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ORIGINAL RESEARCH

Coadministration of Cyclosporin A with Prednisolone in Acute Interstitial Pneumonia Complicating Polymyositis/Dermatomyositis

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Abstract
Objective: To investigate clinical effectiveness of prednisolone (PSL) and cyclosporin A (CyA), particularly continuous intravenous administration of the latter, in patients with interstitial pneumonia (IP) associated with polymyositis/dermatomyositis (PM/DM).
Methods: We reviewed the clinical findings and therapeutic outcomes of patients with PM/DM who had received PSL and CyA (PSL + CyA, n = 21 for DM and 2 for PM) or the former alone (n = 12 for DM and 7 for PM). All patients receiving PSL + CyA had active IP.
Results: Fifteen of the 21 DM patients receiving PSL + CyA showed favorable therapeutic outcomes of IP (recovery group), while the remaining 6 died of respiratory failure (death group). Before treatment PaO_2 in room air and %VC were significantly lower, and the total CT score was significantly higher in the death group than in the recovery one. Continuous intravenous administration of CyA was performed in 6 patients for severe IP requiring oxygen therapy, and of these 2 showed complete recovery from it.
Conclusions: Coadministration of PSL and CyA, particularly continuous intravenous infusion of the latter, from the early phase of illness may be a potent therapeutic option for PM/DM patients with decreases in PaO_2 and %VC and/or a high total CT score suggestive of a poor prognosis.

Keywords: cyclosporin A, intravenous continuous administration, polymyositis, dermatomyositis, interstitial pneumonia

Introduction

Polymyositis (PM) and dermatomyositis (DM) are autoimmune inflammatory systemic disorders primarily targeting skeletal muscles with or without skin involvement. Several recent reports have demonstrated obvious differences in flow cytometry of circulating peripheral blood and immunohistochemistry of skeletal muscles between PM and DM,[1–3] but both disorders are similar with regard to showing an important role of activated T-lymphocytes in the pathogenesis.[4] To control the disease activity of PM and DM via suppression of activated T-lymphocytes, calcineurin inhibitors, such as cyclosporin A (CyA) and tacrolimus, have recently been used for treatment of refractory cases unresponsive to corticosteroid alone, particularly in patients with progressive interstitial pneumonia (IP) in which many CD8-positive cells are frequently detectable in both the alveolar wall and bronchoalveolar fluid.[5–7] Additional use of calcineurin inhibitors in these cases may be able to promote early recovery, save life and also reduce corticosteroid-induced adverse events.[1,8–11]

In the present study we retrospectively investigated the clinical outcomes of prednisolone (PSL) and CyA in acute IP complicating PM/DM in order to clarify therapeutic efficacy and adverse effects. We postulate that additional use of CyA to corticosteroid, particularly continuous intravenous administration of the former in the early phase of illness, may be a potent therapeutic option for PM/DM patients associated with IP probably showing a poor prognosis.

Patients and Methods

Patients

We studied 9 patients with PM (8 women and 1 man; mean age 65 ± 15 years, range 28 to 81) and 33 patients with DM (20 women and 13 men; mean age 52 ± 17 years, range 15 to 83) who had been admitted to our hospital from January 2002 to August 2010. The diagnoses of PM and DM were made according to the classification criteria proposed by Bohan and Peter.[12] None of the patients had received any treatment prior to admission to our hospital, and presented with some of the clinical manifestations and laboratory data suggestive of active disease, such as muscle weakness, skin symptoms and increases in serum creatine kinase (CK). Sixteen of the DM patients were compatible with clinically amyopathic DM (CADM) with regard to showing typical skin symptoms, including heliotrope rash, Gottron's sign and ulcerations, with no or little muscle involvement.[13] No patients had either malignancy on intensive systemic survey or obvious renal dysfunction on routine laboratory examinations. Other clinical information, such as C-reactive protein (CRP) and autoantibodies, was obtained from their medical records. The Local Ethical Committee approved this study.

