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*Review Article*

# Efficacy and safety of tacrolimus in treating pediatric refractory nephrotic syndrome: a meta-analysis

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**Abstract:** To investigate the efficacy and safety of tacrolimus (TAC) in treating pediatric refractory nephrotic syndrome (PRNS). 4 self-controlled studies of tacrolimus were evaluated to verify the therapeutic effect of tacrolimus in PRNS. 3 randomized controlled trials (RCTs) and 1 comparative cohort study were assessed to demonstrate the efficacy and safety of TAC comparing with other immunosuppressive therapies in treating PRNS. The quality of included studies were moderate. The meta-evaluation of the 4 self-controlled studies of TAC stated that TAC significantly decreased urine protein to creatinine ratio (mean difference = -5.78, 95% CI = -8.00 - -3.55, $P < 0.00001$). Further, the 3 RCTs and 1 comparative cohort study showed that compared to mycophenolate mofetil and cyclophosphamide, TAC could achieve higher rates of complete remission (risk ratio = 1.79, 95% CI = 1.11-2.90, P = 0.02, and risk ratio = 3.07, 95% CI = 1.78-5.29, $P < 0.0001$, respectively). Compared with ciclosporin A, no significant difference was found in complete remission rate. But, TAC significantly reduced the adverse events of nephrotoxicity and hypertrichosis (odds ratio = 0.25, 95% CI = 0.08-0.74, $P = 0.01$ and odds ratio = 0.00, 95% CI = 0.00-0.02, $P < 0.00001$, respectively). No obvious evidence of publication bias was found. Therefore, TAC is considered a promising candidate for treating PRNS.

**Keywords:** Efficacy, safety, tacrolimus, pediatric refractory nephrotic syndrome, meta-analysis

## Introduction

The incidence of nephrotic syndrome (NS) is around 16 among 100,000 children, and it is a major challenge in pediatric nephrology [1]. Besides, NS places a huge financial burden on both patient's family and society. NS is the most common glomerulopathy in children. It characterizes as mass of proteinuria, hypoalbuminemia, edema, and hyperlipidemia. NS influences kidneys by enhancing the permeability of the glomerular basement membrane [2]. Although most affected children have steroid-sensitive nephrotic syndrome (SSNS), approximately 20% of children do not acquire complete remission and have steroid-resistant nephrotic syndrome (SRNS) [3]. In addition, about 80%-90% of children with SSNS undergo relapses, among which 50% has relapsed and turned into steroid-dependent nephrotic syndrome (SDNS) [4-6]. Therefore, choosing a better treatment for pediatric refractory nephrotic syndrome (PRNS), including SRNS and SDNS, is crucial and challenging.

The precise pathology of PRNS has not been fully elucidated. Traditional treatment of PRNS is steroid and using it for long time can bring disadvantageous impact on children's growth and development. Encouragingly, it has been reported that immunological factors might play a critical role, and the use of immunosuppressive agents seem to have a positive effect on PRNS [7].

Tacrolimus (TAC) is a macrolide immunosuppressant which inhibits calcineurin and completely blocks the translocation of the cytosolic component of the nuclear factor of activated T cells (NF-AT) [8]. However, only limited reports of treating PRNS with TAC exist, and the efficacy and safety of TAC in treating PRNS remains inconclusive. Therefore, this meta-analysis aims to survey the therapeutic effect of TAC in PRNS, and demonstrate its efficacy and safety

