

Efficacy of tacrolimus and other immunosuppressants in the treatment of systemic lupus erythematosus: A systematic review and meta-analysis

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Abstract. The present systematic review evaluated the efficacy and safety of tacrolimus (TAC) and other immunosuppressants in the treatment of systemic lupus erythematosus (SLE), providing evidence-based recommendations for clinical practice. PubMed, Web of Science, Embase and Cochrane Library databases were searched for clinical studies comparing TAC with other immunosuppressive drugs. A total of 12 studies, including 10 randomized controlled trials and two cohort studies involving 1,217 patients, were identified. The results indicated that TAC was significantly superior to cyclophosphamide (CYC) in complete remission (CR) rates [odds ratio (OR)=1.83, 95% confidence interval (CI): 1.33-2.51], whereas no significant differences were found when compared with mycophenolate mofetil (MMF; OR=0.93; 95% CI: 0.58-1.47] or azathioprine [AZA; OR=0.95; 95% CI: 0.49-1.84]. Thus, significant differences were found in the partial remission rates between TAC and CYC, MMF, or AZA. TAC demonstrated improvements in the short-term SLE disease activity index scores and albumin levels, with long-term efficacy comparable to that of MMF and CYC. Furthermore, the infection rate with TAC was lower than that with MMF (OR=0.48; 95% CI: 0.31-0.75), but similar to those with CYC and AZA. TAC also showed a lower incidence of leukopenia than AZA (OR=0.13; 95% CI: 0.04-0.43). In conclusion, TAC is superior to CYC in achieving CR in patients with SLE, with comparable efficacy to MMF and AZA. TAC improves short-term disease activity and albumin levels, and its long-term efficacy is similar to those of MMF and CYC.

Introduction

Systemic lupus erythematosus (SLE) is recognized globally as one of the three major intractable diseases. It can affect multiple organs, including the heart, lungs and kidneys, and severe cases it can also damage the central nervous system (1). Global epidemiological data (2) show that the annual incidence is 5.14 per 100,000 individuals, with 8.82 and 1.53 cases for women and men, respectively. Significant regional variations have been observed, with higher incidence in Poland, United States and Barbados but higher prevalence in the UAE, Barbados and Brazil. Although the exact cause of SLE remains unknown, it is considered to be influenced by a combination of genetic factors, environmental exposures (such as ultraviolet radiation, toxins and radiation), viral infections, hormone levels and gut microbiota (3-5).

Patients with SLE often experience B-cells overactivation and impaired T-cell function, leading to immune dysregulation and systemic inflammatory responses that disrupt multiple organ functions (6). Currently, the treatment of SLE primarily relies on immunosuppressive agents and corticosteroids. Tacrolimus (TAC), as a calcineurin inhibitor, has high lipophilicity and its mechanism of action is similar to that of cyclosporine. Once inside the cell, TAC binds to the FK506-binding protein in T lymphocytes, forming a complex that disrupts the calcineurin signaling pathway and inhibits the influx of calcium ions (7). This mechanism helps prevent the release of various inflammatory mediators, regulates the function of T lymphocyte subsets, reduces disease activity, and controls SLE progression (8).

TAC has gained increasing attention in recent years. A systematic evaluation of its efficacy compared with other immunosuppressants in the treatment of SLE could provide a more scientific basis for clinical decision-making. In the present study, the efficacy of TAC in treating SLE was systematically assessed by analyzing the existing literature and comparing it with other immunosuppressants.

Materials and methods

Literature search. A literature search was conducted in the databases of PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://www.embase.com/>), Cochrane Library (<https://www.cochranelibrary.com/>) and Web of Science

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Key words: tacrolimus, immunosuppressant, systemic lupus erythematosus, complete response rate

(<https://clarivate.com>) for articles regarding the treatment of SLE with TAC published from database inception up to December 2024. In addition, the reference lists were manually searched to ensure the validity of the included studies. The main search key words included TAC, SLE, lupus nephritis and immunosuppressants, among others. The search strategy involved a combination of subject headings and free terms. The search strategy in PubMed is shown in Table I.

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) The study designs included randomized controlled trials (RCT), cohort studies, single-arm studies; ii) the study participants were patients with clear diagnosis of SLE (9), with no restrictions on sex, age, or region; iii) The treatment group used TAC, and the control group used immunosuppressive agents, such as cyclophosphamide (CYC), mycophenolate mofetil (MMF) and azathioprine (AZA); and iv) the studies analyzed at least one of the following outcomes: complete remission (CR) rate, partial response (PR) rate, SLE disease activity index (SLEDAI) and adverse reactions.

Exclusion criteria were as follows: i) Published similar or duplicate literature; ii) literature from which valid data cannot be extracted or full text cannot be obtained; iii) systematic reviews, reviews, or animal experiment literature; and iv) literature that does not separate the control and treatment groups (Table II).

Literature screening and data extraction. Two researchers independently reviewed all reports and excluded articles that were obviously irrelevant based on the title, abstract and full text. If consensus was not achieved, a third researcher was consulted. Data extraction encompassed the following content: i) basic information; ii) baseline characteristics; iii) interventions; iv) elements of bias risk assessment and v) outcome measures.

Quality evaluation standard. Two researchers independently assessed the risk of bias in the included studies and cross-checked their findings with each other. In the case of disagreements, a third researcher was consulted to resolve the issues. Corresponding quality assessment tools were applied based on the study design. For RCTs, the Cochrane Risk of Bias Tool was used, which is specifically designed for RCTs and allows for a comprehensive assessment of bias risks related to random sequence generation, allocation concealment, blinding, data integrity and selective reporting. For non-RCTs, the Newcastle-Ottawa Scale (NOS) was used, as this tool is specifically designed for non-random studies (such as cohort or case-control studies) and systematically assesses bias risks related to selection, comparability and outcome measurement.

For RCTs, the Cochrane Collaboration's recommended risk-of-bias assessment tool was utilized (10). The assessment encompassed six domains and seven items, namely, random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), completeness of outcome data (attrition bias), selective reporting of results (reporting bias) and other sources of bias (other biases). Each domain was rated as having a low, high, or unclear risk of bias.

Table I. PubMed search strategy.

