Early Intervention with Corticosteroids and Cyclosporin A and 2-hour Postdose Blood Concentration Monitoring Improves the Prognosis of Acute/Subacute Interstitial Pneumonia in Dermatomyositis

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ABSTRACT. ***Objective.*** We retrospectively examined the effect of combination therapy with prednisolone and cyclosporin A (CSA) for dermatomyositis (DM) presenting with acute/subacute interstitial pneumonia (A/SIP), the daily CSA dose, and the time from diagnosis of A/SIP to initiation of CSA treatment.

Methods. Subjects were 16 DM patients with A/SIP. Seven patients were treated initially with 1 mg/kg/day prednisolone. When IP was progressive, CSA was added (Group A). Nine patients were treated initially with 1 mg/kg/day prednisolone and 4 mg/kg/day CSA, and 2-h postdose blood concentration (C2) monitoring was used to maintain the serum CSA level at 1000 ng/ml (Group B).

Results. Four of 7 patients in Group A (57%) and 1 of 9 patients in Group B (11%) died of respiratory failure related to IP ($p = 0.06$). Combination therapy with prednisolone and CSA at ≥ 200 mg/day initiated within 15 days of diagnosis was effective for treatment of DM-A/SIP. The trough level (C0) and daily CSA dose were higher in Group B (201.3 ng/ml and 200.0 mg/day, respectively) than in Group A (140.0 ng/ml and 166.4 mg/day). CSA was continued in all patients without severe side effects. No patient died of infection.

Conclusion. Combination therapy of corticosteroids and CSA should be initiated during the early stage of IP. The daily CSA dose should also be controlled with measurement of serum CSA concentration to achieve maximal immunosuppressive effect. C2 monitoring is a useful tool for this control. (First Release Dec 15 2007; J Rheumatol 2008;35:254–9)

Key Indexing Terms:
DERMATOMYOSITIS INTERSTITIAL PNEUMONIA CYCLOSPORIN A
CYCLOPHOSPHAMIDE C2 MONITORING

Dermatomyositis (DM) is a systemic inflammatory form of myositis characterized by the presence of typical cutaneous manifestations: Gottron's sign and heliotrope rash[1-3]. Interstitial pneumonia (IP) is frequently present in DM and is a poor prognostic factor[4,5]. The histology of DM-IP shows the following 3 types: nonspecific IP, cryptogenic organizing pneumonia, and diffuse alveolar damage (DAD). The prognosis differs among these histologic types, and the mortality rate is the highest in patients with DM-IP presenting with DAD[1-3,6-9].

DM patients with IP are classified to 1 of 2 groups on the basis of clinical course: DM with acute/subacute IP (A/SIP) and DM with chronic IP (CIP). DM-CIP responds well to treatment with corticosteroids and has a good prognosis, whereas DM-A/SIP progresses rapidly and has a poor prognosis. Histologically, DM-A/SIP shows nonspecific IP and DAD that are frequently refractory to corticosteroid treatment[10,11]. In DM patients with A/SIP refractory to corticosteroids, respiratory failure progresses over a period of a few weeks or months, leading to a fatal outcome[7-9]. Additional therapy with immunosuppressive drugs such as cyclosporin A (CSA) and intravenous pulse cyclophosphamide (IVCY) has been performed in these patients.

Recent studies have reported the efficacy of combination therapy with corticosteroids and CSA for DM-A/SIP, and we have also experienced success with simultaneous administration of corticosteroids and CSA. However, the survival rate in response to combination therapy ranges from 42% to 69%[6,12-16], and the prognosis of DM patients with A/SIP remains poor. Previous reports have suggested that early intervention with combination therapy is effective for patients with DM-A/SIP. There are no protocols for combination therapy, and the daily

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dose of CSA for DM-A/SIP has not been reported. Our experience suggests that a higher daily dose of CSA is effective.

