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# Efficacy of combination treatment with cyclosporin A and corticosteroids for acute interstitial pneumonitis associated with dermatomyositis

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**Abstract** Interstitial pneumonitis (IP) associated with polymyositis and dermatomyositis (PM/DM) is a serious complication that affects prognosis. We therefore undertook a retrospective multicenter study to examine the efficacy of a combination treatment with cyclosporin A (CsA) and corticosteroids. Fifty-three IP patients with PM/DM (9 PM, 44 DM) were analyzed. Thirty-two patients treated with CsA plus corticosteroids (9 PM, 23 DM) were included in the study. Four parameters, i.e., subjective symptoms, ausculatory sound, chest radiographs, and respiratory index, were serially evaluated. A general evaluation was performed 4 weeks after the start of the combination treatment. All patients with PM and chronic IP with DM, and 52% of those with acute IP with DM were graded as better than "partially effective" in the general evaluation. In contrast, all patients graded as "progressive" in the general evaluation had acute IP with DM. It is of note that in acute IP with DM, the survival rate of the group primarily treated with CsA and corticosteroids from the early stage of their disease was significantly higher than that of the group initially treated with corticosteroids alone ($P = 0.049$). In conclusion, a combination treatment of CsA and corticosteroids from the early stage of disease may be advantageous for patients with IP with PM/DM, especially acute IP with DM.

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## Introduction

Polymyositis (PM) and dermatomyositis (DM), which are systemic inflammatory diseases characterized by muscular involvement with or without cutaneous manifestation,[1] also affect other organs, including lung, gastrointestinal tract, and heart, with high mortality rates.[2,3]

Interstitial pneumonitis (IP) is a frequent, serious complication among the pulmonary involvements seen in PM/DM. The involvement of IP in PM/DM has been reported to range from 5% to 42% of cases,[4–8] and is one of the common causes of death.[8–10] Although anti-inflammatory and immunosuppressive drugs, including corticosteroids and immunosuppressants, have been widely used for IP with PM/DM, a significant number of cases are refractory to such treatment, a situation that might reflect the heterogeneity of the disease. It is of note that rapidly progressive IP with DM, showing low or absent creatine kinase (CK) elevation and negative anti-Jo-1 antibody, is resistant to conventional treatments and is associated with a poor prognosis.[4,11–14] There is currently no established treatment for this unique subset of the disease.

Recent reports in the literature have noted that cyclosporin A (CsA) in combination with corticosteroids is effective in treating corticosteroid-resistant IP associated with PM/DM.[15–17] Our previous nation-wide survey on the treatment of IP with connective tissue diseases showed that CsA plus corticosteroids was effective for acute IP with PM/DM.[18] However, the number of IP cases associated with PM/DM is not large enough to design a prospective randomized clinical trial to assess the efficacy of a combination treatment with CsA and corticosteroids. We therefore undertook a retrospective multicenter study to examine the efficacy of the combination treatment for IP with PM/DM. We also attempted to determine which subset of the disease responded to this treatment. Our study indicated that the

simultaneous use of CsA and corticosteroids is effective in treating IP with PM/DM, especially acute IP with DM.