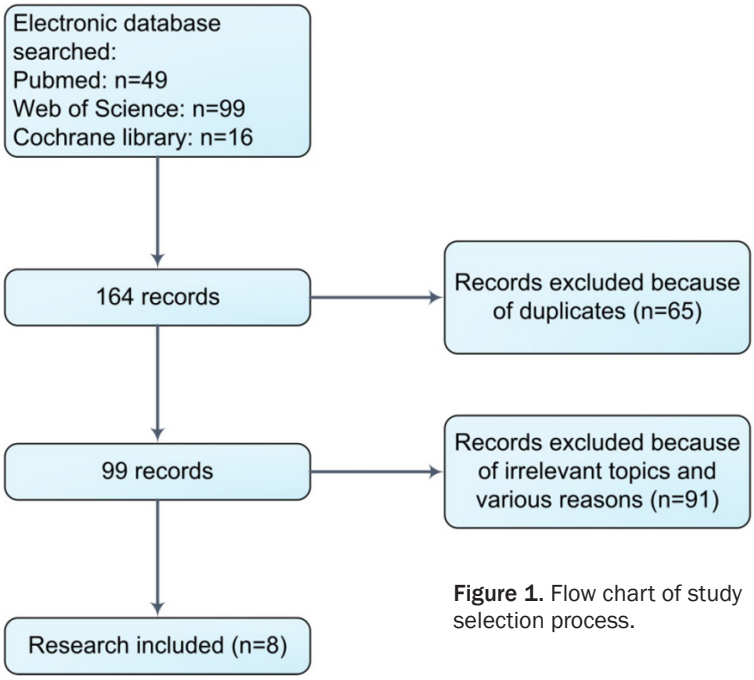


**Figure 1.** Flow chart of study selection process.

comparing with other immunosuppressive therapies in treating PRNS.

## Methods

### *Search strategy*

Utilized PubMed, Web of Science Knowledge, and Cochrane Library databases from inception to August 8, 2017 as searching tools. Search terms included: "tacrolimus", "FK506", and "nephrotic syndrome". The meta-analysis was conducted according to *the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement* [9].

### *Trial inclusion criteria*

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

### *Data extraction*

The search without any language restrictions was performed in duplicate by two independent reviewers (*Dongdong Wang and Xiao Chen*). 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 researches that were not excluded after an initial evaluation were 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 characteristics, (II) study design features, (III) study participants, (IV) study interventions, and (V) study outcomes.

### *Statistical analysis*

Our 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, odds ratios (OR) 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 [10]. If there was significant heterogeneity, we used a random effect model (DerSimonian-Laird method) [11] for the data analysis. Otherwise, we used a fixed effect model (Mantel-Haenszel method) [12]. The Z test was used to assess the pooled MD, RR or OR with significance set at $P < 0.05$. Publication bias was evaluated with Harbord's modified test and Galbraith graph, $P < 0.05$ was considered statistically significant.

## Results

### *Eligible studies*

Total of 164 published articles were collected, of which 49 were from PubMed, 99 from Web of Science, and 16 from the Cochrane Library. By endnote software, 65 duplicated studies were

**Table 1.** Basic characteristics of tacrolimus in treating refractory NS

| Study | Year | Country | Study design | Sex boys/girls | Age (years) | Intervention |
|---|---|---|---|---|---|---|
| EM Yang [16] | 2016 | Korea | Prospective, open-label, single-arm, multicenter trial | 54/23 | Average age 9.9 (range: 1.5-18.9) | TAC was administered in two equal doses of 0.1-0.2 mg/kg per day and the dosage was adjusted to maintain the trough blood level between 5 and 10 ng/mL. An oral dose of glucocorticosteroid was adjusted according to the status of NS. |
| Isabel Roberti [15] | 2010 | USA | Retrospective, single-center, longterm follow-up study | 8/11 | 1.6-18 (median: 10) | The initial tacrolimus dose was 0.1 mg/kg twice daily to keep a blood trough level 5-8 ng/ml. All patients received prednisone at a dose of 1 mg/kg twice daily for 6 weeks (maximum 60 mg/day) followed by rapid tapering over 6 weeks using an alternate day regimen. |
| Kim Loeffler [13] | 2004 | Canada | Retrospective study | 12/4 | Average age 11.4 (range 3.5-18.1) | Tacrolimus was given at 0.1 mg/kg per day divided into two doses over 12 h intervals. The goal for the trough tacrolimus level was 5.0-10.0 ng/mL. All patients initially received prednisone at 2 mg/kg per day. |
| Sanjeev Gulati [14] | 2008 | India | Prospective study | 20/2 | 7.33 ± 5.9 | TAC was initiated with a dose of 0.10 mg/kg/day, and the dose was increased to attain a trough level of 5.0-10.0 ng/mL. These patients were treated with concomitant prednisone, which was subsequently tapered off and stopped. |