Retrieval procedure
#1 Tacrolimus [Mesh]
#2 Prograf
#3 Anhydrous Tacrolimus
#4 FK-506
#5 FR-900506
#6 Lupus Erythematosus, Systemic [Mesh]
#7 Lupus Erythematosus Disseminatus
#8 Systemic Lupus Erythematosus
#9 Libman-Sacks Disease
#10 Disease, Libman-Sacks
#11(#1 OR #2 OR #3 OR #4 OR #5) AND(#6 OR #7 OR #8 OR #9 OR #10)

For non-RCT, the NOS was used to assess the risk of bias (11). The evaluation content included the risk of bias in patient selection, between-group comparability, and outcome exposure or results. The NOS consists of eight aspects and nine entries, with each entry scoring 1 or 0 points. Based on the scores, the studies were categorized into having low quality (<5 points), medium (5-8 points), and high (8-9 points) quality.

Statistical methods. The meta-analysis was conducted using StataMP 17 (StataCorp LLC). For dichotomous variables, odds ratios (OR) and 95% confidence intervals (CI) were used as effect sizes. The random-effects model was used for the meta-analysis, regardless of heterogeneity. Publication bias was assessed by constructing a funnel plot. The significance level was set at $\alpha=0.05$.

Results

Included literature. Of the total of 439 studies searched, 12 (12-23) were finally included after layer-by-layer screening, including 10 RCTs (12-14,16-22) and 2 cohort studies (15,23). The literature screening process and results are shown in Fig. 1.

General characteristics. A total of 12 studies (12-23) enrolled 1,217 patients, which included 582 in the treatment group and 635 in the control group (Table III).

Literature quality evaluation. One RCT (16) did not describe the randomization method; thus, it was rated as 'high risk'. A total of three RCTs (13,14,19) mentioned the methods used, such as sealed envelopes to achieve allocation concealment, therefore they were rated as 'low risk'. For studies that did not employ blinding or did not clearly describe the blinding method (12-23), considering the potential performance bias and detection bias, these studies were assessed as having a 'high risk' of bias. Specifically, in unblinded studies, participants and researchers may be influenced by subjective factors, which could affect the validity and reliability of the study results. All studies (12-23) have reported all the expected collected data and predefined primary and secondary outcome

Table II. Inclusion and exclusion criteria.

Inclusion	Exclusion
1. Randomized controlled trials, cohort studies	1. Published similar or duplicate literature
2. systemic lupus erythematosus patients, with no restrictions on gender, age, or region	2. Literature from which valid data cannot be extracted or full text cannot be obtained
3. Treatment group uses TAC	3. Systematic reviews, reviews, or animal experiment literature
4. Control group uses immunosuppressive agents, such as cyclophosphamide, mycophenolate mofetil and azathioprine	4. Literature that does not separate control and treatment groups
5. Outcome measures such as complete remission rate, partial response rate, Systemic Lupus Erythematosus Disease Activity Index, adverse reactions, etc.	

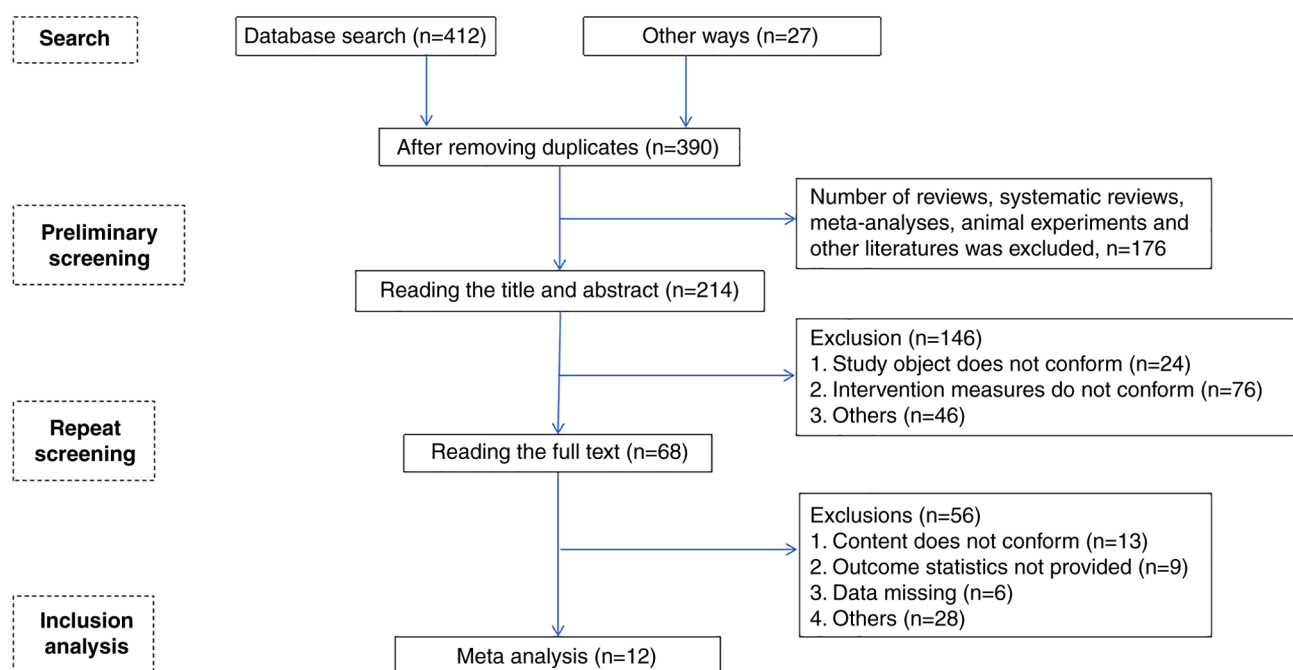


Figure 1. Literature screening process.

measures, therefore they were rated as 'low risk.' However, whether there were other sources of bias was unclear, thus the risk of other bias was rated as unclear (Fig. 2).

One cohort study (23) had an NOS score of 9, whereas the other cohort study (15) did not report matching or adjusting for the exposed and unexposed groups in the analysis, resulting in an NOS score of 8 (Table IV).

Results of meta-analysis

CR. TAC demonstrated significantly superior CR to CYC (OR=1.83; 95% CI: 1.33-2.51; $P<0.001$). No significant difference in CR was found between TAC and MMF or AZA [(OR=0.93; 95% CI: 0.58-1.47; $P=0.753$) OR=0.95; 95% CI: 0.49-1.84; $P=0.884$; Fig. 3].

