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ORIGINAL ARTICLE

**Kazuki Takada · Jun Kishi · Nobuyuki Miyasaka**

# Step-up versus primary intensive approach to the treatment of interstitial pneumonia associated with dermatomyositis/polymyositis: a retrospective study

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**Abstract** Corticosteroids (CS) are the standard initial treatment for interstitial pneumonia (IP) associated with dermatomyositis (DM)/polymyositis (PM). However, many patients fail to respond and have significantly high mortality even if immunosuppressive drugs (ISDs) are subsequently added, while a more intensive initial approach using ISDs is suggested to improve their survival. We conducted a retrospective study to examine the association between initial therapeutic approaches and clinical outcomes of active IP in DM/PM patients. We reviewed medical records of 34 consecutive DM/PM patients who had active IP defined by the presence of pulmonary function abnormality or active symptoms, and compared clinical outcome between those patients to whom ISDs were added if CS alone did not result in a favorable response (a step-up approach) and those who were started on ISDs simultaneously with CS (a primary intensive approach). Clinical endpoints were death, pulmonary death, and progression or improvement of pulmonary function. The step-up approach was used in 20 patients, to 11 of whom ISDs were eventually added after a median of 2.0 weeks, while the primary intensive approach was used in 14 patients. The primary intensive approach group had significantly better survival than the step-up approach group ($P = 0.030$ by the log-rank test). These two groups did not differ significantly in demographic characteristics and baseline clinical and laboratory features. Intensive approach by starting ISDs simultaneously with CS in the initial treatment for active IP in DM/PM patients was associated with better survival, emphasizing the impact of initial treatment on their survival. Prospective clinical investigation of this approach is now needed, but the limited clinical utility of CS as an initial treatment might ethically challenge clinical-trial designing.

K. Takada (✉) · J. Kishi · N. Miyasaka
Department of Medicine and Rheumatology, Graduate School, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
Tel. +81-3-5803-5210; Fax +81-3-5803-5998
e-mail: takada.rheu@tmd.ac.jp

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## Introduction

Since the original description by Mills and Mathews in 1956,[1] interstitial pneumonia (IP) has been recognized to be a common complication of and has a significant impact on the prognosis of patients with dermatomyositis (DM) and polymyositis (PM). Reported prevalence of IP in DM/PM patients varies between 23% and 65%[2–8] depending on criteria applied as well as on clinical settings of studied cohorts, and an earlier overview[9] and a later study[7] reported significantly higher mortality in DM/PM patients with IP than mortality in those without.

However, treatment for this grave complication has not yet been established. Corticosteroids (CS) are considered as the first-line drugs, but no controlled trials have been conducted to prove its efficacy. Indeed, more than 50% of DM/PM patients with IP fail to respond to CS,[3,10,11] and these CS-resistant patients have significantly high mortality,[3] even if immunosuppressive drugs (ISDs) are subsequently added.[11]

Recently, Nagasaka et al.[12] showed, through their nationwide survey of DM patients with IP, that patients to whom cyclosporine was added to CS within the first 2 weeks had significantly better survival. Although their results suggest that more intensive initial approach using ISDs may improve survival of DM patients with IP, methodological shortcomings of their study such as limited data access, potential sampling bias, and indication bias warrant more rigorous evaluation, and it is also not clear whether the implication could be extrapolated to PM patients with IP. To examine the association between initial therapeutic approaches and survival of DM/PM patients with active IP, we conducted a retrospective study and compared clinical outcome between those patients who were started on ISDs simultaneously with CS (a primary intensive approach) and

those to whom ISDs were added if CS alone did not result in a favorable response (a step-up approach).

## Patients and methods

### Patients

The study cohort consisted of consecutive patients diagnosed as having PM or DM, who received medical care for their active IP at the Tokyo Medical and Dental University Hospital between January 1975 and December 2005. The diagnosis of PM or DM was based on Bohan and Peter criteria[13,14]: (1) symmetric muscle weakness, (2) increased serum muscle enzymes, (3) myopathic changes on electromyography, (4) typical histologic findings on muscle biopsy, and (5) characteristic dermatologic manifestations (heliotrope rash, periungal erythema, Gottron's papules, and poikiloderma). The diagnosis was considered definite, probable, or possible, according to the number of criteria fulfilled (at least 4, 3, or 2, respectively).

