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ORIGINAL ARTICLE

Efficacy of mycophenolate mofetil in Japanese patients with systemic lupus erythematosus

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Abstract

Objectives To assess the renal and non-renal efficacy of mycophenolate mofetil (MMF) in Japanese patients with systemic lupus erythematosus (SLE).

Methods We conducted a retrospective study to assess the renal and non-renal efficacies of MMF in Japanese patients with systemic lupus erythematosus (SLE). We analyzed 14 patients with lupus nephritis (LN) who were given MMF, and 13 patients who received monthly intravenous cyclophosphamide (IVCY) as induction therapy, and a further 19 patients without LN who were treated with MMF, and 13 patients who took tacrolimus (TAC) to reduce glucocorticoid dosages. We assessed the therapeutic effects of each therapeutic regime on renal and non-renal disease manifestations over a six-month period after treatment initiation.

Results Median urine protein to creatinine ratios in the MMF and IVCY groups significantly decreased from 2.2 to 0.7 g/gCr and from 3.3 to 0.5 g/gCr, respectively. Significant improvements in serum immunological variables (serum complements C3 and C4 and the anti-double stranded DNA antibody) and reductions in the SLE disease activity index (SLEDAI) and daily prednisolone dosages were observed in each group with LN. MMF and TAC significantly improved SLEDAI and serum immunological variables and reduced daily prednisolone dosages in patients without LN.

Conclusion The present results demonstrated that MMF might be an effective treatment for renal and non-renal manifestations in Japanese patients with SLE and has potential as a good therapeutic alternative and steroid-sparing agent.

Keywords Cyclophosphamide · Lupus nephritis · Mycophenolate mofetil · Systemic lupus erythematosus · Tacrolimus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, and lupus nephritis (LN) is a common manifestation of SLE. LN occurs in up to 60% of patients with SLE and contributes to morbidity and mortality [1, 2]. The conventional induction treatment for LN has been intravenous cyclophosphamide (IVCY) in addition to glucocorticoids; however, this is associated with a risk of adverse effects, including infection, hemorrhagic cystitis, ovarian failure, and secondary malignancy. Mycophenolate mofetil (MMF) is an immunosuppressant, and randomized controlled trials have shown its similar efficacy to IVCY as induction therapy for LN [3, 4]. Based on the findings of these trials, induction therapy for proliferative LN recommended by the American College of Rheumatology (ACR) and European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association is glucocorticoids with IVCY or MMF [5, 6].

Despite the worldwide use of MMF, it was only approved for the treatment of LN in Japan in 2015. Therefore, few studies have evaluated the renal responses of MMF in Japanese patients. Moreover, the effects of MMF on non-renal disease have not yet been studied in detail in the Japanese population. Although a post hoc analysis of the outcomes of the Aspreva Lupus Management Study strongly

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indicated that MMF ameliorated non-renal manifestations [7], we have conventionally used tacrolimus (TAC). TAC is an alternative treatment with demonstrated effectiveness against the various manifestations of SLE and the ability to reduce glucocorticoid dosages [8–11].

Therefore, we conducted a retrospective clinical study to assess the renal and non-renal efficacies of MMF in Japanese patients with SLE and evaluate the validities of MMF, IVCY, and TAC.

Patients and methods

Study design and patients

We conducted a retrospective study. Adult Japanese SLE patients who visited Toho University Omori Medical Center between May 2010 and August 2017 were surveyed by referring to their clinical records. All patients fulfilled the 1997 revised ACR criteria for SLE [12].

The diagnosis of nephritis was made by the detection of elevated serum creatinine, proteinuria, and/or active urine sediments. We assessed the therapeutic effects of MMF and IVCY on renal and non-renal manifestations over a six-month period and those of MMF and TAC on non-renal disease manifestations 1, 3, and 6 months after treatment initiation.

