Non–anti-TNF biologic agents not associated with a worsening of lung disease secondary to rheumatoid arthritis.

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Abstract

Objectives To analyze the effect of disease-modifying antirheumatic drugs (DMARDs) on the outcome of interstitial lung disease secondary to rheumatoid arthritis (RA-ILD).

Patients and methods We performed a multicenter, prospective, observational study of patients with RA-ILD receiving DMARDs between 2015 and 2017. The patients were assessed using high-resolution computed tomography and pulmonary function tests at baseline and at 24 months. The radiological assessment was centralized. The main outcome measure at 24 months was change in lung function (improvement, stabilization, worsening, or death). We recorded the 28-joint Disease Activity Score 28 (DAS28) and adverse events. A logistic regression analysis was performed to identify factors associated with worsening of ILD.

Results After 24 months, lung disease was stabilized in 40 patients (57.1%), improved in 8 (11.4%), and worse in 21 (30.0%). One patient (1.4%) died. The factors associated with worsening of ILD in the multivariate analysis were treatment with abatacept, tocilizumab, or rituximab (OR, 0.102 [95%CI, 0.015-0.686]), DAS28 (OR, 1.969 [95%CI, 1.005-3.857]), and smoking (OR, 6.937 [95%CI, 1.378-4.900]). During follow-up, 30 patients (42.9%) experienced an adverse event, which was severe in 12 cases (17.1%).

Conclusions Lung function is stable and inflammatory activity well controlled in most patients with RA-ILD receiving treatment with DMARDs. Non–anti-TNF DMARDs reduce the risk of worsening of lung disease in 90% of patients. The inflammatory activity of RA and smoking, on the other hand, are associated with worsening.

Introduction

Rheumatoid arthritis (RA) is chronic immune-mediated inflammatory disease of unknown origin that mainly affects the joints, although systemic involvement is also common. The lung is one of the most frequently affected organs, with significant morbidity and mortality (1, 2). Interstitial lung disease (ILD) is the most frequent non pleural lung manifestation in patients with RA, and 8–12% develop clinically relevant ILD. However, subclinical disease, which is detected via systematic screening, is found in 22–33% of patients with established RA (3). Men, smokers, patients with severe joint disease, and patients with positive autoantibody titers are at a greater risk of worsening of ILD (4–6). The disease is associated with poor prognosis and higher mortality (7, 8) and is currently considered the second cause of death in patients with RA after cardiovascular disease (7).

Treatment of arthritis is based on conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted synthetic DMARDs, and biologic DMARDs (bDMARDs). Treatment of ILD in patients with RA (RA-ILD) is usually with corticosteroids combined or not with immunosuppressive agents, such as mycophenolate mofetil (MMF), azathioprine, and cyclophosphamide (9). However, these drugs are of little benefit in joint disease, and patients continue to need treatment for their arthritis.

Studies on the efficacy and safety profile of DMARDs in patients with RA-ILD are scarce, and results are contradictory (10–12). A meta-analysis of randomized controlled trials found an association between methotrexate and the risk of respiratory events and hypersensitivity pneumonitis (13). Leflunomide has also been associated with the risk of lung involvement (14, 15). However, the definition of pneumonitis in these studies was not specific (16), and subsequent studies did not show an association between methotrexate or leflunomide and worsening of RA-ILD (16, 17). Recent years have seen an increase in the number of published cases of RA-ILD during treatment with bDMARDs, and findings have been somewhat controversial. Some studies did not report worsening with anti-TNF agents (18), whereas others did (19), particularly compared with agents such as abatacept (20), rituximab (21), and tocilizumab (22), although treatment with some of these agents has proven fatal (23).

Owing to these contradictory results and the fact that most studies are cross-sectional or retrospective, it is difficult to determine how RA-ILD worsens in patients who continue treatment with DMARDs. The objective of the present study was to perform a prospective analysis of the worsening of RA-ILD in patients treated with DMARDs.

Patients And Methods

Design

We performed a multicenter observational prospective study of a series of cases of RA-ILD in 5 teaching hospitals in Andalucía, Spain. Subjects were recruited between March 2015 and June 2017. The study was approved by the Research Ethics Committee of Hospital Regional Universitario de Málaga (HRUM), Malaga, Spain. All subjects provided their written informed consent before participating in the study.

