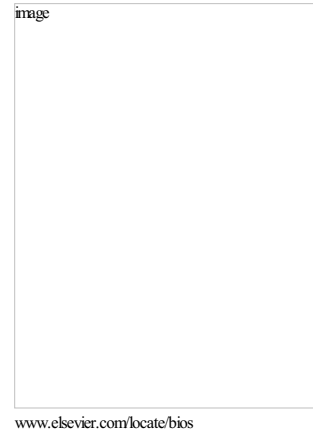


## Author's Accepted Manuscript

Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients

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**ABATACEPT IN PATIENTS WITH RHEUMATOID ARTHRITIS AND INTERSTITIAL LUNG DISEASE: A NATIONAL MULTICENTER STUDY OF 63 PATIENTS****Authors:**

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**Key words:** Rheumatoid arthritis, interstitial lung disease, biologics, abatacept.

**ABSTRACT**

**Objective:** Interstitial lung disease (ILD) is one of the most serious complications of rheumatoid arthritis (RA). In the present study, we aimed to assess the efficacy of abatacept (ABA) in patients with ILD associated to RA.

**Methods:** National multicenter, non-controlled, open-label registry study of RA patients with ILD treated with ABA.

**Results:** 63 patients (36 women) with RA-associated ILD undergoing ABA therapy were studied. The mean±standard deviation age at the time of the study was 63.2±9.8 years. The median duration of RA and ILD from diagnosis were 6.8 and 1 year, respectively. RA was seropositive in 55 patients (87.3%). In 15 (23.8%) of 63 patients the development of ILD was closely related to the administration of synthetic or biologic disease modifying anti-rheumatic drugs. After a follow-up of 9.4±3.2 months, two thirds of patients remained stable whereas one-quarter experienced improvement in the Modified Medical Research Council scale. At that time forced vital capacity remained stable in almost two thirds of patents and improved in one out of five patients assessed. Also, diffusing capacity of the lung for carbon monoxide remained stable in almost two thirds and showed improvement in a quarter of the patients assessed. At 12 months, 50% of the 22 patients in whom chest HRCT scan was performed due persistence of respiratory symptoms showed stabilization, 8 (36.4%) improvement and 3 worsening of the HRCT scan pattern. Eleven of 63 patients had to discontinue ABA, mainly due to adverse events.

**Conclusion:** ABA appears to be an effective in RA-associated ILD.

Interstitial lung disease (ILD) is a common and serious complication of autoimmune diseases, including rheumatoid arthritis (RA)<sup>1,2</sup>. The pathogenesis, clinical presentation and histopathology of RA-associated ILD (RA-ILD) appears to be similar to that of idiopathic interstitial pneumonitis<sup>3,4</sup>.

The prevalence of RA-ILD varies from 19 to 44%<sup>5-7</sup>, and it is an important cause of mortality in patients with RA<sup>8,9</sup>. Currently, it is considered the second cause of death in patients these patients, after cardiovascular disease<sup>10</sup>. Thus, RA-ILD patients have 3-fold higher risk of death than RA patients without this complication<sup>11</sup>.

The management of RA-ILD represents a major clinical challenge. Several conventional synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs) had been considered to be involved in the development or in the exacerbations of ILD. Methotrexate (MTX), leflunomide (LFN), anti-tumor necrosis factor (TNF)- $\alpha$  agents, rituximab (RTX), and tocilizumab (TCZ) have been reported to induce pneumonitis or worsen pre-existing RA-associated ILD<sup>12-15</sup>.

To date, the optimal treatment for RA-ILD has not yet been established<sup>17</sup>. Blockade of T cell costimulation by the cytotoxic T Lymphocyte Antigen 4 (CTLA-4)-Ig, a soluble chimeric fusion protein consisting of the extracellular domain of murine CTLA4 and a mouse IgG2a constant region, led to inhibition of lung inflammation in the murine hypersensitivity pneumonitis<sup>18</sup>. However, the experience on abatacept (ABA), an antagonist of T-lymphocyte co-stimulation, in patients with ILD associated to RA is generally scarce and limited<sup>19,20</sup>.

