Effect of Cotreatment with Corticosteroids in Connective Tissue Related Lung Disease (CTD-ILD) Patients on Mycophenolate Mofetil (MMF)

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Abstract

Introduction: Connective Tissue Disease Related Interstitial Lung Disease (CTD-ILD) is often treated with immunosuppressant medications; common among these is Mycophenolate Mofetil (MMF). We hypothesized that co-treatment with corticosteroids would impact disease progression.

Methods: We examined a consecutive cohort of CTD-ILD patients followed at Temple University Hospital in Philadelphia, PA since 2015 who had pulmonary function tests (PFTs) performed by American Thoracic Society (ATS)/European Respiratory Society (ERS) Criteria at least one year apart. All patients were treated for CTD-ILD with MMF used either as sole therapy or as combination therapy with prednisone. Univariate logistic analyses were performed revealing the odds ratio (OR) for improvement or worsening of several PFT values (including forced vital capacity (FVC), diffusion capacity of carbon monoxide (DL_{CO}), and six-minute walk (6MW)) greater than the minimal clinically important difference (MCID) for each value.

Results: We included 103 patients (74 women) with an average age of 60 ± 11 years, 49% of our cohort were current or former smokers, and mean BMI was 29 ± 7 kg/m². Patients were observed on treatment for an average of 23 months. CTD distribution included 25% mixed connective tissue disease (MCTD), 24% systemic sclerosis (SSc), 17% rheumatoid arthritis (RA), 14% systemic lupus erythematosus (SLE), 10% other idiopathic inflammatory myositis (IIM) syndromes, 7% Antisynthetase Syndrome, 5% Sjögren's syndrome. Non-specific interstitial pneumonia (NSIP) was the majority (45%) ILD pattern noted, Usual Interstitial Pneumonia (UIP) 35%, and other types were less prevalent (20%). The majority of patients received corticosteroids as co-treatment with MMF (75 patients (72%)) with a mean daily dose of 15 ± 16 mg of prednisone. Mean daily MMF dose was 1144 ± 675 mg. Glucocorticoid treatment was not associated with significant improvements in PFT values, including FVC, DL_{CO} , and 6MW distance walked.

Conclusion: In this small cohort, patients with CTD-ILD receiving MMF did not demonstrate improved lung function when receiving co-treatment with corticosteroids, but larger prospective studies are needed to better elucidate the effect of corticosteroids on this vulnerable group of patients.

Introduction

Connective tissue disease-related interstitial lung disease (CTD-ILD) is a form of interstitial lung disease (ILD) common to patients with connective tissue diseases (CTD) including systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myositis (IIM) syndromes, Sjögren's syndrome, mixed connective tissue disease (MCTD), and other forms of CTD.^{1,2} Although ILD is associated with high rates of morbidity and mortality in CTD patients, compared to patients with idiopathic interstitial pneumonias a CTD-ILD diagnosis conveys survival benefit and a potential for symptomatic improvement with immunomodulator therapy.^{1–5}

Medications commonly used in CTD-ILD include mycophenolate mofetil (MMF), Tacrolimus, Cyclophosphamide, Azathioprine, Rituximab, and corticosteroids.⁴ MMF is increasingly used in CTD-ILD and has been found in retrospective analyses to be well tolerated, to have a low rate of discontinuation, to be associated with lower concomitant daily corticosteroid doses, and with stabilization or improvement in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DL_{CO}).^{6–11} CTD-ILD patients benefit from few published randomized controlled trials.^{10,12}

Corticosteroids are often used as co-management with other therapies in CTD-ILD patients. Because clinical trials have focused mainly on SSc-ILD patients, there has been a limited role for corticosteroids at doses > 15mg/d of prednisone due to the risk of renal crisis. For broader populations, corticosteroid use in CTD-ILD has not been studied in detail.^{13,14} Yamano et al. (2018) evaluated high dose methylprednisolone followed by low dose prednisone and Tacrolimus in a population of 26 CTD-ILD patients, a protocol which produced improvements,¹⁵ but to our knowledge no other research has evaluated the benefit of corticosteroids in patients taking other therapies.

We hypothesized that patients taking MMF for CTD-ILD would gain a small benefit from co-treatment with corticosteroids.

Methods

After approval by the Temple University Institutional Review Board, we retrospectively analysed a consecutive cohort of CTD-ILD patients prescribed MMF. Each patient had a diagnosis of CTD per American College of Rheumatology (ACR) classification criteria by a board-certified rheumatologist and had ILD confirmed by high-resolution CT chest (HRCT) or by histology. Each patient also had pulmonary function tests including spirometry, diffusion capacity for carbon monoxide (DL_{CO}), and six-minute walk (6MW).

