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RESEARCH ARTICLE

Mycophenolate mofetil or tacrolimus compared with azathioprine in long-term maintenance treatment for active lupus nephritis

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Abstract **This study aimed to evaluate the efficacy and safety of mycophenolate mofetil (MMF) or tacrolimus (TAC) compared with azathioprine (AZA) as maintenance therapy for active lupus nephritis (ALN). Patients with ALN who responded to 24 weeks of induction treatment were enrolled. Patients who received MMF or TAC as induction therapy continued MMF or TAC treatment during the maintenance period, whereas those who received intravenous cyclophosphamide were subjected to AZA treatment. The primary endpoint was the incidence of renal relapse. Secondary endpoints included extrarenal flares and composite endpoints (deaths, end-stage renal disease, or doubling of serum creatinine levels). A total of 123 ALN patients (47 in the MMF group, 37 in the TAC group, and 39 in the AZA group) were enrolled. The median follow-up time was 60 months. Ten MMF-treated patients, ten TAC-treated patients, and eight AZA-treated patients experienced renal relapses ($P = 0.844$). The cumulative renal relapse rates in the MMF group ($P = 0.934$) and TAC group ($P = 0.673$) were similar to the renal relapse rate in the AZA group. No significant difference in the incidence of severe adverse event was observed among the groups. Long-term maintenance therapies with MMF or TAC might have similarly low rates of renal relapse and similar safety profiles compared with AZA.**

Keywords lupus nephritis; mycophenolate mofetil; tacrolimus; maintenance therapy

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that often affects women of childbearing age. Renal involvement occurs in more than 50% of patients with SLE. Lupus nephritis (LN) is associated with increased risk of end-stage renal disease (ESRD) or mortality [1–3].

The traditional therapeutic schedule in which glucocorticoids (GCs) combined with cyclophosphamide (CYC) are used in the induction phase and azathioprine (AZA) is used in the maintenance phase has saved the lives of many patients with LN. However, some of these patients still failed to respond to traditional therapy. The use of novel immunosuppressive agents, such as mycophenolate mofetil (MMF), tacrolimus (TAC), or cyclosporine, has increased remission rate in patients with SLE and LN and significantly improved their prognosis. Thus, this approach has been widely accepted in the treatment of LN. However, a meta-analysis showed that the risk of developing ESRD decreased significantly from the 1970s to the middle of the 1990s among patients with LN but then plateaued and briefly increased in the late 2000s [4]. This finding has suggested that despite the availability of novel immunosuppressors, the management of LN still needs further investigation. Currently, treatment with active LN (ALN) has two stages: the remission induction and remission maintenance phases. Preventing relapses in the maintenance phase is crucial to prognosis.

AZA is widely used in the maintenance therapy of LN [5,6]. The Aspreva Lupus Management Study (ALMS study) and MAINTAIN Nephritis Trial affirmed the role of MMF in the maintenance of LN remission [7,8]. Although both the ALMS study and the MAINTAIN study had addressed the comparison of AZA and MMF in the maintenance therapy for LN, the present study is of great value due to its different study design and enrolled

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population. Calcineurin inhibitors are alternatives to MMF and have dual effects, that is, they induce immunosuppression and stabilize the actin cytoskeleton of renal podocytes [9,10]. In recent years, several randomized controlled studies have used TAC to induce remission [11–13]. However, owing to the short follow-up time, assessing the long-term role of TAC treatment in LN treatment (decrease in renal flares and preservation of renal function) remains challenging.

We conducted an open-label and prospective randomized controlled trial (RCT) for the induction treatment of ALN. The results showed that MMF and TAC are probable alternatives to intravenous cyclophosphamide (IVC) as induction treatments for ALN in Chinese patients [12]. However, whether MMF and TAC are more effective than AZA in the maintenance phase in Chinese patients is unclear. The present study is the expansion and maintenance part of our previous RCT for the treatment of ALN. The efficacy (preventing renal flares and preserving renal function) and safety of MMF, TAC, and AZA as long-term maintenance treatments for patients with LN were investigated.

Materials and methods

Study population

This study covered the maintenance phase of a prospective randomized controlled trial for the treatment of active LN, which had been partly reported [12]. ALN patients (Classes III, IV, V, V + III or V + IV according to the 2003 International Society of Nephrology/Renal Pathology Society classification) aged between 18 and 65 years who were previously enrolled and randomly assigned to one of the three treatment groups (MMF, TAC, or CYC, all combined with GCs) and who responded to 24 weeks of induction treatment (achieved complete or partial remission, CR or PR) were enrolled in the study. The definitions for CR and PR are provided in Table 1. The exclusion criteria were as follows: (1) failed to sign the written informed consent form, (2) unable or unwilling to abide by the research protocols approved by the researcher, (3) did not need immunosuppressive therapy (except for glucocorticoids) according to the investigator's judgment, (4) known to have allergies to or contraindications for MMF, TAC, AZA, or glucocorticoids, (5) pregnant or breast-feeding, (6) chronic kidney diseases with continuous measurement of estimated glomerular filtration rate (eGFR) < 20 mL/(min·1.73 m^2) more than 3 months, (7) life-threatening complications such as severe infections, cerebral lupus, pancreatitis, gastrointestinal hemorrhage within 6 months or active peptic ulcer within 3 months, severe cardiovascular diseases, bone marrow insufficiency with cytopenia not attributable to SLE.

