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.

| 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)        |
| Sjögren syndrome, n (%)               | 12 (17.1)        |
| Osteoporosis, n (%)                   | 33 (47.1)        |
| **Treatment**                         |                  |
| 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)          |
| Drug                        | n (%)  |
|-----------------------------|--------|
| 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            |        |
| 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)  |         |
| FEV₁, 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)    |         |
| 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; FEV₁, 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)                    |         |
| **Moderate-high activity, n (%)   | 15 (31.3)                            | 15 (68.2)                   | 0.004   |
| 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   |
| **Treatment**                     |                                      |                             | 0.229   |
| Combined therapy, n (%)           | 16 (33.3)                            | 4 (19.0)                    |         |
| **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   |
| 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,**              | 22 (55.0)                            | 17 (81.0)                   | 0.045   |
| Taking corticosteroids, n (%)     |                                      |                             |         |

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.

**References**

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023-38.

2. Hallowell RW, Horton MR. Interstitial lung disease in patients with rheumatoid arthritis: spontaneous and drug induced. Drugs. 2014;74(4):443-50.
3. Gabbay E ea. Interstitial lung disease in recent onset rheumatoid arthritis. 2015.

4. Mori S ea. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. 2015.

5. Alexiou I, Germanis A, Koutroumpas A, Kontogianni A, Theodoridou K, Sakkas LI. Anti-cyclic citrullinated peptide-2 (CCP2) autoantibodies and extra-articular manifestations in Greek patients with rheumatoid arthritis. Clin Rheumatol. 2008;27(4):511-3.

6. Mena-Vazquez N, Perez Albaladejo L, Manrique-Arija S, Romero Barco CM, Gomez Cano C, Urena Garnica I, et al. Analysis of Clinical-Analytical Characteristics in Patients with Rheumatoid Arthritis and Interstitial Lung Disease: Case-Control Study. Reumatol Clin. 2019.

7. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183(3):372-8.

8. Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. Scand J Rheumatol. 2004;33(4):221-7.

9. Saketkoo LA, Espinoza LR. Rheumatoid arthritis interstitial lung disease: mycophenolate mofetil as an antifibrotic and disease-modifying antirheumatic drug. Arch Intern Med. 168. United States2008. p. 1718-9.

10. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheumatol. 2014;66(4):803-12.

11. Ramos-Casals M, Brito-Zeron P, Munoz S, Soria N, Galiana D, Bertolaccini L, et al. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases.
12. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDs and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43(5):613-26.

13. Conway R et al. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. 2015.

14. Ju JH, Kim SI, Lee JH, Lee SI, Yoo WH, Choe JY, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. Arthritis Rheum. 2007;56(6):2094-6.

15. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006;54(5):1435-9.

16. Rojas-Serrano J et al. Methotrexate and lung disease in rheumatoid arthritis: comment on the article by Conway et al. 2015.

17. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Leflunomide Use and Risk of Lung Disease in Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis of Randomized Controlled Trials. J Rheumatol. 2016;43(5):855-60.

18. Detorakis EE, Magkanas E, Lasithiotaki I, Sidiropoulos P, Boumpas DT, Gourtsoyiannis N, et al. Evolution of imaging findings, laboratory and functional parameters in rheumatoid arthritis patients after one year of treatment with anti-TNF-alpha agents. Clin Exp Rheumatol. 2017;35(1):43-52.

19. Nakashita T, Ando K, Kaneko N, Takahashi K, Motojima S. Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis. BMJ Open. 2014;4(8):e005615.

20. Fernandez-Diaz C, Loricera J, Castaneda S, Lopez-Mejias R, Ojeda-Garcia C, Olive A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A
national multicenter study of 63 patients. Semin Arthritis Rheum. 2018.

21. Matteson EL, Bongartz T, Ryu JH, Crowson CS, Hartman TE, Dellaripa PF. Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated Interstitial Pneumonia. Open Journal of Rheumatology and Autoimmune Diseases. 2012;02(03):53.

22. Andreina M, Giulia C, Federica F, Elisa G, Vincenzo V, Fabiola A, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicenter retrospective study. Intern Med J. 2019.

23. Hadjinicolaou AV, Nisar MK, Parfrey H, Chilvers ER, Ostor AJ. Non-infectious pulmonary toxicity of rituximab: a systematic review. Rheumatology (Oxford). 2012;51(4):653-62.

24. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.

25. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733-48.

26. Gaujoux-Viala C, Mouterde G, Baillet A, Claudepierre P, Fautrel B, Le Loet X, et al. Evaluating disease activity in rheumatoid arthritis: which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI. Joint Bone Spine. 2012;79(2):149-55.

27. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ),
Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S4-13.

28. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41(2):256-64.

29. Mera-Varela A, Perez-Pampin E. Abatacept therapy in rheumatoid arthritis with interstitial lung disease. J Clin Rheumatol. 2014;20(8):445-6.

30. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor alpha agents, a retrospective cohort study. Arthritis Res Ther. 2015;17:319.

31. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. Respir Investig. 2016;54(5):376-9.

32. Jimenez-Alvarez L, Arreola JL, Ramirez-Martinez G, Ortiz-Quintero B, Gaxiola M, Reynoso-Robles R, et al. The effect of CTLA-4Ig, a CD28/B7 antagonist, on the lung inflammation and T cell subset profile during murine hypersensitivity pneumonitis. Exp Mol Pathol. 2011;91(3):718-22.

33. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford). 2017.

34. Kawashiri SY, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute
exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. Rheumatol Int. 2012;32(12):4023-6.

35. Wendling D, Vidon C, Godfrin-Valnet M, Rival G, Guillot X, Prati C. Exacerbation of combined pulmonary fibrosis and emphysema syndrome during tocilizumab therapy for rheumatoid arthritis. Joint Bone Spine. 2013;80(6):670-1.

36. Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol. 2017;36(4):817-23.

37. Deane KD, Nicolls MR. Developing better biomarkers for connective tissue disease-associated interstitial lung disease: citrullinated hsp90 autoantibodies in rheumatoid arthritis. Arthritis Rheum. 2013;65(4):864-8.

38. Fabre A, Treacy A, Lavelle LP, Narski M, Faheem N, Healy D, et al. Smoking-Related Interstitial Fibrosis: Evidence of Radiologic Regression with Advancing Age and Smoking Cessation. Copd. 2017;14(6):603-9.

39. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid Arthritis Disease Activity Predicting Incident Clinically Apparent Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Prospective Cohort Study. Arthritis Rheumatol. 2019;71(9):1472-82.

Figures
Figure 1

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