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Efficacy and safety of tacrolimus versus mycophenolate mofetil as induction treatment and low-dose tacrolimus as treatment for lupus nephritis: a meta-analysis

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Abstract

Objective: The purpose of this study was to compare the efficacy and safety of tacrolimus and mycophenolate mofetil (MMF) as induction therapy and low-dose tacrolimus as treatment for lupus nephritis (LN).

Methods: Meta-analysis of randomized controlled trials (RCTs) was conducted to compare the efficacy and safety of tacrolimus and MMF as induction therapy for LN. We systematically reviewed RCTs and prospective cohort studies with a tacrolimus dose of 3 mg daily and performed a meta-analysis of the efficacy and safety of tacrolimus as an induction treatment for LN in comparison to MMF.

Results: The inclusion criteria were satisfied by eight studies (five RCTs and three prospective cohort studies) with a total of 408 individuals (289 for tacrolimus vs. MMF and 119 for low-dose tacrolimus). Tacrolimus and MMF had similar complete remission rates (odds ratio [OR] 1.028; 95% confidence interval [CI] 0.589–1.796; $p = 0.922$). The partial remission rate did not differ between the tacrolimus and MMF groups (OR 1.400; 95% CI 0.741–2.646; $p = 0.300$). Tacrolimus and MMF showed no differences in proteinuria, serum albumin, serum creatinine, creatinine clearance, renal Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), or extra-renal SLEDAI. The incidence of infection, severe infection, leukopenia, and hyperglycemia did not differ between the tacrolimus and MMF groups. However, herpes zoster infection was significantly less common in the tacrolimus group (OR 0.137; 95% CI 0.034–0.546; $p = 0.005$), whereas serum creatinine elevation was significantly higher in the tacrolimus group than in the MMF group (OR 8.148; 95% CI 1.369–48.50; $p = 0.021$). At 3 mg/d, tacrolimus was shown to be safe, well tolerated, and offered therapeutic benefits in all investigations.

Conclusion: Tacrolimus was comparable to MMF in terms of effectiveness and safety as an induction therapy for LN, with the exception of a reduced risk of herpes zoster infection and a rise in serum creatinine. In individuals with LN, 3 mg/d tacrolimus was proven to be efficacious and safe.

Keywords
Tacrolimus · Mycophenolate mofetil · Lupus nephritis · Meta-analysis · Systematic review

Supplementary Information

The online version of this article (https://doi.org/10.1007/s00393-022-01313-2) includes the tables S1 and S2.

Data Availability

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Introduction

Renal involvement affects up to 60% of individuals with systemic lupus erythematosus (SLE), and lupus nephritis (LN) continues to be the leading cause of morbidity and mortality in SLE [1–3]. Despite decades of advancements in treatment, a considerable number of patients have renal impairment, with 10% developing renal failure after 10 years [4]. Cyclophosphamide (CYC) regimens have long since been regarded as the gold standard for achieving renal remission and avoiding

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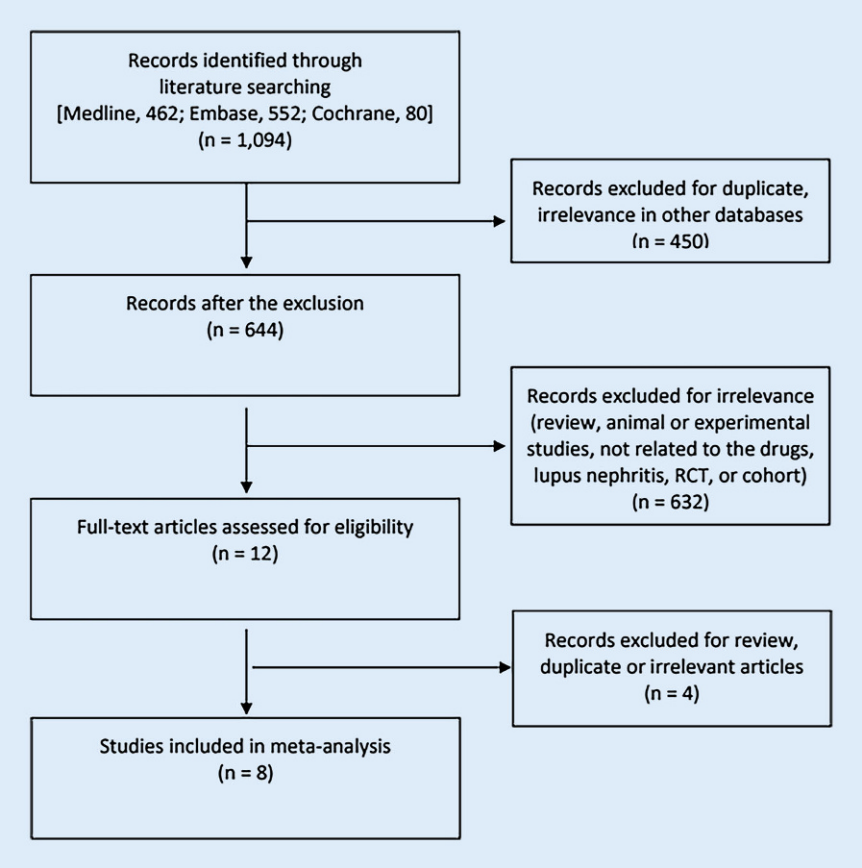