PR. No significant differences in PR were found between TAC and CYC (OR=1.15; 95% CI: 0.78-1.70; $P=0.476$), MMF (OR=1.14; 95% CI: 0.68-1.92; $P=0.610$), or AZA (OR=1.18; 95% CI: 0.55-2.55; $P=0.672$) (Fig. 4).

SLEDAI score. The changes in the SLEDAI scores from eight studies (12,14,15,17-19,21,23) are summarized in Table V. TAC demonstrated therapeutic advantages in reducing the SLEDAI score; however, the results varied across different studies. Szeto *et al* (12) employed a general linear model for repeated measurements, with results indicating no significant difference in SLEDAI scores between the CYC and TAC groups throughout the follow-up period. Wang *et al* (15) revealed that the TAC group showed an improved effect on improving the SLEDAI score compared with the CYC group. Zheng *et al* (21) indicated that at week 24 of treatment, the least squares mean change in the SLEDAI score for the TAC group was -8.6, whereas for the CYC group, it was -6.4, with the TAC group demonstrating significantly improved efficacy. Mok *et al* (18) did not find a significant difference in the effect of TAC and MMF on improving the SLEDAI score after 6 months of treatment. Kamanamool *et al* (19) observed that TAC showed a more pronounced short-term improvement in

Table III. Basic information of the study.

First author/s, year	Age (years)		Grouping situation (sample size)		Course of treatment	Outcome measures	(Refs.)
	C	T	C	T			
Szeto <i>et al.</i> , 2008	36.5 (12.2)	38.2 (10.4)	CYC (n=19)	TAC (n=18)	6 months	①②③	(12)
Chen <i>et al.</i> , 2011	31.9 (10.1)	32.0 (10.8)	CYC (n=39)	TAC (n=42)	6 months	①②④⑤⑥	(13)
Chen <i>et al.</i> , 2012	33.1 (10.9)	30.7 (10.2)	AZA (n=36)	TAC (n=34)	6 months	①②③④⑤⑥	(14)
Wang <i>et al.</i> , 2012	35.7 (11.4)	32.0 (7.7)	CYC (n=20)	TAC (n=20)	12 months	①②③⑤	(15)
Yap <i>et al.</i> , 2012	36.0 (15.7)	40.0 (12.5)	MMF (n=7)	TAC (n=9)	24 months	①②④⑥	(16)
Li <i>et al.</i> , 2012	26.5 (16-62)	29 (17-50)	MMF (n=20)	TAC (n=20)	12 weeks	①②③④⑤⑥	(17)
Mok <i>et al.</i> , 2016	36.1 (13.1)	36.2 (14.0)	MMF (n=76)	TAC (n=74)	6 months	①②③④⑤	(18)
Kamanamool <i>et al.</i> , 2018	34.1 (11.1)	31.7 (10.5)	MMF (n=42)	TAC (n=41)	12 months	①③	(19)
Zhang <i>et al.</i> , 2020	-	-	CYC (n=117)	TAC (n=117)	6 months	①②⑤⑥	(20)
Zheng <i>et al.</i> , 2022	34.1 (9.4)	34.3 (9.6)	CYC (n=142)	TAC (n=157)	24 weeks	①③⑤⑥	(21)
Zhang <i>et al.</i> , 2022	34 (11)	31 (10)	AZA (n=39)	TAC (n=37)	6 months	①②⑤⑥	(22)
Suzuki <i>et al.</i> , 2024	30 (12)	31 (10)	MMF (n=47)	TAC (n=37)	52 weeks	①②⑤⑥	(23)
	36.18 (12.94)	43.92 (11.81)	MMF (n=11)	TAC (n=13)		③	

C, control group; T, treatment group; CYC, cyclophosphamide; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus. Outcome measures: ① complete remission rate ② partial remission rate ③ SLEDAI score ④ serum albumin ⑤ infections ⑥ leukopenia.

Table IV. Evaluation results of the risk of bias in the included cohort studies.

First author/s, year	Research subject				Comparability between groups		Outcome			(Refs.)
	①	②	③	④	⑤A	⑤B	⑥	⑦	⑧	
Wang <i>et al</i> , 2012	1	1	1	1	1	0	1	1	1	(15)
Suzuki <i>et al</i> , 2024	1	1	1	1	1	1	1	1	1	(23)

① Representativeness of the exposed group; ② Selection of the nonexposed group; ③ Ascertainment of exposure; ④ Demonstration that the outcome of interest was not present at the start of study; ⑤ A. The study controlled for the most important confounding factors; ⑤ B. The study controlled for any additional important confounding factors; ⑥ Assessment of outcome; ⑦ Adequacy of follow-up; ⑧ Completeness of follow-up.

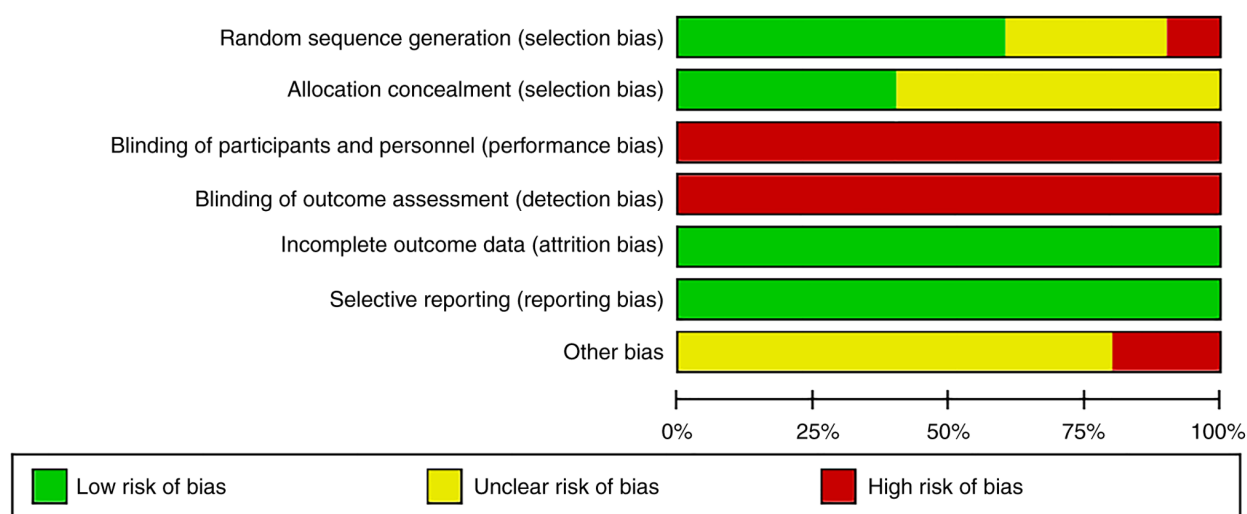


Figure 2. Bias risk bar chart.

the SLEDAI score; however, its long-term effect was slightly inferior to that of MMF. Suzuki *et al* (23) demonstrated that both TAC and MMF significantly improved the SLEDAI score, with no significant difference between the two groups, suggesting the comparable efficacy of TAC and MMF in improving the SLEDAI score. Chen *et al* (14) found that TAC and AZA exhibited significant efficacy in improving the SLEDAI score; however, no significant difference was found between them. Li *et al* (17) reported that CYC, TAC and MMF were all effective in improving the SLEDAI score; however, no significant difference was observed in disease activity control among the three treatment regimens.

