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PAPER

Comparison of disease activity between tacrolimus and mycophenolate mofetil in lupus nephritis: a randomized controlled trial

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We conducted a prospective multicenter, opened-label, parallel, randomized, controlled trial to compare tacrolimus (TAC) and mycophenolate mofetil (MMF) for induction and maintenance therapy in lupus nephritis (LN). Adult patients with biopsy-proven LN International Society of Nephrology/Renal Pathology Society classes III–V and active nephritis were to receive prednisolone (0.7–1.0 mg/kg/day for four weeks of run-in period and tapered) and randomly assigned to receive TAC (0.1 mg/kg/day) or MMF (1.5–2 g/day) as induction therapy for six months. All patients who had remission received azathioprine (AZA) 1–2 mg/kg/day as standard treatment in the maintenance phase. The primary outcome was Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) at six and 12 months, and the secondary outcomes included renal SLEDAI, non-renal SLEDAI, modified SLEDAI-2K, immunity SLEDAI, and disease activity remission. Eighty-four patients were randomized. One patient who was randomized to the TAC group withdrew from the study immediately after randomization. Therefore, 42 patients received MMF and 41 patients received TAC. Disease activity remission rate and time to disease activity remission were similar in both groups. Twelve patients (28.57%) in the MMF group and 10 patients (24.39%) in the TAC group achieved disease activity remission. For disease activity scores, both regimens significantly improved SLEDAI-2K during induction and maintenance therapy. Overall, SLEDAI-2K score in the MMF group decreased more compared with the TAC group. In the MMF group, mean SLEDAI-2K decreased from 11.6 ± 4.8 to 6.3 ± 3.9 after induction therapy and to 5.4 ± 4.4 after maintenance therapy. In the TAC group, mean SLEDAI-2K decreased from 9.0 ± 3.7 to 6.3 ± 5.1 after induction therapy and to 7.1 ± 5.4 after maintenance therapy. Renal SLEDAI and modified SLEDAI-2K showed a similar pattern with SLEDAI-2K. In non-renal SLEDAI and immunity SLEDAI, both regimens also resulted in decreased disease activity scores during the first two months. After that the scores were slightly increased. In the MMF group, the scores were still lower than baseline but in the TAC group were not. In conclusion, disease activity remission rate was similar in the MMF and TAC groups. For disease activity score as measured by SLEDAI-2K, TAC was comparable with MMF during induction but MMF was more effective on disease activity of active LN classes III and IV at 12 months, especially in the renal system. *Lupus* (2017) **0,** 1–10.

Key words: Lupus nephritis; tacrolimus; mycophenolate mofetil; disease activity; SLEDAI; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of autoantibodies. It results in a poor quality of life, morbidity and mortality related to

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itself or its treatment complications. Lupus nephritis (LN) is a common renal manifestation of renal disease, with about 30% of SLE patients developing nephritis by three years after diagnosis.[1] The treatment of LN remains a challenge because of the heterogeneity of the disease and unpredictable outcomes. For induction therapy in proliferative and membranous LN patients, cyclophosphamide (CYC), mycophenolate mofetil (MMF), and tacrolimus (TAC) are the immunosuppressive drugs that have been widely used.[2–6] CYC, a standard treatment for LN, is effective in induction treatment, but has severe adverse events (SAEs). MMF has equivalent efficacy to CYC and may have fewer adverse events than CYC.[2,3] TAC is an alternative regimen that has proven to be more effective and safer than CYC.[6] The efficacy comparison of TAC with MMF is still controversial[5,6] and is explored in this study.

Most clinical trials have concerned only on the renal outcome in LN. However, LN might have systemic manifestations in SLE, so disease activity assessment should be thorough to determine the overall disease effect on patients. Moreover, disease activity has a big impact in terms of need for treatment and cause of hospitalization.[7] Disease activity monitoring might detect early relapse and lead to early treatment, before severe disease has occurred, and ultimate improve patient quality of life. MMF might be effective in extra-renal manifestations such as refractory hemolytic anemia and thrombocytopenia.[8] However, the efficacy of TAC in extra-renal symptoms of SLE has not been evaluated.

Disease activity scores can reflect overall lupus activity. Disease activity measures that have been validated and have been widely used in clinical trials are the British Isles Lupus Assessment Group Scale (BILAG), European Consensus Lupus Activity Measure (ECLAM), Lupus Activity Index (LAI), Systemic Lupus Activity Measures (SLAM) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).[9] SLEDAI, SLAM and BILAG have been shown to be valid when used by investigators from different countries.[10] BILAG and SLAM record symptoms during the preceding month, whereas SLEDAI records disease activity over the past 10 days.[10]

SLEDAI was developed and validated as a clinical index for the measurement of disease activity in SLE.[11] It has recently been updated by Gladman et al. This version is known as the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K). In the original SLEDAI, alopecia, mucous membrane lesions, and rash would be scored if they were new or recurrent, and proteinuria would be scored if there was new onset or a recent increase of more than 0.5 g/24 hours. In the SLEDAI-2K, the presence of any rash, alopecia, or mucosal ulcers and new, recurrent, or persistent proteinuria > 0.5 g/24 hours would be scored.[12] SLEDAI-2K describes disease activity at various activity levels in a comparable manner to the original SLEDAI. It is suitable for use in clinical trials and studies of prognosis in SLE.[13]

Therefore, we conducted a multicenter, randomized, controlled trial to determine the difference of disease severity using SLEDAI-2K in LN compared between TAC and MMF.

