

Comparative efficacy and safety of mizoribine and mycophenolate mofetil for treating systemic lupus erythematosus: a retrospective cohort study

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Abstract

Background: Mizoribine (MZR) is an immunosuppressive agent that selectively inhibits inosine monophosphate dehydrogenase; its actions are considerably similar to those of mycophenolate mofetil (MMF). This study aimed to clarify whether MZR can be a good treatment option for systemic lupus erythematosus (SLE) and to compare the efficacy and safety of MZR and MMF in patients with active SLE.

Methods: We retrospectively compared the efficacy, continuation rate, and safety of MZR (52 patients) and MMF (31 patients) after adjusting for stabilized inverse probability of treatment weighting based on propensity scores. The efficacy endpoints were as follows: cumulative incidence of lupus low disease activity state (LLDAS) or remission attainment and flares and change in prednisolone dose over 2 years. Drug continuation rates were defined as the time from drug initiation to discontinuation for any cause, owing to the lack of efficacy, or owing to adverse events. The safety endpoint was the frequency of adverse events.

Results: Overall, 25 (48.1%) and 13 (25.0%) patients in the MZR group and 18 (58.1%) and 15 (48.3%) in the MMF group achieved LLDAS and remission during the follow-up period, respectively; thus, the cumulative incidence of LLDAS and remission attainment of the two groups was similar after adjustment. Prednisolone dose was steadily reduced in both the groups, and the change in prednisolone dose was nearly identical between the two groups. Drug discontinuation rate due to adverse events and the frequency of all adverse events and infections were higher in the MMF group than in the MZR group, albeit without significance after adjustment.

Conclusion: MZR is as effective as MMF in controlling SLE activity. The adverse events of MZR, whose profile differs from MMF, are comparable to or less than those of MMF. MZR may be a valuable option as an immunosuppressive agent for SLE, as well as MMF.

Keywords: continuation rate, lupus low disease activity, mizoribine, mycophenolate mofetil, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with variable presentations, clinical courses, and prognoses.^{1,2} Although the survival of patients with SLE has improved over recent years, the concern of increased risk of mortality compared with the

general population remains.^{3–5} Long-term use of glucocorticoids, which may lead to several comorbidities and irreversible organ damage, is considered one of the factors associated with excess mortality and requires resolution.^{6–8} Hence, it is important to control disease activity with a minimal dose of glucocorticoids;^{2,9} thus, a combination

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of glucocorticoids with hydroxychloroquine, immunosuppressive agents, and biologics has been the general treatment strategy.^{2,9,10} Because SLE requires long-term treatment and may require treatment with many drugs owing to persistent activity, relapse, and adverse drug events,^{1,11,12} having more alternative drugs with high safety and stable efficacy is beneficial for its appropriate management.

Mizoribine (MZR) is an immunosuppressive agent that inhibits the *de novo* purine biosynthesis by inhibiting inosine monophosphate dehydrogenase, which has inhibitory effects on the proliferation of lymphocytes;^{13–15} its actions are considerably similar to those of mycophenolate mofetil (MMF).^{14,16} MMF is one of the most important immunosuppressive agents used worldwide for SLE. Its effectiveness has been established in patients with lupus nephritis throughout the course of treatment from the initial induction phase to the subsequent maintenance phase.^{17–20} The drug is also widely used in patients with SLE who have other moderate to severe organ involvement than nephritis.^{1,2,21,22} In contrast, MZR, which was developed in Japan and is available in East Asia, has been used as an alternative to MMF especially before MMF was approved for clinical use in Japan in 2016.¹⁵ Post-marketing surveillance of the long-term use of MZR in clinical practice for lupus nephritis and mild active SLE has revealed its efficacy and relatively few adverse events of the drug.²³ Moreover, combination treatment with MZR and tacrolimus was reported to be effective in the induction treatment of lupus nephritis, similar to that with MMF and tacrolimus.^{24–27} Thus, MZR is considered as an effective drug in the treatment of SLE.

Many randomized controlled trials and a meta-analysis have compared the efficacy and safety of MZR and MMF in the field of transplantation, such as kidney transplantation and hematopoietic stem cell transplantation.^{28–30} Reportedly, efficacy, including acute rejection rate and survival, is similar for both drugs.^{28–30} In terms of adverse events, MZR has been reported to have a lower incidence of adverse events than MMF, especially in terms of leukopenia, gastrointestinal symptoms, hepatic dysfunction, and cytomegalovirus reactivation.²⁸ This indicates that MZR may be a safe drug with fewer adverse events that are different from those caused by MMF.²⁸ Although similar results are expected for SLE, this comparison in SLE is limited to an observational study

concerning the induction treatment of lupus nephritis;³¹ whether MMF and MZR have any difference in efficacy and safety in SLE remains unclear.

In this study, we aimed to clarify whether MZR can be a good treatment option for SLE comparable to MMF and compared the efficacy and safety of MZR and MMF in patients with active SLE.

Methods

Patients

We conducted a retrospective analysis of patients with SLE who were treated at the Kyushu University Hospital between January 2013 and August 2020. Patients were consecutively included in this study if they fulfilled the 1997 American College of Rheumatology revised criteria for SLE³² and were newly prescribed MZR or MMF on the basis of consent to treatment obtained from patients in daily clinical practice. Patients were excluded if they were in a lupus low disease activity state (LLDAS);³³ were treated with MZR, MMF, and azathioprine before the study; received other immunosuppressive drugs started just before or at the same time; and were receiving additional intensive treatment, such as cyclophosphamide, rituximab, belimumab, intravenous immunoglobulin, or plasma exchange, during the study. Stable doses of concomitant hydroxychloroquine and calcineurin inhibitors, such as tacrolimus and cyclosporine A, were permitted. MZR at 150 mg/day and MMF at 2 g/day were administered and were adjusted at the discretion of the treating physician. Patients were followed for a maximum of 3 years until the date of drug discontinuation or 31 August 2021.