Active IP was defined by the presence of radiographic abnormalities consistent with IP and by the presence of at least one of the following: (a) the percentage of predicted vital capacity (%VC) that was 80 or less, (b) the percentage of predicted diffusing capacity for carbon monoxide (%$DL_{CO}$) that was 70 or less, or (c) active symptoms (exertional dyspnea, persistent nonproductive cough, or both). Patients were excluded if they had a history of occupational or environmental exposure or of taking drugs known to cause pulmonary fibrosis.

### Data sources and extraction

Clinical data as well as survival and current status were based on hospital medical records, which provided clinical information obtained during hospitalization and follow-up clinic visits. All patients had an initial evaluation for skin and muscle manifestations, for the involvement of other organs, and for underlying malignancy. Autoantibody screen was performed including anti-Jo-1 antibody. Testing for other myositis-specific autoantibodies were not available and thus were not performed.

Pulmonary involvement was systematically evaluated. Pulmonary function tests were performed before and during treatment of IP. The VC was determined by spirometry, while the $DL_{CO}$ was determined by a single-breath method. High-resolution computed tomography (HRCT) examination of the lung was reviewed for the presence of each of the following signs: consolidation, ground glass opacities, traction bronchiectasis, irregular linear opacities, honeycombing, and pleural effusion.

### Treatment

As an initial treatment for IP, prednisolone was used in all patients. The decision for the use of ISDs was made by consensus among our faculty physicians and the patient. We grouped our patients based on initial therapeutic approaches into those to whom ISDs were started simultaneously with CS (a primary intensive approach) and into those to whom CS was started alone and ISDs were added if CS alone did not result in a favorable response (a step-up approach). We excluded those patients who had infection before or at the start of IP treatment, had malignancy, or had other conditions for which the use of moderate to high doses of CS (0.6 mg/kg of body weight or higher of prednisolone or its equivalent) or ISDs were contraindicated. In addition, patients had to be followed until death or until they received treatment for active IP for a minimum of 3 months. Informed consent was obtained from all the patients prior to the use of ISDs.

### Clinical outcome

All death, pulmonary death (death primarily due to IP progression or pulmonary infection), and progression or improvement of pulmonary function were our endpoints. Progression of pulmonary function was defined as ≥10% decrement in %VC as this was shown to correlate with mortality,[15] and we created a combined endpoint of pulmonary death or progression of pulmonary function since patients whose pulmonary condition deteriorate may not undergo pulmonary function test. An improvement of pulmonary function was defined as ≥10% increment in the %VC.

### Statistical methods

For demographic characteristics and baseline clinical and laboratory features between groups, categorical data were compared using Fisher's exact test, and continuous data were compared using the Mann–Whitney *U*-test. Endpoint-free survival curves were estimated by the Kaplan–Meier method, and the significance of differences between groups was tested by using the log-rank test. The results were reported as two-sided *P* values. All statistical analyses were performed with the StatView statistical program package (Version 5; SAS Institute, Cary, NC, USA).

## Results

### Study population and characteristics

Among 117 consecutive patients with PM or DM who received medical care at the Tokyo Medical and Dental University Hospital between January 1975 and December 2005, 53 (45%) patients had radiographic findings consistent with IP, irrespective of their size or extent. Eleven patients were excluded from the analysis because they did not fulfill the criteria for active IP as defined in the method section, 1 patient because the length of follow-up was less than 3 months, and 7 patients because they had medical conditions