Materials and methods

Study design

The Thai Tacrolimus Trial (TTT) was registered at ClinicalTrials.gov (ClinicalTrials.gov identification (ID): NCT01580865, Protocol ID: PRG-LN-11-01). This study was a multicenter, opened-label, parallel, randomized, controlled trial. From April 1, 2012 to March 31, 2016, patients with active, biopsy-proven LN World Health Organization (WHO) Class III, IV or V according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003[14] within 24 weeks of randomization and who were antinuclear antibody (ANA) or anti-double-stranded DNA (anti-dsDNA) positive were included in this study. The exclusion criteria included having severe extra-renal manifestations, previous therapy with calcineurin inhibitor or MMF or CYC within the previous four months before randomization, allergy to macrolide antibiotics, uncontrolled hypertension (systolic blood pressure (SBP) $\geq$ 160 mmHg or diastolic blood pressure (DBP) $\geq$ 100 mmHg), severely deteriorated renal function or rapid progressive crescentic glomerulonephritis, severe myocarditis or cardiomyopathy, requiring plasmapheresis or intravenous immunoglobulin (IVIG), severe infection or active tuberculosis (TB), active hepatitis and evidence of chronic liver disease, human immunodeficiency virus (HIV) infection, diabetes mellitus (DM), pregnancy, hypersensitivity or contraindication to MMF, mycophenolic acid (MPA), TAC, corticosteroids or any components of these drug products.

Study protocol

All patients were treated with prednisolone 0.7–1.0 mg/kg/day (max 60 mg/day) as standard therapy for a period not more than four weeks prior to randomization during the run-in period.

Induction therapy

All consecutive LN patients who fulfilled the inclusion and exclusion criteria were invited to participate in the study. We stratified patients into two strata according to the classification of renal pathology (Class III–IV LN or Class V ± III/IV LN). Patients were randomly assigned 1:1 to a TAC group or an MMF group. To preserve the allocation concealment, the generation of blocks of four to six randomization lists was electronically produced at Ramathibodi Hospital and web-based randomization was used. TAC was started at a dosage of 0.1 mg/kg/day divided into two daily doses at 12-hour intervals, and the dosage was titrated to achieve trough blood concentrations of 6–10 ng/ml in the first and second month and then 4–8 ng/ml thereafter. MMF was initiated at a dose of 500 mg twice daily (for patients > 50 kg and estimated glomerular filtration rate (eGFR) > 60 ml/min) for two weeks. It was then advanced to 750 mg twice daily in LN patients weighing less than 50 kg, or 1000 mg twice daily in LN patients weighing 50 kg or more. Dosage of MMF was prescribed according to the American College of Rheumatology (ACR) recommendations, which suggest MMF 2 g/day for Asians.[15] All patients received concomitant prednisone at a dose of 0.5–0.7 mg/kg/day (maximum 60 mg/day), with tapering by 5–10 mg/day every two weeks until a dose of 5 mg/day had been achieved, and this dosage was maintained until the end of 24 weeks.

Maintenance therapy

All patients who had remission received azathioprine (AZA) 1–2 mg/kg/day for 24 weeks as standard treatment. For patients who did not respond to the induction therapy, treatment depended on physician decision.

Outcome measurements

Overall disease activity

Overall disease activity was measured using SLEDAI-2K at baseline, and at two, four, six, and 12 months. The index measures disease activity in the 10 days before the assessment. Disease remission is defined as a SLEDAI = 0.[16] In this study we considered SLEDAI scores according to organ systems. Renal SLEDAI is the scores of renal system. Non-renal SLEDAI is SLEDAI without the renal system. Modified SLEDAI is SLEDAI without the serological parameters (anti-dsDNA and serum complement). Immunity SLEDAI is the scores of the immunologic system, which are low complement and increased DNA binding.

Renal outcomes

Urine protein creatinine ratio (UPCR) and serum creatinine were measured at baseline, and at two weeks, and one, two, three, four, five, six, and 12 months. Complete remission was defined as return of serum creatinine to previous baseline, plus a decline in UPCR to < 500 mg/g (<50 mg/mmol) according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis 2012.[17]

Statistical analysis

In accordance with TTT, the primary outcome was complete remission. To estimate the sample size, we assumed rate of complete remission after 24 weeks of induction therapy with MMF was 20.5%,[2] and rate of complete remission at 24 weeks from tacrolimus was 52.4%.[18] The sample size of 70 patients was required (35 patients for each group), with 95% confidence and 80% power. The sample size was calculated using the Power and Sample Size Calculation (PS) program. With a dropout rate of 20%, samples of 90 patients had to be recruited (45 patients in each group).

