Myositis-associated Interstitial Lung Disease: Predictors of Failure of Conventional Treatment and Response to Tacrolimus in a US Cohort

Niharika Sharma, Michael S. Putman, Rekha Vij, Mary E. Strek, and Anisha Dua

ABSTRACT. ***Objective.*** Patients with myositis-associated interstitial lung disease (MA-ILD) are often refractory to conventional treatment, and predicting their response to therapy is challenging. Recent case reports and small series suggest that tacrolimus may be useful in refractory cases.

Methods. A retrospective cohort study of patients with MA-ILD comparing clinical characteristics between those who responded to or failed conventional treatment. In those who failed conventional treatment and received adjunctive tacrolimus, response to tacrolimus was measured by the improvement in myositis, ILD, and change in the dose of glucocorticoids.

Results. Thirty-one of 54 patients (57%) responded to conventional treatment based on the predefined variables of improvement in myositis and/or ILD. Patients with polymyositis (PM)-ILD were more likely to respond to conventional treatment than those with dermatomyositis (DM)-ILD (67% vs 35%, $p = 0.013$). Twenty-three patients failed conventional treatment, 18 of whom subsequently received adjunctive tacrolimus. Ninety-four percent had improvements in ILD and 72% showed improvement in both myositis and ILD. The mean doses of prednisone decreased from baseline by 65% at 3–6 months ($p = 0.002$) and 81% at 1 year ($p < 0.001$).

Conclusion. Patients with PM-ILD were more likely to respond to conventional treatment than patients with DM-ILD, but clinical characteristics and serology did not otherwise predict response to therapy. A majority of patients with MA-ILD refractory to conventional therapy improved while receiving tacrolimus and were able to decrease their dose of both glucocorticoids and other disease-modifying antirheumatic drugs. (First Release September 1 2017; J Rheumatol 2017;44:1612–18; doi:10.3899/jrheum.161217)

Key Indexing Terms:
MYOSITIS INTERSTITIAL LUNG DISEASE TACROLIMUS
POLYMYOSITIS DERMATOMYOSITIS

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Accepted for publication June 15, 2017.

The idiopathic inflammatory myopathies are a group of systemic autoimmune diseases characterized by varying types and severities of skeletal muscle inflammation. Polymyositis (PM) and dermatomyositis (DM) are 2 major subtypes that often present with an insidious onset of proximal muscle weakness. In addition to involvement of muscles and skin, other organ systems are frequently affected, including the lungs[1]. One of the most serious pulmonary manifestations is interstitial lung disease (ILD), first described by Mills and Mathews in 1956[2]. It has been estimated that 20–40% of patients diagnosed with PM/DM/clinically amyopathic dermatomyositis (CADM) will have associated ILD during the course of their illness[3]. ILD in PM/DM contributes significantly to morbidity and mortality[4,5,6], and reduces the median survival from 11–12 years in PM/DM[7] to 5–7 years in myositis-associated (MA)-ILD[8]. Moreover, patients with MA-ILD are often refractory to conventional treatment[9].

Corticosteroids remain first-line therapy for patients with MA-ILD[5,10]. In patients with MA-ILD who remain

unresponsive to corticosteroids or experience a relapse, additional disease-modifying antirheumatic drugs (DMARD) have been used, including azathioprine (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF)[11,12,13,14]. Other treatment options for refractory disease include intravenous immunoglobulin, cyclophosphamide (CYC), rituximab, cyclosporine, tacrolimus, and plasmapheresis[10,15,16].

Tacrolimus has been increasingly used in patients with MA-ILD who are refractory to conventional treatment. A systematic review supported the benefit of tacrolimus in treating muscle weakness, improving serum creatine kinase (CK), and stabilization of ILD[17]. Most of the available data on the use of tacrolimus in MA-ILD come from retrospective studies in Japan[9,18,19,20,21,22,23]. Data for patients in the United States are limited to small case series[20,24]. We performed a retrospective study of a single-center MA-ILD cohort in the United States to assess the clinical predictors of failure to conventional treatment. In the subset of patients with MA-ILD who failed to respond to conventional treatment, we assessed the rate of response to tacrolimus, identified clinical variables associated with treatment failure, and examined subsequent doses of prednisone and other DMARD.

