Treatment and follow-up of patients with Sjögren's disease associated interstitial lung disease: a case series

P.K. Panagopoulos[1,2], L.G. Chatzis[1,3,4], K. Malagari[5], A.V. Goules[1,3], A.G. Tzioufas[1,3,4]

[1]Department of Pathophysiology, Joint Academic Rheumatology Program, School of Medicine, National and Kapodistrian University of Athens, Laiko General Hospital, Athens;
[2]Department of Rheumatology, Naval Hospital of Athens;
[3]Research Institute for Systemic Autoimmune Diseases, Athens;
[4]Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens;
[5]2nd Department of Radiology, School of Medicine, National and Kapodistrian University of Athens, Attikon Hospital, Athens, Greece.

Abstract

Objective

To investigate the effect of treatment in a series of patients with Sjögren's disease (SjD) associated interstitial lung disease (ILD).

Methods

Twenty-four primary SjD-ILD patients, followed-up from October 2022 to June 2025 were included in the study. Based on clinical judgment, 12 received treatment for ILD, while 12 did not, following a "watch-and-wait" policy. Participants were evaluated in 2 time points with an interval of 24±6 months. ILD was diagnosed by HRCT according to Fleischner Society definitions, performed at baseline due to respiratory symptoms and/or abnormal pulmonary function tests. Spirometry and diffusing capacity for carbon monoxide (DLCO) were performed at both visits. Progression of ILD was defined as absolute decline of predicted forced vital capacity (FVC) ≥5%.

Results

Treatment regimens of 12 SjD-ILD patients who received treatment included rituximab, mycophenolate mofetil, azathioprine and tocilizumab. Treated group displayed higher extent of ILD on HRCT at baseline visit (median: 20% vs. 10%, p=0.006), more frequently findings of small airways disease on HRCT (58% vs. 8%, p=0.027) and tended to present lower FVC (mean: 81.3% vs. 96.7%, p=0.086) compared to untreated. FVC and DLCO remained stable between baseline and follow-up visit in both groups. However, change in DLCO between the two visits was worse in treated than untreated patients (mean: -11.2% vs. 4.8%, p=0.003). The number of SjD-ILD patients presenting progression of ILD did not differ between the two groups (25% vs. 33%, p=0.999).

Conclusion

SjD-ILD clinical course is variable, with the most aggressive form to be controlled by immunosuppressive treatment.

Key words

Sjögren's disease, interstitial lung disease, small airways disease, targeted treatment, high resolution computed tomography

Panagiotis K. Panagopoulos, MD, PhD
Loukas G. Chatzis, MD, PhD
Katerina Malagari, MD, PhD
Andreas V. Goules, MD, PhD
Athanasios G. Tzioufas MD, PhD

Please address correspondence to:
Athanasios G. Tzioufas
Department of Pathophysiology,
School of Medicine,
National and Kapodistrian
University of Athens,
Mikras Asias 75, 11527 Athens, Greece.
E-mail: agtzi@med.uoa.gr

Received on October 19, 2025; accepted in revised form on November 17, 2025.

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Competing interests: none declared.

Introduction

Sjögren's disease (SjD) is a systemic autoimmune disorder, characterised by peri-epithelial lymphocytic infiltration of salivary and lacrimal glands, while a significant subset of patients develop extra-glandular manifestations including lung involvement (1). Lungs can be affected as part of the inflammatory infiltrate around respiratory epithelium, clinically manifested as xerotrachea or small airways disease (SAD), while pathophysiology of interstitial lung disease (ILD) remains unclear. The prevalence of ILD among SjD patients varies between 16%-25%, depending on diagnostic modality (2) and is considered a severe manifestation, scoring very high in the ESSDAI (3). Furthermore, ILD has been associated with increased morbidity and mortality in SjD (4) and is characterised by variable clinical course, with some patients remaining stable while others progress (5). Interestingly, observational studies have proposed risk factors associated with progression of ILD in SjD (6-8).

Treatment options for SjD-ILD are mainly based on experience from other systemic autoimmune diseases and a small number of case series. Thus, rituximab, mycophenolate mofetil and azathioprine, along with corticosteroids have been reported as efficacious therapeutic interventions (9-11). However, in those case series, there is no comparator group without therapy and there is heterogeneity regarding treatment regimen and duration. The purpose of this prospective study was to explore the effect of ILD treatment on lung function and respiratory symptoms in a series of SjD-ILD patients and investigate potential risk factors for ILD progression in SjD.

