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Original Article

First-line Combination Strategy Provides Favorable 5-year Outcomes for Patients with Lupus Nephritis: A Single-center Observational Study

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This observational study aimed to clarify the long-term results of the combination of mizoribine (MZB), tacrolimus (TAC) and prednisolone as first-line therapy for lupus nephritis (LN). This was our institution's standard therapy between 2009 and 2015, when we saw 36 patients with LN. When a patient thus treated achieved SLEDAI remission (=0) and/or the prednisolone dose could be tapered to 5 mg/day, either MZB or TAC was stopped, and the other was continued for maintenance therapy. If treatment failure or relapse occurred, second-line therapy was introduced. At years 1 and 5, overall complete renal response and SLEDAI remission were 94% and 88%, and 50% and 62%, respectively. Excluding 2 cases lost to follow-up, medications after 5 years were as follows: 20 (59%) were stable on 1 drug (MZB or TAC), 11 (32%) required continuation of both drugs (MZB + TAC), and 3 (9%) required second-line therapy. The 5-year retention rate was 91% (non-second-line), with 0% of relapse in this group. Our first-line combination strategy showed high remission rates in the induction phase, and subsequent maintenance therapy demonstrated good outcomes for up to 5 years. Research that fine-tunes the order of therapeutic agents and institutes appropriate treatment goals may further improve long-term outcomes for patients with LN.

Key words: combination therapy, first-line therapy, lupus nephritis, mizoribine, tacrolimus

Advances in medicine have significantly improved remission rates and long-term prognoses in patients with rheumatoid arthritis (RA), but improvement for patients with systemic lupus erythematosus (SLE)/lupus nephritis (LN) remains limited [1-3]. Standard treatments for LN such as mycophenolate mofetil (MMF) or intravenous cyclophosphamide (IVCY)/azathioprine resulted in two-year remission rates up to 60%, and a 10% rate of end-stage renal disease or death [4]. Since SLE/LN is a more heterogeneous disease than RA, it appears to be difficult to resolve completely with a single therapeutic target [5]. Therefore, combination therapy could improve the remission rate of LN, at least until the knowledge base for personalized medicine is established. However, the concomitant effect of B-cell-activating factor (BAFF) inhibitors [6], IL-12/23 inhibitors [7], or IFN-α inhibitors [8] with standard treatment has been shown to be limited; the difference in efficacy from placebo groups has been relatively small.

The combination therapy of MMF, tacrolimus (TAC) and glucocorticoids showed a high remission rate (46-50% at 6 months) and is considered promising [9, 10], but infectious diseases and lack of long-term results are matters of concern. In recent years, the benefits of combination therapy using MMF and calcineurin inhibitors (CNIs), including a novel CNI, voclosporin [11], has been reviewed as a "new old" treatment for LN [12].

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Mizoribine (MZB), developed in Japan and approved for LN in this country in 1990, has a mode of action similar to that of MMF but has the advantage of an anti-CMV activity [13] that MMF does not possess. In a post-marketing surveillance (PMS) study of MZB in Japan, 44% of subjects used MZB in combination with TAC and showed no increase in adverse events compared to use of MZB alone [14]. Before MMF was approved for LN in 2016, we used a combination regimen of MZB and TAC with glucocorticoids as first-line induction therapy and reported good short-term results [15, 16]. However, in addition to lack of long-term results, the best approach to maintenance therapy following a drug-combination induction phase had remained unclear [17]. Accordingly, in this descriptive study, we sought to uncover the 5-year clinical course of our patients on the MZB and TAC combination and share our experience regarding the lasting efficacy of this combination first-line treatment.

Materials and Methods

Patient selection. This was a single-center observational study. Between July 2009 and September 2015, a total of 40 patients underwent kidney biopsy and received a diagnosis of LN. Of these, 36 received induction therapy with MZB, TAC and prednisolone (PSL) according to our department protocol [16]. All procedures performed in the present study were in accordance with the ethical standards of the institutional review board of the Japanese Red Cross Society Himeji Hospital (IRB approval number 2016-18) and of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study and/or their guardians.