Baseline characteristics of LN patients were described by treatment group using mean ± SD or median (interquartile range) for the continuous data and frequency and percentage for the categorical data. All patients were included in the analyses except one patient who withdrew immediately after randomization (modified intention-to-treat analysis).

For SLEDAI-2K scores, multilevel data analysis (mixed linear model) was used to compare the difference between MMF and TAC groups and the difference between each visit. The data were considered as two-level data, subject and time levels.

The Kaplan-Meier method was used to estimate the median time and rate of disease activity remission in both TAC and MMF groups. Cox's proportion hazard model was used to estimate hazard ratio (HR) of disease activity remission. Disease activity remission was defined as a SLEDAI = 0.[16]

Statistical analyses were performed with STATA version 14. A p value less than 0.05 was considered statistically significant.

Results

Participants

From April 1, 2012 to March 31, 2016, out of 86 eligible patients screened, two patients were excluded (one patient did not meet the study

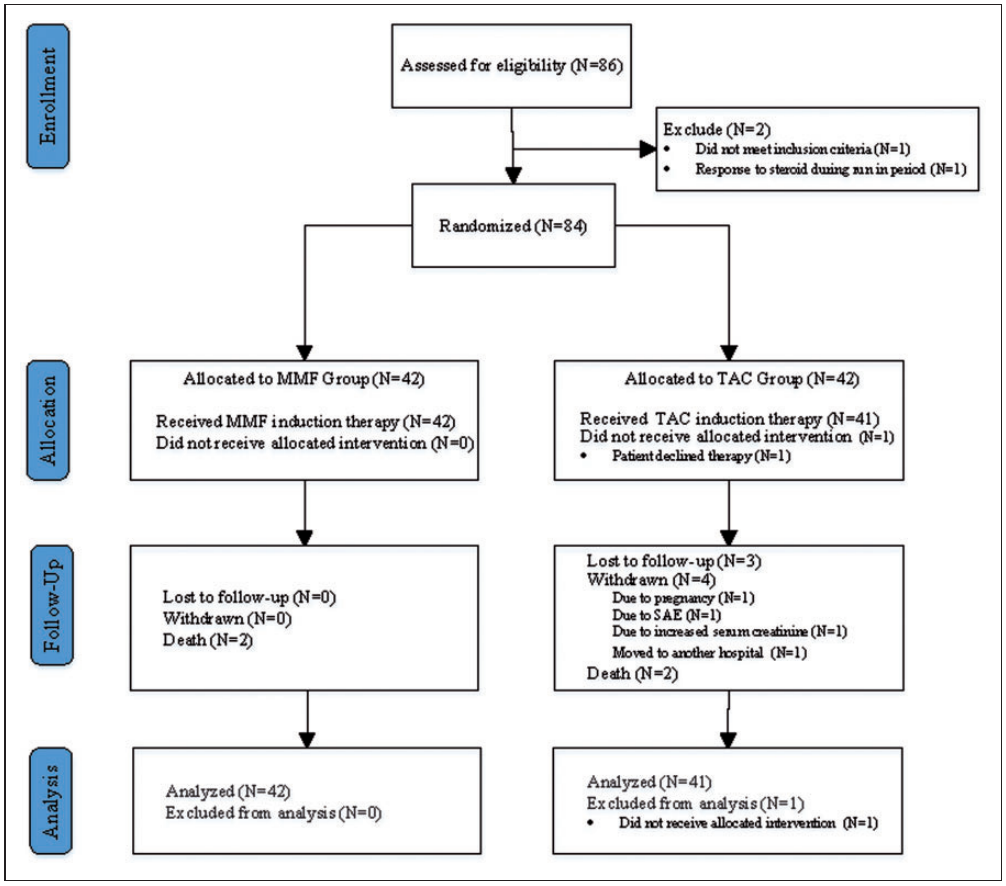

Figure 1 Study flow.
MMF: mycophenolate mofetil; TAC: tacrolimus; SAE: severe adverse effects.

criteria and another one had complete remission during the run-in period). All 84 patients who met the inclusion criteria were randomized at seven study sites. One patient who was randomized to the TAC group withdrew from the study immediately after randomization. Therefore 42 patients received MMF and 41 patients received TAC as induction therapy. In the TAC group, three patients were lost to follow-up (two patients lost to follow-up after hospitalization for acute diarrhea and right basal ganglia hemorrhage and one patient lost to follow-up for unknown reasons) and another four patients withdrew from the study because of pregnancy, SAEs, increased serum creatinine and moved to another hospital. None of the patients in the MMF group were lost to follow-up or withdrew from the study (Figure 1).