Research project

Patients who responded to the 24 weeks of induction treatment entered the maintenance phase. We did not randomize the patients before the maintenance treatment, and the previous grouping was kept. Patients who received MMF or TAC continued to receive MMF (1.0–1.5 g/day) or TAC (0.05 mg/kg/day) during the maintenance period, while those who received intravenous CYC (IVC) switched to AZA (2 mg/kg/day). Patients were excluded if their follow-up time was less than 3 months since the start of the maintenance phase.

In the maintenance phase, MMF was administered twice daily at a dosage of 1.0 g/day in patients weighing 55 kg or less and 1.5 g/day in those weighing over 55 kg. The MMF dosage remained unchanged for the first 2 years. Then, MMF was given at a reduced dosage in the absence of relapse.

TAC was initiated at 0.05 mg/kg/day, given in two doses with an intervening interval of 12 h. Trough concentrations of 5–6 and 3–5 ng/mL were achieved within 48 and 48–96 weeks, respectively, before further tapering according to the patients' clinical status.

AZA was taken after breakfast at a dosage of 2 mg/kg/day and was maintained for 2 years before being reduced to 1 mg/kg/day in the absence of relapse.

All the patients received oral prednisone or prednisolone at < 15 mg/day at the initiation of the maintenance phase. The dosage of corticosteroid was reduced according to clinical status, although it was not reduced to lower than 5 mg/day. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were prohibited unless they had been taken since the induction phase. Blood pressure was maintained at $< 140/90$ mmHg, and antihypertensives, such as calcium channel and beta blockers, were added when necessary. The patients were all treated with hydroxychloroquine (200–400 mg/day) except those with fundus lesions. When extrarenal relapses occurred, the doses of corticosteroids were allowed to be increased to 0.5 mg/kg/day (maximum 40 mg/day) and then tapered after the relapses were controlled. Patients would withdraw when pulse intravenous glucocorticoids, intravenous immunoglobulin, plasmapheresis, or other immunosuppressive therapies not specified in the research protocol were needed.

Follow-up in the maintenance phase

The clinical features and laboratory test data at the beginning of the maintenance phase were collected. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. The patients were assessed every 3 months in the first 24 months and every 6 months thereafter. At each visit, thorough physical examinations and laboratory tests were

performed, and adverse events and episodes of relapse were evaluated. The enrolled patients were asked to come to the outpatient department or make a phone call to the investigator whenever they had new symptoms or any questions about their medical care.

Outcomes and definitions

The primary endpoint was the incidence of renal relapse. The secondary endpoints included extrarenal flares and composite endpoints (including deaths, ESRD, and doubling of Scr levels). The definitions used in the study are provided in Table 1.

Table 1 Definitions used in the study

Definition	Description
Renal relapse	Confirmed when either of the following criteria is met: (1) Proteinuria >1.0 g/24 h in patients with urinary protein excretion ⩽ 0.5 g/24 h after the induction phase or an increase in proteinuria >1.0 g/24 h in patients with urinary protein excretion >0.5 g/24 h after the induction phase (2) A >50% increase in Scr level among patients with normal baseline Scr levels or a >30% increase in Scr levels among those with abnormal baseline levels directly attributed to lupus
CR	Urinary protein excretion <0.3 g/24 h, a serum albumin level >35 g/L, and a stable Scr level (±15% of the baseline level)
PR	Reduction in proteinuria by 50% and proteinuria <3.0 g/24 h, a serum albumin level >30 g/L and a relatively stable Scr level (±30% of the baseline level)
Duration of SLE	The time from the first occurrence of SLE-related symptoms (such as facial erythema, hair loss, joint swelling and pain) to the time when renal biopsy is performed
Duration of LN	The time from the first occurrence of LN-related symptoms (such as proteinuria) until the renal biopsy is performed
Severe infections	Infections necessitating hospitalization or life-threatening infections
Serious adverse events	Doubling of Scr levels, ESRD, severe infections, or death

Scr, serum creatinine; CR, complete remission; PR, partial remission; SLE, systematic lupus erythematosus; LN, lupus nephritis; ESRD, end stage renal disease.

Statistical analysis

Normally distributed data were presented as mean ± SD, skewed data were presented as medians (Q1,Q3), and categorical data were presented as frequencies (%). One-way ANOVA, t-tests, Kruskal–Wallis tests, Mann-Whitney tests, Wilcoxon rank tests, or Fisher's exact tests were used whenever appropriate. Time to renal relapse or extrarenal flares were analyzed using Kaplan–Meier curves and statistically tested for significance with log-rank test. Cox regression analysis was used in calculating the hazard ratio and 95% confidence interval (CI). All statistical analyses were performed using SPSS software (version 22.0).