MATERIALS AND METHODS

Study design. We identified a retrospective cohort of patients with MA-ILD using the International Classification of Diseases, 9th ed codes for DM (710.3), PM (710.4), myalgia and myositis, unspecified (729.1), and ILD (515). These patients were seen every 3–6 months in the rheumatology and/or pulmonology clinics at the University of Chicago between 1998 and 2014. This study was reviewed and approved by the Institutional Review Board at the University of Chicago (IRB #14-0952).

Patients. We included patients > 18 years old who were diagnosed with definite or probable inflammatory myositis by rheumatologists based on the Bohan and Peter criteria[25,26] for DM and PM and the Sontheimer criteria for CADM[27,28]. All patients had ILD diagnosed by pulmonologists based on radiologic abnormalities on high-resolution computed tomography (CT) scan of the chest[29]. In our study, we excluded patients with (1) overlap autoimmune myositis, (2) inclusion body myositis, (3) cancer-associated myositis who received chemotherapy prior to initiation of conventional treatment for MA-ILD, (4) other myopathies not fulfilling the Bohan and Peter criteria, and (5) patients with MA-ILD who did not receive conventional treatment, defined as the use of prednisone with at least 1 of the following DMARD: AZA, MTX, or MMF.

Clinical characteristics. Comprehensive chart review was performed in all patients with MA-ILD to assess clinical characteristics, including race, smoking history, serum CK, serum aldolase, serological data, and treatment with prednisone and DMARD. The severity of ILD was measured by pulmonary function tests [PFT; forced vital capacity (FVC), total lung capacity (TLC), and DLCO], radiographic pattern of ILD (presence or absence of honeycombing), and histopathological findings on lung biopsy when available. Additionally, in patients who started treatment with tacrolimus, data were included on doses of prednisone, doses of DMARD, and hospitalizations for exacerbations of myositis or ILD.

Clinical characteristics were compared between the patients who responded to or failed conventional treatment. In the subset of patients who failed to respond to conventional treatment and received tacrolimus, clinical characteristics were compared between patients who did or did not respond to tacrolimus (Figure 1).

Response to treatment. Patients with MA-ILD were dichotomously classified into treatment responders and treatment failures. Patients were classified as failing conventional treatment or failing tacrolimus if they had refractory myositis and/or refractory ILD. Patients with refractory myositis met at least 1 of 2 criteria: (1) any worsening muscle weakness recorded by their physician or (2) serum CK levels that failed to either normalize or decrease by > 50% from baseline. Patients with refractory ILD met at least 2 of 4 criteria: (1) decrease in FVC by 10%, (2) decrease in TLC by 10%, (3) decrease in DLCO by 15%, or (4) any worsening respiratory symptoms (cough, dyspnea) recorded by their physician. Because the minimum clinically important difference in PFT has not been defined in MA-ILD, these variables for refractory ILD were adapted from an international consensus statement of the American Thoracic Society on the diagnosis and treatment of idiopathic pulmonary fibrosis[4,30]. Data were collected at the index time and 6 months later — refractory myositis or refractory ILD was therefore defined as no response to steroid plus at least 1 other conventional DMARD after at least 6 months of treatment.

Additional data were collected to assess the response of patients who received tacrolimus for treatment of refractory MA-ILD. This included changes in the doses of conventional treatment agents and number of hospitalizations for MA-ILD exacerbations for 1 year after the initiation of tacrolimus. In general, tacrolimus was initiated at doses of 1 mg twice daily with close monitoring of complete blood counts, comprehensive metabolic panels, and tacrolimus trough levels every 14–21 days. Doses were adjusted based on target trough levels of 5–10 ng/ml and tolerability.

Statistical analysis. Continuous variables were reported as means with SD and were compared using a paired Student t test for normally distributed values. Mann-Whitney 2-samples rank-sum test was used for nonparametric interval variables. Categorical variables were reported as counts and percentages and compared using the Pearson chi-square test and Fisher's exact test when n was small (< 5). All analyses were performed using Stata MP v.13 (Stata Corp).

RESULTS

Sixty-seven patients with MA-ILD were identified, 54 of whom met the inclusion criteria (Figure 1). All 54 patients received conventional treatment with prednisone and at least 1 DMARD. Twenty-three patients failed to respond to conventional treatment and received additional therapy with either CYC or tacrolimus, 18 of whom met inclusion criteria and were included in further analysis.

