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Treatment of Antisynthetase-Associated Interstitial Lung Disease With Tacrolimus

Margaret R. Wilkes, Susan M. Sereika, Noreen Fertig, Mary R. Lucas, and Chester V. Oddis

Objective. **To assess the efficacy of tacrolimus in patients with anti–aminoacyl–transfer RNA synthetase (anti-aaRS)–associated interstitial lung disease (ILD) and idiopathic inflammatory myopathy (IIM).**

Methods. **Ninety-eight patients with anti-aaRS autoantibodies were identified in our IIM cohort of 536 patients. The medical records of 15 patients with anti-aaRS–associated ILD treated with tacrolimus between 1992 and 2003 were retrospectively reviewed. Pulmonary parameters of response included forced vital capacity, forced expiratory volume in 1 second, and diffusing capacity for carbon monoxide. Manual muscle testing results, serum creatine kinase (CK) levels, and the daily corticosteroid dosage were used to assess improvement in myositis. Random coefficient modeling considering polynomials of time was used to assess the clinical response to tacrolimus.**

Results. **All patients, except for 1, who had pure ILD, had definite or probable IIM. Two patients received tacrolimus for fewer than 3 months, and their data were not analyzed. For the remaining 13 patients, the mean age at onset of ILD was 46.9 years, and the mean duration of pulmonary disease was 14.7 months. Twelve patients had anti–histidyl–transfer RNA synthetase autoantibody (anti–Jo-1) and 1 had anti–alanyl–transfer RNA synthetase autoantibody (anti–PL-12). Patients received tacrolimus for an average of 51.2 months. A significant improvement was observed in all pulmonary parameters measured. The serum CK level declined significantly, and 10 patients had either an improvement in muscle strength or maintained normal muscle strength. A statistically significant reduction in the corticosteroid dosage was also observed.**

Conclusion. **Tacrolimus is a well-tolerated and effective therapy for managing refractory ILD and myositis in anti-aaRS–positive patients.**

The idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous disorders characterized by skeletal muscle weakness and the presence of inflammatory infiltrates on muscle biopsy. The most common autoantibody in IIM targets the anti–aminoacyl–transfer RNA synthetase (anti-aaRS) specific for histidine (anti–Jo-1); other antibodies are directed against the aaRS for threonine (PL-7), alanine (PL-12), glycine (EJ), asparagine (KS), and isoleucine (OJ). The "antisynthetase syndrome," which is seen in many patients with anti-aaRS autoantibodies, is characterized by myositis, fever, ILD, inflammatory arthritis, and Raynaud's phenomenon.

ILD is a frequent manifestation of polymyositis (PM) and dermatomyositis (DM), and in patients with antisynthetase autoantibodies, the prevalence has been reported to exceed 50% (1–9). Corticosteroids remain the empirical first-line therapy for myositis-associated ILD, but additional immunosuppressive agents are often necessary, including azathioprine, cyclophosphamide, cyclosporine, and tacrolimus. In a previous pilot trial, tacrolimus, a relatively specific inhibitor of lymphocyte proliferation, showed promise in patients with refractory myositis and ILD who were positive for anti–Jo-1 or anti–signal recognition particle (anti-SRP) autoantibody (10).

In the present study, we assessed the efficacy of tacrolimus in a larger population of anti-aaRS autoantibody–positive patients with severe ILD who were refractory to traditional immunosuppressive agents or who presented with severe or life-threatening pulmonary complications.

Margaret R. Wilkes, MD, Susan M. Sereika, PhD, Noreen Fertig, BS, Mary R. Lucas, RN, MPH, Chester V. Oddis, MD: University of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence and reprint requests to Chester V. Oddis, MD, University of Pittsburgh, S703 Biomedical Science Tower, 3500 Terrace Street, Pittsburgh, PA 15261. E-mail: Oddis@dom.pitt.edu.

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PATIENTS AND METHODS

Patient selection. We conducted a computer search of our Rheumatology Research Database at the University of Pittsburgh and identified 536 adult patients with IIM either alone or in overlap with another connective tissue disease. Ninety-eight patients had an anti-aaRS autoantibody, 63 of these patients (64%) had ILD. The medical records of 15 of the latter group of patients who were treated with tacrolimus between December 1992 and February 2003 were retrospectively reviewed. Clinical data and test results, including findings of the medical history, physical examination, laboratory studies, pulmonary function tests, radiographic examinations, and medication profiles, were abstracted from the medical record.

