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CONTRIBUTIONS FROM THE FIELD

Mycophenolate Mofetil for Interstitial Lung Disease in Dermatomyositis

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Objective. **To report our experience using mycophenolate mofetil as first-line treatment for dermatomyositis-associated interstitial lung disease.**

Methods. **We examined the medical records of all 16 dermatomyositis patients with interstitial lung disease seen in our outpatient university hospital dermatology clinic between May 26, 2006, and May 25, 2009. In this retrospective case series, we describe the clinical course of the 4 patients with definitive evidence of interstitial lung disease on radiologic imaging who were treated with mycophenolate mofetil and had pulmonary data available to document their outcome. All of the patients also received prednisone.**

Results. **All 3 patients with at least 1 year of followup receiving mycophenolate mofetil experienced complete normalization of pulmonary function tests (including diffusing capacity for carbon monoxide) and resolution of dyspnea. They were also able to reduce their prednisone doses. The only patient with pre- and posttreatment chest computed tomography imaging had total resolution of her interstitial opacities. The patient with only 5 months of posttreatment followup experienced an improvement in diffusing capacity for carbon monoxide from 44% to 77% predicted, but no change in dyspnea.**

Conclusion. **These promising data indicate that mycophenolate mofetil may be a useful therapy for interstitial lung disease in patients with dermatomyositis, but larger studies are needed to more definitively evaluate the role of this medication in therapy.**

Introduction

Interstitial lung disease (ILD) is commonly observed in patients with dermatomyositis (1), but few studies address treatment of ILD in this population. Prior reports document treatment of polymyositis- and/or dermatomyositis-associated ILD with various immunosuppressants, including cyclosporine, tacrolimus, and cyclophosphamide (2). However, these therapies are all aggressive and are associated with a variety of serious side effects.

Several recent small retrospective and uncontrolled prospective studies of patients with scleroderma and patients with other miscellaneous connective tissue diseases (CTDs) describe treatment of ILD with mycophenolate mofetil (MMF), an immunosuppressive agent with a relatively favorable safety profile. We add to the current literature with this case series of 4 patients with dermatomyositis (1 with skin disease and symptomatic muscle disease, 1 with skin disease and subclinical muscle disease, and 2 with skin disease and no muscle disease) who were successfully treated with MMF for ILD. To our knowledge, this is the first report documenting the use of MMF for ILD specifically in patients with dermatomyositis.

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Patients and Methods

Between May 26, 2006, and May 25, 2009, 16 patients with dermatomyositis seen in our outpatient dermatology clinic were diagnosed with possible or definite ILD. Of these patients, 4 had definitive ILD (per radiologic imaging), were treated with MMF, and had available data to document their pulmonary outcome. These patients are included in this report.

The other 12 patients are not included in the report for the following reasons: not treated with MMF (n = 8), the radiologic diagnosis of ILD was equivocal (n = 2), no radiologic pulmonary images were available (n = 1), and

no pulmonary data (radiologic or pulmonary function tests [PFTs]) were available to document the outcome of MMF treatment (n = 1).

All of the diagnoses of ILD were confirmed by chest high-resolution computed tomography (HRCT). HRCT images were reviewed by a pulmonologist (MEK). The diagnosis of dermatomyositis was made based on clinical skin findings by a dermatologist (VPW). Dermatomyositis patients with proximal muscle weakness and objective evidence of myositis were termed classic dermatomyositis. Although previous studies have used the terms hypomyopathic and amyopathic dermatomyositis to describe patients with minimal or no muscle weakness, respectively, these terms were not used in this study (3). Systemic immunosuppression for 2 months or greater in the first 6 months after skin disease onset is an exclusion criterion for amyopathic and hypomyopathic dermatomyositis (due to the theoretical possibility that such treatment prevented the development of muscle disease), and all of the patients in this report received early immunosuppression for their ILD and/or other symptoms. Patients with minimal or no muscle symptoms were therefore classified as early-treated hypomyopathic dermatomyositis if there was objective evidence of myositis and as early-treated amyopathic dermatomyositis if there was no such evidence.

All of the patients in this case series were part of a previous retrospective cohort study assessing the prevalence of ILD in patients with dermatomyositis. The Institutional Review Board at the University of Pennsylvania granted exempt approval for this study.

Results

All 4 patients experienced the onset of ILD within 1 year of the onset of their dermatomyositis symptoms. Two patients had early-treated amyopathic dermatomyositis, 1 patient had early-treated hypomyopathic dermatomyositis, and 1 patient had classic dermatomyositis. HRCT scans of the chest in all of the patients showed bibasilar-predominant ground-glass and reticular opacities with mild or no honeycombing. The patients were all obese, with body mass indices of 30.7–52.1 kg/m^2. More detailed patient characteristics are shown in Table 1.