Study population

We consecutively recruited adults with RA classified according to the 2010 criteria of the American College of Rheumatology/European League Against Rheumatism (24) and ILD confirmed using pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT) or lung biopsy. Patients had had ILD for different periods of time when they were included in the study and were all receiving DMARDs. We excluded patients with inflammatory or rheumatic diseases other than RA (except secondary Sjögren syndrome), infection, primary pulmonary hypertension, congestive heart failure, and known exposure to fibrosing environmental agents (eg, asbestos). Pregnancy was also an exclusion criterion.

Protocol

Selected patients were seen by a rheumatologist, who followed a pre-established protocol for collection of clinical and laboratory data on the date of inclusion (v0), at 12 months (v12), and at 24 months (v24). PFT was performed at each visit, and HRCT was performed at visits v0 and v24. All HRCT scans were made with axial sections (1.5 or 2 mm in thickness) taken at 1-cm intervals along the thorax. Images were reconstructed with a high spatial frequency algorithm (20–25 slices per patient). The radiological

evaluation was centralized in HRUM and performed blind and independently by 2 experts in radiological imaging of the lung. Discrepancies were resolved by consensus.

Operational definitions and variables

The main variable was “outcome of ILD at v24”, as follows: (1) improvement (i.e. improved forced vital capacity [FVC] ≥ 10% or diffusing capacity of the lung for carbon monoxide [DLCO] ≥ 15% and no radiological worsening), (2) stabilization (stabilization or improvement in FVC ≤ 10% or DLCO < 15% and no radiological worsening), (3) worsening (decrease in FVC > 10% or DLCO > 15% and radiological worsening), and (4) death from a cause associated with ILD (20). Radiological worsening was defined as an increase of 20% or more in the presence and extension of ground-glass opacities, reticulation, honeycombing, diminished attenuation, centrilobular nodules, other nodules, emphysema, or consolidation in comparison with the CT scan from v0.

The different patterns of ILD were defined according to lung biopsy findings or HRCT based on the standard criteria of the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (25). The 3 patterns defined were nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), and other patterns (eg, bronchiolitis obliterans, organizing pneumonia, and mixed patterns). The PFTs included complete spirometry expressed as percent predicted and corrected for age, sex, and height. Abnormal FVC was defined as ≤ 80% of predicted. DLCO was evaluated using the single-breath method (DLCO-SB) and was considered abnormal if its value was ≤ 80%.

RA-related variables included duration of symptoms, systemic manifestations, smoking history (current or past), and respiratory infections during follow-up. Joint involvement was evaluated using the 28-joint Disease Activity Score (DAS28) and its components (26), acute-phase reactants, and physical functioning based on the Health Assessment Questionnaire (HAQ) (27). We also collected variables associated with severity, as follows: rheumatoid factor (reference value, 20 U/ml; high titer > 60 U/ml); anticitrullinated protein antibody (reference value, 10 U/ml, high values > 340 U/mL); radiographic evidence of at least 1 bone erosion. We recorded treatment with csDMARDs, bDMARDs, other immunosuppressants, and corticosteroids at baseline and during the course of the disease. Data on adverse events were collected.

Statistical analysis

A descriptive analysis of the main variables was performed. Qualitative variables were expressed as an absolute number and percentage; quantitative variables were expressed as the mean (SD) or median (IQR), depending on the normality of the distribution as assessed using the Kolmogorov-Smirnov test. The bivariate analysis was performed using a paired t test or Wilcoxon test, as applicable, between v0 and v24. Finally, various binary regression models were constructed (dependent variable: worsening of lung involvement at v24) in order to determine the independent variables associated with worsening of ILD. The analysis was performed using Rcommander.