Patients and methods

This case series included primary SjD patients with ILD followed up in the Center of Expertise for Autoimmune Diseases of the Department of Pathophysiology, School of Medicine and Laiko University Hospital (member of European Reference Network ERN-RECONNET), evaluated at two time points with interval of 24±6 months. Participants fulfilled 2016 ACR/EULAR criteria for SjD (12). ILD and imaging pattern were diagnosed by HRCT according to Fleischner Society definitions, after evaluation from a specialised radiologist (13). HRCT was performed at baseline visit due to respiratory symptoms (dyspnoea and/or dry cough) and/or abnormal pulmonary function tests (PFTs), defined as forced vital capacity (FVC) %predicted <80% and diffusing capacity for carbon monoxide (DLCO) %predicted <70% (14). Spirometry and DLCO were performed at both visits. Progression of ILD was defined as an absolute decline in FVC %predicted ≥5%, based on systemic sclerosis (SSc) literature, since this cut-off has been associated with increased mortality in SSc-ILD patients (15). Patients completed questionnaires for respiratory symptoms at both visits, including St. George's Respiratory Questionnaire (SGRQ), Functional Assessment of Chronic Illness Therapy-Dyspnoea (FACIT-D) and Chronic obstructive pulmonary disease (COPD) assessment (CAT). A more detailed description of definitions of respiratory symptoms, assessment of HRCT scans, PFTs and questionnaires is provided in the Supplementary material.

Patients were treated as part of standard of care according to attending physician's-member of ReCONNET judgment based on ILD extent on HRCT (≥15%) and PFTs impairment (DLCO<70%predicted and/or FVC<80%predicted).

The study was approved by Ethics Committee of the School of Medicine, National and Kapodistrian University of Athens (461/23.03.2022) and all patients provided informed consent.

Statistical analysis for categorical data was performed by Fisher exact test when cell counts <5 patients or chi-square test with Yates correction accordingly; numerical data were analysed with Mann-Whitney test or t-test after applying Shapiro-Wilk normality test. Level of statistical significance was set at 0.05. Statistical analysis was performed in GraphPad 7.0a.

Results

Baseline characteristics of treated and untreated SjD-ILD patients

Twenty-four SjD-ILD patients were evaluated in two visits with time interval of 24±6 months. The mean ± SD age at SjD onset and diagnosis was 52.9±16.2 and 56.3±14.7 years, respectively, and 92% were females. Median disease duration until baseline visit was 9 years (range: 0-38). Thirty eight percent had imaging pattern of cellular NSIP on HRCT, 21% fibrotic NSIP, 8% UIP, 4% LIP, while 29% had non-specific pattern. Median extent of ILD on HRCT was 10% (5-50%), while median ESSDAI was 12 (5-28) at baseline visit.

Twelve of 24 SjD-ILD patients received treatment for ILD between the two visits: 6 received rituximab (median: 4.5 cycles), 3 rituximab and MMF (median: 5 cycles of rituximab, 26 months of MMF), 1 tocilizumab (25 months), 1 MMF (20 months) and 1 azathioprine (26 months).

The twelve treated patients did not differ from untreated patients, regarding sex, age, smoking and history of treatment at baseline visit (Table I). Although difference of main disease duration was not statistically different, untreated patients had numerically much longer disease duration (5.5 *vs*. 12 years). Patients receiving ILD treatment had more severe lung involvement at baseline visit compared to untreated, characterised by greater extent of ILD on HRCT (median: 20% *vs*. 10%, p=0.006), more frequent SAD findings on HRCT (58% *vs*. 8%, p=0.027), and a trend for lower FVC (mean: 81.3% *vs*. 96.7%, p=0.086).

Follow-up of pulmonary function in treated and untreated SjD-ILD patients

FVC %predicted and DLCO %predicted remained stable between baseline and follow-up visit in treated patients (mean: 81.3% *vs*. 82.6%, p=0.908 and 75.8% *vs*. 64.6%, p=0.311, respectively), as well as in untreated patients (mean: 96.7% *vs*. 101.5%, p=0.503 and: 70.4% *vs*. 75.2%, p=0.425, respectively).

