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ORIGINAL ARTICLE

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Cyclosporin A therapy for interstitial pneumonitis associated with rheumatic disease

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Abstract To determine the efficacy of cyclosporin A (CysA) for the treatment of steroid-resistant interstitial pneumonitis (IP), we enrolled 25 patients with various rheumatic diseases and steroid-resistant IP in a pilot study [4 patients with rheumatoid arthritis (RA), 2 with systemic lupus erythematosus (SLE), 11 with polymyositis/dermatomyositis (PM/DM), 4 with systemic sclerosis (SSc), 1 with mixed connective tissue disease (MCTD), 3 with Sjögren syndrome (SS)]. Twelve patients (48%) showed a persistent response to CysA therapy, and 7 of them had PM/DM, including so-called amyopathic DM. Patients with a persistent response had moderately elevated lactate dehydroxygenase (LDH) levels, whereas patients who died had much higher LDH levels and hypoxia. Even patients with low blood levels of CysA achieved a persistent response. In responding patients, the symptoms, chest X-ray findings, arterial oxygen tension, and LDH level all improved after less than 4 weeks. In conclusion, CysA seem to be useful for treating patients with steroid-resistant IP, whose duration is short and severity is mild.

Key words Cyclosporin A · Interstitial pneumonitis (IP) · Polymyositis/dermatomyositis (PM/DM) · Systemic sclerosis (SSc)

Introduction

Cyclosporin (CysA) is widely used for the control of rejection after organ transplantation,[1] and this drug is also used to treat autoimmune diseases such as Behçet's disease[2,3] or psoriasis.[4–6] Among the rheumatic diseases, some authors have used CysA to treat rheumatoid arthritis (RA),[7] systemic lupus erythematosus (SLE),[8] systemic sclerosis (SSc),[9] and polymyositis/dermatomyositis (PM/DM),[10–13] with efficacy being noted for various types of organ involvement. However, further information is needed about which organs respond to CysA therapy.

Interstitial pneumonitis (IP) has an important influence on the prognosis of rheumatic disease and it is a major cause of death in patients with SSc or PM/DM. The manifestations of IP vary widely. For example, it is slowly progressive in SSc and steroids show little efficacy, whereas it is rapidly progressive in PM/DM or SLE and a response to steroids can be expected. Although there is considerable variation in efficacy, the mainstay of therapy for IP in patients with rheumatic disease has been steroids. Unfortunately, some patients show resistance to steroids and they often have a poor prognosis. Recently, we and others have demonstrated the efficacy of CysA for steroid-resistant IP in patients with some kind of rheumatic disease.[10–12,14–16] However, all of the previous studies were only case reports; therefore, the efficacy of this agent for IP has not been clarified and there has been no assessment of the long-term prognosis.

In the present study, we used CysA to treat 25 patients with various rheumatic diseases and steroid-resistant IP. We investigated the efficacy of CysA therapy in relation to the condition of IP and the dose administrated, as well as the outcome after long-term follow-up.

Patients and methods

Patients

This was a pilot study performed on 25 patients who were selected as follows based on the following criteria: (1) they had various rheumatic diseases and IP; (2) they had IP that showed steroid-resistance or their steroid dose could not be increased sufficiently because of side effects. There were 4 patients with RA, 2 with SLE, 11 with PM/DM [including 5

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cases of amyopathic DM (ADM)], 4 with SSc, 1 with mixed connective tissue disease (MCTD), and 3 with Sjögren syndrome (SS). The clinical profile of these patients is shown in Table 1. IP was classified as acute/subacute or chronic, with acute/subacute disease being defined by the progressive dyspnea, X-ray, changes, and hypoxia lasting for less than 1 month. Most patients received 20–60 mg/day of prednisolone and some patients were given steroid pulse therapy. Steroid resistance was defined as follows: (1) no efficacy of steroid therapy (predonisolone 0.5–1 mg/kg/day) after 4 weeks, or (2) difficulty in tapering steroids because of the risk of relapse. However, CysA was started earlier if there was a risk of death from IP. If the improvement was recognized, the dose of steroids decreased by 10% per 2 weeks. None of the patients received methotrexate or cyclophosphamide.