Each patient was followed continuously at Temple University Hospital (Philadelphia, PA) for an average of 23 months between January 1, 2015 and January 1, 2019, with Pulmonary Function Tests (PFTs) performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) Criteria measured at least one year apart.¹⁶ We excluded patients with inadequate PFTs (n = 52), those who did not meet ACR classification criteria for a specific CTD (n = 82), those who did not have ILD by review of HRCT of chest or by histology (n = 51), those who were followed for less than 26 weeks (n = 11), those who received a lung transplant (n = 9), or those with physician-documented MMF nonadherence (n = 5) (Fig. 1).

103 subjects met the above inclusion and exclusion criteria. The following data were extracted from the medical record for each subject: demographics including age, gender, body mass index (BMI), race, ethnicity, and smoking status, pattern of ILD by HRCT or histology, baseline autoantibodies tested, rheumatologic diagnosis by ACR criteria, systemic manifestations of CTD as documented by a board-

certified rheumatologist, and treatment dose and duration for both MMF and corticosteroids (Figs. 2,3; Table 1).

Table 1
Demographic Data of CTD-ILD Patients at Time of MMF Treatment Initiation

	Entire Cohort	MMF Only	Cotreatment with Corticosteroids	p-value
N	103	28	75	
Age (Years), Mean (± SD)	60.1 ± 13	60.6 ± 12.4	60.0 ± 11.8	0.82
Male (n), (%)	29 (28%)	10 (35%)	19 (25%)	0.30
Current or Former Smoking (n), (%)	51 (49%)	12 (42%)	39 (52%)	0.41
BMI (Mean), (± SD)	29.7 ± 7.1	28.3 ± 6.8	30.3 ± 7.2	0.20
Race				
Caucasian (n), (%)	53 (52%)	13 (48%)	40 (54%)	0.41
African American (n), (%)	31 (31%)	11 (43%)	20 (27%)	
Asian (n), (%)	2 (2%)	1 (1%)	1 (4%)	
Other (n), (%)	15 (15%)	2 (7%)	13 (18%)	
Ethnicity				
Hispanic / Latin American	15 (15%)	2 (7%)	13 (17%)	0.35
Rheumatologic Disease by ACR Criteria				
MCTD (n), (%)	26 (25%)	3 (11%)	23 (31%)	0.04
Systemic Sclerosis (n), (%)	25 (24%)	8 (29%)	14 (19%)	0.24
RA (n), (%)	18 (17%)	1 (4%)	17 (23%)	0.02
SLE (n), (%)	15 (14%)	5 (18%)	10 (13%)	0.56
Antisynthetase Syndrome (n), (%)	7 (7%)	6 (8%)	1 (4%)	0.43

Legend: Connective Tissue Disease-Associated Interstitial Lung Disease (CTD-ILD), Mycophenolate Mofetil (MMF), American College of Rheumatology (ACR), Connective Tissue Disease (CTD), Standard Deviation (SD), Mixed Connective Tissue Disease (MCTD), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), milligrams (mg)

	Entire Cohort	MMF Only	Cotreatment with Corticosteroids	p-value
Other Idiopathic Inflammatory Myositis (n), (%)	10 (10%)	3 (11%)	7 (9%)	0.83
Sjögren's Syndrome (n), (%)	5 (5%)	2 (7%)	3 (4%)	0.51
Systemic Manifestations of CTD				
Arthropathy (n), (%)	36 (43%)	10 (36%)	47 (63%)	0.01
Mucocutaneous (n), (%)	27 (40%)	11 (39%)	24 (32%)	0.49
Pulmonary Hypertension, n (%)	39 (37%)	10 (36%)	29 (39%)	0.76
Raynaud Phenomenon (n), (%)	20 (29%)	9 (32%)	23 (31%)	0.89
Myalgia or Myositis (n), (%)	13 (19%)	4 (14%)	13 (17%)	0.71
Nephropathy (n), (%)	2 (2%)	0 (0%)	4 (5.3%)	0.21
Treatment				
MMF Dose, Beginning of Observation Period (mg/day) Mean (± SD)	1144 ± 657	1539 ± 926	1007 ± 469	0.009
MMF Dose, End of Observation Period (mg/day) Mean (± SD)	2144 ± 835	2055 ± 742	2176 ± 870	0.51
Co-treatment with Corticosteroids (n), (%)	75 (72%)	0 (0%)	75 (100%)	< 0.001
Co-treatment with PH Therapy (n), (%)	14 (14%)	5 (17%)	9 (12%)	0.33
Co-treatment with PH Triple Therapy (N), (%)	5 (5%)	2 (7%)	3 (4%)	0.48
Co-treatment with Antifibrotic (N), (%)	9 (9%)	4 (14%)	5 (7%)	0.22
Legend: Connective Tissue Disease-Associated Interstitial Lung Disease (CTD-ILD), Mycophenolate Mofetil (MMF), American College of Rheumatology (ACR), Connective Tissue Disease (CTD), Standard Deviation (SD), Mixed Connective Tissue Disease (MCTD), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), milligrams (mg)				

