Evolution of Pulmonary Function in a Cohort of Interstitial Lung Disease Patients Positive to Antisynthetase Antibodies (ASAB)

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Founding source: none

Conflicts of interest: none declared.

Abstract

OBJECTIVE: To describe the evolution of the pulmonary function in patients with ILD, positive to at least one of the 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 to at least one of the ASAB: Jo1, PL7, PL12, Ej or Oj, were included. The clinical evolution, time until death or censoring, and improvement of lung disease were registered.

RESULTS: 118 patients were included. Most of the patients had a high extent of ground glass opacities in high resolution chest tomography (HRCT) and low extent of fibrosis. In the final evaluation of pulmonary function, (median of follow-up: 749.5 days of follow-up), 67% of the patients had lung disease improvement. The improvement occurred within the first 6 months after initiating medical treatment, and then after, pulmonary function remained stable in most of the patients. A decrease of the extent of ground glass opacities was demonstrated in HRCT at follow up in those patients with pulmonary improvement. No differences were observed in the percentage of patients that achieved improvement between the ASAB groups, neither in survival.

CONCLUSIONS: Improvement of pulmonary function was observed in 67% of the patients, improvement was observed in all ASAB groups and occurred within the 6 months after initiating medical treatment.

KEY WORDS: 1. Interstitial Lung Disease, 2. Idiopathic inflammatory myopathies, 3. Anti Jo1, 4. Anti-synthetase syndrome.

Introduction

The anti-synthetase syndrome (ASSD) is an autoimmune disorder characterized by myositis, arthritis, mechanic's hands, fever, Raynaud´s phenomenon and interstitial lung disease (ILD).(1),(2) The ASSD was first described in patients with inflammatory myopathies (IM) (3), but nowadays, it seems clear that the clinical presentation of the ASSD is more heterogeneous than previously thought (4-6), and patients can only be presented with ILD and ASAB, without fulfilling IM classification criteria(7, 8). ILD is by far the most severe manifestation of ASSD, which is present in about 80% of ASSD patients (60-100%) and is associated with high morbidity and mortality.(9) Although ILD is known to be a severe manifestation of ASSD, little is known about the evolution of the pulmonary function in ASSD patients. Andersson et al(10) described a significantly decline in pulmonary function in ASSD patients with a median of 6 years of evolution as compared with healthy controls. Moreover, Zamora et al,(11) reported that 53% of Jo1 positive ASSD patients had a decline in pulmonary function despite medical treatment. On the contrary, Trallero-Araguás et al(12) recently described that only 16% of ILD patients Jo1 positive progressed to advanced lung disease, and that most patients had a stable lung disease for long periods of time. It is possible that different ASAB autoantibodies may differ in the severity of pulmonary disease. Pinal-Fernandez et al(13) described that patients with PL7 and PL12 had worse pulmonary function compared to Jo1-positive patients,

With this background, the aim of this study is to describe the evolution of the pulmonary function (FVC and DLCO) in a single-center cohort of ASSD patients and whether the evolution of pulmonary function is associated with the type of ASAB.

Patients 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 (INER) 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 of 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 HRCT and be positive to at least one of the following autoantibodies: Jo1, PL7, PL12, Ej or Oj. Patients were managed accordingly physicians' criteria.