Clinical assessment of IP

We assessed pulmonary involvement in the patients using the following indices: chest X-ray, high resolution computed tomography (HRCT), arterial oxygen pressure (PaO_2) in room air, serum KL-6 and respiratory function tests, including a percent vital capacity (%VC) and a percent diffusing capacity for carbon monoxide (%DLco). HRCT was performed using LightSpeed VCT VISION (GE Healthcare Japan; Hino, Japan), with 2-mm collimation at 15-mm intervals at end inspiration from the lung apices to the bases. All images were reconstructed with a high-spatial frequency algorithm, and photographed at window widths of −1500 H.U. and window levels of −600 H.U. To discover interstitial changes in lungs, we focus upon the following CT findings:[14,15] (1) nodular opacities: (2) bronchial dilatation and wall thickening, including consolidation around bronchovascular bundles: (3) reticular opacities, including honeycomb changes: (5) linear opacities and (6) increased lung opacities. When the patients with at least one of these CT findings showed clinical symptoms, such as non-productive cough and exertional dyspnea, with impaired respiratory function, particularly decreases in PaO_2 (<80 mmHg),%VC (<80%) and/or %DLco (<70%), associated IP was regarded as active. To assess IP, we selected 6 transverse CT images taken at the levels of the upper and lower portions each of the aortic arch, the hilus and the lower lobe. Two raters blinded to the clinical information (YS and MM) evaluated the HRCT images focusing the above-mentioned 6 CT findings suggestive of IP, and used the visual estimation method described by Kinoshita et al.[14] Each CT slice level was divided into 4 areas according to a horizontal and a vertical line drawn by a rater, and scored in a semiquatitative manner

Table 1. Comparison of clinical profiles and laboratory data on admission between PSL alone and PSL + CyA.

Treatment	Dermatomyositis		Polymyositis	
	PSL alone	PSL + CyA	PSL alone	PSL + CyA
Number of patients	12 (5*)	21 (11*)	7	2
Age of onset (years)				
Mean	61	46	64	66
SD	16	16	17	7
vs. PSL alone		NS		
Male/Female				
Number	3/9	10/11	0/7	1/1
vs. PSL alone		NS		
Initial dose of PSL (mg/kg/day)				
Mean	0.94	1.00	1.00	1.00
SD	0.16	0.28	0	0
vs. PSL alone		NS		
Clinical symptoms				
Muscle weakness				
Number	8	10	7	2
vs. PSL alone		NS		
Arthralgia				
Number	1	16	0	0
vs. PSL alone		<**0.0001**		
Ulcerative skin lesions				
Number	0	12	0	0
vs. PSL alone		**0.0008**		
Laboratory findings				
WBC (/μL)				
Mean	6235	5228	7363	9830
SD	1993	1251	2397	2772
vs. PSL alone		NS		
Lymphocytes (/μL)				
Mean	674	796	1666	928
SD	529	453	748	146
vs. PSL alone		NS		
CK (IU/L)				
Mean	3261 (6360**)	1825 (3703**)	4348	2558
SD	4616 (4882**)	3513 (4464**)	3124	1190
vs. PSL alone		NS (NS**)		
CRP (mg/dL)				
Mean	0.25	1.54	0.28	1.83
SD	0.25	2.07	0.26	1.61
vs. PSL alone		**0.006**		
Positive for anti-nuclear antibody				
Number	7	3	2	1
vs. PSL alone		NS		
Positive for anti-Jo-1 antibody				
Number	0	1	0	0
vs. PSL alone		NS		
Total CT score				
Mean	0.17	10.75	0.43	10.50
SD	0.58	6.84	0.79	4.95
vs. PSL alone		<**0.0001**		