Determination of autoantibodies. All autoantibody analyses were performed in the Rheumatology Research Laboratory of the University of Pittsburgh. Anti–Jo-1 was identified by immunodiffusion, and anti–PL-12, anti–PL-7, anti-EJ, and anti-OJ were determined by immunoprecipitation using ^{35}S-methionine–labeled extracts of K562 cells. Positive sera were then used in immunoprecipitation reactions with unlabeled extracts of K562 cells. The RNAs were extracted, separated on denaturing polyacrylamide gels, and visualized by silver staining.

Diagnostic criteria for ILD. All patients had ILD, which was defined by the presence of a restrictive physiology and a reduction in the diffusing capacity for carbon monoxide (DLCO), as indicated by the findings on pulmonary function tests and by the presence of infiltrates on chest radiography or on routine or high-resolution computed tomography scanning. The onset of pulmonary disease was defined by the presence of dyspnea or any of the objective criteria noted above.

Tacrolimus treatment. Oral tacrolimus was specifically administered to treat patients with ILD. Tacrolimus was given twice daily (0.075 mg/kg of body weight) to achieve a plasma trough concentration of 5–20 ng/ml. The dosage was subsequently adjusted based on response to therapy and findings of toxicity monitoring.

Assessment of response to tacrolimus. Serial pulmonary function tests assessed disease progression and response to therapy. Pulmonary parameters of response included the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and DLCO, and results were recorded as the percentage of the predicted normal value.

Manual muscle testing (MMT) of the proximal musculature was measured prospectively in all patients. The findings were recorded using a 0–5 scale with +/– designations and were later converted to the modified Kendall muscle grading system using a standardized, published conversion for analysis in this study (11). Data for neck flexor strength and bilateral deltoid, bicep, psoas, hamstring, and quadricep strength were converted to a 10-point scale for each muscle group (maximum total MMT score 110). All corticosteroid dosages were converted to prednisone equivalents (in mg) and were recorded at the time of each patient encounter. Results of all available serum creatine kinase (CK) measurements for each patient were recorded over time.

Statistical analysis. Appropriate descriptive statistics (e.g., frequency counts and percentages for categorical descriptors and measures of central tendency and dispersion for continuous variables) were computed to characterize the subjects in terms of demographic and clinical factors. Random coefficient modeling (i.e., hierarchical linear modeling) considering polynomial functions of time (linear, quadratic, and cubic) was used to assess the clinical response to tacrolimus over time. This statistical approach was chosen to allow for the modeling of multiple data points with variable followup times and an inconsistent number of patient encounters. The outcome measures were evaluated for up to 3 years after initiating tacrolimus. The fixed effects of selected covariates (sex, age at ILD onset, diagnosis, number of months with pulmonary symptoms prior to starting tacrolimus, age at the start of tacrolimus) and their interaction with time were considered individually. Residual analysis was conducted for response, which was modeled to identify the potential outlying observations and to verify that underlying statistical assumptions had been satisfied.

RESULTS

Twelve of the 15 patients treated with tacrolimus were anti–Jo-1 antibody positive and were classified as

Table 1. Characteristics of the study patients*

Patient	Autoantibody	Diagnosis	Age at onset of ILD, years	No. of months of pulmonary disease prior to tacrolimus	Total months of tacrolimus treatment	Immunosuppressive therapy prior to tacrolimus
1/F	Jo-1	DM	41	6	12	MTX/AZA
2/F	Jo-1	PM	58	73	71	MTX/AZA
3/F	Jo-1	PM	54	9	47	CYC
4/F	Jo-1	PM	37	1	120	MTX
5/M	Jo-1	DM	40	1	21	None
6/F	Jo-1	PM	59	2	38	None
7/F	Jo-1	PM	47	14	58	MTX
8/M	Jo-1	PM	69	16	62	MTX
9/F	Jo-1	DM	42	22	87	MTX/AZA
10/M	Jo-1	DM	45	13	23	MTX/AZA
11/M	Jo-1	DM	30	18	6	MTX/AZA
12/M	Jo-1	DM	48	10	103	MTX/CYC
13/F	PL-12	UCTD	40	6	18	None

* ILD = interstitial lung disease; DM = dermatomyositis; MTX = methotrexate; AZA = azathioprine; PM = polymyositis; CYC = cyclophosphamide; UCTD = undifferentiated connective tissue disease.

