

Review Article

Efficacy and safety of tacrolimus in Chinese lupus nephritis patients: a meta-analysis

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Abstract: With a 60% cumulative incidence of renal disease at 5-year post-diagnosis in Chinese systemic lupus erythematosus (SLE) patients, it is necessary to look for better treatment for Chinese lupus nephritis (LN). The aim is to investigate the efficacy and safety of tacrolimus (TAC) in treating Chinese LN. A total of 3 self-controlled studies (SCSs) of TAC were evaluated to verify the therapeutic effect of tacrolimus in Chinese LN. Additionally, 5 randomized controlled trials (RCTs) and 1 cohort study were assessed to demonstrate the efficacy and safety of TAC comparing with other immunosuppressive therapies in treating Chinese LN. Meta-evaluation of the 3 SCSs of TAC stated that TAC significantly decreased daily proteinuria (mean difference = -3.79, 95% CI = -5.63 - -1.95, $P < 0.0001$), SLEDAI scores (mean difference = -8.43, 95% CI = -10.44 - -6.43, $P < 0.00001$), and increased serum albumin (mean difference = 11.31, 95% CI = 8.71 - 13.92, $P < 0.00001$), serum C3 (mean difference = 0.28, 95% CI = 0.19 - 0.37, $P < 0.00001$). Further, the 5 RCTs and 1 cohort study showed that compared to cyclophosphamide (CYC), TAC could achieve higher complete remission rate (risk ratio = 1.53, 95% CI = 1.08 - 2.16, $P = 0.02$). Compared with mycophenolate mofetil (MMF) and azathioprine (AZA), no significant difference was found in complete remission rate. However, TAC significantly reduced the adverse events of infection compared to MMF (risk ratio = 0.54, 95% CI = 0.36 - 0.82, $P = 0.004$) and leukopenia compared to AZA (risk ratio = 0.19, 95% CI = 0.06 - 0.58, $P = 0.004$). No obvious evidence of publication bias was found. TAC is considered a promising candidate for treating Chinese LN.

Keywords: Efficacy, safety, tacrolimus, Chinese lupus nephritis, meta-analysis

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by the production of a large number of autoantibodies in the blood, which deposits in the vascular beds of target tissues and organs including glomeruli and the renal microvasculature, leading to systemic inflammation and lupus nephritis (LN) [1-4].

LN is a major cause of morbidity and mortality in patients with SLE [5]. The treatment and prognosis of LN have advanced when the first breakthrough event in the late 1970s, reporting that the addition of cyclophosphamide (CYC) to the standard corticosteroid regimen could reduce relapse rates in LN [6, 7]. As a new standard therapeutic regimen for LN, CYC has been widely accepted [8-10]. However, patients experiencing CYC therapy have the risk of infection, leucopenia, bladder cancer, etc.

[11, 12]. Since the 1990s, induction therapy with mycophenolate mofetil (MMF) has also appeared as a useful alternative which was proved to be equally or more effective, and safer than CYC [13]. In addition, the efficacy of Azathioprine (AZA) on LN has also been reported and it is a useful option, especially if other drugs are contraindicated or not tolerated [14, 15].

Recently, following encouraging results in trials, more attention has been paid to whether tacrolimus (TAC, previously known as FK506) could have a prominent role in the therapy of LN. TAC is a macrolide immunosuppressant that inhibits calcineurin and completely blocks the translocation of the cytosolic component of the nuclear factor of activated T cells [16].

With a 60% cumulative incidence of renal disease at 5 year post-diagnosis in Chinese SLE patients [17], it is necessary to look for better

treatment for Chinese LN. However, only limited reports of treating Chinese LN with TAC exist, and the efficacy and safety of TAC in treating Chinese LN remains inconclusive. Therefore, this meta-analysis aimed to survey the therapeutic effect of TAC in Chinese LN, and demonstrate its efficacy and safety comparing with other immunosuppressants.