We registered duration of pulmonary symptoms (dyspnea and cough) before baseline evaluation, baseline pulmonary function tests (PFTs), which included DLCO, spirometry, and plethysmography. Also, baseline serum creatinine kinase levels were recorded, as well as the history of proximal muscle weakness, Raynaud's phenomenon, sclerodactyly, dermatomyositis rash, proximal dysphagia and smoking history. Patients were evaluated if they fulfilled Bohan & Peter´s criteria (B&PC) during follow up (14, 15), and if patients meet the new interstitial pneumonia with autoimmune features ATS/ERS 2015 criteria (IPAF).(16). Then after, 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 two visits per year with a pulmonologist, and two visits per year with a rheumatologist. In the first year of follow-up, patients were usually evaluated with spirometry and DLCO at 6 and 12 months after the initiation of a therapy for ILD. After that, PFTs were done according to the attending physician's criteria. Most patients had an annual evaluation of pulmonary function with a spirometry and a DLCO. The baseline PFTs were registered prior to initiation of any therapy for ILD. Also, the last spirometry and DLCO performed on patients, at the end of the follow-up was recorded, and this final evaluation of pulmonary function was used to evaluate the long-term pulmonary function. Disease progression and treatment response on PFTs 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 follow-up were also considered as having progression of lung disease. The local institutional review board approved the study protocol (approval number: C08-17). An informed consent was given when possible to all patients to participate in the study.

Pulmonary Function Tests

PFTs were performed in the Department of Respiratory Physiology, of the Instituto Nacional de Enfermedades Respiratorias, a specialized respiratory physiology laboratory. In every measurement of PFTs, weight and standing height were measured by a digital scale (models 206 and 769, Seca, Hamburg, Germany). Spirometry (to obtain forced vital capacity) and $DLCO_{sb}$ were performed using the commercial equipment Easy One Pro and Easy One Pro Lab (Ndd® Zurich, Switzerland). 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 NHANES tables.(20) studies. All spirometry and DLCO tests fulfilled the acceptability and reproducibility criteria (ATS/ERS 2005)(21, 22)

High-resolution chest tomography (HRCT) evaluation

HRCT was performed at baseline evaluation with a 1.0 or 1.5 mm thick 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 two 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 interpretation was solved by consensus. The fibrotic component, defined by reticular opacities and inflammation by ground glass opacities, was graded according to the Kazerooni(24) and the Goh(25) scores. We evaluated the agreement in the evaluation of the extent of pulmonary disease with the Goh and Kazerooni scores between the two experts. Agreement was better in the Goh score, so, only the Goh score was used in the analysis of the results (Table S1, supplementary material). The evaluation of MM was used in the analysis of the data, MM has a high intra-observer agreement (intraclass correlation coefficient 0.90 (95% CI: 0.84 to 0.94)

Autoantibodies

The IgG ASAB (Jo1, PL7, PL12, Ej, 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 IIM. The overall specificity of the line blot was 100% for anti-Jo1, anti-PL-7 and anti-PL-12. (26)

Statistical Analysis

Variables are described according to their nature: categorical variables with frequencies and percentages, numerical variables with mean ± SD, or medians and interquartile range (IQR) according to the parametric or non-parametric distribution of the variables. To compare baseline with follow up PFTs ang Goh scores, we use paired t test or Wilcoxon Sign Rank as appropriate. The Kruskall Wallis test or one-way ANOVA was used to compare the pulmonary function tests in the baseline evaluation and in the follow-up according to the ASAB profile; if a difference was found, a comparison between each group was done according the Bonferroni correction. In the case of categorical variables, the exact Fischer 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 Odds Ratio (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 Cox regression method to estimate crude Hazard ratios (cHR), then after, a multivariable cox regression analysis was done including variables with P < 0.15 in the univariate analysis. All analyses were two-sided, α was set at 5% unless otherwise specified. The statistical software Stata v. 14.2 was used to perform all analyses.

Results

One hundred and twenty-five ILD patients positive to ASAB were evaluated at the ILD&RU during the study period, 7 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 superposition of autoantibodies, with 17 patients having 2 or 3 concomitant autoantibodies. 60% of the patients were Ro52 positive. Only 18 patients (15.2%) had 3 or more Bohan and Peter´s criteria to be classified as possible or definite IIM during follow up. On the contrary, most patients fulfilled IPAF criteria (74 (63%)). Forty-four patients were smokers (median: 4.5 pack/years (IQR: .7 – 4.7 pack/years). Of these patients, 4 were current smokers at baseline evaluation.