**Table 1.** Demographic, clinical, and laboratory characteristics of the study cohort[a]

| | PM-IP $n = 11$ | DM-IP $n = 23$ | $P$[b] |
|---|---|---|---|
| Demographic characteristics | | | |
| Age, years | 57 (49, 64) | 56 (45, 62) | 0.81 |
| Male/female | 1/10 | 8/15 | 0.21 |
| Malignancy, no. (%) | 1 (9) | 0 | 0.32 |
| Length of illness before IP treatment, weeks | 11.9 (6.9, 32.6) | 5.9 (0.14, 15.1) | 0.019 |
| Onset of IP in relation to the onset of PM/DM | | | |
| Before, no. (%) | 2 (18) | 0 | |
| Concomitant, no. (%) | 7 (64) | 20 (87) | |
| After the onset of PM/DM with flare, no. (%) | 2 (18) | 1 (4) | |
| After the onset of PM/DM while quiet, no. (%) | 0 | 2 (9) | |
| Clinical and laboratory findings at the start of initial treatment | | | |
| Dyspnea on exertion, no. (%) | 10 (91) | 16 (70) | 0.23 |
| Persistent dry cough, no. (%) | 6 (55) | 14 (61) | >0.99 |
| Fine crackles, no. (%) | 10 (91) | 22 (96) | 0.55 |
| CPK, IU/l | 749 (311, 1611) | 366 (122, 2285) | 0.44 |
| Anti-Jo-1 antibody, no./no. of tested (%) | 3/8 (38) | 2/18 (11) | 0.28 |
| $PaO_2$, mmHg[c] | 72 (63, 78) | 75 (73, 88) | 0.19 |
| %VC[d] | 62 (60, 68) | 80 (68, 85) | 0.014 |
| $\%DL_{CO}$[e] | 49 (35, 59) | 54 (48, 60) | 0.50 |
| High-resolution CT findings at the start of initial treatment, no./no. of tested (%) | | | |
| Consolidation | 2/4 (50) | 3/13 (23) | 0.54 |
| Ground glass opacities | 2/4 (50) | 10/13 (77) | 0.54 |
| Traction bronchiectasis | 4/4 (100) | 8/13 (62) | 0.26 |
| Irregular linear opacities | 3/4 (75) | 11/13 (85) | >0.99 |
| Honeycombing | 0/4 | 0/13 | |
| Pleural effusion | 0/4 | 0/13 | |

PM, polymyositis; IP, interstitial pneumonia; DM, dermatomyositis; CPK, creatine phosphokinase; $PaO_2$, partial pressure of oxygen in arterial blood; VC, vital capacity; $DL_{CO}$, diffusing capacity of carbon monoxide; CT, computed tomography

[a] Data for continuous variables are given as the median (25th, 75th percentiles)

[b] $P$ values for comparisons between groups using the Mann–Whitney $U$-test for continuous variables and the Fisher's exact test for categorical variables

[c] Values were available for 9, 16 patients of PM-IP, DM-IP, respectively

[d] Values were available for 8, 16 patients, respectively

[e] Values were available for 7, 14 patients, respectively

for which the use of moderate to high doses of CS or ISDs were contraindicated. Therefore, our study cohort consisted of 11 PM patients (6 definite, 2 probable, and 3 possible PM) and 23 DM patients (15 definite, 5 probable, and 3 possible DM), who received treatment for their active IP. Five of 23 DM patients had abnormal findings in serum muscle enzyme measurements, electromyography, or muscle biopsy, but did not have clinically significant muscle weakness or other clinical findings and thus could be categorized as hypomyopathic dermatomyositis or clinically amyopathic dermatomyositis (CADM) according to the classification criteria proposed by Sontheimer.[16]

The median length of follow-up since the start of treatment in surviving patients was 44.8 months (25th, 75th percentiles, 19.5, 131.0 months). Table 1 shows the demographic characteristics and baseline clinical and laboratory features of our cohort before treatment for active IP was started. DM-IP patients were started on treatment for active IP sooner than PM-IP patients (mean difference, 12.7 weeks [95% confidence interval (CI), 1.9 to 23.6 weeks]). Eighty-seven percent of DM patients developed IP concomitantly with the onset of DM, whereas 36% of PM patients developed IP prior to the onset of PM or while PM was inactive. The prevalence of anti-Jo-1 antibody in tested patients was not significantly different between the groups.

Most patients underwent pulmonary function test and arterial blood gas analysis at the initial evaluation. Both groups showed mild hypoxia. Compared with DM-IP patients, PM-IP patients had lower %VC (mean difference, 13.8% [CI, 2.0% to 25.7%]) (Table 1).

High-resolution CT examination of the lungs was performed and was available for review in 17 patients. Ground-glass opacities, traction bronchiectasis, and irregular linear opacities were the predominant findings in both groups. Bronchoalveolar lavage was performed in 10 patients mainly to rule out underlying pulmonary infection, and lung pathology specimens were obtained through transbronchial or surgical lung biopsy or autopsy in 10 patients (data not shown).