Methods

Search strategy

Utilized PubMed, Web of Science Knowledge, and Cochrane Library databases from March 2000 to March 2018 as searching tools. Search terms included: "tacrolimus or prograf or FK506" and "lupus nephritis or lupus glomerulonephritis or lupus erythematosus nephritis". Meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [18].

Trial inclusion criteria

Self-controlled studies (SCS), randomized controlled trials (RCT) and comparative cohort studies which could estimate the efficacy and safety of TAC in treating Chinese LN were included.

Data extraction

The search only articles written in English was performed in duplicate by two independent reviewers. The initial evaluation was done on the strength of screening the titles and abstracts. Studies that did not meet the trial inclusion criteria were excluded. The research that was not excluded after an initial evaluation was retrieved for full text screening. Additionally, on the basis of the inclusion criteria, it was determined whether the study should be included in our meta-analysis. In cases of disagreement, the terminal decision for inclusion was made by consensus among the authors. Case reports, comments, review articles, meeting abstracts, and editorials were excluded. The data extraction included (I) study location (II) study type, (III) LN biopsy class, (IV) number enrolled, and (V) follow-up period.

Statistical analysis

Meta-analysis was performed with the RevMan software (version 5.30, the Nordic Cochrane

Centre, Copenhagen, Denmark) and Stata software (version 14.0, Stata Corporation, College Station, TX, USA). Continuous variables were analyzed using mean difference (MD) and 95% confidence interval (CI). For complete remission rate, a risk ratio (RR) and its 95% CI were applied for analysis. For adverse events, risk ratios and its 95% CI were calculated. Heterogeneity assumption was evaluated with the Chi-square-based Q-test and a P value < 0.1 for the Q-test or I-squared $> 50\%$ indicated that heterogeneity may exist [19]. If there was significant heterogeneity, a random effect model was used (DerSimonian-Laird method) [20] for the data analysis. Otherwise, a fixed effect model (Mantel-Haenszel method) [21] was used. Publication bias was evaluated with Begg's test and Begg's funnel plot, $P < 0.05$ was considered statistically significant.

Results

Eligible studies

A total of 173 published articles were collected, of which 54 were from PubMed, 93 from Web of Science, and 26 from the Cochrane Library. A total of 164 papers excluded because of duplicates, other interventions or manifestations, laboratory studies, meta-analysis or review articles (Figure 1). Finally, 9 studies were left eligible for meta-analysis, including 3 SCSs [22-24], 5 RCTs [25-29] and 1 comparative cohort study [30] (Table 1).

Therapeutic effect of tacrolimus on Chinese LN

In the 3 SCSs, TAC significantly decreased daily proteinuria (mean difference = -3.79 , 95% CI = -5.63 - -1.95 , $P < 0.0001$), SLEDAI scores (mean difference = -8.43 , 95% CI = -10.44 - -6.43 , $P < 0.00001$), and increased serum albumin (mean difference = 11.31 , 95% CI = 8.71 - 13.92 , $P < 0.00001$), serum C3 (mean difference = 0.28 , 95% CI = 0.19 - 0.37 , $P < 0.00001$), as shown in Figure 2.

Tacrolimus versus other immunosuppressant on complete remission rate

5 RCTs and 1 comparative cohort study were used to demonstrate the complete remission rate of TAC comparing with other immunosuppressive therapies in treating Chinese LN. Compared to CYC, TAC could achieve higher complete remission rate (risk ratio = 1.53 , 95%