Results

Characteristics of patients

A total of 182 patients with LN were recruited for the induction therapy and randomized to the CYC arm (60 cases), MMF arm (63 cases), and TAC arm (59 cases). The inclusion criteria and the therapeutic schedule were based on the preliminary study published [12]. Patients who responded to 24 weeks of induction treatment (achieved CR or PR) entered the maintenance phase. 39 of these patients were in the CYC arm, 47 were in the MMF arm, and 46 were in the TAC arm. Nine patients in the TAC arm withdrew their informed consent because they were not willing to comply with the allocated study regimen in the maintenance phase. The major reasons for withdrawal were financial burdens. A total of 123 patients (47 patients in the MMF group, 37 patients in the TAC group, and 39 patients in the AZA group) were enrolled in the long-term follow-up. The median follow-up time was 60 (31,84) months. No significant difference was observed among the three groups in terms of demographic or clinical characteristics at the beginning of the maintenance phase (Table 2).

Primary endpoint

The survival rates without renal relapse were 97.5%, 83.9%, and 77.8% after 1, 3, and 5 years since the start of the maintenance treatment.

Renal relapses occurred in 28 patients (8 patients in the AZA group (20.5%), 10 patients in the MMF group (21.3%), and 10 patients in the TAC group (27.0%)), and no significant difference was observed among the three groups ($P = 0.844$). The mean dosages of AZA, MMF, and TAC at the time of relapses were 50 mg/day, 0.8 g/day, and 2 mg/day, respectively. The mean concomitant dosages of corticosteroids in the AZA, MMF, and TAC arms were 10.2, 9.5, and 9.5 mg/day, respectively. No relapse was considered due to poor compliance. The trough concentration of TAC was maintained at 5–6 ng/mL within 48 weeks and 3–5 ng/mL within 48–96 weeks according to the protocol. No difference in the median time to first renal relapse was observed among the groups ($P = 0.374$).

Table 2 Baseline clinical, laboratory, and pathological characteristics of patients with lupus nephritis

	Total	AZA group	MMF group	TAC group	*P* value
Number of cases	123	39	47	37	
Age (year)	32±11	34±11	30±12	31±10	0.348
Sex (*n*)					0.218
Male	14	7	5	2	
Female	109	32	42	35	
Duration of SLE before renal biopsy (month)	3 (1,40)	3 (1,53)	2 (2,27)	6 (1,60)	0.413
Duration of LN before renal biopsy (month)	2 (1,6)	2 (1,6)	2 (1,4)	2 (1,14)	0.877
Outcome of remission induction (*n*)					0.843
CR	55	17	20	18	0.874
PR	68	22	27	19	0.874
Glucocorticoid dosage (mg/day)	12.5 (10,15)	15 (10,15)	12.5 (10,15)	10 (10,15)	0.270
Hemoglobin (g/L)	122±13	121±15	123±13	120±12	0.413
Proteinuria (mg/24 h)	251 (117,684)	205 (92,757)	291 (124,644)	252 (124,678)	0.533
Scr (μmol/L)	69±21	72±27	68±18	67±17	0.579
eGFR (mL/(min·1.73 m^2))	104±24	102±24	105±25	105±21	0.802
Alb (g/L)	36±4	35±4	37±4	36±3	0.189
Anti-ds-DNA antibody (ELISA)	150 (99,221)	142 (115,243)	161 (99,251)	145 (87,207)	0.425
Positive anti ds-DNA antibody (*n*)	16	5	8	3	0.483
C3 (mg/dL) (normal: 74–140 mg/dL)	82 (69,99)	93 (73,103)	78 (65,92)	79 (72,95)	0.075
C4 (mg/dL) (normal: 10–40 mg/dL)	16 (12,20)	18 (14,22)	16 (11,19)	16 (13,18)	0.109
Follow-up time (month)	60 (31,84)	60 (24,84)	53 (31,81)	60 (36,84)	0.917

AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus; SLE, systematic lupus erythematosus; LN, lupus nephritis; WHO, World Health Organization; CR, complete remission; PR, partial remission; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; Alb, serum albumin; ds-DNA, double-stranded DNA; C3, serum complement 3; C4, serum complement 4.

During 100 months of follow-up, the renal relapse rates in the MMF group ($P = 0.934$) and the TAC group ($P = 0.673$) were similar to the renal relapse rate in the AZA group (Fig. 1). The renal relapse-free survival rates of the three groups were similar at 1, 3, and 5 years since the start of the maintenance phase ($P > 0.05$).

Secondary endpoints

Extrarenal relapses were mostly presented as new onsets of skin lesions and joint involvements (42.9% in the AZA group, 50% in the MMF group, and 45.5% in the TAC group). No significant change in extrarenal relapse rate was observed in the MMF group ($P = 0.362$) and TAC group ($P = 0.297$) compared with the AZA group (Fig. 2). The TAC group had a lower extrarenal relapse rate than the MMF group, although the difference was nonsignificant ($P = 0.056$). In the maintenance phase, eGFR, proteinuria, albumin, complement C3, C4, and anti-ds-DNA antibody levels remained stable in all the groups, and the differences among the three groups were nonsignificant (Fig. 3).