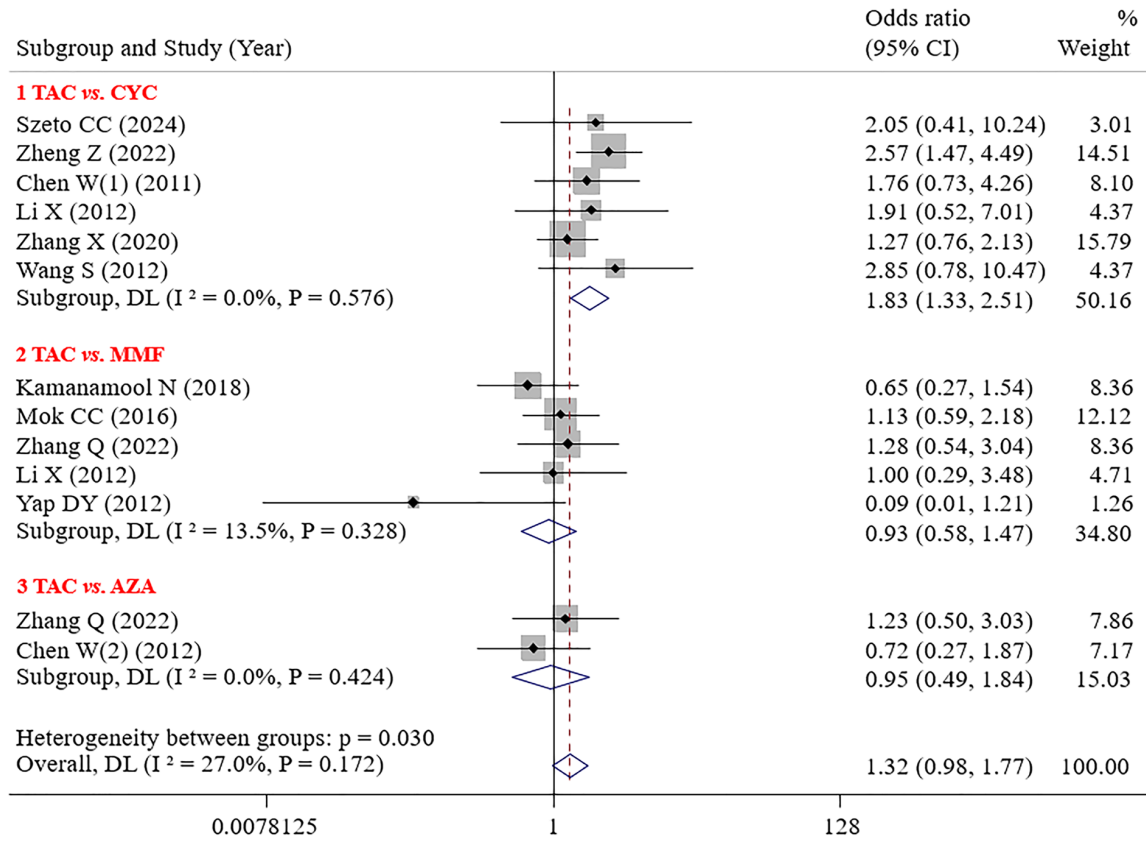
Serum albumin. The results of five studies (13,14,16-18) regarding the TAC-induced changes in serum albumin are summarized in Table VI. The results of Chen *et al* (14) are consistent with the conclusions of Mok *et al* (18), showing no significant difference in serum albumin changes between TAC and AZA. Chen *et al* (13) found that TAC was superior to CYC in reducing proteinuria in the short term (1 month) but slightly increased serum albumin levels. However, in the long-term follow-up (6 months), the two drugs did not show significant differences in proteinuria and serum albumin levels. Li *et al* (17) observed that with short-term treatment (4-8 weeks), TAC is more effective in improving urine protein

and albumin levels, whereas MMF is more beneficial in maintaining higher serum albumin levels with long-term treatment (24 weeks). However, Yap *et al* (16) did not find a significant difference in the serum albumin levels between TAC and MMF in their 24-month study (39.7 ± 5.3 vs. 43.4 ± 2.2 ; $P=0.189$).

Infection. No significant differences were found in infections (such as herpes zoster, urinary tract infections, lung infections, and upper respiratory infections) between TAC and CYC or AZA [(OR=0.96, 95% CI: 0.49-1.85; $P=0.894$) (OR=1.19; 95% CI: 0.13-11.27; $P=0.881$)]. The incidence of infections with TAC was lower than that with MMF (OR=0.48; 95% CI: 0.31-0.75; $P=0.001$; Fig. 5).