CSA is also used as an immunosuppressive drug in organ transplantation. To ensure a maximal immunosuppressive effect, the dose of CSA in transplantation is often controlled by monitoring the serum CSA concentration measured 2 h after administration (C2 monitoring). However, there is marked intra- and inter-patient variability in CSA absorption. We instituted the use of a new protocol for combination therapy starting in 2003. CSA treatment is initiated in the early stage of IP, and the dose is controlled with C2 monitoring. The protocol has good results and was well tolerated. We report the outcome of patients with A/SIP before and after application of this protocol and the effect of the daily dose of CSA and the time from diagnosis of A/SIP to initiation of CSA treatment.

MATERIALS AND METHODS

Patients. Subjects were 33 DM patients with IP (29 women, 4 men), who were admitted to Osaka Medical College Hospital during the period December 1995 to October 2005. DM was diagnosed according to the criteria of Bohan and Peter[17,18]. Clinically amyopathic DM (C-ADM) was diagnosed according to the criteria proposed by Sontheimer[19] and Gerami, *et al*[20]. High-resolution computed tomography (HRCT) of the chest was performed and showed IP in 23 patients. Typical images of IP in DM show ground-glass opacity, consolidation, traction bronchiectasis, linear opacity, and less marked honeycomb lung. All patients with IP were also retrospectively evaluated with respect to clinical characteristics, treatment, and outcome.

Diagnosis of DM-A/SIP and DM-CIP. The 23 patients with DM-IP were classified into 1 of 2 groups on the basis of clinical course: DM patients with A/SIP, and DM patients with CIP. DM patients with A/SIP experience an acute onset of respiratory symptoms and a rapid progressive course of a few weeks with respect to respiratory symptoms and laboratory findings such as chest radiograph, chest HRCT, pulmonary function test, and arterial blood pressure. DM patients with CIP have an insidious onset and a slowly progressive course of many weeks or months. Sixteen of the 23 patients with IP were classified as having DM-A/SIP, and the remaining 7 were classified as having DM-CIP.

Treatment. DM-A/SIP patients were treated with early intervention combination therapy and C2 monitoring after 2002. Seven of the 16 DM-A/SIP patients treated before 2002 were assigned to Group A and were treated initially with 1 mg/kg/day prednisolone. When IP was progressive despite the initial treatment, CSA treatment was added. Dyspnea score (Hugh-Jones classification) progressed in 4 of the 7 patients, alveolar-arterial oxygen pressure gradient (A-aDO_2) increased in 5 of the 7 patients, and ground-glass opacity of the chest HRCT progressed in one patient. Nine of the 16 DM-A/SIP patients treated after 2002 were assigned to Group B and were treated initially with 1 mg/kg/day prednisolone plus 4 mg/kg/day CSA. CSA was administered within 15 days of the diagnosis of A/SIP. The dose of CSA was controlled with C2 monitoring to maintain the serum level at 1000 ng/ml. When IP was progressive despite combination of corticosteroids and CSA in both groups, methylprednisolone (MPDN; 1000 mg × 3 days), or MPDN (1000 mg × 3 days) plus IVCY (200–500 mg/day) therapy was added. All patients with DM-CIP were treated with 1 mg/kg/day prednisolone alone. Trimethoprim-sulfamethoxazole was routinely given to all patients to prevent *Pneumocystis jirovecii* pneumonia.

Infection surveillance. For surveillance of infection, complete blood cell counts (CBC) and serum C-reactive protein (CRP) level were measured 2–3 times a week, serum levels of ß-D-glucan and leukocyte cytomegalovirus pp65 antigen (C7-HRP) were measured every 2 weeks, and bacterial cultures of sputum were performed every 2 weeks during first 3 months from the beginning of treatment. After A/SIP improved, CBC and serum CRP level were measured twice a month and serum levels of ß-D-glucan and C7-HRP were measured once a month.

Statistical analysis. The difference in baseline clinical and laboratory findings between Groups A and B was evaluated using Fisher's exact test or the Mann-Whitney U-test. Endpoint-free survival curves were estimated by the Kaplan-Meier method, and significance of differences between Groups A and B was tested with the log-rank test. The results were regarded as significant when the p value was < 0.05.

