

Risk factors for the recurrence of interstitial lung disease in patients with polymyositis and dermatomyositis: a retrospective cohort study

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Abstract To identify risk factors for the recurrence of interstitial lung disease (ILD) in patients with polymyositis (PM)/dermatomyositis (DM). Forty-four PM/DM-ILD patients who had been treated with glucocorticoid and/or immunosuppressive agents as a remission induction therapy were enrolled. The patients were first classified into two groups: the early recurrence group that recurred within 52 weeks, and the non-early recurrence group, which was further classified into the late recurrence group that recurred after 52 weeks, and the non-recurrence group. The characteristics and treatment regimen between the groups were compared. Recurrence was experienced by 15 of 44 patients. The pulmonary vital capacity of the early recurrence group was significantly lower than the non-early recurrence group (46 vs 76%, $p = 0.0003$), and 60% of the early recurrence group was treated with glucocorticoid alone as a maintenance therapy in contrast to 10% in the non-early recurrence group ($p = 0.004$). The late recurrence was only related with a positivity for autoantibodies against aminoacyl-tRNA synthetases (anti-ARS antibodies, odds ratio 8.4, $p = 0.02$), but calcineurin inhibitors tended to decrease the relapse incidence in patients with anti-ARS antibodies. Low pulmonary vital capacity at disease onset and anti-ARS antibodies positivity are the risk factors for the recurrence of ILD with PM/DM. Calcineurin inhibitors are important in preventing relapse.

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Introduction

Polymyositis (PM) and dermatomyositis (DM) are characterized by a systemic inflammation of proximal skeletal muscles with or without skin involvement [1]. Interstitial lung disease (ILD) is the most common, non-musculoskeletal manifestation of PM/DM, and is identified in 25 to 75% of patients. ILD with these inflammatory myopathies can be refractory to treatment, progress rapidly, and result in high mortality [2]. Immediate intensive immunosuppressive therapy, including a combination of high doses of glucocorticoids and immunosuppressive agents, is currently considered necessary to induce remission at present.

Since recurrence can cause acute life-threatening pulmonary inflammation, and may result in progression of pulmonary fibrosis, maintaining ILD in remission is critical. Although some studies have reported that patients with anti-aminoacyl synthetase autoantibodies (anti-ARS) are inclined to recur, [3, 4] recurrence of ILD is usually unpredictable and little is known about its relevant risk factors.

The aim of the study was to identify risk factors for recurrence of ILD in patients with PM/DM.

Materials and methods

Patients and data collection

We retrospectively reviewed records of patients with PM/DM who received glucocorticoids and/or immunosuppressive agents in Keio University Hospital, from January 2002 to

August 2015 as remission induction therapy for ILD. The diagnosis of PM/DM was made according to specific criteria [1, 5]. Information, including age, sex, smoking history, disease duration, autoantibodies, laboratory data, and pulmonary function tests at disease onset, treatment regimens, and high-resolution computed tomography (HRCT) findings were collected. Anti-ARS antibodies were confirmed by immunoprecipitation assay [6].

We defined induction therapy as treatment provided for ILD within 6 months from the initiation of drug therapy, and maintenance therapy as treatment after 6 months.

The study was approved by the ethics committee (Ethics Committee of Keio University School of Medicine, approval number: 20110136). Informed consent from the patients was waived according to the regulations in Japan.

Recurrence definition

Based on the criteria for the IPF Clinical Research Network, [7] recurrence of ILD was defined as exacerbation of interstitial pulmonary findings in a HRCT assessed by both radiologists and rheumatologists with worsening respiratory symptoms, resulting in re-induction therapy with the increase in glucocorticoid dose. Culture of sputum or bronchoalveolar lavage in all patients showed no evidence of infection. Other diseases such as drug induced pneumonitis, hypersensitivity pneumonitis, or heart failure were excluded by patients' history and clinical course, and physical and serological examinations.