Treatment protocol

Our standard induction therapy for LN is glucocorticoids, with the initiation of prednisolone at a dose of 1 mg/kg/day for 2 to 4 weeks. Glucocorticoids were gradually tapered by 10% of the last dose or 5 mg, as judged by the attending physician. MMF was started at a dose of 250 mg to 1 g daily, and its dosage was increased to a maximum of 2 g, which is the suggested dose by the ACR for Asians [5]. CY was administered intravenously at a dose of 500 to 700 mg monthly for a total of 6 months as per the National Institute of Health protocol [13]. TAC was initiated at a dose of 0.5 to 1 mg daily and increased up to 3 mg according to the national health insurance guidelines in Japan, and we measured blood concentrations of TAC 12 h after its administration in order to avoid exceeding 10 ng/mL in every visit. Each physician involved in this study independently decided dosage adjustments for each drug. We excluded patients being concomitantly treated with other immunosuppressive or biological disease-modifying anti-rheumatic drugs or immunomodulatory drugs. Pulsed methylprednisolone therapy was not given to all patients. Adjunctive treatments, such as an angiotensin-converting enzyme or angiotensin II receptor blocker, were administered if deemed necessary.

Study assessments

Renal responses were measured using serum creatinine, the serum estimated glomerular filtration rate (eGFR), and spot urine protein to creatinine ratio. Serum eGFR was estimated with the aid of revised equations for eGFR from serum creatinine in Japan [14]. Renal pathology was assessed according to the 2003 International Society of Nephrology/Renal Pathology Society classification of LN [15]. Non-renal responses were assessed by measuring immunological variables including the anti-double stranded DNA (dsDNA) antibody and serum complements C3 and C4. We also assessed the SLE disease activity index (SLEDAI) [16] and adverse events from medical records. An adverse event was defined as any unfavorable medical event that newly occurred during the study period. Severe adverse events were defined as those that resulted in death, were life-threatening, or required prolonged inpatient hospitalization.

Statistical analysis

We performed an intention-to-treat analysis. The present results were expressed as medians [interquartile range]. The Wilcoxon rank-sum test was used to compare the baseline data of two groups. Differences between baseline and various time points were compared using Dunnett's multiple comparison test. Fisher's exact test was used to compare categorical data between two groups. P values < 0.05 were considered to be significant. Statistical analyses were performed with Prism ver. 5.0 software (GraphPad Software, San Diego, CA, USA). Missing data were accounted for by the last observation carried forward.

Results

Baseline characteristics

In the first study, we analyzed 14 patients with LN who were treated with MMF and 13 patients who received monthly IVCY as induction therapy for LN. In MMF group, ten patients were administered MMF for LN flares. Their median duration of SLE was 10.5 years, and their median duration until LN flares from remission was 2.8 years. At the LN flares, TAC ($n = 4$), cyclosporine ($n = 2$), or azathioprine ($n = 1$) were concomitantly used. The other four patients of MMF group and all 13 patients of IVCY group were treated for new-onset LN. The baseline demographic and clinical data of these patients are shown in Table 1. Baseline age and sex were similar between the two groups, although the median initial daily prednisolone dose was higher and the median duration of SLE was longer in the IVCY group than in the MMF group. Renal biopsy was performed on 23 out of the 27 patients at