This study was approved by the ethics committee of Kyushu University Hospital (Fukuoka, Japan; Approval No. 2020–803) on 31 March 2021 and was conducted according to the principles of the Declaration of Helsinki. Owing to the retrospective study design, all study information was disclosed at the site of related facilities. Patient consent was waived according to the committee's guidelines. The reporting of this study conforms to the STROBE statement.³⁴

Clinical and laboratory assessment

We collected patients' information after this study was approved and de-identified the details such

that the identity of the patients may not be ascertained in any way. The information extracted from the medical records included demographic data, laboratory findings, disease activities, medications, adverse events, and outcomes. Disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI).³⁵ Patients with a SLEDAI score of ≥ 6 were considered to have moderately to severely active SLE.¹⁰ Active urinary sediment was defined as hematuria, pyuria, red cell casts, and/or white cell casts.³⁶ Platelets of $< 50,000/\text{mm}^3$ were classified on the basis of moderate to severe thrombocytopenia.² LLDAS was defined as a SLEDAI score of ≤ 4 with no major organ activity and no new disease activity, a physician global assessment (scale, 0–3) of ≤ 1 , a prednisolone dose of ≤ 7.5 mg/day, and well-tolerated immunosuppressive dosages.³³ Remission was defined as a clinical SLEDAI score of 0, a physician global assessment (scale, 0–3) of < 0.5 , irrespective of serology, a prednisolone dose of ≤ 5 mg/day, and stable immunosuppressives.³⁷ A flare was identified as a measurable increase in the disease activity requiring an increased prednisolone dose or addition of immunosuppressive drugs.³⁸

Outcomes

In this analysis, we compared the efficacy, continuation rate, and safety of MZR with those of MMF. The efficacy endpoints were the cumulative incidence of LLDAS or remission attainment without additional immunosuppressive agents, which was defined as the time from drug initiation to first LLDAS or remission attainment, respectively; the cumulative incidence of flares, for which a similar definition was used, and the change in prednisolone dose over 2 years. Drug continuation rate was defined as the time from drug initiation to discontinuation for any cause. A similar definition was used for drug discontinuation rate due to the lack of efficacy or adverse events. The safety endpoint was the frequency of adverse events over a 2-year observational period.

Statistical analysis

Continuous variables were summarized as means \pm standard deviations or medians with interquartile ranges. Categorical variables were reported as frequencies and percentages. Differences between the two groups were analyzed using Student's *t*-test for normally distributed continuous variables, Mann–Whitney U-test

for non-normally distributed continuous variables, and Pearson's chi-square test for categorical variables.

Stabilized inverse probability of treatment weighting (IPTW) based on propensity scores was used to adjust for differences in covariates between the two groups.^{39,40} We estimated the propensity score using a multivariable logistic regression model, including the following prespecified confounding factors: age, sex, disease duration, lupus nephritis, SLEDAI score, serum C3, anti-dsDNA antibody titer, prednisolone dose, simultaneous increase in prednisolone dose, hydroxychloroquine use, tacrolimus use, and cyclosporine A use. The factors had no missing data. Log-transformed values of disease duration, SLEDAI score, serum C3, anti-dsDNA antibody titer, and prednisolone dose were used in the analysis. The balance in the baseline clinical characteristics was assessed between the two groups before and after propensity score weighting using the absolute standardized mean differences, with values of < 0.1 indicating a good balance.⁴¹ Comparison of the two groups was performed after adjusting for stabilized IPTW.

The cumulative incidences of LLDAS or remission attainment and flares were analyzed using cumulative incidence function curves, and the Fine and Gray competing risk regression model was used for group comparisons. Drug discontinuation was considered as a competing risk in this analysis. Comparison of changes in prednisolone dose between the two groups was conducted using a linear mixed-effect model; this model included the fixed effects of treatment, month after drug initiation, and treatment \times month interaction, and the random intercept for patient and random slope for month. Drug continuation rate and drug discontinuation rates due to any cause were analyzed using stabilized IPTW-weighted Kaplan–Meier survival curves, and Cox regression-based test was used for group comparisons. Loss of follow-up was considered as censored data.

We conducted sensitivity analyses excluding mildly active patients with a SLEDAI score of < 6 or patients who received concomitant calcineurin inhibitors.

All tests were two-tailed, and *p*-values of less than 0.05 were considered significant. All analyses were performed using STATA version 16.0 (StataCorp, College Station, Texas, USA).

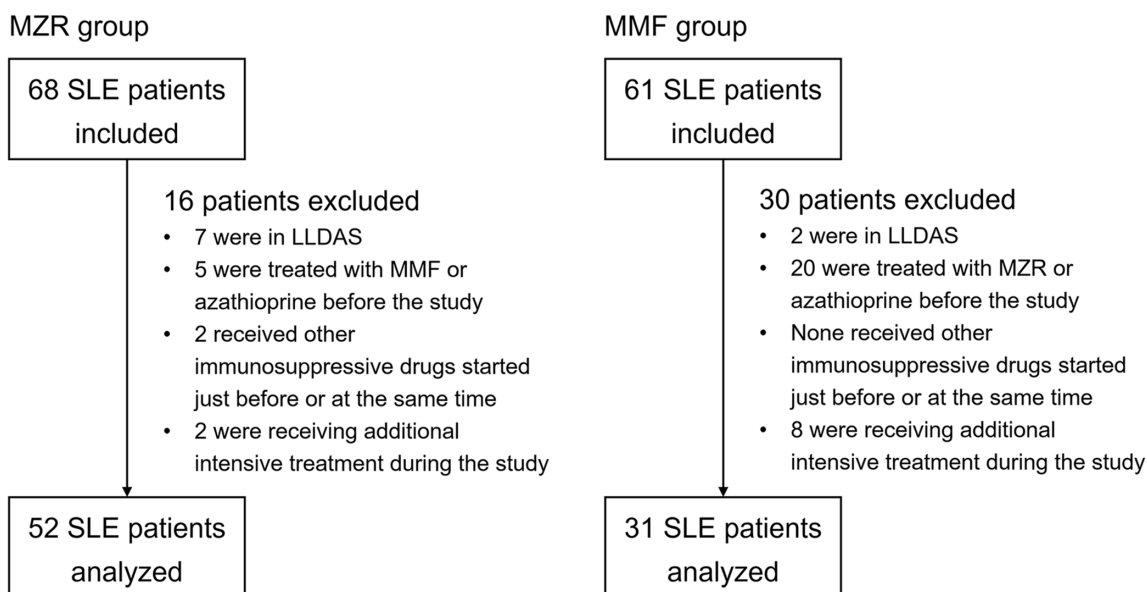


Figure 1. Algorithm for the inclusion and exclusion of the study population.

