Evolution of Pulmonary Function in a Cohort of Patients with Interstitial Lung Disease and Positive for Antisynthetase Antibodies

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ABSTRACT. ***Objective.*** To describe the evolution of the pulmonary function in patients with interstitial lung disease (ILD) who are positive for at least 1 of the antisynthetase antibodies (ASAB) after medical treatment, and to compare whether the evolution of pulmonary function is associated with the type of ASAB.

Methods. Patients with ILD and positive for at least 1 of the ASAB (anti-Jo1, anti-PL7, anti-PL12, anti-EJ, or anti-OJ) were included. The clinical evolution, time until death or censoring, and improvement of lung disease were registered.

Results. The study included 118 patients. Most of the patients had a high extent of ground glass opacities in high-resolution computed tomography (HRCT) and low extent of fibrosis. In the final evaluation of pulmonary function (median 749.5 days of followup), 67% of the patients had lung disease improvement. The improvement occurred within the first 6 months after initiating medical treatment; thereafter, pulmonary function remained stable in most of the patients. A decrease of the extent of ground glass opacities was demonstrated in HRCT at followup in those patients with pulmonary improvement. No differences were observed in the percentage of patients who achieved improvement between the ASAB groups, or in survival.

Conclusion. Improvement of pulmonary function was observed in 67% of the patients. Improvement was observed in all ASAB groups and occurred within 6 months after initiating medical treatment. (First Release November 1 2019; J Rheumatol 2020;47:415–23; doi:10.3899/jrheum.181141)

Key Indexing Terms:
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Antisynthetase syndrome (AS) is an autoimmune disorder characterized by myositis, arthritis, mechanic's hands, fever, Raynaud phenomenon (RP), and interstitial lung disease (ILD)[1,2]. AS was first described in patients with inflammatory myopathies (IM)[3], but today it seems clear that the clinical presentation of the AS is more heterogeneous than previously thought[4,5,6], and patients can present with ILD and antisynthetase antibodies (ASAB) without fulfilling IM classification criteria[7,8]. ILD is by far the most severe manifestation of AS; it is present in about 80% of patients with AS (60–100%) and is associated with high morbidity and mortality[9].

Although ILD is known to be a severe manifestation of AS, little is known about the evolution of the pulmonary function in patients with AS. Andersson, *et al*[10] described a significant decline in pulmonary function in AS patients with a median of 6 years of evolution compared with healthy controls. Moreover, Zamora, *et al*[11] reported that 53% of anti–Jo1–positive patients with AS had a decline in pulmonary function despite medical treatment. In contrast, Trallero-Araguás, *et al*[12] reported that only 16% of patients with ILD who were anti–Jo1-positive progressed to advanced lung disease, and that most patients had stable lung disease

for long periods. It is possible that different ASAB autoantibodies may differ in the severity of pulmonary disease. Pinal-Fernandez, *et al*[13] said that patients with anti-PL7 and anti-PL12 had worse pulmonary function compared to Jo1-positive patients.

With this background, the aim of our study was to describe the evolution of the pulmonary function [forced vital capacity (FVC) and DLCO] in a single-center cohort of patients with AS and to determine whether the evolution of pulmonary function was associated with the type of ASAB.

MATERIALS AND METHODS

All patients were evaluated and managed in the Interstitial Lung Disease and Rheumatology Unit (ILD&RU) at the Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, in México City. Patients from all over the country are referred to the ILD&RU if their attending physicians (primary care, internal medicine specialists, pulmonologists, or rheumatologists) consider that patients may benefit from the clinical evaluation and management at the ILD&RU. Patients referred to the ILD&RU are evaluated by a multidisciplinary group (pulmonologists, radiologists, and a rheumatologist). Included patients were evaluated between January 2008 and January 2018. To be included in this study, patients must have had the diagnosis of ILD confirmed with high-resolution computed tomography (HRCT) and be positive for at least 1 of the following autoantibodies: anti-Jo1, anti-PL7, anti-PL12, anti-EJ, or anti-OJ. Patients were managed according to the attending physicians' criteria.

We registered the duration of pulmonary symptoms (dyspnea and cough) before baseline evaluation. Baseline pulmonary function tests (PFT) included DLCO, spirometry, and plethysmography. Also, baseline serum creatinine kinase levels were recorded, as well as the history of proximal muscle weakness, RP, sclerodactyly, dermatomyositis rash, proximal dysphagia, and smoking history. Patients were evaluated if they fulfilled Bohan and Peter's criteria during followup[14,15], and if patients met the new interstitial pneumonia with autoimmune features (IPAF) criteria of the European Respiratory Society/American Thoracic Society (ATS/ERS; 2015)[16]. The clinical evolution of patients was recorded, including progression, time until death or censoring, improvement or changes in medical treatment for ILD, and the reason for the change.