Table 2. Changes in outcome measures between baseline and up to 3 years after starting tacrolimus*

Patient	FVC			FEV_1			DLCO			Creatine kinase, IU			Manual muscle testing			Corticosteroids, mg/day			No. of months measured during tacro. treatment
	Baseline	After starting tacro.	% improvement	Baseline	After starting tacro.	% improvement	Baseline	After starting tacro.	% improvement	Baseline	After starting tacro.	% improvement	Baseline	After starting tacro.	% improvement	Baseline	After starting tacro.	% improvement	
1	50	67	34	62	77	24	60	69	15	207	100	52	106	110	4	20	5	75	12
2	68	73	7	84	85	1	38	41	8	548	107	80	106	85	−20	10	10	0	36
3	59	67	14	65	79	22	55	75	36	1,088	440	60	110	108	−2	20	5	75	36
4	74	79	7	75	80	7	61	NA	NA	706	21	97	110	110	0	60	1.25	98	36
5	33	55	67	41	60	46	43	43	0	410	59	86	106	110	4	60	10	83	21
6	59	61	3	67	71	6	57	58	2	795	61	92	73	88	21	60	5	92	36
7	47	69	47	52	80	54	32	47	47	386	64	83	110	110	0	60	3	95	36
8	63	67	6	76	77	1	†	†	NA	5,700	236	96	98	89	−9	40	30	25	36
9	73	90	23	80	94	18	45	52	16	3,505	58	98	102	110	8	12.5	0	100	36
10	64	71	11	69	76	10	57	64	12	1,223	285	77	100	110	10	20	7	65	23
11	23	38	65	28	45	61	26	37	42	4,980	2,291	54	59	103	75	30	25	17	6
12	66	71	8	74	79	7	24	57	138	1,432	161	89	102	110	8	40	1	98	36
13	56	73	30	61	81	33	55	72	31	24	19	21	110	110	0	7.5	3.75	50	18

* Values for the pulmonary function tests (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], and diffusing capacity for carbon monoxide [DLCO]) are the percentage of the predicted normal values. tacro. = tacrolimus; NA = not available.
† Data for patient 8 were excluded because of aberrant baseline results.

Table 3. Response to tacrolimus over time*

Outcome	Age at onset of ILD				Linear changes				Quadratic changes				Cubic changes			
	B	SE(B)	*t*	*P*	B	SE(B)	*t*	*P*	B	SE(B)	*t*	*P*	B	SE(B)	*t*	*P*
FVC	0.6790	0.2203	3.08	0.0093	0.6999	0.1363	5.13	<0.0001	−0.0090	0.0025	−3.60	0.0007	0.00003	0.00001	2.75	0.0083
FEV_1	0.8069	0.2104	3.84	0.0024	0.6999	0.1353	5.17	<0.0001	−0.0089	0.0025	−3.64	0.0006	0.00003	0.00001	2.80	0.0072
DLCO†	–	–	–	–	0.2433	0.0814	2.99	0.0046	−0.0012	0.0006	−2.06	0.0444	–	–	–	–
CK	–	–	–	–	−44.686	7.795	−5.73	<0.0001	0.5841	0.1244	4.69	<0.0001	−0.0022	0.0005	−4.10	<0.0001
MMT	–	–	–	–	0.1082	0.0469	2.31	0.0244	−0.0007	0.0003	−2.24	0.0328	–	–	–	–
CS	–	–	–	–	−0.8705	0.1207	−7.21	<0.0001	0.0115	0.0020	5.82	<0.0001	−0.00004	0.00001	−4.90	<0.0001

* The response to tacrolimus over time was analyzed statistically using random coefficient modeling. Time, the independent variable, was initially considered as a linear effect. This relationship between time and the outcome variable was then expanded to include possible nonlinear changes over time by including polynomials of time (i.e., quadratic and cubic). Changes in all outcome measures were considered statistically significant at $P < 0.05$. ILD = interstitial lung disease; B = standardized regression coefficient; SE(B) = standard error of the standardized regression coefficient; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; DLCO = diffusing capacity for carbon monoxide; CK = creatine kinase; MMT = manual muscle testing; CS = corticosteroids.
† Data from patient 8 were excluded because of aberrant baseline results.

