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Antifibrotic treatment adherence, efficacy and outcomes for patients with idiopathic pulmonary fibrosis in Spain: a real-world evidence study

Ana Dolores Romero Ortiz,[1] Beatriz María Jiménez-Rodríguez,[1] Cecilia López- Ramírez,[2] Ángela López- Bauzá,[2] María Pérez- Morales,[3] José Antonio Delgado-Torralbo,[4] Cristina Villalba Moral,[5] Bernardino Alcazar-Navarrete [1,6]

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For numbered affiliations see end of article.

Correspondence to
Dr Bernardino Alcazar-Navarrete; balcazarnavarrete@gmail.com and

Dr Beatriz María Jiménez-Rodríguez; beatriz.jimenez.rodriguez.sspa@juntadeandalucia.es

ABSTRACT

Background Idiopathic pulmonary fibrosis (IPF) is a rare disorder associated with increased mortality and morbidity. There are currently two drugs approved for IPF but their safety and efficacy profile in real-world settings in Spain is not well understood.

Methods An observational, multicentre, prospective study was carried out among patients with IPF who started treatment with pirfenidone or nintedanib from 2015 to 2021. Data regarding clinical characteristics, drug adherence, safety profiles and clinical outcomes between these two drugs were collected.

Results 232 patients were included in the analysis. There were no meaningful differences between both groups at baseline. Patients who started pirfenidone showed a decreased risk for treatment withdrawal compared with those starting nintedanib (HR 0.65 (95% CI 0.46 to 0.94; p=0.002)). Time to first adverse event and all-cause mortality was similar between study groups. Risk factors for withdrawal were female sex, diarrhoea and photosensitivity.

Conclusions in this real-world study, both pirfenidone and nintedanib showed similar efficacy profiles. Pirfenidone was associated with less treatment discontinuations due to side effects.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic pulmonary fibrosis (IPF) is a rare devastating disease which is associated with increased morbidity and mortality.

⇒ Pharmacological therapy for IPF has shown clinical effects in randomised controlled trials; however, the two drugs approved for IPF (pirfenidone and nintedanib) are associated with side effects that can limit their efficacy in real-world populations.

WHAT THIS STUDY ADDS

⇒ In this observational multicentre study, we compared these two drugs in real-life conditions, showing similar efficacy but a better safety profile for pirfenidone which was associated with an increased probability of treatment maintenance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides real-world evidence on the safety and efficacy profiles of these two drugs, highlighting the importance of improving tolerability for treatment adherence.

BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a rare respiratory disease which is characterised by chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring in adults and limited to the lungs. It is associated with the histopathological and/or radiological pattern of usual interstitial pneumonia.[1 2] Although it is infrequent in general population, mortality rates from this disease are high,[3] with a median survival between 2 and 5 years and huge variations due to different trajectories of the disease.[4 5] Several factors such as male gender, older age, poorer lung function (measured either by lung diffusion for carbon monoxide or forced vital capacity), presence of respiratory failure and perceived symptoms are associated with worse long-term prognosis.[6]

After years where no evidence-based therapies were available for patients with this disease, there are currently two approved pharmacological options for patients with IPF which have shown efficacy results in randomised clinical trials: pirfenidone and nintedanib.[7] Nintedanib is a receptor blocker for multiple tyrosine kinases that mediate elaboration of fibrogenic growth factors (eg, platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor). Pirfenidone is an antifibrotic agent that inhibits transforming growth factor

beta-stimulated collagen synthesis, decreases the extracellular matrix and blocks fibroblast proliferation in vitro. Both have effects on disease progression, reduce exacerbation rates and probably have a benefit in all-cause mortality.[8] However, there are patients with IPF who cannot tolerate these treatments due to side effects, a fact that worsens long-term prognosis.[9]

Since the approval of the two antifibrotic drugs by the Spanish Ministry for Health and the Spanish Drug Agency in 2015, many patients have received either pirfenidone or nintedanib prescribed by pulmonologist, mainly at interstitial lung diseases (ILD) specialised units. However, there is scarce data on efficacy and foremost on safety profiles in real-world settings in Spanish populations with IPF.

Given this context, we aimed to describe the safety and efficacy profiles of the two approved treatments for patients with IPF in a real-world observational study among ILD specialised clinics in Andalucia, Spain.