Fig. 1 ▲ Flowchart of the article selection procedure for research. Search strategy identified 1094 studies and finally found eight that met the inclusion criteria

renal flares, because they improve renal outcomes. However, considerable drug-related side effects, such as an increased risk of severe infection and ovarian toxicity, offset these advantages [5].

Mycophenolate mofetil (MMF) is a hypoxanthine nucleotide dehydrogenase inhibitor that specifically decreases T/B lymphocyte proliferation, inhibits antibody generation, controls the immune system, and reduces the formation of circulating immune complexes in renal tissue [6]. Tacrolimus, an effective inhibitor of human T cell proliferation, binds to tacrolimus-binding proteins on T cells and inhibits calcineurin [7]. Immunosuppressive treatments such as tacrolimus are likely to offer therapeutic advantages because of their immunomodulatory effect, as T cell activation is implicated in the etiology of LN [8]. In LN induction therapy, meta-analysis has indicated that MMF seems to be superior to CYC in increasing serum complement C3 and achieving complete remission regardless of ethnicity, as well as having fewer treatment-related side effects [9]. In meta-analysis, tacrolimus was proven to be more efficacious and safer than intravenous CYC as an induction treatment. The general dosing in a tacrolimus regimen was estimated at 3–4 mg twice daily during the induction phase of LN treatment [10]. However, the effectiveness of low-dose tacrolimus in the treatment of LN is uncertain, and it is debatable whether tacrolimus is more effective and safer than MMF in LN therapy. Due to the small number of studies conducted and their small sample sizes, these conclusions are controversial [11–13]. Using meta-analysis and systematic review, this study aimed to assess the efficacy and safety of tacrolimus and MMF as induction therapy and low-dose tacrolimus as a treatment for LN.

Materials and methods

Identification of eligible studies and data extraction

We performed an exhaustive search for studies that examined the efficacy and safety of tacrolimus compared with MMF and tacrolimus at low dose in patients with LN. The PubMed, EMBASE, and Cochrane Controlled Trials Register databases were searched to identify available articles (up to June 2022). The following keywords and subject terms were used in the search: "lupus nephritis," "tacrolimus," and "mycophenolate mofetil." The reference lists of all the retrieved articles were reviewed to identify additional studies that were not included in the electronic databases. Randomized controlled trials (RCTs) were included if they met the following criteria: (1) compared tacrolimus with MMF as induction therapy for LN; (2) provided endpoints for efficacy at 6 months after induction therapy and safety during the follow-up period; or (3) RCT or prospective cohort studies including low-dose tacrolimus for LN. The exclusion criteria were as follows: (1) inclusion of duplicate data and (2) lack of adequate data for inclusion.

The efficacy outcomes were as follows: number of patients who achieved (1) complete remission and (2) partial remissions. Complete or partial remission was defined on the basis of the remission criteria used in each trial. The safety outcome was the number of patients who experienced infection, serious infection, or withdrawal due to adverse events (WAE). The following information was extracted from each study: first author, ethnicity, year of publication, kidney biopsy class, number of patients treated with tacrolimus and MMF, efficacy outcome at 6 months after induction therapy, safety results during the follow-up period, and number of patients treated with low-dose tacrolimus. The methodological quality of the RCTs was determined using Jadad scores [14]. The Jadad score ranged from 0 to 5, with higher scores indicating better trial quality. The Newcastle–Ottawa Scale was used to score the quality of each study included in the meta-analysis [15]. Scores ranging from 6 to 9 indicated high methodological quality. This meta-analysis was conducted in accordance with the