Results

Patients

Among the 129 patients who initiated MZR or MMF during the study period, 16 and 30 patients in the MZR and MMF groups, respectively, were excluded from this study. Thus, 83 patients were finally analyzed: 52 in the MZR group and 31 in the MMF group (Figure 1). The mean \pm standard deviation age of the patients was 40.3 ± 13.4 years, with 75 (90.4%) patients being female; the median (interquartile range) disease duration was 8 (2–17) years; the median (interquartile range) follow-up duration was 2.4 (0.9–3) years. As described in Table 1, patients in the two groups differed in terms of disease activity and concomitant medications. Patients in the MMF group had a higher rate of complications of active nephritis, higher SLEDAI scores, higher prednisolone doses, more concomitant use of hydroxychloroquine, and less concomitant use of tacrolimus than patients in the MZR group. After propensity score weighting, the clinical characteristics of the two groups were well balanced on all baseline covariates, with the absolute standardized mean difference < 0.1 for each. Table 2 shows the details of the activity and severity of SLE. Although patients in the MMF group had a higher rate of active urinary sediment than patients in the MZR group, no obvious difference was found in the disease activity and severity between the two groups after propensity score weighting.

Efficacy endpoints

During the follow-up period, 25 (48.1%) and 13 (25.0%) patients in the MZR group and 18 (58.1%) and 15 (48.3%) patients in the MMF group achieved LLDAS and remission, respectively. Although patients in the MMF group seemed to have a higher rate of achieving LLDAS than those in the MZR group, the cumulative incidences of LLDAS attainment were similar between the two groups after adjusting for stabilized IPTW based on propensity scores [Figure 2(a)]. The same results were obtained for the cumulative incidences of remission attainment after the adjustment [Figure 2(b)].

In terms of flares, 17 (32.7%) patients in the MZR group and 3 (9.7%) patients in the MMF group experienced a flare. Although patients in the MZR group appeared to have a higher rate of flares than those in the MMF group, the cumulative incidences of flare were almost the same between the two groups after adjusting for stabilized IPTW based on propensity scores [Figure 2(c)].

The prednisolone dose was reduced steadily in both the groups over a 2-year follow-up period. The mean predicted prednisolone dose was decreased from 14.4 to 9.4 mg and 8.4 mg at 1- and 2-year post-initiation of MZR, respectively. It was decreased from 14.2 to 8.1 mg and 6.5 mg at 1- and 2-year post-initiation of MMF, respectively. Thus,

Table 1. Baseline clinical characteristics of patients with SLE.

	Unweighted				Stabilized IPTW weighted		
	MZR (n=52)	MMF (n=31)	p	SMD	MZR (n=49)	MMF (n=35)	SMD
Age, years	39.5 ± 14.2	41.8 ± 11.9	0.45	0.176	40.6 ± 14.7	41.6 ± 12.6	0.078
Female, n (%)	48 (92.3)	27 (87.1)	0.44	0.170	44.1 (90.8)	31.0 (90.0)	0.025
Disease durations, years	8.5 [3–16.5]	6 [0.3–18]	0.18		8 [2–17]	8 [3–24]	
Log-transformed duration	1.8 ± 1.4	1.0 ± 2.2	0.03	0.486	1.8 ± 1.4	1.7 ± 1.8	0.039
Lupus nephritis, n (%)	20 (38.5)	18 (58.1)	0.08	0.395	18.7 (38.5)	12.5 (36.3)	0.046
SLEDAI score	6 [3–11]	8 [4–13]	0.18		6 [4–12]	6 [4–10]	
Log-transformed score	1.8 ± 0.8	2.1 ± 0.7	0.18	0.311	1.9 ± 0.8	1.9 ± 0.6	0.082
Serum C3, mg/dl	72 [61.5–87.5]	71 [57–80]	0.47		70 [62–87]	72 [59–74]	
Log-transformed value	4.3 ± 0.4	4.2 ± 0.4	0.45	0.174	4.2 ± 0.4	4.2 ± 0.3	0.066
Anti-dsDNA antibody titer, IU/ml	14.4 [2.2–55.1]	15.1 [1.5–40.4]	0.71		12.1 [1.3–48]	11.6 [1.5–30.8]	
Log-transformed titer	2.4 ± 2.0	2.6 ± 2.1	0.71	0.085	2.3 ± 2.0	2.4 ± 2.0	0.004
Prednisolone dose, mg/day	16.0 ± 10.7	21.6 ± 14.7	0.05		14.4 ± 8.3	14.2 ± 9.0	
Log-transformed dose	2.6 ± 0.6	2.9 ± 0.7	0.07	0.401	2.6 ± 0.6	2.6 ± 0.6	0.052
Simultaneous increase in PSL dose, n (%)	15 (28.8)	16 (51.6)	0.04	0.471	16.7 (34.4)	12.3 (35.6)	0.027
Hydroxychloroquine use, n (%)	4 (7.7)	8 (25.8)	0.02	0.493	6.3 (13.1)	4.6 (13.3)	0.008
Tacrolimus use, n (%)	28 (53.8)	9 (29.0)	0.03	0.514	24.1 (49.5)	18.5 (53.9)	0.087
Cyclosporine A use, n (%)	9 (17.3)	5 (16.1)	0.89	0.031	8.7 (17.9)	5.5 (16.0)	0.051

IPTW, inverse probability of treatment weighting; MMF, mycophenolate mofetil; PSL, prednisolone; SLEDAI, SLE disease activity index in 2000; SMD, standardized mean difference.
Data are presented as means ± standard deviations or medians (interquartile ranges) unless otherwise indicated.

the change in prednisolone dose did not significantly differ between the two groups (Figure 3).