During induction therapy, the average dosage of MMF was 1.69 ± 0.41 g/day and the mean initial dosage of prednisolone was 41.8 ± 12.1 in the MMF group. In the TAC group, the average dosage of TAC was 5.07 ± 2.01 mg/day and the mean 12-hour trough blood concentration was 5.97 ± 4.01 ng/ml. The mean initial dosage of prednisolone in the TAC group was 38.6 ± 10.5.

During maintenance therapy, 39 patients (95.12%) received AZA and two (4.88%) patients received MMF in the MMF group. In the TAC group, 26 patients (81.25%) received AZA, four patients (12.50%) received MMF, and two patients (6.25%) received CYC as maintenance therapy (because of relapse in one patient and increased serum creatinine in another one).

There were four deaths during induction and maintenance treatment (two in the MMF group and two in the TAC group). In the MMF group, one patient died from large bowel perforation with septic shock nine weeks after receiving MMF and another one died from plasmablastic lymphoma 48 weeks after receiving MMF. In the TAC group, one patient died from *pneumocystis carinii* pneumonia, which occurred eight weeks later after receiving TAC and another one died from pulmonary nocardiosis with septic shock 14 weeks after receiving TAC.

Table 1 Baseline demographic data and baseline laboratory investigations

Characteristics of participants	*MMF (n = 42)*	*TAC (n = 41)*
Demographic data		
Age, years, mean (SD)	34.1 (11.1)	31.7 (10.5)
Biopsy age, years, mean (SD)	34.1 (11.1)	31.7 (10.5)
Duration of SLE, years, median (IQR)	6 (1.5–11.5)	5 (0–10)
Duration of LN (years), median (IQR)	1 (0–8)	1 (0–7)
Female, no. (%)	41 (97.6)	38 (92.7)
Physical examinations		
Number of revised ARA criteria met, mean (SD)	4.5 (1.5)	3.9 (1.6)
BMI, kg/m^2, mean (SD)	23.6 (3.9)	22.8 (5.9)
SBP, mmHg, mean (SD)	132.0 (12.8)	127.2 (13.6)
DBP, mmHg, mean (SD)	85.0 (10.2)	82.3 (10.6)
SLEDAI-2K, mean (SD)	11.6 (4.8)	8.6 (4.2)
Renal histopathology		
Renal biopsy, no.(%)		
WHO class III or IV	29 (69.0)	28 (68.3)
WHO class V or V+III/IV	13 (31.0)	13 (31.7)
Activity index, mean (SD)	11.4 (8.9)	5.6 (3.4)
Chronicity index, median (IQR)	3 (1–3.5)	2 (1–3)
Renal function		
Blood urea nitrogen, mg/dl, mean (SD)	20.8 (7.9)	21.9 (12.4)
Serum creatinine, mg/dl, mean (SD)	0.8 (0.3)	0.9 (0.3)
GFR (CKD-EPI), $ml/min/1.73m^2$, mean (SD)	98.7 (25.8)	96.0 (28.2)
Serum albumin, mg/dl, mean(SD)	3.0 (0.7)	2.9 (0.6)
24-hour urine protein/UPCR, g/24 hour, median (IQR)	2.9 (1.3–4.1)	3.4 (1.6–4.7)
Hematuria, no. (%)		
RBC < 5 /HPF	12 (28.6)	20 (48.8)
RBC ≥ 5 /HPF	30 (71.4)	21 (51.2)
Others		
Hematocrit, %, mean (SD)	36.4 (5.4)	35.1 (4.5)
ESR, mm/hour, mean (SD)	30.2 (23.3)	38.6 (30.3)
Fasting blood sugar, mg/dl, mean (SD)	91.5 (25.4)	92.6 (49.8)
ANA positive, no. (%)	42 (100)	37 (90.2)
Anti-dsDNA positive, no. (%)	25 (59.5)	15 (36.6)
Anti-dsDNA titer, IU/ml, median (IQR)	351.5 (105–746)	185 (76–389)
Anticardiolipin antibodies positive, no. (%)	13 (32.5)	13 (36.1)
Serum C3 level, mg/dl, median (IQR)	109.5 (61–546)	89 (65–559)

MMF: mycophenolate mofetil; TAC: tacrolimus; SLE: systemic lupus erythematosus; IQR: interquartile range, LN: lupus nephritis; ARA: American Rheumatism Association; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; WHO: World Health Organization; GFR: glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; UPCR: urine protein to creatinine ratio; RBC: red blood cells; HPF: high-power field; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibodies; Anti-dsDNA: anti-double-stranded DNA.