Notes: *Number of patients with amyopathic dermatomyositis, **Values in patients with non-amyopathic dermatomyositis.
Abbreviations: CK, creatine kinase; CRP, C-reactive protein; CyA, cyclosporin A; NS, not significant; PSL, prednisolone; SD, standard deviation; WBC, white blood cells.
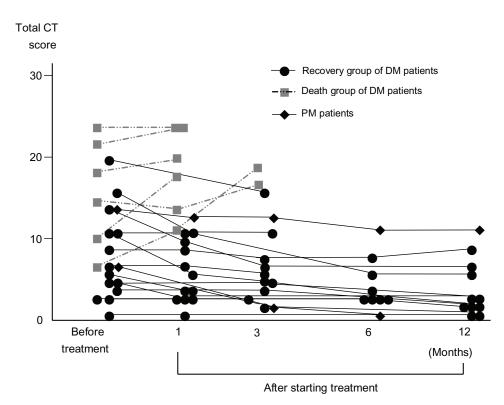
Figure 1. The total CT score before and after treatment in the PSL + CyA group.
Notes: The recovery group of the DM patients showed a significant decrease in the total CT score 1, 3, 6 and 12 months after starting PSL and CyA compared with before ($P < 0.05$), while the death group did not. The total CT score in the PM patients also decreased after starting PSL and CyA.

as follows: 0 = absent; 1 = less than 25% involved; 2 = 25%–50% involved; 3 = 50%–75% involved; and 4 = greater than 75% involved. The final judgment was reached by consensus of the 2 raters. Right and left lungs were evaluated separately, and the sum was expressed as the total CT score. HRCT was serially performed before and after treatment.

Treatment

PSL was started at a dose of approximately 1.0 mg/kg/day in all of the patients soon after the diagnosis of PM/DM. We added CyA to PSL when active IP was evident (PSL + CyA). CyA was orally given twice a day initially at a dose of 75 mg, which was later controlled to keep the trough concentration between 100 and 150 ng/mL. Continuous intravenous administration of CyA was performed when oral intake of it was difficult because of critical care for respiratory failure, such as oxygen therapy with or without mechanical ventilatory support. CyA was started at 0.17 mg/kg/hr, the blood concentration was checked at least twice a day, and in order to keep it at 250–350 ng/mL the administration speed of CyA

was controlled. The dose of CyA was reduced at the development of renal dysfunction.

Statistics

To determine statistical differences between PSL alone and PSL + CyA in PM/DM and also those between recovery and death groups in DM, Mann-Whitney's U and Chi-square for independence tests were employed. Wilcoxon's signed rank test was used for evaluating alterations of the total CT score. The results were expressed as mean ± standard deviation, and a *P*-value less than 0.05 was regarded as statistically significant. Commercially available statistics software was used for data analysis (StatView for Macintosh, Abacus Concepts, Berkeley, CA, USA and Excel for Windows, Microsoft, Redmond, WA, USA).

Results
Clinical profiles and laboratory findings before treatment

CyA was added to PSL (PSL + CyA) in 21 patients with DM, including 11 with CADM, and 2 with PM,

Table 2. Comparison of clinical profiles and laboratory data on adding CyA between the recovery and death groups of DM patients treated with PSL and CyA.

	Recovery group	Death group
Number of patients	15	6
Age (years)		
Mean	44	56
SD	17	10
vs. recovery group		NS
Amyopathic type		
Number	8	3
vs. recovery group		NS
Male/ Females	7/8	4/2
Number		
vs. recovery group		NS
Initial dose of PSL (mg/kg/day)		
Mean	0.94	1.08
SD	0.25	0.20
vs. recovery group		NS
Interval between commencement of PSL and that of CyA (days)		
Mean	32.0	29.4
SD	39.3	18.5
vs. recovery group		NS
Clinical symptoms		
Dyspnea		
Number	9	5
vs. recovery group		NS
Non-productive cough		
Number	9	6
vs. recovery group		NS
Laboratory findings		
KL-6 (U/L)		
Mean	1055	1865
SD	625	2220
vs. recovery group		NS
PaO_2 in room air (mmHg)		
Mean	77.8	59.8
SD	15.0	7.2
vs. recovery group		**0.017**
%VC (%)		
Mean	86.9	58.3
SD	13.6	18.7
vs. recovery group		**0.013**
%DLco (%)		
Mean	57.4	42.1
SD	9.01	11.9
vs. recovery group		NS
Total CT score		
Mean	8.21	16.7
SD	5.55.	6.12
vs. recovery group		**0.013**
Other treatment		
Methylprednisolone pulse		
Number	3	6