Methods

The efficacy of CysA therapy was assessed after 6 weeks, because most responses occurred by this time. If more than two of the following changes were recognized, the therapy was defined as "effective": (1) improvement of symptoms, (2) an increase of PaO_2 by >10 mmHg, (3) an increase of %DLco or %VC by >10%, (4) improvement of the findings on the chest X-ray films (a decrease of the chest X-ray score by more than two points, see following) or computed tomography (CT) scans, (5) a decrease of the steroid dose by more than 10%, or (6) a decrease of the lactate dehydogenase (LDH) level by more than 25%. Patients who died after less than 6 weeks of therapy were defined as "early deaths" and were assigned to the dropout group. The duration of the response to therapy and the short-term prognosis were assessed after 6 months. Patients in whom CyA showed efficacy after 6 months were defined as having a "persistent response," whereas patients with relapse before 6 months were defined as having a "transient response." The patients were then divided into three groups based on the response and outcome: Group A was alive with a persistent response after 6 months, Group B was alive with a transient or no response at 6 months, and Group C was dead after a transient response, no response, or had dropped out before 6 months. The long-term prognosis was also assessed after 1, 2, 3, 4, and 5 years.

The severity of dyspnea was assessed with Borg's score,[17] as follows: 0, no symptoms; 1, very mild dyspnea; 2, mild dyspnea; 3, moderate dyspnea; 4, slightly severe dyspnea; 5, severe dyspnea; 6–8, very severe dyspnea; 9, extremely severe dyspnea; and 10, maximum dyspnea. Chest X-ray films were scored using the method proposed by the Japanese Ministry of Health, Labor and Welfare Autoimmune Diseases Research Committee. This score is assigned as follows: 0, no abnormalities; 1, infiltrates affecting ≦1/4 of the lung fields; 2, infiltrates affecting 1/2 of the lung fields; 3, infiltrates affecting 3/4 of the lung fields; and 4, infiltrates affecting all of the lung.

Differences between the patients with and without a response to CysA were investigated by Fisher's exact test.

Results

Response to CysA and short-term prognosis of IP patients

Fifteen (60%) of the 25 patients showed a response to CysA after 6 weeks and 12 patients (85.7% of the patients with an initial response and 48% of all patients receiving CysA) showed the maintenance of the response for more than 6 months (persistent response) (Table 2). These 12 patients comprised 7 patients with PM/DM (including 4 cases of ADM), 1 with SLE, 2 with SSc, and 2 with SS. Three patients (1 each with RA, PM, and SSc) only showed a transient response to CysA, and two of them (1 each with RA and PM) died after the relapse of IP. Four patients (1 each with RA, SLE, SSc, and MCTD) showed no response to CysA after 6 weeks, and 3 of them (1 each with RA, SLE, and SSc) died of IP. Six patients dropped out of the study and died: three due to early death from respiratory failure caused by IP (one with RA and two with PM/DM) and three because of side effects (infection, leukopenia, and liver dysfunction in one patient each). Three of the patients (one each with RA, DM, and SS) who dropped out due to

Table 1. Clinical profile of the subjects

	RA	SLE	PM/DM	SSc	MCTD	SS
No.	4	2	11	4	1	3
Male	2	0	1	1	0	0
Female	2	2	10	3	1	3
Age (years)	52.1 ± 8.7	38.3 ± 6.2	38.9 ± 12.1	43.8 ± 9.1	42	38.6 ± 8.7
Disease duration (years)	7.2 ± 3.8	7.8 ± 2.4	3.4 ± 1.8	5.1 ± 2.7	2	2.6 ± 1.4
Time from IP onset (years)	1.4 ± 0.7	1.9 ± 1.5	0.9 ± 0.8	4.9 ± 1.9	1	0.8 ± 0.7
Type of IP						
acute/subacute	4	2	11	2	0	3
chronic	0	0	0	2	1	0

Mean ± standard deviation
RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; PM/DM, polymyositis/dermatomyositis; SSc, systemic sclerosis; MCTD, mixed connective tissue disease; SS, Sjögren syndrome; IP, interstitial pneumonitis