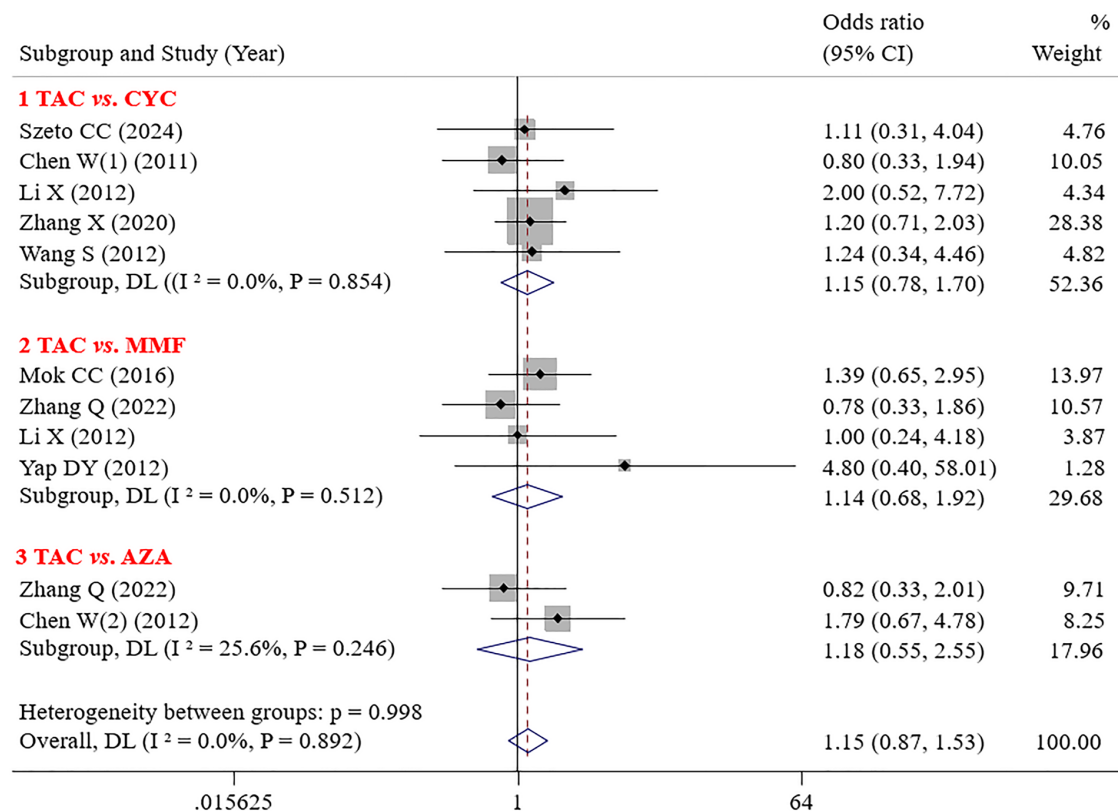
Leukopenia. No significant difference was noted in the incidence of leukopenia between TAC and CYC or MMF [(OR=0.57; 95% CI: 0.07-4.84; $P=0.609$) (OR=0.31; 95% CI: 0.08-1.26; $P=0.102$)]. The incidence of leukopenia caused by TAC was significantly lower than that caused by MMF and AZA (OR=0.13; 95% CI: 0.04-0.43; $P=0.001$; Fig. 6).

Publication bias assessment. A funnel plot was constructed to assess the publication bias for the CR. The funnel plot was approximately symmetrical, indicating no publication bias. The results of the Begg ($P=0.807$) and Egger ($P=0.284$) tests also suggest the absence of publication bias (Fig. 7).



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 3. Forest map of the complete response rate. CYC, cyclophosphamide; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 4. Forest map of the partial response rate. CYC, cyclophosphamide; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.

Table V. SLEDAI scores.

First author/s, year	Group		SLEDAI scores		Course of treatment	Statistical method	(Refs.)
	Control group	Treatment group	Control group	Treatment group			
Szeto <i>et al</i> , 2008	CYC	TAC	No significant difference in the SLEDAI scores between the two groups.		12 months (P=0.2)	General linear model	(12)
Chen <i>et al</i> , 2012	AZA	TAC	5.3±3.1	5.0±2.9	6 months (P=0.18)	t-test	(13)
Suzuki <i>et al</i> , 2024	MMF	TAC	Decreased from 4.000±2.324 to 2.000±1.988 (P=0.021)	Decreased from 4.307±2.287 to 2.833±1.229 (P=0.044)	From 4 to 52 weeks	t-test	(23)
Zheng <i>et al</i> , 2022	CYC	TAC	-5.7 -6.4	-6.7 -8.6	12 weeks (P=0.02) 24 weeks (P<0.001)	Least Square Mean	21
Kamanamool <i>et al</i> , 2018	MMF	TAC	7.0±4.1 5.1±3.9 4.9±3.3 3.9±3.8	5.5±4.7 6.1±4.3 5.3±4.5 5.2±4.3	2 months (P=0.114) 4 months (P=0.223) 6 months (P=0.539) 12 months (P=0.102)	t-test	(19)
Mok <i>et al</i> , 2016	MMF	TAC	3.9±3.1	3.3±3.1	6 months (P=0.25)	t-test	(18)
Li <i>et al</i> , 2012	MMF CYC	TAC	The SLEDAI scores of each group decreased after treatment. No significant difference in the change of SLEDAI score among these three induction treatment regimens		24 weeks	F-test	(17)
Wang <i>et al</i> , 2012	CYC	TAC	4.65±5.11 3.41±2.65	2.80±3.14 1.15±1.54	6 months (P=0.187) 12 months (P=0.003)	t-test	(15)