Meta-analysis of TAC in Chinese LN

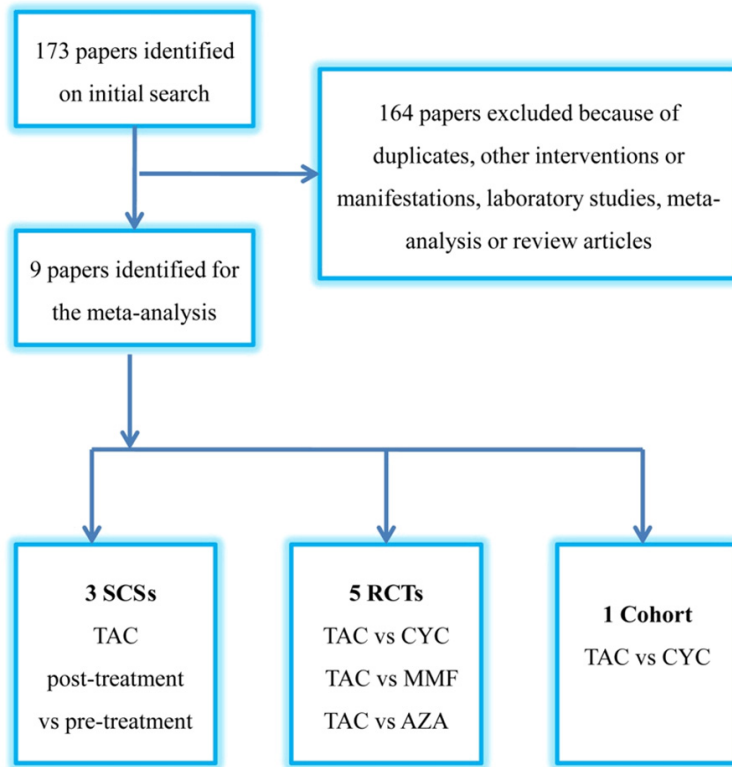


Figure 1. Flow chart of study selection process. SCS: self-controlled study; RCT: randomized controlled trial; TAC: tacrolimus; MMF: mycophenolate mofetil; AZA: azathioprine; CYC: cyclophosphamide.

CI = 1.08 - 2.16, $P = 0.02$) (**Figure 3A**). Compared with MMF and AZA, no significant difference was found in complete remission rate (**Figure 3B** and **3C**).

Tacrolimus versus other immunosuppressant on adverse drug reactions

TAC significantly reduced the adverse events of infection compared to MMF (risk ratio = 0.54, 95% CI = 0.36 - 0.82, $P = 0.004$) and no significant differences were found in infection rate compared to CYC and AZA (**Figure 4**). In **Figure 5**, TAC significantly reduced the adverse events of leukopenia compared to AZA (risk ratio = 0.19, 95% CI = 0.06 - 0.58, $P = 0.004$) and no significant differences were found in leukopenia rate compared to CYC and MMF.

Publication bias

Publication bias was evaluated with Begg's test. The shapes of the Begg's funnel plot did not reveal any obvious asymmetry (**Figure 6**). Next, Begg's test was used to provide statisti-

cal evidence of plot symmetry. The results still did not imply publication bias, for example, the P value of Begg's test for TAC post-treatment vs pre-treatment, TAC vs CYC, and TAC vs MMF were 0.602, 0.602, and 0.296, respectively.

Discussion

Although corticosteroids and immunosuppressants are widely used for treating LN, a few resistant cases have been reported. Therefore, a better treatment has been strongly sought in the clinical setting [31].

TAC is a calcineurin inhibitor and studies have reported that the main immunophilin of TAC is FK-506-binding protein 12 (FKBP-12) in T-cells. The complex of TAC and FKBP-12 inhibits calcineurin phosphatase, an essential enzyme for the activation of nuclear factor of activated T cells (NF-AT). NF-AT

is an important transcription factor for the transcription of cytokine genes in T cells. Thus, TAC inhibits the transcription of T cell cytokines like interleukin-2 (IL-2) and interferon- γ (IFN- γ). The calcineurin-TAC complex is not completely specific for NF-AT and can interfere with other substrates including Na-K-ATPase and nitric oxide synthetase [32]. Besides its effects on IL-2, it has been reported that TAC down-regulates the mRNA levels of IL-3, IL-4, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF), IFN, and c-Myc in activated human peripheral blood T-cells. Therefore, TAC affects the growth and differentiation of T- and B- lymphocytes, inhibiting immunity [33-35].