METHODS

Study design

This study was a multicentre, prospective, observational cohort study conducted in six tertiary pulmonary clinics in Andalusia and included patients diagnosed with IPF between 2015 and 2021, who received at least one dose of antifibrotic treatment during this period and were subsequently followed up in the monographic ILD clinics of each hospital. The baseline visit was made on the day the patient started the drug, and follow-up visits were made every 6 months as part of routine clinical practice. Data from each visit were collected using a predesigned case report form.

Study population

The study population consisted of adult patients (aged >18 years) with a diagnosis of IPF according to the European Respiratory Society/American Thoracic Society guidelines who were seen in the pulmonary clinics.[10] Inclusion criteria were patients diagnosed with IPF according to international guidelines, with no age limit, who had started antifibrotic treatment for >10 days and who signed the informed consent form. Exclusion criteria were other interstitial lung diseases other than IPF, refusal to participate in the study and/or to be contacted for follow-up and those who had not started antifibrotic treatment during the follow-up period or had not taken the medication within the specified number of days.

Main outcomes

The main objective of this study was to determine if there are differences in treatment persistence, time to first adverse event and time to death among the approved antifibrotics in Spain, as well as the factors associated with discontinuation of antifibrotic treatment in patients with IPF.

Treatment persistence was defined as the time a patient received the approved doses of any of the antifibrotics (150 mg/12 hours for nintedanib and 801 mg/8 hours for pirfenidone). Treatment discontinuation was defined as the period during which a patient did not receive the licensed doses of any of the antifibrotics due to dose reduction, temporary or permanent withdrawal.

Secondary outcomes included the influence of comorbidities in patients with IPF as a factor of poor persistence to treatment, using the CCI and the CCI adjusted for age and to assess other features of the patient that may influence the discontinuation of antifibrotic treatment.

Statistical analysis

Study results are presented as sample size (n), range, median (IQR) or mean±SD, as appropriate. Categorical variables were compared using the χ^2 test and continuous variables were compared using analysis of variance, Student's t-test or Mann-Whitney U test, as appropriate. Statistical significance was defined as $p<0.05$.

Based on previous reports of adverse events in clinical trials,[11–14] we hypothesised a 30% withdrawal rate in patients starting nintedanib and a 15% withdrawal rate in patients starting pirfenidone. With an α error of 0.05 and a power of (1–β error) of 0.95, a sample size of 185 patients would be required. Assuming a drop-out rate of 15%, a minimum of 222 patients would be required to detect differences between the study groups.

Kaplan-Meier survival curves and Cox regression analysis were used to compare time to discontinuation, time to adverse events and time to death after adjustment for age, sex, smoking status, Charlson Comorbidity Index and polypharmacy. All statistical analyses were performed using Jamovi V.1.6 software (The Jamovi Project, Sydney, Australia).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

From 2015 to 2021, 232 patients with IPF starting treatment with antifibrotics (either pirfenidone or nintedanib) were identified. Complete data regarding follow-up, treatment persistence and study variables were available for 227 patients.

Baseline characteristics of study population are shown in table 1. Mean age was 69.9 years, 80.2% were male. 85 patients (36.7%) started treatment with nintedanib and 147 (63.3%) started on pirfenidone. The mean time from the initial suspicion of IPF until the start of pharmacological treatment was 267 days. The mean follow-up time from the study population was 716 days. Baseline characteristics of both groups were similar except for an

Table 1 Baseline characteristics of study population according to the starting antifibrotic therapy (pirfenidone or nintedanib)