CYC, cyclophosphamide; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus

Discussion

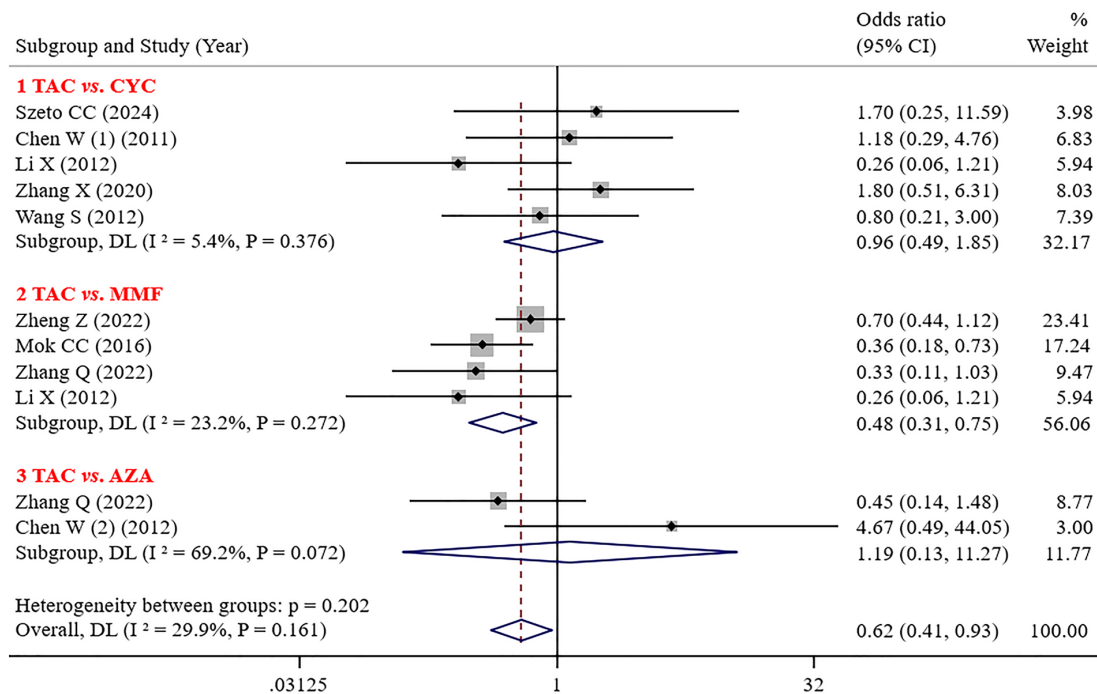
SLE predominantly affects reproductive women, with renal involvement as a frequent and serious complication. Lupus nephritis is one of the most severe manifestations of SLE, with progresses to end-stage renal disease (ESRD) in ~10% of cases, significantly compromising patient outcomes and quality of life (24). Although no definitive cure exists for lupus nephritis, early therapeutic intervention can markedly slow disease progression and improve renal function prognosis, potentially preventing the development of renal failure. MMF and CYC are commonly used immunosuppressive drugs. However, CYC's alkylating agents have adverse reactions such as bone marrow suppression, infection, gonadal suppression, or increased risk of tumors. Meanwhile, certain studies have suggested that MMF may increase the risk of progression to ESRD in certain patients (25), whereas other studies have indicated that MMF could offer improved renal outcomes compared with CYC (26).

Multiple studies have demonstrated the significant efficacy of TAC in treating SLE, as evidenced by improvements in SLEDAI scores, proteinuria reduction, and alleviation of other clinical symptoms (for example, arthritis and skin rash) (8,27-28). Long-term, low-dose TAC therapy

has shown favorable outcomes in certain patient populations with relatively fewer adverse effects (29,30). However, low-dose induction therapy may still carry an increased risk of acute flares. Mechanistic studies have revealed that TAC enhances therapeutic efficacy by inhibiting P-glycoprotein (P-gp) activity, thereby overcoming P-gp-mediated drug resistance (31). Regarding clinical outcomes, 67% of patients achieved a renal response (complete or partial) within 3 months of TAC treatment, with the response rate increasing to 92% by 6 months. Moreover, urine protein levels significantly decreased, and the expression and function of P-gp were also improved (31). Notably, TAC has demonstrated safety for both the mother and fetus during pregnancy (32), and pediatric use has shown comparable efficacy and safety profiles (33). Emerging evidence on TAC-based maintenance therapy for pediatric-onset lupus nephritis indicates that long-term TAC-based immunosuppression demonstrates favorable efficacy and lower cytotoxicity in with pediatric-onset lupus nephritis, suggesting significant potential as maintenance therapy in clinical practice (33). Overall, TAC has shown significant potential in the treating SLE. Owing to the involvement of multiple factors in the treatment of SLE, such as disease activity, organ involvement and patient tolerance, commonly

Table VI. Serum albumin levels.

First author/s, year	Group		SLEDAI scores		Course of treatment	Statistical method	(Refs.)
	Control group	Treatment group	Control group	Treatment group			
Chen <i>et al</i> , 2012	AZA (n=36)	TAC (n=34)	4.08±0.52 g/dl	4.19±0.4 g/dl	6 months (P=0.42)	t-test	(14)
Yap <i>et al</i> , 2012	MMF (n=7)	TAC (n=9)	43.4±12.2 g/l	39.7±15.3 g/l	24 months (P=0.189)	t-test	(16)
Li <i>et al</i> , 2012	MMF (n=20) CYC (n=20)	TAC (n=20)	The serum albumin level in the tacrolimus group significantly increased compared with the baseline after 8 weeks of treatment (P=0.048), while significant changes occurred in the other two groups only after 12 weeks of treatment.			No data	(17)
Mok <i>et al</i> , 2016	MMF (n=76)	TAC (n=74)	33.4±5.7 g/l	34.1±4.5 g/l	2 months (P=0.98)	t-test	(18)
			34.9±6.0 g/l	36.5±4.3 g/l	4 months (P=0.22)		
			36.1±6.3 g/l	37.4±4.8 g/l	6 months (P=0.26)		
Chen <i>et al</i> , 2011	CYC (n=39)	TAC (n=42)	0.50 g/dl (95% CI, 0.47-0.53)	0.54 g/dl (95% CI: 0.51-0.57)	6 months (P=0.05)	No data	(13)