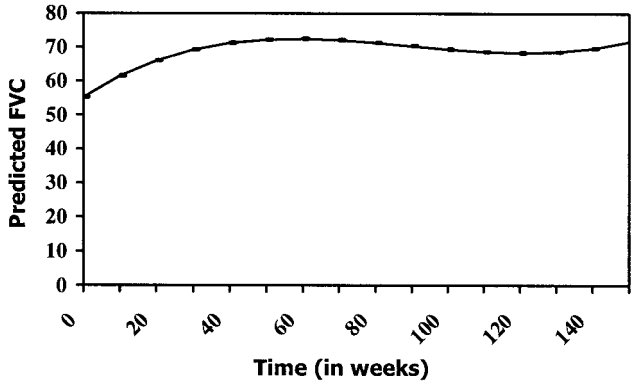

Figure 1. Predicted changes in forced vital capacity (FVC; % predicted) over time in patients treated with tacrolimus. % predicted FVC = 23.4589 + 0.6790 × $age_{interstitial\ lung\ disease\ onset}$ + 0.6999 × time – 0.00889 × $time^2$ + 0.000033 × $time^3$.

having probable or definite PM or DM according to the criteria of Bohan and Peter (12). One patient (patient 13) had the anti–PL-12 autoantibody and ILD with other features of the antisynthetase syndrome but without evidence of myositis after a followup of >3 years. Two patients with the anti–PL-7 autoantibody each received tacrolimus for <3 months and were not included in this analysis. One of them experienced palpitations shortly after beginning tacrolimus and refused to continue the medication; the other one had end-stage pulmonary fibrosis and was given tacrolimus as rescue therapy, but took the drug for <1 month.

Of the remaining 13 patients, 8 were women (62%) and 5 were men (38%). Six patients had a DM rash at some time during their illness, and 6 patients had no defining skin manifestations and were categorized as having PM.

Ten of the 13 patients (77%) whose data were analyzed failed to respond to corticosteroids and at least 1 other immunosuppressive agent for the treatment of ILD. Nine patients (69%) had previously been treated with methotrexate, 5 (38%) with azathioprine, and 2 (15%) with either parenteral or oral cyclophosphamide. Three patients did not previously receive immunosuppressive therapy other than corticosteroids. One of these 3 patients (patient 5) presented with adult respiratory distress syndrome after intravenous pulse methylprednisolone treatment had failed, and tacrolimus was then initiated. The 2 other patients (patients 6 and 13) had active alveolitis superimposed on pulmonary fibrosis, and based on our existing encouraging results with tacrolimus, this immunosuppressive agent was begun (Table 1).

At the time tacrolimus therapy was initiated, all patients had evidence of active ILD, based on worsening results on pulmonary function testing and/or computed tomography and a decline in their clinical status. All but patient 13 had evidence of active myositis, with elevations of serum CK levels, and 9 patients had appreciable muscle weakness prior to starting tacrolimus. Six patients had the simultaneous onset of both alveolitis and myositis, whereas 2 patients had significant pulmonary disease prior to the onset of muscle weakness. Four patients developed myositis prior to the pulmonary symptoms. Patient 13 had only pulmonary involvement.

The mean ± SD age at the onset of pulmonary disease was 46.9 ± 10.6 years (range 30–69 years). Prior to initiating tacrolimus, patients had an average of 14.7 months of pulmonary disease (range 1–73 months). Patients were treated with tacrolimus for a mean of 51.2 months (range 6–120 months). The baseline pulmonary and other outcome measures prior to starting tacrolimus and the last recorded value for each outcome measure up to 3 years after starting therapy are shown in Table 2. A dramatic change in the outcome measures is demonstrated in Table 2; however, only the baseline values and the response to treatment at 1 specific point in time are presented.