Taking into account all these considerations, in the present study we aimed to determine the potential efficacy of ABA in patients with ILD associated to RA.

## **PATIENTS and METHODS**

### ***Design, Enrollment Criteria and Definitions***

A national multicenter, noncontrolled, open-label registry study of patients with ILD associated to RA treated with ABA was conducted. Patients with ILD attending the

Rheumatology divisions of 31 centers from Spain between 2000 and 2016 who had at least a 3-month follow-up period after starting ABA were assessed. Data were retrieved from the clinical records and stored in a computerized database.

RA was diagnosed according to the ACR 1987 classification criteria<sup>21</sup> or the ACR/EULAR 2010 criteria<sup>22</sup> depending on the year of diagnosis. Seropositive RA was considered if the disease was associated to positive Rheumatoid Factor (RF) and/or cyclic citrullinated peptide antibodies (CCPA) in at least two different determinations. One or two senior radiologists, depending on each Center, performed the assessment of the high resolution computed tomography (HRCT) scans of the chest, independently. chest HRCT scans were assessed by a systematic review of all lung fields evaluating the presence and extent of ground glass attenuation, reticulation, honeycombing, decreased attenuation, centrilobular nodules, other nodules, consolidation, and emphysema. There were classified in 3 general radiological patterns according to standardized criteria of the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias<sup>23</sup>. The different pulmonary patterns defined by lung biopsy or chest HRCT scans were as follows: a) usual interstitial pneumonia (UIP), b) non-specific interstitial pneumonia (NSIP); and c) "other patterns" (bronchiolitis obliterans [BO], organized pneumonia [OP] and mixed patterns)<sup>23</sup>.

Disease activity score-28 (DAS28) was evaluated using the erythrocyte sedimentation rate (ESR) [DAS28 ESR]. RF was determined by nephelometry; CCPA were detected by standard commercial enzyme-linked immunosorbent assays (ELISA). Pulmonary function tests were performed based on the 2002 recommendations of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR)<sup>24</sup>.

For the inclusion in the present study RA patients had to be treated with at least one dose of ABA after the ILD diagnosis. Patients were diagnosed as having ILD based on pulmonary function tests and positive chest CT findings or lung biopsy at baseline, before receiving treatment with ABA. Nevertheless, in 3 patients FVC test could not be

performed because they were critically ill and the time of diagnosis of ILD. In these 3 patients a diagnosis of ILD was supported by chest HRCT scan results and other conditions, such as pulmonary infections and heart failure, were excluded. They also received treatment with ABA after the diagnosis of the ILD. Because of that, to provide information on the actual spectrum of severity of ILD associated to RA in patients undergoing ABA therapy, they also were included in the present study.

ABA was prescribed at standard intravenous dose (10 mg/kg/4 weeks) or subcutaneously (125 mg/week). The time period between baseline chest HRCT scans and the ABA onset ranged between 1 and 2 weeks in all the cases.

### ***Outcome Variables***

The efficacy of ABA was evaluated according to the following measurements: **a)** Modified Medical Research Council (MMRC) scale<sup>24</sup>; **b)** Pulmonary Function Tests (PFT) that were performed following international criteria. We considered as significant, changes  $\geq 10\%$  in Forced Vital Capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO)<sup>25,26</sup>; **c)** Improvement, worsening or stability criteria in HRCT scans were evaluated in each center by an experienced radiologist. Confirmation by a second senior radiologist was required in doubtful cases, **d)** DAS28, CRP and/or ESR data were also assessed. All these variables were gathered at baseline and, when available, assessed at 3, 6 and 12 months of follow-up.