Table 1 Characteristics of individual studies included in the meta-analysis of induction therapies for lupus nephritis

Study	Number enrolled		Country (ethnicity)	Comparison		Follow-up period (months)	Results
	E	C		Tacrolimus	MMF		
Kamanamool et al., 2018 [27]	41	42	Thailand (Asian)	0.1 mg/kg and day	1.5–2 g/day	12	Tacrolimus was comparable to MMF during induction. MMF was more effective on disease activity of active LN classes III and IV at 12 months
Mok et al., 2016 [26]	74	76	Hong Kong (Asian)	0.06–0.1 mg/kg and day	2–3 g/day	6	Tacrolimus is non-inferior to MMF for induction therapy of active LN
Li et al., 2012 [22]	20	20	China (Asian)	0.08–0.1 mg/kg and day	1.5–2 g/day	6	MMF and tacrolimus are possible alternatives to IVC as induction therapies for active LN
Yap et al., 2012 [24]	9	7	China (Asian)	0.1–0.15 mg/kg and day	1–2 g/day	6[a]	MMF and tacrolimus are effective treatment options for severe MLN

E experimental group, *C* control group, *I* induction therapy, *MMF* mycophenolate mofetil, *IVC* intravenous cyclophosphamide, *CYC* cyclophosphamide, *ND* no difference was found between the MMF and IVC groups with regard to response rate and adverse events, *MLN* membranous LN
[a]Follow-up period of 24 moths for safety outcomes

guidelines provided by the PRISMA statement [16].

Evaluation of statistical associations

The effect size of the study outcomes was represented as an odds ratio (OR) for dichotomous data or standardized mean difference (SMD) for continuous data and the corresponding 95% confidence intervals (95% CIs). We assessed intra- and inter-study variations and heterogeneities using Cochran's Q-statistics [17]. The heterogeneity test was used to evaluate the null hypothesis that all studies evaluated the same effect. When a significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random-effects model was used for the meta-analysis; otherwise, the fixed-effects model was used. The fixed-effects model assumes that all studies estimate the same underlying effect and considers only intra-study variations. We quantified the impact of heterogeneity using [18]:

$$I^2 = 100\% \times (Q - df)/Q \quad [18] \quad (1)$$

where I^2 measures the degree of inconsistency between studies and determines whether the percentage of total variation across studies is due to heterogeneity rather than chance. I^2 values ranged between 0% and 100%, and 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively. Statistical manipulations were performed using the Comprehensive Meta-Analysis Program (Biostat, Englewood, NJ, USA).

Evaluation of publication bias

Funnel plots are normally used to detect publication bias. However, because they require a range of studies with different sizes and subjective judgements, we evaluated publication bias using Egger's linear regression test [19], which measures funnel plot asymmetry using a natural logarithmic scale of ORs or SMD.

Results

Studies included in the meta-analysis

Electronic and manual searches identified 1094 studies; of these, 12 were selected for full-text review based on the title and abstract details. However, four were excluded because they contained duplicate data or did not contain outcome data (**Fig. 1**). Thus, eight studies (five RCTs and three prospective cohort studies) including 408 participants (289 for tacrolimus vs. MMF and 119 for low-dose tacrolimus) met the inclusion criteria ([20–27]; **Tables 1 and 2**). Four studies addressed tacrolimus vs. MMF for LN induction therapy [22, 24, 26, 27], and four studies addressed a low fixed dose of tacrolimus therapy ([20, 21, 23, 25]; **Table 3**). Oral daily doses of tacrolimus and MMF were taken. Tacrolimus 0.05–0.1 mg/kg and day was titrated to maintain a 12-hour blood concentration of 5–15 ng/ml in trials of tacrolimus vs. MMF. The Jadad scores ranged from 2 to 3, and the quality assessment scores of the prospective cohort ranged between 5 and 6. The relevant features of studies included in the systematic review and meta-analysis are provided in **Tables 1, 2 and 3** (Supplementary data).