	Nintedanib (n=85)	Pirfenidone (n=147)	Total (n=232)	P value
Age (years), mean (SD)	69.0 (8.3)	70.4 (7.7)	69.9 (7.9)	0.190*
Sex male, n (%)	69 (81.2%)	117 (79.6%)	186 (80.2%)	0.771†
Smoking history				
Current smoker, n (%)	9 (10.6%)	9 (6.1%)	18 (7.8%)	0.325†
Pack years, mean (SD)	31.8 (26.7)	29.9 (27.7)	30.6 (27.3)	0.622*
BMI, mean (SD)	28.9 (3.4)	29.0 (4.1)	28.9 (3.9)	0.891*
Comorbidities				
Any, n (%)	49 (57.6%)	101 (68.7%)	150 (64.7%)	0.090†
Charlson Comorbidity Index, mean (SD)	3.6 (1.6)	4.1 (1.7)	3.9 (1.7)	0.017*
Respiratory comorbidities, n (%)	30 (35.3%)	50 (34.0%)	80 (34.5%)	0.843†
Cardiovascular comorbidities, n (%)	21 (24.7%)	53 (36.1%)	74 (31.9%)	0.074†
GORD, n (%)	22.0 (26.2%)	30.0 (20.4%)	52.0 (22.5%)	0.311†
Type II DM, n (%)	15.0 (17.6%)	38.0 (25.9%)	53.0 (22.8%)	0.152†
CKD, n (%)	10.0 (11.8%)	8.0 (5.4%)	18.0 (7.8%)	0.083†
Depression, n (%)	8.0 (9.4%)	10.0 (6.8%)	18.0 (7.8%)	0.126†
Days since diagnosis, mean (SD)	280.0 (698.3)	260.3 (686.5)	267.5 (689.4)	0.834*
GAP index, n (%)				0.729†
Stage I	25 (30.1%)	43 (29.3%)	68 (29.6%)	
Stage II	43 (51.8%)	71 (48.3%)	114 (49.6%)	
Stage III	15 (18.1%)	33 (22.4%)	48 (20.9%)	
HRCT pattern, n (%)				0.245†
UIP pattern	48 (57.1%)	75 (51.4%)	123 (53.5%)	
Probable UIP pattern	27 (32.1%)	55 (37.7%)	82 (35.7%)	
Indeterminate UIP pattern	8 (9.5%)	15 (10.3%)	23 (10.0%)	
Alternative pattern	1 (1.2%)	1 (0.7%)	2 (0.9%)	
Pulmonary function test				
FEV1 % predicted, mean (SD)	85.2 (17.6)	84.8 (15.3)	85.0 (16.6)	0.875*
FVC % predicted, mean (SD)	83.1 (20.6)	79.7 (17.5)	80.9 (18.7)	0.174*
DLCO % predicted, mean (SD)	50.4 (17.7)	50.5 (14.5)	50.4 (15.7)	0.979*
6MWT m, mean (SD)	447.7 (120.0)	408.8 (119.4)	422.9 (120.7)	0.068*
SpO2%, mean (SD)	95.6 (2.6)	95.6 (2.4)	95.6 (2.5)	0.848*
Medical therapy				
Oxygen therapy, n (%)	26 (30.6%)	61 (41.5%)	87 (37.5%)	0.098†
Oral corticosteroids, n (%)	16 (18.8%)	32 (21.8%)	48 (20.7%)	0.594†
PPI, n (%)	69 (81.2%)	120 (81.6%)	189 (81.5%)	0.931†
Polypharmacy, n (%)	25 (29.8%)	65 (44.2%)	90 (39.0%)	0.030†

*Linear model analysis of variance.
†Pearson's χ^2 test.
BMI, body mass index; CKD, chronic kidney disease; DLCO, lung diffusion for carbon monoxide; DM, diabetes mellitus; FEV1, forced espiratory volume in the first second; FVC, forced vital capacity; GORD, gastro-oesophageal reflux disease; HRCT, high-resolution CT scan; GAP index, gender, age and pulmonary characteristics (reported in reference 6); 6MWT, 6 min walking test; PPI, proton pump inhibitor; SpO2, transcutaneous oxygen saturation; UIP, usual interstitial pneumonia.

increased proportion of patients with comorbidities and polypharmacy in the pirfenidone group.

During follow-up, 135 patients discontinued antifibrotic treatment: 55 in the nintedanib group (64% of the initial population) and 80 in the pirfenidone group (54.4% of the initial population). More patients discontinued antifibrotic treatment in the nintedanib group (31 patients, 36.5%) than in the pirfenidone group (29

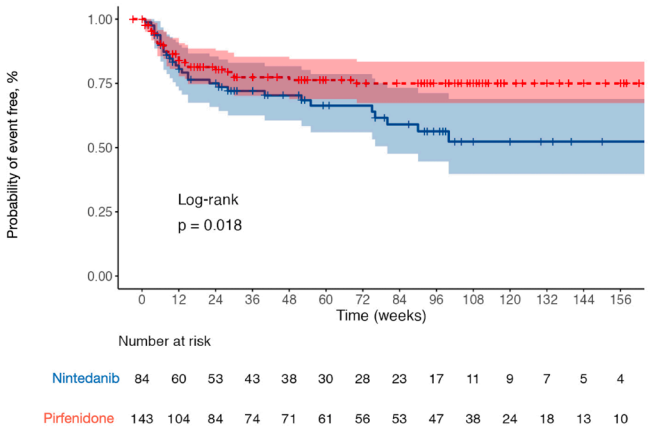

Figure 1 Kaplan-Meier survival curves showing time (with shadow lines reflecting 95% CI) to definitive discontinuation (withdrawal) from either nintedanib (blue) or pirfenidone (red) among new antifibrotic users.

patients, 19.7%), resulting in an HR 0.65 (95% CI 0.46 to 0.94; p=0.002) for persistence in pirfenidone group. 15 patients withdrawn from pirfenidone reported photosensitivity and 27 patients withdrawn from nintedanib reported gastrointestinal (GI) side effects. Time to withdrawal was longer in pirfenidone group compared with nintedanib group (figure 1).

