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Treatment of primary sjögren's syndrome-related interstitial lung disease: a retrospective cohort study

Barkha Amlani[1], Ghada Elsayed[2], Umang Barvalia[3], Jeffrey P Kanne[4], Keith C Meyer[5], Nathan Sandbo[5], Zhanhai Li [6], Sara S McCoy[7]

[1] Division of Rheumatology, Department of Internal Medicine Santa Clara Valley Medical Center, San Jose, CA; [2] Rheumatology, Proclinic Center, Cairo, Egypt; [3] Division of Pulmonary & Critical Care, Department of Internal Medicine, Santa Clara Valley Medical Center, San Jose, CA; [4] Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI; [5] Division of Pulmonary & Critical Care, Department of Internal Medicine, University of Wisconsin School of Public Health, Madison, WI, 53705, U.S.A; [6] Department of Biostatistics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; [7] Division of Rheumatology, Department of Internal Medicine, University of Wisconsin School of Public Health, Madison, WI;

Abstract. *Background:* Interstitial lung disease (ILD) is a common complication of primary Sjögren's syndrome (pSS). Because there is a paucity of literature on the management of pSS-associated ILD (pSS-ILD), this retrospective cohort study assessed the efficacy of azathioprine and mycophenolate therapy in adult patients with pSS-ILD. *Methods:* A retrospective cohort study was performed using electronic health records to identify adults meeting the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for pSS. The presence of pSS-ILD was confirmed by characteristic high-resolution computed tomography and/or histopathology findings. Sociodemographic, clinical, and pulmonary function test (PFT) data were abstracted for patients meeting the criteria and followed longitudinally from the date of their ILD diagnosis. PFT values were anchored on time of treatment start, and linear mixed-effects modeling was used to analyze changes in diffusion capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) before and after treatment initiation. *Results:* We identified 19 subjects who had pSS-ILD, of whom seven were treated with azathioprine and seven were treated with mycophenolate. Within the azathioprine treated group, FVC% slope change trended toward improvement from a rate of -9.8% per month pre-treatment to 2.1% per month post-treatment (p = 0.13). Within the mycophenolate treated group, FVC% slope change improved from a rate of 1.5% per month pre-treatment to 4.3% per month post-treatment (p = 0.02) and DLCO% slope changed from a rate of -3.8% to −1.3% per month (p = 0.01) after therapy start. *Conclusions:* Mycophenolate treatment was associated with significant improvement in PFTs of pSS-ILD patients over time, and azathioprine treatment followed a similar non-significanttrend. Additional prospective studies are needed to further evaluate these findings. *(Sarcoidosis Vasc Diffuse Lung Dis 2020; 37 (2): 136-147)*

Key words: Sjögren's Syndrome, Interstitial Lung Disease, Treatment

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Correspondence: Sara McCoy, MD
University of Wisconsin
School of Medicine and Public Health
1685 Highland Avenue
Madison, WI 53705-2281
ssmccoy@medicine.wisc.edu
Email: ssmccoy @medicine.wisc.edu
Phone: (608) 262-0908
Fax: (608) 263-7353

Introduction

Primary Sjögren's syndrome (pSS), a chronic, multisystem autoimmune disease, is characterized by focal lymphocytic infiltration of the lacrimal and salivary glands resulting in dry eyes and dry mouth (1-3). As the second most common multisystem rheumatologic disease, pSS has an estimated incidence between 0.1-0.5% of the general population (1, 4). Systemic involvement is common and can be the initial manifestation of pSS (1, 5). Interstitial lung disease (ILD) is a life-threatening systemic complication of pSS; patients with ILD have a higher mortality than those without ILD (3, 6, 7). Pulmonary involvement is common in pSS, and at least 9-20% of pSS patients have lung involvement (1, 8), with some studies suggesting much higher rates (3, 8, 9). Finally, ILD can precede the diagnosis of pSS in up to 25% of patients (8).

Azathioprine and mycophenolate are commonly utilized for treatment of pSS-ILD. Despite the common use of azathioprine for pSS-ILD, there is only one study (n = 13 patients) that evaluated the effect of azathioprine on lung function in a well-defined cohort of patients with pSS-ILD, and this study did not evaluate differential longitudinal trends in pulmonary function test (PFT) pre- and post-therapy (10). No studies exist that have evaluated the effect of mycophenolate in a well-defined cohort of patients with pSS-ILD. Other studies evaluating azathioprine or mycophenolate in larger mixed cohorts of patients with connective-tissue disease associated ILD had small percentages of pSS patients, and therapeutic effect was not reported for pSS (11, 12). Thus, despite the high frequency and morbidity of pSS-ILD, the effectiveness and safety of commonly utilized immunosuppressive treatments for pSS-ILD remains unknown. This lack of an evidential base to inform the choice of treatment in pSS-ILD creates uncertainty in clinical decision making and potentially delays the initiation of efficacious treatments.

To address this gap in knowledge, we hypothesized that treatment with azathioprine or mycophenolate, with or without rituximab, would attenuate PFT decline over time. To test this hypothesis, we retrospectively analyzed a well-defined cohort of patients with pSS-ILD to evaluate the effect of initiation of azathioprine and mycophenolate on lung function decline. In this manuscript we describe the characteristics of this cohort and report the longitudinal change in PFTs before and after initiation of therapy.