The two most frequent HRCT findings were organized pneumonia (OP) pattern, followed by the non-specific interstitial pneumonia (NSIP) pattern. Patients with OP

and NSIP had Goh scores reflecting a very high extent of ground glass (46.83 ± 16.08 and mean 47.14 ± 17.43, respectively) and low scores of fibrosis (median 3.75 (1.33 - 5.68) and 6.68 (4.2-11.4), respectively). 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) (Graph S1 Supplementary material) Two patients had concomitant signs of emphysema in the HRCT scan and 3 patients had pneumomediastinum. Thirteen patients died during follow up. 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). In the supplementary material, there is a complete description of the treatments that patients received to treat ILD at the ILD&RU (table 1A).

Baseline and at follow-up pulmonary function.

The percentage baseline median of predicted FVC was of 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. The reason patients could not perform the

DLCO at baseline evaluation was due to the severity of lung disease. In the final evaluation of pulmonary function, (median of follow-up: 749.5 days of follow-up (328 –1428 days of follow-up)), 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 that did not. In the univariate analysis, age at the 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, Adjusted OR (aOR) are presented in Table 2. In this model, only age at baseline, showed a tendency towards statistical significance.

Graph 1 describes the evolution of pulmonary function at baseline, 6 months of follow up (data from 70 patients), 12 months of follow up (data from 45 patients) and at the final evaluation of PFTs. The improvement in pulmonary function was observed in the first 6 months of follow up, after that, pulmonary function remains stable in most of the patients. Improvement was observed in all ASAB groups, and no differences were observed in the percentage of patients that achieved improvement between the ASAB groups, neither in the baseline or follow up values of DLCO and FVC (Table 3.)

Extent of pulmonary disease evaluated by HRCT scan at baseline and at one year of follow up.

A HRCT scan at one year of follow up was available in 89 patients. Table 4. compares baseline Goh scores with those of follow up in these 89 patients. Also, the evolution of the most frequent HRCT patterns is provided. Both OP. and NSIP had lower Goh scores at the 12 months of follow up compared to baseline Goh scores. On the contrary, patients with UIP HRCT pattern, had higher extent of pulmonary disease at one year follow up. Importantly, patients with improvement had lower extent of lung disease in HRCT at follow up that patients without improvement (Table 4. $P < 0.045$) Figure S1 in online supplementary material 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 to lung disease progression (Table 5.). A multivariable logistic regression analysis including age at baseline, extent of ground glass in HRCT, no baseline DLCO and UIP HRCT pattern was performed. In the multivariable analysis, the inability to perform DLCO at baseline was associated to lung disease progression. UIP HRCT pattern had a tendency towards lung disease progression.

Finally, we performed a survival analysis. Of the 13 patients that died in the follow up period, 8 (61.5%) died in the first year of follow up, (survival function at one year of follow up 0.92). Risk factors associated with worst survival were older age at baseline, a low percentage of expected DCLO and being unable to perform DLCO due to the severity of pulmonary disease (Table S3. Online supplementary material)

The survival of Jo1 patients was compared with non-Jo1 patients and no difference was found (Graph S2, online supplementary material).

DISCUSSION

The purpose of this study was to describe the evolution of the pulmonary function in a single-center ASSD cohort, and to compare whether the evolution of pulmonary function is associated with the type of ASAB. We found that 67% of ASSD 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, then after pulmonary function remains stable in most of the 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 follow up are similar to the recent report of Yamakawa et al(27), who reported that 64% ILD associated to ASAB autoantibodies improved in PFTs at one year of follow up, after initiating anti-inflammatory therapy (prednisone with calcineurin inhibitors 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. Now, we can assume that around of 67% of patients with ILD positive to ASAB, achieve a significant improvement in pulmonary function after

medical treatment with anti-inflammatory therapy whiting 6 months after initiating medical management, then after, most patients remain stable in PFTs.