The recurrence within 52 weeks of induction therapy was defined as early recurrence and a recurrence after 52 weeks as late recurrence. In the analyses, patients were firstly classified into the early recurrence group and the non-early recurrence group. Subsequently, the non-early recurrence group was classified into the late recurrence group and the non-recurrence group. We reviewed patients' charts from the beginning of induction therapy to their last visit on August, 2015. Observation period was defined in this study as the duration from the initiation of induction therapy to the recurrence of ILD in patients who had recurrence or to the last follow-up in patients who did not have recurrence. Follow-up period was the duration from the beginning of induction therapy to the last visit in all patients.

Statistics

Mean or median values and proportions were compared between two groups using the Mann-Whitney *U* test, Student's *t* test, or chi-square test. Recurrence-free survival was depicted with Kaplan-Meier method, and in comparisons of four groups the Logrank test was used to compare the differences between each two groups with Bonferroni correction. The annual risk was calculated by one-sample sign test. Odds ratio was calculated by univariate logistic regression analysis. A *p*

value of < 0.05 was regarded as significant. All statistical analyses were performed with JMP Software 11.2.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient flow and recurrence rates

Flowchart for patient selection is shown in Fig. 1a. Of the 46 patients with PM/DM-ILD, two patients were excluded (death or lost-to-follow-up within 1 month), and 44 patients were enrolled in the study. All 44 patients underwent HRCT both before and after induction therapy, which confirmed improvement of ILD.

During the observation period (6.6 ± 6.5 years), 15 patients experienced recurrence of ILD (34%). The overall recurrence rate was 5 per 100 person-years (Fig. 1b). The median time from the induction therapy to the recurrence was 152 (41–271) weeks. Five patients recurred within 52 weeks (early recurrence group), and nine patients after 52 weeks (late

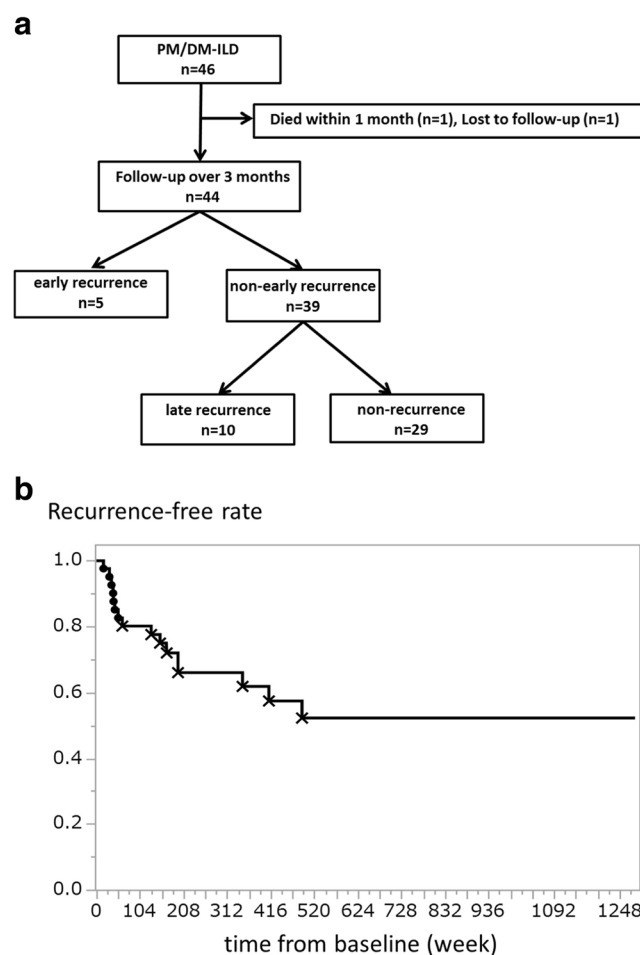


Fig. 1 Flowchart for patient selection with recurrence rates. **a** Patient flow. **b** Estimated recurrence-free rate by Kaplan-Meier method. Bullet, early recurrence; small letter “x,” late recurrence