Meta-analysis of the efficacy of tacrolimus vs. MMF in RCTs

The complete remission rate was comparable between tacrolimus and MMF (OR 1.028; 95% CI 0.589–1.796; $p = 0.922$; **Table 4**; **Fig. 2**). The partial remission rate did not differ between tacrolimus and MMF (OR 1.400; 95% CI 0.741–2.646; $p = 0.300$) (**Table 4**; **Fig. 2**). Proteinuria, serum albumin, serum creatinine, creatinine clearance, renal systemic lupus erythematosus disease activity index (SLEDAI), and extrarenal SLEDAI did not differ between tacrolimus and MMF (**Table 4**). Creatinine clearance was comparable between tacrolimus and MMF groups (tacrolimus vs. MMF: 79.7 ± 32 vs. 71.4 ± 31 mL/min, and 87.8 ± 18.7 vs. 75.6 ± 17.9 mL/min, respectively) [24, 26].

Meta-analysis of the safety of tacrolimus vs. MMF in RCTs

The incidence of infection, severe infection, leukopenia, hyperglycemia, and WAE did not differ between tacrolimus and MMF (**Table 4**). However, herpes zoster infection was significantly less common in the

Table 2 Characteristics of the studies included in this systematic review of low-dose tacrolimus therapy in lupus nephritis

Study	Number enrolled		Study type	Country (ethnicity)	Subject	Follow-up period (months)	Results
	T	C					
Miyasaka et al. 2009 [20]	28	35	RCT	Japan (Asian)	LN (III–V) with persistent proteinuria on glucocorticoid ≥ 10 mg/day for at least 8 weeks	6	Tacrolimus was safe and effective addition to glucocorticoid therapy
Fei et al. 2013 [25]	26	NA	PC	China (Asian)	LN (III–V) with persistent proteinuria who were resistant to CYC treatment (> 8 g in less than 6 months)	12	Tacrolimus at low dosage and serum level to be potentially effective and safe for treatment in patients with LN resistant to sufficient CYC therapy
Tanaka et al. 2013 [23]	19	NA	PC	Japan (Asian)	LN (II–V) treated with prednisolone combined with/without cytotoxic agents	42	Long-term, low-dose tacrolimus-based immunosuppressive treatment is beneficial and has low cytotoxicity
Tanaka et al. 2009 [21]	11	NA	PC	Japan (Asian)	LN (II, IV, V) treated with prednisolone combined with cytotoxic agents	24	Low-dose tacrolimus treatment is an effective and safe method for managing selected young patients with pediatric-onset, long-standing LN

RCT randomized controlled trial, *PC* prospective cohort study, *LN* lupus nephritis, *CYC* cyclophosphamide, *NA* not available

Table 3 The studies included in this systematic review of tacrolimus at 3 mg/day therapy in lupus nephritis

Study	Tacrolimus daily dose	Tacrolimus level (mean ± SD)	Primary end point or efficacy	Relapse or flare	Adverse events
Miyasaka et al. 2009 [20]	3 mg/day vs. placebo	4.35 ± 1.53 ng/ml	Daily proteinuria, urinary RBC count, Cr, C3, anti-dsDNA, Lupus Nephritis Disease Activity index (LNDAI)	NC	All AEs: tacrolimus (92.9%) vs. placebo (80.0%; $p = 0.277$). M/F: infection 57.1% vs. 57.1%
Fei et al. 2013 [25]	2 mg/day (body weight < 60 kg) or 3 mg/day (body weight ≥ 60 kg)	2.46 ± 1.13 ng/mL	Change in 24-hour urinary protein excretion and serum albumin levels, complete or partial remission, changes in serum creatinine, serum C3 values	Flare (1)	Severe pulmonary infection with *Aspergillus fumigatus* and cytomegalovirus (1), new-onset hypertension (1), and one patient had alopecia (1)
Tanaka et al. 2013 [23]	3 mg/day	1.5–7.9 ng/ml	U-pro/U-creat ratio, Cr, C3, C4, CH50, anti-dsDNA, ECLAM	Flare (3), no response (2)	Herpes zoster (2), acute bronchitis (1), perioral herpes (1)
Tanaka et al. 2009 [21]	3 mg/day	1.5–7.5 ng/ml	U-pro/U-creat ratio, Cr, C3, C4, CH50, anti-dsDNA, ECLAM	No response (1)	Acute bronchitis (4), herpes zoster (6)

SD standard deviation, *NC* no comment, *AEs* adverse effects, *LNDAI* calculated as the total of the scores of five parameters (daily urinary protein excretion, urinary RBC count, serum creatinine, anti-ds-DNA antibody, and the complement (C3) level), *U-pro/U-creat ratio* urinary protein/creatinine ratio, *Cr* creatinine, *ECLAM* European Consensus Lupus Activity measurement index

tacrolimus group than in the MMF group (OR 0.137; 95% CI 0.034–0.546; $p = 0.005$), while elevation in serum creatinine was considerably higher in the tacrolimus group than in the MMF group (13/103 vs. 0/103; OR 8.148; 95% CI 1.369–48.50; $p = 0.021$; ◘ **Table 4**; ◘ **Fig. 3**).