During the follow-up period, four patients died (one in the AZA group, one in the MMF group, and two in the TAC group), and the causes of death were infections (two patients), heart failure (one patient), and an unknown reason (one patient). The Scr levels of two patients (both in the MMF group) doubled. One of these patients subsequently developed ESRD. Among the three groups, the

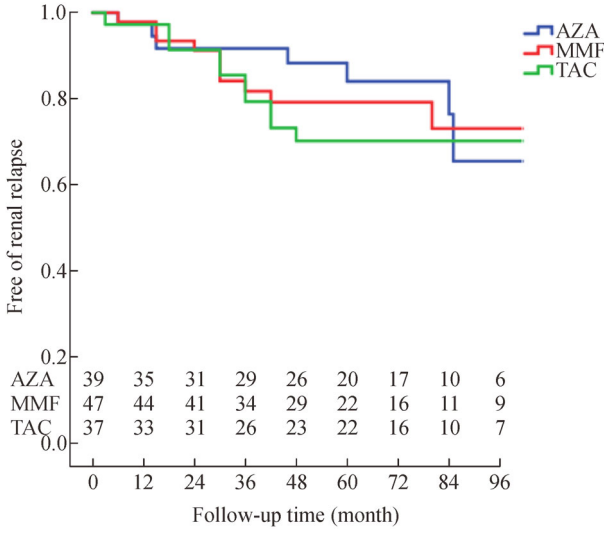

Fig. 1 Comparison of renal relapse rates in the three groups during the follow-up period. During follow-up, the renal relapse-free survival rates in the MMF and TAC groups were similar to the renal relapse-free survival rate in the AZA group. AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.

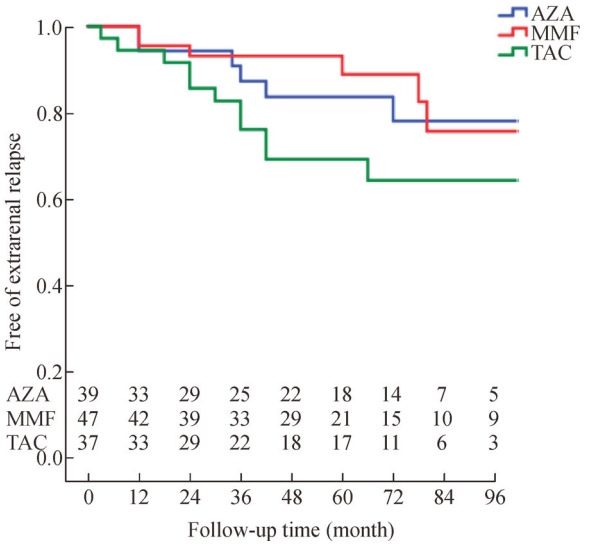

Fig. 2 Comparison of extrarenal relapses in the three groups during the follow-up period. No significant change in extrarenal relapse rate was observed in the MMF and TAC groups compared with the AZA group. AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.

incidence rates of the composite endpoint (including death, ESRD, or the doubling of Scr levels) were similar (P = 0.589; Fig. 4).

Adverse events

Mild infections, hyperlipidemia, leucopenia, and liver dysfunction were common adverse events, and their incidence rates in the three groups were similar (all $P > 0.05$). No difference was found among the groups with respect to other adverse events (Table 3). Definitions of the adverse events are provided in the supplementary material.

Discussion

The ideal maintenance therapy for LN treatment after the induction phase should be effective in preventing renal or systemic flares, minimizing side effects, and preserving renal function. Oral AZA or quarterly intravenous injections of CYC and low-dose corticosteroids have been used as classic treatments in the maintenance phase but have been challenged because of the side effects, such as liver dysfunction, bone marrow suppression, amenorrhea, and lupus relapses, which frequently occur [14–17]. Other immunosuppressors, such as MMF, CsA, and TAC, have been used in the maintenance phase. However, which of these immunosuppressors is optimal remains controversial [6–8,11]. The experience in Asian patients is limited. Our previous study suggested that MMF and TAC as induction therapies for ALN are possible alternatives to IVC for Chinese patients. TAC possibly accelerates the resolution of proteinuria and hypoalbuminemia [12]. In the present study, we further observed the efficacy and safety of MMF and TAC as maintenance therapies and compared them with those of oral AZA in patients who had responded to the induction therapy. This study was a continuation of our previous study. Given the limited sample size, to observe the long-term efficacy and safety of the study drugs, we did not rerandomize the patients before the start of the maintenance phase. The MMF arm contained more cases because more patients in the TAC group withdrew their informed consent before the maintenance phase and a relatively lower number of patients in the CYC group responded after the induction phase. No significant difference with respect to baseline characteristics was observed among the groups.

The efficacy and safety of MMF as a maintenance therapy for LN have been assessed in several studies. However, whether MMF is superior to AZA in the maintenance phase during long follow-up periods is unclear.