Treatment protocol. The treatment protocol was described in a previous publication [16]. Briefly, patients initially received intravenous methylprednisolone pulse therapy (0.5 g/day for 3 days) followed by oral PSL. The daily dose of PSL was started at 60 mg/day (80 mg/day for patients weighing > 60 kg) and then reduced by 10 mg/day every week to reach 30 mg/day, which was followed by further tapering by 5 mg/day at 2-week intervals until the dose reached 20 mg/day. Further tapering to 5 mg/day was allowed if the patient's condition was stable. The target doses of PSL at months 2, 6 and 12 were 20, 10 and 5 mg/day, respectively.

The initial MZB dose was 300 mg/day once daily for 3 days per week [15, 16]. Peak blood concentration (C3) was measured once or twice during the hospital stay to assess the therapeutic range [16]. The initial TAC dose was 3 mg/day once daily. Blood trough concentration was measured every week during the hospital stay and at every outpatient visit, and the dose was reduced if the blood trough concentration was > 10 ng/ml or the serum creatinine level was dangerously elevated [16]. The maximum doses of MZB and TAC were 300 and 3 mg/day, respectively.

When a patient displayed SLE Disease Activity Index (SLEDAI) remission (= 0) and/or the PSL dose reached 5 mg/day, either MZB or TAC was stopped, and the other was continued for maintenance therapy. The choice between MZB and TAC was made in consultation with the patient according to each patient's situation (desire for childbearing, adverse events, drug blood concentration, drug price, *etc.*). When further intensification of current treatment was required, second-line therapy (MMF or IVCY) was introduced.

Data collection. Data collected at baseline (before the remission induction therapy) included demographics and disease characteristics. The following parameters were assessed at baseline and months 2, 4, 6, 12, 24, 36, 48 and 60: urinary protein level, serum creatinine level, estimated glomerular filtration rate (eGFR), serum albumin level, urinary sediment, serum C3 level, anti-double-stranded DNA (anti-dsDNA) antibody titer, SLEDAI-2K score, daily prednisolone dose and concomitant immunosuppressants. The urinary protein/creatinine ratio was used as a substitute for 24-h urinary protein excretion when 24-h urine excretion could not be measured. There were no missing data with respect to the above parameters.

Clinical outcomes. The main outcomes were overall proteinuria remission, complete renal response and SLEDAI remission rates at 5 years, as well as drug requirement at the end of year 5 of first-line combination strategy. Proteinuria remission was defined as a 24-h urinary protein excretion of ≤ 0.2 g. Complete renal response was defined as a composite of 24-h urinary protein excretion of ≤ 0.5 g and an eGFR of ≥ 60 ml/min/1.73 m^2 or decline of ≤ 20% from baseline [11]. SLEDAI remission was defined as a SLEDAI-2K score of 0. Other renal outcomes included eGFR, annual eGFR decline, daily urinary protein, absence of active urine sediment, absence of doubling of serum

creatinine and absence of end-stage renal disease. The serological outcomes were anti-dsDNA titer, serum C3 level and SLEDAI-2K score. Pharmacological outcomes included the number and kind of immunosuppressants and the PSL maintenance dose.

Adverse events were assessed for all 36 patients. Serious adverse events were defined as events necessitating hospitalization. Infectious adverse events were defined as events requiring oral antibiotics or additional outpatient visits due to infectious symptoms. CMV disease was defined by the need for ganciclovir/valganciclovir treatment. By contrast, CMV viremia was defined as pp65 antigenemia test positivity without the need for antiviral treatment.

Statistical analysis. Data are presented as means (standard deviations, SD) or numbers of patients (percentages), unless otherwise specified. Continuous variables were compared using Student's *t*-test or Mann–Whitney's *U* test depending on the data distribution, and categorical variables were compared using Fisher's direct probability test. A *p*-value of less than 0.05 indicated a statistically significant difference. All statistical analyses were performed using EZR ver. 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Clinical course of 36 patients over 5 years. Baseline demographics and disease characteristics are shown in Table 1. Of 36 patients, 13 (36%) were nephrotic and 28 (78%) had low serum C3 levels. Fig. 1 shows the clinical course of all 36 patients over 5 years. Two patients were lost to follow-up: a 29-year-old female moved to get married during the remission maintenance phase with TAC in the third year, and a 62-year-old female was transferred to a university hospital in the fourth year during second-line IVCY therapy. Immunosuppressant medications in the remaining 34 cases at the end of year 5 were as follows: 20 cases (59%) were stable on 1 drug (MZB or TAC, Group A), 11 cases (32%) required continuation of both drugs (MZB + TAC, Group B), and 3 cases (9%) required second-line therapy (MMF + TAC or IVCY, Group C).