Clinical characteristics are summarized in Table 1. The mean age of patients with MA-ILD was 44.9 years (SD 14.9), 70.4% were women, and 48.2% were African American. Thirty patients had PM, 20 had DM, and 4 patients had CADM. The baseline mean serum CK level was 2933.4 U/l. The most commonly observed positive antibodies were an ANA > 1:80 (59.3%), anti-Jo1 (50.0%), and SSA (40.7%). Thirty-five patients (64.8%) received AZA, 17 patients (31.5%) received MTX, and 11 patients (20.4%) received MMF.

At the time of diagnosis of ILD, 29.6% of patients with MA-ILD had honeycombing on chest CT scan, mean FVC was 61.7% predicted, mean TLC was 68.6% predicted, and mean DLCO was 57.9% predicted. Fourteen patients underwent surgical lung biopsy. Five patients had organizing pneumonia (OP), 3 had usual interstitial pneumonia (UIP), and 3 had nonspecific interstitial pneumonia (NSIP). The remaining 3 patients had combined findings of cryptogenic

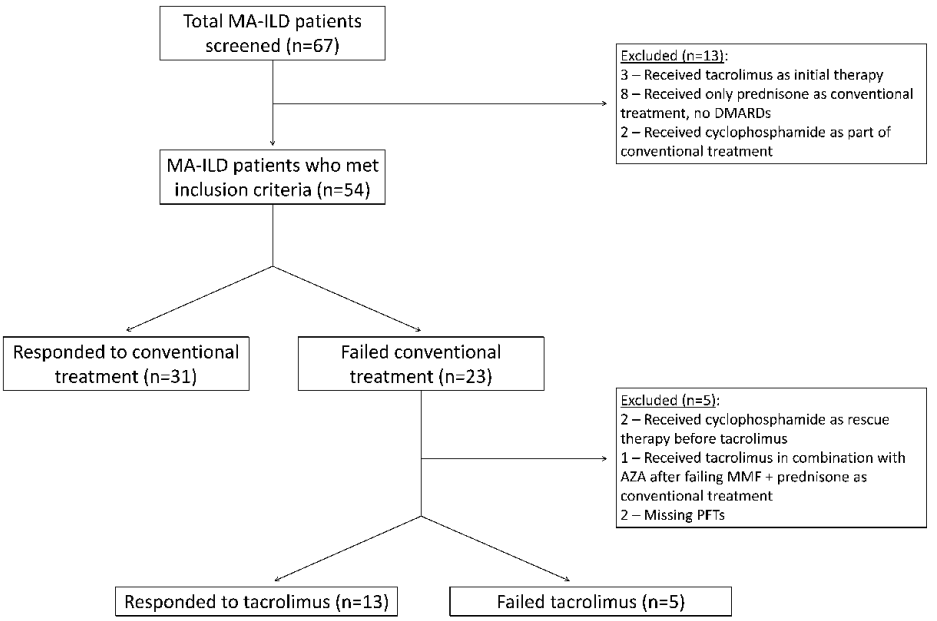

Figure 1. Study design: Patients responding to or failing conventional treatment and tacrolimus. MA-ILD: myositis-associated interstitial lung disease; DMARD: disease-modifying antirheumatic drugs; AZA: azathioprine; MMF: mycophenolate mofetil; PFT: pulmonary function tests.

OP (COP) with NSIP, COP with hypersensitivity pneumonitis, and COP with diffuse alveolar damage.

Response to conventional treatment. All 54 patients who met inclusion criteria received conventional treatment (prednisone and at least 1 DMARD). Clinical characteristics were compared between the 31 patients who responded to conventional treatment and 23 patients who failed to respond to conventional treatment (Table 2). Patients with PM-ILD were more likely to respond to conventional treatment than patients with DM-ILD (67% vs 35%, respectively, p = 0.013). Women were more likely to respond, though this was not statistically significant (66% vs 38%, p = 0.055). There were no significant differences between responders and nonresponders to conventional treatment with respect to age, race, serologic tests, radiographic pattern, or severity of ILD as measured by PFT.