Table 2. Response to CysA therapy

	Persistent response	Transient response		No response		Dropped out and died
		alive	dead	alive	dead	
RA ($n = 4$)	0	0	1	0	1	2
SLE ($n = 2$)	1	0	0	0	1	0
PM/DM ($n = 11$)	7	0	1	0	0	3
SSc ($n = 4$)	2	1	0	0	1	0
MCTD ($n = 1$)	0	0	0	1	0	0
SS ($n = 3$)	2	0	0	0	0	1
Total	12	1	2	1	3	6

CysA, cyclosporin A

Table 3. Relationship between the response and clinical findings

	Group A[a] ($n = 12$)	Group B[b] ($n = 2$)	Group C[c] ($n = 11$)
Disease duration (months)	23 ± 35.2	42 ± 30	55.4 ± 78.6
Duration of steroid therapy (months)	23 ± 35.2	22 ± 22	38.3 ± 57.1
Maximum steroid dose (mg/day)	51.2 ± 12.2	35.0 ± 5.0*	57.3 ± 14.1
Dose of steroids at the start of CysA therapy (mg/day)	51.2 ± 12.2	35.0 ± 5.0*	57.3 ± 14.1
Onset to CysA therapy (weeks)	5.4 ± 7.1	1.5 ± 0.5	3.6 ± 3.1
LDH (U)	690.2 ± 239.8	443 ± 39**	1174 ± 462.3***
PaO_2 (mmHg)	67.8 ± 14.6	69.2 ± 17.5	56 ± 14.8****

LDH, lactate dehydroxygenase
* Group B versus A, C: $P < 0.05$
** Group B versus A: $P < 0.01$
*** Group C versus A: $P < 0.01$
**** Group C versus A: $P < 0.05$
[a] Alive with a persistent response
[b] Alive with a transient or no response
[c] Dead after transient/no response or dropout

side effects subsequently died of IP, because there was no other therapy available. However, the death of these patients was not thought to related to toxicity of CysA.

Relationship between efficacy and laboratory data on CysA level

The patients were divided into three groups based on their response to CysA therapy (group A; $n = 12$, group B; $n = 2$, group C; $n = 11$) as previously described, and the differences of clinical manifestations and laboratory findings among these groups were assessed. As shown in Table 3, the patients in Group A (persistent response) tended to have a shorter duration of illness when compared with the other groups, although there was no significant difference. There were no differences among the groups in the time between the onset of IP and the start of therapy.

However, group A had a significantly higher LDH level than did group B and a significantly lower LDH level than did group C, whereas group C had a significantly lower PaO_2 level than did the other groups. Thus, efficacy of CysA was recognized in patients with a shorter duration of illness, a moderate increase of LDH, and no hypoxia. Gallium scintigraphy was performed in four patients, and one who showed accumulation had a persistent response to CysA. In one patient with SS and a persistent response, open lung biopsy was performed and nonspecific interstitial pneumonitis was diagnosed histologically. Bronchoalveolar lavage was not performed in any of the patients. Although Group B had a significantly lower maximum steroid dose and dose of steroid at the start of CysA therapy than did either Group A or Group C (both $P < 0.05$), this related to the fact that patients belonging to Group B had SSc and MCTD and slowly progressive IP.

Table 4. Relationship between response to therapy and the trough level of cyclosporin

	<50	50–100	100–150	150–200 (ng/ml)
Group A ($n = 11$)	3	4	3	1
Group B ($n = 2$)	0	0	1	1
Group C ($n = 8$)	0	2	3	3

We also examined the relationship between the trough CysA concentration and the response to CysA. As shown in Table 4, even patients with a level of less than 100 ng/ml were among the responders.