The classic studies on the maintenance therapies of LN may be the MAITAIN and ALMS studies. However, the present study differed from them in terms of study design and enrolled population.

In the present study, all enrolled patients were Asian. In the MAINTAIN study, the patients included were mostly Caucasians [8]. In the MAINTAIN study, no clear boundary was observed between the induction and maintenance periods. Patients switched to MMF or AZA since week 12 regardless of whether they responded or not [8]. While in the present study, only the patients who responded after the induction therapy were included.

The ALMS study included 76 (33.5%) Asian patients in the maintenance phase. The conclusion was that MMF was superior to AZA in maintaining renal responses and preventing relapses in patients with LN who responded to the induction therapy [7]. The conclusion in our study was slightly different from that of the ALMS study. In our study, MMF or TAC as maintenance therapies had similar renal relapse rates compared with AZA. Some differences between the study designs may explain the discrepancy. First, the initial dose of MMF as maintenance therapy was lower in our study (1.0–1.5 g/day in our study and 2.0 g/day in ALMS study unless not tolerated) [7]. The lower dose may weaken the advantage of MMF over AZA in preventing renal relapses. However, given the relatively higher incidence of severe infections in the MMF group among Asian patients during the induction phase [18], a relatively lower MMF dose with acceptable renal relapse rate during the maintenance phase can be considered in Asian patients. Second, racial differences with respect to sensitivity to AZA may be present. Asians may be more sensitive to AZA [19]. In the ALMS study, the incidence