Table 1 Demographics and clinical data at baseline of the study population

	With LN		*P*	Without LN		*P*
	MMF ($n = 14$)	IVCY ($n = 13$)		MMF ($n = 19$)	TAC ($n = 19$)	
Age (years)	40.5 [30.5–48.5]	33.0 [25.5–44.0]	0.67	34.0 [27.0–45.0]	33.0 [23.0–45.0]	0.63
Male/Female	6/8	2/11	0.21	3/16	0/19	0.23
Duration of SLE (years)	10.5 [3.5–17.3]	0.0 [0.0–4.0]	0.04	7.0 [1.0–11.0]	1.0 [0.0–8.0]	0.34
Initial prednisolone dose (mg/day)	19.0 [9.8–50.0]	50.0 [50.0–50.0]	0.02	12.5 [8.0–40.0]	12.0 [8.0–25.0]	0.12
Renal pathological findings						
III, no.	1	1				
III+V, no.	2	2				
IV, no.	3	6				
IV+V, no.	2	3				
V, no.	3	0				
Unknown, no.	3	1				
Serum creatinine (mg/dL)	0.92 [0.68–1.7]	0.76 [0.62–1.3]	0.38			
eGFR (ml/min/1.73m^2)	51.0 [35.8–100.1]	74.2 [51.1–86.8]	0.68			
Urine P/Cr ratio (g/gCr)	2.2 [0.88–3.8]	3.3 [1.5–6.1]	0.17			
SLEDAI	12.0 [6.8–14.5]	16.0 [13.0–17.0]	0.02	4.0 [3.0–5.0]	4.0 [2.0–4.0]	0.32
Serum C3 (mg/dL)	84.0 [41.0–104.0]	46.0 [31.0–60.0]	0.04	52.5 [46.0–67.8]	68.0 [46.5–82.5]	0.16
Serum C4 (mg/dL)	16.5 [5.8–26.0]	4.0 [3.5–6.5]	< 0.01	9.0 [5.0–17.0]	13.0 [5.5–16.5]	0.89
Anti-dsDNA antibody (IU/mL)	26.5 [10.0–111.5]	54.0 [13.5–315.5]	0.12	31.0 [11.0–61.0]	36.0 [19.5–56.5]	0.62

Data are expressed as medians [interquartile range]. *$P < 0.05$ versus baseline by the Wilcoxon rank-sum test

MMF mycophenolate mofetil, *IVCY* intravenous cyclophosphamide, *TAC* tacrolimus, *LN* lupus nephritis, *P/Cr* protein to creatinine ratio, *SLEDAI* systemic lupus erythematosus disease activity index

treatment initiation. All patients who had undergone renal biopsy had proliferative and/or membranous LN. Baseline renal parameters were similar, whereas significant differences were observed in SLEDAI scores and serum complements C3 and C4 between the MMF and IVCY groups.

In the second study, we analyzed 19 patients without LN who were treated with MMF and TAC to reduce glucocorticoid dosages. The baseline demographic and clinical data of these patients were similar (Table 1).

Efficacies of MMF and IVCY in patients with LN

In the MMF group, improvements in proteinuria from baseline were observed in months 2 to 6 (Fig. 1a). In the IVCY group, improvements from baseline were noted in months 1 to 6. The median urine protein to creatinine ratio decreased from the baseline value of 2.2 to 0.7 g/gCr in month 6 ($P < 0.01$) in the MMF group (Table 2), and from the baseline value of 3.3 to 0.5 g/gCr in month 6 ($P < 0.01$) in the IVCY group. Median serum creatinine levels decreased from 0.92 to 0.66 mg/dL and from 0.80 to 0.70 mg/dL after the initiation of therapy in the MMF and IVCY groups, respectively. Although no significant changes were observed in serum eGFR, it gradually increased after the initiation of therapy in both groups (median MMF, 51.0 to 82.7 ml/min/1.73m^2; IVCY, 74.2 to 74.6 ml/min/1.73m^2). Increases in eGFR were greater in the MMF group than in the IVCY group. Moreover, significant reductions were observed in SLEDAI in both groups (Fig. 1b and Table 2). Median SLEDAI significantly decreased from 12.0 to 4.0 in the MMF group and from 16.0 to 2.0 in the IVCY group. Serum titers of the anti-dsDNA antibody also significantly decreased in month 6 from baseline in both groups, and serum levels of complements C3 and C4 significantly increased in month 6 from baseline in both groups