Patients had at least 2 visits per year with a pulmonologist and 2 visits per year with a rheumatologist. In the first year of followup, patients were usually evaluated with spirometry and DLCO at 6 and 12 months after the initiation of a therapy for ILD. After that, PFT were done according to the attending physician's criteria. Most patients had an annual evaluation of pulmonary function with a spirometry and DLCO. The baseline PFT were registered prior to initiation of any therapy for ILD. Also, the last spirometry and DLCO (performed at the end of the followup) was recorded, and this final evaluation of pulmonary function was used to evaluate the longterm pulmonary function. Disease progression and treatment response on PFT were defined as a decrease or increase in FVC by more or less than 10% of those predicted, respectively, and/or a decrease or increase in DLCO by more or less than 15% of those predicted, respectively, similar to the established criteria for idiopathic pulmonary fibrosis[17,18]. Patients who died in the followup were also considered as having progression of lung disease. The local institutional review board approved the study protocol (approval number: C08-17). Informed consent was given when possible by all patients to participate in the study.

Administration of PFT. PFT were performed in the Department of Respiratory Physiology of the Instituto Nacional de Enfermedades Respiratorias, a specialized respiratory physiology laboratory. In every measurement of PFT, weight and standing height were measured by a digital scale (models 206 and 769, Seca). Spirometry (to obtain FVC) and single-breath DLCO were performed using the commercial equipment EasyOne Pro and EasyOne Pro Lab (Ndd Medizintechnik AG). The data were expressed as percentages of the predicted values. The predicted values for each subject, according to sex, age, height, and weight, were obtained from the PLATINO study[19] and US National Health and Nutrition Examination Survey tables[20]. All spirometry and DLCO tests fulfilled acceptability and reproducibility criteria (ATS/ERS 2005)[21,22].

HRCT evaluation. HRCT was performed at baseline evaluation with a 1.0 or 1.5 mm axial section taken at 1 cm intervals and was reconstructed using a high spatial frequency algorithm. Between 20 and 25 CT scan images were acquired for each patient. HRCT was blindly evaluated by 2 experts (MM and HN M-T). Experts evaluated the HRCT and classified the images according to the official ATS/ERS Statement of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias[23]. Any discrepancies in the interpretations were solved by consensus. The fibrotic component, defined by reticular opacities, and inflammation, defined by ground glass opacities, was graded according to the scores described by Kazerooni, *et al*[24] and Goh, *et al*[25]. We evaluated the agreement of the extent of pulmonary disease with the Goh and Kazerooni scores between the 2 experts. Agreement was better in the Goh score, so only the Goh score was used in the analysis of the results (Supplementary Table 1, available with the online version of this article). The evaluation of MM was used in the analysis of the data; it had a high intraobserver agreement (intraclass correlation coefficient 0.90; 95% CI 0.84–0.94).

Autoantibodies. The IgG ASAB (anti-Jo1, anti-PL7, anti-PL12, anti-EJ, anti-OJ) was measured using EUROIMMUN immunoblot strips (EUROLINE: Myositis Profile 3) according to the manufacturer's instructions. This commercial line blot assay for myositis diagnosis was assessed on its diagnostic accuracy against RNA immunoprecipitation in a multicenter cohort of patients with idiopathic IM (IIM). The overall specificity of the line blot was 100% for anti-Jo1, anti-PL7, and anti-PL12[26].

Statistical analysis. Variables are described according to their type: categorical variables with frequencies and percentages, numerical variables with mean ± SD, or medians and interquartile range (IQR) according to the parametric or nonparametric distribution of the variables. To compare baseline with followup PFT and Goh scores, we use paired t test or Wilcoxon signed-rank test, as appropriate. The Kruskal-Wallis test or 1-way ANOVA was used to compare the PFT in the baseline evaluation and in the followup according to the ASAB profile; if a difference were found, a comparison between each group was done according to the Bonferroni correction. In the case of categorical variables, Fisher's exact test was used to evaluate whether there was a difference in the frequencies of lung function improvement or progression of lung disease.

