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ORIGINAL ARTICLES

Antifibrotics in rheumatoid arthritis-associated interstitial lung disease – real-world data from a nationwide cohort

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ABSTRACT

Introduction: Interstitial lung disease (ILD) is the most common pulmonary manifestation of rheumatoid arthritis (RA) and is associated with an increased mortality. Clinical trials have shown that antifibrotics (nintedanib and pirfenidone) can slow the progression of connective tissue disease-associated ILD. This study aims to evaluate the effectiveness and tolerability of antifibrotics in a national, real-world cohort of patients with RA-ILD.

Material and methods: We conducted an observational multicenter study of RA-ILD patients treated with antifibrotics, who were prospectively followed in Reuma.pt. Demographic and clinical data, pulmonary function tests (PFTs) results and adverse events (AEs) were collected. A linear mixed model with random intercept was used to compare PFT results within 12 (±6) months before to 12 (±6) months after antifibrotic initiation. Drug persistence was evaluated using Kaplan-Meier curves.

Results: We included 40 RA-ILD patients, 27 (67.5%) initially treated with nintedanib and 13 (32.5%) with pirfenidone. Most of the patients were female (55%), and current or past smokers (52.5%). At antifibrotic initiation, mean age was 70.9 ± 7.1 years and median ILD duration 5.0 [IQR 2.3-7.5] years. A total of 20 patients were included in effectiveness analysis, with the use of antifibrotics interrupting the decline of forced vital capacity (FVC; decline 300 ± 500 mL in the year before antifibrotic initiation vs. improvement of 200 ± 400 mL in the year following antifibrotic initiation, p=0.336) and total lung capacity (TLC; decline 800 ± 300 mL in the year before antifibrotic initiation vs. improvement of 600 ± 900 mL in the year following antifibrotic initiation, p=0.147). However, diffusion capacity for carbon monoxide remained in decline (3% decline in the year before antifibrotic initiation vs. 2.9% decline in the year following antifibrotic initiation, p=0.75). AEs were reported in 16 (40%) patients and led to drug discontinuation in 12 (30%). Median duration of drug persistence was 150.3 weeks (95 %CI 11.0-289.6), with no difference between nintedanib and pirfenidone (p = 0.976).

Conclusion: This study with real-world data corroborates the usefulness of antifibrotics in stabilizing lung function, based on FVC and TLC. However, AEs were frequently reported and were the main cause for drug discontinuation.

Keywords: Pirfenidone; Interstitial lung disease; Rheumatoid arthritis; Antifibrotics; Nintedanib.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can affect 0.5–1% of the population worldwide[1]. It mainly affects joints[2], in particular small joints of the hands and feet, but can also have several extra-articular manifestations. Pulmonary complications are common, occurring in 60-80% of RA patients[3] and all lung compartments can be involved, including parenchyma, large and small airways, pleura, and less

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commonly, vasculature[3].

Interstitial lung disease (ILD) is the most prevalent manifestation of RA-associated lung disease. Its prevalence ranges widely, mainly due to different diagnostic strategies[4]. ILD can be detected in up to 70% of RA patients, based on chest high resolution computed tomography (HRCT) systematically performed, regardless of the presence of symptoms, or on autopsy series[3,5]. However, the prevalence of symptomatic, clinically relevant, RA-ILD is lower, ranging from 2 to 10%[4–6].

The predominance of usual interstitial pneumonia (UIP) pattern distinguishes RA from most other connective tissue diseases (CTDs), where non-specific interstitial pneumonia (NSIP) is the most frequent pattern[2]. UIP pattern, in particular the presence of honeycombing, is associated with a worse prognosis in RA-ILD[2,7,8]. Published data have demonstrated that RA-UIP and idiopathic pulmonary fibrosis (IPF) share several clinical, radiographic and genetic features[9], which can have implications for the treatment of RA-ILD.

Antifibrotic therapies, including nintedanib and pirfenidone, initially approved for IPF treatment, have demonstrated efficacy in inhibiting fundamental processes in the pathogenesis of lung fibrosis[10]. More recently, both drugs were tested in CTD-ILD, including RA-ILD, showing promising results, particularly with regard to delaying disease progression[11–13]. These results led to the approval of nintedanib for the treatment of chronic fibrosing ILD with a progressive phenotype. However, real-world data on the use of nintedanib and pirfenidone in CTD-ILD, particularly RA-ILD, are scarce. Therefore, this study aims to evaluate the effectiveness and tolerability of antifibrotics in a national, real-world cohort of patients with RA-ILD.