Efficacy and safety of low-dose tacrolimus in LN

Four studies on tacrolimus at low and fixed doses were conducted for the treatment of LN. One RCT included patients receiving tacrolimus (3 mg/day) or placebo therapy for LN [20]. The primary endpoint was the change in LN Disease Activity Index (LNDAI), calculated from the scores for daily urinary protein excretion, urinary red cells, serum creatinine, anti-double-stranded DNA antibody, and serum complement. The LNDAI was decreased by 32.9 ± 31.0% (mean ± SD) in the tacrolimus group ($n = 28$) and was increased by 2.3 ± 38.2% in the placebo group ($n = 35$) at 6 months. Significant improvement was observed in the tacrolimus group. Treatment-related adverse events occurred in 92.9% of the tacrolimus group and 80.0% of the placebo group, but the difference was not statistically significant. In patients receiving glucocorticoid therapy for LN, the addition of 3 mg tacrolimus to basal therapy achieved significant improvement compared to placebo. Fei et al. [25] conducted a prospective cohort study to assess the efficacy and safety of low-dose tacrolimus therapy in patients with refractory LN resistant to CYC. A total of 26 patients with LN accompanying persistent proteinuria who were resistant to CYC treatment (> 8 g in less

Table 4 Meta-analysis of randomized controlled trials of tacrolimus versus MMF in lupus nephritis

Efficacy/ safety	Outcome	No. of studies	Test of association			Test of heterogeneity		
			OR or SMD*	95% CI	*p*-value	Model	*p*-value	I^2
Efficacy	CR	4	1.028	0.589–1.796	0.922	F	0.306	17.0
	PR	3	1.400	0.741–2.646	0.300	F	0.555	0
	CR and/or PR	4	1.028	0.589–1.796	0.922	F	0.306	17.0
	Proteinuria	3	−0.116	−0.389–0.158	0.408	F	0.968	0
	Serum albumin	2	−0.205	−1.260–0.851	0.704	R	0.046	74.8
	Serum creatinine	2	0.191	−0.335–0.718	0.477	F	0.611	0
	CrCl	2	0.030	−0.595–1.020	0.952	R	0.056	72.5
	Renal-SLEDAI	2	−0.088	−0.345–0.169	0.502	F	0.281	13.8
	Extra-renal-SLEDAI	2	−0.005	−0.262–0.252	0.971	F	0.235	29.0
Safety	Infection	3	0.622	0.327–1.181	0.147	F	0.149	47.3
	Severe infection	3	0.597	0.225–1.587	0.301	F	0.106	55.4
	H. Zoster infection	2	0.137	0.034–0.546	0.005	F	0.742	0
	Leukopenia	2	0.539	0.062–4.712	0.576	F	0.510	0
	Hyperglycemia	3	2.236	0.681–7.337	0.184	F	0.877	0
	Elevation in serum creatinine	3	8.148	1.369–48.50	0.021	F	0.606	0
	Withdrawal due to AE	4	1.501	0.382–5.905	0.561	F	0.298	17.4

OR odds ratio, *SMD** standardized mean difference, *CI* confidence interval, *F* fixed-effect model, *R* random-effect model, *MMF* mycophenolate mofetil, *CR* complete remission, *PR* partial remission, *CrCl* creatinine clearance, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *H. Zoster* herpes zoster, *AE* adverse events