Table 1 Baseline characteristics and treatment

	Early recurrence vs. non-early recurrence			Late recurrence vs. non-recurrence		
	Early recurrence (n = 5)	Non-early recurrence (n = 39)	p value	Late recurrence (n = 10)	Non-recurrence (n = 29)	p value
Demographics						
Age (year)	45.2 ± 19.8	48.9 ± 12.6	0.56	49.4 ± 8.6	48.8 ± 13.9	0.89
Female (n, %)	4 (80)	26 (66.7)	0.55	7 (70)	19 (65.5)	0.80
Myositis type						
Dermatomyositis (n, %)	4 (80)	18 (47.4)		3 (33.3)	15 (51.7)	
Polymyositis (n, %)	1 (20)	12 (30.8)		6(60)	6 (20.7)	
Clinically amyopathic dermatomyositis (n, %)	0	9 (23.7)		1 (11.1)	8 (27.6)	
Disease duration (months)	6 (2–13.5)	3 (2–7)	0.60	3 (2–13)	3 (2.5–19)	0.87
Observation period (weeks)	40 (24–43)	242 (159–653)		195 (130–365)	276 (162–764)	
Follow-up period (weeks)	158 (74–230)	319 (166–697)	0.04	352 (248–425)	276 (162–764)	0.72
Physical findings						
Heliotrope rash (n, %)	0	8 (20.5)	0.26	2 (20)	6 (20.7)	0.96
Gottron papules (n, %)	0	5 (12.8)	0.72	1 (10)	4 (13.8)	0.76
Gottron signs (n, %)	4 (80)	24 (61.5)	0.42	4 (40)	20 (69.0)	0.10
MMT ≤ 4 (n, %)	4 (80)	25 (64.1)	0.48	6 (60)	19 (65.5)	0.75
Laboratory test						
Anti-ARS antibody (n, %)	5 (100)	24 (61.5)	0.09	9 (90)	15 (51.7)	0.03
CRP (mg/dL)	0.44 (0.30–1.29)	0.16 (0.04–0.53)	0.16	0.19 (0.04–1.44)	0.14 (0.03–0.47)	0.50
KL-6 (U/mL)	1277 (643–2089)	707 (530–2378)	0.78	1277 (883–2095)	935 (455–2089)	0.46
LDH (IU/L)	279 (219–477)	263 (246–371)	0.85	293 (223–532)	279 (219–476)	0.83
CK (IU/L)	277 (79–444)	91 (70–628)	0.73	83 (69–878)	119 (71–767)	0.66
PaO ₂ /FiO ₂ ratio	465 ± 37	450 ± 51	0.53	458 ± 49	420 ± 48	0.11
HRCT findings						
Irregular linear opacities (n, %)	3 (60)	28 (73.7)	0.52	8 (88.9)	20 (69.0)	0.24
Consolidation (n, %)	2 (40)	18 (46.2)	0.79	7 (70)	11 (37.9)	0.08
Ground glass opacities (n, %)	5 (100)	38 (97.4)	0.72	10 (100)	28 (96.6)	0.55
Honeycombing (n, %)	0 (0)	1 (2.63)	0.71	0 (0)	1 (3.5)	0.57
Traction bronchiectasis (n, %)	1 (20)	16 (42.1)	0.34	2 (22.2)	14 (48.3)	0.17
Micronodules (n, %)	1 (20)	1 (2.63)	0.08	1 (11.1)	0 (0)	0.07
HRCT pattern						
UIP pattern (n, %)	0 (0)	1 (2.63)	0.71	0 (0)	1 (3.5)	0.57
Possible UIP pattern (n, %)	0 (0)	0 (0)		0 (0)	0 (0)	
NSIP pattern (n, %)	5 (100)	35 (89.7)	0.45	9 (90)	26 (89.7)	0.98
OP pattern (n, %)	0 (0)	1 (2.63)	0.71	0 (0)	1 (3.5)	0.57
Unclassifiable pattern (n, %)	0 (0)	2 (5.26)	0.6	1 (11.1)	1 (3.5)	0.37
Pulmonary function test						
%VC (%)	46 ± 7	76 ± 3a	0.0003	59 ± 12b	79 ± 17c	0.19
DLC0/VA	3.5 ± 0.8	3.9 ± 0.8d	0.34	3.8 ± 0.9e	3.9 ± 0.8f	0.61
Induction therapy						
Prednisolone dose (mg/kg/day)	0.96 ± 0.09	0.91 ± 0.16	0.46	0.90 ± 0.16	0.91 ± 0.16	0.65
GC pulse (n, %)	0	10 (25.6)	0.20	4 (40)	6 (20.7)	0.23
GC mono (n, %)	3 (60)	18 (46.2)	0.56	5 (50)	13 (44.8)	0.78
GC + IVCY ± calcineurin inhibitor (n, %)	2 (40)	14 (35.9)	0.86	4 (40)	10 (34.5)	0.75
GC + calcineurin inhibitor (n, %)	0	8 (20.5)	0.26	1 (10)	7 (24.1)	0.34
PSL tapered to half of the initial dose within 8 weeks (n, %)	4 (80)	14 (37.8)g	0.07	1 (12.5%)h	13 (44.8)	0.10