Materials and Methods

Inclusion/exclusion

This study was performed in accordance with the Declaration of Helsinki and approved by the UW Health Sciences Institutional Review Board (IRB) (2013-1121) with a waiver of individual informed consent due to the minimal risk represented by this retrospective study. This is a retrospective cohort study of adults ≥ 18 years old with pSS complicated by ILD. We used the electronic health record (EHR) from an academic health system to create this cohort. Patients were identified who had both CD9/10 codes for pSS and ii) and a diagnosis of ILD. Specific ILD types were identified as nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphoid interstitial pneumonia (LIP), diffuse alveolar damage, or organizing pneumonia (OP). Patients were included if they were evaluated by both pulmonology and rheumatology within our health care system and had clinically confirmed pSS (Figure 1). Records were individually reviewed by a board certified (SM) rheumatologist to ensure each patient met the 2016 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria for pSS (13). Patients with another autoimmune condition in addition to pSS were excluded so that we only included patients who had pSS. The diagnosis of ILD was confirmed either by the presence of characteristic changes on high resolution computed tomography (HRCT), as determined by a thoracic radiologist (J.K), or by characteristic findings of ILD on lung specimen histopathology at the time of diagnosis. Medical records were manually abstracted by MD reviewers (B.A., U.B., and G.A.) for all clinical and serologic data using a standardized case review tool.

Outcome/data collection

Our primary outcome of interest was a significant change in percent predicted forced vital capacity (FVC%) and percent predicted diffusing capacity of carbon-monoxide (DLCO%) between pre- and post-treatment slope determined by linear effects models.

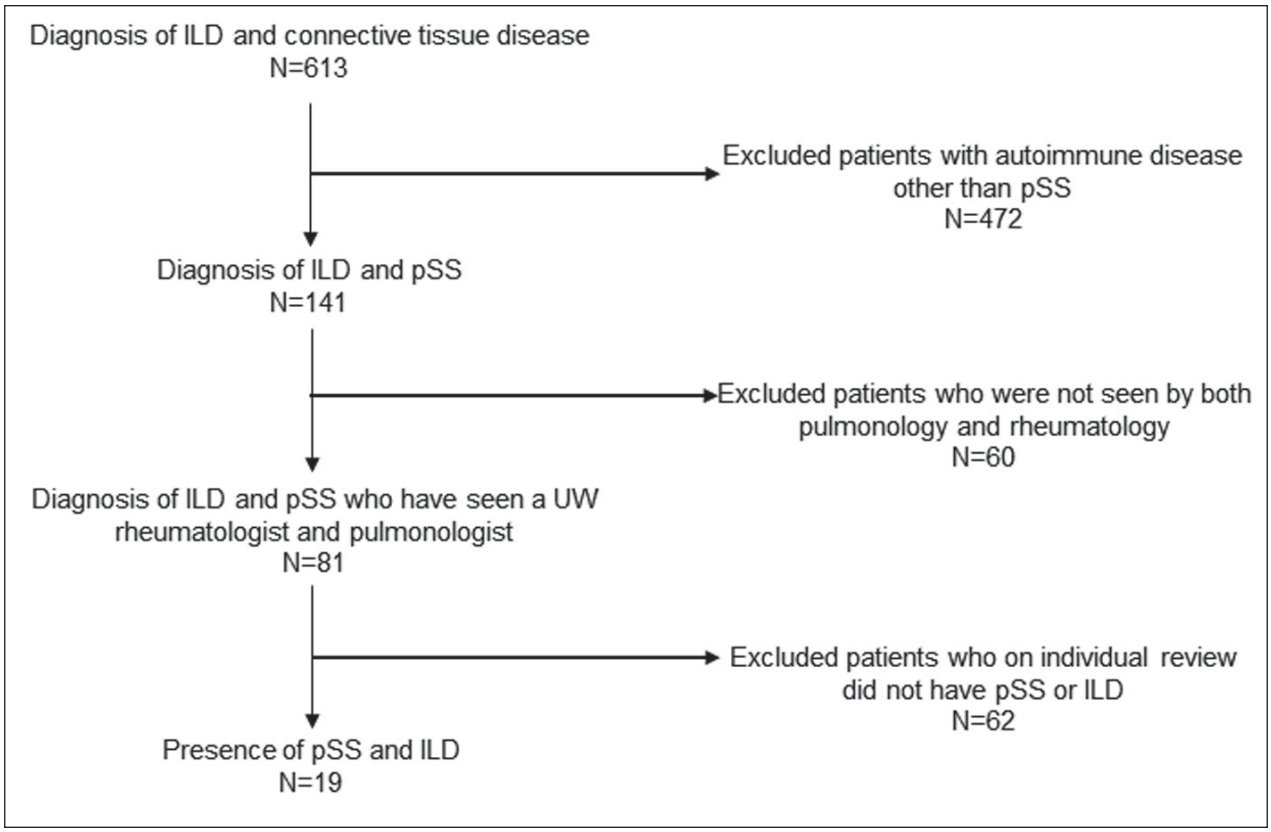

Fig. 1. Cohort flow diagram demonstrating exclusion and inclusion of patients who meet criteria for primary Sjögren's Syndrome (pSS) and interstitial lung disease (ILD) diagnosis and who have seen both pulmonology and rheumatology within the UW health system.