RESULTS

Clinical and laboratory findings of DM patients with A/SIP before (Group A) and after application of the new treatment protocol (Group B) are listed in Tables 1 and 2, respectively. Group A consisted of 7 patients with a mean age of 64.7 years (range 56–75 yrs): 4 with definite DM and 3 with probable DM. Group B consisted of 9 patients with a mean age of 52.8 years (range 43–68 yrs): 4 with definite DM and 5 with probable DM. The male-to-female ratios in Groups A and B were 1:6 and 3:6, respectively. Although patients in Group B were significantly younger than those in Group A ($p < 0.05$), there were no statistically significant differences in the indices of disease activity of DM-A/SIP between Groups A and B: body temperature, dyspnea score, percentage volume capacity, forced expiratory volume in 1 s/forced vital capacity, DLCO, chest HRCT findings, and A-aDO_2. Poor prognostic factors of DM-IP were described as follows: (1) C-ADM; (2) creatine kinase (CK)/lactate dehydrogenase (LDH) ratio < 2; (3) negative test results with antinuclear antibodies and anti-Jo-1; and (4) presence of pneumomediastinum[13,21]. In Group A, 6 of 7 (86%) patients had C-ADM and a CK/LDH ratio < 2. Pneumomediastinum was present in one (14%) patient. In Group B, 7 of 9 (78%) patients had C-ADM, and 6 patients had a CK/LDH ratio < 2. Clinical features related to the prognosis of DM were similar in both groups. There were no statistically significant differences in the poor prognostic factors of DM-IP between Groups A and B.

Results of combination therapy were markedly better after early intervention and C2 monitoring. Four of 7 (57%) patients in Group A died of respiratory failure due to IP progression. In Group B, 1 of 9 (11%) patients died of gastric cancer despite improvement of IP, and one (11%) patient died of IP progression. The survival curve of patients with A/SIP is shown in Figure 1. There was a trend toward a higher survival rate for patients in Group B than in Group A (89% vs 43%; $p = 0.06$).

The average time from diagnosis of IP to initiation of CSA treatment was 3.8 days in Group B and 20.0 days in Group A ($p = 0.033$). The average time from the onset of respiratory symptoms of IP to initiation of CSA treatment was 64.6 days in Group B and 42.0 days in Group A. The trough level (C0) and daily dose of CSA were higher in Group B (201.3 ng/ml and 200.0 mg/day, respectively) than those in Group A (140 ng/ml and 166.4 mg/day). Although the C2 level in Group A was not measured, the average C2 level in Group B was 976.8

Table 1. Patient profiles (clinical findings).

Group		Age, yrs	Sex	Diagnosis	BT, °F	Hugh-Jones Classification	Complications	CSA Administration (time from respiratory symptoms, days)	CSA Administration (time from diagnosis, days)	CSA Dose, mg/day	CSA Trough/Peak, ng/ml	Additional Treatment	Outcome of IP
A	1	64	F	D	103.6	II	Pneumomediastinum	NT	53	100	240/NT	MPDN, IVCY	Dead
	2	75	F	P	99.3	IV	—	74	30	250	110/NT	MPDN	Dead
	3	62	F	P	99.7	IV	Pneumothorax	32	16	165	150/NT	MPDN	Dead
	4	56	M	D	99.0	V	—	27	3	250	NT/NT	MPDN	Dead
	5	64	F	P	98.1	II	—	34	15	100	100/NT	—	Alive
	6	62	F	D	97.5	IV	—	33	3	200	100/NT	MPDN, IVCY	Alive
	7	70	F	D	99.0	IV	—	52	22	100	NT/NT	MPDN, IVCY	Alive
Average		64.7			99.5			42.0	20.0	166.4	140/NT		
B	1	54	M	P	98.4	V	Gastric cancer**	8	1	200	191/659	MPDN	Dead**
	2	52	M	P	97.9	III	—	47	12	250	150/911	—	Alive
	3	47	M	P	101.5	IV	Pneumomediastinum	55	2	225	164/982	MPDN, IVCY	Alive
	4	68	F	P	98.2	III	—	24	3	175	456/1600	MPDN, IVCY	Dead
	5	43	F	D	99.7	III	—	12	1	175	136/825	MPDN	Alive
	6	44	F	P	98.6	II	—	138	4	200	119/909	—	Alive
	7	50	F	D	100.2	IV	—	35	5	175	199/1096	—	Alive
	8	56	F	D	100.0	III	—	245	5	200	187/814	—	Alive
	9	61	F	D	100.8	V	—	17	1	200	201/987	MPDN, IVCY	Alive
Average		52.8			99.5			64.6	3.8	200.0	201.3/976.8		
p*		0.01	0.59	1.0	0.29	0.54		0.86	0.033	0.59	0.02/NT		