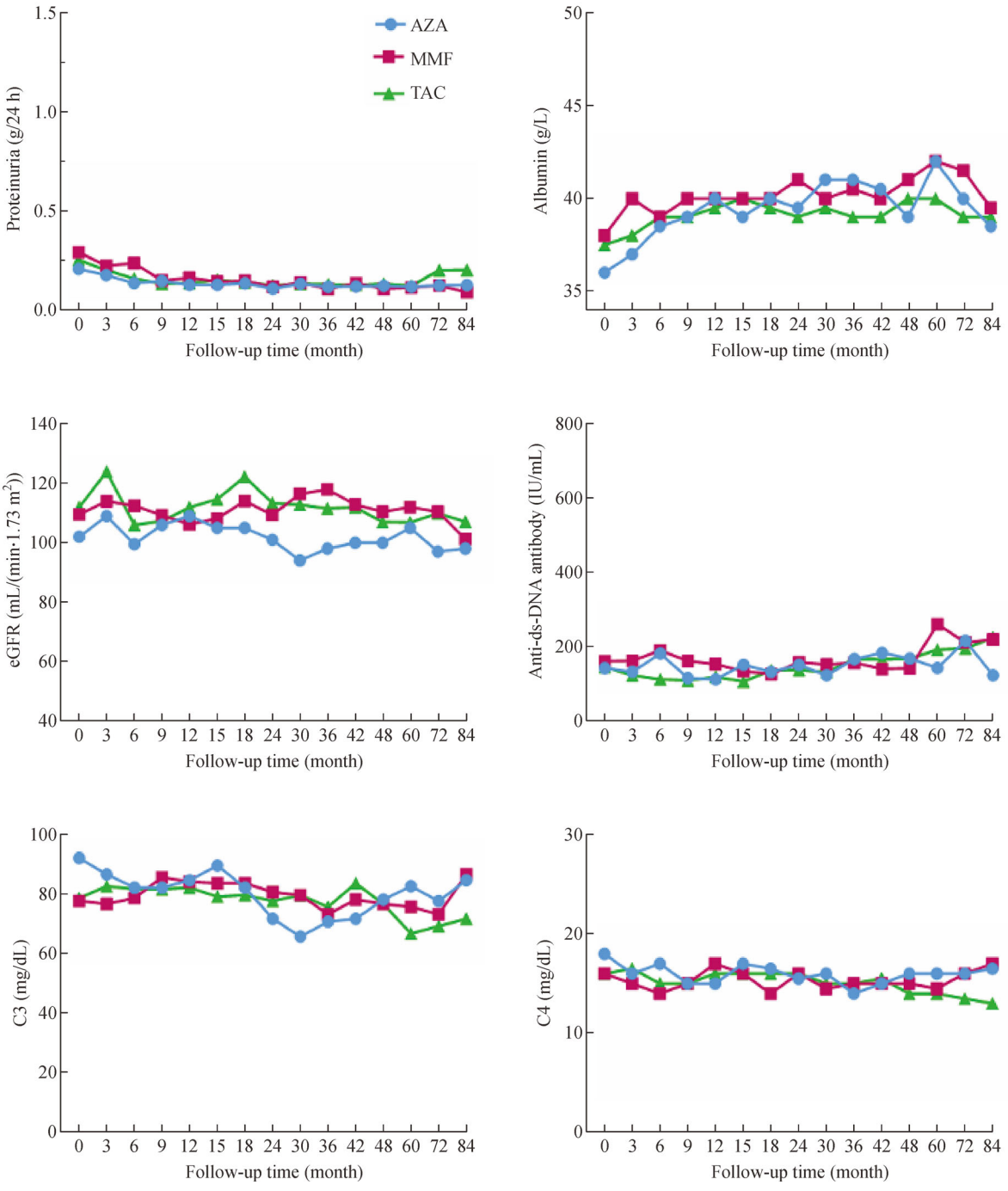

Fig. 3 Changes and comparison of proteinuria, eGFR, and albumin, anti-ds-DNA antibody, serum C3, and serum C4 levels during the follow-up period in the three groups. During the maintenance phase, the eGFR, proteinuria, and albumin, complement C3, C4, and anti-dsDNA antibody levels remained stable in all the groups. The differences among the three groups were nonsignificant. AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus; eGFR, estimated glomerular filtration rate; ds-DNA, double-stranded DNA; C3: serum complement 3; C4, serum complement 4.

rates of treatment failure in the AZA group were 12.8, 18.7, and 34.3 (events per 100 person-years) in Asian, White, and Black patients, respectively. When AZA was used as the maintenance therapy, the incident rate of treatment failure was lower in Asian than in White and Black patients [7]. Given that all the included patients in our study were Asian, the small gap of the renal relapse rates between AZA and other groups might be partly

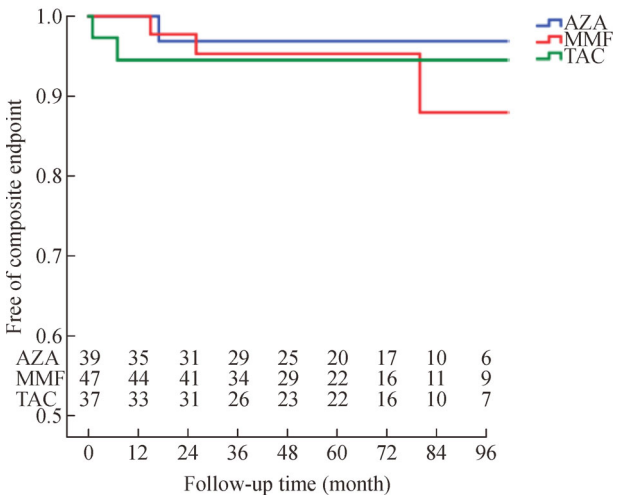

Fig. 4 Comparison of the composite endpoints in the three groups during the follow-up period. Among the three groups, the incidence rates of the composite endpoint (including death, ESRD, or the doubling of Scr levels) were similar. AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.

explained. Third, given the limited sample size, we did not rerandomize the patients before the maintenance treatment for the observation of the effect of sequential treatment (MMF–MMF, IVC–AZA, and TAC–TAC). Patients who received MMF or TAC continued to receive MMF or TAC, whereas those who received IVC switched to AZA during the maintenance period. The differences among the grouping may lead to different findings.

In recent years, several studies have shown that TAC combined with GC can effectively induce active LN to enter remission [12,20,21]. However, few studies have established the efficacy and safety of TAC as a maintenance therapy in comparison with AZA [11]. In the study of Chen *et al.* [11], 70 patients with biopsy-proven LN who achieved remission were randomized to the TAC or AZA group, and TAC and AZA were combined with low-dose oral prednisone. After 6 months of maintenance therapy, 2/36 patients in the AZA group and 0/34 in the TAC group developed renal relapses. However, no significant difference was found ($P = 0.49$).

In the present study, we compared the efficacy and safety of MMF, TAC, and AZA as maintenance therapies for LN. Patients with active LN who responded after the induction phase were assigned to one of the three groups according to the randomized grouping before the induction phase. Renal relapses occurred in 10 patients (21.3%) in the MMF group, 10 patients (27.0%) in the TAC group, and eight patients (20.5%) in the AZA group. No significant difference was found among the groups in terms of renal relapse rate ($P = 0.844$), although there seemed to be a trend that the patients in the TAC group had a higher renal relapse rate. Given the possible renal toxicity with the long-term use of TAC, TAC was administered at a relatively low dose in the present study. This procedure may lead to the weakening of its effectiveness in preventing renal relapses. A higher number of cases and the layering of the drug dose maybe needed in future studies for the determination of the optimal dose of TAC for maintenance treatment for LN. The renal relapse rate in the MMF group in the present study was similar to the renal relapse rates reported in the MAINTAIN study [8]. However, the doses of MMF in the maintenance phase in the present study were lower (1–1.5 g/day in this study and 2 g/day in the MAINTAIN study), indicating a lower dose of MMF can be taken into account in Asian patients during the maintenance phase. With respect to the AZA group, the renal relapse rate in the present study (20.5%) was similar to the previously reported rates (ALMS study: 23.4%; MAINTAIN study: 25%) [7,8]. The above results in the present study suggested that AZA and MMF might have similar effects with regard to the prevention of renal flares after induction therapy in Asian patients at these doses. However, multicenter double-blind RCTs with larger sample sizes might be needed to illustrate the point.