Drug continuation rate

Of 52 patients in the MZR group, 26 (50%) patients discontinued the drug throughout the observation period. The major reason for MZR discontinuation was lack of efficacy in 11 patients, followed by adverse events in 5 patients, and preparation for pregnancy in 4 patients (Table 3). In contrast, 9 of 32 (32%) patients in the MMF group discontinued the drug within the first year

of treatment, and the most common reason for MMF discontinuation was adverse events in 6 patients (Table 3). As a result, MZR discontinuation persisted after 1 year, and the drug continuation rates of the two groups crossed over at approximately 2 years [Figure 4(a)]. In terms of drug discontinuation owing to a lack of efficacy, drug discontinuation rates were almost the same between the two groups after adjusting for stabilized IPTW based on propensity scores [Figure 4(b)]. The drug discontinuation rate due to adverse events was higher in the MMF group than in the MZR group, but the differences

Table 2. Details of the activity and severity of patients with SLE.

	Unweighted			Stabilized IPTW weighted		
	MZR (n=52)	MMF (n=31)	p	MZR (n=49)	MMF (n=35)	p
Lupus nephritis						
Proteinuria	18 (34.6)	13 (41.9)	0.50	17.0 (35.1)	9.4 (27.2)	0.50
UPCR of > 2g/g	8 (15.4)	8 (25.8)	0.24	7.7 (15.9)	4.7 (13.6)	0.78
Active urinary sediment	10 (19.2)	13 (41.9)	0.03	9.2 (19.0)	8.8 (25.7)	0.50
Urinary casts	11 (21.2)	9 (29.0)	0.42	10.9 (22.4)	4.8 (14.1)	0.31
Chronic kidney disease	11 (21.2)	8 (25.8)	0.63	10.6 (21.8)	4.8 (14.0)	0.35
Active cutaneous lupus						
Rash	14 (26.9)	8 (25.8)	0.91	13.8 (28.5)	10.6 (30.7)	0.87
Inflammatory arthritis						
Arthritis	5 (9.6)	1 (3.2)	0.28	4.7 (9.6)	2.1 (6.1)	0.66
Hematological disorders						
Thrombocytopenia	2 (3.8)	3 (9.7)	0.28	3.2 (6.5)	2.1 (6.2)	0.95
Platelets of < 50,000/mm ³	1 (1.9)	1 (3.2)	0.71	0.8 (1.6)	0.5 (1.3)	0.89
Leukopenia	1 (1.9)	3 (9.7)	0.11	1.2 (2.4)	1.4 (3.9)	0.66
Active hemolytic anemia	0 (0)	0 (0)	1	0 (0)	0 (0)	1
Serological activity						
Low C3	26 (50.0)	16 (51.6)	0.89	25.4 (52.3)	15.9 (46.3)	0.66
Low C4	23 (44.2)	12 (38.7)	0.62	21.2 (43.8)	15.3 (44.5)	0.96
Positive anti-dsDNA antibody	29 (55.8)	20 (64.5)	0.43	25.9 (53.4)	23.3 (67.7)	0.27
SLEDAI score						
>4	31 (59.6)	21 (67.7)	0.46	30.8 (63.3)	22.9 (66.6)	0.79
>12	9 (17.3)	8 (25.8)	0.35	9.6 (19.8)	4.0 (11.6)	0.28
IPTW, inverse probability of treatment weighting; MMF, mycophenolate mofetil; SLEDAI, SLE disease activity index in 2000; UPCR, urinary protein-to-creatinine ratio. Data are presented as n (%). Proteinuria, urinary casts, rash, arthritis, thrombocytopenia, and leukopenia are based on the SLEDAI definition.						

observed did not reach statistical significance [Figure 4(c)].

Safety endpoints

The frequency of all adverse events, infections, and adverse events resulting in hospitalization was higher in the MMF group than in the MZR

group; however, no significant difference was noted between the two groups after adjusting for stabilized IPTW based on propensity scores. Table 4 shows adverse events that occurred in more than two patients. Infections were the most frequent adverse events observed and resulted in hospitalization. Among infections, herpes zoster was the most common in both the groups,

