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BRIEF REPORT

Mycophenolate mofetil treatment with or without a calcineurin inhibitor in resistant inflammatory myopathy

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Abstract

To evaluate the efficacy and tolerability of mycophenolate mofetil (MMF) with or without calcineurin inhibitors (CNIs) in patients with inflammatory myopathy taking prednisolone, but refractory to conventional immunosuppressive therapy. The records of patients with inflammatory myopathy who had previously failed treatment with at least one immunosuppressant were retrospectively evaluated. We selected patients treated with MMF and divided them into two groups depending on whether or not there was concomitant use of CNIs. We investigated the efficacy by changes in creatine kinase (CK) levels, forced vital capacity (%FVC), prednisolone dose, and high-resolution computed tomography (HRCT) findings. Interstitial lung disease (ILD) progression was defined by more than 10% decline of %FVC from baseline. We identified 19 patients on MMF treatment. There were seven (36.8%) patients on MMF and CNIs, including five on cyclosporine and two on tacrolimus. At baseline, no significant difference was seen in the prevalence of ILD between patients taking or not taking CNIs (85.7% vs. 75.0%, $P = 0.68$). Improvement in CK was seen in patients treated with CNIs ($P = 0.04$) but not in those without ($P = 0.39$). No significant improvement in %FVC and HRCT findings were found in patients with ILD in either group, and there were no differences in death or ILD progression. The combination of CNIs and MMF might be more effective for decreasing CK levels than MMF alone. Neither treatment arm had a beneficial effect on ILD over a variable observation period.

Keywords Dermatomyositis · Drug therapy · Inflammatory myopathy/CO · Interstitial lung disease · Mycophenolate mofetil · Polymyositis · Tacrolimus

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic rheumatic diseases that include adult polymyositis (PM) and adult dermatomyositis (DM) [1]. Glucocorticoids are the standard first-line therapy for patients with PM/DM, but approximately 50% of patients fail to respond when the glucocorticoids were tapered. Patients refractory to glucocorticoid therapy have been treated with a variety of immunosuppressants, most commonly methotrexate (MTX), azathioprine (AZA), intravenous immunoglobulin (IVIg), and calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (TAC) [2]. Mycophenolate mofetil (MMF) is an immunosuppressant widely used in organ transplantation and currently used for autoimmune conditions, mostly systemic lupus erythematosus (SLE) [3]. Recently, combination therapy with MMF and TAC showed significant efficacy in lupus nephritis in a 6-month trial [4]. Although MMF has been found efficacious in connective tissue disease-associated interstitial lung disease (CTD-ILD) [5] and refractory myositis [6–10], the efficacy of combination therapy with MMF and TAC in PM/DM or myositis-associated ILD has not been elucidated.

Here, we analyzed the efficacy and tolerability of MMF with or without CNIs in patients with inflammatory myopathy on prednisolone (PSL) refractory to conventional immunosuppressive therapy.

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Material and methods

Patients

We performed a retrospective study of Japanese patients with PM/DM. We selected patients who met Bohan and Peter's criteria [11] and who visited St. Marianna University Hospital from 2006 through 2015, and who had failed therapy with at least one immunosuppressant and had started MMF treatment. Of 150 PM/DM cases, 48 patients had been treated with only PSL. We found 28 patients with AZA, 25 patients with TAC, 19 patients with CsA, 11 patients with MTX, and 19 patients with MMF. In this study, we enrolled the 19 patients who had been treated with MMF. We further divided the patients into two groups according to whether or not they also received therapy with a CNI. This study was approved by the Ethics Committee of St. Marianna University School of Medicine (approval number 3502). Since this study was conducted under a retrospective cohort design without any samples taken besides those for clinical use, written informed consent was not required, in accordance with the guidelines of the Ministry of Health, Labour, and Welfare of Japan.

Data collection

Clinical information was obtained from all records at baseline and at the final time point, defined as the last follow-up examination or discontinuation of MMF, whichever occurred first. All prior treatments were documented, including steroid dose and previous immunosuppressive therapies. Manual muscle testing 8 (MMT8) was scored as previously reported in which eight proximal, distal, and axial muscle groups tested unilaterally [12] on available records. Efficacy was measured by changes in creatine kinase (CK) level and PSL dose pre- and post-MMF treatment. For those with ILD, percent forced vital capacity (%FVC) was measured. ILD progression was defined by more than 10% decline of %FVC from baseline [13].