Reasons and types of discontinuations are shown in table 2. Main reasons for treatment discontinuation were adverse effects, resulting in 42.4% of the discontinuations among nintedanib starters and 23.1% of the pirfenidone starters.

Regarding adverse effects, 64.1% of the entire population reported significant adverse effects to the clinician. Most frequent adverse events are described in table 3. GI side effects were the most common reported by the patients in both pirfenidone and nintedanib groups, with diarrhoea being reported by 63.1% of the patients taking nintedanib. Photosensitivity was reported by 23.1% of the patients taking pirfenidone. Time to first side effect was similar between pirfenidone and nintedanib groups (figure 2). Females were more likely to withdraw due to side effects, especially for those concerning GI area (13 females, 28.2% vs 25 males, 13.4%).

Survival between both treatment groups was similar, with 15 deaths among nintedanib users and 41 among pirfenidone ones, with a 2-year mortality rates of 88.6% and 85.5%, respectively (HR 0.89, 95% CI 0.58 to 1.36, p=0.586) (figure 3).

Multivariate analysis assessing drug withdrawal showed that female sex, diarrhoea and photosensitivity were independent factors associated with an increased risk for definitive discontinuation from therapy (figure 4).

DISCUSSION

The main results of this study show that the efficacy of the antifibrotics is similar in the real world (in terms of mortality), but their safety profiles are different, with pirfenidone being associated with a lower number of withdrawals, mainly due to fewer side effects. Both treatments had a similar time to patient-reported adverse events, suggesting that side effects associated with pirfenidone were less intense or severe. Risk factors for discontinuation were female sex and adverse events, and were not influenced by disease severity or comorbidities. Given the importance of adherence to treatment for the long-term prognosis of IPF, our results should help clinicians to identify early risk factors for discontinuation.

Most of the adverse events reported by patients in our study have been extensively documented in both randomised controlled trial (RCTs) and real-world evidence (RWE) settings. For example, pirfenidone was reported to increase the risk of photosensitivity in 28% of ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis) participants and 12% of CAPACITY (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes) participants,[11 12] although the discontinuation rate due to adverse events in these trials was 4.4%, while diarrhoea was reported by nearly 60% of

Table 2 Number and types of drug discontinuations among new antifibrotic users

	Nintedanib	Pirfenidone	Total	P value
Discontinuation, n (%)	55 (64.0%)	80 (54.4%)	135 (58.1%)	0.016*
Cause of discontinuation				
Adverse events, n (%)	36 (42.4%)	34 (23.1%)	70 (30.2%)	0.012*
Lung transplantation, n (%)	4 (4.7%)	5 (3.4%)	9 (3.9%)	0.346*
Death	15 (17.6%)	41 (27.8%)	56 (14.2%)	0.834*
Type of discontinuation				
Dose reduction, n (%)	31 (36.5%)	35 (23.8%)	66 (28.4%)	0.039*
Drug change, n (%)	31 (36.5%)	23 (15.6%)	54 (23.3%)	<0.001*
Temporary discontinuation, n (%)	13 (15.3%)	18 (12.2%)	31 (13.4%)	0.511*
Withdrawal, n (%)	31 (36.5%)	29 (19.7%)	60 (25.9%)	0.005*

*Pearson's χ^2 test.

Table 3 Types of most common adverse events reported to clinicians by new antifibrotic users

	Nintedanib	Pirfenidone	Total	P value
Adverse event, any; n (%)				0.020*
Yes	62.0 (73.8%)	86.0 (58.5%)	148.0 (64.1%)	
Liver function test abnormality n (%)				0.140*
Yes	9.0 (10.7%)	8.0 (5.4%)	17.0 (7.4%)	
Photosensitivity n (%)				<0.001*
Yes	0.0 (0.0%)	34.0 (23.1%)	34.0 (14.7%)	
Gastrointestinal complaints n (%)				0.012*
Yes	39.0 (46.4%)	44.0 (29.9%)	83.0 (35.9%)	
Anorexia n (%)				0.349*
Yes	21.0 (25.0%)	29.0 (19.7%)	50.0 (21.6%)	
Blood count abnormality n (%)				0.449*
Yes	0.0 (0.0%)	1.0 (0.7%)	1.0 (0.4%)	
Diarrhoea n (%)				<0.001*
Yes	53.0 (63.1%)	16.0 (10.9%)	69.0 (29.9%)	

*Pearson's χ^2 test.