The use of random coefficient modeling allowed for the inclusion of multiple data points for each measured outcome in assessing the changes in response to tacrolimus over time. The changes demonstrated over time in all outcome measures using this statistical model were considered significant, as shown in Table 3.

As depicted in Figures 1 and 2, statistically sig-

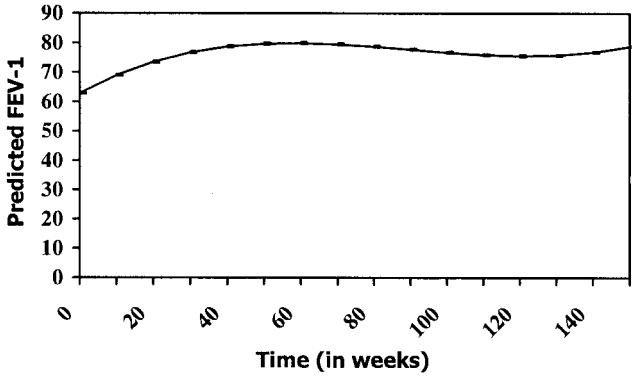

Figure 2. Predicted changes in forced expiratory volume in 1 second (FEV_1; % predicted) over time in patients treated with tacrolimus. % predicted FEV_1 = 24.9727+ 0.8069 × $age_{interstitial\ lung\ disease\ onset}$ + 0.6999 × time – 0.00891 × $time^2$ + 0.000033 × $time^3$.

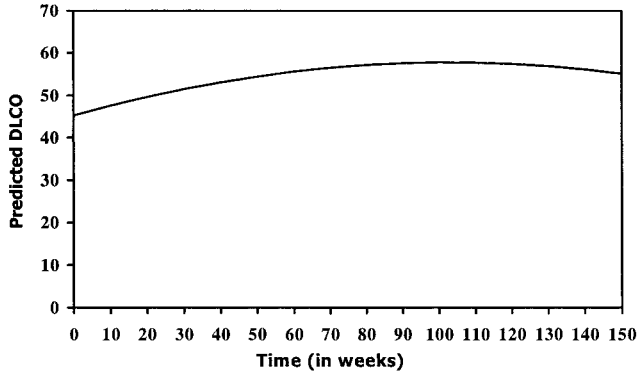

Figure 3. Predicted changes in diffusing capacity for carbon monoxide (DLCO; % predicted) over time in patients treated with tacrolimus. Quadratic curve: % predicted DLCO = 45.2507 + 0.2433 × time – 0.00118 × time^2.

nificant nonlinear changes were observed in the predicted outcomes of both the FVC and the FEV_1 when measured over time. A statistically significant response over time was also observed for the predicted DLCO. Considering the predicted trajectory for each of these pulmonary outcomes, the responses tended to improve in a nonlinear manner until ~60 weeks. Following a slight decline, the predicted FVC and FEV_1 again began to improve over time at ~120 weeks. For each of these pulmonary responses, the age at onset of ILD was identified as an important covariate ($P < 0.01$) and was included in the model. No significant interactions between age at onset of ILD and time were observed.

Due to a strikingly elevated baseline DLCO value (>135% predicted) in patient 8, which was incongruent with the patient's clinical status, this individual's DLCO results were excluded from the analysis. When the DLCO responses of the remaining patients were analyzed, a statistically significant improvement was predicted when comparing pre-tacrolimus DLCO measurements with post-tacrolimus measurements as depicted in Figure 3. No significant covariates were identified.

Improvement in muscle disease was similarly noted over time with tacrolimus treatment. Patients had a marked and statistically significant reduction in the serum CK level ($P < 0.0001$). An improvement in muscle strength was also observed when evaluating the MMT score over time ($P < 0.05$), since 10 patients (77%) either maintained normal muscle strength or experienced an improvement in muscle strength. Tacrolimus had a dramatic steroid-sparing effect, with statistically significant reductions in corticosteroid dosing ($P < 0.0001$). No significant covariates were identified.

Three patients were deceased at the time of our review. Patient 2 died after a myocardial infarction and subsequent respiratory failure. Patient 8 died of a pulmonary *Aspergillus* infection. Patient 9 died of severe acute respiratory failure that developed 7.25 years after tacrolimus was begun.