### ***Statistical Analysis***

Results were expressed as mean $\pm$ standard deviation (SD) or as median [interquartile range (IQR), 25<sup>th</sup>-75<sup>th</sup>] as appropriate. Wilcoxon's test was used to compare continuous variables before and after ABA therapy (at 3, 6 and 12 months). Qualitative variables were compared by the Chi-squared test or Fisher test, as appropriate. STATISTICA software (StatSoft Inc., Tulsa, Oklahoma, USA) was used for the statistical analysis.



**RESULTS*****Baseline clinical characteristics at abatacept onset***

We studied 63 patients (36 women/27 men) with RA-associated ILD treated with ABA. Baseline features of the series before ABA onset are summarized in **Table 1**. The mean age at ABA onset was  $63.2 \pm 9.8$  years. At that time, the duration of RA and ILD from diagnosis were 6.8 (IQR 2-13.6) and 1 (IQR 0.3-3.3) years, respectively. Patients were positive for RF or CCPA in 55 (87.3%) and 54 (85.7%) of the 63 cases, respectively. In addition to the use of HRCT for the diagnosis of ILD, histological confirmation of ILD by lung biopsy was obtained in 18 of 63 patients.

The most common patterns of RA-associated ILD were UIP (n=29 [43%]) and NSIP (n=17 [27%]). Before ILD diagnosis, 59 patients had received synthetic DMARDs and 19 biologic agents. At the time of the ILD diagnosis, patients were receiving the following conventional synthetic and biologic agents: MTX (n=38), LFN (n=15), hydroxychloroquine (HCQ) (n=7), etanercept [ETN] (n=7), adalimumab [ADA] (n=3), infliximab [IFX] (n=2), certolizumab pegol [CZP] (n=2), azathioprine (AZA) (n=4), sulfasalazine (SSZ) (n=1), gold salts (n=1), RTX (n=1) and TCZ (n=1). In 15 (23.8%) of 63 patients, the development of ILD was closely related to the administration of synthetic DMARDs (MTX, n=5 and LFN, n=1) or biologic DMARDs (ETN], n=3, ADA, n=3, CZP, n=2 and IFX, n=1).

Regarding glucocorticoids, the median dose of prednisone at baseline was 10 [5-13.1] mg/day.

**TABLE 1.** Baseline clinical features of 63 patients with Rheumatoid Arthritis associated with Interstitial Lung Disease treated with abatacept.

<b>Age</b> , years, mean $\pm$ SD	63.2 $\pm$ 9.8
<b>Sex</b> , female/male	36/27
<b>Smoker or ex-smoker</b> , n (%)	38 (60.3%)
<b>Rheumatoid factor</b>	
Positive, n (%)	55 (87.3%)
Titer, median [IQR] (normal values, U/mL)	316 [140-735] (0-22)
<b>CCPA</b>	
Positive, n (%)	54 (85.7%)
Titer, median [IQR] (normal values, U/mL)	330 [248-743] (0-50)
<b>Duration of RA*</b> , years, median [IQR]	6.8 [IQR 2-13.6]
<b>Duration of ILD**</b> , years, median [IQR]	1 [IQR 0.3-3.3]
<b>Chest HRCT pattern of ILD</b> , n (%)	
Usual interstitial pneumonia	29 (46%)
Non-specific interstitial pneumonia	17 (27%)
Others	17 (27%)

CCPA: Cyclic Citrullinated Peptide Antibodies; DMARD: Disease-Modifying Anti-Rheumatic Drugs, HRCT: High Resolution Computed Tomography; ILD: Interstitial Lung Disease.

\*Since the disease diagnosis. \*\*From the diagnosis of RA to the diagnosis of ILD.