*p < 0.05 between groups, Mann-Whitney U-test for continuous variables, Fisher's exact test for categorical variables (Group A vs Group B). ** Patient died of gastric cancer despite improvement of IP. D: definite DM; P: probable DM; BT: body temperature; IP: interstitial pneumonia; NT: not tested; CSA: cyclosporin A; MPDN: high-dose methylprednisolone therapy; IVCY: intravenous pulse cyclophosphamide.

Table 2. Patient profiles (laboratory findings).

Group		CK/LDH Ratio	Anti Jo-1 Antibody	KL-6, U/ml	VC, %	FEV1/ FVC, %	DLCO, %	Chest HRCT					PaO_2 (torr)	A-aDO_2	Outcome of IP
								Co	GGO	LO	TBE	Ho			
A	1	41/279	Neg	NT	73.1	91.9	42.1	+	+	+	+	–	74.4 (rm air)	29.6	Dead
	2	58/256	NT	NT	95.2	85.2	48.0	+	+	+	+	–	75.1 (rm air)	16.1	Dead
	3	98/295	Neg	NT	NT	NT	NT	+	+	+	+	–	139.1 (O_2 5 l)	109.7	Dead
	4	193/349	Neg	NT	44.6	96.5	24.2	+	+	+	+	–	79.3 (rm air)	15.8	Dead
	5	550/387	Neg	NT	86.3	79.2	30.9	+	+	–	–	–	67.3 (rm air)	39.7	Alive
	6	42/26	Neg	737	93.8	80.5	41.9	+	+	+	–	–	67.9 (rm air)	33.3	Alive
	7	926/329	Pos	489	50.6	87.5	NT	+	+	+	+	–	91.6 (O_2 3 l)	87.2	Alive
Average					73.9	86.8	37.4							47.3	
B	1	1774/814	Neg	3880	79.9	95.5	NT	+	+	+	–	–	53.2 (rm air)	46.5	Dead**
	2	265/344	Neg	2770	48.8	87.1	31.8	+	+	+	+	–	89.4 (rm air)	8.5	Alive
	3	224/876	Neg	1220	53.3	91.5	24.5	+	+	+	+	–	54.1 (rm air)	55.5	Alive
	4	194/425	Neg	512	56.0	70.4	NT	+	+	+	+	–	50.7 (rm air)	51.2	Dead
	5	9100/960	Pos	740	100.5	83.8	67.5	+	+	+	–	–	67.5 (rm air)	29.0	Alive
	6	217/285	Neg	1530	92.9	83.0	59.7	+	–	+	+	–	59.7 (rm air)	42.4	Alive
	7	320/451	Neg	1630	58.9	83.1	42.1	+	+	+	+	–	67.6 (rm air)	19.0	Alive
	8	13574/1463	Pos	337	97.8	77.4	50.4	+	–	+	–	–	75.3 (rm air)	17.7	Alive
	9	490/726	Neg	213	NT	NT	NT	+	+	+	+	–	53.3 (O_2 15 l)	487.0	Alive
Average					73.5	84.0	46.0							84.1	
p*		0.60	1.0		0.83	0.71	0.24							0.95	