Results

1. Baseline clinical characteristics

We included 70 patients with RA-ILD treated with DMARDs. The main baseline characteristics are shown in Table 1. Patients were aged around 70 years, with a similar percentage of men and women. While most patients were not smokers at inclusion, two-thirds reported having smoked in the past. Almost all patients had chronic seropositive erosive joint disease. On entering the study, they had had ILD for a mean of 3.5 years. The most frequent radiological pattern was UIP in 46/70 patients (65.7%), followed by NSIP in 15/70 (21.4%), and fibrotic NSIP in 9/70 (14.8). UIP-type ILD was histologically confirmed in 2 patients.

Table 1

Baseline characteristics of 70 patients with RA-ILD receiving treatment with DMARDs

Variable	Patients (n = 70)
Epidemiological characteristics	
Female sex, n (%)	39 (55.7)
Male sex, n (%)	31 (44.3)
Caucasian race, n (%)	68 (97.1)
Age, y, mean (SD)	68.8 (7.8)
Clinical-laboratory characteristics	
Smoking	
Nonsmokers, n (%)	57 (81.4)
Smokers, n (%)	13 (18.6)
Smoking history	
Never smoked, n (%)	23 (32.9)
Smoked, n (%)	47 (67.1)
Body mass index, mean SD	28.6 (4.9)
Duration of RA, (months), mean (SD)	161.0 (125.9)
Time since diagnosis of ILD, (months), mean (SD)	42.3 (48.3)
Positive rheumatoid factor (> 10), n (%)	65 (92.0)
ACPA (> 20), n (%)	58 (82.9)
Double seropositivity (RF + and ACPA +), n (%)	56 (81.2)
Erosive disease, n (%)	43 (61.4)
Systemic manifestations	
Serositis (pleuritis or pericarditis), n (%)	14 (20.3)
Vasculitis, n (%)	2 (2.9)
Rheumatoid nodules, n (%)	13 (18.6)
Anemia of chronic disease, n (%)	19 (27.5)

Abbreviations. RA, rheumatoid arthritis; ILD, interstitial lung disease; DMARD, disease-modifying antirheumatic drug; SD, standard deviation; RF, rheumatoid factor; ACPA, anticitrullinated protein antibody.

Variable	Patients (n = 70)
Sjögren syndrome, n (%)	12 (17.1)
Osteoporosis, n (%) Treatment	33 (47.1)
Synthetic DMARDs	64 (91.4)
Methotrexate, n (%)	30 (42.9)
Leflunomide, n (%)	16 (22.9)
Sulfasalazine, n (%)	8 (11.4)
Hydroxychloroquine, n (%)	10 (14.3)
Biologic DMARDs	27 (38.1)
Infliximab, n (%)	1 (1.4)
Etanercept, n (%)	4 (5.7)
Adalimumab, n (%)	1 (1.4)
Golimumab, n (%)	1 (1.4)
Certolizumab, n (%)	0 (0.0)
Tocilizumab, n (%)	5 (6.2)
Abatacept, n (%)	5 (6.2)
Rituximab, n (%)	10 (14.3)
Other immunosuppressants	
Mycophenolate, n (%)	4 (5.7)
Azathioprine, n (%)	1 (1.4)
Corticosteroids	
Baseline, n (%)	39 (55.7)
Baseline dose, median (IQR)	5.0 (5.0–10.0)
Previous corticosteroids, n (%)	70 (100.0)
Previous treatment	
Synthetic DMARDs	

Abbreviations. RA, rheumatoid arthritis; ILD, interstitial lung disease; DMARD, disease-modifying antirheumatic drug; SD, standard deviation; RF, rheumatoid factor; ACPA, anticitrullinated protein antibody.

Variable	Patients (n = 70)
Methotrexate, n (%)	40 (55.2)
Leflunomide, n (%)	24 (34.8)
Sulfasalazine, n (%)	11 (15.7)
Hydroxychloroquine, n (%)	7 (10.0)
Biologic DMARDs	
Infliximab, n (%)	1 (1.4)
Etanercept, n (%)	3 (4.3)
Adalimumab, n (%)	5 (7.1)
Golimumab, n (%)	1 (1.4)
Certolizumab, n (%)	0 (0.0)
Tocilizumab, n (%)	2 (2.9)
Abatacept, n (%)	1 (1.4)
Rituximab, n (%)	3 (4.3)
Abbreviations. RA, rheumatoid arthritis; ILD, interstitial lung disease; DMARD, disease-modifying antirheumatic drug; SD, standard deviation; RF, rheumatoid factor; ACPA, anticitrullinated protein antibody.	