Demographic characteristics and baseline laboratory investigations are described in Table 1. Mean age of patients in the MMF group was 34.1 ± 11.1, which was slightly older than the TAC group (31.7 ± 10.5). Forty-one patients (97.6%) in the MMF group and 38 patients (92.7%) in the TAC group were female. The renal histopathology classes were III or IV 29 (69.0%), V ± III/IV 13 (31%) in the MMF group and III or IV (28 (68.3%), V ± III/IV 13 (31.7%) in the TAC group. Mean activity index was also higher in the MMF group (11.4 ± 8.9) compared with the TAC group (5.6 ± 3.4). Most baseline characteristics were similar between the two treatment groups except for mean activity index, anti-dsDNA positivity, hematuria and SLEDAI-2K score. More patients in the MMF group were anti-dsDNA positive, had more hematuria and higher mean modified SLEDAI-2K score compared with the TAC group.

Disease activity outcomes

Time to disease activity remission

During induction therapy, 12 patients (28.57%) in the MMF group and 10 patients (24.39%) in the

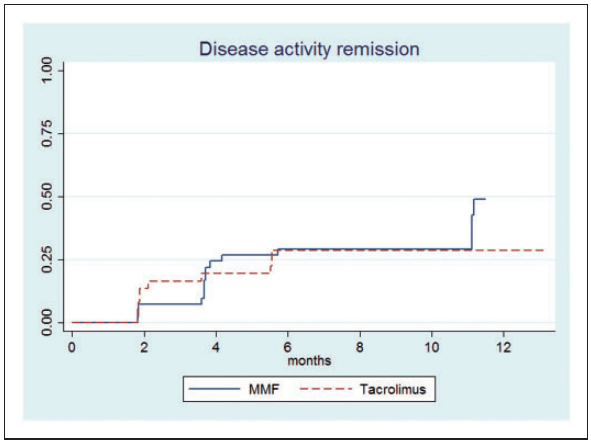

Figure 2 Probability of disease activity remission according to treatment groups: Kaplan-Meier method.
MMF: mycophenolate mofetil.

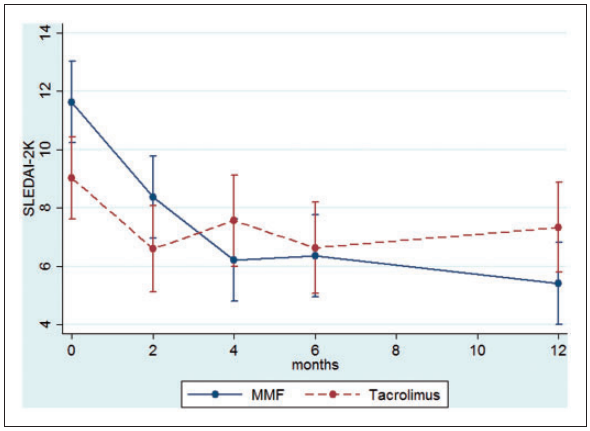

Figure 3 Changes in SLEDAI-2K during induction and maintenance therapy.
SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; MMF: mycophenolate mofetil.

TAC group achieved disease activity remission. In addition, five more patients in the MMF group achieved disease activity remission during maintenance therapy. The Kaplan-Meier analysis was used to estimate the probability of disease activity remission (Figure 2). Time to disease activity remission was similar in both groups: 4.17 months in the MMF group and 5.55 months in the TAC group ($p = 0.403$).

Randomization balanced baseline characteristics between the MMF and TAC groups except baseline SLEDAI-2K and anti-dsDNA positivity. However, anti-dsDNA positivity was included in SLEDAI-2K. Therefore, we further adjusted only baseline SLEDAI-2K in the multivariate analysis. Patients in the TAC group had about a 34% lower chance of achieving disease activity remission compared with the MMF group, but it was not statistically significant (HR = 0.66; 95% confidence interval (CI) 0.29 to 1.52; $p = 0.331$). Every one-point increase in SLEDAI-2K score had about a 2% lower chance of disease activity remission ($p = 0.614$).

Disease activity scores

The SLEDAI-2K was significantly improved at two, four, six, and 12 months compared with baseline ($p < 0.001$) in both groups (Figure 3). In the MMF group, mean SLEDAI-2K was decreased from 11.6 ± 4.8 to 6.3 ± 3.9 after induction therapy and to 5.4 ± 4.4 after maintenance therapy. In the TAC group, mean SLEDAI-2K was decreased from 9.0 ± 3.7 to 6.3 ± 5.1 after induction therapy and to 7.1 ± 5.4 after maintenance therapy. At two months, SLEDAI-2K in the TAC group was lower than the MMF group's –1.8 score (95% CI: −3.8, 0.3). Because patients in the MMF group had a higher mean SLEDAI-2K score compared with the TAC group at baseline, baseline SLEDAI was adjusted in multilevel data analysis. After adjusting for baseline SLEDAI, SLEDAI-2K in the TAC group was lower than the MMF group's –0.3 score (95% CI: –2.2, 1.5) at two months. However, SLEDAI-2K in the TAC group was statistically higher than in the MMF group at four months ($p = 0.005$) and 12 months ($p < 0.001$) as shown in Table 2.