**Table 2.** Basic characteristics of tacrolimus in treating refractory NS comparing with other immunosuppressive therapies

| Study | Year | Country | Study design | Group | Case | Intervention |
|---|---|---|---|---|---|---|
| Aditi Sinha [19] | 2017 | India | Open-label, one-to-one randomized, controlled trial | TAC vs MMF | 31 29 | Patients received tacrolimus at a dose of 0.12 ± 0.04 mg/kg per day or MMF at 32.2 ± 8.8 mg/kg per day. Cotreatment with alternate day prednisolone. |
| Ashima Gulati [18] | 2012 | India | A multicenter, randomized, controlled trial | TAC vs CTX | 63 61 | The dose of tacrolimus and cyclophosphamide was 0.12 ± 0.03 mg/kg/day and 554.1 ± 98.2 mg/m$^2$/dose, respectively. The dose of enalapril was 5.8 ± 2.1 and 5.5 ± 2.3 mg/day in tacrolimus and cyclophosphamide groups, respectively. The respective cumulative doses of prednisolone were 0.44 ± 0.19 and 0.39 ± 0.19 mg/kg/day for the first 6 months (P = 0.18), and 0.35 ± 0.15 and 0.34 ± 0.12 mg/kg/day for 12 months (P = 0.74). |
| Swati Choudhry [17] | 2009 | India | Randomized, controlled trial, single-center study | TAC vs CsA | 21 20 | Tacrolimus (0.1 to 0.2 mg/kg/d) or CsA (5 to 6 mg/kg/d). Cotreatment with alternate day prednisolone and enalapril. |
| Wenjing Wang [20] | 2012 | China | Comparative cohort study | TAC vs CsA | 26 8 | The dose of tacrolimus according to each patient's trough blood level, with a target of 5-12 ng/mL. The overall final dose of tacrolimus was 86.9 ± 27.6 μg/kg/day for these patients. The dose of CsA was adjusted according to each patient's trough blood level, with a target of 100-150 ng/mL. The overall final dose of CsA was 2.72 ± 0.59 mg/kg/day. Cotreatment with prednisolone. |