At v0, all patients were taking a DMARD, mostly an csDMARD, with somewhat more than one-third taking a bDMARD. A total of 41 patients (58.6%) were taking an csDMARD in monotherapy, 23 (32.9%) were taking a combination of DMARDs, and 4 (5.7%) were taking a bDMARD. The different DMARDs prescribed at v0 are shown in Table 1. Five patients combined a DMARD with MMF or azathioprine. More than half of the patients were taking corticosteroids at < 7.5 mg/d. Most patients (49 [70%]) had received at least 1 csDMARD before v0, 14 patients (19%) had taken a bDMARD for a median of 24 (17.0–26.0) months and 21 (30%) were taking their first csDMARD.

2. Outcome of ILD at 24 months

After 24 months, a total of 69 patients remained in follow-up. As shown in Table 2, mean lung function values worsened significantly, particularly FVC and DLCO-SB (Fig. 1). However, progression according to the HRCT scan was observed at 24 months in only one-third of the patients, who fulfilled the criteria for worsening of ILD. One patient died because of worsening and lung infection while receiving leflunomide and rituximab.

Table 2

Progress of symptoms and lung involvement after 24 months of follow-up in patients with RA-ILD receiving treatment with DMARDs.

Variable	Baseline	24 months	p value
Pulmonary function tests			
Oxygen saturation, mean (SD)	96.2 (1.9)	95.8 (2.7)	0.225
FVC, mean (SD)	71.9 (19.0)	67.6 (20.9)	0.016
FVC < 80%, n (%)	42 (60.0)	46 (65.5)	0.157
FVC ≥ 80%, n (%)	28 (40.0)	24 (34.5)	
FEV_1, mean (SD)	76.9 (18.3)	73.5 (23.0)	0.164
DLCO, mean (SD)	63.3 (14.7)	57.2 (10.2)	0.015
HRCT scan			
Radiological type			0.220
UIP, n (%)	46 (65.7)	50 (71.4)	
NSIP, n (%)	15 (21.4)	13 (18.5)	
Fibrotic NSIP, n (%)	9 (14.8)	6 (8.5)	
Outcome			
Progression, n (%)	-	21 (30.4)	
Stabilization, n (%)	-	42 (60.8)	
Worsening, n (%)	-	6 (8.6)	
Pulmonary outcome, overall*			
Improvement, n (%)	-	8 (11.4)	
Stabilization, n (%)	-	40 (57.1)	
Worsening, n (%)	-	21 (30.0)	
Death, n (%)	-	1 (1.4)	

Abbreviations. RA, rheumatoid arthritis; ILD, interstitial lung disease; DMARD, disease-modifying antirheumatic drug; SD, standard deviation; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; DLCO, diffusing capacity of the lung for carbon monoxide; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; HRCT, high-resolution computed tomography; DAS28, 28-joint Disease Activity Score; NPJ, number of painful joints; NIJ, number of inflamed joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; *Lung outcome, overall, taking into account HRCT and LFTs (FVC and DLCO).

Variable	Baseline	24 months	p value
Inflammatory activity			
DAS28, mean (SD)	2.9 (1.4)	2.6 (1.1)	0.124
C-reactive protein, median (IQR)	5.0 (2.9–13.0)	4.5 (2.6–15.0)	0.132
HAQ, mean (SD)	0.70 (0.1)	0.84 (0.1)	0.600

Abbreviations. RA, rheumatoid arthritis; ILD, interstitial lung disease; DMARD, disease-modifying antirheumatic drug; SD, standard deviation; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; DLCO, diffusing capacity of the lung for carbon monoxide; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; HRCT, high-resolution computed tomography; DAS28, 28-joint Disease Activity Score; NPJ, number of painful joints; NIJ, number of inflamed joints; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; *Lung outcome, overall, taking into account HRCT and LFTs (FVC and DLCO).