## Treatments

As an initial treatment for IP, all 34 patients received prednisolone (a median dose, 0.97 mg/kg of body weight [25th, 75th percentiles, 0.87, 1.07]) for at least 4 weeks, which was subsequently tapered according to the general rule of 10% decrement every 4 weeks if clinically feasible until it reached the maintenance dose of 5 to 10 mg/day. Twelve patients also received 1 to 3 courses of intravenous methylpred-

nisolone pulse therapy (1 g/day for 3 consecutive days). The decision for the use of ISDs was made by consensus among our faculty physicians and the patient. A step-up approach was used in 20 patients (a step-up approach group) to whom ISDs were added if CS alone did not result in a favorable response. The favorable response was not defined prospectively, but in most cases response to CS was judged by 2 or more of the following: (1) a decrease in symptoms (exertional dyspnea); (2) reduction of parenchymal abnormalities on chest radiograph or HRCT; (3) an improvement of $PaO_2$. Among these 20 patients, ISDs were eventually added to 11 patients after a median of 2.0 weeks (25th, 75th percentiles, 1.3, 4.7 weeks), and included cyclosporine ($n = 4$) and cyclophosphamide ($n = 7$). A primary intensive approach was used in the remaining 14 patients who were started on ISDs simultaneously with CS (a primary intensive approach group). Initially used ISDs were cyclosporine ($n = 6$), cyclophosphamide ($n = 3$), azathioprine ($n = 2$), and tacrolimus ($n = 3$). These two groups did not differ significantly in demographic characteristics and baseline clinical and laboratory features (Table 2).

## Survival

Eleven patients died during follow-up. Causes of death were respiratory failure, which was primarily due to IP progression ($n = 8$) or pulmonary infection ($n = 1$), cerebral hemorrhage ($n = 1$), and unknown (sudden cardiopulmonary arrest of unclear etiology) ($n = 1$). We evaluated the association between initial therapeutic approaches and survival on the entire cohort. As shown in Fig. 1A, the primary intensive approach group had significantly better survival than the step-up approach group ($P = 0.030$ by the log-rank test). None died within the first 12 months in the primary intensive approach group, whereas 7 patients (35%) died in the step-up approach group. The similar trend favoring the primary intensive approach was observed when we controlled our analysis for the year in which treatment for IP was started in each patient (data not shown).

We also evaluated the association between initial therapeutic approaches and other endpoints. Although only 1 patients died in the primary intensive approach group, 2 surviving patients, both receiving CS and cyclosporine as an initial treatment, reached the endpoint of progression of pulmonary function (≥10% decrement in %VC) within the first 3 months, and thus the probability of pulmonary death- or progression-free survival was not significantly different between the groups (Fig. 1B) ($P = 0.085$ by the log-rank test). Of note, after reaching the endpoint, cyclosporine was switched to tacrolimus in one and to intravenous pulse cyclophosphamide in the other, both of which stabilized their IP. On the other hand, among 24 patients whose baseline %VC values were available, 8 patients (67%) in the primary intensive approach group achieved the improvement of pulmonary function (≥10% increment in %VC) after a median of 2.4 months, whereas 6 patients (50%) in the step-up approach group did (Fig. 1C) ($P = 0.15$ by the log-rank test).