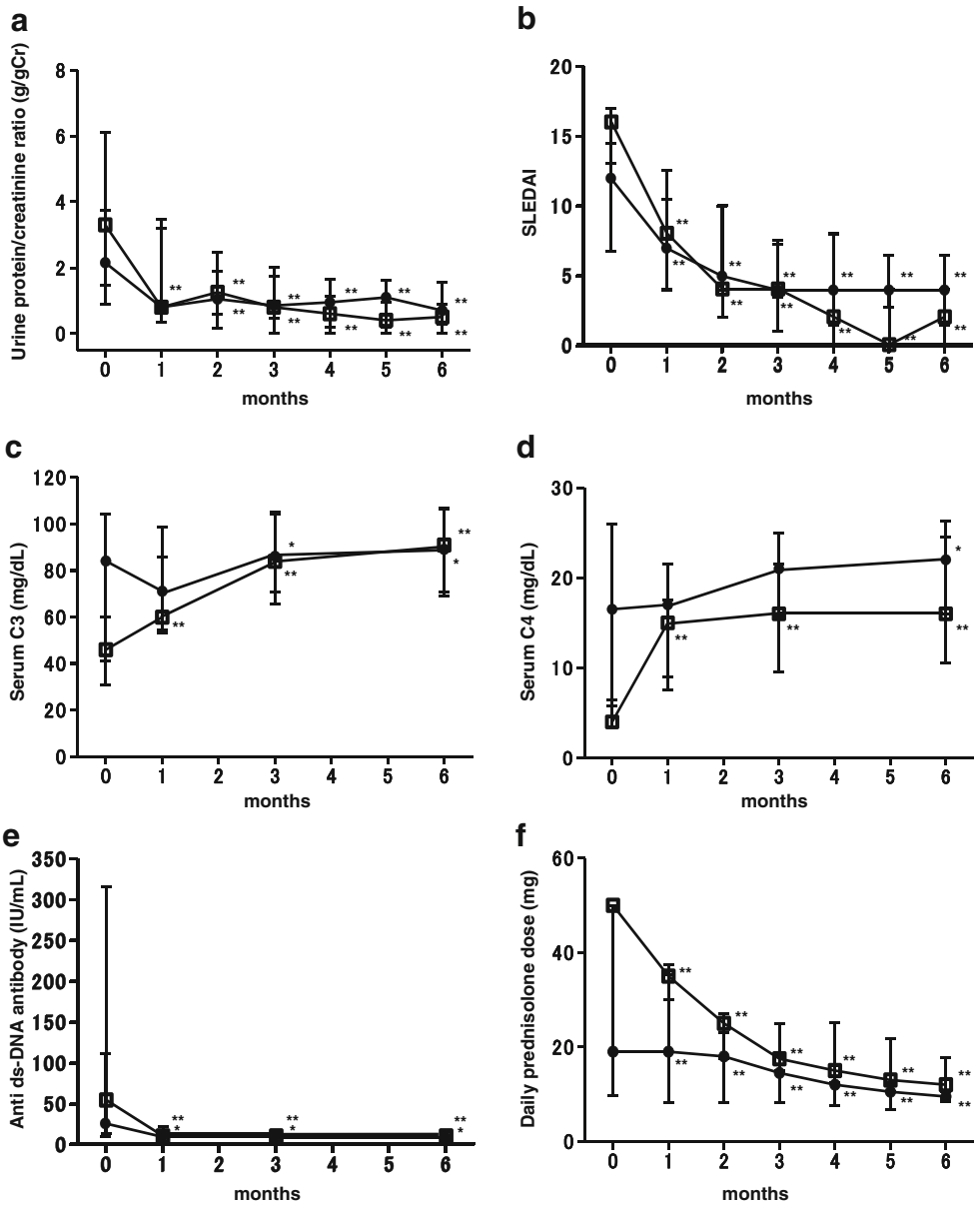

Fig. 1 Changes in the urine protein/creatinine ratio (**a**), SLEDAI (**b**), serum C3 (**c**), serum C4 (**d**), serum anti-dsDNA antibody (**e**), and daily prednisolone dose (**f**) in the MMF group (circles) and IVCY group (empty squares) during glucocorticoid therapy. Data are expressed as medians [interquartile range]. $*P < 0.05$ versus baseline; $**P < 0.01$ versus baseline by Dunnett's multiple comparison test

(Fig. 1c–e and Table 2). Daily prednisolone dosages also significantly decreased in months 1 to 6 from baseline in both groups (Fig. 1f).