Use of tacrolimus in refractory MA-ILD. Table 3 displays the clinical characteristics and response rates of 18 patients who failed to respond to conventional treatment, received tacrolimus in addition to conventional therapy, and had sufficient data for analysis. Fourteen patients (78%) had improvement in myositis, 17 patients (94%) had improvement in ILD, and 13 patients (72%) had improvement in both. Only 1 patient was hospitalized for an exacerbation of MA-ILD. Patients with more severe ILD as measured by lower FVC and lower TLC at the time of initiation of tacrolimus were more likely to fail treatment (63.7 vs 42.4, p = 0.010 and 65.9 vs 45.0, p = 0.042, respectively). All 6 patients with anti-Jo1 antibody responded to tacrolimus, which trended toward statistical significance (p = 0.09). There was no difference in age, sex, race, or radiographic pattern between patients who responded to or failed tacrolimus.

Change in the doses of DMARD. In patients who responded to conventional therapy, the mean dose of prednisone at baseline was 35.4 mg ± 21.5 mg and decreased to 11.4 mg ± 8.8 mg (p < 0.001) by 6 to 12 months. In those who failed conventional therapy, the mean baseline dose of prednisone was 44.7 mg ± 5.2 mg and decreased to 31.2 mg ± 18.9 mg by 6 to 12 months (p = 0.08). Those who responded to conventional therapy were being treated with a significantly lower dose of prednisone at 6–12 months than those who failed (11.4 mg vs 31.6 mg, p < 0.001).

For patients who failed conventional therapy and were treated with tacrolimus, the mean dose of prednisone at the time of initiation of tacrolimus was 35.1 mg ± 18.6 mg, which decreased to 12.4 mg ± 8.0 mg at 3–6 months (65% decrease, p = 0.002) and 6.8 mg ± 6.8 mg at 1 year (81% decrease, p < 0.001). At the time of initiation of tacrolimus, 11 patients were taking AZA, most commonly at a dose of 150 mg (n = 7) and with a mean dose of 143.2 mg ± 28.6 mg. This decreased 89.6 mg ± 67.8 mg at 3–6 months (37% decrease, p = 0.04) and 84.1 mg ± 69.2 mg at 1 year (41.2% decrease, p = 0.010), with 4 patients able to discontinue AZA entirely. Five patients were taking MTX, most commonly at a dose of 25 mg (n = 3) and with a mean dose of 25.0 mg ± 3.5 mg. This decreased to 17.5 mg ± 16.8 mg at 3–6 months (30.0% decrease, p = 0.30) and 23 mg ± 14.4 mg at 1 year (8%

Table 1. Clinical characteristics of patients with MA-ILD (n = 54). Values are n (%) unless otherwise specified.

Clinical Characteristics	Values
Age at onset, yrs, mean (SD)	44.9 (14.9)
Sex	
Male	16 (29.6)
Female	38 (70.4)
Race	
Black	26 (48.2)
White	22 (40.7)
Hispanic	4 (7.4)
Asian	2 (3.7)
Smoking history	
Never	38 (70.4)
Former	12 (22.2)
Active	4 (7.4)
Myositis	
Polymyositis	30 (55.6)
Dermatomyositis	20 (37.0)
CADM	4 (7.4)
Baseline CK, U/l, mean (SD)	2933.4 (4724.8)
Baseline aldolase, mean (SD)	31.6 (32.2)
Serologic data	
ANA	32 (59.3)
Anti-Jo1	27 (50.0)
SSA	22 (40.7)
Mi-2	3 (5.6)
PL-7	1 (1.9)
SRP	2 (3.7)
Ku	1 (1.9)
PFT, %, mean (SD)	
FVC	61.7 (19.6)
TLC	68.6 (17.1)
DLCO	57.9 (24.1)
CT chest	
Honeycombing absent	38 (70.4)
Honeycombing present	16 (29.6)
Lung histopathology	
OP	5 (35.7)
NSIP	3 (21.4)
UIP	3 (21.4)
Others*	3 (21.4)
Conventional DMARD	
AZA	35 (64.8)
MTX	17 (31.5)
MMF	11 (20.4)

*COP with NSIP, COP with hypersensitivity pneumonitis, and COP with diffuse alveolar damage. MA-ILD: myositis-associated interstitial lung disease; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; ANA: antinuclear antibody; SRP: signal recognition particle; PFT: pulmonary function test; FVC: forced vital capacity; TLC: total lung capacity; CT: computed tomography; OP: organizing pneumonia; COP: cryptogenic OP; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; DMARD: disease-modifying antirheumatic drugs; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil.

decrease, p = 0.70). Three patients were taking MMF at a mean dose of 2166.7 mg ± 288.7 mg, which decreased to 1333.3 mg ± 1258.3 mg at 3–6 months (38.4% decrease, p = 0.30) and 0 mg at 1 year (p = 0.006). At 1 year, 2 patients had initiated treatment with MMF.