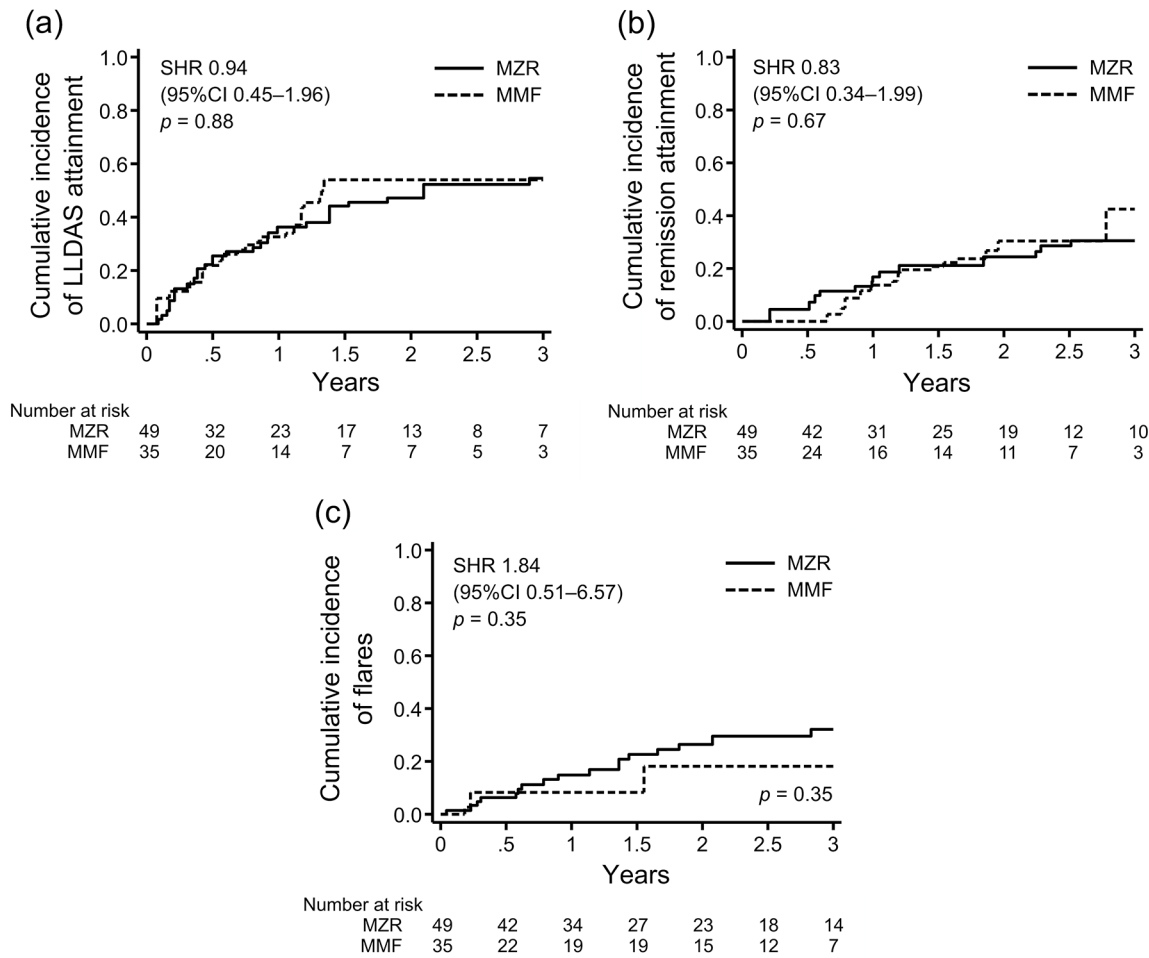


Figure 2. The cumulative incidence of (a) LLDAS attainment, (b) remission attainment, and (c) flares in the MZR and MMF groups after adjusting for propensity score-based stabilized IPTW. CI, confidence interval; SHR, sub-distribution hazard ratio.

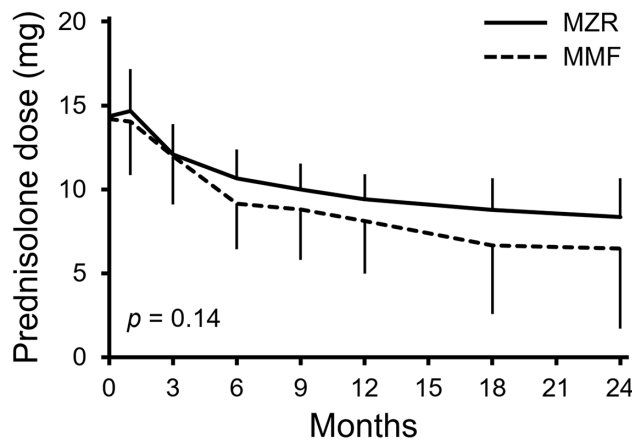


Figure 3. Predicted changes in prednisolone dose in the MZR and MMF groups. Data and error bars represent means and 95% confidence intervals.

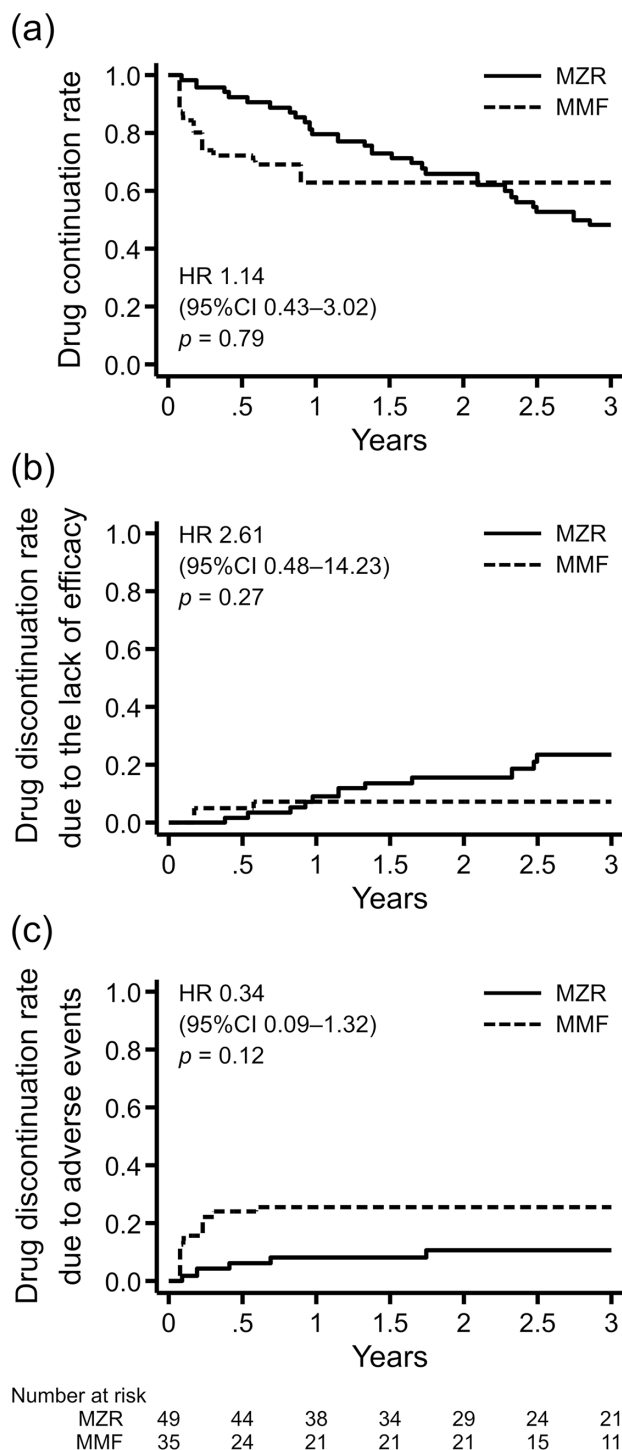


Figure 4. (a) Drug continuation rates, (b) drug discontinuation rates due to the lack of efficacy, and (c) drug discontinuation rates due to adverse events in the MZR and MMF groups after adjusting for propensity score-based stabilized IPTW.

CI, confidence interval; HR, hazard ratio.

followed by urinary tract infections, bronchitis, pneumonia, and cellulitis. No cytomegalovirus reactivation was noted in both the groups. In

Table 3. Reasons for drug discontinuation.