In terms of joint involvement, patients remained stable. Forty patients continued taking csDMARDs in monotherapy, 19 were taking a combination of DMARDs, and 10 continued taking bDMARDs in monotherapy. One patient switched leflunomide for hydroxychloroquine owing to a nonsevere adverse effect. The remaining DMARDs were modified owing to lack of efficacy against joint disease (5 with csDMARDs and 1 with tocilizumab); 2 patients started abatacept owing to poor control of joint disease, and 1 patient initiated MMF owing to worsening of lung disease.

3. Factors associated with worsening of lung disease at 24 months of follow-up

Table 3 shows the main differences between patients with RA-ILD and worsening of lung disease and the others. We can see that more marked worsening was observed in active smokers and exsmokers and in patients with a higher DAS28. Similarly, these patients more frequently received treatment with leflunomide, MMF, and corticosteroids and less frequently with a non–anti-TNF bDMARD. There were no differences in sociodemographic variables, time since diagnosis, the frequency of autoantibodies, or the presence of erosions.

Table 3

Factors associated with progression of lung disease in patients with RA-ILD after 24 months of follow-up

Variable	Improvement or stabilization (n = 48)	Worsening or death (n = 22)	p value
Clinical characteristics			
Smoking			0.205
Nonsmoker, n (%)	41 (85.4)	16 (72.7)	
Never smoker, n (%)	19 (39.6)	4 (18.2)	0.047
Smoked in past, n (%)	29 (60.4)	18 (81.8)	0.047
Smokers, n (%)	7 (14.6)	6 (27.3)	
Mild-moderate infection, n (%)	18 (37.5)	12 (54.5)	0.181
Severe infection, n (%)	8 (16.7)	4 (18.2)	0.876
DAS28, mean (SD)	2.8 (1.0)	3.5 (1.1)	0.011
Remission-low activity, n (%)	33 (68.8)	7 (31.8)	0.004
Moderate-high activity, n (%)	15 (31.3)	15 (68.2)	0.004
HAQ, mean (SD)	0.89 (0.7)	1.30 (0.9)	0.200
Treatment			
Combined therapy, n (%)	16 (33.3)	4 (19.0)	0.229
Type of DMARD			
scDMARDs, n (%)	39 (81.3)	19 (90.5)	0.335
Methotrexate, n (%)	24 (50.0)	7 (33.3)	0.200
Leflunomide, n (%)	4 (8.3)	6 (28.6)	0.028
Sulfasalazine, n (%)	6 (15.0)	2 (9.5)	0.722
Hydroxychloroquine, n (%)	5 (12.5)	4 (19.0)	0.327
Immunosuppressants	2 (4.2)	4 (18.2)	0.052
Mycophenolate, n (%)	1 (2.5)	4 (19.0)	0.025

Abbreviations: RA, rheumatoid arthritis; ILD, interstitial lung disease; SD, standard deviation; BMI, body mass index; DAS28, 28-joint Disease Activity Score; ACPA, anticitrullinated protein antibodies; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying antirheumatic drug.

Variable	Improvement or stabilization (n = 48)	Worsening or death (n = 22)	p value
Azathioprine, n (%)	1 (2.5)	0 (0.0)	0.465
bDMARDs, n (%)	23 (47.9)	6 (28.6)	0.134
Anti-TNF, n (%)	3 (6.3)	4 (18.2)	0.122
Infliximab, n (%)	0 (0.0)	1 (4.8)	0.164
Etanercept, n (%)	2 (5.0)	2 (9.5)	0.498
Adalimumab, n (%)	0 (0.0)	1 (4.8)	0.164
Golimumab, n (%)	1 (2.5)	0 (0.0)	0.465
Certolizumab, n (%)	0 (0.0)	0 (0.0)	-
Non–Anti-TNF, n (%)	20 (41.7)	2 (9.1)	0.006
Tocilizumab, n (%)	3 (6.3)	1 (4.8)	0.681
Abatacept, n (%)	8 (16.7)	0 (0.0)	0.042
Rituximab, n (%)	9 (18.8)	1 (4.8)	0.129
Corticosteroids,			
Taking corticosteroids, n (%)	22 (55.0)	17 (81.0)	0.045

Abbreviations: RA, rheumatoid arthritis; ILD, interstitial lung disease; SD, standard deviation; BMI, body mass index; DAS28, 28-joint Disease Activity Score; ACPA, anticitrullinated protein antibodies; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying antirheumatic drug.