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 PFTs, remained below the normal limits for age and gender. These results are in accordance with what was reported by Andersson et al,(10) that ASSD patients have a significant decline in pulmonary function. In Yamakawa et al report, patients received therapy within 6 months after diagnosis, in this report, included patients had a median of pulmonary symptoms at baseline of 12 months. Is still to be defined, if treating patients early is associated with better outcomes in PFTS. There are important differences between our cohort and the one reported by Yamakawa. 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´s scores, and low fibrosis Goh´s scores. NSIP pattern can have an inflammatory predominance over fibrosis, what it 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 follow up HRCT, both OP and the NSIP pattern had a significative decrease in the extent of lung disease. Also, patients with improvement had lower extent of lung disease at follow up compared to those without improvement. Interestingly, Patients with UIP like

HRCT pattern, had longer pulmonary symptoms onset before baseline evaluation, indeed, patients with OP HRCT pattern, had the shorter duration of pulmonary symptoms at baseline, compared both to NSIP and UIP HRCT patterns, this may suggest that a path towards lung fibrosis may occur in ASSD patients if not treated early, and that OP is an early pulmonary disease stage in ASSD that may evolve to NSIP and finally towards UIP like pattern. Another possible explanation to this finding, is that UIP patients differ in the pathophysiology of pulmonary disease, leading to a subtler clinical course, resulting in longer referral times.

Aggarwal et al(30) described that the prognosis of non-Jo1 patients in the ASSD is worse than that of the Jo1 patients. Later, Pinal-Fernández et al(13) described that ASSD patients, positive to PL7 or PL12, had a more severe interstitial lung disease 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 the autoantibody profile. Nevertheless, the small sample of the PL7 and PL12 patients may result in a small statistical power to find differences between the groups both in the evaluation of survival and the severity of pulmonary disease. A small group of patients had two or three 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 neither in the HRCT pattern, severity of lung disease or response to medical treatment. We believe that including this group of patients in the study contributes with clinically relevant information to the practical physician: patients with ILD and positive to two or three ASAB, have a good chance of improving with anti-inflammatory 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 fact results in very heterogeneous treatments. An important fact that we observed while gathering the data for the study was that many patients had treatment changes during the follow-up, which is secondary to an inadequate response based on the treating physician's criteria. For us, it is important to mention that the most frequent treatment at the end of the follow-up 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 120,000,000 inhabitants. Therefore, the referred patients may not be representative of ASSD patients evaluated elsewhere.

In conclusion, we found that 67% of ASSD patients have a significant clinical improvement of lung function, this improvement occurs within 6 months after initiating medical therapy, and was observed in all ASAB groups, then after, most patients remain stable.