A total of four patients needed second-line therapy: a 62-year-old female and a 45-year-old female both had persistent proteinuria, with active disease on repeat kidney biopsies, and a 17-year-old male and 27-year-old female both achieved complete renal response, but serological deterioration precluded further dose reduction of PSL.

Excluding one case in Group A who did not meet the drug reduction criteria but discontinued TAC due to chronic kidney disease (CKD) progression, all remaining 19 cases were able to reduce their immunosuppressant to 1 drug at a median of 17 months (interquartile range, 12.5 to 26) and maintain remission until year 5. Complete renal response and SLEDAI remission at year 5 in Groups A, B, and C were 90%, 91% and 67%, and 85%, 27% and 33%, respectively. The PSL maintenance dose at year 5 in Groups A, B and C were 5.8 (1.9), 8.1 (2.3) and 9.8 (2.8) mg/day, respectively. The 5-year retention rate was 91% (Groups A and B), with 0% relapse in the study period.

Overall 5-year outcomes of the first-line combination strategy. Fig. 2 shows the overall efficacy of the first-line combination strategy. Proteinuria remission, complete renal response and SLEDAI remission were

Table 1 Baseline demographics and disease characteristics

Variables	Data (n = 36)
Age, years	43.3 (16.0)
Female sex, no. (%)	33 (92)
First time LN, no. (%)	32 (89)
Previous treatment	
Glucocorticoids, no. (%)	6 (17)
Immunosuppressants, no. (%)	3 (8)
Biopsy class, no. (%)	
Pure Class V	2 (6)
Class III/IV	9 (25)/10 (28)
Class III + V and IV + V	15 (42)
Urinary protein (g/day)	3.31 (2.74)
Serum creatinine (mg/dl)	0.76 (0.35)
eGFR (ml/min 1.73 m^2)	80.4 (30.0)
Anti-dsDNA positive, no. (%)	32 (89)
Anti-dsDNA titer (IU/ml)	157 (140)
Serum C3 level (mg/dl)	49.4 (24.9)
SLEDAI-2K scores	20.8 (6.4)
Initial PSL dose (mg/day)	61.4 (7.6)
Initial hydroxychloroquine use, no. (%)	0 (0)

[a]Data are shown as the mean (standard deviation) or the number of patients (percentage).
[b]eGFR, estimated glomerular filtration rate; anti-dsDNA, anti-double-stranded DNA; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.
[c]Approval of hydroxychloroquine in Japan was late, in 2015, and there were no cases of use during the induction phase in this study. By the end of the fifth year, hydroxychloroquine had been introduced in 5 cases.