The multivariate analysis revealed that treatment with a non–anti-TNF bDMARDs—abatacept, rituximab, or tocilizumab, in that order—was associated with a 90% reduced relative risk of worsening of RA-ILD, whereas smoking—current or past—was associated with an almost 7-fold greater probability of worsening of lung disease (Table 4).

Table 4
Multivariate analysis. Variables independently associated with progression of lung disease in RA-ILD patients.

Predictor	OR	(95% CI)	p value
Non–anti-TNF biologics	0.102	0.015–0.686	0.019
Average DAS28	1.969	1.005–3.857	0.048
History of smoking	6.937	1.378-4.900	0.019
Nagelkerke R2 = 0.465			

Abbreviations: RA, rheumatoid arthritis; ILD, interstitial lung disease; DAS28: 28-joint Disease Activity Score; Independent variables: sex, age, anti-TNF treatment (infliximab, adalimumab, etanercept, golimumab, certolizumab), non–anti-TNF treatment (rituximab, abatacept, tocilizumab); scDMARDs (methotrexate, leflunomide, hydroxychloroquine, sulfasalazine), immunosuppressants (azathioprine, mycophenolate), corticosteroids, smoking history, DAS28.

Adverse events

During follow-up, 30 patients (42.9%) experienced adverse events; these were mainly mild (25.7%), although 12 (17.1%) were severe. Mild adverse events were mainly respiratory infection (15 patients, 21.4%), labial herpes (1 patient, 1.4%), dental infection (1 patient, 1.4%), and cellulitis (1 patient, 1.4%). The severe events included respiratory infection requiring admission to hospital in 9 patients (12.8%), urosepsis in 2 patients (2.8%), and death in 1 patient (1.4%). Medication was discontinued permanently in only 2 patients: the patient who died while taking rituximab and leflunomide, and a patient with severe lung infection taking leflunomide.

Discussion

We prospectively evaluated lung and joint function in 70 patients with RA-ILD receiving treatment with various DMARDs. We observed worsening of lung disease in a minority of patients after 24 months of follow-up, although arthritis continued to be well-controlled. Mean PFT values fell gradually during follow-up; however, most decreases were detected in 30% of patients.

In our study, csDMARDs were not generally associated with more marked worsening of lung disease after 24 months of follow-up, although individually, more patients presented worsening of lung involvement when receiving leflunomide, MMF, and corticosteroids, probably because patients with poorer lung outcomes were more likely to require corticosteroids and MMF (both are frequently used for treatment of ILD) (9). The same bias arises with leflunomide, especially in patients with more poorly controlled arthritis, since a systematic review and meta-analysis covering 4579 patients suggested a lower risk of noninfectious respiratory adverse events (RR, 0.64) with leflunomide than with methotrexate or placebo (17).

bDMARDs have also been reported to be possible triggers of ILD. They can worsen pre-existing ILD or increase susceptibility to infection (28). Similar to findings reported by other authors at 12 months (18), we found that lung disease had not worsened at 24 months in patients who took anti-TNF agents. However, other studies (19) reported more marked worsening of RA-ILD in patients treated with anti-TNF agents (24.1%) than in those treated with other biologics, thus suggesting that non–anti-TNF inhibitors are a good therapeutic option in this population. Our multivariate analysis revealed that non–anti-TNF biologics reduce the risk of worsening of lung disease at 24 months by 90%, with more importance given to abatacept, followed by rituximab and tocilizumab. We do not know whether these biologic agents have an intrinsic effect on RA-ILD, although in recent years, abatacept has been associated with improvement and stabilization of lung function in patients with RA-ILD in small case series (29–31). More recently, Fernández-Díaz et al. (20) reported the results of a multicenter prospective study of 63 patients with RA treated with abatacept, in which pulmonary function was stable after 12 months of treatment. In our study, 8 patients were receiving abatacept at 24 months, and none presented worsening of lung involvement. In experimental studies, cytotoxic T-lymphocyte antigen 4 has been tested as a major target in lung inflammation in other lung diseases such as hypersensitivity pneumonitis. In this context, abatacept may be a potential therapy for RA-ILD (20, 32).