Change in FVC %predicted from baseline to follow-up visit did not differ significantly between treated and untreated patients (mean: 1.3% *vs*. 4.8%, p=0.594) (Table II). The number of patients presenting progression of ILD did not differ either between the two groups (25% *vs*. 33%, p=0.999). Interestingly, treated patients presented decline of DLCO compared to untreated (mean change: -11.2% *vs*. 4.8%, p=0.003). Change in respiratory questionnaires scores did not differ between two groups.

Seven of 24 (29%) SjD-ILD patients presented progression of ILD between two visits. The 7 progressors did not differ regarding sex, age, disease duration, smoking history, treatment modalities, ESSDAI, from the 17 non-progressors. Furthermore, the two groups did not differ regarding FVC, DLCO and extent of ILD on HRCT at baseline visit (Table III). However, progressors presented numerically more frequently fibrotic NSIP pattern on HRCT compared to non-progressors (43% *vs*. 12%, p=0.127).

Table I. Comparison of clinical, functional and radiological features at baseline visit between treated and untreated SjD-ILD patients.

Features on baseline visit	Treated SjD-ILD patients (n=12)	Untreated SjD-ILD patients (n=12)	*p*-value
Female gender*	10 (83)	12 (100)	0.478
Age at SjD onset**	55.5 ± 18.1	50.4 ± 14.7	0.462
Age at baseline visit**	65.8 ± 11.8	67.0 ± 13.1	0.823
Disease duration of SjD until baseline visit#	5.5 (1-35)	12 (2-27)	0.432
Smoking history*	5 (42)	4 (33)	0.999
History of csDMARDs ever*¶	6 (50)	1 (8)	0.069
History of bDMARDs ever*§	4 (33)	3 (25)	0.999
ESSDAI #	12 (6-22)	12 (5-28)	0.727
ESSDAI excluding pulmonary domain#	3 (0-12)	2 (0-18)	0.525
FVC (%)**	81.3 ± 22.0	96.7 ± 20.0	0.086
DLCO (%)**	75.8 ± 25.3	70.4 ± 15.1	0.537
FEF_{25-75} (%)**	73.9 ± 40.0	78.3 ± 48.8	0.814
FEF_{25-75} <60%*	5 (42)	5 (42)	0.999
Extent of ILD on HRCT#	20 (10-50)	10 (5-30)	**0.006**
SAD findings on HRCT*	7 (58)	1 (8)	**0.027**
FACIT-D **	37.9 ± 7.4	35.9±8.0	0.555
SGRQ **	21.6 ± 19.6	15.1±15.9	0.432
CAT score #	7 (0-17)	2 (0-16)	0.134

csDMARDs: conventional synthetic disease modifying antirheumatic drugs; bDMARDs: biologic disease modifying antirheumatic drugs; ESSDAI: EULAR Sjögren's syndrome disease activity index; FEF_{25-75}: forced expiratory flow after an expiration of 25% to 75% of forced vital capacity.
*Data are expressed as n(%). **Data are expressed as mean±standard deviation. #Data are expressed as median (range). ¶methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclophosphamide. § rituximab.

Table II. Comparison of changes in pulmonary function indices and respiratory symptoms between treated and untreated SjD-ILD patients.

	Treated SjD-ILD patients (n=12)	Untreated SjD-ILD patients (n=12)	*p*-value
Change in FVC (mL) *	-59.2±345.9	35.8±0.338	0.504
Change in FVC predicted (%)*	1.3±17.2	4.8±14.4	0.594
Number of patients with decline in FVC predicted > 5%**	3 (25)	4 (33)	0.999
Change in DLCO predicted (%)*	-7.0±14.9	4.8±11.1	**0.042**
Change in FEF_{25-75} predicted (%)#	-4 (-42 – 34)	-3 (-118 – 43)	0.921
Change in FACIT-D*	1.6±5.9	3.1±5.7	0.564
Change in SGRQ#	2.1 (-4.7 – 13.7)	0.0 (-5.7 – 20.5)	0.742
Change in CAT*	-2.2±5.4	0.6±3.1	0.168

*Data are expressed as mean±standard deviation. **Data are expressed as n(%). # Data are expressed as median (range).

Discussion

In this small case series, the effect of immunosuppressive treatment on the

Table III. Comparison of clinical, functional and radiological features at baseline visit between SjD-ILD progressors vs. non-progressors patients.