*p < 0.05 between groups, Mann-Whitney U-test for continuous variables, Fisher's exact test for categorical variables (Group A vs Group B). ** Patient died of gastric cancer despite improvement of IP. CK: creatine kinase; LDH: lactate dehydrogenase; VC, % volume capacity; FEV1/FVC: forced expiratory volume in 1 s/forced vital capacity; DLCO: carbon monoxide diffusing capacity; HRCT: high-resolution computed tomography; Co: consolidation; GGO: ground-glass opacity; LO: linear opacity; TBE: traction bronchiectasis; Ho: honeycomb; A-aDO_2: alveolar-arterial oxygen pressure gradient; IP: interstitial pneumonia; NT: not tested.

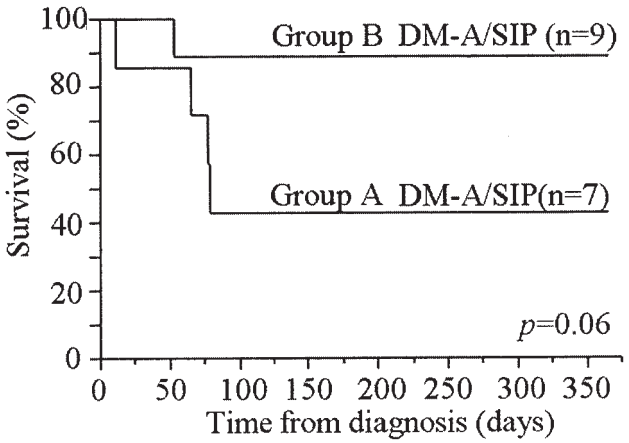

Figure 1. Kaplan-Meier curves comparing survival of patients in Group A and Group B. P value was obtained by the log-rank test. DM-A/SIP: dermatomyositis with acute/subacute interstitial pneumonia.

ng/ml. These results suggested that both CSA dose and time between diagnosis of IP and initiation of CSA treatment are related to the effect of combination therapy with CSA and corticosteroids.

Patient prognosis and daily CSA dose and the time from diagnosis of A/SIP to initiation of CSA treatment were analyzed (Table 3). Three of 7 (43%) patients treated with ≤ 199 mg/day CSA died due to respiratory failure, whereas 2 of 9 (22%) patients treated with ≥ 200 mg/day CSA died. Two of 12 (17%) patients given CSA within 15 days of diagnosis died, whereas 3 of 4 (75%) patients given CSA after 16 days died. DM patients with A/SIP were classified into 4 groups based on the daily CSA dose and the time from diagnosis to CSA treatment. Patients treated with ≥ 200 mg/day CSA within 15 days of diagnosis had a better outcome than did the other groups. Thus, the efficacy of CSA is related to both daily CSA dose and time from diagnosis to CSA treatment.

Additional treatments were also examined (Figure 2). Five of 16 (31%) patients were successfully treated with combination therapy alone. The remaining 11 patients (69%) required additional immunosuppressive therapy because of no or low response to combination therapy. Five patients were treated additionally with MPDN alone, and 3 (60%) died. The remaining 6 patients were treated additionally with MPDN plus IVCY, and 2 (33%) died. MPDN plus IVCY appeared to be more effective as an additional therapy than did MPDN alone.

Table 3. Effects of daily CSA dose and time from diagnosis of A/SIP to initiation of CSA treatment on patient outcome. Data in parentheses are number of patients treated with combination therapy of high-dose methylprednisolone and intravenous pulse cyclophosphamide.

	CSA Administration (time from diagnosis)		
	≤ 15 days	≥ 16 days	Total
	Dead/Alive		
CSA dose, mg/day			
≤ 199	1 (1)/3	2 (1)/1 (1)	3 (2)/4 (1)
≥ 200	1/7 (3)	1/0	2/7 (3)
Total	2 (1)/10 (3)	3 (1)/1 (1)	5 (2)/11 (4)

A/SIP: acute/subacute interstitial pneumonia; CSA: cyclosporin A.