## Materials and methods

### Patients

This work was carried out as part of a study by the Autoimmune Disease Research Committee, Ministry of Health, Welfare and Labour, Japan. Questionnaires were sent to 32 hospitals in Japan which have rheumatology divisions, and based on the responses, we reassessed the data of CsA-treated IP patients with PM/DM as well as the data of acute IP patients with DM initially treated with corticosteroids between 1989 and 2000. We were able to enroll 53 patients (9 PM, 44 DM) retrospectively with sufficient data for analysis. PM/DM was diagnosed according to the criteria of Bohan and Peter.[1] Patients who had characteristic rashes such as heliotropic rash, Gottron's papules, or Gottron's sign were diagnosed as having DM. Patients whose rashes were characteristic of DM and who had normal CK levels were diagnosed as having amyopathic dermatomyositis according to the criteria of Euwer and Sontheimer.[19] These patients were analyzed with the DM patients. The diagnosis of IP was made according to clinical symptoms that included nonproductive cough and dyspnea, fine crackles on ausculatory examination, deteriorated arterial blood oxygen pressure ($PaO_2$), and a reticular pattern on chest radiographs. Computed tomography was performed for 50 of 53 patients, and showed ground-glass opacities and/or linear shadows in all 50 cases. Pulmonary function tests were given to 32 of 53 patients, and 31 patients showed a decreased vital capacity and/or carbon monoxide diffusion capacity. IP was classified as acute or chronic based on the clinical course of subjective symptoms, and changes in physical and laboratory findings as determined by at least two independent physicians in each institution. As in a previous study,[18] the acute type was defined as having an acute onset of subjective symptoms, including cough and dyspnea, and a rapidly progressive course of a few weeks, whereas the chronic type was defined by an insidious onset and a slowly progressive course of many weeks. Patients who had malignancy, respiratory infection, or drug-induced pneumonitis at the time IP was diagnosed were excluded from the study.

Thirty-two patients treated with CsA plus corticosteroids (9 PM, 23 DM) were included in the study. CsA was administered orally to maintain serum trough levels between 100 and 200 ng/ml, and the resultant doses of CsA were within the range 147–156 mg/day on average (see Table 1). CsA was used in combination with corticosteroids or added to basal administrations of corticosteroids without any change in the corticosteroid dosage. Patients who failed to be treated with CsA for at least 2 weeks, and those treated with CsA plus other immunosuppressants during the first 4 weeks, were excluded from the group that received CsA plus corticosteroids.

The remaining 21 patients had acute IP with DM and were initially treated with corticosteroids alone. When IP was progressive in spite of the initial treatment, either a 500–1000 mg cyclophosphamide (CPA)-pulse or 50–100 mg/day oral CPA treatment was subsequently given. Methylprednisolone (mPSL)-pulse therapy (500 or 1000 mg mPSL for 3 days) was also administered. These decisions were made by the individual physician in charge, and written consent forms that accorded with the Declaration of Helsinki were obtained from the patients.

### Assessment of IP patients with PM/DM

The four parameters of subjective symptoms (dyspnea according to the Hugh–Jones classification[20]: 0, I; 1, II; 2, III; 3, IV; 4, V; nonproductive cough: 0, none; 1, 1–5 times/day; 2, 6–10 times/day; 3, more than 10 times/day; sputum: 0, none; 1, a little; 2, observed almost all day; 3, observed all day); ausculatory sound (fine crackles: 0, none; 1, mild; 2, moderate; 3, severe); chest radiographs (number of quadrants[21] with reticular pattern: 0, none; 1, 1 quadrant; 2, 2 quadrants; 3, 3 quadrants; 4, 4 quadrants); and respiratory index ($PaO_2$/fraction of inspired oxygen ($FiO_2$))[21] were serially scored before and 4 weeks after treatment according to the established criteria[18,22] as modified in this unit. We regarded data obtained from 3 to 5 weeks after treatment as 4 weeks' data when data were not available at 4 weeks. For subjective symptoms, ausculatory sound, and chest radiographs, we defined an improvement as a decrease of more than 1 point, exacerbation as an increase of more than 1 point, and no change as no difference. For respiratory index, improvement was defined as an increase of more than 50, exacerbation as a decrease of more than 50, and no change as within the range $-50$ to 50.

A general evaluation was performed 4 weeks after the start of the combination treatment using the modified criteria.[18,22] We defined "remarkably effective" as an improvement in at least three parameters, "moderately effective" as an improvement in two parameters, "partially effective" as an improvement in only one parameter, "no change" as showing no improvement, and "progressive" as showing a significant worsening in any of the parameters. The outcome was assessed at the latest time each physician examined an IP patient, and "remission" was defined as an improvement in all parameters without exacerbation under maintenance treatment. The follow-up period was calculated as the period between the day when the combination treatment or initial corticosteroid treatment was started and the latest time a physician interviewed the patient.