In our study, 10 patients were taking rituximab, and in most (9/10), their condition improved or stabilized, although 1 patient died owing to worsening of lung disease. In the study of Yusof et al. (33), the authors observed that in most patients with RA-ILD treated with rituximab, their condition stabilized (23/44; 52%) or improved (7/44; 16%), although it worsened in 14 patients (32%). Of these, 9 died from worsening of lung involvement. As these patients had more severe RA-ILD before treatment, the results may have been subject to an indication bias.

The number of patients treated with tocilizumab in our study was too low to draw conclusions, although pulmonary function improved/stabilized in 3 of 4 patients treated with this agent. Some authors have reported isolated cases of worsening of RA-ILD after 24 months of follow-up (34, 35), whereas others (22) reported stabilization of lung disease after 30 months of follow-up.

It is noteworthy that the percentage of patients whose condition stabilized, improved, and worsened (57%, 12%, and 31%) in our study is similar to those reported in other prospective studies (18, 20, 33) and retrospective studies (22) with bDMARDs. Therefore, these findings can only be explained by the natural history of RA-ILD. In fact, during the prospective follow-up of the study patients, we observed no significant impairment in lung function at 12 months of follow-up, although we did record significant worsening at 24 months. Several authors have reported DLCO to be the earliest indicator of worsening of lung function in these patients (6, 36).

Our results also show that smoking and inflammatory activity in joints act independently in the worsening of lung disease. On the one hand, smoking and other stimuli could contribute to citrullination of proteins (37) and to other respiratory conditions, such as emphysema, which further impair lung function (38). On the other, systemic inflammation associated with poor disease control could be

associated with worsening of lung involvement in RA-ILD (39) and control of arthritis with stabilization of lung involvement (20). We made a similar observation in our study.

Our study is subject to a series of limitations. First, the fact that this was a multicenter study could lead to differences in the evaluation of lung function. In order to mitigate this risk, HRCT was centralized by taking advantage of the fact that the radiological findings could be reported online. In addition, the prospective follow-up meant that no data were missing. Second, patients had already been treated at the start of the follow-up period. Third, we had no control group. This makes it difficult to interpret the effect of each of the drugs on the natural course of ILD. Nevertheless, our objective was to evaluate the clinical course of patients with RA-ILD treated under conditions of daily clinical practice. This did not prevent us from comparing different treatment groups. In fact, one of the strengths of the study was the prospective evaluation of different treatment groups in patients with RA-ILD in both joint and lung assessments.

Conclusions

In conclusion, lung function stabilizes, and inflammatory activity is well controlled in most patients with RA-ILD receiving treatment with DMARDs. Neither csDMARDs nor anti-TNF agents were associated with a significant risk of worsening of lung disease, whereas non–anti-TNF bDMARDs could reduce the risk of worsening of lung disease. Smoking and poor control of joint involvement were the main factors associated with worsening of lung disease.

Abbreviations

bDMARDs
Biologic DMARDs
DAS28
Disease Activity Score.
DLCO
Diffusing capacity of the lung for carbon monoxide [DLCO]
DMARDs
Disease-modifying antirheumatic drugs.
FVC
Forced vital capacity.
HRCT
High-resolution computed tomography.
HRUM
Hospital Regional Universitario de Málaga.
ILD
Interstitial lung disease.
MMF
Mycophenolate mofetil.

Non–anti-TNF agents
Biologic DMARDs non anti-tumor necrosis factor alpha.
PFTs
Pulmonary function tests.
RA
Rheumatoid arthritis.
RA-ILD
Interstitial lung disease secondary to rheumatoid arthritis.
csDMARDs
Conventional synthetic disease-modifying antirheumatic drugs.