To evaluate the factors associated with improved lung function and lung disease progression, a crude OR (cOR) was estimated using a univariate logistic regression analysis. Then, the confounding factors were adjusted in a multivariate logistic regression analysis to estimate the adjusted OR (aOR). To elaborate on these models, variables with $p < 0.15$ in the univariate regression analysis were included. A survival analysis was performed using the Cox regression method to estimate crude HR (cHR), and then a multivariable Cox regression analysis was done including variables with $p < 0.15$ in the univariate analysis. All analyses were 2-sided and α was set at 5% unless otherwise specified. The statistical software Stata (v. 14.2) was used to perform all analyses.

RESULTS

There were 125 patients with ILD positive to ASAB who were evaluated at the ILD&RU during the study period. Seven patients did not have baseline spirometry, so 118 patients, with a median of pulmonary symptoms of 12 months at baseline evaluation, were included (Table 1). The most frequent autoantibody was Jo1 in 42.4% of the patients. Autoantibodies were not mutually exclusive and there was

Table 1. Description of the cohort.

Variables	N = 118
Age at baseline evaluation, yrs, mean ± SD	53.69 ± 11.53
Age at followup evaluation, yrs, mean ± SD	56.42 ± 11.23
Males: females	33 (28): 85 (72)
Pulmonary symptom onset before baseline evaluation, mos, median (IQR)	12 (5–24)
Jo1-positive patients	50 (42)
Non-Jo1 patients	
PL7-positive patients	14 (12)
PL12-positive patients	19 (16)
EJ-positive patients	15 (13)
OJ-positive patients	3 (2.5)
Patients with 2 or 3 autoantibodies (11 patients had 2 concomitant autoantibodies and 4 had 3 concomitant autoantibodies)	17 (14.5)
Ground glass and consolidation with or without reticulation (OP pattern)	51 (43)
Ground glass, reticulation without consolidation (NSIP pattern)	46 (39)
Basal predominant reticular abnormality with peripheral and subpleural distribution (UIP pattern)	15 (13)
Overlapping of HRCT patterns	6 (5)
Extent of lung disease in HRCT according to Goh score, mean ± SD	49.75 ± 22.15
Extent of ground glass in HRCT according to Goh score, mean ± SD	43.71 ± 18.98
Extent of fibrosis in HRCT according to Goh score	6 (2.64–11.4)
Baseline % of predicted value of FVC, median (IQR)	56 (42–77)
Baseline % of predicted value of DLCO*, mean ± SD	52 ± 27.3
Creatine-kinase serum levels at baseline u/l, median (IQR)	94 (48–462) min, max (18–7460)
Arthritis	88 (74.6)
Fever	72 (61)
Mechanic's hand sign	59 (50)
Proximal muscle weakness	85 (72)
Sclerodactyly/scleroderma	25 (21)
Ro52-positive	64/106 (60)
Former smokers	40/118 (33)
Current smokers	4/118 (3)
Patients with smoking history (former + current smokers)	44/118 (37)

* Data from 105 patients; 13 patients were unable to perform DLCO because of the severity of lung disease. Values are n (%) unless otherwise specified. IQR: interquartile range; FVC: forced vital capacity; OP: organized pneumonia; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography.

superposition of autoantibodies, with 17 patients having 2 or 3 concomitant autoantibodies. Sixty percent of the patients were Ro52-positive. Only 18 patients (15.2%) had 3 or more Bohan and Peter criteria to be classified as possible or definite IIM during followup. On the contrary, most patients fulfilled IPAF criteria (n = 74; 63%). Forty-four patients were smokers [median: 4.5 pack/years (IQR 0.7–4.7 pack/years)]. Of these patients, 4 were current smokers at baseline evaluation.

The 2 most frequent HRCT findings were organized pneumonia (OP) pattern, followed by the nonspecific interstitial pneumonia (NSIP) pattern. Patients with OP and NSIP had Goh scores reflecting a very high extent of ground glass (49.75 ± 22.15 and mean 43.71 ± 18.98, respectively) and low score of fibrosis [6 (2.64–11.4)]. Thirteen percent of the patients had usual interstitial pneumonia (UIP) HRCT pattern. This group of patients had higher extent of fibrosis in the Goh scores compared to OP and NSIP (median 21.4; 13.44–31.2) and lower ground glass extent in the Goh score (22.37 ± 19.34). Also, HRCT patterns differed in the duration of pulmonary symptoms before baseline evaluation: patients with OP HRCT pattern had the shorter duration of pulmonary symptoms and UIP patients had the longer duration. These differences were statistically significant after Bonferroni correction (α set at < 0.016; Supplementary Graph 1, available with the online version of this article). Two patients had concomitant signs of emphysema in the HRCT scan and 3 patients had pneumomediastinum. Thirteen patients died during followup. The causes of death were sepsis in 5 patients (4 of them secondary to pneumonia), respiratory failure due to the progression of ILD in 7 patients, and acute myocardial infarction in 1 patient. Before baseline evaluation, 84% of the patients received antibiotic treatment in variable doses and amounts, and 25% of the patients received corticosteroids and immunosuppressive drugs (cyclophosphamide and azathioprine). Supplementary Table 2 describes the treatments that patients received for ILD at the ILD&RU (available with the online version of this article).