The CK/lactate dehydrogenase (LDH) index was determined as the corrected CK′/LDH′ (CK′ and LDH′ were corrected values in which each value was divided by the normal maximum value of each institution). We devised this index to delineate IP patients with normal CK levels in PM/DM because refractory IP has been reported to occur in a subset of patients with normal CK levels.[11,17,23] The serum concentration of KL-6 antigen was measured by enzyme immunoassay (Eisai, Tokyo, Japan). Pulmonary function

**Table 1.** Features of IP patients with PM/DM treated with CsA plus corticosteroids

| | PM | | DM | |
|---|---|---|---|---|
| | Acute | Chronic | Acute | Chronic |
| No. of cases | 1 | 8 | 17 | 6 |
| Male/female | 0/1 | 0/8 | 5/12 | 2/4 |
| Age (years) | 46 | 49.4 ± 9.52 | 47.5 ± 11.0 | 56.7 ± 6.29 |
| CK/LDH index | 6.05 | 4.60 ± 5.46 | 0.779 ± 1.17* | 5.23 ± 5.41 |
| Anti-Jo-1 antibodies | 1/1 | 2/8 | 0/15 | 1/6 |
| Dose of CsA (mg/day) | 150 | 147 ± 38.8 | 156 ± 48.8 | 156 ± 35.1 |
| Oral corticosteroids (PSL mg/day) | 40 | 44.4 ± 19.7 | 46.5 ± 19.9 | 55 ± 13.8 |
| mPSL pulse | 1 | 2 | 14** | 0 |

Plus-minus values are means ± SD
IP, interstitial preumonitis; PM, polymyositis; DM, dermatomyositis; CsA, cyclosporin A; CK, creatine kinase; LDH, lactate dehydrogenase; PSL, prednisolone; mPSL, methylprednisolone
* $P < 0.01$ by the Kruskal–Wallis test and the Mann–Whitney *U*-test (acute IP with DM versus chronic IP with PM/DM)
** $P = 0.0011$ by $\chi^2$ analysis

tests and bronchoalveolar lavage (BAL) were carried out according to standard protocols.[24,25] After signed consent forms had been obtained, a lung biopsy was performed to determine the treatment regimen and also to predict the prognosis. The indication for a lung biopsy was determined by the physician in charge.

### Statistical analyses

Statistical analyses were done using StatView 5.0 software (SAS Institute, Cary, NC, USA). Survival curves were drawn using the Kaplan–Meier method. $\chi^2$ analysis, the Kruskal–Wallis test, the Mann–Whitney *U*-test, the Spearman rank correlation coefficient, and the log-rank test were used for the statistical analyses. $P < 0.05$ was considered to be significant.

## Results

### Clinical features of IP patients with PM/DM treated with CsA plus corticosteroids (Table 1)

Thirty-two patients treated with CsA plus corticosteroids (9 PM, 23 DM) were analyzed in four subsets: acute IP with PM ($n = 1$), chronic IP with PM ($n = 8$), acute IP with DM ($n = 17$), and chronic IP with DM ($n = 6$). The PM patients were all female and had a higher CK/LDH index and a high ratio of positive anti-Jo-1 antibodies (3 of 9). In contrast, acute IP patients with DM ($n = 17$) had some unique clinical features, including an increased ratio of males, a lower CK/LDH index ($P < 0.01$, Kruskal–Wallis test and Mann–Whitney *U*-test for acute IP with DM vs. chronic IP with PM and DM, respectively), negative anti-Jo-1 antibodies, and frequent episodes of mPSL-pulse therapy ($P = 0.0011$, $\chi^2$ analysis). The clinical features of chronic IP patients with DM were similar to those of PM patients except for the sex ratio. There were no statistically significant differences in the doses of CsA and corticosteroids among the patient groups.

### General evaluation after 4 weeks of combination treatment with CsA and corticosteroids, and outcome (Table 2)

The acute IP patient with PM ($n = 1$), who was graded "remarkably effective" in the general evaluation, went into remission in the outcome. In chronic IP with PM ($n = 8$), 3 patients (37.5%) were graded as "remarkably effective," 2 patients (25%) as "moderately effective," and 3 patients (37.5%) as "partially effective" in the general evaluation. All patients improved within 1 month, and 5 of 8 (62.5%) obtained remission.