Table 1 (continued)

	Early recurrence vs. non-early recurrence			Late recurrence vs. non-recurrence		
	Early recurrence (n = 5)	Non-early recurrence (n = 39)	<i>p</i> value	Late recurrence (n = 10)	Non-recurrence (n = 29)	<i>p</i> value
Maintenance therapy						
GC mono (n, %)	3 (60)	4 (10.3)	<i>0.004</i>	2 (20)	2 (6.9)	0.24
GC + calcineurin inhibitor (n, %)	2 (40.0)	27 (69.2)	0.19	5 (50)	22 (75.9)	0.13
GC + methotrexate (n, %)	0	1 (2.6)	0.72	0	1 (3.5)	0.55
GC + azathioprine (n, %)	0	6 (15.4)	0.35	1 (10)	5 (7.2)	0.58
GC + daily oral CY (n, %)	0	3 (7.7)	0.52	2 (20)	1 (3.5)	0.09
PSL dose at the recurrence/at the last observation (mg/day)	10 ± 2.7	8 (4–11)	0.21	7 (4–12.9)	7.4 ± 3.2	0.94

Different letters beside the values have the following numbers: a, $n = 27$; b, $n = 7$; c, $n = 20$; d, $n = 26$; e, $n = 6$; f, $n = 20$; g, $n = 37$; and h, $n = 8$. A p value of < 0.05 was shown in italics

Values are mean (standard deviation) or median (first quartile, third quartile) unless otherwise indicated

MMT manual muscle testing, *Anti-ARS antibodies* autoantibodies against aminoacyl-tRNA synthetases, *CRP* C-reactive protein, *KL-6* Krebs von den Lungen-6, *LDH* lactate dehydrogenase, *CK* creatine kinase, *PaO₂* arterial pressure of oxygen, *FiO₂* fraction of inspiratory oxygen, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *%VC* the percentage of vital capacity, *DLCO* diffusing capacity of the lung carbon monoxide, *VA* alveolar ventilation, *GC* glucocorticoid, *IVCY* intravenous cyclophosphamide, *mono* monotherapy, *CY* cyclophosphamide, *PSL* prednisolone

recurrence group). Recurrence rates were 2 per 100 person-years in the early recurrence group, and 3 per 100 person-years in the late recurrence group. The annual risk of recurrence was higher for the first year than for the subsequent observation period (0.13 vs, 0.05 $p = 0.07$), although no statistical difference was found.