MATERIAL AND METHODS

Study design and population

We conducted an observational, retrospective, multicenter study of RA-ILD patients prospectively followed in Rheumatic Diseases Portuguese Registry (Reuma.pt). Data were collected until March 2024. This work is part of a Reuma.pt project entitled "Lung involvement in rheumatoid arthritis: the portrait of a national cohort". This sub-analysis includes ten centers with registered RA-ILD patients undergoing antifibrotic treatment.

We included patients having i) diagnosis of RA made by the treating rheumatologist, ii) ≥ 18 years old at initial diagnosis, iii) ILD diagnosis based on chest HRCT and iv) treatment with antifibrotics for RA-ILD. Patients who started antifibrotics for an indication other than RA-ILD were excluded.

The index date was date of initiation of the first antifibrotic.

We assessed demographic data (age, race and sex), smoking habits, RA and RA-ILD duration, positivity for rheumatoid factor and/or anti-citrullinated peptide antibodies and previous/concomitant disease modifying antirheumatic drugs (DMARDs).

Effectiveness

We collected chest HRCT and pulmonary function tests (PFTs) at baseline and follow-up. All exams were performed as part of routine clinical practice.

ILD pattern was defined base on chest HRCT images and classified according to the American Thoracic Society/ European Respiratory Society international multidisciplinary classification of idiopathic interstitial pneumonias[14]. Data collected from PFTs included forced vital capacity (FVC; in L and percent predicted [pp] when available), total lung capacity (TLC; in L and pp when available) and diffusion capacity for carbon monoxide (DLCO; pp).

The use of supplementary oxygen was also documented.

In patients who died, the date and the cause of death were retrieved.

Data was collected until March 2024.

Tolerability

We recorded adverse events (AEs) reported and the type of event until last visit confirmed to be on antifibrotic, loss to follow-up or death, whichever occurred first. The date of discontinuation as well as reason for discontinuation or last date verified to be on drug were also retrieved to evaluate drug persistence. If a patient started a second antifibrotic, we also reviewed this drug for tolerability.

Statistical analysis

A descriptive analysis was performed. Continuous variables were expressed as mean ± standard deviation (S.D.) or median with interquartile range (IQR). Categorical variables were presented as absolute values and frequencies. Shapiro-Wilk test was used to evaluate the normality of data distribution.

For the effectiveness analysis, patients having at least one value for FVC, TLC and DLCO 12 (±6) months before and 12 (±6) months after antifibrotic initiation (index date) were included in a linear mixed-effect model with random intercept. Date of antifibrotic initiation (time 0) was used to compare each variable before and after antifibrotic initiation. Since each patient served as their own control, analysis was performed without covariate adjustment.

For tolerability analysis, we used a Kaplan Meier curve with log rank test to assess drug persistence since first antifibrotic initiation. Patients were censored at the time of their last visit confirmed to be under antifibrotic, first antifibrotic cessation or death (whichever came first).
A significance level of 5% was considered. SPSS version 28.0 (IBM Corp, Armonk NY, USA) was used.

Ethics

This study was conducted according to the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies and approved by the ethics committee of Hospital Garcia de Orta. All patients signed the Reuma.pt informed consent and pseudonymised data was processed in accordance with the EU General Data Protection Regulation.

RESULTS

We included 40 patients with RA-ILD treated with antifibrotics, mostly females (55%) and current or past smokers (52.5%). At antifibrotic initiation, mean age was 70.9 ± 7.1 years and median ILD duration 5.0 [IQR 2.3-7.5] years. Nintedanib was used as first antifibrotic drug in 27 (67.5%) patients and pirfenidone in 13 (32.5%). From the 13 patients receiving pirfenidone as first-drug, two were switched to nintedanib due to AEs. Despite UIP being the most prevalent ILD pattern (85.3%), more than half of patients in our cohort were receiving concomitant immunosuppression, with rituximab being the most prescribed biological drug. The detailed patients' characteristics at antifibrotic initiation are showed in Table I.

A total of 20 patients have at least one respiratory functional parameter 12 (±6) months before and 12 (±6) months after antifibrotic initiation in order to be were included in effectiveness analysis. In these patients, the use of antifibrotics interrupted the decline of FVC (decline 300 ± 500 mL in the year before antifibrotic initiation vs. improvement of 200 ± 400 mL in the year following antifibrotic initiation, p=0.336) and total lung capacity (decline 800 ± 300 mL in the year before antifibrotic initiation vs. improvement of 600 ± 900 mL in the year following antifibrotic initiation, p=0.147). DLCO decline documented before the introduction of the antifibrotic drug, persisted after its initiation. Detailed results are reported in Table II.