Pulmonary function at baseline and at followup. The percentage baseline median of predicted FVC was 56 (42–77), and the mean baseline percentage of the predicted DLCO was 52 ± 28.1. The DLCO was estimated with the data from 106 patients. Patients could not have the DLCO test at the baseline evaluation because of the severity of their lung disease. In the final evaluation of pulmonary function [median of followup: 749.5 days (328–1428 days)], 79 patients (67%) had lung disease improvement. The final median percentage of expected FVC was 71 (50–90; data from 106 patients; $p < 0.0001$ compared to baseline FVC 56, 42–77) and the mean final percentage of expected DLCO was 62.8 ± 30.9 (data from 91 patients; $p < 0.002$ compared to baseline DLCO 52 ± 28.1). Table 2 compares baseline characteristics of patients achieving improvement with those who did not. In the univariate analysis, age at baseline, UIP HRCT pattern, and pneumomediastinum were negatively associated with the improvement of pulmonary lung function. After excluding possible interactions, a multivariable logistic regression was elaborated on: aOR are presented in Table 2. In this model, only age at baseline showed a tendency toward statistical significance.

Figure 1 describes the evolution of pulmonary function at baseline, 6 months of followup (data from 70 patients), 12 months of followup (data from 45 patients), and the final evaluation of PFT. The improvement in pulmonary function was observed in the first 6 months of followup; after that, pulmonary function remained stable in most of the patients. Improvement was observed in all ASAB groups, and no differences were observed in the percentage of patients who achieved improvement between the ASAB groups, in neither the baseline nor followup values of DLCO and FVC (Table 3).

Extent of pulmonary disease evaluated by HRCT scan at baseline and at 1 year of followup. An HRCT scan at 1 year of followup was available in 89 patients. Table 4 compares baseline Goh scores with those at followup in these 89 patients. Also, the evolution of the most frequent HRCT patterns is provided. Both OP and NSIP had lower Goh scores at 12 months of followup compared to baseline Goh scores. Patients with UIP HRCT pattern had higher extent of pulmonary disease at 1 year of followup. Importantly, patients with improvement had lower extent of lung disease in HRCT at followup than patients without improvement (Table 4; $p < 0.045$). Supplementary Figure 1 (available with the online version of this article) shows representative HRCT images before and after treatment of the 3 most frequent HRCT patterns.

Factors associated with lung disease progression. In the univariate analysis, age at baseline evaluation, being unable to perform DLCO, and UIP HRCT pattern were factors associated with lung disease progression (Table 5). A multivariable logistic regression analysis was performed including age at baseline, extent of ground glass in HRCT, no baseline DLCO, and UIP HRCT pattern. In the multivariable analysis, the inability to perform DLCO at baseline was associated to lung disease progression. UIP HRCT pattern had a tendency toward lung disease progression.

Finally, we performed a survival analysis. Of the 13

Table 2. Comparison of patients achieving improvement in PFT with those without improvement.

Variables	Patients with Improvement, n = 79	Patients without Improvement, n = 39	cOR (95% CI); p	aOR (95% CI); p
Age at baseline evaluation, yrs, mean ± SD	51.84 ± 11.85	57.43 ± 9.98	0.95 (0.9–0.99); 0.02	0.96 (0.92–1.001); 0.06
Male sex	18 (23)	15 (38.5)	0.47 (0.20–1.08); 0.08	0.61 (0.24–1.51); 0.29
Extent of lung disease in HRCT according to Goh score	50 (38–62)	52 (36-68)	0.99 (0.97–1.009); 0.31	
Extent of ground glass in HRCT according to Goh score	41.68 (34–56)	44.2 (28.2–58.2)	1.002 (0.98–1.02); 0.80	
Extent of fibrosis in HRCT according to Goh score	5.94 (2.64–8.66)	6.27 (2.88–17.92)	0.97 (0.93–1.009); 0.14	
Baseline % of DLCO*	50.3 ± 27.5	55.9 ± 26.8	0.99 (0.97–1.007); 0.32	
Baseline % of FVC	53 (42–77)	61 (43–80)	0.99 (0.97–1.01); 0.46	
Patients unable to perform baseline DLCO because of the severity of lung disease	7 (9)	6 (15.4)	0.53 (0.16–1.71); 0.30	
UIP HRCT pattern	6 (7.6)	9 (23)	0.27 (0.09–0.83); 0.023	0.46 (0.13–1.59); 0.22
Anti-Jo1 positivity	34 (43)	16 (41)	1.08 (0.49–2.36); 0.83	
Smoking history (current/former)	28 (37)	16 (42)	0.80 (0.36–1.77); 0.58	
Ro52-positive	44/72 (61)	20/34 (58)	1.1 (0.47–2.52); 0.82	
Pneumomediastinum**	0	3 (7.6)	Not estimated; p = 0.03	