than 6 months) were enrolled. Tacrolimus was initiated at 2 mg/day (if the patient's weight was < 60 kg) or 3 mg/day (if the patient's weight was ≥ 60 kg). Mean urinary protein significantly decreased from 6.91 ± 4.50 g at baseline to 1.11 ± 1.10 g at 6 months ($p < 0.001$). Mean SLEDAI score decreased from 11.42 ± 6.74 at baseline to 3.61 ± 2.73 at 6 months ($p < 0.001$). A complete or partial response was observed in 88.46% of the patients receiving tacrolimus therapy at 6 months. Tacrolimus was well tolerated at 2–3 mg/day, although one patient developed a severe lung infection. A tacrolimus dosage of 2–3 mg daily appears to be effective and safe. The study by Tanaka et al. [23] was an open-label, prospective, long-term cohort study on tacrolimus once daily at a dose of 3 mg as induction- or reinduction/maintenance treatment in 19 patients with biopsy-proven LN. The median follow-up duration was 42 months. A complete response was achieved in 12 patients (63%) and a partial response was achieved in five patients (26%). The remaining two patients showed no response. Serious adverse effects were not observed. This long-term, low-dose, tacrolimus-based immunosuppressive treatment is beneficial and has low cytotoxicity, suggesting it is an attractive option for the treatment of young patients with LN in daily clinical practice. The study by Tanaka et al. [21] was a prospective cohort study on a once-daily dose of tacrolimus (3 mg/day) in young patients with pediatric-onset, long-standing LN. The U-protein/U-creatinine ratio gradually decreased after treatment commencement and dropped significantly 24 months after the start of treatment. Complete responses were achieved in eight patients (73%) and partial responses in two patients (18%), but the remaining patients showed no response. Serious adverse effects were not observed.

Heterogeneity and publication bias

Between-study heterogeneity was not found during the meta-analysis of the efficacy and safety of tacrolimus versus MMF, except for serum albumin and creatinine clearance. It was difficult to correlate the funnel plot, which is typically used to detect publication bias, because the number of studies included in the analysis was too small. However, no publication bias was observed (Egger's regression test, $p > 0.1$).

Discussion

We systematically reviewed the clinical data from four RCTs that examined the use of low-dose tacrolimus for treatment of LN and merged the clinical data from four RCTs on tacrolimus vs. MMF as induction therapy. Tacrolimus was shown to be as effective and safe as MMF as an induction therapy for LN, with the exception of a reduced risk of herpes zoster infection and a rise in serum creatinine. Tacrolimus at a dose of 3 mg/day was found to be efficacious and safe in patients with LN.

SLE is a heterogeneous autoimmune disorder characterized by autoantibody overproduction and T and B cell abnormalities that contribute to immune complex accumulation in the kidneys. The formation of an immunological complex triggers an inflammatory reaction in glomeruli, resulting in lymphocyte and macrophage infiltration [28]. It was shown that tacrolimus and MMF had comparable efficacies in terms of inducing renal remission. Long-term outcome of an RCT confirmed non-inferiority of tacrolimus to MMF as induction therapy for LN [29]. However, tacrolimus reduces the risk of herpes zoster infection and increases the risk of serum creatinine elevation. Cy-

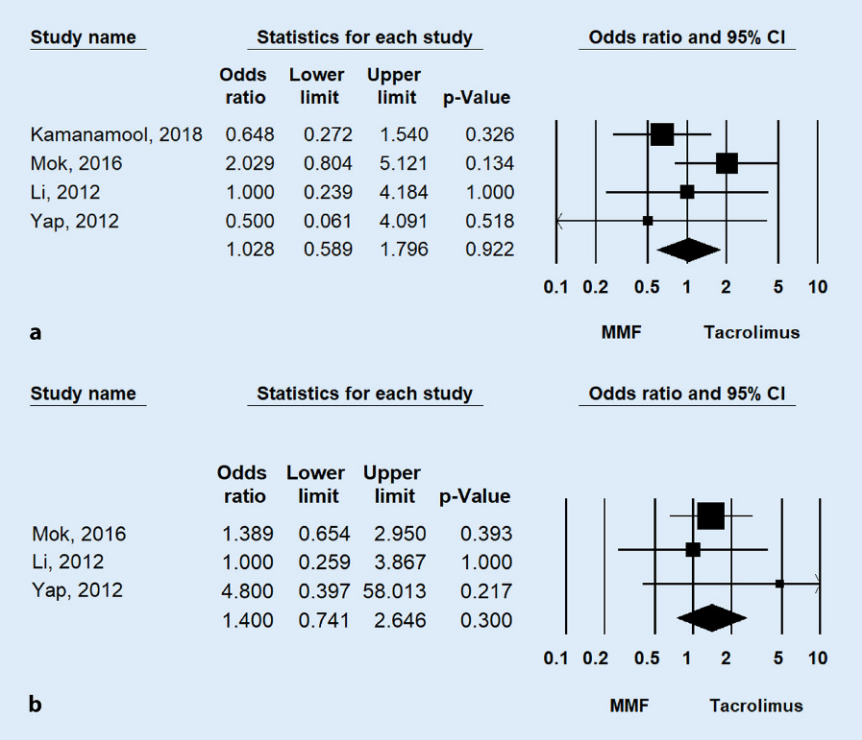

Fig. 2 ▲ Meta-analysis of the efficacy of tacrolimus and mycophenolate mofetil (MMF) in patients with lupus nephritis. **a** Complete remission, **b** Partial remissions. The complete and partial remission rates were comparable between tacrolimus and MMF