***Treatment with abatacept and outcome variables***

ABA was used at standard intravenous dose for RA (10 mg/kg/4 weeks) after an induction period with 2 intravenous injections every other week in 26 patients. In the other 37 patients, this agent was administered subcutaneously (125 mg/week). These numbers did not allow us to draw conclusions on differences in the efficacy of the route of administration of ABA. It was prescribed as monotherapy (n= 26) or along with the following conventional DMARDs: LFN (n=15), MTX (n= 6), HCQ (n=10), SSZ (n= 4), AZA (n=4), chloroquine (CQ) (n=1) and cyclosporine A (CyA) (n=1).

At the time of ABA onset, the degree of dyspnea using MMRC scale was as follows: a) asymptomatic (grade 0 MMRC) (n=19); b) mild dyspnea (grade 1 MMRC) (n=17); c) mild-moderate dyspnea (grade 2 MMRC) (n=17); d) moderate-severe dyspnea (grade 3 MMRC) (n=8) and e) severe dyspnea (grade 4 MMRC) (n=2). At that time, DLCO and FVC measurements were performed in 48 and 60 patients with mean $\pm$  SD values of 64.4 $\pm$ 16.1% and 87.1 $\pm$ 15.6%, respectively.

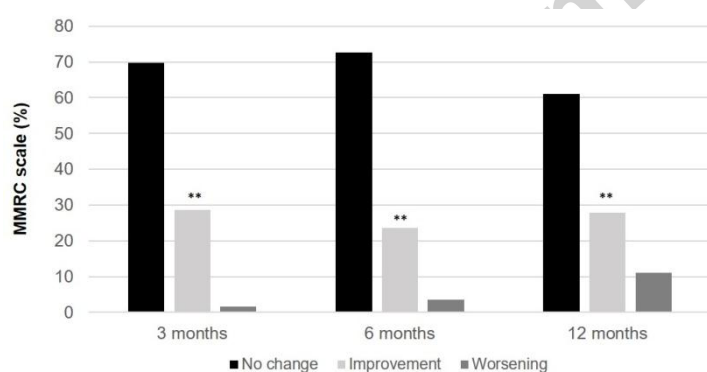
The number of patients assessed at each time period (baseline, at 3, 6 and 12 months) was the following: MMRC: at baseline 63 patients, at 3 months 63, at 6 months 55 (87% of the 63 assessed at baseline) and 36 patients at 12 months. FVC: at baseline 60 patients, at 3 months 33, at 6 months 33 (55% of the 60 assessed at baseline) and 26 patients at 12 months. DLCO: at baseline 48 patients, at 3 months 28, at 6 months 22 (46% of the 48 assessed at baseline) and 23 patients at 12 months.

The outcome of these parameters during the follow-up period is detailed in **Figure 1**. At 3 months after the onset of ABA therapy, maintained clinical stabilization or improvement was seen in most cases. After a mean follow-up of 9.4 $\pm$ 3.2 months, the following findings were found: **a)** 1 of 19 patients who were asymptomatic at baseline developed mild dyspnea (grade 1); **b)** about two thirds of patents remained stable whereas one-quarter experienced improvement of at least 1 point on the MMRC scale (**Figure 1A**); **c)** Regarding respiratory function tests, FVC remained stable in almost two thirds of patents whereas it showed an improvement of at least 10% from baseline