High-resolution computed tomography and scoring

Thin-section CT (1-mm thickness) was taken at 10-mm intervals from the apex to base of the lung. Baseline and the final high-resolution computed tomography (HRCT) findings were assessed by two physicians (H.H. and H.I.) in a blinded manner. The lesion of ILD on HRCT was scored as previously described [14]. Briefly, three CT levels were pre-selected: mid-arch of the aorta, tracheal carina, and 1 cm above the dome of the right diaphragm. Allowance was made for differences in lung volume at each level. The weighting ratios for the three levels were 1.0, 1.20, and 1.45, respectively. The estimated percentage (to the nearest 5%) of the lung lesions at each level was multiplied by the corresponding ratio and calculated, which was designated as the CT score of the total extent of ILD.

Statistical analysis

Continuous values are shown as mean ± standard deviation (SD). Differences between the groups were analyzed using the Mann-Whitney *U* test for nonparametric data and the chi-squared or Fisher's exact test for categorical data. Change in CK, %FVC, and PSL dose between baseline and final time point were analyzed using the Wilcoxon *t* test. Deterioration-free rates were calculated using the Kaplan-Meier method, and differences between the two groups were tested with a log-rank test.

Results

Clinical characteristics

Demographic and clinical features when MMF was started are shown in Table 1. Seven patients had undergone therapy with MMF and CNIs, and 12 had received MMF only. Average observational periods were 14.3 ± 13.7 months in patients with MMF and 18.6 ± 20.5 months in those with the MMF and CNIs ($P = 0.29$). Patients given therapy with MMF and CNIs had a significantly longer disease duration ($P = 0.01$), received a larger dose of MMF ($P = 0.04$), and were more likely to have received previous CsA compared to those treated with MMF only. Since all the patients with MMF and CNIs had taken CNIs when MMF was newly added, more patients had received CNIs comparing to MMF group. Previous average use of immunosuppressants was 1.9 ± 0.7 in the MMF and 3.0 ± 0.8 in the MMF and CNIs group ($P = 0.35$) and they were intravenous cyclophosphamide (41.7 vs 28.5%, $P = 0.52$), AZA (58.3 vs 71.4%, $P = 0.56$), TAC (25.0 vs 57.1%, $P = 0.16$), CsA (25.0 vs 85.7%, $P = 0.01$), and MTX (16.7 vs 14.8%, $P = 0.89$).

Efficacy evaluations

We next focused on the efficacy of MMF vs. MMF and CNIs combination therapy. Figure 1a shows a reduction in CK levels between the baseline and final visit. A borderline significant reduction was seen in patients on MMF and CNIs but not in those on MMF alone ($P = 0.05$ and $P = 0.33$, respectively). CK levels at the final visit were lower in the patients with MMF and CNIs compared to those on MMF ($P = 0.04$). We evaluated %FVC change in patients with ILD (Fig. 1b) and found there was no significant difference between baseline and final visits in either group. Figure 1c shows a reduction in daily PSL dose in both groups between baseline and final visit ($P = 0.03$ and $P = 0.03$, respectively). In analysis on CT score, no difference was observed between baseline and final visit in either group (Fig. 1d). There were two deaths due to ILD exacerbation in the MMF group and no patient in the

Table 1 Clinical features of patients with inflammatory myopathy treated with mycophenolate mofetil alone or in combination with calcineurin inhibitor