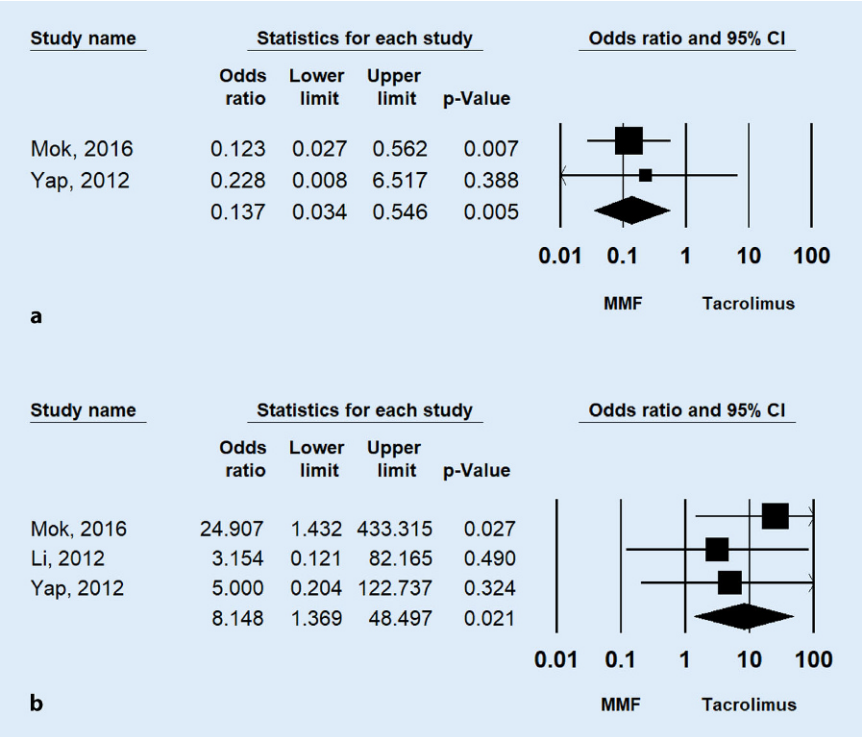

Fig. 3 ▲ Meta-analysis of safety outcomes for tacrolimus versus mycophenolate mofetil (MMF) in patients with lupus nephritis. **a** Herpes zoster infection, **b** elevation in serum creatinine. Herpes zoster infection was significantly less common in the tacrolimus group than in the MMF group, while elevation in serum creatinine was higher in the tacrolimus group than in the MMF group (13/103 vs. 0/103)

closporin, another calcineurin inhibitor, is an effective and safe treatment for patients with LN [30]. Multitarget therapy such as tacrolimus + MMF showed a higher complete remission rate than monotherapy [31]. However, cases of infection and pneumonia were numerically elevated in the multitarget therapy group compared to the monotherapy group [32].

This meta-analysis differs from a previous meta-analysis by Hannah et al. [33], as the current study included one new study and 42 more patients with LN in the tacrolimus group and 41 more patients in the MMF group. Our meta-analysis is more comprehensive in terms of efficacy and safety. The conclusion of this meta-analysis that tacrolimus is comparable to MMF in terms of effectiveness agrees with previous research; however, our investigation revealed a difference in safety between tacrolimus and MMF.

Due to the limitations of this study, our findings should be considered with care. First, the possibility of publication bias is always a concern. It should be emphasized that it is difficult to rule out publication bias with certainty, particularly when the number of studies considered is low, as in this analysis. Second, variances in clinical characteristics such as race, sex, age, extent of renal impairment, proportion of patients with class III and IV LN, and research quality are likely to skew the meta-analysis findings. Third, because tacrolimus was only studied in Asian patients, further studies are required to determine whether tacrolimus therapy is successful in non-Asian patients with LN. Fourth, the number of studies included and the sample sizes in these studies were small. Especially, the numbers of study participants for the side effects were substantially small (83 vs. 83 for herpes zoster infection and 103 vs. 103 for elevation in serum creatinine). Fifth, the three prospective cohort trials used uncontrolled designs, resulting in a lack of clear evidence for the specific effects of low-dose tacrolimus. However, this meta-analysis and systematic review had some benefits. The number of patients with LN in different studies varied from 11 to 150; nonetheless, 408 individuals were included in this pooled analysis. We generated more accurate data by merging the findings of multiple investigations and per-

forming a systematic review rather than conducting independent research [34–36]. This improved statistical power and resolution, enabling collection of more accurate data.