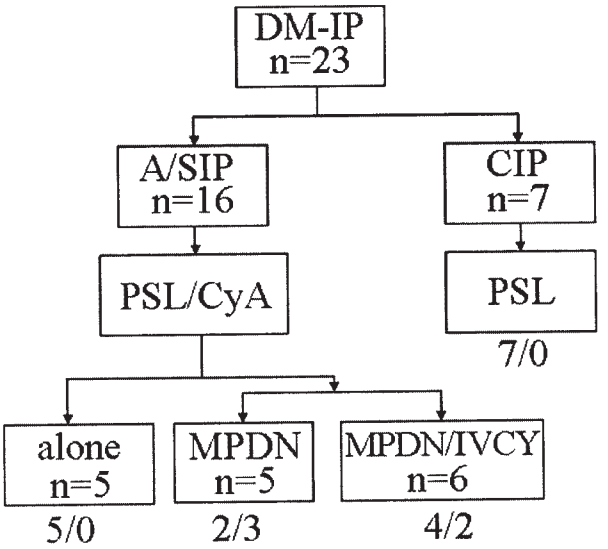

Figure 2. Outcomes of combination therapy and additional treatment. The ratio of alive to dead patients is indicated below the boxes. DM: dermatomyositis; IP: interstitial pneumonia; A/SIP: acute/subacute IP; CIP: chronic IP; PSL: prednisolone; CyA: cyclosporin A; IVCY: intravenous pulse cyclophosphamide; MPDN: high-dose methylprednisolone; alone: combination therapy of PSL and CSA alone.

Adverse events in response to combination treatment with corticosteroids and CSA in 16 DM patients with A/SIP are listed in Table 4. One of 16 (6%) patients showed hypertension and was treated with 40 mg/day nifedipine. Eleven (69%) patients showed increased serum creatinine (Cr) levels. Cr levels were < 2 mg/dl in all patients, and CSA treatment was continued without severe renal damage. Infections were identified in 12 (75%) patients (18 events) and were caused mainly by fungus, herpes virus, or cytomegalovirus. No patient died of infection.

Table 4. Adverse events in 16 DM patients with A/SIP treated with combination therapy.

CSA Side Effects, n = 12		Adverse Infections, n = 18	
Hypertension	1	Fungus	5
Serum Cr, mg/dl	11	Candida	1
> 2.0	0	Pulmonary aspergilloma	2
> 1.5 ≤ 2.0	1	Trichophytosis unguium	2
≥ 1.0 ≤ 1.5	5	Herpes virus	5
< 1.0	5	Herpes zoster	4
		Herpetic corneitis	1
		Bacteria	3
		Bacterial enteritis	2
		Bacterial pneumonia	1
		Cytomegalovirus C7-HRP-positive	5

DM: dermatomyositis; A/SIP: acute/subacute interstitial pneumonia; CSA: cyclosporin A; Cr: creatinine; C7-HRP: leukocyte cytomegalovirus pp65 antigen.

DISCUSSION

DM-A/SIP is a progressive and fatal disease that is treated with a combination of corticosteroids and immunosuppressive drugs such as CSA. The clinical efficacy of combination therapy with corticosteroids and CSA has been reported[13-17]. However, there are no guidelines for combination therapy, and the prognosis of DM-A/SIP has remained poor. We report the successful treatment of DM-A/SIP by early initiation of combination therapy and C2 monitoring. Our results suggest that the efficacy of CSA in treatment of DM-A/SIP is related to both the daily CSA dose and the time from diagnosis of IP to initiation of CSA treatment.

The maximal immunosuppressive effect of CSA occurs during the first 4 h after administration [area under curve (AUC) 0–4][22,23]. Serum concentrations of CSA before and 2 h after administration (C0 and C2, respectively) are measured to ensure a sufficient immunosuppressive effect and to avoid adverse events. C2 monitoring is also performed in organ transplantation to achieve maximal immunosuppressive effect; the C2 level reflects the AUC_{0-4} but not the C0 level[24]. Recent studies have indicated that the C2 level must reach approximately 1000 ng/ml to achieve maximal immunosuppressive effect[24,25].