Patients were then divided into two groups, those who received only MMF, and those who received MMF and a corticosteroid. Chi-squared or paired t-tests were used to compare demographic and baseline data

between the two groups, and to describe the change in PFT values and medication doses over time in the entire cohort (Table 1,2).

Table 2
Pulmonary Function Tests, Exercise Capacity, Oxygen Requirement, and Corticosteroid Dose Over 23 Months of Observation on MMF, Entire Cohort

	N	Observation Period		P Value
		Start	Finish	
FVC (L), (Mean ± SD)	96	2.05 ± 0.63	1.98 ± 0.71	0.07
FVC % Predicted, (Mean ± SD)	98	63 ± 16	62 ± 19	0.21
DLCO (ml/min/mmHg), (Mean ± SD)	77	10.2 ± 5.2	8.5 ± 3.6	0.01
DL _{CO} % Predicted, (Mean ± SD)	76	39 ± 16	35 ± 15	0.01
6MW Distance (meters), (Mean ± SD)	79	272 ± 116	277 ± 112	0.61
Oxygen Required On Exercise During 6MW (L/min), (Mean ± SD)	80	2.7 ± 3.4	2.7 ± 4.0	0.35
Corticosteroid Dose (mg prednisone), (Mean ± SD)	103	15.7 ± 18.6	7.9 ± 9.1	< 0.001
MMF Dose (mg/day), (Mean ± SD)	101	1275 ± 827	2143 ± 835	< 0.001
Legend: Mycophenolate Mofetil (MMF), Forced Vital Capacity (FVC), Liters (L), Standard Deviation (SD), Diffusion Capacity of Carbon Monoxide (DL _{CO}), Milliliters (ml), Minute (min), Millimeters of Mercury (mmHg), Percent (%), Six Minute Walk (6MW), Milligrams (mg)				

Univariate logistic analyses were then performed revealing the odds ratio (OR) for improvement or worsening of several PFT values between the two groups (including forced vital capacity (FVC), DL_{CO}, and 6MW distance greater than the minimal clinically important difference (MCID) for each value. Given the small number of patients in the study, improvement of FVC, DL_{CO}, and/or 6MW distance greater than the MCID for each test was analysed as a combined variable. Data are presented as percent (%), mean ± standard deviation (SD) or OR ± confidence interval. P-values < 0.05 were considered statistically significant.

Results

We included 103 patients who were observed on treatment with MMF for an average of 23 months. The baseline characteristics of the 103 consecutive patients are summarized in Table 1 and compared between groups. Patients were predominantly female had an average age of 60 ± 11 years, a mean BMI

of 29 ± 7 , and 49% were current or former smokers. The racial breakdown of our cohort was 52% Caucasian, 31% African American, 2% Asian, and 15% other race or mixed race. 15% of patients identified as being of hispanic ethnicity (Table 1).

The distribution of CTD in the patient cohort was 25% MCTD, 24% SSc, 17% RA, 14% systemic lupus erythematosus (SLE), 10% other IIM syndromes, 7% Antisynthetase Syndrome, 5% Sjögren's syndrome. The baseline autoantibodies found to be positive according to standard laboratory reference ranges in our patient cohort are summarized in Fig. 3, with a majority (52.4%) having Antinuclear Antibodies (ANA), which was defined as "positive" at titre $\geq 1:320$, 34% Rheumatoid Factor (RF), 15.5% Sjögren's Syndrome-Related-Antigen A/Anti-Rho (SS-A), and the remainder having other antibodies (Sjögren's Syndrome-Related-Antigen B/Anti-La (SS-B), citric citrullinated peptide (CCP), anti-Jo1, Anti-Smith, etc.)

Clinical manifestations of CTD in this cohort included arthropathy (43%), mucocutaneous disease (40%), pulmonary hypertension (37%), Raynaud Phenomenon (29%), myalgia or myositis (19%), and nephropathy (2%) (Table 1).