Upon being diagnosed with ILD, all of the patients were treated with 3,000 mg daily of MMF in divided doses (titrated up from a starting dosage of 1,000–2,000 mg daily) as first-line therapy. Three of 4 patients were also treated with high-dose prednisone (maximum dosage 40–60 mg daily). The fourth patient had already been receiving prednisone for 8 months (maximum dosage 60 mg daily) prior to her diagnosis with dermatomyositis and ILD, and her prednisone was tapered when MMF was added. All 3 patients with at least 1 year of followup while receiving MMF experienced complete normalization of PFTs and resolution of dyspnea. These patients were also able to substantially decrease their prednisone doses while receiving MMF (starting dosage 15–60 mg daily, final dosage 0–4 mg daily). The remaining patient had been treated with MMF for only 5 months at the latest date of followup and did not report improvement in her dyspnea, but did have a large increase in diffusing capacity for carbon monoxide (DLco; from 44% to 77% predicted) while taking MMF. A summary of the outcome of each patient is shown in Table 1.

Although 1 patient had an episode of tinea pedis and onychomycosis while immunosuppressed with MMF and prednisone, the 4 patients reported no other adverse effects attributed to the MMF.

Patient 1. Patient 1 was referred to our dermatology clinic 6 months after beginning prednisone for newly diagnosed ILD (confirmed by HRCT and a DLco of 46% predicted). Although her pulmonary disease and skin symptoms had responded well to high-dose prednisone (60 mg daily for 2 weeks, then 40 mg daily), tapering her prednisone below 40 mg daily had resulted in worsening skin and respiratory symptoms. On presentation to our dermatology clinic, the patient was diagnosed with early-treated amyopathic dermatomyositis. For treatment of her skin and lung disease, she was started on MMF, and her prednisone was increased to 60 mg daily.

After beginning MMF, the patient's pulmonary symptoms slowly improved, and her prednisone was carefully tapered over a time span of greater than 2 years. Thirteen months after starting MMF (receiving prednisone 10.5 mg daily), the patient denied dyspnea, her PFTs were essentially within the normal limits (DLco was borderline low at 79% predicted), and HRCT chest imaging showed complete resolution of her previous parenchymal opacities (Figure 1). Her skin symptoms also improved on MMF and remained stable as her prednisone was tapered. At her latest followup, approximately 3 years after starting MMF, the patient's PFTs were normal, she was asymptomatic from a respiratory standpoint, and her skin disease was stable. The details of the patient's serial PFTs and her associated respiratory symptoms and prednisone and MMF doses are shown in Table 2.

Patient 2. Patient 2 denied dyspnea when he was diagnosed with classic dermatomyositis, but screening PFTs performed at the time of his diagnosis revealed a DLco of 37% predicted. He was started on MMF and 60 mg daily prednisone for his muscle disease, skin symptoms, and suspected ILD. His ILD was later confirmed with HRCT imaging. The patient experienced a dramatic improvement in his energy level and skin and muscle symptoms during the 3 months after he started prednisone and MMF. He also reported that his breathing was improved (noting in retrospect that he had been short of breath for a year). Five months after initiating MMF, he began a prednisone taper. At his latest date of followup (14 months after beginning MMF), he was receiving 4 mg daily of prednisone, he denied muscle or respiratory symptoms, his skin disease was stable, and his PFTs had completely normalized. HRCT imaging at this time showed stable ILD in comparison with imaging from 8 months prior, but no pre-MMF HRCT scans were available. The details of the patient's serial PFTs and his associated respiratory symptoms and prednisone and MMF doses are shown in Table 2.