Available PFT data were collected for all patients, averaged in 3-month time intervals, and anchored with the values (T_0) for each patient just prior to the date on which treatment with azathioprine or mycophenolate was initiated. For the grouped analysis, if patients were treated with more than one medication, T_0 was anchored on the start date of the first of the combined treatments. Analysis of the untreated group was anchored with T_0 on date of ILD diagnosis. All HRCT scans were reviewed by a subspecialist thoracic radiologist (J.K.), and morphologic patterns were determined (NSIP, OP, NSIP with OP overlap, LIP, other) according to radiographic patterns.

Variable definitions

Our primary exposures of interest included azathioprine, mycophenolate, and rituximab. Mycophenolic acid was considered equivalent to mycophenolate mofetil for the purposes of this study. Exposure start and end dates were recorded using manual review of EHR prescription data. Sensitivity analysis analyzed treated UIP patients versus a composite of other treated patients. The composite group was composed of diagnoses including NSIP, LIP, and OP.

Additional clinical data abstracted included age, sex, tobacco use, cardiovascular disease (CVD) (defined as coronary artery disease, congestive heart failure, or cerebrovascular disease), gastroesophageal reflux (GERD), obstructive sleep apnea (OSA), malignancy, pulmonary arterial hypertension (PAH), and pulmonary embolism (PE). Clinical features abstracted included pulmonary symptoms at ILD diagnosis, constitutional symptoms, lymphadenopathy, glandular swelling, inflammatory arthritis, cutaneous manifestations of pSS, renal involvement with pSS, muscular involvement with pSS, peripheral or central nervous system manifestations of pSS, immunosuppressive/immunomodulatory therapy, and adverse effects of azathioprine, mycophenolate, or rituximab. Laboratory data on pSS and pSS disease activity were also collected.

Statistical methods

Baseline characteristics between treated group and untreated group were compared with chi-squared test or Fisher's exact test for categorical variables and t-tests for continuous variables. Within the treated group, linear mixed-effects models were used to evaluate for change in PFT slopes (FVC% and DLCO%) per month before and after therapy. Analysis was performed for each treatment group (azathioprine, mycophenolate, and rituximab) as well as for the entire treated cohort. When the entire cohort was evaluated, patients who were treated sequentially with multiple drugs were anchored at the start time of the initial drug. Plots were created illustrating PFTs two years pre- and post-therapy. Pre-treatment PFT slope was projected into the post-treatment portion of the graph for visual comparison of slope change. A p value of < 0.05 was considered to be significant. Statistical analyses were performed using SAS 9.4 (Cary, NC) and GraphPad Prism software (GraphPad Software, La Jolla, CA, USA).

Results

Study population and baseline characteristics

613 patients with ILD and sicca symptoms were identified. 472 patients carried diagnoses of other autoimmune diseases and were excluded (Figure 1). Patients not seen by both pulmonology and rheumatology consultants were also excluded to allow for accurate diagnosis and longitudinal PFT follow-up. After individual chart review, 19 patients with ILD who met the 2016 ACR/EULAR criteria for pSS were identified and comprised our study cohort.

Demographics and clinical characteristics were similar between the treatment groups (Table 1). The mean age for patients who received immunosuppressive treatment was 58 (± 11) years, and the mean age for patients who received no immunosuppressive therapy was 70 (± 11) years.

Symptoms including cough, dyspnea, dry eyes or mouth, joint pain and other constitutional symptoms did not vary significantly between treated versus untreated groups. Other clinical characteristics including cryoglobulinemia, anemia, cytopenia, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), low complement, presence of RF, anti-SSA antibody, anti-Jo1 antibody, anti-neutrophil cytoplasmic antibody (ANCA), anti-ribonucleoprotein (anti-RNP) antibody, anti-Smith antibody, lymphadenopathy, CVD, GERD, malignancy, OSA and PE were similar between the groups (Table 1).

The number of patients treated with azathioprine (n = 7), mycophenolate (n = 7), rituximab (n = 6), or untreated (n = 5) were similar. Indications for treatment initiation were functional decline combined with worsening HRCT or PFTs. The reasoning for therapy choice was explained in three patients. Two patients were started on rituximab for concomitant arthralgias and one was started on rituximab over azathioprine or mycophenolate due to the general increased risk of lymphoma in pSS. Otherwise, no explicit reasoning was provided for the choice of therapy. Five out of six patients who received rituximab also received azathioprine or mycophenolate, one of whom received all three treatments. Of the five patients who received combined therapy, two patients were started on mycophenolate for ILD and rituximab was ultimately added for progression of ILD. A third patient started rituximab initially for ILD and mycophenolate was added for progression of ILD. A fourth patient started azathioprine for ILD and rituximab was added for arthralgias. A fifth patient started mycophenolate for ILD, mycophenolate was stopped and rituximab was started for pSS-related inflammatory myositis. Azathioprine was ultimately added as a steroid sparing agent after an initial rituximab course.