However, a few studies have investigated TAC therapies in Chinese LN, and the sample size was limited. As a result, this survey aimed to evaluate the efficacy and safety of TAC in Chinese LN. Meta-analysis included 3 SCSs, 5 RCTs and 1 cohort study involving 481 patients. No obvious evidence of publication bias was found, according to the Begg's test.

Meta-analysis of TAC in Chinese LN

Table 1. Trials included in the meta-analysis and their key characteristics

Study	Study location	Study type	LN biopsy class	Number enrolled				Follow-up period (months)
				TAC	MMF	AZA	CYC	
Chen 2011	Guangzhou, Chengdu, Nanning, Kunming, Fuzhou, Foshan	RCT	III, IV-S, IV-G, V, V+III, V+IV	42	--	--	39	6
Chen 2012	Guangzhou, Chengdu, Guilin, Kunming, Fuzhou, Foshan	RCT	III, V, IV-S or IV-G, or Combination	34	--	36	--	6
Fei 2013	Beijing	SCS	III, IV, V, III+V, IV+V	26	--	--	--	6
Li 2012	Shanghai	RCT	III, IV, V or Combination	20	20	--	20	6
Mok 2005	Hong Kong	SCS	NR	9	--	--	--	6
Mok 2014	Hong Kong	RCT	III, IV, V	74	76	--	--	6
Wang 2012	Hangzhou	Cohort	IV, V, V+IV, V+III	20	--	--	20	12
Yap 2012	Hong Kong, Guangzhou, Beijing, Shanghai	RCT	V	9	7	--	--	24
Yap 2014	Hong Kong	SCS	III/IV or V	29	--	--	--	36

LN, lupus nephritis; RCT, randomized controlled trial; SCS, self-controlled study; TAC, tacrolimus; MMF, mycophenolate mofetil; AZA, azathioprine; CYC, cyclophosphamide; NR, not report.