	MZR (n = 52)	MMF (n = 31)
Lack of efficacy	11	2
Adverse events	5	6
Skin rash	2	0
Uric acid elevation	1	0
Hepatic dysfunction	1	0
General fatigue	1	0
Diarrhea	0	2
Cytopenia	0	2
Pneumonia	0	1
Renal dysfunction	0	1
Preparation for pregnancy	4	1
Others	6	0

MMF, mycophenolate mofetil.

terms of adverse events leading to drug discontinuation, skin rash, and uric acid elevation were characteristic to the MZR group, whereas diarrhea and cytopenia were characteristic to the MMF group (Table 3).

Sensitivity analyses

For sensitivity analyses, we first limited our analysis to moderately to severely active patients with a SLEDAI score of ≥ 6 . A total of 49 patients were analyzed; 28 and 21 patients were categorized into the MZR and MMF groups, respectively. Although the time to achieve LLDAS appeared shorter in the MMF group than in the MZR group, no significant difference was found in the cumulative incidences of LLDAS attainment [Figure 5(a)]. The drug discontinuation rates certainly differed between the two groups, with more cases of discontinuation due to the lack of efficacy in the MZR group [Figure 5(b)] and more cases of discontinuation due to the adverse events in the MMF group [Figure 5(c)].

We next limited our analysis to patients who received no concomitant calcineurin inhibitors. A total of 32 patients were analyzed; 15 and 17 patients were categorized into the MZR and MMF groups, respectively. The cumulative

Table 4. Adverse events.

	Unweighted			Stabilized IPTW weighted		
	MZR (n=52)	MMF (n=31)	<i>p</i>	MZR (n=49)	MMF (n=35)	<i>p</i>
All adverse events	26 (50.0)	23 (74.2)	0.03	23.7 (48.7)	23.9 (69.2)	0.13
Adverse events resulted in hospitalization	9 (17.3)	11 (35.5)	0.06	8.7 (17.8)	9.3 (27.1)	0.37
SLE-related complications	6 (11.5)	6 (19.4)	0.33	6.1 (12.4)	4.4 (12.7)	0.97
Other complications	3 (5.8)	5 (16.1)	0.12	2.6 (5.4)	5.0 (14.4)	0.19
Adverse events leading to drug discontinuation	5 (9.6)	6 (19.4)	0.21	4.7 (9.7)	8.6 (24.8)	0.15
Treatment-related adverse events						
Infections	13 (25.0)	15 (48.4)	0.03	10.9 (22.4)	12.6 (36.5)	0.22
Infections requiring hospitalization	3 (5.8)	4 (12.9)	0.26	2.8 (5.9)	2.4 (6.9)	0.83
Herpes zoster	4 (7.7)	5 (16.1)	0.23	3.2 (6.6)	3.5 (10.0)	0.55
Urinary tract infections	3 (5.8)	2 (6.5)	0.90	2.9 (5.9)	1.2 (3.4)	0.57
Bronchitis	1 (1.9)	3 (9.7)	0.11	0.9 (1.8)	1.8 (5.1)	0.35
Pneumonia	1 (1.9)	1 (3.2)	0.71	0.7 (1.4)	0.5 (1.3)	0.96
Cellulitis	1 (1.9)	1 (3.2)	0.71	0.7 (1.4)	1.2 (3.4)	0.52
Cerebral infarction	3 (5.8)	1 (3.2)	0.60	3.2 (6.6)	1.4 (4.1)	0.69
Diarrhea	0 (0)	3 (9.7)	0.02	0 (0)	5.5 (16.1)	0.09
Hypertension	2 (3.8)	1 (3.2)	0.88	1.7 (3.6)	1.0 (3.0)	0.86
Osteonecrosis	1 (1.9)	2 (6.5)	0.29	0.8 (1.6)	1.3 (3.7)	0.46
Skin rash	2 (3.8)	0 (0)	0.27	1.7 (3.5)	0 (0)	0.24
Cytopenia	0 (0)	2 (6.5)	0.06	0 (0)	2.7 (7.9)	0.14
Renal dysfunction	1 (1.9)	1 (3.2)	0.71	0.9 (1.9)	0.5 (1.3)	0.79
Hepatic dysfunction	1 (1.9)	1 (3.2)	0.71	0.9 (1.9)	0.4 (1.2)	0.74

IPTW, inverse probability of treatment weighting; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus. Data are presented as *n* (%). Adverse events that occurred in more than two patients are shown.

incidences of LLDAS attainment and the drug discontinuation rates were nearly identical between the two groups (Figure 6). The results were superior to those of all patients in both the groups, although the number of patients in the analysis was small, and no drug discontinuation due to the lack of efficacy was observed in the MZR group.

Discussion

This study demonstrated that the efficacy of MZR and MMF was nearly identical in terms of the cumulative incidence of LLDAS or remission attainment and flares, the change in prednisolone dose, and drug continuation rates. In addition, adverse events, such as infections and the drug discontinuation rate due to adverse events, were