Seventeen patients who had acute IP with DM were evaluated very thoroughly. In the general evaluation, 3 patients (18%) were graded as "remarkably effective," 5 patients (28%) as "moderately effective," 1 patient (6%) as "partially effective," 3 patients (18%) as "no change," and 3 patients (18%) as "progressive." Two patients (12%) died. In terms of outcome, a majority of "remarkably effective" or "moderately effective" patients (5 of 8) obtained remission. However, of 3 "moderately effective" patients, one patient died of progressive IP, one of hepatitis B, and one of aspiration pneumonia. The "partially effective" patient obtained remission after the simultaneous use of 500 mg CPA-pulse treatment with CsA and corticosteroids. Furthermore, two patients in the "no change" group discontinued the combination treatment of CsA and corticosteroids because of its inefficacy, and one of these eventually obtained remission after 500 mg CPA-pulse treatment with corticosteroids. Two of three "progressive" patients died of progressive IP with respiratory infection. These findings suggest that, in comparison with other subsets, acute IP patients with DM might be relatively resistant to CsA plus corticosteroids. In contrast, in chronic IP with DM ($n = 6$), all patients were evaluated as either "remarkably effective" or "partially effective." Four patients obtained remission, but one patient died of respiratory infection and one of malignant lymphoma.

There was a statistically significant correlation between the general evaluation and the outcome among patients treated with CsA plus corticosteroids ($\rho = 0.36$, $P = 0.048$,

**Table 2.** General evaluation 4 weeks after combination treatment, and patient outcome

| General evaluation | No. of cases | Outcome | | | | Cause of death |
|---|---|---|---|---|---|---|
| | | Remission | No change | Progressive | Death | |
| PM | | | | | | |
| Acute IP ($n$ = 1) | | | | | | |
| Remarkably effective | 1 | 1 | 0 | 0 | 0 | |
| Moderately effective | 0 | | | | | |
| Partially effective | 0 | | | | | |
| No change | 0 | | | | | |
| Progressive | 0 | | | | | |
| Death | 0 | | | | | |
| Chronic IP ($n$ = 8) | | | | | | |
| Remarkably effective | 3 | 2 | 0 | 1 | 0 | |
| Moderately effective | 2 | 2 | 0 | 0 | 0 | |
| Partially effective | 3 | 1 | 1 | 0 | 1 | Respiratory infection |
| No change | 0 | | | | | |
| Progressive | 0 | | | | | |
| Death | 0 | | | | | |
| DM | | | | | | |
| Acute IP ($n$ = 17) | | | | | | |
| Remarkably effective | 3 | 3 | 0 | 0 | 0 | |
| Moderately effective | 5 | 2 | 0 | 0 | 3 | IP, hepatitis B, aspiration pneumonia |
| Partially effective | 1 | 1[a] | 0 | 0 | 0 | |
| No change | 3 | 2[b] | 0 | 1[c] | 0 | |
| Progressive | 3 | 1 | 0 | 0 | 2 | IP with respiratory infection |
| Death | 2 | 0 | 0 | 0 | 2 | IP, IP with respiratory infection |
| Chronic IP ($n$ = 6) | | | | | | |
| Remarkably effective | 3 | 2 | 0 | 0 | 1 | IP with respiratory infection |
| Moderately effective | 0 | | | | | |
| Partially effective | 3 | 2 | 0 | 0 | 1 | Malignant lymphoma |
| No change | 0 | | | | | |
| Progressive | 0 | | | | | |
| Death | 0 | | | | | |

[a] Simultaneous use of cyclophosphamide (CPA)-pulse treatment with CsA and corticosteroids
[b] One case changed to CPA-pulse treatment with corticosteroids
[c] Alteration to CPA-pulse treatment with corticosteroids

Spearman rank correlation coefficient). The follow-up periods for acute IP with PM, chronic IP with PM, acute IP with DM, and chronic IP with DM were 13.5, 36.2 ± 22.4, 17.8 ± 17.8, and 13.7 ± 7.41 (mean ± SD) months, respectively, showing no statistically significant differences.