Table 2. Clinical characteristics of patients with MA-ILD who responded to or failed conventional treatment (n = 54). Values are n unless otherwise specified.

Clinical Characteristics	Responders, n = 31	Nonresponders, n = 23	p
Age at onset of myositis, yrs	46.8	42.2	0.34
Sex			
Male	6	10	0.055
Female	25	13	
Race			
Black	14	12	0.12
White	13	9	
Asian	4	0	
Hispanic	0	2	
Smoking history			
Never	20	18	0.068
Former	10	2	
Active	1	3	
Myositis			
Polymyositis	20	10	0.013
Dermatomyositis	7	13	
CADM	4	0	
Baseline CK, U/l	2588.9	3431.0	0.20
Baseline aldolase	29.6	34.4	0.29
Serologic data			
ANA	16	16	0.18
Anti-Jo1	18	9	0.17
SSA	13	9	0.84
Mi-2	1	2	0.39
PL-7	0	1	0.43
SRP	1	1	0.68
Ku	0	1	0.43
PFT, %			
FVC	62.5	60.4	0.39
TLC	68.8	68.3	0.46
DLCO	58.3	57.3	0.62
CT chest			
Honeycombing absent	21	17	0.62
Honeycombing present	10	6	
Lung histopathology			
COP	3	2	0.60
UIP	1	2	
NSIP	0	3	
Others*	1	2	
Conventional DMARD			
AZA	19	16	0.53
MTX	8	9	0.30
MMF	6	5	0.55

*COP with NSIP, COP with hypersensitivity pneumonitis, and COP with diffuse alveolar damage. MA-ILD: myositis-associated interstitial lung disease; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; ANA: antinuclear antibody; SRP: signal recognition particle; PFT: pulmonary function test; FVC: forced vital capacity; TLC: total lung capacity; CT: computed tomography; COP: cryptogenic organizing pneumonia; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; DMARD: disease-modifying antirheumatic drugs; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil.

DISCUSSION

In this US cohort of patients with MA-ILD, the majority of patients showed stabilization or improvement in MA-ILD

Table 3. Clinical characteristics of patients with MA-ILD who failed conventional treatment and received adjunctive tacrolimus (n = 18). Values are n unless otherwise specified.

Clinical Characteristics	Responders, n = 13	No Response, n = 5	p
Age at onset of myositis, yrs	41.8	43.0	1.00
Sex			
Male	6	2	0.62
Female	7	3	
Race			
Black	5	4	0.49
White	7	1	
Asian	0	0	
Hispanic	1	0	
Smoking history			
Never	10	4	1.00
Former	2	0	
Active	1	1	
Myositis			
Polymyositis	6	3	0.50
Dermatomyositis	7	2	
CADM	0	0	
Baseline CK, U/l	4353.5	1975.7	0.60
Baseline aldolase	31.0	43.8	0.64
Serologic data			
ANA	10	2	0.18
Anti-Jo1	6	0	0.09
SSA	5	2	0.68
Mi-2	2	0	0.51
PL-7	0	1	0.28
SRP	1	0	0.72
Ku	1	0	0.72
PFT, %			
FVC	63.7	42.4	0.010
TLC	65.9	45.0	0.042
DLCO	52.2	56.4	0.49
CT chest			
Honeycombing absent	9	5	0.23
Honeycombing present	4	0	
Lung histopathology			
COP	2	0	N/A
UIP	2	0	
NSIP	2	0	
Others*	1	0	
Conventional DMARD			
AZA	8	5	0.15
MTX	4	4	0.088
MMF	3	1	0.70

*COP with NSIP, COP with hypersensitivity pneumonitis, and COP with diffuse alveolar damage. MA-ILD: myositis-associated interstitial lung disease; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; ANA: antinuclear antibody; SRP: signal recognition particle; PFT: pulmonary function test; FVC: forced vital capacity; TLC: total lung capacity; CT: computed tomography; COP: cryptogenic organizing pneumonia; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; DMARD: disease-modifying antirheumatic drugs; AZA: azathioprine; MTX: methotrexate; MMF: mycophenolate mofetil; N/A: not applicable.

when treated with conventional therapy (glucocorticoid with AZA, MTX, or MMF). Patients with PM-ILD were more likely to respond to conventional treatment than patients with DM-ILD. A large majority of those with refractory disease who received adjunctive tacrolimus experienced stabilization or improvement of disease and subsequently tapered both prednisone and azathioprine.