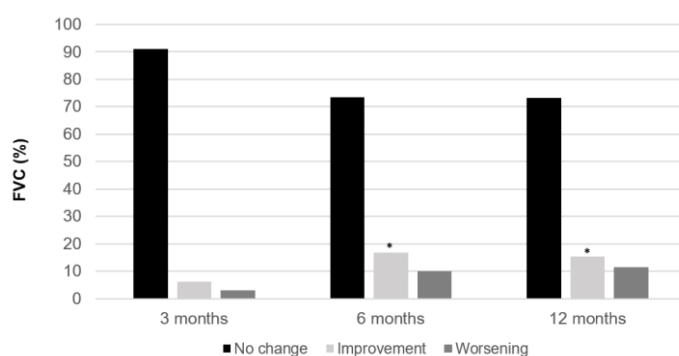
in one out of five patients assessed (**Figure 1B**); **d**) DLCO remained stable in almost two thirds and showed at least 10% improvement in a quarter of the patients assessed. (**Figure 1C**); **e**) the mean DAS28 ESR score decreased from  $5.03 \pm 1.42$  at baseline to  $3.34 \pm 1.25$  at month 6 and  $3.51 \pm 1.24$  at month 12 (**Figure 2**). A decrease in the median prednisone dose from 10 [5-13.1] mg/day at baseline to 5 [5-7.5] mg/day at month 12 was also achieved (**Figure 3**). At 12 months, chest HRCT scans were performed in 22 patients with persistence of respiratory symptoms. At that time, 11 of 22 patients showed stabilization of the ILD radiological features. Radiological improvement was found in 8 (36.4%) whereas worsening of the chest HRCT scan pattern was observed in 3 cases.

**FIGURES 1A, 1B and 1C.** Dyspnea (MMRC scale) and lung function tests results (FVC and DLCO) at 3, 6 and 12 months in our series

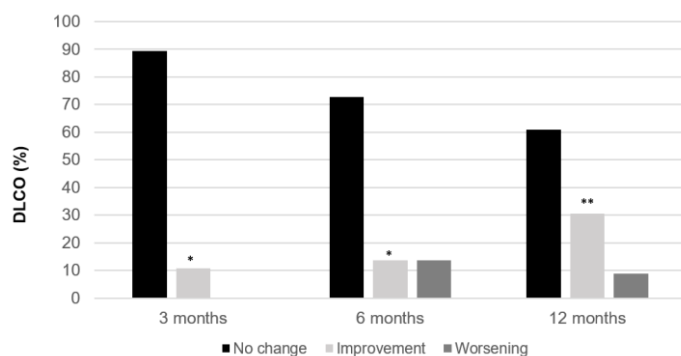
**Figure 1A**



**Figure 1B**



**Figure 1C**

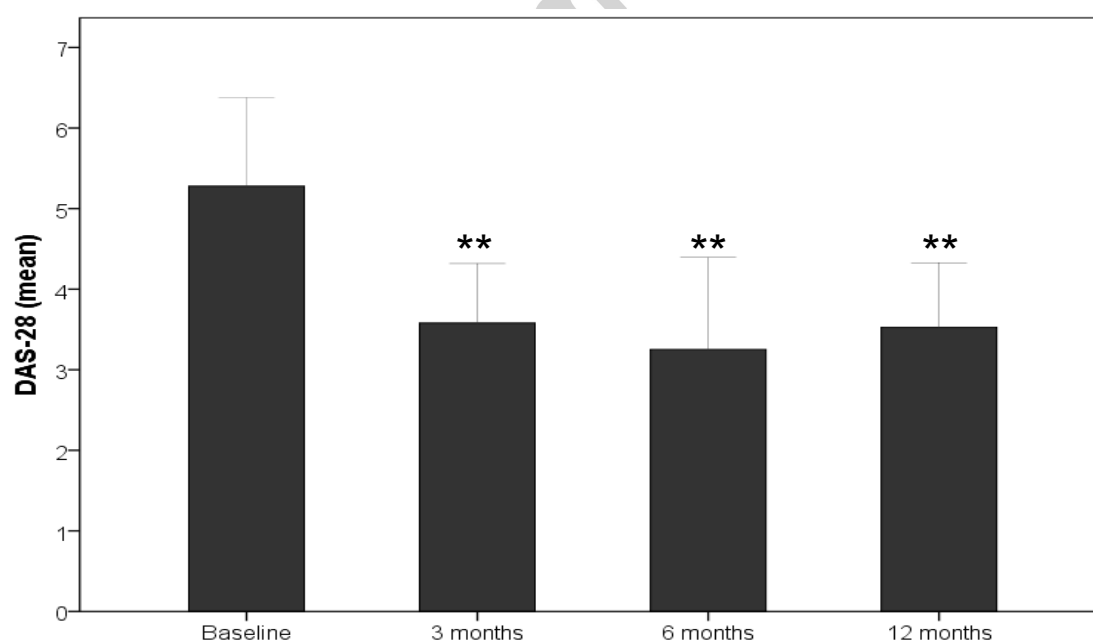


**Abbreviations (in alphabetical order):** DLCO: Diffusion of the Lung for Carbon

monoxide; FVC: Forced Vital Capacity; MMRC: Modified Medical Research Council.