INPULSIS-1 (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients) and INPULSIS-2 participants, leading to discontinuation in nearly 20% of the population.[13]

Our results showed similar safety profiles to what RCTs have previously shown, although withdrawal rates in our study are higher than those reported in RCTs.[14–16] This is not surprising as the study populations of RCTs tend to differ from those of RWE studies, which tend to include older patients with more comorbidities and more concomitant pharmacological treatments. Many authors have reported higher rates of drug discontinuation in populations with IPF, with pirfenidone showing a more favourable safety profile.[9 17–23] However, we have to acknowledge that some of these RWE studies have shown a better safety profile for nintedanib, which could be explained by different study populations or different susceptibility to side effects among study participants.

In our study, women were more likely to withdraw from antifibrotic treatment due to side effects, especially GI side effects, which led to a higher number of withdrawals. Although we must be cautious due to the small number of women included in this cohort, this observed gender effect should warrant further study in the future.

About 20% of our study population were receiving systemic corticosteroids as background therapy for IPF, which may have increased the risk of side effects and/or discontinuation. However, there was no effect of corticosteroid use on overall efficacy and safety in the multivariate analysis.

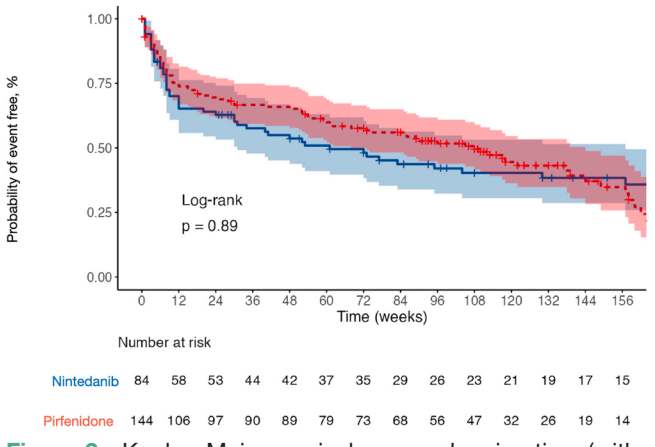

Figure 2 Kaplan-Meier survival curves showing time (with shadow lines reflecting 95% CI) for first reported adverse event from either nintedanib (blue) or pirfenidone (red) among new antifibrotic users.

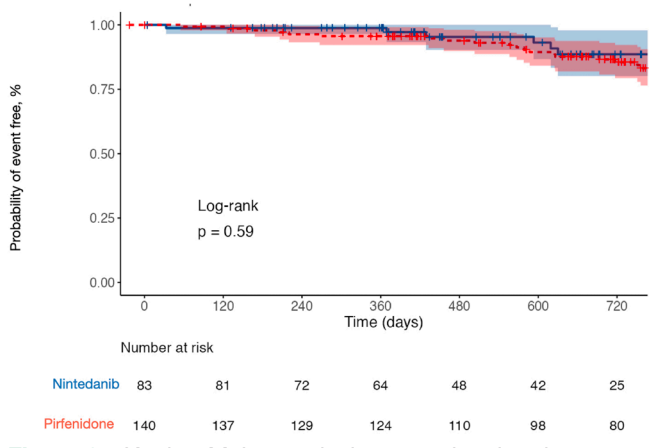

Figure 3 Kaplan-Meier survival curves showing time (with shadow lines reflecting 95% CI) to death from either nintedanib (blue) or pirfenidone (red) among new antifibrotic users.