In conclusion, our RCT-based meta-analysis indicated that tacrolimus was comparable to MMF in terms of effectiveness and safety as an induction therapy for LN, with the exception of a lower risk for herpes zoster infection and a greater rate of serum creatinine increase due to tacrolimus. In this systematic review, tacrolimus was shown to be efficacious and safe at a dose of 3 mg/day in patients with LN. Further research is required to assess the long-term effectiveness and safety of tacrolimus therapy in individuals with LN from various ethnic groups.

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Declarations

Conflict of interest. Y.H. Lee and G.G. Song declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

Zusammenfassung

Wirksamkeit und Sicherheit von Tacrolimus vs. Mycophenolat-Mofetil als Induktionstherapie und niedrigdosiertem Tacrolimus zur Behandlung der Lupusnephritis: eine Metaanalyse

Ziel: Ziel der Studie war es, die Wirksamkeit und Sicherheit von Tacrolimus und Mycophenolat-Mofetil (MMF) als Induktionstherapie und von niedrigdosiertem Tacrolimus zur Behandlung der Lupusnephritis (LN) zu untersuchen.
Methoden: Es wurde eine Metaanalyse randomisierter kontrollierter Studien (RCT) durchgeführt, um die Wirksamkeit und Sicherheit von Tacrolimus und Mycophenolat-Mofetil (MMF) als Induktionstherapie bei LN zu vergleichen. Dazu wurden RCT und prospektive Kohortenstudien mit einer täglichen Tacrolimusdosis von 3 mg systematisch überprüft und eine Metaanalyse der Wirksamkeit und Sicherheit von Tacrolimus als Induktionstherapie bei LN im Vergleich zu MMF durchgeführt.
Ergebnisse: Die Einschlusskriterien wurden von 8 Studien (5 RCT und 3 prospektive Kohortenstudien) mit insgesamt 408 Personen (289 für Tacrolimus vs. MMF und 119 für niedrigdosiertes Tacrolimus) erfüllt. Tacrolimus und MMF wiesen ähnliche komplette Remissionsraten auf (Odds Ratio [OR]: 1,028; 95%-Konfidenzintervall [95%-KCI]: 0,589–1,796; $p = 0{,}922$). Die partielle Remissionsrate unterschied sich nicht zwischen der Tacrolimus- und der MMF-Gruppe (OR: 1,400; 95%-KI: 0,741–2,646; $p = 0{,}300$). Bei Tacrolimus und MMF gab es keine Unterschiede in Bezug auf Proteinurie, Serumalbumin, Serumkreatinin, Kreatininclearance, den renalen Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) oder den extrarenalen SLEDAI. Auch die Inzidenz von Infektionen, schweren Infektionen, Leukopenien und Hyperglykämien unterschied sich nicht zwischen der Tacrolimus- und der MMF-Gruppe. Allerdings war eine Herpes-zoster-Infektion in der Tacrolimusgruppe signifikant weniger häufig (OR: 0,137; 95%-KI: 0,034–0,546; $p = 0{,}005$), während der Serumkreatininanstieg in der Tacrolimusgruppe signifikant höher war als in der MMF-Gruppe (OR: 8,148; 95%-KI: 1,369–48,50; $p = 0{,}021$). Bei Gabe von 3 mg/Tag erwies sich Tacrolimus als sicher und gut verträglich und bot in sämtlichen Untersuchungen therapeutische Vorteile.
Schlussfolgerung: Tacrolimus war in Bezug auf Wirksamkeit und Sicherheit als Induktionstherapie bei LN mit MMF vergleichbar, außer im Hinblick auf ein vermindertes Risiko für eine Herpes-zoster-Infektion und in Bezug auf einen Anstieg des Serumkreatinins. Bei Personen mit LN stellte sich Tacrolimus in der Dosis von 3 mg/Tag als wirksam und sicher heraus.

Schlüsselwörter
Tacrolimus · Mycophenolat-Mofetil · Lupusnephritis · Metaanalyse · Systematische Übersichtsarbeit

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