Table 1. Patient characteristics*

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	65	65	37	62
Sex	Female	Male	Female	Female
Race	White	White	White	White
BMI, kg/m^2	36.0	30.7	52.1	38.6
Smoking history	40 pack-years, quit when she was diagnosed with ILD	17 pack-years, quit ~30 years before DM onset	36 pack-years, quit 3 years before DM onset	Never smoked
Relevant past medical history	Obstructive sleep apnea	Type 2 diabetes mellitus	Obstructive sleep apnea	None
DM type	Early-treated amyopathic	Classic	Early-treated amyopathic	Early-treated hypomyopathic
Years since DM onset	4	3	1.5	2
Skin findings	Gottron's papules, V-neck and back of the neck erythema, cuticular dystrophy, mechanic hands, periorbital edema	Gottron's sign, periungual erythema, mechanic hands, periorbital edema	Gottron's sign, periungual erythema, dystrophic cuticles, erythematous scaly plaques on elbows	Gottron's papules, V-neck and back of neck erythema, mechanic hands, heliotrope rash, periorbital edema
Muscle findings	Minimal/no muscle symptoms, normal CK and aldolase levels, normal MRI (bilateral thighs)	Proximal muscle weakness, CK 639 units/liter, aldolase 18.6 units/liter, EMG abnormal (inflammatory myopathy)	Minimal/no muscle symptoms, normal CK and aldolase levels	Minimal/no muscle symptoms, normal CK and aldolase levels, EMG abnormal (possible chronic myopathy)
Antibody status				
ANAs	Negative	Negative	Negative	Negative
Anti–Jo-1	Negative	Negative	Not tested	Negative
Years since ILD onset	4	2.5	0.75	2
Duration of MMF treatment	3 years, 2 months	1 year, 2 months	5 months	1 year, 1 month
Outcome of respiratory symptoms	Improved (no dyspnea)	Improved (no dyspnea)	No change	Improved (no dyspnea)
Outcome of PFTs, % predicted				
DLCO				
MMF start	70	37	44	66
Final	88	82	77	82
Lowest	46	37	44	66
FVC				
MMF start	99	76	65	73
Final	121	87	69	83
Lowest	77	76	65	64
TLC				
MMF start	99	77	73	56
Final	89	85	71	86
Lowest	70	77	71	56
Outcome of chest HRCT changes	Improved (interstitial opacities completely resolved)	NA (no chest HRCT before treatment)	NA (no chest HRCT after treatment)	NA (no chest HRCT before treatment)
Prednisone dosage at MMF start, mg daily	60	60	40	15
Prednisone dosage at latest date of followup, mg daily	0	4	40	4

*BMI = body mass index; ILD = interstitial lung disease; DM = dermatomyositis; CK = creatine kinase; MRI = magnetic resonance imaging; EMG = electromyography; ANAs = antinuclear antibodies; MMF = mycophenolate mofetil; PFTs = pulmonary function tests; DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; TLC = total lung capacity; HRCT = high-resolution computed tomography; NA = not applicable.

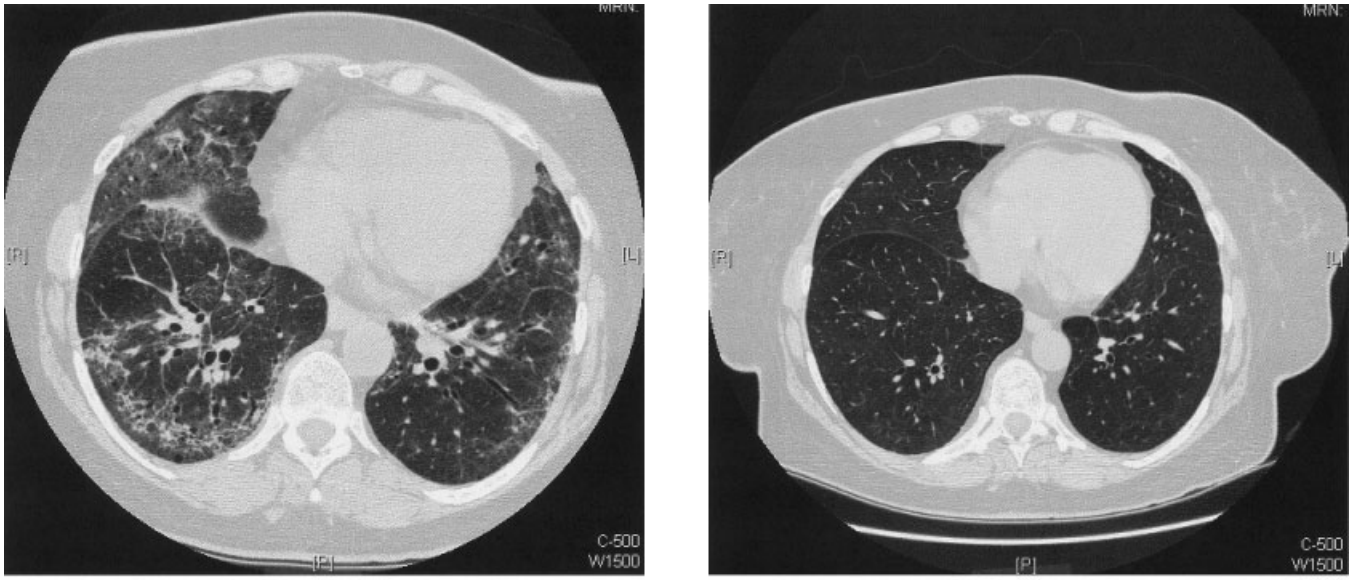

Figure 1. Chest high-resolution computed tomography image of patient 1 **A**, before, and **B**, after receiving mycophenolate mofetil.