Values are n (%) unless otherwise specified. Variables with $p < 0.15$ in the univariate analysis were included in a multivariable logistic regression analysis to adjust for confounding. * Data from 105 patients; 13 patients were unable to perform DLCO because of the severity of lung disease. ** Because some cell entries were zero, the OR could not be estimated. This variable was not included in the multivariable logistic regression analysis. PFT: pulmonary function test; cOR: crude OR; aOR: adjusted OR; FVC: forced vital capacity; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography.

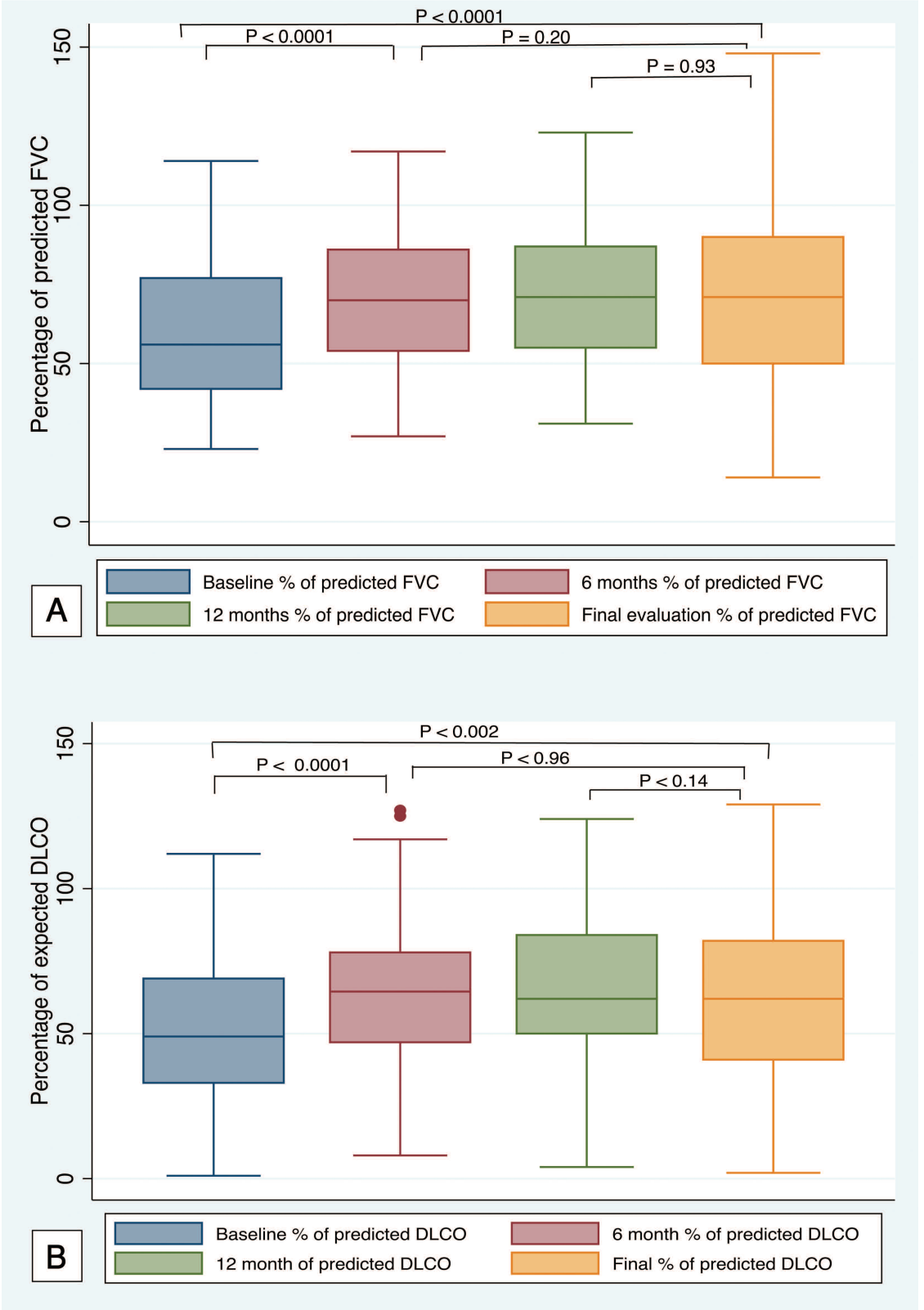

Figure 1. The evolution of pulmonary function at baseline, 6 months of followup, 12 months of followup, and the final evaluation of PFT. PFT: pulmonary function test; FVC: forced vital capacity.

Table 3. Comparison of pulmonary function tests, percentages of patients unable to perform spirometry or DLCO according to the autoantibody profile. Patients with 2 or 3 ASAB were considered as an independent group.

Variables	Jo1-positive Patients, n = 50	PL7- positive Patients, n = 14	PL12-positive Patients, n = 19	EJ-positive Patients, n = 15	OJ-positive Patients, n = 3	Patients with 2 or 3 ASAB, n = 17	p
Baseline % of predicted value of FVC*	61.5 (41–83)	62.5 (38–82)	53 (45–66)	53.6 (39–74)	43 (38–59)	52 (44–72)	0.76
Baseline % of predictive value of DLCO, mean ± SD	55.6 ± 28.6	58 ± 37.2	45 ± 19.8	46.7 ± 25.5	34.6 ± 17.6	53.7 ± 26.5	0.52
Patients unable to perform DLCO because of the severity of lung disease**	7 (14)	3 (21)	1 (5.3)	2 (13)	0 (25)	0 (6)	0.39
Patients with improvement in FVC (> 10%) or in DLCO (> 15%)**	34 (68)	6 (43)	11 (58)	11 (73)	3 (100)	14 (82)	0.19
Followup % of predicted value of FVC*	72 (58–91)	68 (41–79)	63 (42–74)	70 (45–77)	64 (43–85)	84 (55–97)	0.31
Followup % of predicted value of DLCO, mean ± SD	71.63 ± 29.8	61.2 ± 27.4	46.3 ± 28.9	58.3 ± 22.0	28.25 ± 25.4	69.2 ± 37.7	0.32

Values are n (%) unless otherwise specified. * Medians (interquartile range). ** Categorical variables are described with percentages. ASAB: antisynthetase antibodies; FVC: forced vital capacity.