In addition, the overall renal relapse rate in the present

Table 3 Adverse events of the three groups

	Total, *n* (%)	AZA group, *n* (%)	MMF group, *n* (%)	TAC group, *n* (%)	*P* value
Hyperlipidemia	24 (19.5)	8 (20.5)	9 (19.1)	7 (18.9)	1
Hyperglycemia	7 (5.7)	3 (7.7)	3 (6.4)	1 (2.7)	0.707
Liver dysfunction	18 (14.6)	5 (12.8)	7 (14.9)	6 (16.2)	0.949
Leucopenia	7 (5.7)	4 (10.3)	2 (4.3)	1 (2.7)	0.380
Mild infections	16 (13)	4 (10.3)	9 (19.1)	3 (8.1)	0.324
Serious infections	14 (11.4)	6 (15.4)	6 (12.8)	2 (5.4)	0.426
Osteonecrosis	8 (6.5)	5 (12.8)	2 (4.3)	1 (2.7)	0.209
Doubling of Scr	1 (0.8)	0	1 (2.1)	0	1
ESRD	1 (0.8)	0	1 (2.1)	0	1
Died	4 (3.3)	1 (2.6)	1 (2.1)	2 (5.4)	0.686

AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus; Scr, serum creatinine; ESRD, end-stage renal disease.

study was lower than that reported in the literature. The renal relapse rate in the present study was 22.8%, whereas those in the literature were generally 27%–66% [14–16,22]. In addition, the incidence rates of infections, ESRD, and death were lower in our study, indicating better prognosis in these patients [7,8,14]. We postulated that this finding is related to the high CR rates at baseline. In this study, patients with LN entered the maintenance phase after receiving sufficient induction therapies for 6–9 months. Therefore, the proportion of CR patients (over 40% in this study) at the baseline of the maintenance phase was relatively high. We presumed that a high CR rate at the baseline of the maintenance phase might be related to a lower renal relapse rate in the maintenance phase.

No significant change in risk of extrarenal relapse was observed in the two groups when compared with the AZA group. Therefore, MMF or TAC as maintenance treatments might be as effective as AZA in preventing extrarenal relapses in patients with LN. The incidences of the composite endpoint (including death, ESRD, or doubling of Scr levels) were similar among the three groups (P = 0.589).

No difference was found among the MMF, TAC, and AZA groups with regard to common side effects, such as liver dysfunction and serious infections. The incidence rates of mild infections in the MMF group seemed higher than in the AZA group (19.1% vs. 10.3%), and the incidence rate of femoral head necrosis seemed lower (4.3% vs. 12.8%). However, these differences were not statistically significant. Hyperglycemia and nephrotoxicity may be the two problems nephrologists address when considering the long-term use of TAC. Interestingly, in the present study, the proportion of patients with hyperglycemia in the TAC group was similar to the proportions in the MMF and AZA groups. No TAC-related nephrotoxic events were observed in the present study. The presumed reason was that in the maintenance phase, TAC was prescribed in a low dose and thus had little effect on blood glucose level and deterioration of renal function. In previous studies, most TAC-related nephrotoxicity events were reported in renal transplant recipients. Those patients might differ from patients with LN. Tanaka *et al.* [21] reported 19 children with LN using GC combined with TAC as the induction and maintenance regimen. No serious adverse events were observed during the 42-month follow-up period. Considering that there were fewer side effects of gonadal suppression with MMF and TAC, patients with LN who are young and have fertility requirements can select MMF combined with GC or TAC combined with GC as an integrated treatment regimen in the induction and maintenance phases.

This study has both advantages and disadvantages. First, although some studies have compared the efficacy of MMF with that of AZA in the maintenance phase of ALN, whether TAC is superior to MMF and AZA in the maintenance phase is unclear, and limited data with limited follow-up time illustrate the point. In the present study, we compared the efficacy and safety of these medications at the same period. Second, in the selection of drug dosage in the maintenance phase, the physiques of Asian population were considered. The results may be of particular interest to some clinicians. Third, the median follow-up time in this study was as long as 60 months. The present study reflected the efficacy and safety of long-term maintenance therapies for ALN. However, this study has some limitations. First, this study was a single center study. Given the limited sample size in a single center, the study may be under-powered. Second, difference in the number of patients was observed among the groups due to various reasons (less responders in the CTX induction group, although no statistical difference was found among groups; cost concerns of long-term TAC; etc.), which may lead to potential selection bias. Multicenter double-blind RCTs might be needed. Third, no layering in the dose of immunosuppressors was performed. Data on the optimal dose of TAC in the maintenance phase is limited, and thus TAC was administered at a relatively low dose for the prevention of side effects. This procedure may weaken its effectiveness in preventing renal relapses. More detailed dose groups might be needed in further studies.

The results of this study provide additional evidence for the selection of immunotherapies in the maintenance treatment for LN. We conclude that long-term maintenance therapies with MMF or TAC might have the same low rates of renal relapse and safety profiles as long-term maintenance therapy with AZA for ALN.