Factors relevant to the early recurrence

Demographic characteristics at initiation of induction therapy and the treatment regimens were compared between the early recurrence and the non-early recurrence groups, and then, between the late recurrence and the non-recurrence groups (Table 1).

Between the early recurrence group and the non-early recurrence group, no differences were identified in demographics or laboratory tests, including markers reflecting the severity of ILD (serum C-reactive protein, lactate dehydrogenase, Krebs von den Lungen-6, creatine kinase and PaO₂ (arterial pressure of oxygen)/FiO₂ (fraction of inspiratory oxygen) ratio). HRCT findings at disease onset were also summarized in Table 1 [8, 9]. No statistical difference was found in HRCT findings between the early recurrence group and the non-early recurrence group. In the early recurrence group, percentage vital capacity (%VC) at the initiation of induction therapy was significantly lower when compared to the non-early recurrence group (46 vs. 76%, $p = 0.0003$). While the induction therapy regimen was not different between the two groups, 60% of patients in the early recurrence group were treated with glucocorticoids monotherapy without immunosuppressive agents for the maintenance, compared to 10% of

the non-early recurrence group ($p = 0.004$). In 80% of patients in the early recurrence group, the glucocorticoid dose was decreased by 50% within 8 weeks, compared to 38% of the non-early recurrence group ($p = 0.07$). Univariate logistic regression analysis identified low %VC at induction therapy (odds ratio 0.6, 95% confidential interval 0.3–0.9, $p < 0.001$) and glucocorticoid maintenance monotherapy (odds ratio 13.1, 95% confidential interval 1.7–127.4, $p = 0.01$) as risk factors for early recurrence of ILD.

Factors relevant to the late recurrence

Table 1 also compares the characteristics between the late recurrence and non-recurrence groups. Autoantibodies against aminoacyl-tRNA synthetases (anti-ARS) were significantly more frequent in the late recurrence group, when compared to the non-recurrence group (90 vs. 52%, $p = 0.03$). In the non-recurrence group, more patients were treated with calcineurin inhibitors combined with glucocorticoids, when compared to the late recurrence group although it was not statistically significant (75.9 vs. 50%, $p = 0.13$). Univariate logistic regression analysis showed an odds ratio of recurrence of 8.4 (95% confidential interval 1.3–165.2, $p = 0.02$) for patients positive for anti-ARS antibodies.

Figure 2 shows the ILD recurrence-free rates in patients with PM/DM analyzed by the Kaplan-Mayer method. Patients were divided into four groups based on the use of calcineurin inhibitors and the presence of anti-ARS antibodies. Patients positive for anti-ARS antibodies, not treated with calcineurin inhibitors, had trend to recur compared to other groups ($p = 0.04$). Although the significance of difference

Recurrence-free rate

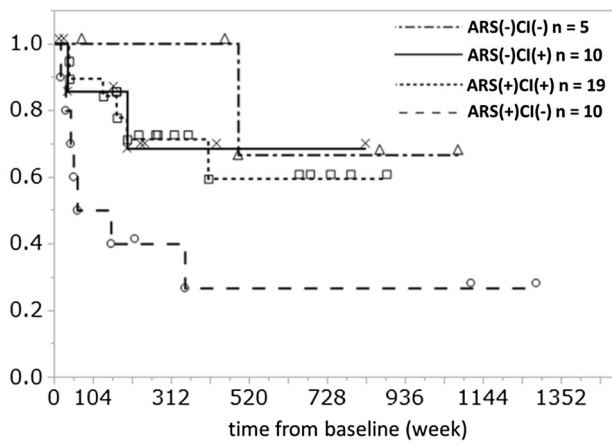


Fig. 2 Recurrence-free rate of four groups divided according to the presence of anti-ARS antibodies and the use of a calcineurin inhibitor. Recurrence-free rates in four groups divided according to the presence, ARS(+), or absence, ARS(-), of anti-ARS antibodies and the use, CI(+), or non-use, CI(-), of a calcineurin inhibitor. Anti-ARS antibodies, autoantibodies against aminoacyl-tRNA synthetases; CI, calcineurin inhibitors

disappeared after Bonferroni correction ($p = 0.07$) presumably because of the small number of patients, those data suggests that calcineurin inhibitors may help to prevent recurrence.