Clinical course and long-term prognosis of responders

The changes of various parameters were examined in 8 of 12 patients with a persistent response (Group A). Dyspnea (Borg's score) improved after 8 weeks in most patients, as shown in Fig. 1. Along with the improvement of symptoms,

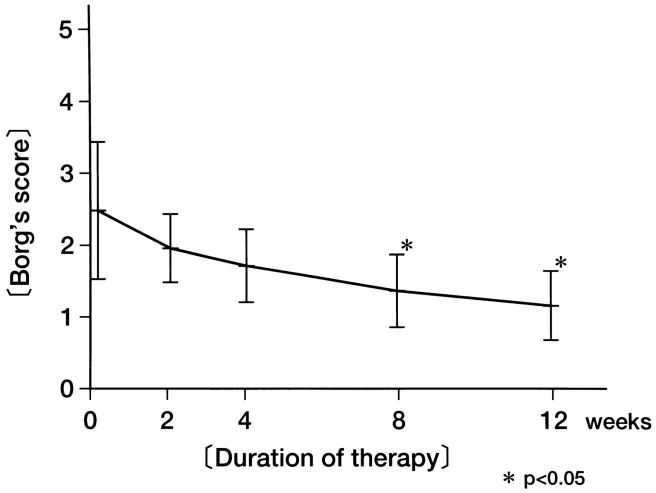

Fig. 1. Changes of symptoms shown by Borg's score. The *vertical bars* represent the mean ± standard deviation. Improvement was recognized after 8 weeks, and a significant change was recognized at 8 and 12 weeks (both $P < 0.05$) (2.5 ± 0.9 → 1.6 ± 0.4 at 8 weeks, 1.5 ± 0.4 at 12 weeks)

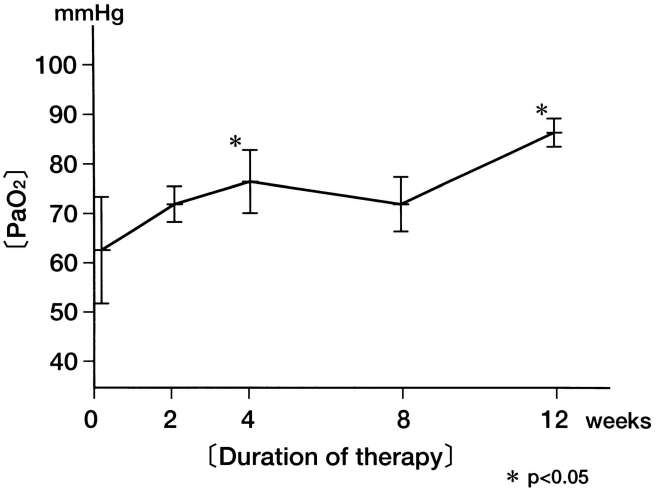

Fig. 2. Changes of PaO_2. The *vertical bars* represent the mean ± standard deviation. Improvement was recognized after 4 weeks, and a significant change was recognized at 4 weeks and 12 weeks (both $P < 0.05$) (62.1 ± 10.3 → 75.2 ± 6.2 at 4 weeks, 85.0 ± 3.7 at 12 weeks)

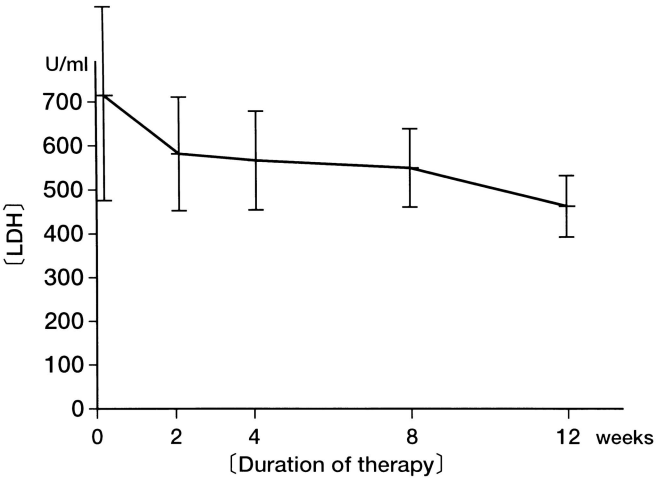

Fig. 3. Changes of lactate dehydroxygenase (*LDH*). The *vertical bars* represent the mean ± standard deviation. Improvement was recognized after 2 weeks, but there was no significant change