45% of patients had a non-specific interstitial pneumonia (NSIP) pattern noted on HRCT, 35% had a usual interstitial pneumonia (UIP) pattern, and the remainder (20%) had other ILD patterns including bronchiolitis, mixed patterns, and organizing pneumonia (Fig. 2).

The majority of patients ($n = 75$, 72%) received corticosteroids as co-treatment with MMF, and the remainder received MMF as sole therapy ($n = 28$, 28%). Overall, patients received a mean daily dose of 15 ± 16 mg of prednisone and mean daily MMF dose of 2000 mg. Additionally, 14 patients (14%) received pulmonary hypertension (PH) cotreatment. Only 5 of these patients (5%) received three concurrently prescribed PH medications. 9 patients (9%) received cotreatment with an antifibrotic (Table 1).

Significant differences were noted between patients receiving MMF as sole therapy when compared to patients receiving corticosteroids as co-treatment with MMF. Patients receiving co-treatment with corticosteroids were more likely to have diagnoses of RA or MCTD, were more likely to report arthropathy, and received lower starting doses of MMF (1007 ± 469 milligrams (mg) per day vs 1539 ± 926 mg/day ($p = 0.009$) (Table 1).

For the entire cohort, decreases were noted in mean FVC, mean DL_{CO} , and mean $DL_{CO}\%$ predicted over the follow-up interval, but ambulatory oxygen requirement in liters/minute via nasal cannula and distance walked on 6MW testing did not change significantly. The mean prescribed prednisone dose decreased significantly ($p < 0.001$) from 15.7 to 7.9 mg and the mean MMF dose increased significantly ($p < 0.001$) from 1275 to 2143 mg/day over the course of the study period (Table 2).

We hypothesized that patients taking MMF for CTD-ILD would gain a small benefit from cotreatment with corticosteroids. There were no significant differences in changes in PFT values between those treated with corticosteroids in addition to MMF versus those treated only with MMF. Over the observation period,

there was no between-groups difference in change in FVC, DL_{CO}, or 6MW distance walked over the MCID for each test (Table 3).

Table 3

Odds Ratio of Improvement of PFT Values Greater Than the MCID in Patients with CTD-ILD Treated with Corticosteroids and MMF vs Those Treated Only with MMF

Univariate Logistic Analysis			
Outcome	Odds Ratio	Confidence Interval	P value
FVC (% predicted)	1.08	0.38–3.01	0.89
Improvement (MCID ≥ 5%)			
DL _{CO} Improvement (MCID > 1.1 ml/min/mmHg)	2.18	0.67–7.07	0.19
6MW Distance Improvement (MCID > 30 meters)	1.56	0.52–4.68	0.43
Combined Variable*	1.44	0.60–3.47	0.41
Legend: Connective Tissue Disease-Associated Interstitial Lung Disease (CTD-ILD), Forced Vital Capacity (FVC), Diffusion Capacity of Carbon Monoxide (DL _{CO}), Milliliters (ml), Minimum Clinically Important Difference (MCID), Minute (min), Millimeters of Mercury (mmHg), Mycophenolate Mofetil (MMF), Percent (%), Six Minute Walk (6MW), *Combined Variable Including FVC (% predicted) Improvement (MCID ≥ 5%), DLCO Improvement (MCID > 1.1 ml/min/mmHg), or 6MW Distance Improvement (MCID > 30 meters)			

Interpretation

Corticosteroids are a mainstay of treatment in CTD-ILD, but there are few studies investigating their efficacy and there are presently no guidelines directing their use. In our study, there was no effect of steroid cotreatment in CTD-ILD patients taking MMF.

Corticosteroids are frequently prescribed as both monotherapy and cotherapy for CTD-ILD due to anti-inflammatory and immunosuppressive effects on endothelial, fibroblast, and leukocyte cell function.¹⁷ The use of chronic low-dose steroids as co-management in the maintenance phase of disease has been shown to improve CTD-related arthropathy and myopathy.¹⁶ Although long-term steroid use in ILD patients has been implicated in the development of dose-dependent steroid-induced myopathy, it has not been shown to have an overall effect on exercise capacity or ability to tolerate activities of daily living (ADL) in CTD patients.¹⁸

Steroid-sparing agents such as MMF may reduce steroid requirements while stabilizing DL_{CO} and FVC.⁷ Our cohort as a whole suffered a small decrease in FVC and DL_{CO} over the follow up interval, but had no change in exercise capacity while taking decreasing steroid dosages and increasing MMF dosages over the course of the study period. This finding is reflective of the progressive impact of CTD-ILD on

pulmonary physiology, but suggests a discrepancy between physiological effects and overall clinical significance to patients. These findings highlight the need for further study to better correlate effects on pulmonary physiology to functional status and overall quality of life.

