REAL-WORLD CLINICAL EFFECTIVENESS AND SAFETY OF ANTIFIBROTICS IN PROGRESSIVE PULMONARY FIBROSIS ASSOCIATED WITH RHEUMATOID ARTHRITIS

Javier Narváez, Martí Aguilar-Coll, Juan José Alegre, Montserrat Roig-Kim, Laia de Daniel, Aina Fabregat, Mónica Cubells, Vanesa Vicens-Zygmunt[1], Guadalupe Bermudo[1], Joan Miquel Nolla, María Molina-Molina[1]
Servicios de Reumatología y [1]Neumología. Hospital Universitario de Bellvitge. Barcelona

OBJECTIVE

Interstitial lung disease (ILD) is one of the most severe complications of rheumatoid arthritis (RA). Real-world data on antifibrotic treatment are needed. Our objective was to evaluate the real-world effectiveness and tolerability of antifibrotic agents in patients with progressive fibrosing RA-ILD.

METHODS

A longitudinal, retrospective, observational study was conducted on a cohort of RA-ILD patients treated with either nintedanib or pirfenidone. The data collected included pulmonary function test (PFT) results, adverse events (AEs), tolerability, and drug retention.

RESULTS

Study population.

Twenty-seven patients were included; 25 (92.5%) initiated nintedanib, while 2 initiated pirfenidone. During follow-up, nintedanib was switched to pirfenidone in 5 patients because of adverse effects; thus, 7 (26%) patients received pirfenidone at some point during the follow-up period.

The key baseline characteristics of this cohort are summarised in Table 1. At the onset of antifibrotic therapy, 10 (37%) patients exhibited moderate to high RA activity according to the DAS28 ESR score (> 3.2). The mean %pFVC was 86.6 ± 15 (IQR 25th–75th percentile, 73–97.1), and the mean %pDLCO was 54.3 ± 14.8 (IQR 44–66). Fourteen (52%) patients presented a decline of ≥10% in %pFVC.

Radiologically, 21 patients (78%) were classified as having UIP, 5 (18%) as fibrotic NSIP, and 1 (4%) as combined pulmonary fibrosis and emphysema (CPFE). A smoking history was reported in 18 patients (67%).

Efficacy endpoints.

Changes in the primary efficacy outcome measures assessed at 6 months and 1 year following the initiation of antifibrotic therapy are presented in Tables 2 and 3 and illustrated in Figure 1. Across the entire study population, prior to starting therapy, the mean decline in %pFVC and %pDLCO from the time of ILD diagnosis to the initiation of antifibrotic treatment (T0) was -8.9% (95% CI: 7.81 to 16.02; p=0.0001) and -14.8% (95% CI: 9.53 to 20.16; p=0.0001), respectively.

In 3 patients, antifibrotic therapy was discontinued due to adverse effects before completing 6 months of treatment. In the remaining 24 patients (twenty-one UIP and three non-UIP patterns), a slower decline in PFT parameters was observed after 6 months of therapy (delta: percentage change from baseline): Δ%pFVC +1.2% (95% CI: -5.67 to 3.41; p=0.611 compared with T0) and Δ%pDLCO +3.9% (95% CI: -13.51 to 5.63; p=0.400).

At 1 year of treatment, data were unavailable for nine patients: three had died due to ILD progression, four had discontinued treatment due to adverse effects, and two had not yet completed 12 months of therapy. Among the 18 patients who completed one year of therapy (fifteen UIP and three NSIP patterns), a modest improvement in %pFVC was observed (Δ+4.7%, 95% CI: -8.66 to -0.74; p=0.023), along with a slowing in %pDLCO decline (Δ-3.8%, 95% CI: -1.82 to -9.25; p=0.175).

Nine of the 24 patients completed 2 years of treatment (seven UIP and two NSIP), maintaining a response in PFTs: Δ%pFVC: +7.7% (95% CI: -16.07 to -0.66; p=0.037) and Δ%pDLCO: -2.2% (95% CI: -7.67 to -12.07; p=0.621).

A comparison of pre- and post-treatment pulmonary variables revealed that PFT deterioration either slowed or stabilized in approximately three-quarters of the patients (Table 3 and figure 2). Additionally, prednisone doses were reduced in 10 out of 25 patients (40%) following the initiation of antifibrotic therapy, with a mean reduction of -5.8 mg/day (SD: 3.5 mg; 95% CI: 7.73 to 15.62; p<0.046). Efficacy comparisons between radiological patterns could not be performed due to the low number of non-UIP patterns.

Antifibrotic tolerability and retention.

Seventeen patients (63%) continued treatment after a median follow-up period of 25 months (IQR 7–27) following the initiation of antifibrotic therapy. Among the 10 patients who discontinued treatment, the reasons were death due to ILD progression and infectious complications in 4 patients (15%), lung transplantation in 1 patient (4%), and adverse events leading to treatment discontinuation in 5 patients (18.5%). The retention rate of patients initially treated with nintedanib was 52% (13/25).