Cases with two times recurrence

We identified six patients who recurred again after the second induction therapy (Table 2). They were all positive for anti-ARS. Although most of them had received intensive induction therapy and continuous calcineurin inhibitors, recurrence still occurred when glucocorticoids were decreased to 5–13 mg/day, suggesting that a more innovative treatment strategy is

necessary to prevent recurrence of ILD in a part of patients with anti-ARS antibodies. We did not identify specific characteristics of twice recurrent patients in spite of comparable observation period (352 weeks for one recurrence vs 233 weeks for twice recurrence, $p = 0.29$).

Discussion

This study demonstrates that ILD for patients with PM/DM recurred at the rate of 5 per 100 person-years, and risk factors for recurrence within 52 weeks were low %VC at the time of induction therapy and glucocorticoid monotherapy, whereas the risk for recurrence during the long-term was the presence of anti-ARS antibodies. Calcineurin inhibitors could prevent relapse in patients with anti-ARS antibodies.

The incidence of ILD in patients with PM/DM varies between 25 and 75% depending on the definition of ILD. However, the recurrence rate of ILD after improvement, or during non-progressive status, is unclear. A cross-sectional study reported that eight of 45 patients (17.8%) had a recurrence of ILD [3]. A retrospective longitudinal study of 49 patients, with the median observation period of 25.7 months, showed approximately 30% of patients treated with tacrolimus died or had recurrence, compared to 55% in the conventional therapy group [4]. The recurrence rates in our long-term, longitudinal study were consistent with those findings; however, a larger observational cohort study is needed to clarify the incidence rate of the recurrence.

Recurrence within 52 weeks following induction therapy was related to low %VC at induction therapy and glucocorticoid maintenance monotherapy. Recurrence may also be related to the rapid reduction in glucocorticoid dose. As previously reported, lower %VC predicts unfavorable outcome, [10] and

Table 2 Details of six patients with more than one recurrence of interstitial lung disease

No.	Sex	PM/DM	Anti-ARS antibodies	Recurrence	Age	%VC (%)	Induction therapy	Initial PSL dose (mg/kg/day)	Maintenance therapy	Duration from the induction to the recurrence (week)	PSL dose at the recurrence (mg/day)
1	M	DM	Jo-1	1st	46	45.2	GC + CyA + IVCY	1	GC + CyA	41	6
				2nd	47	66.3	GC + CyA	0.5	GC + CyA	47	5
2	F	DM	EJ	1st	44	42.2	GC	1	GC	44	12
				2nd	50	39.7	GC	1	GC	287	11
3	F	DM	EJ	1st	52	57.4	GC	0.67	GC	52	8
				2nd	54	73	GC + CyA	0.67	GC + CyA	124	8
4	M	PM	Jo-1	1st	61	59	GC + FK	1	GC + FK	271	7
				2nd	65	98.1	GC + CyA + IVCY	0.5	GC + CyA	242	6
5	F	PM	ARS	1st	50	35.1	GC + FK + IVCY	1	GC + FK	40	13
				2nd	51	47.5	GC + CyA + IVCY	1	GC + CyA	57	8
6	F	PM	Jo-1	1st	41	87	GC + CyA + IVCY	1	GC + CyA	152	8
				2nd	43	104	GC + CyA	0.5	GC + CyA	124	4