## Adverse effects of the combination treatment

Twenty-seven adverse events were seen in 19 patients. Ten patients died during the combination treatment of CsA and corticosteroids. Among these, 2 patients died as a result of the progression of IP. The remaining 8 patients died because of adverse effects with or without IP progression (Table 3). Respiratory infection was frequently observed, and 6 of 8 of these patients (75%) died. Among the 6 patients who died of infection, 4 died of respiratory failure because of progressive IP and simultaneous infection seen in the terminal stage, whereas 2 died as a result of infection without IP progression. Two patients with *Pneumocystis carinii* pneumonia recovered successfully. Patients suffering from hepatitis B and malignant lymphoma died despite the remission of IP. All other events were treated successfully.

**Table 3.** Adverse events during the combination treatment

| Event | No. of patients | No. of deaths |
|---|---|---|
| Respiratory infection | 8 | 6 |
| Fungi | (2) | (2) |
| *Pneumocystis carinii* | (2) | |
| *Pneumocystis carinii* and *Cytomegalovirus* | (1) | (1) |
| *Cytomegalovirus* and fungi | (1) | (1) |
| *Pseudomonas aeruginosa* and MRSA | (1) | (1) |
| Aspiration pneumonia | (1) | (1) |
| Liver dysfunction | 3 | |
| Diabetes mellitus | 2 | |
| Hyperlipemia | 2 | |
| Herpes zoster | 2 | |
| Hepatitis B | 1 | 1 |
| Malignant lymphoma | 1 | 1 |
| Subcutaneous abscess | 1 | |
| Pneumothorax | 1 | |
| Thrombocytopenia | 1 | |
| Hyperpotassemia | 1 | |
| Edema | 1 | |
| Gingival hypertrophy | 1 | |
| Hypertrichosis | 1 | |
| Nasal bleeding | 1 | |

MRSA, methicillin-resistant *Staphylococcus aureus*

### Clinical and laboratory parameters predicting the efficacy of the combination treatment

Since the efficacy of the combination treatment varied among patients, we looked for parameters that might predict the efficacy or inefficacy of this treatment. The patients treated with CsA plus corticosteroids ($n = 32$) were divided into an effective group (graded as better than "partially effective"; $n = 24$) and a non-effective group (graded as worse than "no change"; $n = 8$) in the general evaluation, and clinical parameters, including the subset with IP ($n = 32$), fever at the beginning of treatment ($n = 32$), and laboratory parameters, including CK/LDH index ($n = 32$), serum KL-6 level ($n = 11$), respiratory index ($n = 32$), pulmonary function tests ($n = 21$), and BAL cell profiles ($n = 18$), were compared. The effective group contained all the IP patients with PM and chronic IP with DM, and 9 patients who had acute IP with DM, while all the patients in the ineffective group had acute IP with DM. Thus, the ineffective group contained significantly more acute IP patients with DM ($P = 0.023$, $\chi^2$ analysis). However, neither fever nor any of the laboratory parameters could distinguish the effective group from the noneffective group (data not shown). The assessment of acute IP patients with DM yielded similar results (data not shown).

### Histological analysis of IP patients treated with CsA plus corticosteroids

In this study, 9 IP patients treated with CsA plus corticosteroids were evaluated histologically, and all were found to have DM. Samples were obtained by transbronchial lung biopsy in 5 patients, video-assisted thoracoscopic lung biopsy in 3 patients, and autopsy in 1 patient. The histological findings were heterogeneous: 3 cases of diffuse alveolar damage (DAD), 2 of bronchiolitis obliterans organizing pneumonia (BOOP) pattern, 2 of nonspecific interstitial pneumonia (NSIP) pattern, and 2 of usual interstitial pneumonia (UIP) pattern. Two of the 3 DAD patients, 1 of the 2 BOOP patients, and 1 of the 2 NSIP patients died, indicating that DAD had the worst prognosis. Of note is that all the DAD patients and the 1 NSIP patient who died clinically manifested the acute type of IP, and the one surviving DAD patient had been treated with a combination of CsA and corticosteroids from the initiation of treatment. In contrast, except for the 1 NSIP patient, the majority of patients with a histological pattern other than DAD had the chronic type of IP, which had a better prognosis than DAD.