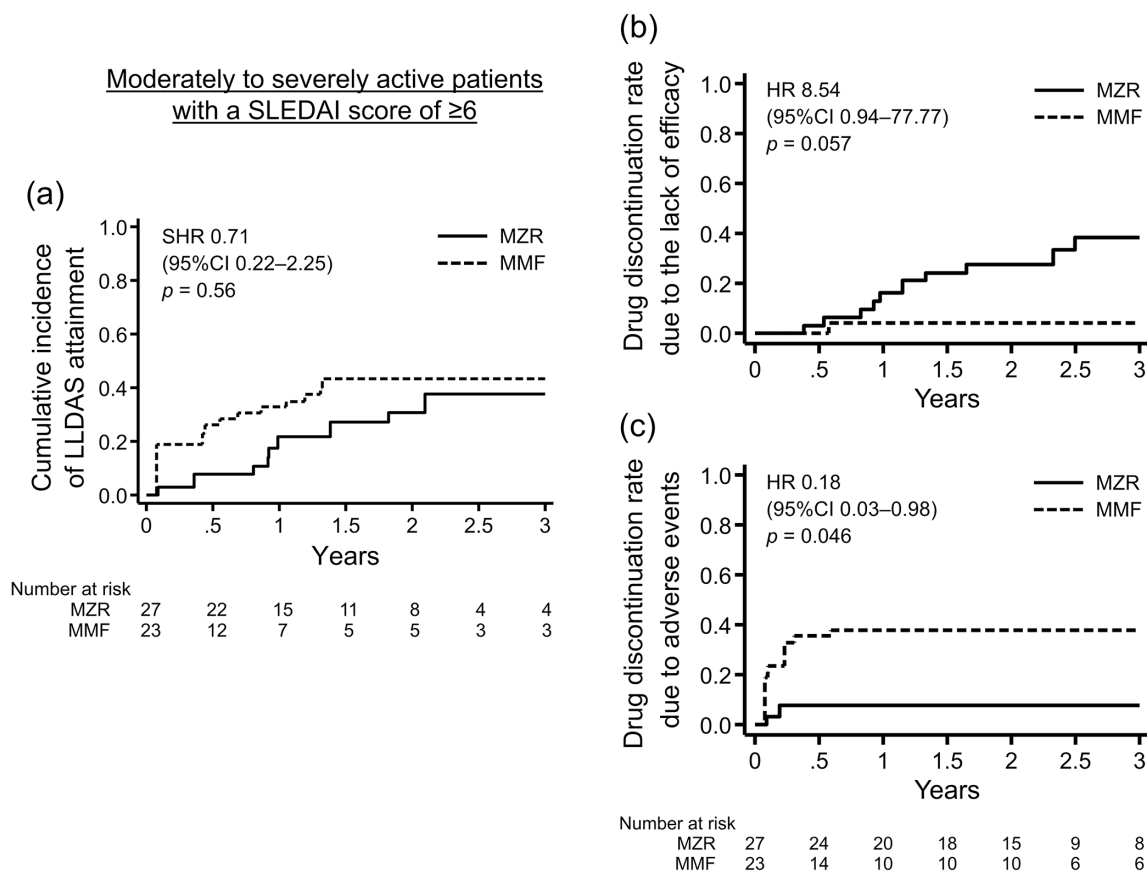


Figure 5. (a) The cumulative incidence of LLDAS attainment, (b) drug discontinuation rates due to the lack of efficacy, and (c) drug discontinuation rates due to adverse events in the MZR and MMF groups after adjusting for propensity score-based stabilized IPTW. The analysis was limited to moderately to severely active patients with a SLEDAI score of ≥ 6 . CI, confidence interval; HR, hazard ratio; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index 2000; SHR, sub-distribution hazard ratio.

somewhat lower in the MZR group than in the MMF group.

This study compared the efficacy and safety of MZR and MMF using data from clinical use in daily practice. Because some differences were observed in the clinical characteristics of patients between the groups, we performed a comparative analysis using propensity score weighting to correct selection bias to the maximum extent appropriate^{40,42} and conducted sensitivity analyses excluding mildly active patients or patients who received concomitant calcineurin inhibitors. The patients analyzed in this study were those with mild to moderate activity, aiming to achieve remission or at least low disease activity, prevent flares, and reduce the dose of glucocorticoids to the lowest possible.^{2,9} Thus, we used the cumulative incidence of LLDAS or remission attainment and flares, and change in glucocorticoids as

efficacy endpoints. As a result, this study showed no obvious difference in the efficacy outcomes, although MMF may be more effective, for which further investigation is needed, compared with MZR in moderately to severely active patients with SLE. The results indicate that the additional initiation of MZR in the maintenance phase or at mild to moderate flare may be as useful as MMF. In addition, a previous report on the induction treatment of lupus nephritis showed no significant difference in the complete remission rates following treatment with MZR and MMF at week 24.³¹ These results suggest that MZR may be as effective as MMF, which is beneficial in various settings of SLE treatment. Although randomized controlled trials, which have been conducted in patients undergoing transplantation and have revealed that the efficacy of MZR was equivalent to that of MMF, are needed in patients with SLE as well, MZR may be a worthwhile drug for