(Continued)

Table 2. (*Continued*)

	Recovery group	Death group
IVIg		
Number	0	5
PE		
Number	0	2
IVCY		
Number	0	3

Abbreviations: CyA, cyclosporin A; DLco, diffusing capacity for carbon monoxide; DM, dermatomyositis; IVCY, cyclophosphamide pulse; IVIg, high-dose intravenous immunoglobulin; NS, not significant; PE, plasma exchange; PSL, prednisolone; SD, standard deviation; VC, vital capacity.

all of whom showed active IP on or after admission. Possibilities of infection were excluded on the basis of blood examinations, including serum antibodies to infectious agents, and analyses of bronchoalveolar lavage fluid in all of these patients. Twelve DM patients, including 5 with CADM, and 7 with PM were treated only with PSL (PSL alone). Among them 1 DM and 2 PM patients revealed mild consolidation around bronchovascular bundles and/or honey-comb changes on CT, which were regarded as old and inactive IP based on the lack of clinical symptoms with well-preserved respiratory function. Comparison of clinical profiles and laboratory data on admission between PSL alone and PSL + CyA is shown in Table 1. There was no significant difference in the initial dose of PSL between PSL alone and PSL + CyA. Among the clinical symptoms of DM, arthralgia and ulcerative skin lesions were significantly more frequent in PSL + CyA ($P < 0.0001$ and $P < 0.001$, respectively) than in PSL alone. No significant difference was seen in laboratory data between the 2 groups except for CRP in the DM patients, which showed a significantly higher value in PSL + CyA than in PSL alone ($P < 0.01$). The total CT score in DM showed a significantly higher level in PSL + CyA than in PSL alone ($P < 0.0001$).

Therapeutic outcomes

Fifteen of the 21 DM patients receiving PSL + CyA (recovery group) showed favorable therapeutic outcomes of IP, including complete recovery, and no serious adverse events except for mild pneumocystis pneumonia in 2. The remaining 6 patients receiving PSL + CyA (death group) died of respiratory failure due to active IP despite methylprednisolone pulse

therapy and other intensive immunomodulatory treatment, such as plasma exchange and high-dose intravenous cyclophosphamide. Three of the 6 patients had CADM. The total CT scores of each patient before and after starting coadministration of PSL and CyA are shown in Figure 1. All DM patients in the recovery group showed decreases or at least no increase in the total CT score from 1 month after starting coadministration of PSL and CyA. There were significant decreases in the total CT scores 1, 3, 6 and 12 months after starting coadministration of PSL and CyA compared with before ($P < 0.05$). All DM patients in the death group showed increases in the total CT score suggestive of worsening of IP even after starting coadministration of PSL and CyA, and died within approximately 3 months after admission. In PM 2 patients received PSL and CyA, and both recovered from active IP without serious adverse events, although the total CT score in 1 remained at a slightly high level owing to inactive interstitial sequellae 12 months after starting this treatment. No patients receiving PSL alone showed any life-threatening complications.

To investigate clinical indices predicting therapeutic outcomes in IP complicating PM/DM, we compared clinical symptoms and laboratory data on adding CyA in the death group with those of the recovery one (Table 2). PaO_2 in room air and %VC were significantly lower in the death group than in the recovery one ($P < 0.05$).