### Superiority of the primary use of CsA in combination with corticosteroids over the primary use of corticosteroids in acute IP with DM

Since our present study revealed that acute IP patients with DM were relatively resistant to 4 weeks of CsA treatment combined with corticosteroids when compared with the other three subsets, and since more than just a few acute IP patients with DM died following a rapidly progressive course, the initial treatment was considered to be very important to rescue this subset. We therefore attempted to evaluate the long-term efficacy of the combination treatment, focusing on the primary use of CsA plus corticosteroids in acute IP with DM. Among the acute IP patients with DM treated with CsA and corticosteroids ($n = 17$), 13 patients were initially treated with CsA plus corticosteroids, while the remaining 4 patients were initially treated with corticosteroids alone. Three of these 4 patients were given CsA plus corticosteroids secondarily, and the fourth patient received it as a third treatment. These patients were added to those initially treated with corticosteroids alone.

We then compared the survival rates of patients with acute IP with DM between the group primarily treated with CsA plus corticosteroids from the beginning of treatment ($n = 13$) and that initially treated with corticosteroids alone ($n = 25$). Both groups revealed similar clinical features in terms of sex, age, initial symptoms, and physical and laboratory findings (Table 4). In the group primarily treated with CsA plus corticosteroids from the beginning of treatment, 10 patients were solely treated with this combination, and the remaining 3 patients were given 500 mg CPA-pulse treatment as a secondary treatment after 8.37 ± 7.92 (mean ± SD) months of the combination treatment because of the

**Table 4.** Features of patients with acute IP and DM in the CsA + corticosteroids group and the corticosteroid group

| | CsA + corticosteroids group | Corticosteroid group |
|---|---|---|
| Initial treatment | CsA + corticosteroids | Corticosteroids alone |
| No. of cases | 13 | 25 |
| Male/female | 4/9 | 8/17 |
| Age (years) | 48.8 ± 9.60 | 52.2 ± 11.3 |
| CK/LDH index | 0.923 ± 1.32 | 0.975 ± 2.02[a] |
| Initial symptoms (points) | 4.15 ± 2.61 | 3.82 ± 2.56[b] |
| Physical findings (points) | 2.07 ± 0.862 | 2.30 ± 0.876[c] |
| Chest radiographs (points) | 2.23 ± 1.01 | 2.71 ± 1.08[a] |
| $pO_2/FiO_2$ (Torr) | 337 ± 98.2 | 295 ± 105[a] |
| Oral corticosteroids (PSL mg/day) | 48.3 ± 20.2 | 52.0 ± 12.6 |
| mPSL pulse | 10 | 21 |

Plus–minus values are means ± SD
[a] $n = 24$; [b] $n = 22$; [c] $n = 23$

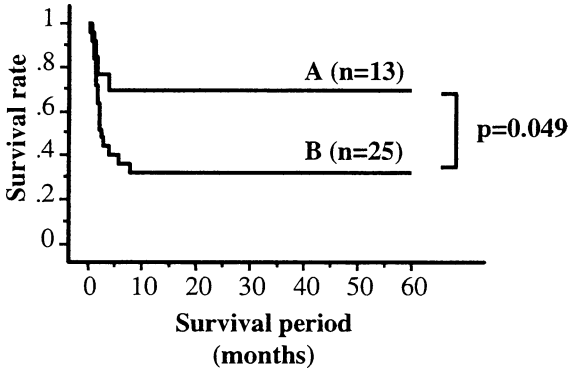


**Fig. 1.** Survival curves of the group treated with cyclosporin A (CsA) plus corticosteroids and that treated with corticosteroids alone. Survival curves were drawn using the Kaplan–Meier method. All patients had acute interstitial pneumonitis with dermatomyositis. Patients in the group given CsA plus corticosteroids ($A$, $n = 13$) were primarily treated with CsA and corticosteroids, while patients in the corticosteroid group ($B$, $n = 25$) were initially treated with corticosteroids alone. Primary use of CsA plus corticosteroids resulted in a better survival rate than the initial use of corticosteroids alone ($P = 0.049$, log-rank test)