Patient 3. Patient 3 had no pulmonary symptoms when she was diagnosed with early-treated amyopathic dermatomyositis, but screening PFTs revealed a DLCO of 44% predicted, and a subsequent HRCT confirmed ILD. After her diagnosis of ILD, she noted in retrospect that she had experienced exertional dyspnea for the past few months. The patient was already receiving methotrexate and prednisone (7.5 mg daily) for treatment of inflammatory arthritis. Following her diagnosis of ILD, her prednisone was increased to 40 mg daily, and she was started on MMF. Her methotrexate was also discontinued at this time because ILD is a rare but well-known toxicity of methotrexate. Five months after she started MMF (the latest date of followup), the patient's skin symptoms had improved. Her dyspnea was unchanged, but her DLCO had increased from 44% to 77% predicted. Given the impressive improvement in DLCO and the likely multifactorial nature of her dyspnea (morbid obesity, obstructive sleep apnea), a prednisone taper was started. Notably, this patient's history of methotrexate use prevents us from definitively determining the etiology of her ILD (methotrexate versus dermatomyositis) and the cause of her improved DLCO (addition of MMF and prednisone dose increase versus methotrexate discontinuation). However, dermatomyositis was believed to be a much more likely source of the patient's ILD than methotrexate due to the time course of her ILD (chronic symptom onset and no rapid improvement following methotrexate withdrawal) and the rarity of methotrexate-induced ILD (particularly chronic ILD) (4,5). The details of the patient's serial PFTs and her associated respiratory symptoms and prednisone and MMF doses are shown in Table 2.

Patient 4. Patient 4 had already completed 8 months of prednisone (maximum dosage 60 mg daily) therapy for her rash and cough when she was referred to our dermatology clinic and diagnosed with early-treated hypomyopathic dermatomyositis and ILD. At the time of her diagnosis, she was started on MMF and began a gradual taper of her prednisone (from 15 mg daily). The patient experienced an improvement in her respiratory symptoms over the subsequent months. One year after starting MMF (her latest date of followup), she was down to 4 mg of prednisone daily, her PFTs were within the normal limits, and she denied dyspnea. However, she still had active skin disease at this time. The details of the patient's serial PFTs and her associated respiratory symptoms and prednisone and MMF doses are shown in Table 2.

Discussion

In this small case series, all 3 patients with dermatomyositis-associated ILD who were treated for at least 1 year with MMF and prednisone experienced complete normalization of PFTs (including DLCO) and resolution of dyspnea. These patients were also able to reduce their daily prednisone dosages. Although MMF has been disappointing in patients with idiopathic pulmonary fibrosis (6), this medication has recently begun to emerge as a potential treatment for ILD in patients with CTD.

Several small retrospective studies (10–28 patients each) of CTD/ILD patients, including 2 scleroderma-only studies (7,8) and 2 studies of patients with miscellaneous CTDs (9,10), document stabilization of PFTs in the majority of patients after treatment with MMF (some patients also received glucocorticoids). Some of these studies also report improvement of respiratory symptoms (10) and decreased prednisone doses following MMF therapy (9,10). Two small (<10 patients each) uncontrolled prospective studies focusing on scleroderma patients with recent-onset ILD who were treated with MMF and glucocorticoids as first-line therapy show improved PFTs (including DLCO), HRCT imaging, and symptoms in most patients (11,12). Notably, in some of these studies (and in our report), many patients were treated with glucocorticoids and MMF,