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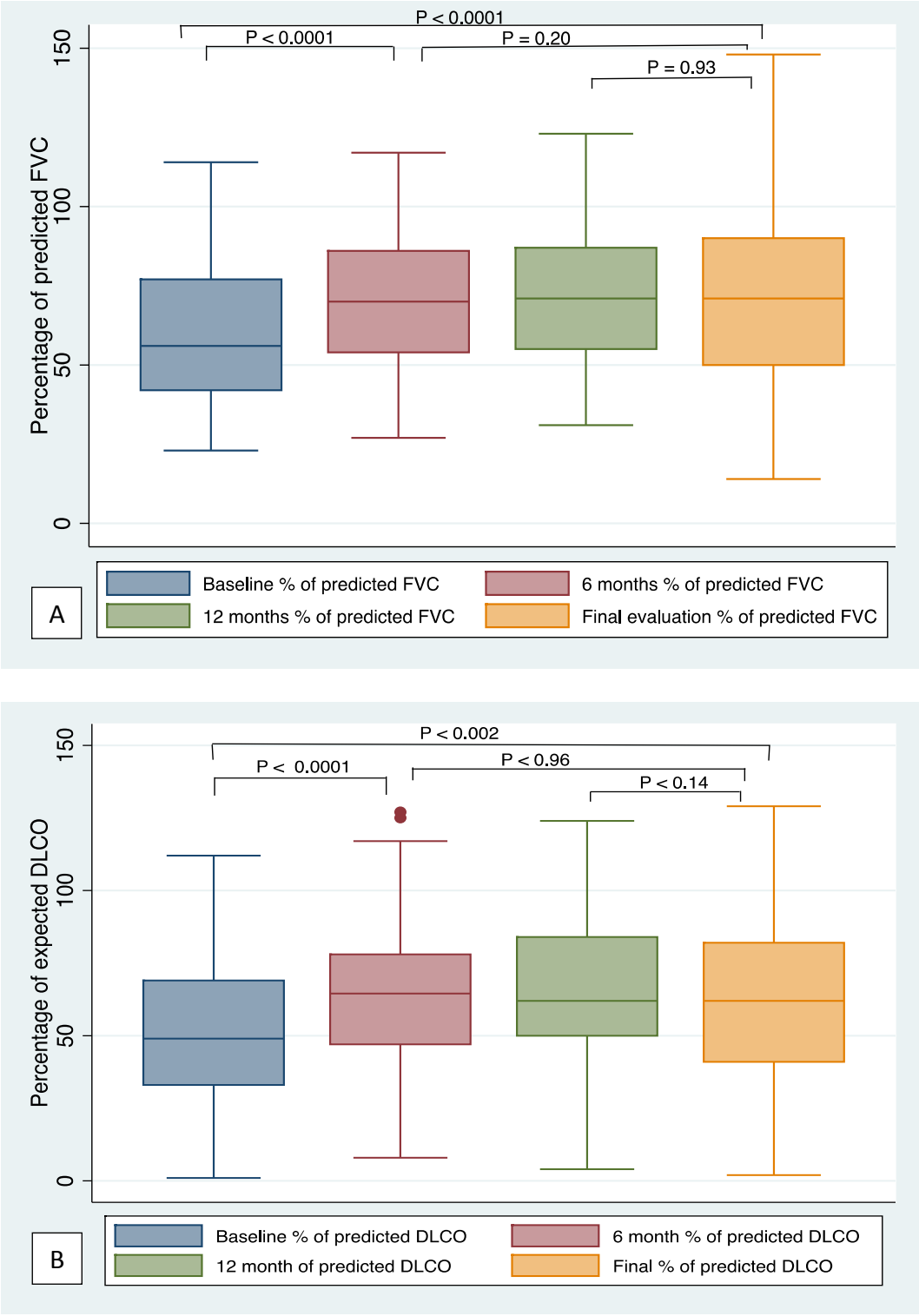

Graph 1. Evolution of pulmonary function at baseline, 6 months of follow-up (data from 70 patients), 12 months of follow-up (data from 45 patients), and at the final evaluation of PFTs. A) Evolution of the percentage of expected of FVC. B) Evolution of the percentage of expected of DLCO.

Variable	N: 118
Age at baseline evaluation	53.69 ± 11.53
Age at follow up evaluation	56.42 ± 11.23
Males: Females	33 (28%): 85 (72%)
Pulmonary symptoms onset before baseline evaluation (months, median (IQR))	12 (5 – 24) months
Jo 1 positive patients	50 (42 %)
Non-Jo1 patients	
PL 7 positive patients	14 (12%)
PL 12 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 (organized pneumonia pattern).	51 (43 %)
Ground glass, reticulation without consolidation (nonspecific interstitial pneumonia pattern)	46 (39 %)
Basal predominant reticular abnormality with peripheral and subpleural distribution (usual interstitial pneumonia pattern).	15 (13 %)
Overlapping of HRCT patterns	6 (5 %)
Extent of lung disease in HRCT according the Goh score	49.75 ± 22.15
Extent of ground glass in HRCT according the Goh score	43.71 ± 18.98
Extent of fibrosis in HRCT according the Goh score	6 (2.64 – 11.4)
Baseline % of predicted value of forced vital capacity (FVC) (median, (IQR)	56 (42-77)
Baseline % of predicted value of diffusing capacity of the lungs for carbon monoxide (DLCO)**	52 ± 27.3
Creatin-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.