Eighty-one-point five percent (22/27) of patients experienced adverse events (AEs) attributed to antifibrotic treatment. Their frequency and types are detailed in Table 4. As expected, the most common events were gastrointestinal events and hepatitis.

In 48.1% (13/27) of patients, antifibrotic therapy was temporarily suspended (mean number of suspensions: 1.38 ± 0.5; range: 1–2), and in 63% (17/27) of patients, the recommended dosage was temporarily reduced (mean number of dose reductions: 1.53 ± 0.5; range: 1–3).

The most frequent AEs leading to treatment discontinuation or permanent dose reduction were diarrhea and hepatitis.

As previously reported, a second antifibrotic agent was prescribed for 5 (18.5%) patients; all were initially treated with nintedanib and were switched to pirfenidone due to adverse events. Among these 5 patients, three (60%) remained on pirfenidone after a median follow-up of 13 months.

Table 1. Characteristics of patients with RA-ILD at the initiation of initial antifibrotic medication.

Demographics and RA Characteristics	N = 27
Age at age at initiation of antifibrotic treatment, years (mean ± SD)	67 ± 10
Sex, woman/man	12 (44.5%)/15 (55.5%)
Body mass index (BMI), missing data = 4 (mean ± SD)	28.3 ± 5.3
Smoker or ex-smoker	18 (67%) Current: 1 (4%)
Positive rheumatoid factor	23 (85%)
Positive ACPA	22 (81.5%)
Median duration of RA, months (IQR 25th–75th)	70.5 (27.5–114)
DAS28-ESR at initiation of antifibrotic treatment	
Remission or low activity	17 (63%)
Moderate or high activity	10 (37%)
ILD characteristics	
Median duration of ILD, months (IQR 25th–75th)	29 (20–50)
HRCT pattern of ILD	
Usual interstitial pneumonia (definite or probable)	21 (78%)
Fibrotic non-specific interstitial pneumonia	5 (18%)
Combined pulmonary fibrosis and emphysema	1 (4%)
%pFVC at initiation of initial antifibrotic medication	86.6 ± 15
%pDLCO at initiation of initial antifibrotic medication	54.3 ± 14.8
Prior treatments	
Glucocorticoids	26 (96%)
Mean dose (± SD), mg/day (IQR 25th–75th)	8.3 ± 5.4 (5–10)
csDMARDs or immunosuppressants *	22 (81.5%)
Number of previous csDMARDs or immunosuppressants	1.4 (minimum 1, maximum 2)
Methotrexate	7 (26%)
Leflunomide	18 (67%)
Sulfasalazine	2 (8%)
Mycophenolate mofetil	2 (8%)
bDMARD *	20 (74%)
Number of previous bDMARD	1.5 (minimum 1, maximum 6)
Rituximab	10 (37%)
Number of cycles	4.4 (minimum 1, maximum 10)
Abatacept	11 (41%)
TNFi	4 (15%)
Tocilizumab	1 (4%)
Antifibrotic medication	
Nintedanib	25 (92%)
Pirfenidone	
As initial antifibrotic medication/After nintedanib	2 (8%)/5 (18.5%)
Concomitant medication	
Glucocorticoids	25 (93%)
Dose of prednisone at initiation of initial antifibrotic medication, (mean ± SD)	7.9 ± 5
csDMARDs or immunosuppressants	21 (78%)
Leflunomide	16 (59%)
Mycophenolate mofetil	4 (15%)
Methotrexate	1 (4%)
bDMARD or JAKi *	22 (81.5%)
Abatacept	13 (48%)
Rituximab	10 (37%)
TNFi	1 (4%)
JAKi	2 (8%)
Need for oxygen therapy at initiation of initial antifibrotic medication	7 (26%)

* Some patients received more than one. Abbreviations ACPA: anticitrullinated protein autoantibodies; bDMARD biologic disease-modifying antirheumatic drugs; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28-ESR: Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; IQR: interquartile range; JAKi: Janus kinase inhibitors; %pDLCO: percent predicted diffusing capacity for carbon monoxide corrected for hemoglobin; %pFVC: percent predicted forced vital capacity; RA: rheumatoid arthritis; SD: standard deviation; TNFi: tumor necrosis factor inhibitor.

Table 2. Changes before and after 6 months and after 1 and 2 years of treatment with antifibrotic medication.