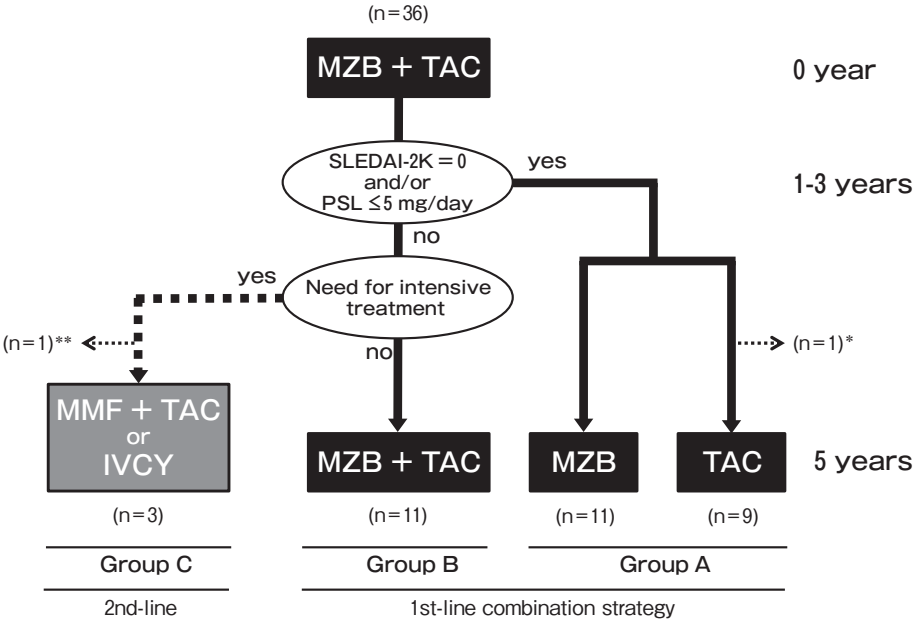
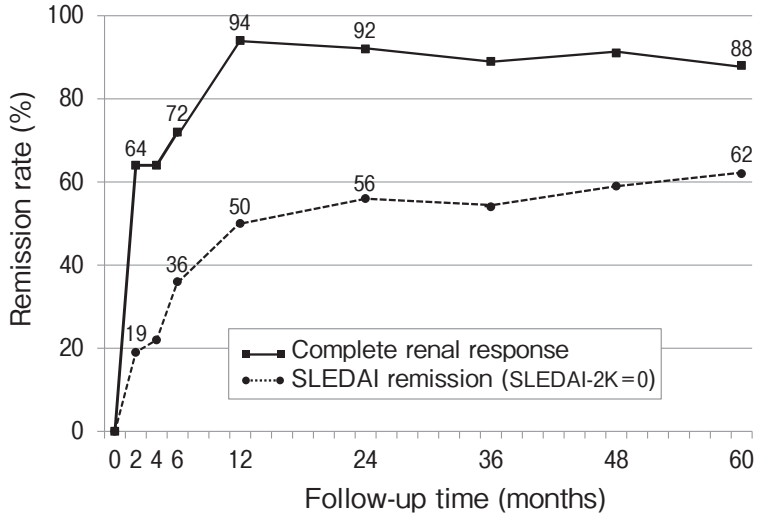


Fig. 1 Clinical course of 36 patients over 5 years. Between 2009 and 2015, 36 patients with LN were initially treated with MZB, TAC and prednisolone (PSL). When a patient achieved SLEDAI remission and/or the PSL dose reached 5 mg/day, either MZB or TAC was stopped, and the other was continued for maintenance therapy. If treatment failure or relapse occurred, second-line therapy was introduced.
*29-year-old female moved to get married during the remission maintenance phase with TAC in the third year. **62-year-old female was transferred to a university hospital in the fourth year during second-line IVCY therapy.



	n=36	n=36	n=36	n=35	n=34	n=34
Group A, no.	0	5	14	19	19	20
Group B, no.	36	31	21	14	12	11
Group C, no.	0	0	1	2	3	3

Fig. 2 Overall efficacy of first-line combination strategy. Complete renal response was defined as a composite of 24-h urinary protein excretion of ≤0.5 g and eGFR of ≥60 ml/min/1.73 m^2 or decline of ≤20% from baseline. SLEDAI remission was defined as a SLEDAI-2K score of 0. The bottom row shows the number of patients in each year for one-drug (Group A), two-drug (Group B), and second-line therapy (Group C).

92%, 94% and 50% at year 1; 89%, 92% and 56% at year 2, and 88%, 88% and 62% at year 5, respectively. The median time to remission was 2, 2, and 12 months for proteinuria remission, complete renal response, and SLEDAI remission, respectively.

The eGFR levels at years 1, 2, and 5 were 74.7 (20.9), 77.1 (23.2), and 72.2 (20.3) ml/min 1.73 m^2, respectively. One patient (3%) in group C was initiated on maintenance hemodialysis in the fifth year, and only that same patient met the doubling of serum creatinine limit. The mean PSL maintenance doses at years 1, 2, and 5 were 8.8 (2.6), 7.0 (2.4), and 6.9 (2.5) mg/day,

respectively.