After a median follow-up of 12.9 years [IQR 6.9-24.3] there were nine deaths, that occurred in average 6.7 ± 3.5 years after RA-ILD diagnosis. Four deaths were related to ILD progression and other four were due to infection (two SARS-CoV-2, one *Pneumocystis jirovecii*, one unknown agent). One patient died of unknown cause.

The initial antifibrotic was discontinued in eighteen (45%) patients (thirteen nintedanib, five pirfenidone). Reasons for discontinuation were AEs (n=12), death (n=5) and patient decision (n=1). The median duration of drug persistence was 150.3 weeks (95% CI 11.0-289.6) with no difference between nintedanib and pirfenidone (Figure 1).

At the end of follow-up, AEs were reported in 16 patients (40%), thirteen (81.2%) receiving nintedanib and three (18.8%) pirfenidone. Only six patients (four nintedanib, two pirfenidone) had the type of AE specified, all being gastrointestinal. Among patients who reported AEs with nintedanib, the dose was reduced to 100mg bid in four of them, with AEs resolution. From the three patients who developed AEs with pirfenidone, two were switched to nintedanib, which they kept until last appointment with good tolerability.

DISCUSSION

This is one of the few real-world studies evaluating the effectiveness and tolerability of antifibrotics in RA-ILD[15]. The use of real-world data allows for the inclusion of more heterogeneous populations and, consequently, more representative of daily clinical practice. Besides, real-world studies also provide information on long-term safety, particularly concerning rare AEs. In our cohort, the use of antifibrotics slowed the rate of decline of FVC and TLC. Similarly, in the INBUILD trial[11], which included patients with a progressive fibrotic ILD phenotype other than IPF treated with nintedanib, the annual rate of decline in FVC was significantly lower among patients who received nintedanib than among those who received placebo (–80.8 ml per year with nintedanib vs. –187.8 ml per year with placebo, p<0.001). These results were confirmed in the sub-analysis of 89 patients with RA-ILD (–82.6 mL per year in the nintedanib group vs. –199.3 mL/year in the placebo group; p =0.037)[12]. TRAIL1[13] aimed to evaluate the use of pirfenidone in RA-ILD, but was early terminated due to slow recruitment and the COVID-19 pandemic. However, it still demonstrated that patients treated with pirfenidone had a slower rate of decline in lung function, measured by estimated annual change in absolute FVC (-66 vs -146; p=0·0082)[13].

This disparity concerning DLCO might be related to the fact that more than half of the patients in our cohort were current/past smokers and smoking is a leading cause of emphysema, which has been documented in two patients of our cohort, in combination with pulmonary fibrosis. Apart from a decline in FVC,

Table I. Characteristics of patients with RA-ILD at initiation of first antifibrotic drug

	Overall (N=40)	Nintedanib (N=27; 67.5%)	Pirfenidone (N=13; 32.5%)
Demographic and lifestyle			
Age (mean ± SD)	70.9 ± 7.1	70.3 ± 7.2	72.2 ± 6.8
Male sex	18 (45%)	9 (33.3%)	9 (69.2%)
Caucasian, missing data = 7	31 (93.9%)	20 (95.2%)	11 (91.7%)
Smoking habits, missing data = 2			
Current	6 (15.8%)	5 (20%)	1 (7.7%)
Past	15 (39.5%)	6 (24%)	9 (69.2%)
Never	17 (44.7%)	14 (56%)	3 (23.1%)
RA characteristics			
RA duration (median [IQR]), missing data = 10	12 [5.5-21.75]	15 [5.75-30]	12 [IQR 2.5-20]
Positive RF, missing data = 2	35 (92.1%)	24 (96%)	11 (84.6%)
Positive ACPA, missing data = 2	36 (94.7%)	24 (96%)	12 (92.3%)
Concomitant RA medication			
Corticosteroids	25 (62.5%)	17 (63%)	8 (61.5%)
MTX	15 (37.5%)	9 (33.3%)	6 (46.2%)
Other csDMARDs	15 (37.5%)	10 (37%)	5 (38.5%)
Rituximab	21 (52.5%)	18 (66.7%)	3 (23.1%)
TNFi	3 (7.5%)	1 (3.7%)	2 (15.4%)
Abatacept	3 (7.5%)	2 (7.4%)	1 (7.7%)
IL6i	1 (2.5%)	0	1 (7.7%)
ILD characteristics			
ILD duration (median [IQR]), missing data = 5	5 [2.3-7.5]	5.25 [3-7.38]	5 [1-7.5]
HRCT ILD pattern, missing data = 6			
UIP	29 (85.3%)	18 (81.8%)	10 (83.3%)
Fibrotic NSIP	4 (11.7%)	3 (13.6%)	2 (16.7%)
Unclassifiable	1 (3%)	1 (4.5%)	0
Mean FVC % (L), missing data = 13	80.4 (2.5)	79.6 (2.5)	81.2 (2.5)
Mean TLC % (L), missing data = 21	80.3 (4.5)	82 (4.6)	78.5 (4.4)
Mean DLCO %, missing data = 19	58.1	54.9	61.4
Supplemental oxygen therapy	6 (15%)	4 (14.8%)	2 (15.4%)