The number of patients receiving hydroxychloroquine, leflunomide, and methotrexate were similar between the groups. The mean dose of azathioprine was 150 mg daily with duration of therapy ranging from three to thirteen years with mean of 7 years. The mean dose used for mycophenolate was 2000 mg daily with duration of therapy ranging from six months to five years with mean of 2 years. The average latency period from ILD diagnosis to the initiation of immunosuppressant therapy did not vary significantly between the three groups but the azathioprine group trended to shorter treatment latency. Between the four groups, there was no significant difference between duration of high dose prednisone use (months ≥ 40 mg), pre-immunosuppression prednisone dose or duration, six month post-immunosuppression prednisone dose or duration, or median prednisone

maintenance dose. The average dose of prednisone before azathioprine start was 9 (± 10) mg and after 6 months of therapy was 6 (±8) mg (p = 0.3). The average dose of prednisone before mycophenolate start was 32 (±26) mg and after 6 months of therapy was 19 mg (±9) (p = 0.03).

Baseline PFTs including FEV1%, FVC%, FEV1/FVC% and DLCO% and baseline oxygen use were similar between the four groups (Table 1). The mean FVC% and DLCO% for five patients in the untreated group was 67% and 39% respectively. Baseline 6-minute walk tests varied between groups but were only reported in two patients each in the azathioprine and mycophenolate groups and in one patient in each of the rituximab and untreated

Table 1. Demographics and Patient Characteristics

	AZA (n=7)	Msg	MMF (n=7)	Msg	Ritux (n=6)	Msg	No Therapy (n=5)	Msg
Mean Age (± SD)	57.7 ± 14.2		58.9 ± 10.6		55.7 ± 10.1		69.6 ± 11.3	
Demographics n(%)								
Alive	6 (86)		5 (71)		5 (83)		2 (40)	
Caucasian	6 (100)	1	6 (100)	1	5 (100)	1	1 (100)	4
Female	6 (86)		5 (83)		5 (83)		5 (100)	
Tobacco ever*	1 (17)	1	5(71)		4 (67)		3 (75)	
Labs n(%)								
ANA positive	6 (86)		6 (86)		6 (100)		4 (100)	1
ANA Titer≥1:320	3 (60)	2	5 (83)	1	4 (67)		4 (100)	1
Nucleolar	1(20)	2	1 (14)	1	1 (17)		0 (0)	1
Speckled	2(40)	2	5 (71)	1	4 (67)		3 (75)	1
Other	2(40)	2	1 (14)	1	1 (17)		1 (25)	1
Cryoglobulinemia	0 (0)	4	0 (0)	3	0 (0)	4	1 (33)	1
Elevated CRP	3 (50)	1	3 (43)		2 (33)		2 (50)	1
Elevated ESR	7 (100)		5 (83)	1	5(83)		2 (50)	1
Low C3/C4	0 (0)		1 (14)		0 (0)		1 (33)	2
RF	3 (50)	1	4 (57)		3 (50)		2 (50)	1
SSA	6 (86)		6 (86)		5 (83)		3 (75)	1
Comorbidities n(%)								
#CVD	1 (17)		1 (17)		1 (25)	2	1 (25)	1
GERD	5 (71)		7 (100)		4 (67)		4 (100)	1
Malignancy	2 (33)	1	0 (0)	2	0 (0)	2	1 (25)	1
OSA	2 (33)	1	1 (20)	1	1 (25)	2	1 (33)	2
PE	1 (17)		1 (20)	1	1 (25)	2	0 (0)	
PAH	1 (17)		3 (50)		2 (50)	2	2 (67)	2
Diagnosis to IS start (Months ± SD)	4.3 ± 6.4		29.1 ± 46.7		44.4 ± 9.6	1	N/A	
Treatment n(%)								
HCQ	5 (71)		5 (71)		5 (83)		1 (25)	1
Leflunomide	1 (14)		1 (14)		1 (17)		0 (0)	