\* $p < 0.05$ ; \*\* $p < 0.01$  vs. baseline. Only the “improvement” variable was considered in the calculations.

**FIGURE 2.** Mean DAS28 ESR score at baseline, at 3, 6 and 12 months.

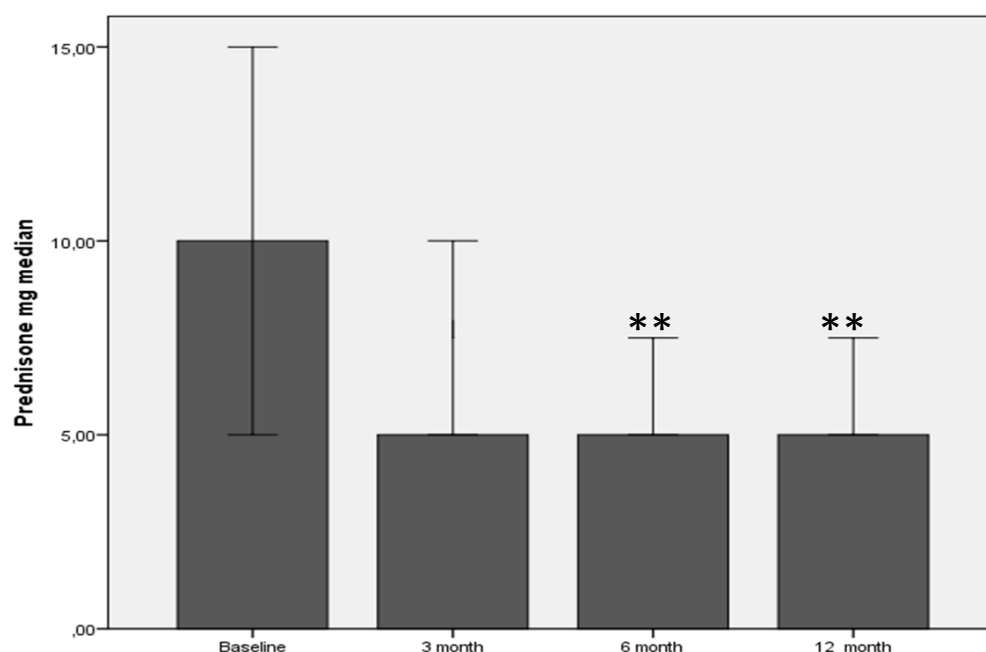


Bars represent 95% confidence interval (CI).

\*\* $p < 0.01$  vs baseline values.

**Abbreviations:** DAS28: Disease activity score with 28 joints count.

**FIGURE 3.** Median prednisone dose at baseline, at 3, 6 and 12 months.



Bars represent 95% confidence interval (CI).

\*\* $p < 0.01$  vs baseline values.

### **Adverse events**

During the follow-up period, ABA had to be withdrawn in 11 of 63 patients. Due to inefficacy to improve the rheumatic manifestations in 3 of them (no improvement or worsening of DAS28), because of pulmonary worsening and joint inefficacy in 1 patient and due to adverse events in 7 patients. The main adverse effects were severe respiratory infections ( $n=2$ ), severe urinary infection ( $n=1$ ) and serious cutaneous infusion reaction ( $n=1$ ). One patient died during the follow-up due to ischemic heart disease. Another patient died two months after ABA withdrawal because of a flare of ILD.