Baseline characteristics	Treatment group		*P*
	MMF ($n = 12$)	MMF + CNIs ($n = 7$)	
Gender (% female)	9 (75.0)	6 (85.7)	0.68
Age (years)	52.8 ± 16.6	57.1 ± 10.4	0.42
Polymyositis (%)	4 (33.3)	1 (14.3)	0.45
Dermatomyositis (%)	8 (66.6)	6 (85.7)	0.45
Disease duration (months)	31.8 ± 38.9	88.4 ± 65.8	0.01
Observation period (months)	14.3 ± 13.6	18.6 ± 20.5	0.29
Interstitial lung disease (%)	9 (75.0)	6 (85.7)	0.68
Anti-nuclear antibody (%)	7 (58.3)	3 (42.9)	0.51
Anti-ARS antibody (%tested)	2 (33.3)	5 (71.4)	0.24
Ani-Jo-1 antibody (%tested)	0 (0)	1 (20.0)	0.53
Anti-Ro/SSA antibody (%tested)	4 (40.0)	1 (16.7)	0.32
CK (IU/L)	213.2 ± 191.2	263.1 ± 254.6	0.32
Aldolase (U/L)	8.6 ± 3.9	10.3 ± 8.6	0.32
LDH (U/L)	277.3 ± 74.1	271.3 ± 80.8	0.44
Ferritin (ng/mL)	949.6 ± 2174.1	115.8 ± 121.4	0.26
KL-6 (U/mL)	846.2 ± 564.2	730.2 ± 518.0	0.34
%FVC (%)	72.3 ± 24.2	87.2 ± 15.3	0.09
%DLCO (%)	50.6 ± 27.6	56.7 ± 5.2	0.34
MMT8	72.0 ± 8.2	76.0 ± 5.6	0.29
Muscle biopsy performed (%)	10 (83.3)	6 (85.7)	0.89
Initial treatment			
Prednisolone (mg/day)	15.6 ± 8.8	13.6 ± 8.9	0.31
Tacrolimus (%)	–	2 (28.6)	–
Cyclosporine (%)	–	5 (71.4)	–
MMF max dose (mg/day)	1270.8 ± 558.6	1785.7 ± 566.9	0.04
Previous treatment			
IVCY (%)	5 (41.7)	2 (28.5)	0.52
AZA (%)	7 (58.3)	5 (71.4)	0.56
Tacrolimus (%)	3 (25.0)	4 (57.1)	0.16
Cyclosporine (%)	3 (25.0)	6 (85.7)	0.01
MTX (%)	2 (16.7)	1 (14.8)	0.89
IVIg (%)	3 (25.0)	3 (42.9)	0.41

MMF mycophenolate mofetil, *CNi* calcineurin inhibitors, *ARS* aminoacyl tRNA synthetase, *CK* creatinine kinase, *LDH* lactate dehydrogenase, *KL-6* Krebs von den Lungen-6, *FVC* forced vital capacity, *DLCO* diffusing capacity of the lung carbon monoxide, *MMT* manual muscle testing, *IVCY* intravenous cyclophosphamide, *AZA* azathioprine, *MTX* methotrexate, *IVIg* intravenous immunoglobulin

MMF + CNIs group (Table 2) and no significant difference was observed in cumulative survival rate ($P = 0.29$) (Fig. 2a). A slightly higher ILD progression-free rate was observed in the combination group, although the difference was not significant ($P = 0.51$) (Fig. 2b). Nine patients (75.0%) in MMF alone and four (57.1%) in MMF and CNIs combination discontinued MMF in this study. (Table 2). Frequency of other complications, including infection abnormal liver dysfunction, cytopenia, proteinuria, and tremor, was not different between these groups.

Discussion

We found a significant reduction in CK levels in patients taking the MMF and CNIs in combination but not in those on MMF only. Both treatments allowed reductions in PSL dose but neither treatment arm had a beneficial effect on ILD over a variable observation period.

Treatment of inflammatory myopathies is very challenging. Although the small number of randomized, double-blind controlled clinical trials have been completed, there are currently