Meta-analysis of TAC in Chinese LN

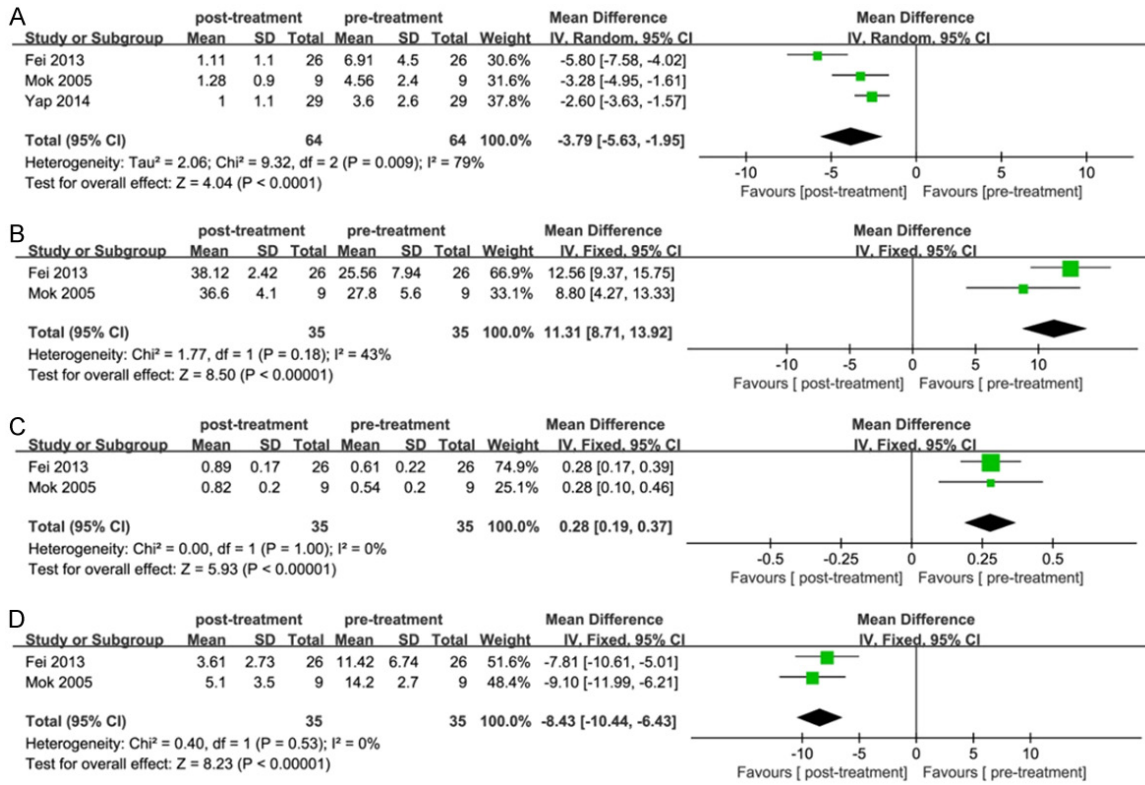


Figure 2. Forest plot showing a meta-analysis for tacrolimus post-treatment versus pre-treatment. A: Daily proteinuria; B: Serum albumin; C: Serum C3; D: SLEDAI scores.