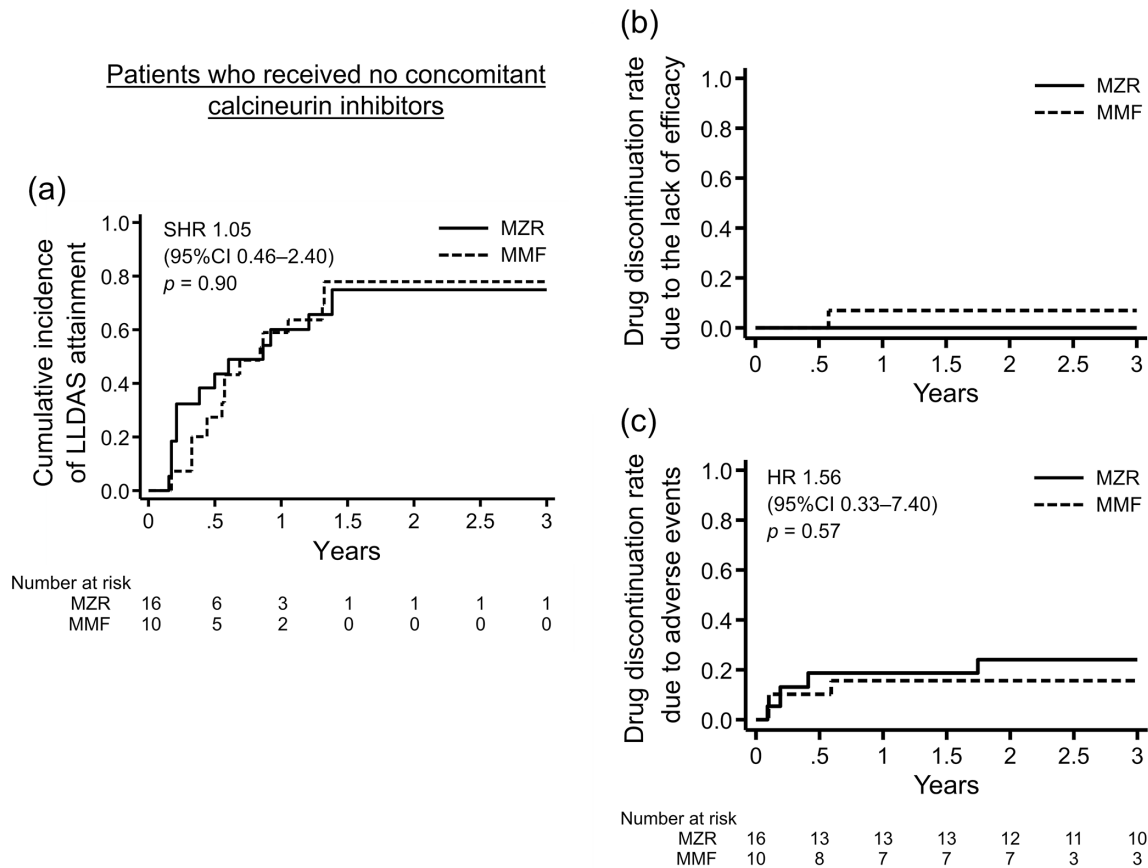


Figure 6. (a) The cumulative incidence of LLDAS attainment, (b) drug discontinuation rates due to the lack of efficacy, and (c) drug discontinuation rates due to adverse events in the MZR and MMF groups after adjusting for propensity score-based stabilized IPTW. The analysis was limited to patients who received no concomitant calcineurin inhibitors.

CI, confidence interval; HR, hazard ratio; SHR, sub-distribution hazard ratio.

achieving remission or at least low disease activity based on the treat-to-target strategy for SLE.

In this study, we compared the overall continuation rate and the discontinuation rates owing to the lack of efficacy or adverse events between MZR and MMF. Although the continuation rates of the two drugs showed no clear difference, the continuation rates crossed over during the course of the study. MMF had a relatively high incidence of discontinuation owing to adverse events in the first year but otherwise could be continued stably for a long time. In contrast, MZR discontinuation due to lack of efficacy persisted after 1 year, probably because hydroxychloroquine, MMF, and belimumab became available sequentially in Japan during the use of MZR, which may have influenced the choice of drugs. The reason for this finding may be that the group of patients who had already received calcineurin inhibitors, who were common in the MZR group, possibly

included many patients with difficult-to-treat disease. These results may reflect the characteristics of MZR, which is considered safe with few adverse events and has relatively mild immunosuppressive effects.

The frequency of all adverse events and infections was higher in the MMF group than in the MZR group, but not significantly so after adjusting for propensity score weighting. This indicates that not only the use of MMF but also the differences in disease activity and prednisolone dose are involved in the observed effects. In addition, adverse events leading to the discontinuation of MMF, such as diarrhea and cytopenia, were more common early in the course, unlike that observed with MZR. Thus, the profile of adverse events is different in both drugs, and MZR may have fewer adverse events than MMF. This finding is consistent with those of a previous meta-analysis showing that MZR had a significantly lower

incidence of adverse events than MMF, especially leukopenia, gastrointestinal symptoms, and hepatic dysfunction.²⁸ Furthermore, MZR has been shown to reduce the risk of cytomegalovirus reactivation,^{28,43,44} although no related findings were obtained in this study. This may be because the patients analyzed in this study were mainly outpatients and in the maintenance phase, and thus, monitoring of cytomegalovirus reactivation was not fully conducted. The comparison should be performed with patient populations in the induction phase or with high doses of concomitant glucocorticoids.

This study has several limitations that must be considered. First, our study had a small sample size and was conducted at a single institution. Thus, the results should be validated in a multicenter study with a larger sample size. Second, the analysis was performed retrospectively using clinical data from daily practice. Concomitant medications, including calcineurin inhibitors and hydroxychloroquine, and prednisolone dose differed in the two groups. Although propensity score weighting was used to correct selection bias, there may be residual differences that have not been examined in the clinical characteristics of patients and concomitant medications between the MZR and MMF groups. We also conducted sensitivity analyses excluding mildly active patients or patients who received concomitant calcineurin inhibitors; however, because of the small number of patients included in the sensitivity analyses, the results must be confirmed by comparison with a larger number of patients with similar background clinical characteristics. In addition, there was no standardized protocol for the use of MZR, MMF, and glucocorticoids; thus, drug adjustment was at the discretion of the treating physician. More rigorous comparisons need to be verified using randomized controlled trials or prospective studies. Third, the concomitant use of hydroxychloroquine was relatively low because most patients in this study were included before September 2015, when the drug was approved for clinical use in Japan or had a long disease duration. Finally, the standard dose of MZR in this study was 150 mg/day. The efficacy and safety of a higher dose of MZR were not examined. Because studies in the field of transplantation have shown that a higher dose of MZR is more effective than a standard dose of MZR,²⁸ determining the optimal dose of MZR for SLE is a future challenge.

Conclusion

MZR is as effective as MMF in controlling SLE activity. In addition, the adverse events of MZR, the profile of which differs from MMF, are comparable to or less than those of MMF. MZR may be a valuable option as an immunosuppressive agent for SLE, as well as MMF.

Ethics approval and consent to participate

This study was approved by the ethics committee of Kyushu University Hospital (Fukuoka, Japan; Approval No. 2020–803) on 31 March 2021 and was conducted according to the principles of the Helsinki Declaration. Owing to the retrospective study design, all study information was disclosed at the site of related facilities. Patient consent was waived according to the committee's guidelines.

Author contribution(s)

Masahiro Ayano: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Resources; Visualization; Writing – original draft.

Yasutaka Kimoto: Investigation; Writing – review & editing.

Hiroki Mitoma: Investigation; Writing – review & editing.

Mitsuteru Akahoshi: Investigation; Writing – review & editing.

Nobuyuki Ono: Investigation; Writing – review & editing.

Yojiro Arinobu: Investigation; Writing – review & editing.

Koichi Akashi: Conceptualization; Supervision; Writing – review & editing.

Takahiko Horiuchi: Conceptualization; Writing – review & editing.

Hiroaki Niiro: Conceptualization; Investigation; Supervision; Writing – review & editing.

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Conflict of interest statement

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Availability of data and materials

The datasets generated for this study are available on request to the corresponding author.

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