	AZA (n=7)	Msg	MMF (n=7)	Msg	Ritux (n=6)	Msg	No Therapy (n=5)	Msg
MTX	1 (14)		1 (14)		1 (17)		0 (0)	
Prednisone	4 (57)		7 (100)		5 (83)		2 (40)	
Duration prednisone ≥40 mg (months ± SD)	0.5 ± 0.55	1	1.3 ± 2.05		0.7 ± 0.8		0.5 ± 0.6	
Duration prednisone pre-IS (months ± SD)	3.8 ± 4.6	1	4.2 ± 4.4		7.3 ± 5.5		N/A	
Dose prednisone pre-IS (mg ± SD)	9.2 ± 10.2	1	31.7 ± 25.6		23.3 ± 15.1		N/A	3
Duration prednisone post-IS (months ± SD)	45.6 ± 69.1	1	22.3 ± 22.7		26.4 ± 32.4		N/A	
Dose prednisone 6 months post-IS (mg ± SD)	6.3 ± 7.5	1	19 ± 8.9		12.1 ± 7.5	1	0.8 ± 2.0	
Median prednisone maintenance dose* (mg ± SD)	2.5 ± 2.7	1	12.9 ± 10.8		7.5 ± 6.9		0.8 ± 2.0	
Baseline PFTs (% ± SD)								
FEV1%	84 ± 2.9		70 ± 11.7	2	70 ± 19.6	3	59 ± 14.6	3
FVC%	86 ± 26.0		64 ± 7.9	1	74 ± 15.5	2	67 ± 17.9	2
FEV1/FVC%	88 ± 15.9	3	88 ± 7.0	3	91 ± 11.7	3	73 ± 14.7	2
DLCO%	57 ± 23.6		45 ± 9.1	1	59 ± 14.84	2	39 ± 16.0	4
Baseline 6MWT distance (feet ± SD)*	993 ± 151	5	1267 ± 208	5	1119 ± 0	5	450 ± 0	4
Oxygen at baseline n(%)	1 (17)		3 (43)		1 (17)		0	
BAL n(%)								
+Eosinophilic	0 (0)	3	1 (50)	5	0 (0)	4	0 (0)	2
^Lymphocytic	2 (50)	3	1 (50)	5	2 (100)	4	1 (33)	2
Normal	2 (50)	3	0 (0)	5	0 (0)	4	2 (67)	2
HRCT pattern n(%)								
LIP	4 (57)		1 (14)		2 (33)		1 (25)	1
NSIP	1 (14)		5 (71)		3 (50)		1 (25)	1
OP	1 (14)		0 (0)		0 (0)		0 (0)	1
UIP	0 (0)		0 (0)		0 (0)		0 (0)	1
Other	1 (14)		1 (14)		1 (17)		2 (50)	1
Lung biopsy n(%)								
LIP	2 (33)	1	1 (20)	2	2 (50)	2	0 (0)	3
NSIP	1 (17)	1	3 (60)	2	1 (25)	2	0 (0)	3
UIP	1 (17)	1	1 (20)	2	1 (25)	2	0 (0)	3
Other	2 (33)	1	0 (0)	2	0 (0)	2	2 (100)	3

AZA: Azathioprine; MMF: Mycophenolate; Ritux: Rituximab; SD: Standard deviation; *p < 0.05; ANA: Antinuclear antibody; CVD: Cardiovascular disease; #CVD history includes coronary artery disease, congestive heart failure, or cerebrovascular event; GERD: Gastroesophageal reflux disease; OSA: Obstructive sleep apnea; PE: Pulmonary embolism; PAH: Pulmonary arterial hypertension; HCQ: Hydroxychloroquine; MTX: Methotrexate; IS: immunosuppression; 6MWT: 6-Minute Walk Test; BAL: Bronchoalveolar lavage; +≥2% eosinophilic; ^≥15% lymphocytic; HRCT: High resolution computed tomography LIP: Lymphoid interstitial pneumonia; NSIP: Non-specific interstitial pneumonia; OP: Organizing pneumonia; UIP: Usual interstitial pneumonia

groups. Oxygen use was similar between these groups at baseline.

Imaging, biopsy, and bronchoalveolar lavage

Patients in azathioprine treatment group predominantly had a LIP pattern (n = 4) compared to the mycophenolate treated group, which predominantly had a NSIP pattern (n = 5). The untreated group included one patient with LIP and one patient with NSIP. The differences were not statistically significant. None of the patients in either treatment group had a UIP pattern on HRCT. Two patients had changes consistent with significant aspiration on HRCT.

Histopathology results for 13 patients who had undergone native lung biopsy were available. The different patterns of involvement are included in Table 1. Additional findings included chronic bronchiolitis (n = 2) and hypersensitivity pneumonia (n = 1). Six patients did not have a biopsy despite imaging consistent with ILD. Of the four HRCT-diagnosed NSIP patients who did not receive biopsy, three were untreated and one was treated with mycophenolate. Biopsy was not performed in one untreated patient because the ILD was mild and stable. One patient with NSIP on HRCT was not biopsied due to presentation with severe exacerbation and was considered too high risk for biopsy before their ultimate death. Two cases of NSIP were not biopsied and no justification was provided. Of the two patients with HRCT-diagnosed LIP without histopathologic confirmation, one patient was in the untreated group and one patient was treated with azathioprine. The two patients with LIP were not biopsied because their clinical course was stable.

Bronchoalveolar lavage (BAL) results from 11 patients showed a majority of patients (n = 5) with lymphocytosis (≥15% lymphocytes). Four patients had a normal BAL nucleated immune cell profile, one had BAL that showed an increase in eosinophils, and one had a contaminated sample with numerous squamous epithelial cells.

Adverse effects of therapy

Azathioprine was discontinued in one patient after ten years of use because of recurrent uncomplicated lower urinary tract infections. Azathioprine was stopped in another patient after three years out of concern for bleeding risk when the patient presented with uncomplicated rectal bleeding. One patient was switched from mycophenolate to azathioprine because of an ILD exacerbation. One NSIP patient on mycophenolate developed respiratory failure secondary to rhinovirus infection and died. One LIP patient who received mycophenolate and one dose of rituximab died while in hospice care for ILD symptoms. One patient had mild neutropenia due to mycophenolate (lowest 1.95 K/μL; normal 2.3-8.6 K/μL). without and associated infections. The cause of death was unknown for two patients (one who was receiving azathioprine and the other was not on treatment). No patients had liver enzyme elevation.