Serious adverse events, infectious events, and management of glucocorticoid-related adverse events over 5 years. There were no withdrawals due to death or adverse events including infectious diseases. All adverse events experienced by 36 patients during the first year were elaborated in our previous paper [13]. Four serious adverse events (23/100 patient-years) were observed: a 54-year-old female hospitalized due to bronchitis for 3 days in the first year, a 58-year-old female hospitalized due to cholangitis for 20 days in the third year, a 76-year-old male hospitalized due to pyelonephritis for 13 days in the fifth year, and the same 76-year-old male hospitalized due to pneumonia for 46 days in the fifth year. A total of 41 infectious events (23/100 patient-years) were observed in the 5-year period. Although four CMV viremias were observed in the first year, none progressed to CMV disease: all improved spontaneously without the need for ganciclovir or valganciclovir treatment.

Table 2 shows the management of glucocorticoid-related adverse events. Obesity, hypertension, diabetes, and dyslipidemia were all well-controlled throughout the 5-year period. At year 5, the mean levels of BMI, systolic blood pressure, HbA1c, and LDL-cholesterol were 21.6, 126 mmHg, 5.7%, and 105 mg/dl, respectively.

Discussion

This study was the first to report 5-year outcomes of a first-line combination strategy for LN. Several important findings were obtained. First, a widespread response with this strategy was seen in both renal and systemic/serological measurements. SLEDAI remission, an ideal therapeutic target [18], seems to be an "achievable goal" in this strategy. As shown in Fig. 2, the complete renal response of 88% and SLEDAI remission of 62% at year 5 were higher than those previously reported [19, 20]. From the perspective of the time to remission, complete renal response at months 2 and 6 were 64% and 72%, respectively, predicting good long-term outcomes. In addition, there were no cases of withdrawal due to adverse events including infectious diseases, suggesting a good safety profile.

Second, 19 cases in Group A (95% of Group A, 56% of all groups) were able to switch to monotherapy within a median of 17 months and remain in remission through year 5 (Table 3). Regarding this "durable remission," we decided on immunosuppressant reduction based on treatment response (achievement of SLEDAI remission and/or PSL 5 mg/day), which may be useful as therapeutic targets.

Third, even patients in whom the immunosuppressants could not be reduced (Group B) showed accept-

Table 2 Management of glucocorticoid-related adverse events

Adverse events	Baseline	Year 1	Year 2	Year 5
Obesity				
BMI	20.2 (3.0)	21.1 (2.9)	21.5 (3.1)	21.6 (3.0)
Hypertension				
SBP (mmHg)	119 (14)	119 (13)	118 (14)	126 (15)
SBP ≤130, no. (%)	28 (78)	28 (78)	29 (81)	24 (67)
No. (%) receiving medication	8 (22)	15 (42)	22 (61)	18 (50)
Diabetes				
HbA1c (%)	6.0 (0.8)	5.8 (0.4)	5.7 (0.4)	5.7 (0.4)
HbA1c ≤6.0, no. (%)	21 (58)	25 (69)	26 (72)	27 (75)
No. (%) receiving medication	3 (8)	13 (36)	6 (17)	5 (14)
Dyslipidemia				
LDL-C (mg/dl)	136 (44)	103 (27)	96 (29)	105 (29)
LDL-C ≤120, no. (%)	11 (31)	30 (83)	29 (81)	27 (75)
No. (%) receiving medication	2 (6)	21 (58)	29 (81)	26 (72)

[a]Data are shown as the mean (standard deviation) or the number of patients (percentage).
[b]BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol.
[c]Data at year 5 for the two cases lost to follow-up were substituted with values at the last visit. Baseline data were presented as values at hospital discharge, except that the numbers of patients receiving medication were presented as values at admission (*i.e.*, pre-existing conditions).

Table 3 Baseline characteristics and 5-year outcomes of the 3 groups based on treatment strategy