None of the side effects attributed to tacrolimus were severe according to the National Cancer Institute Common Terminology Criteria for Adverse Events. All patients experienced at least a transient increase in serum creatinine levels. Eleven patients had grade 1 increases and 2 patients had grade 2 changes in serum creatinine levels. Elevated serum creatinine levels improved within several weeks after discontinuing tacrolimus or decreasing the dosage. Hypomagnesemia was observed in 10 of the 13 patients (77%), but was easily treated with oral magnesium supplementation. Tremors occurred in more than one-half of our patients (69%). Mild to moderate hypertension or worsening of existing hypertension was seen in 6 patients (46%). One case each of gynecomastia and headache was attributed to tacrolimus. Hypertension, tremor, hypomagnesemia, and headache were grade 1 adverse events, while gynecomastia was a grade 2 adverse event.

DISCUSSION

ILD is a common and serious complication of IIM, particularly in the subset of patients with an anti-aaRS autoantibody. Pulmonary symptoms may dominate the clinical picture, and a chronic decline in pulmonary function or rapidly progressive ILD can be fatal (13–15). Aggressive therapy is warranted in patients with interstitial pneumonitis, particularly in those with presumed active and treatable alveolitis as demonstrated on high-resolution computed tomography.

The most effective treatment regimen for IIM-associated ILD is unknown because of a lack of placebo-controlled trials. Corticosteroids remain the mainstay of therapy, but many patients fail to respond to this treatment or manifest recurrent flares when the steroid dosage is tapered. Observational studies of patients with corticosteroid-resistant ILD have shown variable results with cyclophosphamide, azathioprine, and methotrexate treatment (16–18). Cyclosporin A, a potent T cell inhibitor, has been used in the treatment of adult and pediatric patients with ILD of unknown etiology and in patients with myositis-associated ILD, and the results have been favorable (19–22).

The success of cyclosporine prompted a previous pilot study at our institution evaluating the efficacy of tacrolimus, another T cell inhibitor, in treating refractory myositis. Tacrolimus showed promising results, since patients with anti–Jo-1 autoantibody and patients with anti-SRP autoantibodies had an improvement in their myopathy, with the former patients also demonstrating a response in their ILD (10). Five of the 13 patients included in the present study (patients 2, 4, 8, 9, and 12) were also included in the previously published study. The previous study emphasized the use of tacrolimus in refractory myositis, hence, the inclusion of anti-SRP–positive patients. However, a marked improvement in ILD was noted in this small number of patients and led to its use as a specific treatment of ILD. These preliminary findings prompted the present study to assess the efficacy of tacrolimus in treating the interstitial pneumonitis of IIM, a particularly devastating and potentially fatal complication.

Although the pathogenesis of myositis-associated ILD is unknown, a recent study indicated that activated Th1-type pulmonary T cells play an important role in the development of corticosteroid-resistant ILD in patients with PM and DM (23). These findings suggest that a T cell inhibitor, such as tacrolimus, may be of benefit in patients with interstitial pneumonitis.

Tacrolimus (FK-506), is a macrolide immunosuppressant with actions similar to those of cyclosporin A, but with much greater potency (24). Tacrolimus binds to immunophilins in lymphocytes, alters the activity of calcineurin, and leads to the inhibition of T cell activation (24–26). Since its approval for use in the prophylaxis of orthotopic liver transplantation rejection, tacrolimus has been used to treat a variety of immunologically mediated diseases, including Behçet's disease, pyoderma gangrenosum, and psoriasis (27–29). It is relatively well tolerated, with many patients continuing to take tacrolimus indefinitely, even during pregnancy (30,31). The major adverse effects are similar to those seen with cyclosporine: nephrotoxicity, neurotoxicity, disturbances in glucose metabolism, hypertension, and gastrointestinal symptoms (24–26). We have demonstrated that patients with anti-aaRS–associated ILD refractory to conventional immunosuppressants or patients with anti-aaRS–associated ILD presenting with acute severe pulmonary disease responded favorably to tacrolimus and tolerated the medication with manageable side effects. In our patient cohort, all but 1 of the patients were anti–Jo-1 antibody positive and had PM or DM. The patient without myositis had the anti–PL-12 autoantibody. Patients with this antibody have previously been shown to have ILD and manifest features of the antisynthetase syndrome (32).