## DISCUSSION

We studied 63 patients with RA-associated ILD treated with ABA. We assessed the following data: dyspnea, lung function tests (FVC and DLCO) and HRCT findings. Most patients yielded stabilization or improvement of these variables.

The pathogenesis of RA-associated ILD remains unknown. There are several predisposing factors such as male gender, older age, and cigarette smoking, that are also predictors of mortality<sup>27,28</sup>. Indeed, cigarette smoking may represent an upstream trigger leading to *in situ* development of citrullinated proteins, which may play an important role in both idiopathic pulmonary fibrosis and RA-associated ILD<sup>29</sup>. Association between positivity of RF and CCPA and the development of ILD-RA has also been reported<sup>26,27,30,31</sup>. RF and CCPA have been detected in smokers with ILD even without clinical signs of RA<sup>29</sup>.

The predisposing factors discussed above are consistent with our data since in our series the mean age was  $63.1 \pm 9.6$  years, more than 40% were men although the disease itself is more common in women, 87.3% and 85.7% were RF positive or CCPA positive, and 60.3% of them were active smokers or ex-smokers.

Paulin et al.<sup>29</sup> proposed two potential mechanisms to explain the co-existence of RA and ILD. An immune response against citrullinated peptides taking place at the joints, which subsequently shifts to the lungs, leading to an interstitial lung inflammation, mainly to a NSIP pattern<sup>32</sup>. It was also postulated that individuals with a genetic susceptibility to RA may develop an immune response against citrullinated peptides in the lung, causing inflammation that subsequently affects the joints<sup>33</sup>.

On the other hand, it is well-known that several conventional DMARDs, especially MTX and LFN, have been involved in *de novo* development or in exacerbations of ILD.<sup>12,14,15</sup>. Furthermore, biological DMARDs may be the trigger of severe lung injuries by inducing idiosyncratic reactions, accelerating pre-existing ILD, modifying ILD into a more injurious phenotype, or increasing the susceptibility to infections<sup>20,34,35</sup>.

Pérez-Álvarez et al.<sup>35</sup> published 122 cases of new-onset ILD or exacerbation of ILD secondary to administration of biologic therapy, including 108 patients with RA. These authors observed that RA-associated ILD occurred in these patients after a mean of 26 weeks from the onset of the biologic therapy and had a high rate of mortality (29% of patients), mainly during the first 5 weeks of treatment. Panopoulos and Sfikakis<sup>36</sup> reported 144 patients of new-onset or exacerbation of RA-associated ILD with the use of anti-TNF- $\alpha$  drugs. Nakashita et al.<sup>37</sup> reported 58 patients with RA with a pre-existing ILD and observed that the incidence of exacerbation of RA-associated ILD was higher in patients receiving anti-TNF- $\alpha$  agents (24.1%). Although no increase in the prevalence of ILD following TCZ or ABA therapy has been reported, Kawashiri et al.<sup>38</sup> reported a fatal case of exacerbation of ILD during treatment with TCZ. Also, Wendling et al.<sup>39</sup> reported a patient with acute worsening of pre-existing RA associated to pulmonary fibrosis and emphysema after 2 years of the TCZ onset.

Dixon et al.<sup>40</sup> studied 367 patients with pre-existing RA-associated. These authors did not find an increase of mortality in patients with RA-associated ILD following treatment with anti-TNF therapy when compared with that related to the use traditional DMARDs. In our series, following ABA onset, 4 of 9 patients who had suffered ILD related to anti-TNF- $\alpha$  drugs experienced an improvement of dyspnea (measured by MMRC), and 2 and 3 of these 4 patients also had improvement of FVC and HRCT scan, respectively. The remaining 5 patients remained stable in terms of dyspnea, respiratory function tests and radiological findings.