Efficacies of MMF and TAC in patients without LN

As shown in Fig. 2a and Table 3, median SLEDAI significantly decreased in months 1 to month 6 from baseline and from 4.0 to 2.0 in both groups. Serum titers of the anti-dsDNA antibody also significantly decreased in month 6 from baseline in both groups, while serum levels of complements C3 and C4 significantly increased in month 6 from baseline in both groups (Figs. 2b–d and Table 3). Significant reductions in daily prednisolone dosages were observed in months 2 to 6 from baseline, and median daily prednisolone doses in the MMF and TAC groups decreased from 12.5 to 10.0 mg and from 12.0 to 9.0 mg, respectively (Fig. 2e and Table 3).

Adverse events

Table 4 summarizes the adverse events of each treatment. There were 11 adverse events reported from 65 patients during the follow-up period; however, serious adverse events did not occur in any group. Six adverse events were reported in the MMF group between months 1 and 2: nausea in 2, diarrhea in 1, bacterial pneumonia in 1, genital bleeding in 1, and leukopenia in 1; therefore, MMF was discontinued in these patients.

Table 2 Summary of the changes in biochemical parameters after treatment

	MMF ($n = 14$)		P	IVCY ($n = 13$)		P
	Baseline	Month 6		Baseline	Month 6	
Serum creatinine (mg/dL)	0.92 [0.68–1.7]	0.66 [0.58–1.25]	ns	0.80 [0.62–1.3]	0.70 [0.58–0.92]	< 0.05
eGFR (ml/min/1.73m^2)	51.0 [35.8–100.1]	82.7 [51.0–96.0]	ns	74.2 [51.1–86.8]	74.6 [54.4–86.3]	ns
Urine P/Cr ratio (g/gCr)	2.2 [0.88–3.8]	0.7 [0.28–1.6]	< 0.01	3.3 [1.5–6.1]	0.5 [0.0–0.9]	< 0.01
SLEDAI	12.0 [6.8–14.5]	4.0 [1.5–6.5]	< 0.01	16.0 [13.0–17.0]	2.0 [0.0–5.5]	< 0.01
Serum C3 (mg/dL)	84.0 [41.0–104.0]	89.0 [70.5–106.5]	< 0.05	46.0 [31.0–60.0]	91.0 [69.0–107.0]	< 0.01
Serum C4 (mg/dL)	16.5 [5.8–26.0]	22.0 [16.0–26.3]	< 0.05	4.0 [3.5–6.5]	15.5 [9.8–25.8]	< 0.01
Anti-dsDNA antibody (IU/mL)	26.5 [10.0–111.5]	10.0 [10.0–10.5]	< 0.05	54.0 [13.5–315.5]	10.0 [10.0–15.0]	< 0.01

Data are expressed as medians [interquartile range]. *$P < 0.05$ versus baseline by the Wilcoxon rank-sum test

MMF mycophenolate mofetil, *IVCY* intravenous cyclophosphamide, *eGFR* estimated glomerular filtration rate, *P/Cr* protein to creatinine ratio, *SLEDAI* systemic lupus erythematosus disease activity index

TAC was discontinued in two patients due to nausea and diarrhea in month 3. Three patients withdrew from IVCY therapy because of bacterial pneumonia, nausea, and leukopenia in month 3.

Discussion

This retrospective study demonstrated that MMF exerted therapeutic effects on renal and non-renal disease manifestations in Japanese patients with SLE.