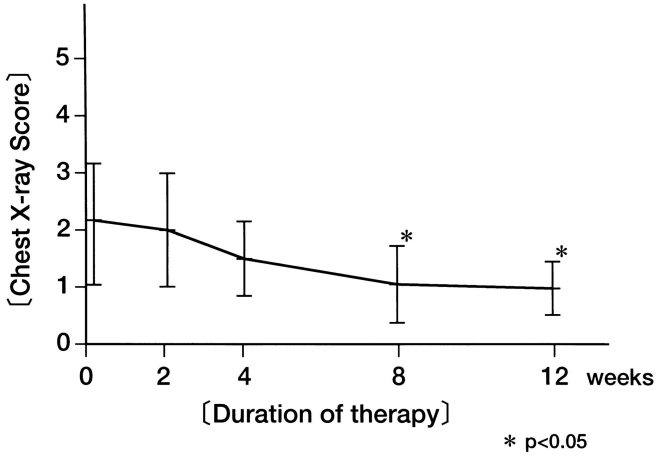

Fig. 4. Changes of the chest X-ray score. The chest X-ray score reflects the extent of interstitial pneumonitis. The *vertical bars* represent the mean ± standard deviation. Improvement was recognized after 8 weeks, and a significant change was recognized at 8 and 12 weeks (both $P < 0.05$) (2.2 ± 1.1 → 1.1 ± 0.8 at 8 weeks, 1.0 ± 0.4 at 12 weeks)

the PaO_2 increased after 4 weeks, as shown in Fig. 2. Although the LDH level decreased earlier than the improvement of symptoms and PaO_2, there was no significant decrease (Fig. 3). Improvement of chest X-ray findings was recognized after 8 weeks (Fig. 4), and the findings on computed tomography showed a similar course (data not shown).

We could further examine the long-term prognosis in 11 of 12 patients (one patient was transferred to another hospital). These 11 patients were all followed for more than 6 months, and the longest duration of follow-up was 5 years. Treatment was stopped in one patient because of an increased creatinine level, and death from the relapse of IP occurred after 10 months. Another patient suffered the relapse of IP after 1 year and died after 2 years. The remaining 9 patients have all lived for more than 1 year, although 1 patient had a relapse after 1 year. All surviving patients continue to receive CysA and show no side effects of this therapy.

Discussion

IP can be caused by various factors, including drugs such as bleomycin or methotrexate; radiation; viruses such as cytomegalovirus; allergy; and rheumatic diseases. Immunological mechanisms are closely related to the onset of IP in association with rheumatic disease, but are also involved in IP with other causes. Humoral immunity is mainly involved in the pathogenesis of IP. In brief, the production of autoan-

tibodies, the formation of immune complexes, and the activation of complement are important in the pathogenesis of various rheumatic diseases, especially SLE, RA, and polyarteritis nodosa. However, some components of cellular immunity, such as cytotoxic T cells and natural killer cells, are also involved. For example, a role of cytotoxic T cells has been reported in the pathogenesis of PM.[18,19] As the cause/pathogenesis of IP, a relationship with cytotoxic T cells has also been reported. For example, activated CD8-positive T cells are increased in patients with PM/DM and IP,[20] whereas interleukin-12, interferron-γ, and activated CD8 T cells are increased in patients with SLE and IP.[21] Thus, activation of T cells (especially cytotoxic T cells) seems to be important in the pathogenesis of IP.

Although steroids are the main therapy for IP in patients with rheumatic diseases (especially PM/DM, SLE, or SS), some patients show resistance to steroids and need additional therapy. In such cases, immunosuppressants have commonly been used. However, some immunosuppressive agents (especially methotrexate and cyclophosphamide) have pulmonary toxicity; therefore, there is a limited choice available for the treatment of IP. CysA does not show pulmonary toxicity and acts on T cells, suggesting that it could be effective for steroid-resistant IP. In fact, CysA has already been used to treat some patients with steroid-resistant IP and its efficacy has been recognized. However, these patients have shown various responses, so the efficacy of CysA needs to be assessed in a larger group of subjects.