Table 1. Description of the cohort

Table 1. Description of the cohort

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

Variable	Patients with improvement n=79	Patients without improvement n=39	cOR (95% CI) P	aOR (95% CI) P
Age at baseline evaluation	51.84 ± 11.85	57.43 ± 9.98	0.95 (0.92 – 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 the Goh score	50 (38 -62)	52 (36 -68)	0.99 (0.97 – 1.009) 0.31	
Extent of ground glass in HRCT according the 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 the 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 due to the severity of lung disease[ǂ]	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 Jo 1 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. 0.03	

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 due to the severity of lung disease.
⊗ Due to some cell entries are zero, the OR could not be estimated, neither this variable was included in the multivariable logistic regression analysis.

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

Variable	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	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 due to 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
Follow up % 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
Follow up % of predicted value of DLCO	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

*Categorical variables are described with percentages.
**Medians (IQR).

Variable	Baseline evaluation n:89	One year follow up n: 89	P
Extent of lung disease in HRCT according the Goh score	50.46 ± 23.10	42.85 ± 23.47	0.005
Extent of ground glass in HRCT according the Goh score	44.57 ± 19.45	35.88 ± 18.77	0.0001
Extent of fibrosis in HRCT according the Goh score	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.			
Organized pneumonia pattern	**Baseline evaluation n:36**	**One year follow up n: 36**	
Extent of lung disease in HRCT according the Goh score	46.36 ± 22.32	36.5 ± 20.37	0.03
Extent of ground glass in HRCT according the Goh score	47.03 ± 16.69	31.95 ± 16.92	0.0001
Extent of fibrosis in HRCT according the Goh score	3.54 (0.46 - 5.88)	2.52 (0.48 – 6.48)	0.76
Nonspecific interstitial pneumonia pattern	**Baseline evaluation n: 39**	**One year follow up n: 39**	
Extent of lung disease in HRCT according the Goh score	54.94 ± 22.91	44.87 ± 25.09	0.01
Extent of ground glass in HRCT according the Goh score	48.09 ± 18.37	37.64 ± 20.17	0.003
Extent of fibrosis in HRCT according the Goh score	6.8 (3.6-11.7)	2.88 (0.72-11.2)	0.003
Usual interstitial pneumonia pattern	**Baseline evaluation n:9**	**One year follow up n: 9**	
Extent of lung disease in HRCT according the Goh score	39.88 ± 17.59	50.44 ± 17.71	0.16
Extent of ground glass in HRCT according the Goh score	16.19 ± 11.91	29.28 ± 16.68	0.02
Extent of fibrosis in HRCT according the Goh score	21.4 (13.44 – 31.2)	17.4 (8.64 -27.84)	0.09
Comparison of follow 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 the Goh score	39.58 ± 22.88	50.37 ± 23.50	0.045
Extent of ground glass in HRCT according the Goh score	33.23 ± 18.03	38.68 ± 20.19	0.21
Extent of fibrosis in HRCT according the Goh score	2.48 (0.52 – 9)	8.64 (1.76 – 16.8)	0.005

Table 4. comparison of baseline Goh scores with those of follow-up 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 follow-up than patients without improvement

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

Variable	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*	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 the Goh score	48.3 ± 18.19	50.2 ± 23.3	0.99 (0.97 – 1.02) 0.70	
Extent of ground glass in HRCT according the Goh score*	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 the Goh scoreψ	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 Jo 1 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 (.31 – 1.95) 0.60	
Smoking history (current/former)	9 (32 %)	35 (39 %)	0.74 (0.30 -1.82) 0.52	

* 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 due to the severity of lung disease.

ψ This variable was not included in the multivariable analysis due to its colliniarity with UIP HRCT pattern.