The death group showed lower % DLco compared with the recovery one, but no statistical difference was present. The total CT score was significantly higher in the death group than in the recovery one ($P < 0.05$). There was no significant difference in clinical symptoms, such as non-productive cough and dyspnea, KL-6, initial dose of PSL or the interval from commencement of PSL to that of CyA between the death and recovery groups. Other treatments, such as methyprednisolone pulse therapy and high-dose intravenous immunoglobulin, were more frequently performed in the death group than in the recovery one in order to avoid worsening of respiratory failure.

Continuous intravenous administration of CyA

Continuous intravenous administration of CyA was performed in 6 DM patients, including 2 with CADM. Clinical profiles and therapeutic outcomes of these patients are summarized in Table 3. All of the patients required oxygen therapy on or after admission because of severe dyspnea and non-productive cough with low levels of PaO_2 in room air, %VC and %DLco, although respiratory function tests could not be performed in some of them. The duration of continuous intravenous administration of CyA was 7 to 15 days (mean 12.5 ± 3.3 days), and the interval between admission to our hospital and commencement of this treatment was 0 to 44 days

Table 3. Clinical profiles of patients treated with continuous intravenous administration of CyA.

Patient	Age/Sex	Diagnosis	Clinical symptoms		Respiratory function tests			Total CT score on starting intravenous CyA	Methyl PSL pulse therapy	PSL
			Dyspnea	Cough	PaO$_2$ in room air	%VC	%DLco			
1	65/F	DM	+	+	62.8	ND	ND	19	+	+
2	55/F	CADM	+	+	68.0	45.0	ND	16	+	+
3	56/M	CADM	+	+	61.8	43.6	ND	22	+	+
4	54/F	DM	+	+	50.8	ND	ND	24	+	+
5	52/F	DM	+	+	60.6	45.5	31.5	16	+	+
6	57/M	DM	+	+	61.2	61.4	63.6	14	+	+

(mean 9.2 ± 17.3 days). Three patients started to receive continuous intravenous administration of CyA right after admission to our hospital because of rapidly progressive respiratory failure, and of these 2 (patients 5 and 6) completely recovered from IP. After reaching stable general status the administration route of CyA was changed from intravenous to oral in both patients. As a representative case the clinical course of patient 6 is shown in Figure 2. IP quickly improved in parallel with a decrease in serum CK and an increase in SaO$_2$ after starting continuous intravenous infusion of CyA and methylprednisolone pulse therapy followed by PSL. The administration route of CyA was successfully changed from intravenous to oral 2 weeks after admission. Nevertheless, the remaining 1 (patient 4), who had already shown consciousness disturbance due to hypoxia on admission, showed improvement of IP only when the blood concentration of CyA was raised to 450 ng/mL or higher. Renal dysfunction ascribable to CyA quickly worsened, and the patient died of respiratory failure during tapering continuous intravenous infusion of this drug.

Discussion

In the present study we reviewed the clinical profiles of PM/DM patients who had received coadministration of CyA and PSL in order to treat associated active IP. All of the patients receiving PSL + CyA, therefore, had active IP, while those receiving PSL alone did not. Considering that the PSL + CyA group showed a significantly higher frequency of ulcerative skin lesions and arthralgia than PSL alone before treatment, DM associated with active IP may have a systemic inflammatory process affecting visceral organs, such as vasculitis, in the background, as shown in the previous report.[16] A significantly higher level of CRP in PSL + CyA than in PSL alone also supports the possible presence of systemic vasculitis in DM associated with active IP.