Declarations

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Author contributions statement

NMV participated in the design of the study, carried out patient recruitment and statistical analysis, and drafted the manuscript. FJGN and SMA were a contributor in including patients. They were a major contributor in writing the manuscript and they were a contributor in analyzing and interpreting the patient data. MCAH and MIPM collected radiology data. IUG, MCRB, FGJN, IAO, LPA and CGC were a major contributor in including patients. AFN: A contributor in writing the manuscript. He was a contributor in analyzing and interpreting the patient data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Málaga (“Comité de Ética de la Investigación de Málaga”). (Project identification code 4/2015, P15).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

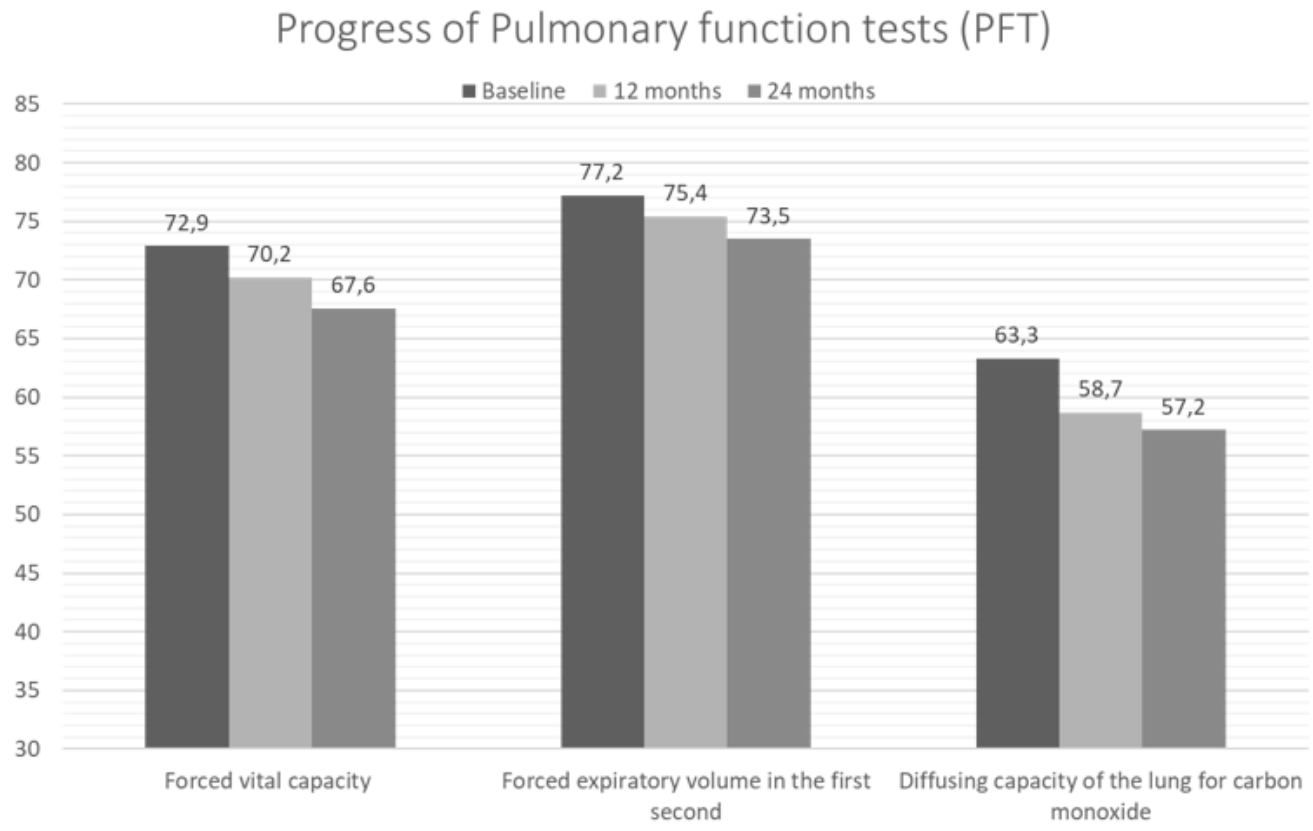

Figure 1

Progress of pulmonary function tests after 24 months of follow-up in patients with RA and ILD receiving treatment with DMARDs.