	At Time of RA-ILD Diagnosis Mean ± SD (IQR, 25th–75th)	At Time of Initiation of Initial Antifibrotic Medication Mean ± SD (IQR, 25th–75th)	Delta (Mean)	*p* Value (95% CI)
Before Antifibrotics				
Total sample (N = 27)				
%FVC predicted	95.5 ± 14.6 (88.1–107.5)	86.6 ± 15 (73–97.1)	−8.9%	0.0001 (7.81 to 16.02)
%DLCO predicted	69.1 ± 18.8 (55.4–79.5)	54.3 ± 14.8 (44–66)	−14.8%	0.0001 (9.53 to 20.16)
After 6 months of treatment				
	At time ofinitiation of initial antifibrotic medication mean ± SD (IQR, 25th–75th)	**6 months post-treatment mean ± SD (IQR, 25th–75th)**	**Delta (mean)**	***p* value (95% CI)**
Total sample (N = 24)				
UIP: 21/Non-UIP: 3				
%FVC predicted	88.2 ± 19 (73.7–102.7)	89.4 ± 22.7 (74.4–105.5)	+1.2%	0.611 (−5.67 to 3.41)
%DLCO predicted	57.4 ± 16.6 (46.2–68.1)	61.3 ± 24.9 (40.5–79.6)	+3.9%	0.400 (−13.51 to 5.63)
After 1 year of treatment				
	At time ofinitiation of initial antifibrotic medication mean ± SD (IQR, 25th–75th)	**12 months post-treatment mean ± SD (IQR, 25th–75th)**	**Delta (mean)**	***p* value (95% CI)**
Total sample (N = 18)				
UIP: 15/NSIP: 3				
%FVC predicted	87.5 ± 20.7 (71.8–108.6)	92.2 ± 24.8 (76–115.8)	+4.7%	0.023 (−8.66 to 0.74)
%DLCO predicted	58.2 ± 17.9 (45.7–69.9)	54.4 ± 16.7 (42.7–67)	−3.8%	0.175 (−1.82 to −9.25)
After 2 years of treatment				
	At time ofinitiation of initial antifibrotic medication mean ± SD (IQR, 25th–75th)	**24 months post-treatment mean ± SD (IQR, 25th–75th)**	**Delta (mean)**	***p* value (95% CI)**
Total sample (N = 9)				
UIP: 7/NSIP: 2				
%FVC predicted	89.1 ± 19.7 (71.6–111.4)	97.4 ± 19.7 (84.3–120.1)	+7.7%	0.037 (−16.07 to 0.66)
%DLCO predicted	60.8 ± 20.3 (43.8–81.9)	58.6 ± 15.1 (45.5–73.1)	−2.2%	0.621 (−7.67 to −12.07)

%pFVC = predicted forced vital capacity; %pDLCO = predicted diffusing capacity for carbon monoxide, corrected for hemoglobin; UIP: usual interstitial pneumonia and NSIP: fibrotic non-specific interstitial pneumonia.

Table 3. Lung function test results according to the definitions of ATS after antifibrotic therapy.

After 6 Months of Treatment N = 24	Improvement	Stabilization	Worsening
%FVC predicted	12.5% (3)	75% (18)	12.5% (3)
%DLCO predicted	21% (5)	58% (14)	21% (5)
After 12 months of treatment N = 18			
%FVC predicted	22.2% (4)	66.7% (12)	11.1% (2)
%DLCO predicted	11.1% (2)	61.2% (11)	27.7% (5)
After 24 months of treatment N = 9			
%FVC predicted	44.5% (4)	55.5% (5)	0
%DLCO predicted	22.2% (2)	44.5% (4)	33.3% (3)

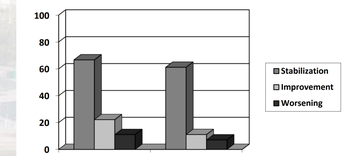

Figure 2. Lung function test results (as defined by the ATS) after 12 months of antifibrotic therapy.

Table 4. Adverse events associated with antifibrotic therapy.

	N = 27
Any adverse event	22 (81.5%)
Most frequent adverse events	
Diarrhea	17 (63%)
Nausea/Vomiting	9 (33%)
ALT o AST increased	7 (26%)
Decreased appetite/weight loss	10 (37%)
Asthenia	2 (7.4%)
Abdominal pain	3 (11%)
Adverse event leading to permanent dose reduction	
Nintedanib (N = 25)/Pirfenidone (N = 7)	10 (40%)/1 (14%)
Adverse event leading to treatment discontinuation	5 (18.5%)

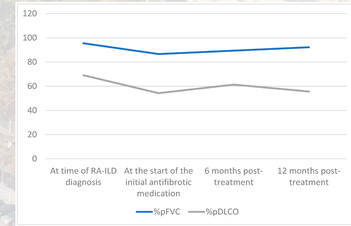

Figure 1. Evolution of the predicted forced vital capacity (%pFVC) and the predicted diffusing capacity for carbon monoxide corrected for hemoglobin (%pDLCO) before initiation of antifibrotic therapy and after 1 year of treatment.

CONCLUSION

According to our results, antifibrotic initiation was associated with a modest improvement in the trajectory of %pFVC and stabilization in %pDLCO. The discontinuation rate in our cohort (37%) was higher than that reported in clinical trials but similar to that reported in previously published real-world studies.

fjnarvaez@bellvitgehospital.cat

Generalitat de Catalunya
Departament de Salut
Institut Català de la Salut
Gerència Territorial
Metropolitana Sud
Bellvitge
Hospital Universitari
IDIBELL
Institut d'Investigació Biomèdica de Bellvitge
Universitat de Barcelona
N.º 018