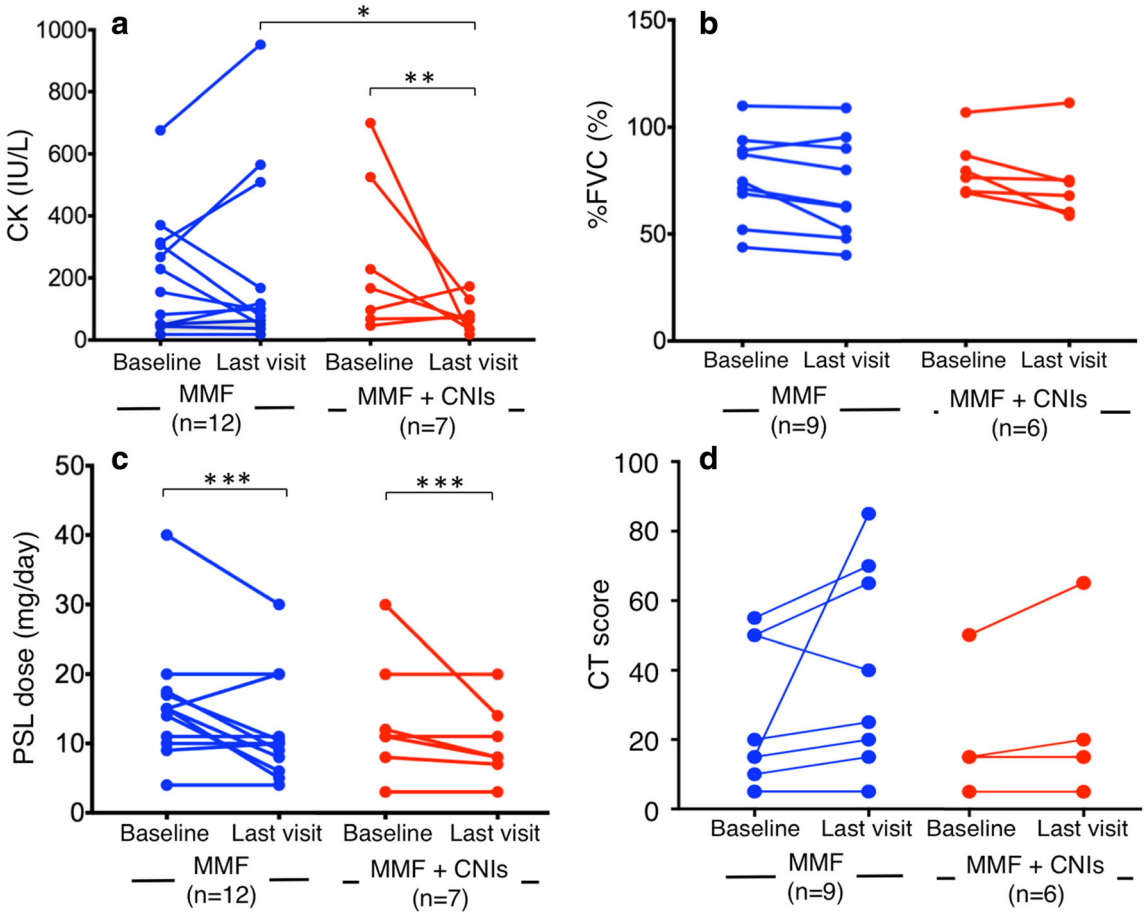

Fig. 1 Therapeutic effect of MMF and the combination therapy. **a** Reduction of CK levels between baseline and final visit. A significant reduction was seen in patients on MMF and CNIs therapy ($P = 0.05$). CK levels at the final visit were significantly lower in the MMF and CNIs group than the MMF therapy group ($P = 0.04$). **b** Significant changes in %FVC were not seen in either treatment group. **c** Daily PSL dose was significantly lower in both groups compared with the baseline ($P = 0.03$ in MMF, $P = 0.03$ in MMF and CNIs). **d** No significant difference in CT scores was observed between baseline and final visit in both MMF and MMF + CNIs group. MMF, mycophenolate mofetil; CNI, calcineurin inhibitors; CK, creatinine kinase; FVC, forced vital capacity; PSL, prednisolone. *$P = 0.04$, **$P = 0.05$, ***$P = 0.03$

no standard therapeutic guidelines. Since most of the patients with PM/DM fail to respond to glucocorticoids monotherapy for long-term observation, additional immunosuppression may be required to allow a reduction in the dose of glucocorticoids without disease flare [15]. The first-line conventional immunosuppressive drug is generally MTX or AZA [2] and use of CNIs has been reported in particularly those with coexisting ILD [16]. In our study, AZA was most frequently used and MTX was less frequently used in previous treatment. Since most of the patients were complicated by ILD, MTX may not be preferred in attending physicians for safety concerns [2].

Table 2 Comparison of complications in patients with inflammatory myopathy treated with mycophenolate mofetil alone or in combination with calcineurin inhibitor

Complications	Treatment group		*P*
	MMF ($n = 12$)	MMF + CNIs ($n = 7$)	
Death	2 (16.7)	0 (0)	0.28
Infection	1 (8.3)	1 (14.3)	0.59
Abnormal liver function	1 (8.3)	1 (14.3)	0.59
Cytopenia	1 (8.3)	0 (0)	0.47
Proteinuria	1 (8.3)	0 (0)	0.47
Tremor	1 (8.3)	0 (0)	0.47
Oral ulceration	0 (0)	1 (14.3)	0.15

MMF mycophenolate mofetil, *CNI* calcineurin inhibitors;

Several small case series have reported on the efficacy of MMF in IIMs [6–10]. MMF has been successful in treating refractory PM/DM when conventional treatment was ineffective or poorly tolerated. Furthermore, MMF has also been increasingly used in myositis-associated ILD. In the largest cohort of CTD-ILD, 32 patients with PM or DM treated with MMF for a median of 897 days showed significant improvements in %FVC at 52, 104, and 156 weeks [5]. In our study, adding MMF to glucocorticoid treatment did not show significant efficacy in terms of CK reduction, %FVC improvement,