RA – rheumatoid arthritis; ILD – interstitial lung disease; RF – rheumatoid factor; ACPA – anti-citrullinated peptide antibodies; csDMARDs – conventional synthetic disease modifying antirheumatic drugs; MTX – methotrexate; TNFi – Tumor necrosis factor inhibitors, IL-6i – Interleukin 6 inhibitors; HRCT – high resolution computed tomography; UIP – usual interstitial pneumonia; NSIP – nonspecific interstitial pneumonia; FVC – forced vital capacity; TLC – total lung capacity; DLCO – diffusion capacity for carbon monoxide

a reduced DLCO is a hallmark of the disease. More recently, a new syndrome of combined pulmonary fibrosis and emphysema (CPFE) has been described[16]. It typically occurs in male smokers and has also been reported as a pulmonary manifestation within the spectrum of CTD-associated lung disease, including RA[17]. It is characterised by the presence of upper lobe emphysema and lower lobe fibrosis in imaging and a severely impaired DLCO [18]. Its recognition is crucial, as it has a distinctive physiological profile, associated with an increased risk of complications (pulmonary hypertension, lung cancer and mortality) compared to those with IPF and no emphysema or emphysema less than 10–15%[19].

On the other hand, pulmonary hypertension (PH) can also be responsible for a disproportionate reduction in DLCO. Although the prevalence of PH in the course of RA is less frequent than in other CTDs[20], it can also occur in RA. Several causes can lead to development of PH in RA[21], but ILD is the most frequent[22]. PH is also rather frequent in patients with CPFE syndrome and its presence is associated with a poorer[17]. However, the presence of PH was not evaluated in our study.

Table II. Comparison between mean FVC, TLC and DLCO before and after antifibrotic initiation, using a linear mixed-effect model

	12 (±6) months before antifibrotic initiation	Antifibrotic initiation	12 (±6) months after antifibrotic initiation	p-value
	Mean ± S.D.	Mean ± S.D.	Mean ± S.D.	
FVC (L)	2.4 ± 0.6	2.1 ± 0.5	2.3 ± 0.7	0.336
FVC (pp)	78.4 ± 15.0	70.7 ± 20.8	71.4 ± 23.3	0.496
TLC (L)	4.7 ± 0.8	3.9 ± 0.6	4.5 ± 0.9	0.147
TLC (pp)	80.0 ± 17.0	80.3 ± 24.0	81.7 ± 14.9	0.974
DLCO (pp)	54.1 ± 18.9	51.1 ± 18.3	48.2 ± 21.4	0.750

FVC – forced vital capacity; TLC – total lung capacity; DLCO – diffusion capacity for carbon monoxide; pp – percentage predicted