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Compliance with ethics guidelines

Qianying Zhang, Peng Xing, Hong Ren, Xiaonong Chen, Jingyuan Xie, Wen Zhang, Pingyan Shen, Xiao Li, and Nan Chen declare that they have no conflict of interest. The study was approved by the Ethics Committees of Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, and the registration number in the Chinese Clinical Trial Registry is ChiCTR-TRC-10000896. All patients signed written informed consent forms.

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References

1. Bomback AS, Appel GB. Updates on the treatment of lupus nephritis. J Am Soc Nephrol 2010; 21(12): 2028–2035
2. Danila MI, Pons-Estel GJ, Zhang J, Vilá LM, Reveille JD, Alarcón GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford) 2009; 48(5): 542–545
3. Campbell R Jr, Cooper GS, Gilkeson GS. Two aspects of the clinical and humanistic burden of systemic lupus erythematosus: mortality risk and quality of life early in the course of disease. Arthritis Rheum 2008; 59(4): 458–464
4. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and Bayesian meta-analysis. Arthritis Rheumatol 2016; 68 (6): 1432–1441
5. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, Lau CS, Wong AK, Tong MK, Chan KW, Lai KN; Hong Kong–Guangzhou Nephrology Study Group. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. N Engl J Med 2000; 343(16): 1156–1162
6. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed ER, Danieli MG, Abramovicz D, Blockmans D, Mathieu A, Direskeneli H, Galeazzi M, Gül A, Levy Y, Petera P, Popovic R, Petrovic R, Sinico RA, Cattaneo R, Font J, Depresseux G, Cosyns JP, Cervera R. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002; 46(8): 2121–2131
7. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, Eitner F, Appel GB, Contreras G, Lisk L, Solomons N; ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011; 365(20): 1886–1895
8. Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, Fiehn C, de Ramon Garrido E, Gilboe IM, Tektonidou M, Blockmans D, Ravelingien I, le Guern V, Depresseux G, Guillevin L, Cervera R; MAINTAIN Nephritis Trial Group. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis 2010; 69(12): 2083–2089
9. Bensman A, Niaudet P. Non-immunologic mechanisms of calcineurin inhibitors explain its antiproteinuric effects in genetic glomerulopathies. Pediatr Nephrol 2010; 25(7): 1197–1199
10. Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med 2008; 14(9): 931–938
11. Chen W, Liu Q, Chen W, Tang X, Fu P, Liu F, Liao Y, Yang Z, Zhang J, Chen J, Lou T, Fu J, Kong Y, Liu Z, Li Z, Yu X. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. Lupus 2012; 21(9): 944–952
12. Li X, Ren H, Zhang Q, Zhang W, Wu X, Xu Y, Shen P, Chen N. Mycophenolate mofetil or tacrolimus compared with intravenous cyclophosphamide in the induction treatment for active lupus nephritis. Nephrol Dial Transplant 2012; 27(4): 1467–1472
13. Kamanamool N, Ingsathit A, Rattanasiri S, Ngamjanyaporn P, Kasitanont N, Chawanasuntorapoj R, Pichaiwong W, Anutrakulchai S, Sangthawan P, Ophascharoensuk V, Avihingsanon Y, Sumethkul V. Comparison of disease activity between tacrolimus and mycophenolate mofetil in lupus nephritis: a randomized controlled trial. Lupus 2018; 27(4): 647–656
14. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, Roth D. Sequential therapies for proliferative lupus nephritis. N Engl J Med 2004; 350(10): 971–980
15. Mosca M, Bencivelli W, Neri R, Pasquariello A, Batini V, Puccini R, Tavoni A, Bombardieri S. Renal flares in 91 SLE patients with diffuse proliferative glomerulonephritis. Kidney Int 2002; 61(4): 1502–1509
16. Ioannidis JP, Boki KA, Katsorida ME, Drosos AA, Skopouli FN, Boletis JN, Moutsopoulos HM. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. Kidney Int 2000; 57(1): 258–264
17. Mok CC, Ho CT, Chan KW, Lau CS, Wong RW. Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. Arthritis Rheum 2002; 46(4): 1003–1013
18. Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, Sánchez-Guerrero J, Wofsy D, Yu X, Solomons N. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. Rheumatology (Oxford) 2010; 49(1): 128–140
19. Yamamoto K, Okada Y, Nakamura K, Hiromura K, Nojima Y, Nakamura T. Inosine triphosphate pyrophosphatase 94C > A polymorphism: clinical implications for patients with systemic lupus erythematosus treated with azathioprine. Expert Opin Drug Saf 2010; 9(3): 447–457
20. Chen W, Tang X, Liu Q, Chen W, Fu P, Liu F, Liao Y, Yang Z, Zhang J, Chen J, Lou T, Fu J, Kong Y, Liu Z, Fan A, Rao S, Li Z, Yu X. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis 2011; 57(2): 235–244
21. Tanaka H, Watanabe S, Aizawa-Yashiro T, Oki E, Kumagai N, Tsuruga K, Ito E. Long-term tacrolimus-based immunosuppressive treatment for young patients with lupus nephritis: a prospective study in daily clinical practice. Nephron Clin Pract 2012; 121(3–4): c165–c173
22. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. Kidney Int 1996; 50(6): 2047–2053