Baseline characteristics	Group A MZB or TAC (n=20)	Group B MZB+TAC (n=11)	Group C second-line (n=3)
Age, years	46.9 (18.8)	40.2 (6.2)	29.7 (14.2)
Female sex, no. (%)	18 (90)	11 (100)	2 (67)
First time LN, no. (%)	19 (95)	8 (73)	3 (100)
Biopsy class, no. (%)			
Pure Class V	1 (5)	1 (9)	0 (0)
Class III/IV	3 (15)/6 (30)	3 (27)/2 (18)	2 (67)/1 (33)
Class III+V and IV+V	10 (50)	5 (45)	0 (0)
eGFR (ml/min/1.73 m^2)	82.6 (35.0)	81.4 (20.3)	74.5 (28.2)
Urinary protein (g/day)	4.22 (3.14)	2.00 (1.47)	3.02 (2.52)
Anti-dsDNA positive, no. (%)	19 (95)	8 (73)	3 (100)
Anti-dsDNA titer (IU/ml)	162 (140)	129 (146)	173 (181)
Serum C3 level (mg/dl)	52.8 (29.6)	50.3 (18.0)	32.0 (12.2)
SLEDAI-2K scores	21.7 (5.6)	16.7 (6.8)	27.3 (1.5)
MZB conc. (μg/ml)	2.19 (1.03)	2.50 (1.40)	1.68 (0.79)
TAC conc. (ng/ml)	4.86 (2.03)	5.18 (1.86)	3.43 (0.80)
Outcomes at 5 years	**Group A MZB or TAC (n=20)**	**Group B MZB+TAC (n=11)**	**Group C second-line (n=3)**
eGFR (ml/min per 1.73 m^2)	74.4 (18.0)	73.2 (17.9)	54.4 (42.5)
Annual change in eGFR (ml/min 1.73 m^2)	−1.6	−1.6	−4.0
Urinary protein (g/day)	0.09 (0.19)	0.11 (0.07)	1.33 (2.13)
Proteinuria remission, no. (%)	19 (95)	9 (82)	2 (67)
Complete renal response, no. (%)	18 (90)	10 (91)	2 (67)
Normal urine sediment, no. (%)	20 (100)	10 (91)	2 (67)
Anti-dsDNA titer (IU/ml)	3.6 (4.6)	6.4 (9.1)	5.0 (2.8)
Serum C3 level (mg/dl)	87.9 (17.9)	71.1 (14.5)	74.7 (8.5)
SLEDAI-2K scores	0.5 (1.4)	2.0 (1.8)	2.7 (2.3)
SLEDAI remission, no. (%)	17 (85)	3 (27)	1 (33)
PSL dosage (mg/day)	5.8 (1.9)	8.1 (2.3)	9.8 (2.8)

[a]Data are shown as the mean (standard deviation) or the number of patients (percentage).
[b]Group A included one patient who did not meet the drug reduction criteria but discontinued TAC due to CKD progression.

able renal outcomes of complete renal response of 91% at 5 years (Table 3). The number of patients in Group B was larger than expected, mainly because the immunosuppressant was reduced based on strict clinical targets. The two groups showed no distinguishing characteristics at baseline, but Group A showed early improvement in serum C3 level. Of the items on the SLEDAI-2K, serological indices and skin rash were the least likely to improve.

Fourth, compared to previous studies starting with standard monotherapy, a smaller number of intractable cases with irreversible CKD progression was observed. Three out of 4 cases who transitioned to second-line therapy (Group C, MMF + TAC or IVCY) achieved remission, while one developed end-stage renal disease in the fifth year. Because Group C had high baseline disease activity and tended to have low blood levels of MZB and TAC (Table 3), cases having high SLE activity may be suited to the treatment option of starting with IVCY or MMF plus TAC. In Japan as well, high efficacy of the MMF plus TAC combination therapy for initial or relapsed cases has been reported [21].

Fifth, although a simple comparison cannot be made in our observational study, MZB or TAC seemed to offer equivalent maintenance therapies in our clinical setting (Table 4). Therefore, patients who meet our criteria may choose either MZB or TAC for subsequent monotherapy, regardless of the histological type of LN.

There are pros and cons to using combination therapy as the first-line treatment. However, delayed treatment worsens the long-term prognosis [22]. There are many reports that long-term prognosis correlates with remission or proteinuria improvement in the first 3 months [23], 6 months [22], 1 year [24-26], and 2 years [4]. Furthermore, even a mild or moderate phenotype of SLE at disease onset often progresses to the severe form [27]. Accordingly, the first-line treatment is very important. Therefore, a treatment strategy should be developed considering the order of therapeutic agents. In addition, safety and cost-effectiveness should be considered together. Our combination strategy seemed to be suitable for first-line therapy because it showed high 5-year retention and remission rates, with low dropout due to treatment failure/flares or side effects.