The daily CSA dose for the treatment of DM-A/SIP ranges from 100 to 300 mg/day[13,15,16,26]. CSA treatment with a C0 level of 160–200 ng/ml is effective[26]. The C0 level, but not the C2 level, is frequently checked. Because the absorption of CSA varies widely between individuals, we have controlled the daily CSA dose with C2 monitoring to maintain the C2 level at 1000 ng/ml since 2003. The survival rate of patients subjected to this C2 monitoring and treatment was improved in our study. The average daily CSA dose and average C0 in the patients not undergoing C2 monitoring were lower than those in patients subjected to C2 monitoring. Therefore, although C2 levels in patients without C2 monitoring were not measured in our study, they were likely lower. The survival rate was higher in patients treated with 200 mg/day CSA. Considering the characteristics of CSA absorption, the daily CSA dose should be controlled in the treatment of DM-A/SIP.

The efficacy of CSA in the treatment of DM-A/SIP was also related to the time from diagnosis of A/SIP to initiation of CSA treatment. It has been reported that CSA was effective in treatment of DM-AIP when given early during the course of IP[16]. Nagasaka, *et al* reported that simultaneous administration of corticosteroids and CSA was more effective than initial treatment with corticosteroids followed by CSA[13]. In our study, initiation of CSA treatment within 2 weeks of diagnosis of A/SIP provided good results. Thus, early administration of CSA minimizes irreversible lung damage in DM-A/SIP.

Some DM patients with A/SIP experienced a rapidly progressive and fatal course despite combination therapy with corticosteroids and CSA in our study. Thirty-one percent of patients were successfully treated with combination therapy alone. The remaining 69% required additional immunosuppressive therapy. MPDN plus IVCY appeared to improve the survival rate of these patients compared to MPDN alone. Recent pilot studies have reported the efficacy of high doses of corticosteroids, CSA, and IVCY in DM patients with fulminant IP[14]. Thus, IVCY might also be useful during the early course of A/SIP refractory to combination therapy of corticosteroids and CSA.

Side effects of CSA include predominantly renal damage, hypertension, diabetes mellitus, and liver damage. Min, *et al* reported that the incidence of side effects increased significantly when the C0 level exceeded 200 ng/ml[27]. When the C2 level was maintained at 1000 ng/ml, the C0 level was approximately 200 ng/ml in our study. One patient showed hypertension, and 11 patients showed increased serum Cr levels. CSA was continued in all patients without severe side effects. Considering the high mortality rate of DM-A/SIP, the efficacy of CSA appears to be relatively more important than its toxicity.

Infection should be considered during combination therapy. Infection due to fungi, *P. jirovecii*, and cytomegalovirus occurs frequently[13,14]. Nagasaka, *et al* reported that respiratory infections were observed frequently during combination therapy, and 75% of patients with respiratory infection died regardless of IP progression[13]. Kameda, *et al* reported that repeated surveillance could detect early-stage infection and decrease the number of patients who die of infection[14]. In our study, infection was observed in 12 of 16 (75%) patients (18 episodes) during combination therapy. Fungal and viral infections were observed frequently, but *P. jirovecii* infection was not. None of the patients died of infection. Thus, repeated surveillance should be performed, and trimethoprim-sulfamethoxazole should be given routinely to all patients.

We have reported successful treatment of DM-A/SIP by early combination therapy and C2 monitoring. This protocol was effective and well tolerated. Combination therapy should be applied during the early stage of IP (within 15 days of diagnosis of A/SIP), as described. Because of variable CSA absorption, the daily CSA dose should also be controlled with measurement of serum CSA concentration to achieve a maximal immunosuppressive effect. C2 monitoring is a useful tool for this control. Further studies are needed to establish a standard protocol for the treatment of DM patients with A/SIP.

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