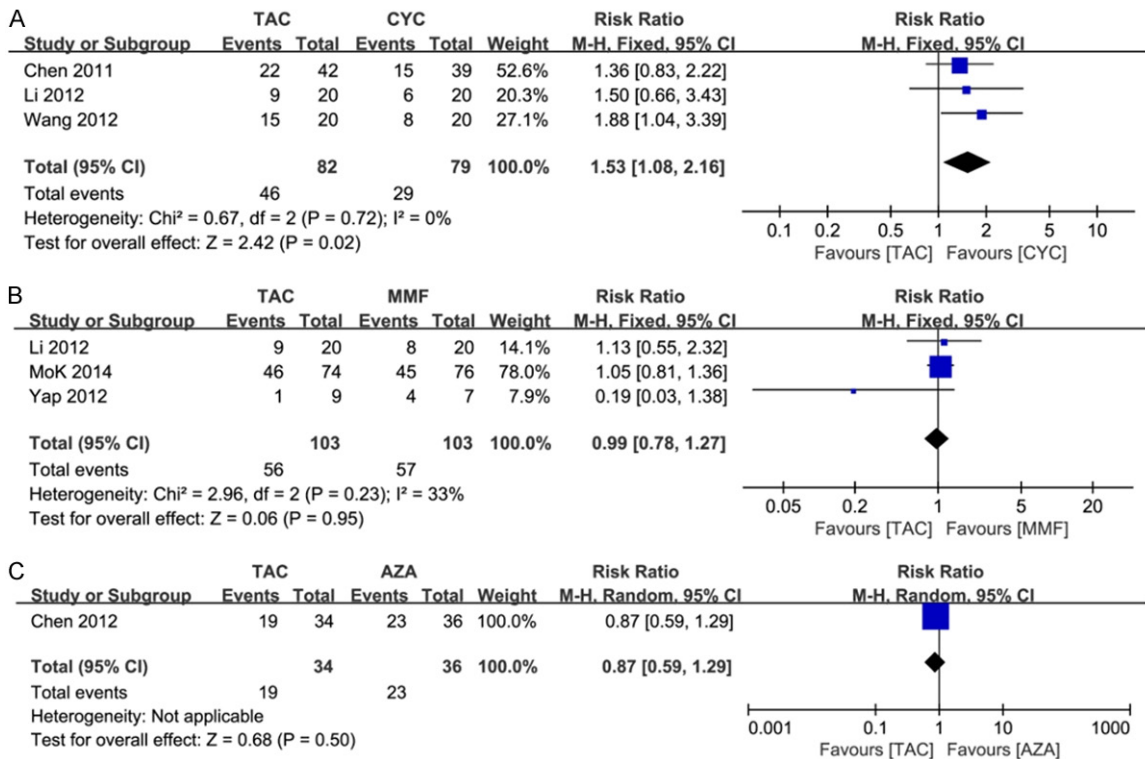


Figure 3. Forest plot showing a meta-analysis for tacrolimus versus other immunosuppressive control treatment on complete remission rate. A: TAC vs CYC; B: TAC vs MMF; C: TAC vs AZA.

Meta-analysis of TAC in Chinese LN

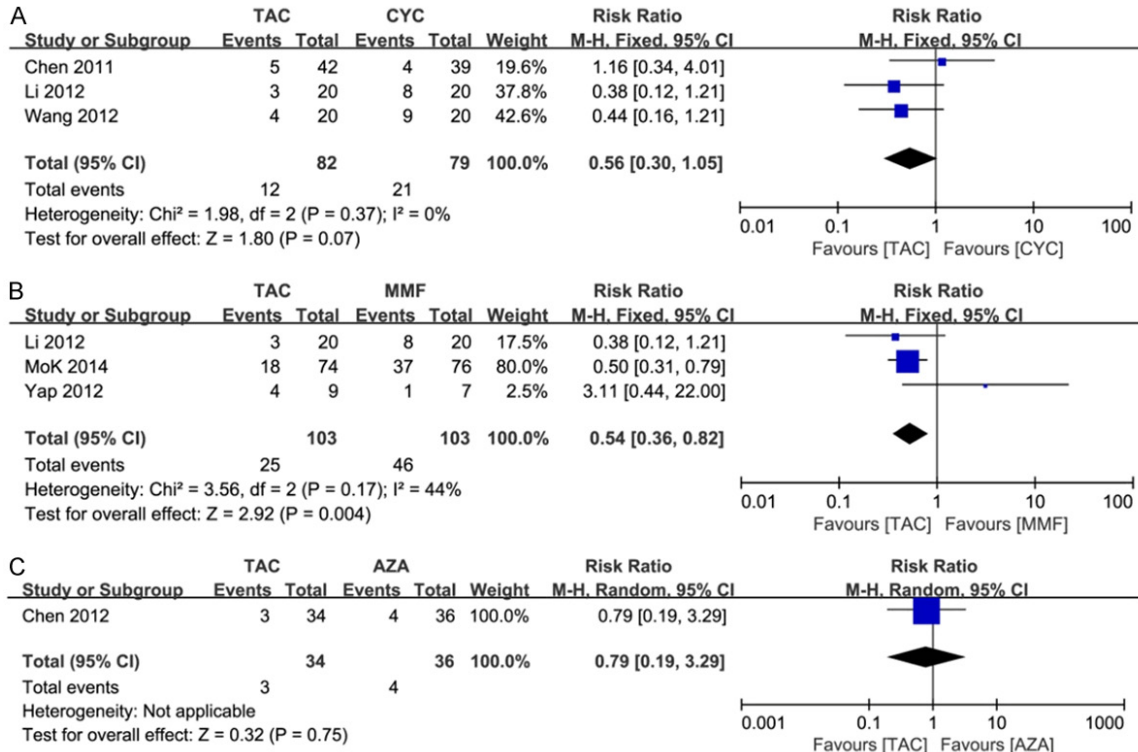


Figure 4. Forest plot showing a meta-analysis for tacrolimus versus other immunosuppressive control treatment on adverse drug reaction (infection). A: TAC vs CYC; B: TAC vs MMF; C: TAC vs AZA.