The present results demonstrated the effects of MMF on renal responses in Japanese patients with LN. The similar efficacies of MMF and IVCY as induction therapy for LN have already been reported in various races/ethnicities [3, 4]. However, IVCY had been more widely used in Japan since MMF was off-label for that purpose until 2015. Therefore, most patients with LN who were administered MMF in the present study were treated for LN flares, whereas all patients in the IVCY group received the treatment for new-onset LN. Consequently, significant differences were observed in the duration of SLE and initial daily prednisolone doses between the MMF and IVCY groups. In comparisons of patients with new-onset and flared LN, significant differences were observed in initial daily prednisolone doses and SLEDAI (median [interquartile range]; 50.0 [35.0–50.0] vs 10.0 [8.3–30.0], 17.0 [13.0–21.8] vs 7.5 [6.0–12.0], respectively). This result indicated, in view of the treatment of LN flares, that LN flares are treatable with MMF and minimum increases in the dosage of prednisolone. A small trial that compared the efficacy of MMF in combination with standard-dose or reduced-dose glucocorticoids as induction therapy for LN reported that a reduced dose of prednisolone lowered the risk of infection in LN patients treated with MMF [17]. Since the side effects of glucocorticoids, including infection, need to be considered, this result suggests that the use of MMF reduces additional increases in prednisolone dosages during the treatment of LN and is worthwhile.

Furthermore, MMF appeared to be more effective than IVCY for improving eGFR in the present study. A post hoc analysis of ALMS in patients with eGFR < 30 mL/min/1.73m^2 showed markedly faster and higher rates of improvements in eGFR in patients treated with MMF than in those receiving IVCY [18]. Since the number of patients with eGFR < 30 mL/min/1.73m^2 in the present study was small ($n = 3$ in the MMF group, $n = 2$ in the IVCY group), we were unable to examine whether the extent of the change in eGFR varied with renal function. In patients with eGFR > 30 mL/min/1.73m^2 in the present study, median eGFR improved from 76.0 to 88.0 mL/min/1.73m^2 in the MMF group and from 76.1 to 80.2 mL/min/1.73m^2 in the IVCY group. Therefore, the present results suggest that MMF improves eGFR regardless of renal function.

We also investigated whether MMF effectively improved non-renal manifestations in Japanese patients with SLE. In patients with LN, a previous randomized controlled clinical trial assessed the non-renal effects of MMF and IVCY using the Systemic Lupus Activity Measure (SLAM) score and immunological variables (serum levels of complements C3 and C4 and the anti-dsDNA antibody) as well as renal efficacy. All of these parameters improved, and there were no significant