patients who died in the followup period, 8 (61.5%) died in the first year of followup (survival function at 1 year of followup was 0.92). Risk factors associated with worst survival were older age at baseline, a low percentage of expected DLCO, and being unable to perform DLCO because of the severity of pulmonary disease (Supplementary Table 3, available with the online version of this article). The survival of anti-Jo1 patients was compared with that of non-Jo1 patients and no difference was found (Supplementary Graph 2).

DISCUSSION

The purpose of our study was to describe the evolution of the pulmonary function in a single-center AS cohort, and to compare whether the evolution of pulmonary function is associated with the type of ASAB. We found that 67% of AS patients with a median of 12 months of pulmonary symptoms at baseline had a significant clinical improvement of lung function. This improvement occurred within the first 6 months after initiating medical treatment and was observed in all ASAB groups. After the first 6 months, pulmonary function remained stable in most patients. The results of this study give us a better understanding of the evolution and response to medical treatment of ILD associated to ASAB.

The percentage of patients achieving improvement in the pulmonary function at followup is similar to the recent report of Yamakawa, *et al*[27], who reported that 64% of ILD cases associated to ASAB autoantibodies improved in PFT at 1 year of followup, after initiating antiinflammatory therapy (prednisone with calcineurin inhibitor immunosuppressants). The definition of improvement that we used in this study is very similar to the one used by Yamakawa, *et al*. In our cohort, the improvement occurred within the 6 first months after initiating medical treatment for the management of ILD. Around 67% of patients with ILD positive to ASAB achieved a significant improvement in pulmonary function after medical treatment with antiinflammatory therapy within 6 months; most patients then remained stable in their PFT.