The market share of MZB has been declining in recent years due to the approval of MMF in 2016, which has a similar mode of action with stronger effect, and the publication of the LN guideline in Japan in 2019. On the other hand, MZB has been shown to have unique beneficial effects such as antiviral activity [13], regulation of the glucocorticoid receptor via 14-3-3 proteins [28], inhibition of activation of integrin-linked kinase (ILK) and phosphorylation of glycogen synthase kinase-3beta (GSK3beta) [29], and inhibition of cyclin A [30], in addition to selective inhibition of inosine monophosphate dehydrogenase (IMPDH). As the efficacy issue can be addressed at high doses as in our protocol [16], we recommend utilizing MZB, especially in combination therapy, for LN.

Since our initial PSL dose was higher than that of the current guideline recommendation, it might be inter-

Table 4 The MZB sub-group and the TAC sub-group within Group A

Baseline characteristics	MZB (n = 11)	TAC (n = 9)
Age, years	54.7 (15.8)	37.3 (18.5)
Female sex, no. (%)	9 (82)	9 (100)
First time LN, no. (%)	11 (100)	8 (89)
Biopsy class, no (%)		
Pure Class V	1 (9)	0 (0)
Class III/IV	2 (18)/3 (27)	1 (11)/3 (33)
Class III + V and IV + V	5 (45)	5 (56)
eGFR (ml/min/1.73 m^2)	81.0 (39.8)	84.6 (30.4)
Urinary protein (g/day)	5.59 (3.24)	2.55 (2.15)
Anti-dsDNA positive, no. (%)	10 (91)	9 (100)
Anti-dsDNA titer (IU/ml)	114 (121)	221 (145)
Serum C3 level (mg/dl)	63.2 (30.5)	40.1 (24.4)
SLEDAI-2K scores	20.6 (5.3)	23.0 (5.9)
MZB conc. (μg/ml)	2.52 (1.03)	1.70 (0.89)
TAC conc. (ng/ml)	4.73 (2.43)	5.03 (1.54)
Outcomes at 5 years	**MZB (n = 11)**	**TAC (n = 9)**
eGFR (ml/min 1.73 m^2)	71.2 (21.2)	78.4 (13.2)
Annual change in eGFR (ml/min 1.73 m^2)	−2.0	−1.2
Urinary protein (g/day)	0.12 (0.25)	0.06 (0.04)
Proteinuria remission, no. (%)	10 (91)	9 (100)
Complete renal response, no. (%)	10 (91)	8 (89)
Normal urine sediment, no. (%)	20 (100)	10 (91)
Anti-dsDNA titer (IU/ml)	4.3 (6.2)	2.7 (1.0)
Serum C3 level (mg/dl)	89.2 (16.6)	86.3 (20.4)
SLEDAI-2K scores	0.7 (1.9)	0.2 (0.7)
SLEDAI remission, no. (%)	9 (82)	8 (89)
Cumulative SLEDAI remission, no. (%)	10 (91)	9 (100)
PSL dosage (mg/day)	6.1 (2.3)	5.4 (1.2)

[a]Data are shown as the mean (standard deviation) or the number of patients (percentage).
[b]The MZB sub-group included one patient who did not meet the drug reduction criteria but discontinued TAC due to CKD progression.

preted that glucocorticoids contributed to the favorable outcomes. However, it is also possible that the high initial dose of PSL was associated with the higher SLEDAI remission rate and the subsequent lower relapse rate, and therefore the recommended initial PSL dose should be revisited in an RCT. To date, combination therapy of MMF and CNI [11] and repeated biweekly methylprednisolone pulses [31] have been reported to be effective in reducing the initial and total doses of PSL.

There are some limitations to this study. This study reports results from a modest number of cases in daily practice and is not a clinical trial. Although our treatment strategy is a potential treatment option, its superiority or non-inferiority to standard therapies as a first-line therapy has yet to be proven. Fig. 1 shows the treatment protocol of our department. It has been adhered to for 10 years, but there have been some deviations as every clinical decision is made in consultation with the patient. Also, although MZB is a relatively inexpensive immunosuppressant, its overall cost-effectiveness has not been investigated. Future studies will be needed to compare treatment strategies that consider the order of therapeutic agents and adapt combination therapy to personalized medicine. We are planning a clinical trial to compare this study population using first-line combination strategy as a historical control group in comparison to a more recent group receiving first-line treatment of MMF.

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