Table 2. Longitudinal pulmonary details*

Patient	Months since MMF start	MMF dosage, mg daily	Prednisone dosage, mg daily	DLCO	FVC	FEV_1/FVC, %	TLC	SpO_2 on room air, %	Weight, pounds	Medication changes after PFT results	Dyspnea
1	−6	0	0	46	77	81	70	84 walk, 93 rest	217	Began prednisone 60 mg daily	DOE for 2 months
1	−3	0	40	80	125	79	119	94 walk, 97 rest	217	Began prednisone taper	DOE improved
1	−1	0	30	70	99	82	99	NA	217	1 month later: increased prednisone to 60 mg daily (taper after 2 months), MMF added	DOE increased
1	13	3,000	10.5	79	106	78	99	96 rest	200	Continued prednisone taper	No DOE
1	24	3,000	3	83	104	79	97	96 rest	217	Finished prednisone taper over the next 4 months	No DOE
1	37	2,000	0	88	121	78	89	95 rest	230	Continued MMF taper (began taper 4 months ago)	No DOE
2	0	0	0	37	76	83	77	NA	200	Began prednisone 60 mg daily and MMF	Noted DOE in retrospect
2	7	3,000	25	76	82	77	83	97 rest	216	Continued prednisone taper (began taper 2 months ago)	No DOE
2	14	2,000	4	82	87	78	85	98 rest	214	Continued prednisone taper	No DOE
3	−1	0	7.5	44	65	87	73	NA	305	1 month later: added MMF, increased prednisone to 40 mg daily, stopped methotrexate (12.5 mg weekly)	Noted DOE in retrospect
3	5	3,000	40	77	69	86	71	100 rest	363	Started prednisone taper	No change in DOE
4	−1	0	15	66	73	69	56	NA	210	1 month later: MMF added, prednisone taper started	Mild DOE
4	6	3,000	10	69	64	78	77	99 rest	207	Continued prednisone taper	DOE improved
4	12	3,000	4	82	83	83	86	100 rest	211	Continued prednisone taper	No DOE

* Values are the percentage of predicted value unless otherwise indicated. MMF = mycophenolate mofetil; DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; TLC = total lung capacity; SpO_2 = saturation of peripheral oxygen; PFT = pulmonary function test; DOE = dyspnea on exertion; NA = not available.

which limits our ability to determine the contribution of each individual drug to the clinical outcome.

The clinical outcome of our patients was excellent in comparison with the existing literature. Due to the small number of patients in our report, it is difficult to make any inferences from our data. However, given that our report is limited to dermatomyositis patients (including 2 patients with early-treated amyopathic dermatomyositis and 1 with early-treated hypomyopathic dermatomyositis) with newly-diagnosed ILD, our experience suggests that this patient population may be particularly responsive to first-line therapy with MMF.

To our knowledge, this is the first report specifically documenting the use of MMF for the treatment of dermatomyositis-associated ILD and the first report of CTD/ILD patients treated with MMF to include dermatomyositis patients with minimal or no muscle symptoms. One of the case series of CTD/ILD patients treated with MMF includes 2 patients with polymyositis but no patients with dermatomyositis (10). The other case series includes 5 patients with polymyositis/dermatomyositis and 1 patient with dermatomyositis/Sjögren's syndrome, but the authors group all of the CTD types together when reporting their results and do not detail the clinical courses of individual patients or CTD groups (9).

Although our retrospective data collection may have underestimated the incidence of MMF-related side effects experienced by our patients, no patients were forced to reduce their MMF dosages or to discontinue MMF due to side effects. The low rate of side effects observed in this

study is consistent with what has been reported in other CTD/ILD studies and with the favorable safety profile of MMF. Common side effects of MMF include gastrointestinal and urinary symptoms (usually resolve with continued use) and hematologic abnormalities (usually reversible with dose reduction or discontinuation) (13). MMF is also associated with an increased risk of infection, but opportunistic infections appear to be rare in the dermatology population (13). The risk of malignancy conferred by MMF treatment is uncertain; malignancies have been reported in psoriasis patients treated with MMF, but a cohort study of 85 patients with psoriasis demonstrated no increased risk in MMF-treated patients relative to the general population (13).

Of note, all 4 patients in this report were obese. Although this finding may be merely coincidental, it is interesting because there is no known association between obesity and ILD or obesity and dermatomyositis.

Mycophenolic acid, the active form of mycophenolate mofetil, inhibits inosine monophosphate dehydrogenase, a rate-limiting enzyme for de novo synthesis of guanosine nucleotides (14). The end result is decreased T and B lymphocyte proliferation. MMF has also been shown to inhibit fibrosis via direct suppression of fibroblast function (14). The combination of immunosuppressive and antifibrotic properties may be especially helpful for treatment of autoimmune-associated fibrotic disease, including ILD.

Our own clinical experience and a recent retrospective review of 12 patients with dermatomyositis demonstrate that MMF can be an effective steroid-sparing agent for recalcitrant skin and muscle manifestations of dermatomyositis (15). Although the small number of patients in this report limits our ability to make generalizations, our pulmonary data indicate that MMF may also be useful for ILD in patients with dermatomyositis. Hopefully our promising results will encourage further exploration of this medication for treatment of dermatomyositis-associated ILD.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Werth had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Morganroth, Werth.
Acquisition of data. Morganroth, Werth.
Analysis and interpretation of data. Morganroth, Kreider, Werth.

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