Although more than 60% of our patients achieved a significant improvement in pulmonary function, the percentage median of expected FVC and mean percentage of expected DLCO at the final evaluation of PFT remained below the normal limits for age and sex. These results are in accordance with what was reported by Andersson, *et al*[10], that patients with AS have a significant decline in pulmonary function. In the study by Yamakawa, *et al*, patients received therapy within 6 months after diagnosis[27]; in our study, included patients had a median of pulmonary symptoms at baseline of 12 months. It is still to be defined whether treating patients early is associated with better outcomes in PFT. There are important differences between our cohort and the one reported by Yamakawa, *et al*. The most obvious is that in our cohort no patient received calcineurin inhibitors. One task for future research is to evaluate which medical treatment is the most optimal in this group of patients.

The most frequent HRCT patterns were OP and NSIP. Patients with these HRCT patterns had high ground glass Goh scores, and low fibrosis Goh scores. NSIP pattern can have an inflammatory predominance over fibrosis, in what has been called the cellular NSIP pattern[28,29]. Both OP and cellular NSIP have good prognosis compared to fibrotic interstitial pneumonias[29]. In the followup HRCT, both OP and the NSIP pattern had a significant decrease in the extent of lung disease. Also, patients with improvement had a lower extent of lung disease at followup compared to those without improvement. Interestingly, patients with UIP-like HRCT pattern had longer pulmonary symptom onset before baseline evaluation. Indeed, patients with OP HRCT pattern had the shorter duration of pulmonary symptoms at baseline, compared to NSIP and UIP HRCT patterns. This may suggest that a path toward lung fibrosis may occur in patients with

Table 4. Comparison of baseline Goh scores with those of followup in these 89 patients. In addition, the evolution of the most frequent HRCT patterns is provided. Patients with improvement had a lower extent of lung disease in HRCT at followup than patients without improvement.

Variables	Baseline Evaluation, n = 89	1-year Followup, n = 89	p
Extent of lung disease in HRCT according to Goh score, mean ± SD	50.46 ± 23.10	42.85 ± 23.47	0.005
Extent of ground glass in HRCT according to Goh score, mean ± SD	44.57 ± 19.45	35.88 ± 18.77	0.0001
Extent of fibrosis in HRCT according to Goh score, median (IQR)	6 (2.64–8.88)	3.36 (0.96–11.52)	0.015
Stratified analysis by HRCT pattern. Data of the 3 most frequent HRCT patterns:			
OP pattern	Baseline Evaluation, n = 36	1-year Followup, n = 36	
Extent of lung disease in HRCT according to Goh score, mean ± SD	46.36 ± 22.32	36.5 ± 20.37	0.03
Extent of ground glass in HRCT according to Goh score, mean ± SD	47.03 ± 16.69	31.95 ± 16.92	0.0001
Extent of fibrosis in HRCT according to Goh score, median (IQR)	3.54 (0.46–5.88)	2.52 (0.48–6.48)	0.76
NSIP pattern	Baseline Evaluation, n = 39	1-year Followup, n = 39	
Extent of lung disease in HRCT according to Goh score, mean ± SD	54.94 ± 22.91	44.87 ± 25.09	0.01
Extent of ground glass in HRCT according to Goh score, mean ± SD	48.09 ± 18.37	37.64 ± 20.17	0.003
Extent of fibrosis in HRCT according to Goh score, median (IQR)	6.8 (3.6–11.7)	2.88 (0.72–11.2)	0.003
UIP pattern	Baseline Evaluation, n = 9	1-year Followup, n = 9	
Extent of lung disease in HRCT according to Goh score, mean ± SD	39.88 ± 17.59	50.44 ± 17.71	0.16
Extent of ground glass in HRCT according to Goh score, mean ± SD	16.19 ± 11.91	29.28 ± 16.68	0.02
Extent of fibrosis in HRCT according to Goh score, median (IQR)	21.4 (13.44–31.2)	17.4 (8.64–27.84)	0.09
Comparison of followup HRCT extent of pulmonary disease in patients with improvement with patients without improvement			
	Patients with Improvement, n = 62	Patients without Improvement, n = 27	
Extent of lung disease in HRCT according to Goh score, mean ± SD	39.58 ± 22.88	50.37 ± 23.50	< 0.045
Extent of ground glass in HRCT according to Goh score, mean ± SD	33.23 ± 18.03	38.68 ± 20.19	0.21
Extent of fibrosis in HRCT according to Goh score, median (IQR)	2.48 (0.52–9)	8.64 (1.76–16.8)	0.005

OP: organized pneumonia; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; HRCT: high-resolution computed tomography; IQR: interquartile range.

