anti-fibrotic agents approved for the treatment of IPF. They both met similar endpoints in phase III trials that led to their approval and are accompanied by the same side effects, particularly in the gastrointestinal system[4,5,16]. Post-approval, observational studies[15,19] for both medicines have demonstrated a reduction in mortality, compared to untreated disease. However, many areas of uncertainty remain. Our study offers new insights for the safety and tolerability of nintedanib in patients that had to discontinue treatment with pirfenidone due to adverse reactions that could not be managed conservatively. Moreover, the alteration in treatment did not seem to negatively affect the disease course and the observed side-effects were as expected, considering the known safety profile and the most common side effects of nintedanib.

Our study is not the first one in literature to address this issue. Milger et al[30] reported the results of seven patients treated with nintedanib for six months after discontinuation of pirfenidone treatment, due to either adverse reactions or disease progression. The authors concluded that switching treatment to nintedanib is feasible and safe in selected patients[30]. In another study, Brunnemer et al[29] reported real-life observations from patients treated with nintedanib. While some of them received pirfenidone previously, there are no data in this study that focus on this specific subgroup[29]. Finally, Vianello et al[31] reported an acceptable safety profile for nintedanib in 12 patients who interrupted treatment with pirfenidone due to side effects or due to disease progression. In contrast to previous reports, our study does not include patients who have discontinued treatment, due to disease progression but includes only patients whose treatment cessation was due to adverse reactions. Additionally, data regarding treatment with nintedanib were collected prospectively, thus surveillance for possible side effects was high.

Our results add to the knowledge produced by the previous studies and altogether converge to the conclusion that switch of treatment to nintedanib in patients who have discontinued pirfenidone is a safe, well-tolerated and possibly efficient practice.

This study exhibits certain limitations. First, while data for treatment with nintedanib were gathered prospectively, those regarding treatment with pirfenidone were gathered retrospectively, thus susceptible to related biases. However, no prospective initial phase could be initiated because interrupting treatment in patients without side effects for the purpose of a prospective study would violate ethical standards. Second, the number of patients is limited and thus our results should be interpreted with caution. As demonstrated previously, the sample size in previous studies were similar to ours. Finally, due to prescription particularities in Greece, patients remained without treatment for up to three to four weeks after the discontinuation of pirfenidone. Nevertheless, this limitation provided a wash-out period between the administration of the two agents.

Conclusions

In conclusion, treatment switch to nintedanib is a safe option for patients with IPF who had to discontinue pirfenidone due to adverse reactions. Despite the similar adverse reactions reported for the two compounds, treatment modification to nintedanib was well-tolerated. Still, our study includes a limited number of patients and thus larger studies are necessary to draw definite conclusions regarding efficacy.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare. This study received no external funding. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors' Contribution

The 'Author contributions' section should be presented as follows: (I) Conception and design: PN, PS. (II) Administrative support: PS. (III) Provision of study materials or patients: PN, KA, SA, KB, NP, AV, MF, PS. (IV) Collection and assembly of data: PN, KA, PS. (V) Data analysis and interpretation: PN, KA, PS. (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors.

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