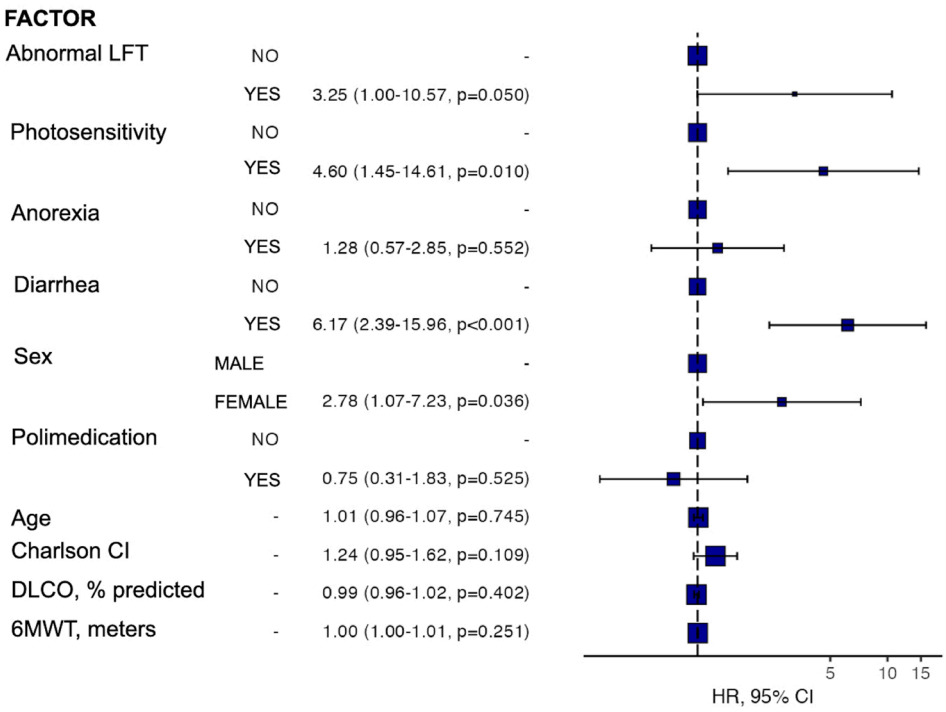

Figure 4 Multivariate analysis for definitive discontinuation from antifibrotic therapy. Results are expressed as HR (mean, 95% CI) for each variable. 6MWT, 6 min walking test; Charlson CI, Charlson Comorbidity Index; DLCO, lung diffusion for carbon monoxide; LFT, liver function test.

Nonetheless, our results are in line with smaller studies performed in Spain[24] or descriptive studies which were not designed for safety events.[25]

Our study has some strengths, such as its multicentre design and being conducted in ILD clinics within the same health system (which reduces the risk of bias due to different clinical care). It also includes all patients initially treated for IPF since approval by health authorities. However, it has some weaknesses, such as its observational nature, where we could not adjust for confounding variables that might explain differences in drug tolerance. With regard to adverse events, the occurrence of adverse events was self-reported by the patients at the visit and could not be completely accurate. Another limitation is that the sample size may not have captured some rare adverse events such as liver function test abnormalities. Another weakness is that we could not assess adherence to treatment because it was self-reported by the patients.

CONCLUSIONS

In this real-world study, conducted in specialised ILD clinics in Andalusia, we observed a similar efficacy profile for both nintedanib and pirfenidone as compared with first-line IPF treatment, with a better safety profile for patients on pirfenidone, resulting in a lower risk of withdrawal due to adverse events. Risk factors for discontinuation were mainly related to female gender and adverse events such as diarrhoea and photosensitivity, with no signal related to comorbidities, IPF severity or polypharmacy.

Author affiliations
[1]Respiratory Department, Hospital Universitario Virgen de las Nieves, Granada, Spain
[2]Hospitales Universitarios Virgen del Rocío, Sevilla, Spain
[3]Respiratory Department, Hospital Universitario Costa del Sol, Marbella, Spain
[4]Respiratory Department, Hospital Universitario Virgen Macarena, Sevilla, Spain
[5]Respiratory Department, Complejo Hospitalario de Jaen, Jaen, Andalucía, Spain
[6]Medicine Department, Universidad de Granada, Granada, Spain

X Bernardino Alcazar-Navarrete @banavarrete

Contributors ADRO conceived and designed the study, collected the data, contributed data analysis and wrote the paper; BMJ-R collected the data and contributed to data analysis; MP-M collected the data; CVM collected the data; CL-R collected the data; AL-B collected the data; JAD-T collected the data; BAN contributed to data analysis, performed the analysis, wrote the paper, and is the guarantor of the study

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The study protocol was approved by local ethics committee (CEIM Granada 0318-N-21). The study was conducted in accordance with national and international standards for medical research in human beings (Declaration of Helsinki and Tokyo) and with the Organic Law on the Protection of Personal Data and Digital Rights (5 December 2018). All participants gave signed informed consent.

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Data availability statement Data are available on reasonable request. Data includes database & statistical analysis.

ORCID iD

Bernardino Alcazar-Navarrete http://orcid.org/0000-0003-2356-9366

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