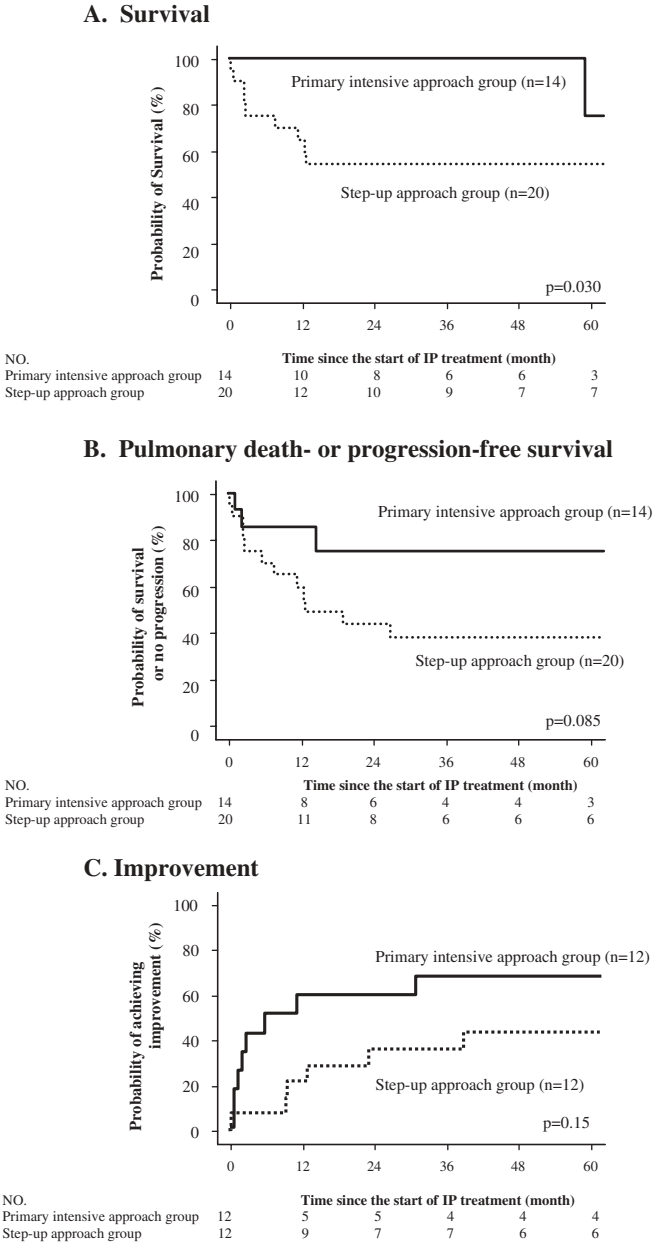


**Fig. 1.** Association between initial therapeutic approaches and clinical outcome. Kaplan–Meier curves comparing time to death (**A**), the combined endpoint of pulmonary death or the progression in pulmonary function as defined by ≥10% decrement in the percentage of vital capacity (%VC) (**B**), and the improvement in pulmonary function as defined by ≥10% increment in %VC (**C**) between patients with dermatomyositis or polymyositis and associated active interstitial pneumonia to whom immunosuppressive drugs were added if corticosteroids (CS) alone did not result in a favorable response (a step-up approach group) and those who were started on ISDs simultaneously with CS (a primary intensive approach group). The analysis for the improvement in pulmonary function (**C**) was limited to those patients whose baseline %VC values were available (12 patients in each group). *P* values were obtained by the log-rank test

Survival was not significantly different between PM-IP and DM-IP (Fig. 2) ($P = 0.76$ by the log-rank test), even after controlling for initial therapeutic approaches ($P = 0.67$ by Cox proportional hazards regression analysis, data not shown).