Oral administration of immunosuppressive agents, particularly CyA, is often employed for treatment of acute IP complicating DM in addition to PSL and methylprednisolone pulse therapy.[9,17–19] In the present study 15 DM patients in the recovery group showed quick decreases or at least no increase in the total CT score after starting coadministration of CyA and PSL. Nevertheless, oral CyA has been reported to sometimes fail to sufficiently avoid deterioration of IP, resulting in unfavorable outcomes even if this drug is started from the early phase of illness.[20] In the present study 6 DM patients died of respiratory failure due to acute IP despite administration of oral CyA. Among them 4 patients showed an evident delay in commencement of CyA, but in the remaining 2 both PSL and oral CyA were started almost simultaneously right after admission to our hospital in good general status with relatively low values of the total CT score. One possible cause of the unfavorable outcome is that IP was rapidly progressive. In other words, IP may

CyA				Other treatments	Adverse effects	Therapeutic outcome
Interval from admission to commencement of CyA (days)	Duration of oral CyA before intravenous administration (days)	Duration of continuous intravenous administration of CyA (days)	Oral CyA after intravenous administration			
7	0	15	–	PE, IVIg	Renal dysfunction Eruptions	Death
39	5	14	–	IVCY, IVIg	–	Death
0	4	15	–	PE, IVIg	–	Death
0	0	10	–	IVCY, IVIg	Renal dysfunction	Death
0	0	7	+	–	–	Recovery
0	0	15	+	–	–	Recovery

Abbreviations: CADM, clinically amyopathic dermatomyositis; CyA, cyclosprin; DLco, diffusing capacity for carbon monoxide; DM, dermatomyositis; IVCY, intravenous cyclophosphamide; IVIg, intravenous high-dose immunoglobulin; ND, not done; PE, plasma exchange; PSL, prednisolone; VC, vital capacity.
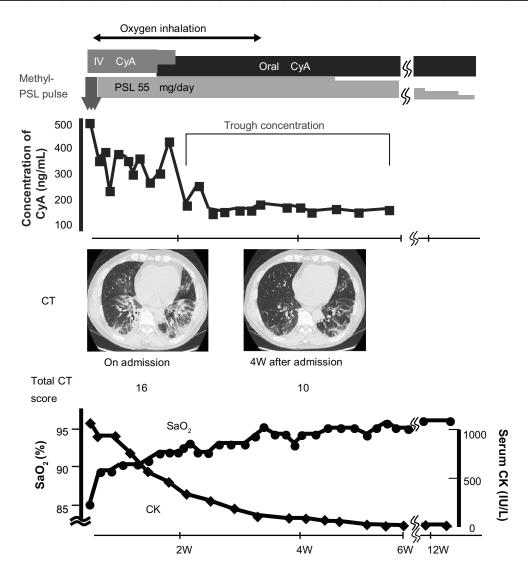
Oxygen inhalation

IV CyA

Oral CyA

Methyl-
PSL pulse

PSL 55 mg/day

Concentration of CyA (ng/mL)

500
400
300
200
100

Trough concentration

CT

On admission

4W after admission

Total CT
score

16

10

SaO₂ (%)

95

90

85

SaO₂

CK

Serum CK (IU/L)

1000

500

0

2W

4W

6W

12W

Figure 2. The clinical course of patient 6, showing a decrease in CK and an increase in SaO₂ during continuous intravenous infusion of CyA and methylpred-nisolone pulse therapy followed by PSL. The administration route of CyA was successfully changed from intravenous to oral 2 weeks after admission.
Abbreviations: CK, creatine kinase; CT, computed tomography; CyA, cyclosporin A; IV, intravenous; PSL, prednisolone; SaO₂, arterial oxygen saturation.