This study had several limitations. Our cohort of only 103 patients was small and recruited from a single center. However, this cohort is valuable for study, as most research on CTD-ILD patients thus far includes a large number of patients with systemic sclerosis.^{6,9,12} Our cohort had a diverse distribution of CTD and may be more representative of the diversity of disease encountered in clinical practice outside of systemic sclerosis specialty centers. Larger studies across multiple treatment centers are needed to avoid confounding variables and to increase confidence in the results. Our cohort was recruited at a specialty lung center, which may confer referral bias.

As there are no guidelines for corticosteroid treatment in patients with CTD-ILD, more research is needed to elucidate the optimal dosing and duration of therapy, and to clarify the goals of therapy. It remains unclear whether the addition of corticosteroids to steroid-sparing therapy benefits patients with CTD-ILD, and if so, in which subgroups and to what degree. Our patients received a minimum of 26 weeks and average of 23 months of follow-up. Longer term analyses may further uncover corticosteroid side effects which may affect their long-term tolerability.

Conclusion

In this small cohort, patients with CTD-ILD receiving treatment with MMF did not demonstrate improved lung function when receiving co-treatment with corticosteroids. Larger prospective studies are needed to better elucidate the effect of corticosteroids on this vulnerable group of patients.

Abbreviations List

ACR American College of Rheumatology

ADL Activities of Daily Living

ATS American Thoracic Society

BMI Body Mass Index

CTD-ILD Connective Tissue Disease Related Interstitial Lung Disease

DL_{CO} Diffusing Capacity of the lung for Carbon Monoxide

ERS European Respiratory Society

FVC Forced Vital Capacity

HRCT High Resolution Computed Tomography

IIM Idiopathic Inflammatory Myositis

ILD Interstitial Lung Disease

MCID Minimal Clinically Important Difference

MCTD Mixed Connective Tissue Disease

MMF Mycophenolate Mofetil

NSIP Non-Specific Interstitial Pneumonia

PH Pulmonary Hypertension

SScSystemic Sclerosis

SSc-ILD Systemic Sclerosis-related ILD

UIP Usual Interstitial Pneumonia

6MWD 6-Minute Walking Distance

Declarations

This research was conducted after IRB approval and was deemed exempt from ethics committee approval by Temple University, and in compliance with all relevant guidelines and regulations.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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J.R. and E.N. conceived of the presented idea. J.R., R.T., S.C., J.S.K., A.K., and E.N. collected and processed experimental data. J.R., E.N., and H.Z. performed the analysis and verified the statistical methods. G.C., R.C., and E.N. aided in interpreting the results. S.L., E.N., and R.C. wrote and edited the manuscript. All authors contributed input to the manuscript, discussed the results, and contributed meaningfully to the project.

All authors consent to the publication of the manuscript and have approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures

Figure 1

Inclusion and Exclusion Criteria

Figure 2

Pattern of ILD by HRCT or Histology in CTD-ILD Patients on MMF. Legend: Interstitial Lung Disease (ILD), High-Resolution Computed Tomography (HRCT), Connective Tissue Disease Interstitial Lung Disease (CTD-ILD), Mycophenolate Mofetil (MMF), Usual Interstitial Pneumonia (UIP), Non-Specific Interstitial Pneumonia (NSIP), Other ILD Pattern (Other)

Figure 3

Baseline Autoantibodies in CTD-ILD Patients on MMF. Legend: Connective Tissue Disease Interstitial Lung Disease (CTD-ILD), Mycophenolate Mofetil (MMF), Antinuclear Antibody (ANA) $\geq 1:320$ (ANA), anti-RNP antibody (RNP), Anti-centromere antibody (Anti-centromere), Anti-Double-Stranded DNA antibody (ds-DNA), Sjögren's Syndrome-Related-Antigen A/ Anti-Rho (SS-A), Sjögren's Syndrome-Related-Antigen B/ Anti-La (SS-B), Anti-Smith Antibody (Anti-Smith), Topoisomerase-1 (SCL-70), Antihistidyl transfer-RNA [t-RNA] synthetase (Anti-Jo 1), Anti-Citric Citrullinated Peptide (Anti-CCP), Rheumatoid Factor (RF), Anti-Smith Antibody (Anti-Smith), Anti-RNA Polymerase 3 Antibody (RNA Polymerase 3), Antineutrophil Cytoplasmic Antibodies (ANCA)