The results showed a similar pattern with respect to renal SLEDAI and modified SLEDAI (Table 2). Both regimens significantly decreased renal SLEDAI and modified SLEDAI-2K at two, four, six, and 12 months compared with baseline ($p < 0.001$) in both groups as shown in Figure 4. Renal SLEDAI was close to SLEDAI-2K, which demonstrated that the renal system played a major role in SLEDAI-2K. After adjusting for baseline SLEDAI, renal SLEDAI in the TAC group was statistically higher than in the MMF group at four months ($p = 0.016$) and 12 months ($p = 0.003$). Modified SLEDAI in the TAC group was statistically higher than the MMF group at four months ($p = 0.004$), six months ($p = 0.049$) and 12 months ($p < 0.001$).

However, there were slightly different patterns in non-renal SLEDAI and immunity SLEDAI. Both regimens sharply decreased non-renal SLEDAI and immunity SLEDAI during the first two months. Then the scores were slightly increased, but still lower than baseline at four and six months ($p < 0.05$). At 12 months, non-renal SLEDAI and immunity SLEDAI scores in the MMF group were

Table 2 Changes in SLEDAI-2K, renal SLEDAI, modified SLEDAI, non-renal SLEDAI and immunity SLEDAI scores at two, four, six, and 12 months

	Mean (SD)		*Crude mean difference*		*Adjusted mean difference*	
Time (months)	*TAC*	*MMF*	*(95% CI)*	p *value*	*(95% CI)*	p *value*
SLEDAI-2K						
0	9.0 (3.7)	11.6 (4.8)				
2	6.5 (5.2)	8.3 (4.7)	−1.8 (–3.8, 0.3)	0.090	−0.3 (–2.2, 1.5)	0.724
4	7.4 (4.4)	6.2 (5.0)	1.3 (–0.8, 3.5)	0.209	2.8 (0.9, 4.7)	0.005
6	6.3 (5.1)	6.3 (3.9)	0.3 (–1.8, 2.4)	0.802	1.7 (–0.2, 3.7)	0.085
12	7.1 (5.4)	5.4 (4.4)	1.9 (–0.2, 4.0)	0.072	3.6 (1.6, 5.5)	0.000
Renal SLEDAI						
0	7.2 (3.8)	8.8 (3.9)				
2	5.5 (4.7)	7.0 (4.1)	−1.4 (–3.2, 0.3)	0.114	−0.4 (–2.1, 1.3)	0.619
4	6.1 (4.3)	5.1 (3.9)	1.1 (–0.7,3.0)	0.223	2.2 (0.4, 3.9)	0.016
6	5.3 (4.5)	4.9 (3.3)	0.6 (–1.3,2.4)	0.539	1.6 (–0.2, 3.4)	0.075
12	5.2 (4.3)	3.9 (3.8)	1.5 (–0.3,3.3)	0.102	2.7 (0.9, 4.5)	0.003
Modified SLEDAI						
0	7.9 (3.7)	9.9 (4.6)				
2	6.0 (5.0)	7.5 (4.5)	−1.4 (–3.4, 0.5)	0.143	−0.3 (–2.1, 1.6)	0.780
4	6.8 (4.5)	5.3 (4.3)	1.6 (–0.4, 3.6)	0.122	2.8 (0.9, 4.7)	0.004
6	5.6 (4.9)	5.2 (3.5)	0.7 (–1.3, 2.7)	0.496	1.9 (0.0, 3.8)	0.049
12	5.9 (5.3)	4.1 (3.8)	2.1 (0.1, 4.1)	0.038	3.4 (1.5, 5.3)	<0.001
Non-renal SLEDAI						
0	1.8 (2.0)	2.9 (2.5)				
2	1.0 (1.7)	1.3 (1.9)	−0.3 (–1.2, 0.5)	0.452	0.1 (–0.7, 0.9)	0.818
4	1.3 (1.9)	1.1 (1.7)	0.2 (–0.7, 1.1)	0.638	0.7 (–0.2, 1.5)	0.144
6	1.1 (2.1)	1.5 (1.6)	−0.3(–1.2, 0.6)	0.516	0.1 (–0.7, 1.0)	0.750
12	1.9 (2.4)	1.5 (1.7)	0.4 (–0.5, 1.3)	0.366	0.9 (0.0, 1.8)	0.039
Immunity SLEDAI						
0	1.1 (1.3)	1.8 (1.5)				
2	0.5 (0.9)	0.8 (1.2)	−0.3 (–0.9, 0.2)	0.210	−0.1 (–0.6, 0.4)	0.683
4	0.7 (1.0)	0.9 (1.3)	−0.2 (–0.8, 0.3)	0.391	0.0 (–0.6, 0.5)	0.990
6	0.8(1.0)	1.2(1.3)	−0.4 (–1.0,0.1)	0.113	−0.2 (–0.8, 0.3)	0.460
12	1.2(1.1)	1.3(1.5)	−0.2 (–0.7, 0.4)	0.492	0.1 (–0.4, 0.7)	0.688

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; CI: confidence interval; TAC: tacrolimus; MMF: mycophenolate mofetil.

still lower than baseline, but in the TAC group were not. After adjusting for baseline SLEDAI, non-renal SLEDAI and immunity SLEDAI in the TAC group and the MMF group were similar during induction therapy as shown in Table 2. After maintenance therapy, non-renal SLEDAI in the TAC group was significantly higher than the MMF group's 0.9 score (95% CI: 0.0, 1.8).