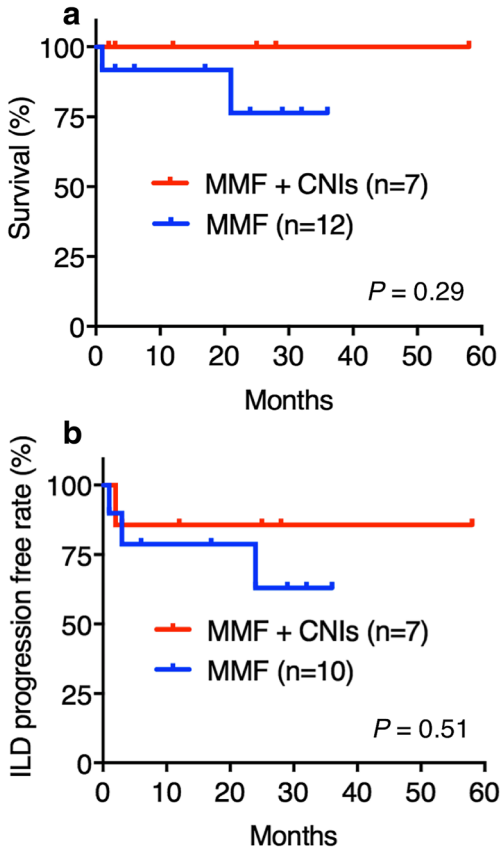

Fig. 2 Death and interstitial lung disease progression-free rate. Survival (**a**) or interstitial lung disease (ILD) progression-free rate (**b**) was not different between the treatment groups ($P = 0.29$ and $P = 0.51$, respectively)

HRCT findings, or ILD progression. Adding a MMF and CNI, however, showed a significant reduction in CK levels. Since this study was conducted retrospectively, and because of the rarity of the disease, the enrolled patients had heterogeneous clinical histories and observational period was varied. The dose of MMF was significantly lower in the MMF group than in the MMF and CNIs group. Although we have tried to enroll the patients who had taken MMF at more than 1000 mg/day, too small number of patients was obtained to draw the conclusion. Since a previous study reported improvement in %FVC at 52 weeks after initiation [5], our observational periods may have been too short. These baseline clinical differences may have been behind the lower apparent efficacy in the MMF treatment group.

Adding CNIs to MMF and glucocorticoid treatment resulted in a fairly good prognosis. Examination of muscle biopsy samples shows a deep association between lymphocytes including T cells or B cells and inflammation in PM/DM [1]. Recently, C protein-induced myositis was established as murine model of PM [17]. Its histologic examination revealed a common pathologic feature of PM, involving abundant infiltration of CD8 cells in the endomysial site of the injured muscle and suppression of myositis was achieved by depletion of both CD4 and CD8 cells. Thus, T cells have long been suggested as therapeutic targets in PM/DM. Furthermore, B cells have been reported to play a critical pathogenic role in myositis [18]. They localized to the perivascular regions of DM muscle and are found in the inflammatory infiltrates of both PM and DM [18]. B cells present antigen to T cells and secrete pro-inflammatory cytokines and contribute to establishment of myositis. Its contribution has been suggested by clinical efficacy with rituximab initiation in PM or DM patients [19]. Since CNIs, including CsA and TAC, inhibit IL-2-induced activation of T cells [2] and MMF, a reversible inhibitor of inosine monophosphate dehydrogenase induces the inhibition of T and B cells proliferation [5], dual inhibition of T cells and B cells by CNIs and MMF may be beneficial for some PM/DM patients with resistant disease.

The present study is limited by its single-center, retrospective design, variable observational periods, and small sample size, which may have limited the significance of some findings. Since the enrolled patients had heterogeneous clinical histories and attending physicians decided to add MMF on CNIs in MMF + CNIs group, they were likely to be more treatment resistant. Serial change of muscle weakness (MMT), Health Assessment Questionnaire (HAQ), and total improvement score [20] were not collected in all the patients and only muscle enzyme was compared in this study. Since therapeutic response in IIMs is mainly assessed by the change of the composite measure shown above, our results may only indicate a part of improvement. A multi-center, prospective study is required to confirm our findings.

In conclusion, combination of MMF and CNIs may be more effective for decreasing CK levels than MMF, but neither treatment arm exerted a beneficial effect on ILD over short-term observation.

Compliance with ethical standards

This study was approved by the Ethics Committee of St. Marianna University School of Medicine (approval number 3502). Since this study was conducted under a retrospective cohort design without any samples taken besides those for clinical use, written informed consent was not required, in accordance with the guidelines of the Ministry of Health, Labour, and Welfare of Japan.

Disclosures None.

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