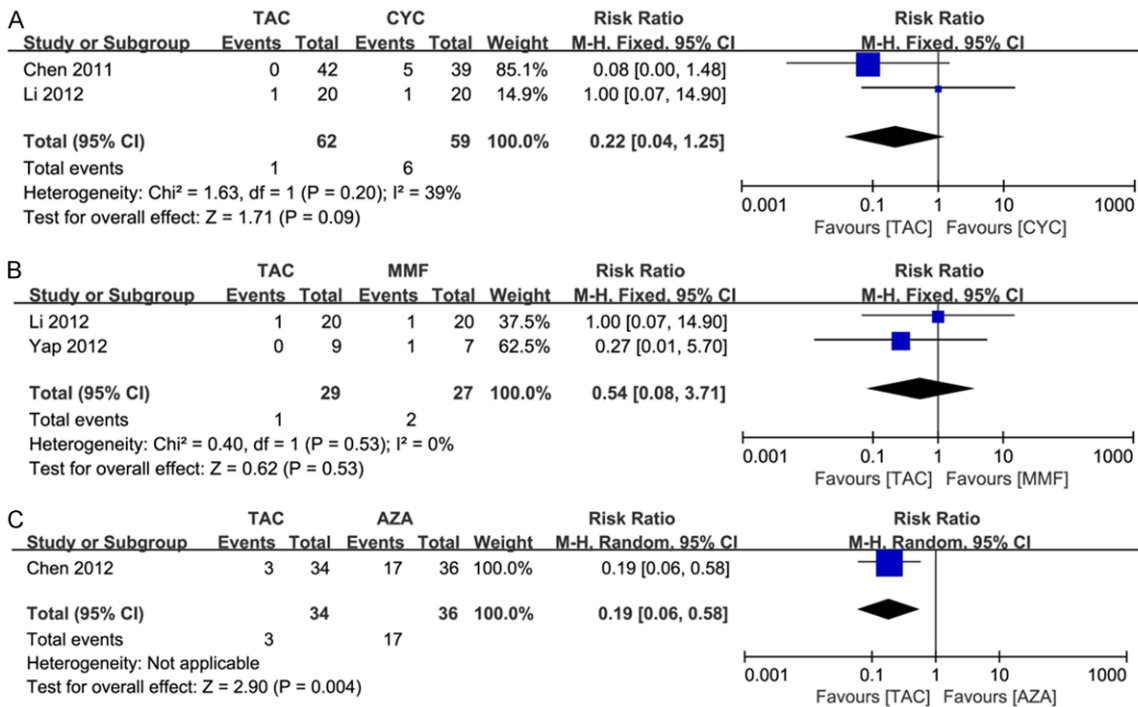


Figure 5. Forest plot showing a meta-analysis for tacrolimus versus other immunosuppressive control treatment on adverse drug reaction (leukopenia). A: TAC vs CYC; B: TAC vs MMF; C: TAC vs AZA.