Renal outcomes

During the 12 months, 19 out of 41 patients in the TAC group (46.3%) and 24 out of 42 patients in the MMF group (57.1%) had achieved complete remission. The complete remission rates were similar between both groups ($p = 0.325$). Proteinuria was improved at two to six months compared with baseline in both groups. In the TAC group, UPCR decreased from 4.17 ± 3.76 g/day to 1.22 ± 1.52 g/day after induction therapy and then increased to 1.85 ± 1.96 g/day after maintenance therapy. In the MMF group, UPCR was decreased from 3.23 ± 2.16 g/day to 1.13 ± 1.29 g/day after induction therapy and 1.08 ± 1.18 g/day after maintenance therapy. The reductions in UPCR were similar between the two groups during the induction period, but there was a significant increase in UPCR in the TAC group at 12 months ($p = 0.036$). The results of serum creatinine were different. The TAC regimen increased serum creatinine from 0.88 ± 0.31 mg/dl to 0.95 ± 0.27 mg/dl during induction, but returned to baseline after maintenance therapy (0.86 ± 0.37 mg/dl). There were no changes in serum creatinine in the MMF group during 12 months of follow-up. Mean serum creatinine at baseline, and at six months and 12 months, were 0.82 ± 0.27 mg/dl, 0.78 ± 0.20 mg/dl, and 0.85 ± 0.32 mg/dl, respectively.

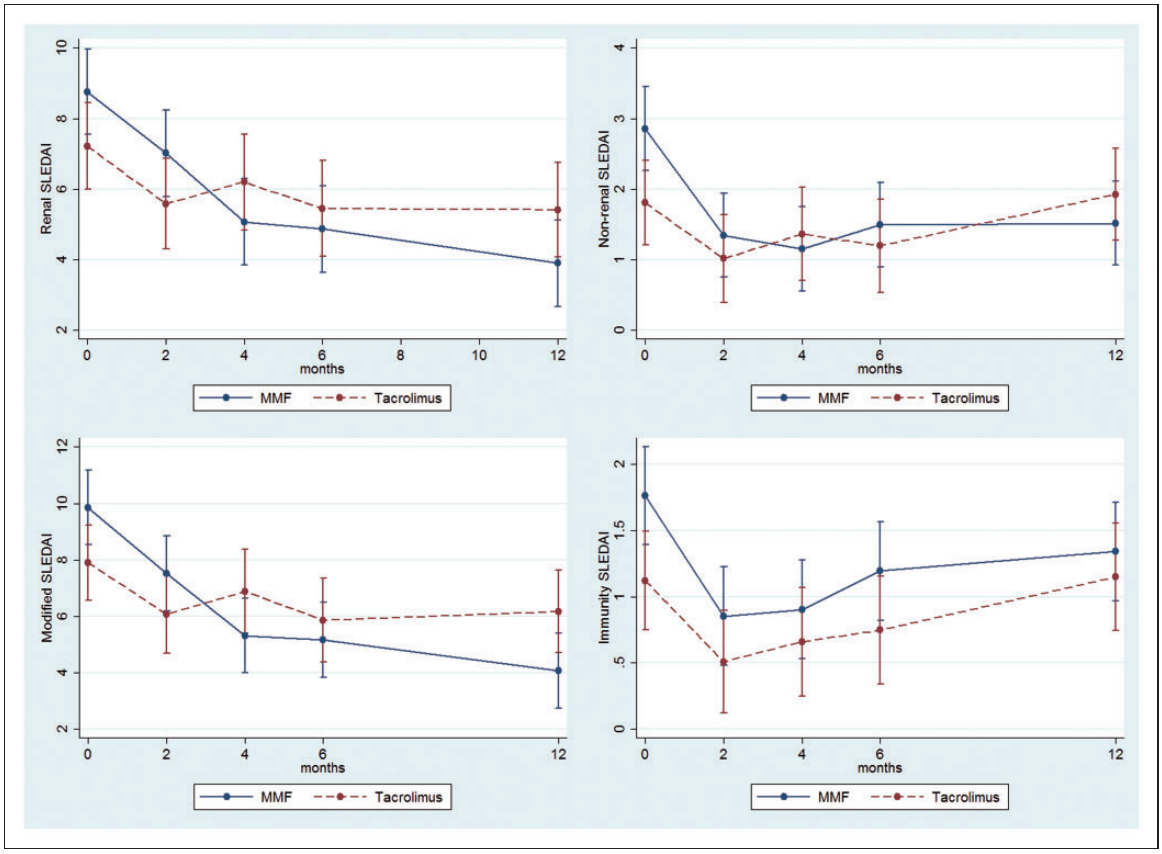

Figure 4 Changes in renal SLEDAI, modified SLEDAI, non-renal SLEDAI and immunity SLEDAI during induction and maintenance therapy.
SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; MMF: mycophenolate mofetil.