The role of RTX in RA-associated ILD has been recently questioned due to the report of some cases of drug-induced ILD. Hadjinicolaou et al.<sup>41</sup> performed a systematic literature review to document all reported cases of RTX-associated interstitial lung disease. A total of 121 cases of potential ILD related with RTX were identified being fatal in 18 patients.



Different radiological patterns of pulmonary involvement associated with RA have been described, usually extrapolated from those of idiopathic pulmonary fibrosis<sup>23</sup>. The patterns commonly associated with RA in decreasing frequency are the following: UIP, NSIP, BO and OP. Classically, UIP has been associated with lower 5-year survival when compared to the other radiological patterns<sup>42</sup>. In our series, 46% of the patients presented with UIP, 27% had NSIP and 27% had other radiological findings including OP, OB and mixed patterns. After a follow-up of 12 months, we observed an improvement in HRTC scans in 33.3% of patients with UIP, whereas 50% remained stable from a radiological point of view.

The diagnosis and treatment of RA-associated ILD represent a challenge for the clinicians for several reasons. First, respiratory infections and drug-induced pulmonary diseases need to be excluded. Second, some patients have progressive RA-associated ILD while others have a stable disease. This fact implies the need for regular clinical, imaging and pulmonary function test monitoring to effectively discriminate between these different courses of the disease. Third, the clinical evidence of the efficacy and safety of specific drugs for RA-associated ILD is quite limited<sup>43</sup>. Glucocorticoids have been traditionally the first-line treatment for RA-associated ILD. However, the mean dose of glucocorticoids in our series was relatively small, so we do not believe that they may have influenced the outcome of our patients. In cases of refractory disease, the use of other DMARDs such as mycophenolate, azathioprine or cyclophosphamide has been reported with controversial results<sup>44-46</sup>.

ABA is a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4. It binds human B7 (CD80/86) more strongly than CD28. ABA has demonstrated his efficacy on RA in different studies<sup>47,48</sup>. In experimental studies, CTLA-4 has been tested as an important target in lung inflammation in other pulmonary diseases such as hypersensitivity pneumonitis. In this setting, this biologic agent may be a potential therapy on RA- associated ILD<sup>49</sup>.

Unfortunately, only small case series of RA-associated ILD patients treated with ABA

have been published<sup>19,20,50</sup>. Mera-Varela et al.<sup>19</sup> reported 4 patients who developed ILD or exacerbation of preexisting ILD while they were undergoing anti-TNF- $\alpha$  therapy. They were subsequently treated with ABA without deterioration of respiratory function tests or remarkable side effects, suggesting that ABA may provide a better control of RA in patients with ILD unresponsive to conventional DMARD therapy. In contrast, Curtis et al.<sup>20</sup> performed a retrospective cohort study to evaluate ILD incidence and exacerbation among 109 ABA and 59 TCZ new users compared with those on anti-TNF- $\alpha$  agents. However, these authors did not find significant differences. Recently, Nakashita et al.<sup>50</sup> reported 16 patients with RA-associated ILD treated with ABA without worsening of ILD in any of them. In addition, DAS28-ESR score and serum metalloproteinase-3 levels decreased and the dose of glucocorticoids was also tapered. Our study has limitations due to its retrospective design, the variable duration of the ILD before the onset of abatacept and the relatively short follow-up time. Another potential limitation was the absence of a control group. Nevertheless, no prospective studies on RA-associated ILD are available. Moreover, a good number of our patients had clinical improvement and they remained stable during the follow-up. Finally, although the number of patients in whom a control CT-scan of the chest was performed at 1 year may appear to be low, it was only carried out in the patients who at that time had clinical manifestations related to the ILD, since in the rest of patients the symptoms were stable or had improved.

Taken together, our findings speak in favor of the potential use of ABA in ILD related to RA.

In conclusion, herein we report one of the largest series of RA-associated ILD patients treated with ABA. In this study, ABA seems to be an effective treatment for these patients. Large randomized prospective studies are needed to confirm these promising results.

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