Although ILD encompasses a heterogeneous group of disorders with varying disease mechanisms and histopathologic types, the unifying factor in the ILD in our patients was the presence of an antisynthetase autoantibody. Routine lung biopsies were not performed prior to more aggressive immunosuppressive therapy, since lung biopsies often fail to yield a specific diagnosis and were unlikely to change the requirement for immunosuppressive therapy. Potentially diverse forms of ILD may have been treated with tacrolimus, and the treatment response may be dependent on the histopathologic type. However, in this retrospective review, the data were too limited to report any useful observations regarding the response to therapy based on immunohistopathologic classification.

In previous studies of idiopathic pulmonary fibrosis, the FVC and DLCO have been the physiologic parameters of choice for the assessment of disease progression (33,34). We also used the FEV_1 as an outcome variable since it is less dependent on patient effort and reflects a more accurate measure of restrictive lung disease in our patient population than does the FVC, which requires a considerable effort from the patient. Our cohort demonstrated a significant improvement in all 3 pulmonary parameters, in addition to a dramatic and statistically significant decrease in the requirement for corticosteroids. Myopathy parameters, as measured by the serum CK levels and MMT scores, also showed statistically significant improvement with tacrolimus treatment over time.

Because of a concern that concomitant immunosuppression would adversely increase the risk of infection, none of the patients received any immunosuppressive therapy concomitantly with tacrolimus other than prednisone. All previous immunosuppressive therapy (except prednisone) was discontinued prior to the initiation of tacrolimus because of the perceived failure of that therapy, based on worsening findings on pulmonary function tests and imaging studies and declines in clinical status. In this retrospective analysis, there was no standardized approach to a reduction in the corticosteroid dosage, but an attempt to decrease the dosage by 20–25% every 4 weeks was made. Ultimately, the patient's clinical response dictated the reduction of the steroid dosage.

Although it is difficult to discriminate between the effects on outcome measures that were due to tacrolimus and those that were due to prednisone, it is important to recognize that all but 3 patients had

progression of their disease during previous immunosuppression with methotrexate, azathioprine, or cyclophosphamide along with corticosteroids. Also, there was a dramatic and statistically significant reduction in the corticosteroid dosage with improvement in the pulmonary outcome measures while taking tacrolimus; this was not appreciated when the patients were taking other immunosuppressive agents. Quantifying the effect of prednisone on the improvement in outcomes is difficult, but prednisone was clearly not the sole factor in the pulmonary improvement of these patients. We attribute the improvement in outcome measures to treatment with tacrolimus.

This study was neither prospective nor placebo controlled and is limited by its small sample size. However, our data and those from previously published studies (19–23) suggest that a T cell inhibitor such as cyclosporine or tacrolimus may be effective in treating connective tissue disease–associated ILD.

Cyclosporine has been shown to be effective in treating ILD in patients with myositis. However, there are currently no data that definitively favor either tacrolimus or cyclosporine. Although both cyclosporine and tacrolimus are T cell inhibitors, tacrolimus is a more potent immunosuppressive agent. In addition, they have different mechanisms of action and differing effects on Th2 cell cytokines as well as other aspects of humoral immunity (24). Side-effect profiles may influence the selection of therapy, since tacrolimus has a lower incidence of significant hypertension and hypercholesterolemia compared with cyclosporine. Conversely, tacrolimus has a higher incidence of alopecia, diabetes mellitus, and tremor than cyclosporine (24–26). In this study, tacrolimus was well tolerated, and no severe adverse reactions were documented.

In summary, this study demonstrates that patients with anti-aaRS autoantibodies and refractory or severe ILD had significant improvements in pulmonary outcomes when treated with tacrolimus. Tacrolimus should be considered an important therapeutic alternative for managing patients with IIM-associated interstitial pneumonitis. Prospective investigations of connective tissue disease–associated ILD or early idiopathic pulmonary fibrosis should consider studying this agent in a more rigorous and controlled manner.

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