**Table 2.** Clinical and laboratory characteristics of patients in each group[a]

| | Primary intensive approach group: ($n$ = 14) | Step-up approach group: ($n$ = 20) | $P$[b] |
|---|---|---|---|
| Patient characteristics | | | |
| Age, years | 56 (49, 62) | 58 (44, 63) | 0.94 |
| Male/female | 4/10 | 5/15 | >0.99 |
| PM/DM | 4/10 | 7/13 | >0.99 |
| CADM, no (%) | 3 (21) | 2 (10) | 0.63 |
| Dysphagia, no. (%) | 2 (14) | 4 (20) | >0.99 |
| Malignancy, no. (%) | 0 | 1 (5) | >0.99 |
| Length of illness before treatment, weeks | 6.6 (2.3, 21.4) | 7.1 (0.86, 17.5) | 0.70 |
| Clinical and laboratory findings at the start of initial treatment | | | |
| Dyspnea on exertion, no. (%) | 11 (79) | 15 (75) | >0.99 |
| Persistent dry cough, no. (%) | 9 (64) | 11 (55) | 0.73 |
| Fine crackles, no. (%) | 13 (93) | 19 (95) | >0.99 |
| CPK, IU/L | 244 (184, 1801) | 1278 (165, 2305) | 0.37 |
| Anti-Jo-1 antibody, no./no. of tested (%) | 3/12 (25) | 2/14 (14) | 0.63 |
| $PaO_2$, mmHg[c] | 77 (72, 87) | 73 (67, 86) | 0.47 |
| %VC[d] | 81 (64, 89) | 69 (62, 77) | 0.27 |
| $\%DL_{CO}$[e] | 52 (38, 60) | 52 (48, 60) | 0.89 |
| High-resolution CT findings at the start of initial treatment, no./no. of tested (%) | | | |
| Consolidation | 3/10 (30) | 2/7 (29) | >0.99 |
| Ground glass opacities | 8/10 (80) | 4/7 (57) | 0.59 |
| Traction bronchiectasis | 8/10 (80) | 4/7 (57) | 0.59 |
| Irregular linear opacities | 9/10 (90) | 5/7 (71) | 0.54 |
| Honeycombing | 0/10 | 0/7 | |
| Pleural effusion | 0/10 | 0/7 | |
| Treatment[f] | | | |
| Initial CS dose, mg/day | 50 (45, 55) | 50 (40, 60) | 0.90 |
| Use of IV MPS pulse therapy, no. (%) | 2 (14) | 10 (50) | 0.066 |
| ISD ever used, no. (%) | 14 (100) | 11 (55) | |
| Initially used ISD, no. | | | |
| Cyclophosphamide | 3 | 7 | |
| Cyclosporine | 6 | 4 | |
| Azathioprine | 2 | 0 | |
| Tacrolimus | 3 | 0 | |
| Prophylaxis for pneumocystis pneumonia, no. (%) | 8 (57) | 6 (30) | 0.11 |
| CS dose at the endpoint, mg/day | 11.3 (8, 20) | 10 (6.5, 27.5) | 0.77 |
| ISD being used at the endpoint, no. | | | |
| Cyclophosphamide | 1 | 4 | |
| Cyclosporine | 4 | 3 | |
| Azathioprine | 1 | 0 | |
| Tacrolimus | 6 | 3 | |
| Outcome | | | |
| Follow-up, months | 25.6 (10.6, 59.2) | 21.5 (5.2, 127) | 0.78 |
| All death, no. (%) | 1 (7) | 10 (50) | 0.030 |
| Pulmonary death (death primarily due to IP progression or pulmonary infection), no. (%) | 1 (7) | 8 (40) | 0.051 |
| Death primarily due to IP progression, no. (%) | 1 (7) | 7 (35) | 0.078 |
| Death primarily due to infection, no. (%) | 0 | 2 (10) | |

PM, polymyositis; DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis; CPK, creatine phosphokinase; $PaO_2$, partial pressure of oxygen in arterial blood; VC, vital capacity; $DL_{CO}$, diffusing capacity of carbon monoxide; CS, corticosteroids; IV MPS, intravenous methylprednisolone; ISD, immunosuppressive drug; CT, computed tomography

[a] Data for continuous variables are given as the median (25th, 75th percentiles)

[b] $P$ values for comparisons between groups using the Mann–Whitney $U$-test for continuous variables, the Fisher's exact test for categorical variables, and the log-rank test for survival (all death and death primarily due to IP progression)

[c] Values were available for 10, 15 patients in the primary intensive approach group and the step-up approach group, respectively

[d] Values were available for 12, 12 patients, respectively

[e] Values were available for 11, 10 patients, respectively

[f] Doses of ISDs were as follows: oral cyclophosphamide: initial dose of 1 mg/kg/day, increased as tolerated up to 2 mg/kg/day; intravenous pulse cyclophosphamide: initial dose of 0.5 g/m$^2$ of body surface area, increased as tolerated up to 1 g/m$^2$; cyclosporine: daily doses adjusted for a target trough level of 100–200 ng/ml; azathioprine: initial dose of 3 mg/kg/day; tacrolimus: daily doses adjusted for a target trough level of 5–10 ng/ml