AS if not treated early, and that OP is an early pulmonary disease stage in AS that may evolve to NSIP and finally toward UIP-like pattern. Another possible explanation is that patients with UIP differ in the pathophysiology of pulmonary disease, leading to a subtler clinical course and resulting in longer referral times.

Aggarwal, *et al*[30] described that the prognosis of non-Jo1 patients in AS is worse than that of anti-Jo1 patients. Later, Pinal-Fernandez, *et al*[13] described that AS patients positive for PL7 or PL12 had a more severe ILD compared to Jo1 patients. In this cohort, we did not observe a worse survival in non-Jo1 patients. Also, there were no differences in the percentage of patients achieving pulmonary improvement according to the autoantibody profile. Nevertheless, the small sample of the PL7 and PL12 patients may result in too little statistical power to find differences between the groups in both the evaluation of survival and the severity of pulmonary disease. A small group of patients had 2 or 3 concomitant autoantibodies. Although this observation must be confirmed with immunoprecipitation as the gold standard for the detection of ASAB, this group of patients did not differ in the HRCT pattern, severity of lung disease, or response to medical treatment. Including this group of patients in the study contributes clinically relevant information to the practicing physician: patients with ILD and positive to 2 or 3 ASAB have a good chance of improving with antiinflammatory therapy.

Our study has several limitations. One is the sample size. Another limitation is that patients in the cohort were treated according to the physician's judgment. This results in very

Table 5. Comparison of patients with progression (drop in FVC > 10%, and/or drop in DLCO > 15% or death in followup) with patients with no progression or with improvement.

Variables	Patients with Progression, n = 28 (24%)	Patients without Progression or with Improvement, n = 90 (76%)	cOR (95% CI), p	aOR (95% CI), p
Age at baseline evaluation*, mean ± SD	57.75 ± 10.47	52.43 ± 11.60	1.04 (1.002–1.08), 0.04	1.02 (0.97–1.07), 0.34
Male sex	8 (28.6)	25 (28)	1.04 (0.40–2.66), 0.93	
Extent of lung disease in HRCT according to Goh score, mean ± SD	48.3 ± 18.19	50.2 ± 23.3	0.99 (0.97–1.02), 0.70	
Extent of ground glass in HRCT according to Goh score*, mean ± SD†	37.82 ± 19.66	45.51 ± 18.51	0.97 (0.95–1.002), 0.08	0.98 (0.95–1.01), 0.42
Extent of fibrosis in HRCT according to Goh score†	7.2 (2.9–19.2)	5.76 (2.64–8.64)	1.03 (0.99–1.07), 0.097	
Baseline % of DLCO**	52.2 ± 26.2	52 ± 27.7	1.0002 (0.98–1.01), 0.97	
Baseline % of FVC	60 (43–81.5)	53.3 (42–74)	1.009 (0.99–1.02), 0.35	
Patients unable to perform DLCO at baseline due to the severity of lung disease**	6 (21.5)	7 (8)	3.23 (0.98–10.60), 0.053	5.95 (1.34–26.41), 0.02
UIP HRCT pattern*	8 (28.6)	7 (8)	4.74 (1.53–14.62), 0.007	3.45 (0.85–13.99), 0.082
Anti-Jo1 positivity	12 (42.8)	38 (42.2)	1.02 (0.43–2.41), 0.95	
Ro52-positive	14/28 (56)	50/81 (62)	0.78 (0.31–1.95), 0.60	
Smoking history (current/former)	9 (32)	35 (39)	0.74 (0.30–1.82), 0.52	

Values are n (%) unless otherwise specified. * Variables with $p < 0.15$ in the univariate analysis were included in a multivariable logistic regression analysis to adjust for confounding. All possible interactions were evaluated, and none was found. ** Data from 105 patients; 13 patients were unable to perform DLCO because of the severity of lung disease. † This variable was not included in the multivariable analysis because of its collinearity with UIP HRCT pattern. FVC: forced vital capacity; cOR: crude OR; aOR: adjusted OR; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

heterogeneous treatments. An important fact that we observed while gathering the data for the study was that many patients had treatment changes during the followup, which were secondary to an inadequate response based on the treating physician's criteria. It is important to mention that the most frequent treatment at the end of the followup was the combination of methotrexate plus leflunomide, with or without prednisone. Finally, our unit is a national referral center of the country with more than 120 million inhabitants. Therefore, the referred patients may not be representative of patients with AS evaluated elsewhere.

We found that 67% of patients with AS have a significant clinical improvement of lung function that occurs within 6 months after initiating medical therapy. This improvement was observed in all ASAB groups; afterward, most patients remained stable.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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