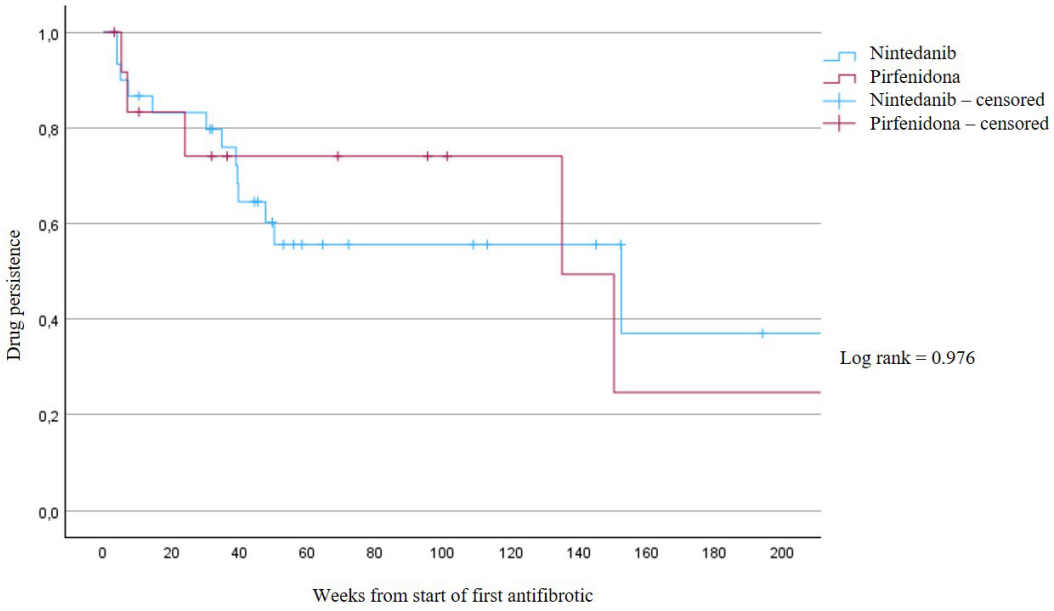

Figure 1. Kaplan Meier curves comparing drug persistence after starting the first antifibrotic

Despite the use of antifibrotics, ILD progression was responsible for the death of four patients, accounting for almost 50% of mortality in our cohort. However, we must be aware that antifibrotics are mostly prescribed to patients with more severe and progressive forms of ILD.

Regarding concomitant treatment, at least half of the patients in our cohort was receiving concomitant immunosuppression, targeting both inflammatory and fibrotic processes present in the pathogenesis of RA-ILD[23]. Rituximab was the most prescribed biological drug probably due to the fact that its use has been associated with lung disease stabilization/improvement[4,25].

AEs are not negligible in this class of drugs. In previous trials including IPF (CAPACITTY[26], INPULSIS[27]) and non-IPF patients (INBUILD[11], TRAIL1[13] and SENSCIS[11]) treated with both antifibrotics, gastrointestinal AEs were the most prevalent AEs, but with a higher prevalence than the one reported in our cohort. Similar to our results, AEs were also more frequently reported in patients treated with nintedanib compared to pirfenidone in INPULSIS[27] and CAPACITY[26] trials. LOTUSS trial[28], which was designed to evaluate the tolerability of pirfenidone in systemic sclerosis-associated ILD, concluded that longer titration may be associated with better tolerability. In daily clinical practice, the presence of possible AEs should be evaluated in all appointments, as this could be compromising therapeutic adherence.

Discontinuation rate in our cohort was higher than the ones reported in clinical trials (INBUILD[11] 19.6%; TRAIL 1[13] 24%; SENSCIS[29] 16%), but similar to real-world studies previously published [15,30].

Our study does not include a control group (RA-ILD

without antifibrotics). However, in clinical practice, patients receiving antifibrotics typically have more severe and progressive ILD, usually associated with a longer RA duration and seropositivity, while those that remain untreated usually have milder forms of the disease. Therefore, the creation of a control group without blind randomization would be biased regarding ILD severity.

Other limitations can be pointed out, such as the absence of symptomatic and imaging assessment for lung disease progression.

The small sample size may have decreased the power to detect significant differences in change of lung function and also limits the performance of other sub-analyses, namely the combination of antifibrotics with rituximab vs. other immunosuppressants.

The fact that most of these patients are concomitantly followed by pulmonologists, who are responsible for managing antifibrotic therapy, may result in more data being missing from Reuma.pt, particularly with regard to PFTs. The absence of a standardized protocol can also lead to inconsistencies in definitions and practices over time and sites, particularly when there are no specific recommendations regarding RA-ILD treatment. On the other hand, the absence of strict inclusion and exclusion criteria in our study enables the inclusion of a not so-controlled population, but wider and consequently more heterogeneous and representative of real-world practice.

The management of RA patients has greatly improved over the last years, with the introduction of several new drugs, leading to an overall reduction in mortality[31]. However, ILD remains an important cause of death in RA, with RA-ILD patients having a 2 to 10 times higher mortality rate than those without RA-ILD[32,33]. Some data have even shown that respiratory diseases, including ILD, may have supplanted cardiovascular diseases as a major contributor of mortality in RA[34]. With increased clinicians' awareness for ILD in RA and the current approval of nintedanib for the treatment of chronic fibrosing ILD with a progressive phenotype, which includes RA-ILD, we hope that care provided to RA-ILD patients will improve, and ultimately their prognosis. Therefore, sharing real-world data can reinforce the promising results demonstrated in clinical trials and lead to a widespread use of these drugs.

CONCLUSION

Our real-world data showed that the use of pirfenidone and nintedanib stabilizes lung function in RA-ILD, when considering FVC and TLC. However, particular attention must be paid to AEs, as they are quite common in patients receiving antifibrotics, and a major cause of drug discontinuation. In the future, studies with larger sample size are essential to obtain more robust results, particularly regarding effectiveness analysis and comparisons between different treatment strategies.

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