exacerbation of the IP. Nine patients (69%) (6 CsA, 3 CPA-pulse) survived, and 4 patients (31%) died. In the group initially treated with corticosteroids alone, 10 patients were treated solely with corticosteroids, while the remaining 15 patients were treated with corticosteroids alone for at least the first 2 weeks, and then further treated with immunosuppressants in addition to corticosteroids because of progressive IP after 1.49 ± 3.55 months of corticosteroid treatment (9 patients had 748 ± 179 mg CPA-pulse; 3 had CsA; 2 had 800 mg CPA-pulse plus 50 mg/day oral CPA; 1 had 100 mg/day oral CPA). As a result, 8 patients (32%) (5 patients given corticosteroids alone; 2 given CPA-pulse; 1 given CsA) survived, and 17 patients (68%) died. No significant difference was found between these groups regarding the cause of death and the frequency of opportunistic infection (data not shown). The follow-up periods of the two groups were 21.1 ± 18.8 and 23.4 ± 37.4 months, respectively, and no significant difference was found between them. The survival rate of the group primarily treated with CsA plus corticosteroids was significantly higher than that of the group initially treated with corticosteroids alone ($P = 0.049$, log-rank test) (Fig. 1), suggesting that the primary use of CsA with corticosteroids might improve the prognosis of patients with acute IP with DM.

## Discussion

In this study, the combination treatment of CsA and corticosteroids was effective for patients with IP with PM and chronic IP with DM. All IP patients with PM were graded as better than "partially effective," and two-thirds of them as "remarkably effective" or "moderately effective" after 4 weeks of the combination treatment, suggesting that this treatment was effective for IP patients with PM irrespective of their clinical course. Chronic IP patients with DM also responded to the combination treatment. In contrast, the efficacy of the combination treatment was less dramatic in patients with acute IP with DM. Although approximately one-half of the patients showed responses which were better than "partially effective" in the general evaluation, the other half did not respond to the treatment, suggesting that this subset might be resistant not only to conventional medication, but also to the combination therapy with CsA and corticosteroids.

The general evaluation after 4 weeks of the combination treatment was correlated with the outcome for the patients. Although some patients showed a discrepancy between the general evaluation and their outcome, this was mainly ascribed to opportunistic infection occurring in the later stages of the disease. Therefore, it might be reasonable to conclude that the efficacy of the combination treatment with CsA and corticosteroids can be determined after 4 weeks of treatment.

Opportunistic infection was a serious complication during the combination treatment of CsA and corticosteroids, since it significantly influenced the patients' prognoses. In this study, 11 events occurred (8 cases of respiratory infection, 2 of herpes zoster, 1 of hepatitis B), and 7 patients died. The most frequent event was respiratory infection, and 6 of 8 patients died. Nephrotoxicity, a serious and common adverse effect of CsA, was not observed, and other complications were well tolerated. Under the combination treatment for IP with PM/DM, opportunistic infections should be carefully monitored, and the prophylactic use of antibiotics should be considered to reduce mortality when prospective clinical trials are conducted.