Features on baseline visit	SjD-ILD patients with progression of ILD (n=7)	SjD-ILD patients without progression of ILD (n=17)	*p*-value
Female gender*	7 (100)	15 (88)	0.999
Age at SjD onset**	58.3 ± 12.6	50.5 ± 17.4	0.300
Disease duration**	10.1 ± 9.1	13.7 ± 11.2	0.472
Smoking history*	1 (14)	8 (47)	0.191
ESSDAI**	13.7 ± 7.1	11.9 ± 11.3	0.496
ESSDAI excluding pulmonary domain#	2 (0-18)	2 (0-17)	0.726
FVC (%)**	97.7 ± 23.3	85.4 ± 21.1	0.219
FVC <80%*	2 (29)	7 (78)	0.669
DLCO (%)**	67. 9± 15.3	75.3 ± 22.3	0.436
DLCO <70%*	4 (57)	6 (38)	0.650
cNSIP*	1 (14)	9 (47)	0.191
fNSIP*	3 (43)	2 (12)	0.127
LIP*	0 (0)	1 (6)	0.999
UIP*	0 (0)	1 (6)	0.999
Extent of ILD on HRCT#	10 (10-40)	10 (5-50)	0.865
SAD findings on HRCT*	2 (29)	6 (35)	0.999
FACIT-D **	35.9 ± 7.0	37.4 ± 8.0	0.681
SGRQ**	16.2 ± 16.4	19.3 ± 18.6	0.722
CAT score#	4 (0-8)	3 (0-17)	0.665

*Data are expressed as n(%). **Data are expressed as mean±standard deviation. #Data are expressed as median (range).

course of SjD-ILD was explored, by comparing treated vs. untreated SjD-ILD patients in terms of respiratory parameters. Treated patients who had more severe disease at baseline, reflected by extent of ILD on HRCT and a tendency for worse FVC, displayed stable FVC and DLCO after treatment but deteriorating change of DLCO compared to untreated. Furthermore, SjD-ILD progression defined as deterioration of FVC predicted ≥5%, was associated with fibrotic NSIP on HRCT, independently of receiving or not treatment.

In previous small cases series where SjD-ILD patients were evaluated before and after treatment with rituximab, MMF and AZA, respiratory parameters remained largely stable with some patients exhibiting improvement in DLCO. However, there was no control/comparator group without treatment, the extent and ILD pattern were not considered and follow-up period was relatively small (9-11). Regarding treated SjD-ILD group in our study, it appears that immunosuppression modified ILD course by stabilizing FVC and DLCO, although DLCO change was significant towards a lower value, pointing out an aggressive form of ILD. The difference of ILD severity between the two groups is obvious considering that treated patients had: i) more extended ILD on HRCT at baseline which led to treatment initiation, ii) tendency for worse FVC at baseline and iii) deteriorating DLCO change compared to untreated despite treatment. Given these observations and considering that disease duration was numerically longer in untreated patients, it is reasonable to assume that there may be two ILD forms in SjD; a mild occurring later during disease course or early but evolving slowly and a more aggressive becoming clinically evident close to disease onset or diagnosis.

It was also shown, that SjD-ILD patients can be classified into progressors or not, with the first group associated with fibrotic NSIP. In a recent study, proportion of SjD-ILD progressors after 1 year of evaluation was 34.5%, using definition of FVC predicted decline ≥5% (7), but without considering treatment, while in another study the proportion was higher and associated with UIP, although definition of progression was more complex (6). Given that UIP is rare among SjD-ILD patients, it seems that most cases with NSIP in SjD have variable course with two distinct patterns as described previously. Whether cNSIP or fNSIP may affect the course of ILD in SjD remains to be addressed.

Our case series has some limitations. Firstly, the number of patients is small and SjD-ILD patients receiving treatment were not completely matched in terms of ILD extent and disease duration compared to the untreated group, which may have potentially affected the observed results. Secondly, the heterogeneity of different treatment modalities and duration may have also influenced response to treatment. Thirdly, the small number of patients did not allow investigating risk factors for the progressive form of ILD.

In conclusion, the clinical course and prognosis of SjD-ILD is variable following either a mild or a more aggressive form which seems to be at least in part, controlled by immunosuppressive treatment. Future studies with larger, matched cohorts are anticipated to clarify treatment efficacy and reveal risk factors for early therapeutic intervention and close follow-up of SjD-ILD patients.

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