Regarding malignancies, one patient developed mucosa-associated lymphoid tissue (MALT) lymphoma of the lung 12 years after azathioprine was discontinued. This patient had a biopsy at the time of the initial diagnosis that showed LIP and repeat lung biopsy twelve years later diagnosed MALT lymphoma. One untreatated patient developed MALT lymphoma of the parotid gland. This patient did not have a lung biopsy. Finally, one patient had uterine cancer decades before development and treatment of ILD.

Pulmonary Function Tests

Azathioprine Group

The slope of FVC% trended toward improvement after azathioprine treatment (Figure 2A). The FVC% slope for patients in azathioprine group before treatment was increasing at a rate of 2% per month and after treatment was increasing at a rate of 4% per month (p = 0.13) (Table 2). The mean FVC% before treatment in the azathioprine group was 72% and the mean FVC% after treatment was 76%. Only one patient had a recorded DLCO% before treatment in the azathioprine group so evaluation of DLCO% in this group was limited (Figure 2B, Table 2).

Mycophenolate Group

The change in slope of FVC% before and after mycophenolate therapy significantly improved after treatment. The change in FVC% slope was declining at a rate of -10% per month before therapy, and after therapy the slope improved to a rate of 2% per month (p = 0.02) (Figure 3A, Table 2).

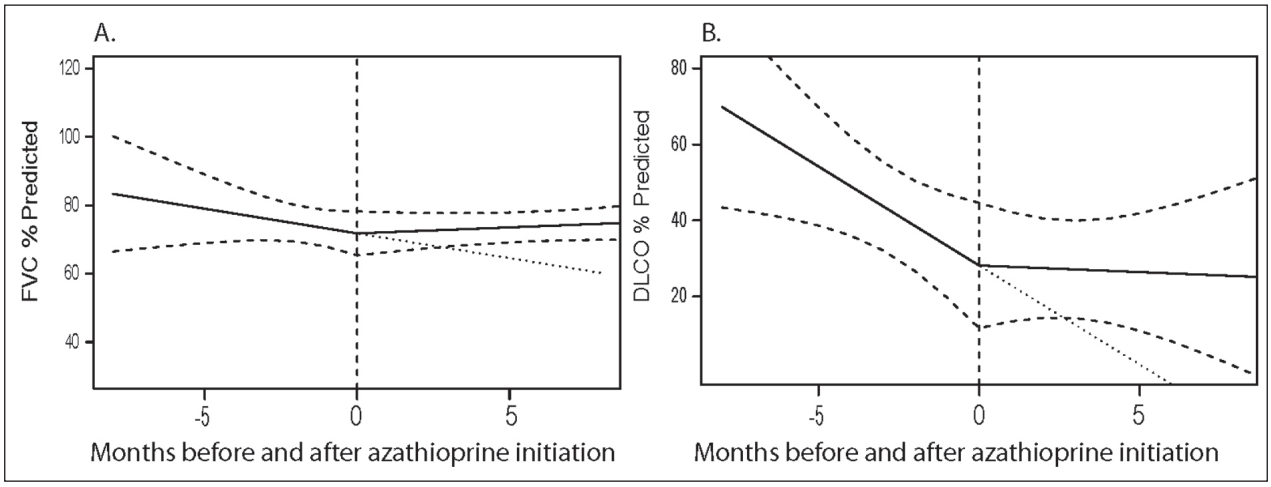

Fig. 2. Mixed-effects model estimate of FVC% and DLCO% slope before and after initiation of azathioprine plotted 12 months before and 12 months after azathioprine start. The bold perforated line represents the 95% confidence interval. The light perforated line represents the trajectory of the pre-treatment slope. (a) FVC% slope before treatment was declining at a rate of 1.5% per month and after treatment was increasing at a rate of 4.3% per month (p=0.13); (b) DLCO% slope after treatment was declining at a rate of -0.3% per month (p=0.96).

Table 2. FVC% and DLCO% Before and After Azathioprine and Mycophenolate Treatment

	AZA			MMF		
	Before IS	**After IS**	**P value**	**Before IS**	**After IS**	**P value**
FVC%						
Mean	71.9	75.7	0.46	54.9	60.5	0.34
Slope Change	1.5 ± 11.4	4.3 ± 7.6	0.13	-9.8 ± 11.7	2.1 ± 7.7	0.02
DLCO%						
Mean	47.3	28.7	0.17	45.2	41.6	0.59
Slope Change	0	-0.3 ± 4.5	0.96	-3.8 ± 3.7	-1.3 ± 3.2	0.01

FVC% and DLCO% mean included mean PFTs performed every 3 months before and after therapy start. FVC% and DLCO% slope is calculated as change per month before and after treatment start. AZA: Azathioprine; MMF: Mycophenolate; IS: Immunosuppression

The mean FVC% before mycophenolate therapy was 55%, and the mean FVC% after therapy was 61% (p = 0.34). DLCO% slope was declining at a rate of -4% change per month before therapy and -1% after therapy (p = 0.01) (Figure 3B, Table 2). The mean DLCO% before therapy was 45% and after was 42% (p = 0.59).