Acute IP patients with DM showed some unique clinical features: an increased ratio of males, low CK/LDH index and negative anti-Jo-1 antibodies. In this regard, Fergusson et al.[11] and Fudman and Schnitzer[26] have both reported two DM patients with rapidly progressive IP and normal CK levels. The term "amyopathic DM" has been widely used for this subset of patients.[19,27] Takizawa et al.[23] also reported that a majority of IP patients with DM showed normal CK levels and had a poor prognosis. In addition, there have been sporadic reports in the literature of patients with rapidly progressive IP and amyopathic DM.[28–32] These patients showed common clinical features, including low CK levels, negative anti-Jo-1 antibodies, and a poor prognosis. Although patients with anti-Jo-1 antibodies tend to have mild chronic IP,[33] none of our acute IP patients with DM possessed anti-Jo-1 antibodies (0 of 15). Thus, it is possible that patients with acute IP and DM might form a unique subset with increased resistance to medication. Our study also indicated that approximately one-half of patients with acute IP and DM were resistant to treatment with CsA plus corticosteroids, and had a higher mortality in their outcome.

We next looked for parameters that could predict the efficacy of the combination treatment in IP patients with PM/DM. Recent studies have demonstrated that serum KL-6 reflects the disease activity of IP associated with PM/DM.[34,35] Since acute IP with DM was more resistant to the combination treatment than other subsets, the clinical subset of IP might predict the effectiveness of the combination

treatment. In contrast, other parameters, including fever, CK/LDH index, serum KL-6 levels, respiratory index, pulmonary function tests, and BAL fluid profile, could not predict the prognosis in our study. This might be because the number of patients in this study was limited, because adverse effects influenced the general evaluation, or because these parameters did not precisely reflect the disease activity of IP in PM/DM. Although many factors that might influence the prognosis, including delays in diagnosis and treatment, anti-SRP antibodies and anti-Mi-2 antibodies, have been reported,[36] we were not able to assess these parameters in our study. A prospective study on a large series of patients would clarify this point.

It has been reported that a histological classification of the lung is useful in predicting the prognosis of IP patients with PM/DM.[37,38] Tazelaar et al.[37] demonstrated that histological features on open lung biopsy may be a better predictor of survival than either radiographic findings or clinical course. In our study, although the number of cases was not sufficient to draw definitive conclusions, DAD was shown to be more refractory to treatment than other types such as BOOP, NSIP, and UIP, findings similar to those of previous reports. However, it is also true that there were fatal non-DAD cases. Furthermore, 3 of 4 (75%) acute IP patients showed poor prognoses, whereas 4 of 5 (80%) chronic IP patients survived irrespective of their histology, suggesting that clinical course might predict the prognosis for IP patients without histology.

In order to demonstrate the long-term efficacy of CsA, the survival rate should be examined. In this regard, Maeda et al.[16] reported that 3 of 4 IP patients with DM survived when CsA and corticosteroids were employed from an earlier phase of IP. Moreover, Nawata et al.[17] recently reported that CsA was effective in all of 5 patients with corticosteroid-resistant IP with DM, and their 1-year survival rate was 80%. In our acute IP patients with DM, the primary use of CsA with corticosteroids rescued 9 of 13 patients (69%). In contrast, an initial corticosteroid treatment rescued only 8 of 25 patients (32%). In this regard, Takizawa et al.[23] emphasized that the response to corticosteroids was poor in IP patients with DM, noting that in their study, 6 of 9 IP patients (67%) with DM died of respiratory failure. Further, among the group initially treated with corticosteroids in our study, 2 of 3 patients (67%) died in spite of the secondary use of CsA. These findings stress the importance of the primary use of CsA with corticosteroids for acute IP patients with DM. Indeed, in our study, the group treated with CsA plus corticosteroids showed a significantly higher survival rate than the group given corticosteroids.

It should be pointed out that our retrospective study was subject to certain limitations, since the number of patients included was not sufficient, and no corticosteroid-treated group was used as a control in IP with PM and chronic IP with DM. Furthermore, the standardization of treatment may have been less than stringent because of the nature of retrospective studies. However, our findings suggest that under careful observation and the prevention of opportunistic infection, a combination therapy with CsA and corticosteroids may be advantageous for IP patients with PM/DM, and that the primary use of CsA with corticosteroids significantly improves the survival rate in patients with acute IP with DM. Further prospective clinical trials will need to be conducted to ascertain the efficacy of this treatment.

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