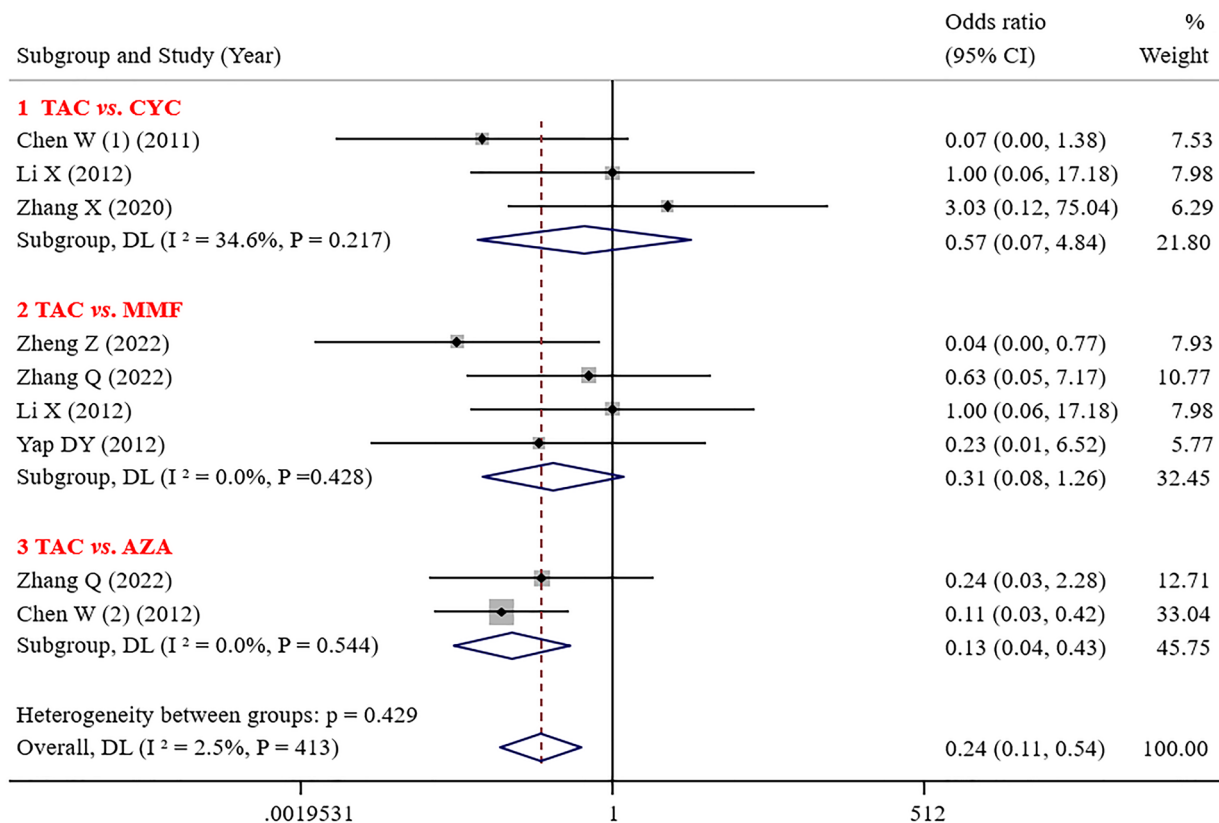


NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 5. Forest map of the infection incidence. CYC, cyclophosphamide; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.

used clinical immunosuppressants include MMF, CYC and AZA. However, these drugs have different efficacy and safety

profiles. To clarify the role of TAC in SLE, its effectiveness and safety were systematically analyzed and compared with those



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Figure 6. Forest map of leukopenia. CYC, cyclophosphamide; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus.

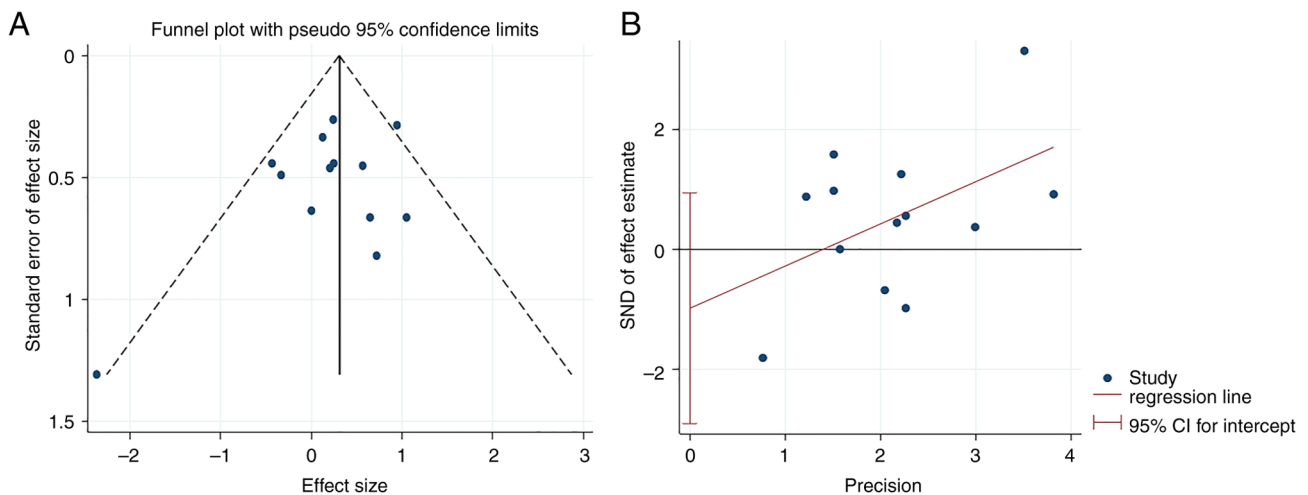


Figure 7. Publication bias assessment. (A) Funnel plot. (B) Egger's funnel diagram.

of MMF, CYC and AZA to provide clinicians with a more comprehensive treatment option and optimization strategy.

The present systematic review revealed that TAC demonstrated significantly superior CR rates to CYC, consistent with previous findings (34). Specifically, the advantage of TAC in CR may be related to its lower immunosuppressive toxicity and improved clinical efficacy. Therefore, for patients who do not respond well to CYC, TAC may offer greater potential as an alternative, particularly in avoiding CYC-associated infectious complications. In addition, TAC did not show significant

differences in PR from MMF or AZA, suggesting that it may exert similar effects to these drugs during the maintenance phase of treatment. The results further support findings from previous meta-analyses (35,36), indicating that TAC and MMF have comparable efficacy in CR and PR, particularly with long-term treatment, where both drugs may contribute similarly to the control of the immune response. Although TAC demonstrated improved short-term efficacy, the differences in its effect compared with those of MMF and AZA during the maintenance phase were not significant. Notably,

the MMF group showed a lower relapse rate, suggesting the potential advantages of MMF in long-term immunosuppressive therapy (35). Therefore, for patients who have successfully controlled immune response, MMF or AZA may be considered for maintenance therapy to reduce the relapse risk. Overall, TAC is superior to CYC in terms of CR and has potential advantages in personalized treatment strategies, particularly for patients who have an inadequate response to CYC. Moreover, the combination of TAC with MMF, AZA, or other immunosuppressive drugs may become an ideal treatment option in long-term therapy (37,38). Therefore, to explore the best treatment combinations and individualized treatment strategies for patients, future studies could focus on the combined use of TAC with other immunosuppressive agents.