Patients with PM-ILD were significantly more likely to respond to conventional treatment than those with DM-ILD. This result corroborates the findings of Fujisawa, *et al*[31], who demonstrated that patients with DM-ILD had decreased survival rate, poorer response to prednisone, and longer duration of treatment as compared to PM-ILD. Although the precise explanation for this finding is unclear, differences in immune-pathogenesis between PM and DM[32] may contribute.

The presence of anti-Jo1 antibodies is associated with ILD in patients with idiopathic inflammatory myopathies and has been shown to have favorable prognostic value[4]. In our study, the presence of a Jo1 antibody did not distinguish responders from nonresponders to conventional treatment. However, all patients with anti-Jo1 antibody who were refractory to conventional treatment improved after the addition of tacrolimus. This is consistent with previous case reports and case series of patients with anti-Jo1 antibody who showed improvement in myositis and ILD with tacrolimus[16,17,20,24]. Our findings further support the therapeutic efficacy of tacrolimus in the subset of patients with antisynthetase syndrome who are anti-Jo1–positive.

The SSA antibody is a myositis-associated antibody that has been identified in patients with the antisynthetase syndrome[33,34]. We found that 40% of our patients with MA-ILD had a positive SSA antibody without xerostomia or keratoconjunctivitis sicca. In a small case series of anti-Jo1–positive patients by Mileti, *et al*, SSA was associated with pulmonary fibrosis[34]. Our findings confirm an association between the SSA antibody and MA-ILD, but its presence was not associated with treatment response. Similarly, our study confirms previous literature demonstrating that OP and NSIP are the most frequent histopathological patterns in patients with MA-ILD[35,36], but this was not associated with response to either conventional treatment or tacrolimus.

In idiopathic interstitial pneumonia and scleroderma-ILD, the presence of honeycombing on CT chest indicates a poorer prognosis[37,38]. In our study, there was no statistically significant difference in the prevalence of honeycombing between patients with MA-ILD who responded to or failed conventional treatment, suggesting that the presence of honeycombing in MA-ILD may not predict a response to conventional treatment. Interestingly, all 6 patients with honeycombing who were refractory to conventional treatment improved after receiving tacrolimus. Therefore, it may be reasonable to treat patients with MA-ILD with radiographic evidence of fibrosis at the time of diagnosis of ILD with immunosuppressive agents.

Our study suggests that tacrolimus may be a useful therapeutic option in refractory MA-ILD. This supports the

findings of a systematic review of patients with MA-ILD treated with tacrolimus and demonstrates similar favorable outcomes[17]. Of particular note, patients with refractory MA-ILD are at risk for adverse effects from prolonged exposure to prednisone. In our cohort, the addition of tacrolimus was associated with decreased doses of prednisone at 3–6 months and at 1 year. This is similar to the findings of Shimojima, *et al* in patients with PM/DM without ILD[39]. We also found that the addition of tacrolimus allowed for a decreased dose of AZA by the end of 1 year.

There are several limitations to our study. Because this was a retrospective study, we were unable to apply strict response criteria for myositis, and were limited in the data available for prednisone doses and the presence of certain antibodies including anti-MDA5 that were not routinely tested at our institution. Further, causation cannot be inferred from these findings. Second, as a single-center study, these findings may not be generalizable and need to be validated. At our center, tacrolimus doses are adjusted to a serum trough level of 5–10 ng/ml, which may not reflect the practice of other centers. Finally, the dose of prednisone is often increased during an exacerbation of MA-ILD, which may limit both the clinical improvement attributable to tacrolimus and the reductions in steroid doses we observed.

In the largest (to our knowledge) MA-ILD cohort in the United States to receive tacrolimus reported to date, we found that patients with PM-ILD are more likely to respond to conventional treatment as compared with DM-ILD. For patients with refractory MA-ILD, treatment with tacrolimus was associated with both treatment response and tapering of both prednisone and other DMARD. Randomized, prospective, multicenter studies in patients with MA-ILD analyzing the efficacy and safety of tacrolimus earlier in the disease course may be helpful.

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