Rituximab Group

Five out of six patients treated with rituximab had received or were receiving treatments with mycophenolate or azathioprine. Only three patients had PFTs available before and after treatment. Overall, an improvement in FVC% and decline inDLCO% after treatment with rituximab was noted. The FVC% change of slope before treatment was a rate of 9% per month and after treatment was 3% per month (p = 0.18). The DLCO% slope before therapy was 5% per month and after therapy was -2% per month (p = 0.43).

UIP vs. Composite Group

To determine if treatment response to immunosuppression varied between UIP and other ILD patterns, sensitivity analysis of UIP versus a composite group (LIP, NSIP, and OP) before and after treatment was performed. In the analysis of UIP versus other ILD patterns we found that FVC% slope improved an average of 9% per month for UIP and 3% for the composite group (p = 0.06). DLCO%

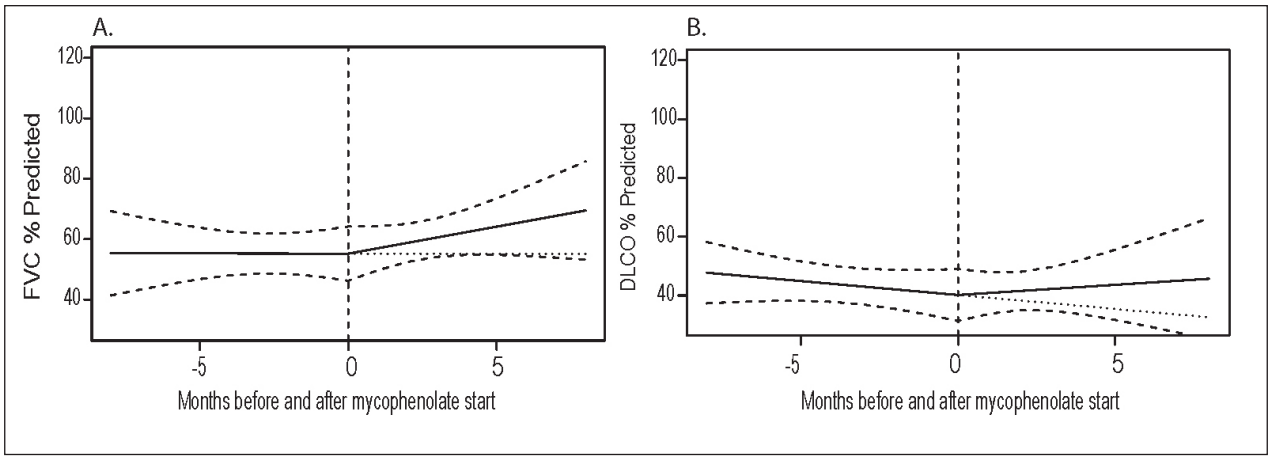

Fig. 3. Mixed-effects model estimate of FVC% and DLCO% slope before and after initiation of mycophenolate plotted 12 months before and 12 months after mycophenolate start. The bold perforated line represents the 95% confidence interval. The light perforated line represents the trajectory of the pre-treatment slope. (a) FVC% slope before treatment was declining at a rate of -9.8% per month and after treatment was increasing at a rate of 2.1% per month (p = 0.02); (b) DLCO% slope before treatment was declining at a rate of -3.8% per month and after treatment was declining at a rate of -1.3% per month (p = 0.01).

improved by a mean 1% per month in the UIP group and 1% in the composite group (p = 0.96).

Discussion

ILD is a common complication of pSS that significantly increases morbidity and mortality. Despite these implications for patient's well-being, the optimal management of pSS-ILD remains unknown. Because there is no well-defined or standard approach to therapy that is supported by clinical trial data, we sought to determine the real-world efficacy of commonly utilized immunosuppressive medications.

In this retrospective, observational cohort study we identified well-matched cohorts of patients with pSS-ILD who had received either azathioprine or mycophenolate as the primary steroid-sparing immunosuppressive agent. Analysis of pre- and post- treatment PFTs showed that initiation with azathioprine was associated with a trend toward improvement in PFT parameters. Fitting these findings using a mixed effects model, comparison of pre-treatment FVC% decline compared with post-treatment FVC% decline suggested a trend toward stabilization, although the study may have been underpowered to directly test this outcome. In the second cohort of patients treated with mycophenolate, we observed improved PFTs after initiation of therapy with the mixed effects model showing a similar stabilization in FVC% and DLCO% decline. Of clinical importance, prednisone use decreased significantly after start of mycophenolate therapy and a similar trend was noted with azathioprine therapy.

Chart review of both of these cohorts found that both azathioprine and mycophenolate were well-tolerated with most patients able to remain on therapy for an extended time (median 7.3 years for azathioprine and 1.9 years for mycophenolate). Taken together, these data support the use of mycophenolate as a treatment for pSS-ILD, and suggest that azathioprine may have a similar efficacy.