have become irreversible and extensive before CyA extended immunosuppressive action. The other possible cause is that blood concentrations of CyA were not high enough to suppress the disease activity of IP. We raised the administration dose of oral CyA within several days after commencement in these 2 patients in order to keep the trough concentration between 100 and 150 ng/mL, but IP quickly worsened during this period. Oral CyA suppresses autoreactive T cells in conjunction with an increase in blood concentrations after absorption from the gastrointestinal tract. As many exogenous factors, such as food and drugs, can affect the therapeutic efficacy of oral CyA by readily modifying its absorption and metabolism, continuous intravenous administration is often employed for

treatment of rejection in organ transplantation[21,22] and inflammatory bowel disorders, including ulcerative colitis.[23,24] In the present study 6 DM patients with active IP received continuous intravenous administration of CyA because of respiratory failure requiring oxygen therapy with or without mechanical ventilatory support. Four patients showed extensive and probably irreversible damage in both lungs at commencement of the continuous intravenous administration of CyA, finally resulting in death, while the remaining 2 received this treatment from admission to our hospital, and quickly recovered from IP. These results suggest that the continuous intravenous administration of CyA may be a potent therapeutic option in IP complicating DM, particularly in the early phase

of illness, with regard to its capability of quickly elevating the blood concentration and stabilizing it.

With continuous intravenous administration of CyA both therapeutic effects and adverse events, such as renal dysfunction, depend on its blood concentration. For therapeutic efficacy the appropriate blood concentration with continuous intravenous infusion has been reported to be approximately 2.55-times as high as the trough level with oral administration.[22] Considering that the appropriate trough level of CyA in the oral administration is 80–150 ng/mL, therefore, the blood concentration should be kept at approximately 200–380 ng/mL in continuous intravenous infusion. In the present study we controlled the administration speed of CyA in order to keep the blood concentration at 250–350 ng/mL. In the term of safety, adverse events ascribed to CyA have been reported to be dependent on the length of continuous intravenous administration but not on the blood concentration at 300–500 ng/mL.[23,25,26] To reduce the possibility of adverse events, therefore, we need to switch the continuous intravenous infusion of CyA to oral administration as soon as possible after reaching stable general status. In the present study 2 patients showed successful transition from continuous intravenous infusion of CyA to oral administration in at most 2 weeks. Renal dysfunction with or without skin eruptions occurred in 2 patients, and of these it rapidly worsened in 1 because the blood concentration of CyA had to be maintained at 450 ng/mL or higher for 10 days in order to treat IP.

According to several recent reports the presence of autoantibodies to CADM-140 in serum and hyperferritinemia are strongly relevant to poor prognosis in IP complicating PM/DM.[27,28] At the present time, however, the anti-CADM-140 antibody remains commercially unavailable. To discover other clinical factors suggestive of poor prognosis, we investigated whether or not there was a difference in laboratory data, respiratory function and the total CT score between the death and recovery groups of DM associated with IP. No significant difference was seen in laboratory data, including KL-6, but PaO_2 and %VC were significantly lower and the total CT score was significantly higher in the death group than in the recovery one. Respiratory function tests showed a lower level also in %DLco in the death group than in the recovery one, although there was no statistical difference. These results suggest that respiratory function, such as PaO_2, %VC and %DLco, may be useful as clinical indices predicting a poor prognosis. The continuous intravenous administration of CyA is probably adequate for DM patients with active IP who show malfunction in respiratory function tests from the early phase of illness.

In conclusion, coadministration of oral CyA with PSL is effective for IP complicating PM/DM, but its efficacy is sometimes insufficient, particularly in rapidly progressive cases. To more consistently and quickly suppress the disease activity of IP, the continuous intravenous administration of CyA might be a potent therapeutic option. Further prospective study of a larger set of patients is necessary in order to clarify the clinical usefulness of this treatment.

Author Contributions

Conceived and designed the experiments: Y. Shimojima, WI, MM. Analysed the data: Y. Shimojima, NK, KT, MM. Wrote the first draft of the manuscript: Y. Shimojima. Contributed to the writing of the manuscript: MM, SI. Agree with manuscript results and conclusions: Y. Shimojima, WI, MM, NK, KT, Y. Sekijima, SI. Jointly developed the structure and arguments for the paper: Y. Shimojima, WI, Y. Sekijima, NK, KT, MM. Made critical revisions and approved final version: WI, MM. All authors reviewed and approved of the final manuscript.

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Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders

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