The key to therapeutic intervention lies in the complete or partial improvement of the clinical manifestations of kidney injury. The present study indicated that although results across different studies vary, TAC demonstrates certain short-term efficacy advantages in improving the SLEDAI score and serum albumin levels in patients with SLE. In terms of SLEDAI score improvement, the present findings align with those of Wang *et al* (15), indicating that the TAC group performance was improved compared with the CYC group. However, Szeto *et al* (12) did not observe a significant difference. This may be attributed to differences in the baseline characteristics of patients, disease severity and treatment regimens across studies. In addition, while the SLEDAI score is sensitive in assessing disease activity, its ability to predict treatment response may be influenced by various factors. Regarding serum albumin levels, TAC exhibited some improvement in the short term compared with AZA and MMF; however, long-term follow-up results revealed no significant differences in efficacy. This finding is consistent with the results of previous meta-analyses (36), which concluded the lack of significant differences between TAC and MMF in terms of proteinuria, serum albumin, serum creatinine, creatinine clearance and SLEDAI score. The early efficacy advantage of TAC may stem from its rapid immune modulation, whereas the convergence of long-term efficacy suggests that various immunosuppressive agents can ultimately achieve disease stabilization. This finding indicates that TAC is more suitable as a short-term induction therapy, whereas maintenance therapy may require a combination with other immunosuppressive agents. This conclusion aligns with the results of previous research and supports the necessity of personalized treatment strategies.

For continuous outcomes such as SLEDAI scores and serum albumin levels, a narrative review was preferred over a meta-analysis, primarily due to the significant heterogeneity in the available research data. Specifically, considerable differences were observed in the assessment criteria, time points and data collection methods for SLEDAI scores and serum albumin levels across studies, making data integration challenging. In addition, some studies had small sample sizes and missing data, particularly in the measurement of serum albumin levels, which could compromise the accuracy and robustness of the meta-analysis results. The use of different statistical analysis methods across studies further complicated the direct application of a meta-analysis. Therefore, to ensure the reliability of the findings and avoid bias arising from data

heterogeneity, a narrative review was employed. This approach allows for a clearer presentation of the differences between studies and ensures a more accurate interpretation of the research outcomes.

Regarding safety, Li *et al* (34) considered TAC as the safest treatment option, with the lowest likelihood of infection events. The results of the present study demonstrate a lower incidence of infection events (such as herpes zoster and urinary tract infections) in the TAC group than in the MMF group, with no significant difference when compared with those in the CYC and AZA groups. An observational study found that MMF was significantly associated with the overall infection risk in SLE (adjusted OR=1.90), as well as with specific types of infections, such as bacterial (adjusted OR=2.07), viral (adjusted OR=1.92) and opportunistic (adjusted OR=2.13) infections (39). Moreover, the longer the duration and the higher the MMF dosage, the higher the infection risk (39). As a calcineurin inhibitor, TAC reduces excessive immune responses by inhibiting T-cell activation and proliferation. By suppressing the production of interleukin-2, TAC helps control inflammatory reactions and alleviates immune-mediated damage, thereby limiting T-cell proliferation (7,8,40). Although MMF and CYC also alleviate inflammatory reactions through immunosuppression, their mechanisms and modes of action differ. MMF primarily inhibits immune cell proliferation by suppressing deoxyadenosine triphosphate synthesis (41), whereas CYC directly targets immune cells by inhibiting DNA synthesis (42). By contrast, the immunosuppressive effect of TAC is more specific, avoiding the broad suppression of the immune system, which may reduce the risk of infection. The meta-analysis showed that leukopenia was significantly less reported in the TAC groups. The results of the present study align with the analysis finding of Kraaij *et al* (43), who also found a lower incidence of leukopenia in the TAC treatment group than in the AZA groups. This may be related to the mechanism of TAC, which selectively inhibits T-cell function, thus avoiding widespread effects on bone marrow production, thereby reducing the incidence of leukopenia. By contrast, AZA, by inhibiting cell proliferation, affects a broader range of immune cells, including B cells, T cells and bone marrow hematopoietic cells, making them more likely to induce leukopenia. However, owing to the limited number of the included studies, this conclusion still needs further validation.

In the present meta-analysis, a total of 12 studies were included. It is important to note that none of the included studies employed blinding. This design choice was determined by the respective research teams and may have been influenced by the initial objectives of the studies, resource constraints, or ethical considerations at the time of their design. The absence of blinding could potentially introduce bias, either overestimating or underestimating the treatment effects. Specifically, without blinding, there may be a risk of performance or detection bias, which could lead to an overestimation of the therapeutic benefits due to subjective assessment or reporting. However, the results of these studies were carefully assessed and found to be consistent across multiple trials, providing some confidence in the validity of the findings despite the absence of blinding.

The present study also has some limitations that need to be addressed in future research. First, the long-term efficacy of TAC remains uncertain. Among the studies included, only one analyzed the relapse rates at 3 and 5 years. Although TAC demonstrates favorable efficacy in short-term treatment, its long-term effects, particularly in maintaining remission and preventing disease relapse, have not been fully validated. Thus, further validating these findings and establishing robust evidence for clinical practice require large-scale RCT with long-term follow-up. These studies should focus on standardized dosing protocols and employ a prospective cohort design to evaluate relapse rates, safety profiles and long-term renal outcomes. Second, regarding the TAC dosage, existing studies have not provided a detailed discussion on its optimal dosage. In immunosuppressive therapy, choosing the correct drug dosage is crucial for both efficacy and safety; however, no standardized dosage has been established for TAC in clinical practice. Third, given the limited reporting in the current studies, a comprehensive analysis of other adverse events has not been conducted. Fourth, although TAC demonstrates similar long-term efficacy to other immunosuppressive agents such as MMF, CYC and AZA, selecting the most appropriate immunosuppressive drug based on the characteristics of patient groups remains an important issue for further exploration. Finally, the studies included lacked blinding, which may introduce bias into the results and affect the validity and reliability of the outcomes. Non-blinded studies may be influenced by observer or participant bias, leading to the overestimation or underestimation of treatment effects. Nevertheless, therapeutic effect data in these studies are consistent across multiple studies, and most of them have strictly controlled other variables. Although the lack of a blinded design may affect the accuracy of some data, the overall therapeutic effect still demonstrates a higher credibility. Of course, future research should strive to adopt double-blind or at least single-blind designs to reduce the effect of observer and participant bias. Strictly controlling these bias factors may yield more accurate and reliable estimates of treatment effects.

In conclusion, TAC has demonstrated significant short-term efficacy in the treatment of SLE, particularly in improving the CR, SLEDAI scores, and serum albumin levels. Its long-term efficacy is comparable with those MMF, CYC and AZA. However, it exhibits a lower risk of infections and leukopenia when considering safety. Nevertheless, potential limitations should be acknowledged in clinical applications, and continuous monitoring remains essential.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XL contributed to the conception and design of the study and drafted the manuscript. JZ and YL performed the data collection and statistical analysis. All authors read and approved the final version of the manuscript. XL and JZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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