Discussion

In this study, we've found that disease activity remission rate and time to disease activity remission were similar in both groups. For disease activity scores, both regimens significantly improved SLEDAI-2K during induction and maintenance therapy. Overall, SLEDAI-2K score in the MMF group decreased more compared with the TAC group. Although patients in the MMF group had higher SLEDAI-2K compared with the TAC group at baseline, they had lower SLEDAI-2K after induction and maintenance therapy. Renal SLEDAI and modified SLEDAI-2K showed similar patterns with SLEDAI-2K. The renal system plays a major role in SLEDAI-2K. In non-renal SLEDAI and immunity SLEDAI, both regimens also decreased disease activity scores during the first two months. After that the scores were slightly increased. In the MMF group, the scores were still lower than baseline, but in the TAC group they were not.

Previous multicenter randomized clinical trials assessed the non-renal effects of MMF and CYC using disease activity scores, including BILAG, the Safety of Estrogens in Lupus Erythematosus National Assessment version of SLEDAI (SELENA-SLEDAI), and immunologic variables (levels of complement C3, C4, and CH50 and titers of anti-dsDNA antibodies).[19] There was a reduction in both disease activity indexes (BILAG and SLEENA-SLEDAI) in both the MMF and CYC groups and this was sustained through the induction period. Disease activity remission (SELENA-SLEDAI score ≤ 2) was achieved in 18.4% of the patients in the MMF group and 13.0% in the CYC group. SELENA-SLEDAI scores in both treatment groups were driven by the renal domain. Their finding was consistent with our finding in the MMF group. A recent systematic review summarized 20 relevant case series or open-label trials of MMF for non-renal manifestations of SLE. The limited evidence suggested that MMF might be effective in refractory hematologic and dermatologic manifestations of SLE.

There was no evidence to support treating serological activity by MMF.[8] Our study showed that MMF decreased immunity SLEDAI during the induction period. However, the immunity SLEDAI scores at 12 months were not different from baseline in the MMF group.

In our study, the incidence of death was 4.8% during induction and maintenance treatment (4.7% in the MMF group and 4.9% in the TAC group), which was similar to other randomized controlled trials among LN, which ranged from 3.6% to 7.3%.[20–22] Infection was the major cause of death. TAC and MMF showed similar therapeutic responses for induction of complete renal remission in LN class III–V patients. The UPCR in both groups was significantly improved during induction therapy. However, UPCR in the TAC group was higher than in the MMF group at 12 months. TAC has a tendency to relapse earlier than MMF. The results were consistent with a previous report.[23] Patients in the TAC group also had transient increased serum creatinine during induction therapy, but had recovery after one year.

MMF is a prodrug of MPA. MPA is an inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo purine biosynthesis. MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, resulting in suppression of cell-mediated immune responses and antibody formation. MPA also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation.[24] TAC is a T-cell-specific calcineurin inhibitor that reduces production of interleukin 2 (IL-2) and other cytokines such as tumor necrosis factor α, interferon γ, IL-6 and IL-10 by inhibiting T cell activation.[25] Signals for B cell activation and IG production are indirectly decreased.[2]

SLE is a heterogeneous autoimmune disease with a wide range of clinical and serological manifestations characterized by overproduction of autoantibodies and T and B cell abnormalities that lead to immune complex deposition in the kidneys.[26] Deposition of immune complex initiates an inflammatory response that results in lymphocyte and macrophage infiltration in the glomeruli. In our study, the MMF regimen had significantly more reduced disease activity scores (SLEDAI-2K, renal SLEDAI and modified SLEDAI) during induction and maintenance therapy compared with the TAC regimen, which might result from the mechanism of action by which MMF inhibits both T and B lymphocytes, but only TAC directly inhibits T lymphocytes.

The strengths of our study include it being the first study considering the effect of TAC on disease activity scores in LN compared with MMF and having a long follow-up period. Our protocol adjusted dosage of MMF according to patients' body weight and lower dosage of TAC, and included multiple centers across the country that represent all regions in Thailand. We prevented co-intervention by strict protocol and prevented bias by objective outcome measurement.

Limitations of our study include using the sample size from the main study that calculated sample size from complete remission and our open-label trials. In conclusion, disease activity remission rate and time to disease activity remission were similar in the MMF and TAC groups. For disease activity scores, both regimens significantly improved SLEDAI-2K during induction and maintenance therapy. Overall, SLEDAI-2K score in the MMF group decreased more compared with the TAC group.

Further research should also be conducted to compare the effect of MMF and TAC on disease activity scores in LN patients with double-blind, double-dummy, placebo-controlled, non-inferiority trials with larger sample size.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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