PM polymyositis, DM dermatomyositis, Anti-ARS antibodies autoantibodies against aminoacyl-tRNA synthetases, %VC the percentage of vital capacity, PSL prednisolone, GC glucocorticoid, IVCY intravenous cyclophosphamide, CyA cyclosporine, FK FK506, mono monotherapy, rapid PSL reduction PSL tapered to half of the initial dose within 8 weeks

reflects the severity of ILD [11]. In our study, patients with low %VC at disease onset were more likely to have recurrence of ILD early after remission induction, suggesting that ILD with low %VC may need more intensive induction therapy. It is not surprising that glucocorticoid monotherapy dose is related to recurrence within 52 weeks, since the importance of combination immunosuppressant therapy, including calcineurin inhibitors, cyclophosphamide, azathioprine, and methotrexate, has been reported [12–14]. Moreover, the relationship of rapid decrease in glucocorticoid dose with early re-worsening of ILD indicates that it could be regarded as remission induction failure rather than recurrence in spite of improved finding by HRCT, meaning subsiding inflammation in the lungs requires some time.

Recurrence of ILD after 52 weeks is associated only with the presence of anti-ARS antibodies. Our results, suggesting that maintenance therapy with calcineurin inhibitors can inhibit recurrence of ILD, is in agreement with previous clinical and basic science studies [4, 12, 15]. A retrospective study showed that the addition of tacrolimus to conventional therapy significantly improved the prognosis [4]. Calcineurin inhibitors inhibit T cell proliferation by inhibiting IL-2 production, and targeting CD8 T cells could be a reasonable strategy for ILD in PM/DM as the local CD4/CD8 ratio in bronchoalveolar fluid was low in ILD with PM/DM [16]. Six patients positive for anti-ARS antibodies, however, experienced repetitive recurrence, despite the combination calcineurin inhibitors with glucocorticoids. While calcineurin inhibitors are effective to decrease recurrence risk, a part of patients are still at risk of recurrence after glucocorticoid tapering. Further studies are required to identify more effective treatment strategies to prevent those recurrence of ILD.

This study had a longer observation period than previous studies. Although the frequent recurrence of interstitial lung disease with PM/DM is problematic, little is known about the long-term information about it because of the difficulty in collecting those rare diseases. This long-term observational study is valuable. This study has added evidence on the importance of concomitant use of calcineurin inhibitors. The necessity of establishing innovative treatment strategy is revealed by showing that a part of patients are still at risk of recurrence despite the use of calcineurin inhibitors. This study has some limitations. First, this is a single-center, retrospective study with a small sample size. Although the patient number was rather large for these rare diseases, the small sample size could result in bias and obscure statistical significance. Second, this analysis included patients with PM, DM, and amyopathic DM as a single group, despite the clinical and pathological differences because the small sample size hampered the stratified analyses. Third, all patients were Japanese, and a specific genetic background may affect clinical and therapeutic outcomes.

In conclusion, the use of immunosuppressive agents such as calcineurin inhibitors is vital to manage ILD in patients

with PM/DM, especially in patients with low %VC at disease onset and positive for anti-ARS antibodies. Calcineurin inhibitors can be favorable in maintenance therapy; however, inhibiting recurrence in a long time still needs innovative treatment strategy.

Compliance with ethical standards

Conflict of interest M.N. has none to disclose. Y.K. has received consulting fees, speaking fees, and/or honoraria from AbbVie, Astellas Pharma, Chugai Pharmaceutical, Bristol-Myers K.K., Eisai, Tanabe Mitsubishi Pharma, Pfizer Japan, UCB, Eli Lilly, Taisho-Toyama, Janssen, EA Pharma, Ayumi Pharmaceutical, and Takeda Pharmaceutical. T.T. has received consulting fees, speaking fees, and/or honoraria from Pfizer Japan, Mitsubishi Tanabe Pharma, Eisai, Astellas Pharma, and UCB (less than \$10,000 each), and from Chugai Pharmaceutical, Bristol-Myers K.K., Daiichi Sankyo, AbbVie, Janssen Pharmaceutical K.K., Pfizer Japan, Asahi Kasei Pharma, Takeda Pharmaceutical, AstraZeneca K.K., Eli Lilly Japan K.K., and Novartis Pharma K.K. (more than \$10,000 each).

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