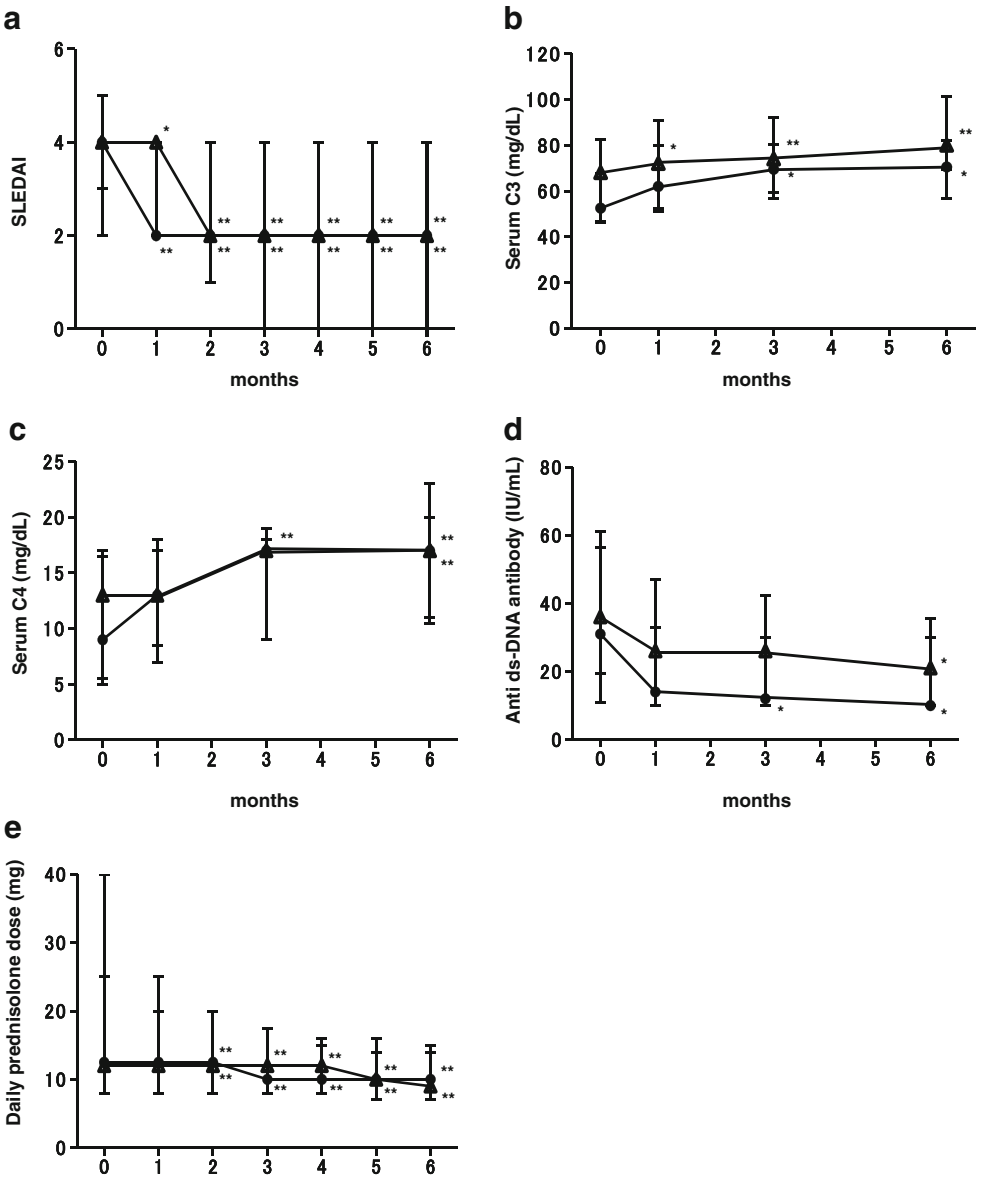

Fig. 2 Changes in SLEDAI (**a**), serum C3 (**b**), serum C4 (**c**), serum anti-dsDNA antibody (**d**), and daily prednisolone doses (**e**) in the MMF group (circles) and TAC group (triangle) during glucocorticoid therapy. Data are expressed as medians [interquartile range]. $*P < 0.05$ versus baseline; $**P < 0.01$ versus baseline by Dunnett's multiple comparison test

Table 3 Summary of the changes in biochemical parameters after treatment

	MMF ($n = 19$)		P	TAC ($n = 19$)		P
	Baseline	Month 6		Baseline	Month 6	
SLEDAI	4.0 [3.0–5.0]	2.0 [0.0–4.0]	< 0.01	4.0 [2.0–4.0]	2.0 [0.0–4.0]	< 0.01
Serum C3 (mg/dL)	52.5 [46.0–67.8]	71.0 [56.8–82.0]	< 0.01	68.0 [46.5–82.5]	80.0 [69.5–101.5]	< 0.01
Serum C4 (mg/dL)	9.0 [5.0–17.0]	17.0 [11.0–20.0]	< 0.01	13.0 [5.5–16.5]	17.0 [10.5–23.0]	< 0.01
Anti-dsDNA antibody (IU/mL)	31.0 [11.0–61.0]	10.0 [10.0–30.0]	< 0.05	36.0 [19.5–56.5]	21.0 [10.0–35.5]	< 0.05
Daily prednisolone dose (mg)	12.5 [8.0–40.0]	10.0 [7.0–14.0]	< 0.01	12.0 [8.0–25.0]	9.0 [7.0–15.0]	< 0.01