Meta-analysis of TAC in Chinese LN

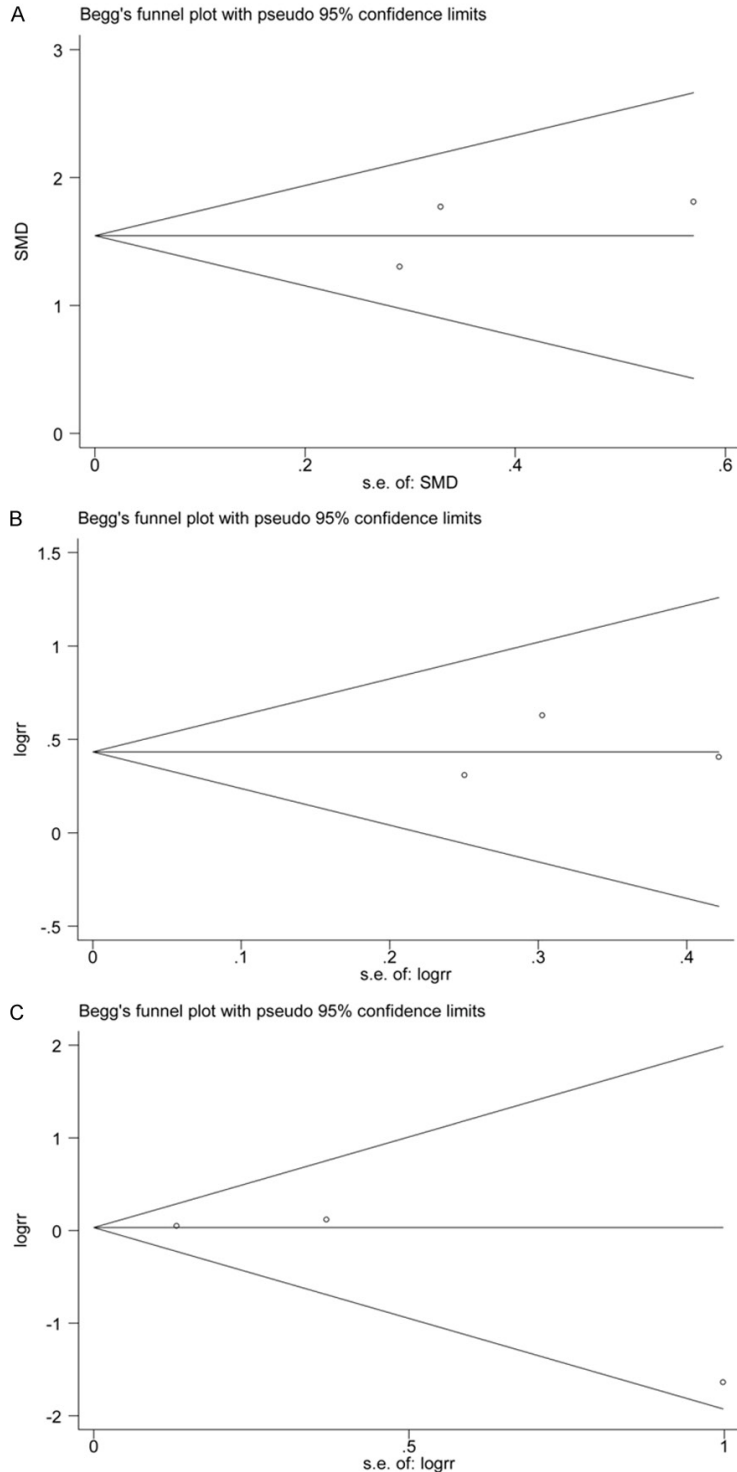


Figure 6. Publication bias. A: TAC post-treatment vs pre-treatment; B: TAC vs CYC; C: TAC vs MMF.

The 3 SCSs confirmed that treatment of TAC significantly decreased daily proteinuria, SLEDAI scores and increased serum albumin, serum C3. Additionally, the 5 RCTs and 1 cohort

study were used to prove the efficacy and safety of TAC comparing with other immunosuppressive therapies in Chinese LN. Compared to CYC, TAC could achieve higher complete remission rate. Compared with MMF and AZA, no significant difference was found in complete remission rate. Infection and leucopenia are common side effects of immunosuppressants. Compared to MMF and AZA, TAC significantly reduced the adverse events of infection and leucopenia, respectively. Therefore, curative effect of TAC was superior to CYC, equivalent to MMF and AZA on complete remission rate, however, showed better safety.

This paper also has some limitations that should be pointed out. First, our 9 papers for meta-analysis included 3 SCSs, 5 RCTs and 1 cohort study, whose clinical evidence may not be strong enough. Second, the number of included cases were small. Future studies should address these issues.

In conclusion, TAC is considered to be a promising candidate for treating Chinese LN because it can significantly decrease daily proteinuria, SLEDAI scores, and adverse reactions. However, on the other hand, it can increase serum albumin, serum C3, and complete remission rate.

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Disclosure of conflict of interest

None.

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