In the present study, we used CysA to treat 25 patients who had IP associated with various rheumatic diseases. Efficacy was recognized in patients with a moderate increase of LDH, but not in those with normal or high LDH levels or in those with severe hypoxia. Because we performed the study to determine the indications for CysA therapy, patients with various underlying diseases and different condition of IP were enrolled. When these patients were divided into three groups based on the outcome of treatment, and their clinical findings were compared, the following features were recognized. The patients with a persistent response had significantly higher LDH levels when compared with survivors who showed transient or no efficacy, and patients who died had significantly higher LDH levels or lower PaO_2 values when compared with the other groups. These results suggest that CysA should be used to treat patients with active or subacute IP and mild hypoxia. Most of the patients with a persistent response had PM/DM, which is frequently associated with acute progressive IP. Some patients with SSc, which is generally associated with chronic IP, also showed persistent responses and this finding supported our previous report.[22] However, because half of the patients with SSc had a transient or no response, we believe that IP with SSc generally had poor efficacy for CysA. Thus, we should determine the indications for CysA based on the underlying disease and the features of IP itself. We should also remember that patients with hypoxia are unlikely to show a response to CysA and have a high risk of early death. Because the trough levels of CysA measured in these patients were not as high, it is possible that the lack of efficacy was related to an inadequate dose of drug. Therefore, the dosage of CysA in patients with severe hypoxia should be considered further.

We have also used azathioprine as an immunosuppressant to treat patients with steroid-resistant IP, but CysA seems to achieve an earlier response than does this agent. In fact, the response to azathioprine generally occurs after 2 months, whereas in the present study we found a response to CysA appeared after less than 1 month. On the other hand, we do not use intravenous cyclophosphamide(IVCY), which also shows rapid efficacy, because of its plumonary toxicity; thus, we cannot investigate a comparison of CysA and IVCY.

Efficacy of CysA was recognized in some patients with ADM. As described in previous reports,[23,24] most patients with ADM and acute progressive IP die after less than 1 year; therefore, new therapy has been needed for IP associated with this disease. Some recent reports[25] have suggested the efficacy of CysA in ADM, we also treated five patients with ADM plus IP in the present series and four of them improved. Three of these patients had acute progressive IP, but lived for more than 1 year. These results suggest the possibility that CysA may be a useful therapy for acute progressive IP associated with ADM.

Interestingly, efficacy was recognized at a low blood concentration of CysA (less than 150 ng/ml). We recently reported similar results in a small series,[26] and the present study confirms that report. Because CysA can have adverse effects on renal function, efficacy at low doses would be desirable and the present study suggested that high doses may not be needed for the treatment of IP. However, low blood concentrations are below the so-called effective dose, suggesting that a different mechanism of action might be involved at this low concentration.

This study had the following limitations. First, the extent of prior steroid therapy was not assessed, although this point is potentially very important. In fact, the steroid dose of the patients with a transient response or no response (Group B) was significantly lower than in the other groups. A controlled trial would be needed to resolve this problem, but because the study would have to be performed in patients with a very poor prognosis, this would give rise to ethical and practical difficulties. Second, the optimum duration of CysA therapy was not determined. In this study, 11 patients showed a response for more than 6 months, 8 patients survived for more than 1 year without relapse (all of them continued to receive CysA long term), and 1 patient died from the relapse of IP after ceasing therapy. These results may suggest that continuous CysA therapy is needed to maintain the improvement of IP. However, because the number of patients was small and the duration of follow-up was relatively short, the need for long-term therapy and its adverse effects could not be assessed in this study. Therefore, a further multicenter study will be needed. Third, some patients suffered a relapse and died of IP. Among two patients with a transient response, one relapsed after 2 months when the steroid dose was reduced, and one patient on maintenance steroid therapy suffered a relapse after 6 months. In addition, two patients with a persistent response also relapsed after 8 months and 1 year; thus, relapse oc-

curred after a short or longer period and was difficult to predict. Therefore, we cannot relax our vigilance, even if patients show persistent responses to CysA therapy. Finally, most of the nonresponders and dropouts died, suggesting that new therapy other than CysA is also needed for steroid-resistant IP.

In conclusion, IP has an important influence on the prognosis of rheumatic disease, and this study showed that CysA was effective for some patients with steroid-resistant IP, whose duration is short and severity is mild, although, unfortunately, other patients showed no response and died. Therefore, CysA may be able to contribute to an improvement of the prognosis of patients with rheumatic diseases.

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