Data are expressed as medians [interquartile range]. $*P < 0.05$ versus baseline by the Wilcoxon rank-sum test

MMF mycophenolate mofetil, *TAC* tacrolimus, *SLEDAI* systemic lupus erythematosus disease activity index

Table 4 Adverse events of the treatment

	MMF ($n = 33$)	TAC ($n = 19$)	IVCY ($n = 13$)
Serious adverse event	0	0	0
Gastrointestinal			
Nausea	2	1	1
Diarrhea	1	1	0
Infection			
Pneumonia	1	0	1
Genital bleeding	1	0	0
Laboratory data			
Leukopenia	1	0	1

All values for each treatment group indicate n

MMF mycophenolate mofetil, *TAC* tacrolimus, *IVCY* intravenous cyclophosphamide

differences between the MMF and IVCY groups [19]. A similar retrospective study in Japanese LN patients showed improvements in these immunological variables, with no significant differences between the two groups [20]. These findings were consistent with the present results.

Most clinical trials have primarily focused on renal outcomes; few studies have examined the efficacy of MMF for non-renal manifestations in patients without LN. Bijl et al. [21] treated patients with SLE and an elevated anti-dsDNA antibody titer without clinical signs of disease activity with MMF for 6 months to prevent clinical relapse, and observed a significant reduction in the antibody titer, but failed to demonstrate a reduction in SLEDAI. Riskalla et al. [22] found significant decreases in SLEDAI and prednisone dosages at 3 months and approximately 12 months in SLE patients with and without LN.

In clinical practice in Japan, as in the present study, TAC has been used to treat SLE patients with mild disease activity and non-renal manifestations as well as minor flares of SLE. However, few studies have evaluated the efficacy of TAC [8, 9]. A recent randomized controlled trial compared the effectiveness of MMF and TAC on disease activity measured using SLEDAI-2000 in patients with LN, and showed that MMF was similar to TAC during induction therapy [23]. Our results are consistent with these findings, although we used SLEDAI as a disease activity score.

The occurrence of side effects was similar between the MMF and IVCY groups during induction therapy for LN, which is in agreement with previous findings [3, 4]. The most frequent adverse events observed with MMF were gastrointestinal intolerance (nausea and diarrhea); however, they were not as frequent as previously reported. Based on previous findings, the incidence of gastrointestinal intolerance in the Japanese population appears to be low [24, 25], which may be attributed to the lower induction and maintenance doses of MMF administered to patients.

The limitations of the present study need to be considered. The main limitation is its single-center, retrospective design, small sample size, and short observational period. In addition, we were unable to compare the efficacy of each treatment directly because the baseline demographic and clinical data of patients varied. Further large, prospective, and protocol-based studies with sufficient study populations need to be conducted.

In conclusion, MMF might be an effective treatment for renal and non-renal disease manifestations in Japanese patients with SLE. Moreover, MMF has potential as a good therapeutic alternative and steroid-sparing agent. Further studies in the Japanese population are needed to prove the efficacy and safety of MMF, which has already been shown in other races.

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Compliance with ethical standards

Ethical standards This study was approved by the Ethics Committee at Toho University Omori Medical Center (approval no. M17140) and was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments, and Ethical Guidelines for medical research targeting people by Ministry of Health, Labour and Welfare of the Japanese Government.

Conflict of interest HS received speaker fee from Chugai Pharmaceutical Co., Ltd. SM received speaker fee from Chugai Pharmaceutical Co., Ltd., and Pfizer Japan Inc. SK received research grants from Astellas Pharma Inc., Ayumi Pharmaceutical Co., and Chugai Pharmaceutical Co., Ltd. TN received grant/research support from Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Ayumi Pharmaceutical Co., Pfizer Japan Inc., and Shionogi & Co., Ltd., consultant fees from Chugai Pharmaceutical Co., Ltd., and speaker fees from Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Ayumi Pharmaceutical Co., and Pfizer Japan Inc.

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