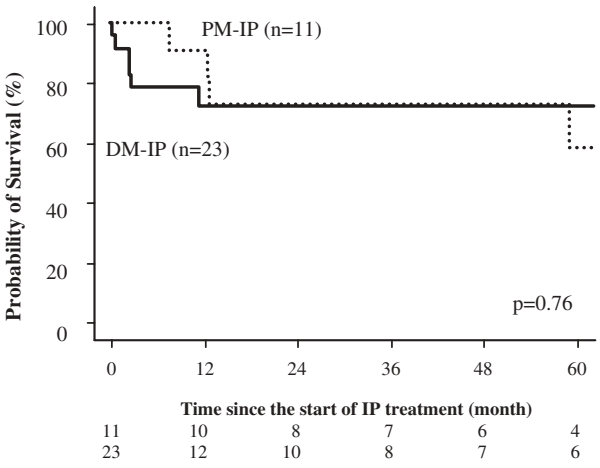


**Fig. 2.** Survival by disease. Kaplan–Meier curves comparing survival of patients with polymyositis and associated active interstitial pneumonia with that of patients with dermatomyositis and associated active interstitial pneumonia. *P* value was obtained by the log-rank test

## Discussion

In this study, we examined the association between initial therapeutic approaches and clinical outcome of active IP in DM/PM patients. We found that more intensive approach in the initial treatment was associated with better survival. Specifically, patients who were started on ISDs simultaneously with CS (the primary intensive approach) had significantly better survival than those to whom ISDs were added if CS alone did not result in the favorable response (the step-up approach).

Our study extends the impact of initial treatment on survival of DM/PM patients with active IP suggested by the previous study. Nagasaka et al.[12] showed, through their nationwide survey of DM-IP patients, that those patients to whom cyclosporine was added to CS within the first 2 weeks had significantly better survival. However, unspecified decision-making rational or criteria regarding whether and when to use cyclosporine make it difficult to interpret their finding. Instead, we grouped our cohort by different initial approaches regarding the use of ISDs and thus convey more practical implication for clinicians who are about to start initial treatment for active IP on DM/PM patients.

Our study re-emphasizes the limited clinical utility of CS alone as an initial treatment for active IP in DM/PM patients. In our study, 9 patients (45%) in the step-up approach group died within 14 months even though ISDs were subsequently added in 4 of them. Significantly high mortality associated with the step-up approach may be related to its inability to suppress inflammation promptly and effectively and to an increased risk of infection, especially due to opportunistic pathogens. Indeed in the step-up approach group, ISDs could not be added in 1 patient due to the development of infection, and 3 of 10 patients who died developed severe infection, which led to or contributed to their death. These findings underscore the limited clinical utility of CS as the initial treatment for active IP in DM/PM patients when given alone. It is also noteworthy that 6 patients (30%) in the step-up approach group did not reach the combined endpoint of pulmonary death or progression of pulmonary function, and could be categorized as CS responders. When we compared demographic characteristics and baseline clinical and laboratory features between these CS responders and the remaining 14 patients in the step-up approach group (CS nonresponders), statistically significant difference was noted only for the length of illness before treatment ($P = 0.048$) with the median length of 17.7 and 4.2 weeks, respectively (data not shown). It could be speculated that a delay in initiating treatment in CS responders reflected a slowly progressing nature of their illness and therefore that those with slowly progressive IP may have relatively good prognosis. However, larger studies are needed to further define predictors for good prognosis.

Contrary to previous reports, survival was not significantly different between PM-IP and DM-IP (Fig. 2), even after controlling for initial therapeutic approaches. Nawata et al.[3] previously reported in their cohort treated only with CS that the survival of PM-IP patients was better than that of DM-IP, and Fujisawa et al.[11] also reported the similar findings in their cohort treated with CS and ISDs. This discrepancy between our findings and those of earlier reports may be due to differences in patient cohort. Firstly, our PM-IP cohort may have included more patients from the subgroup with poorer prognosis than others. Nawata and colleagues showed, in the same report, that DM/PM patients who had the onset of IP concomitant with the onset of myositis had better prognosis than others. Indeed, 10 of 12 PM-IP patients (83%) in Nawata's report and 13 of 16 PM-IP patients (81%) in Fujisawa's report[11] had the onset of IP concomitant with the onset of myositis, whereas only 7 of 11 PM-IP patients (64%) of our cohort did. Secondly, our cohort may have had more active and severe IP than others. We included only those patients who had active IP defined by the presence of characteristic radiographic abnormalities and by the presence of pulmonary function abnormality (%VC ≤80 or $\%DL_{CO}$ ≤70) or active symptoms, whereas other studies did not provide specific criteria for their patient selection. Indeed, 91% of our PM-IP cohort had dyspnea on exertion at the start of IP treatment whereas only 63% of Fujisawa's cohort did, and the similar trend could be found in pre-treatment %VC as well. Thirdly, our cohort may have included more patients with advanced IP than others. Although the number of PM-IP patients in whom HRCT images were available was limited, all of them had traction bronchiectasis whereas 67% of Fujisawa's cohort did. Lastly, our cohort may have included more patients with histological types associated with worse prognosis. However, histological types are known in only few patients in these studies and thus conclusive comments could not be made.