A further strength of this study is the granular examination of longitudinal PFT data, which enabled us to utilize a mixed effects model to estimate the magnitude of effect on PFT decline pre- and post-initiation of therapy. This model suggests that, in aggregate, mycophenolate completely attenuated the FVC% decline, which fits with the observed change in pre- and post-FVC% values. This finding adds to our understanding of the potential effect of mycophenolate on lung function decline for this subset of ILD, as other efficacious therapies for idiopathic ILDs such as IPF are known to decrease the FVC% decline, but do not fully stabilize disease in aggregate (14, 15). Too few subjects were available that had received only rituximab and who had

sufficient PFT data available before and after therapy initiation to adequately evaluate its potential efficacy.

These findings add to the limited existing published data studying the efficacy of mycophenolate in pSS-ILD. Mycophenolate has been studied as part of a large CTD-ILD cohort including pSS patients and reported to possibly improve lung function, but only four of a total of 67 patients with CTD-ILD had pSS (12). Thus, definitive conclusions about its efficacy in pSS-ILD could not be drawn. Our cohort significantly adds to our understanding of the effects of mycophenolate on pSS-ILD. Our work represents the largest reported well-characterized cohort of pSS-ILD patients treated with mycophenolate for lung function decline. Furthermore, along with the observed stable lung function post mycophenolate initiation, we identified a significant reduction in prednisone dosage, which is often an important aim of initiating this therapy in patients. In aggregate, these findings lend further support to the potential efficacy of mycophenolate in this patient population.

Similar to mycophenolate, this study adds to the limited existing published data studying the efficacy of azathioprine in pSS-ILD. In the largest published cohort of pSS-ILD patients treated with azathioprine, Deheinzelin et al. found that the FVC improved in seven of eleven patients (10). While other studies have reported potentially improved outcomes in patients with pSS-ILD on azathioprine, these studies grouped pSS patients into a larger CTD cohort, precluding analysis of individual disease types (11). Thus, in this report we describe the second largest cohort of patients with pSS-ILD treated with azathioprine. Although our study was likely underpowered to detect differences in pre- and post- FVC% changes, mixed effects modeling suggested that there is stabilization of FVC% decline after treatment initiation.

Although an analysis of the efficacy of rituximab was a goal of this study, we had limited data available on pre- and post-treatment PFTs in the rituximab group. Previous studies reporting rituximab efficacy have been small, ranging from one to eight pSS-ILD patients treated with rituximab (16-18). Our limited series of patients treated with rituximab had mixed PFT change after therapy. Of the three patients with pre- and post-PFT data, all were treated with another immunosuppressive agent prior to initiation of rituximab, confounding the interpretation of these data.

We performed sensitivity to evaluate pre and post FVC% and DLCO% when comparing UIP to composite ILD (LIP, NSIP, and OP). No significant difference was seen in treatment response between UIP and NSIP, supporting that histopathology pattern did not significantly influence our reported findings. Further, the distribution of UIP was similar between the three treatment cohorts. Interestingly, there was a trend toward greater improvement of FVC% in the UIP group compared to the composite group, although this did not reach significance. Previous series have suggested that pSS UIP prognosis is similar to that of NSIP, while others show pSS UIP is progressive and resistant to immunosuppressive therapy (3, 9).

Limitations of our study include its retrospective nature and the small number of patients who met inclusion criteria that allowed them to be placed in the treatment cohorts. The retrospective nature of this study may confer bias and limits our ability to draw conclusions concerning causal relationships of specific therapies with outcomes. Intrinsic to a retrospective study, there was variability between comparator groups. For example, the untreated group had an overall older age than the treated groups. Despite older age, the untreated group had a similar baseline functional capacity including baseline PFT values and oxygen requirement. Although baseline 6-minute walk tests varied between the four groups at baseline, interpretation of these results are limited by a paucity of data. Additionally, many patients were treated with other immunosuppressive therapy such as corticosteroids, however doses of corticosteroids were similar between the groups and declined after initiation of azathioprine and mycophenolate, making this less likely to have confounded our results. Two patients treated with immunosuppressive therapy were diagnosed by HRCT alone without pathology. In the case of HRCT-diagnosed NSIP, a histopathologic diagnosis of UIP might falsely reduce the significance of the results. Reassuringly, despite this limitation, we did find significant improvement in FVC% with mycophenolate therapy. One case of LIP treated with azathioprine was not biopsied. Biopsy of LIP is important because both pulmonary amyloidosis and lymphoma can appear similar to LIP. However, in this case the patient was followed

over 15 years for stable ILD, making the presence of occult amyloidosis or lymphoma unlikely. Also, because out center is a tertiary referral center, our pSS-ILD cohort may have referral bias toward more severe disease. Finally, improved PFT values may only reflect a survival effect that was not linked to a beneficial treatment response.

In conclusion, in this retrospective cohort analysis of well-characterized pSS-ILD patients treated with either azathioprine or mycophenolate we found that mycophenolate treatment was associated with a significant improvement in pulmonary function that appeared durable by mixed effects modeling. These findings significantly expand the limited available data supporting the use of azathioprine and mycophenolate as therapies for these patients. This study has found compelling associations between the use of azathioprine and mycophenolate in pSS-ILD and lung function stabilization. However, due to the retrospective and observational nature of this study, adequately powered prospective studies are still needed to further validate the potential efficacy of these immunomodulatory therapies on disease progression in pSS-ILD.

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