The optimal choice for ISD to be used in the initial treatment for active IP in DM/PM patients remains uncertain and warrants further investigation. In our study, choice of ISD was not controlled but was based on individual cases

and the best available evidence at each time. Azathioprine[2,17] and cyclophosphamide[2,18–21] have long been used and been reported to be beneficial in refractory cases. Recently, several groups demonstrated that T lymphocytes are abundant in the inflammatory lung tissue and most of CD8+ T lymphocytes have phenotypic characteristics of activation,[22–25] implicating the potentially important roles of T lymphocytes in PM/DM-IP. Clinicians therefore resorted to a T-lymphocyte specific immunosuppressive drug, cyclosporine, in refractory cases and often experienced a favorable response.[3,12,22,25–27] Tacrolimus has a mode of action similar to cyclosporine but is up to 100-fold more potent in vitro with more favorable safety profile in vivo than cyclosporine,[28,29] and reports of favorable experiences with tacrolimus have been accumulating. Notably, Wilkes et al.[30] reported significant improvement in pulmonary function in 13 refractory IP patients with anti-tRNA synthetase antibodies, the largest case series reported in the literature for the treatment of IP in DM/PM. We have also recently reported favorable experiences with tacrolimus in five refractory DM/PM patients with IP all of whom had previously failed to respond to cyclosporine.[31,32] However, most of these experiences were in refractory patients and ISDs were used late. Therefore, clinical utility of specific ISDs as an additional agent in the initial treatment should be formally investigated.

Our study had several limitations. Firstly, choice of initial therapeutic approach was not controlled. In some patients, the primary intensive approach was chosen because IP was severe on presentation or in order to limit the exposure to CS for their side effects. Although this potential indication bias would have favored the step-up approach group, their survival was worse. In others, the primary intensive approach was chosen based on the accumulating evidence and experiences showing limited clinical utility of CS alone as an initial therapy. This could lead to a noncontemporaneous control bias: the primary intensive approach was used more frequently in later years than in earlier years, and we cannot be confident that advances in general medical care did not contribute to better survival associated with the primary intensive approach. However, the trend favoring the primary intensive approach was observed when we controlled our analysis for the year in which treatment for IP was started in each patient (data not shown). Additionally, %VC values and $PaO_2$ in the primary intensive approach group were higher. However, these values were not available for all the patients in both groups and thus the comparison is imperfect. Furthermore, neither of them was associated with the examined endpoints in our cohort (data not shown). Therefore, we believe that these differences do not account for the better survival of the primary intensive approach group. Of note, prophylaxis for opportunistic infection was similarly undertaken regardless of approach. Secondly, choice of ISD was not controlled. Some ISDs used in our patients may not have as much impact as others, and thus the observed impact may not be generalized to all ISDs. Thirdly, since very few of our patients had histological specimens available, we could not control our findings for histological differences. Lastly, because of referral filter bias, our study cohort may have consisted of patients who had more severe or complicated disease, and thus the results of our study may not be generalized to patients in other settings.

Caution is warranted in extrapolating the results of our study to the general population of DM/PM patients with IP. The IP is common in DM/PM patients, but a certain proportion of IP patients remain asymptomatic and IP will not progress or will progress slowly. In our study, we included only those patients with active IP, and therefore our results will not apply to those patients with asymptomatic and subclinical IP, which is only detectable by sensitive radiographic examination.

In summary, we have shown that intensive approach by starting ISDs simultaneously with CS in the initial treatment for active IP in DM/PM patients was associated with better survival, emphasizing the impact of initial treatment on their survival. Prospective clinical investigation for the efficacy as well as safety of this approach is now needed. Theoretically it is preferable that this approach is compared with the step-up approach. However, the limited clinical utility of CS as an initial treatment demonstrated in our study and others might ethically challenge clinical-trial designing.

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