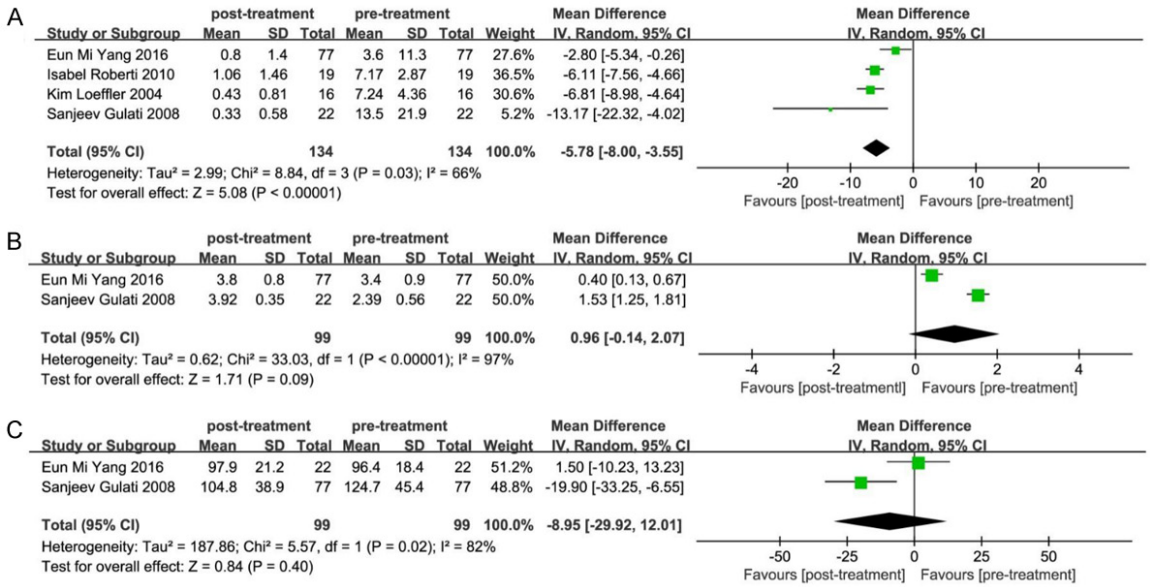


**Figure 2.** Forest plot showing a meta-analysis for tacrolimus post-treatment versus pre-treatment. A: Urine protein to creatinine ratio. B: Serum albumin. C: Glomerular filtration rate.

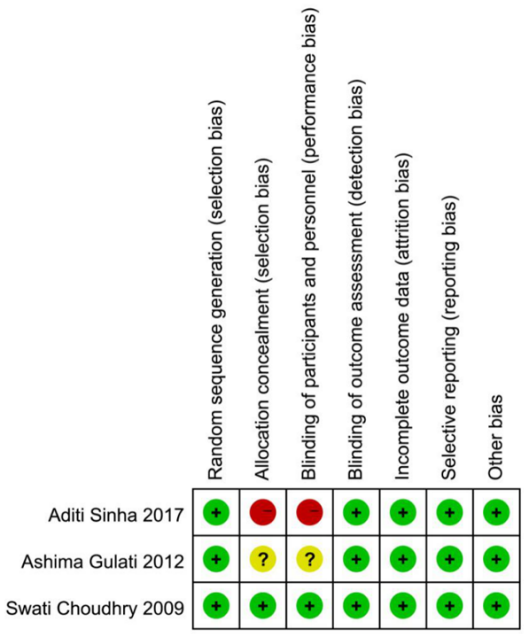


**Figure 3.** Risk of bias summary of three RCTs. "+": low risk of bias. "-": unclear risk of bias. "-": high risk of bias.

excluded. After reading the rest researches in detail, 91 articles were excluded because of irrelevant topics or various reasons (**Figure 1**). Finally, 8 studies were left eligible for meta-analysis, including 4 self-controlled studies [13-16] (**Table 1**), 3 RCTs [17-19] and 1 comparative cohort study [20] (**Table 2**).

*Therapeutic effect of tacrolimusin on PRNS*

In the 4 self-controlled studies, TAC treatment has significantly reduced urine protein to creatinine ratio (mean difference = -5.78, 95% CI = -8.00-3.55, $P < 0.00001$; **Figure 2A**). However, no statistically significant difference was found in serum albumin and glomerular filtration rate (mean difference = 0.96, 95% CI = -0.14-2.07, $P = 0.09$; and mean difference = -8.95, 95% CI = -29.92-12.01, $P = 0.40$, respectively; **Figure 2B** and **2C**).

*Efficacy and safety of tacrolimus comparing with other Immunosuppressive therapies*

3 RCTs and 1 comparative cohort study were used to demonstrate the complete remission rate of TAC comparing with other immunosuppressive therapies in treating PRNS. Risk of bias summary of the 3 RCTs were shown in **Figure 3**.

Compared with mycophenolate mofetil and cyclophosphamide, TAC achieved higher rates of complete remission (risk ratio = 1.79, 95% CI = 1.11-2.90, $P = 0.02$ and risk ratio = 3.07, 95% CI = 1.78-5.29, $P < 0.0001$, respectively; **Figure 4**). Compared with ciclosporin A, no significant difference in complete remission rate was determined (risk ratio = 1.31, 95% CI = 0.51-3.40, $P = 0.57$; **Figure 4**); However, TAC signifi-

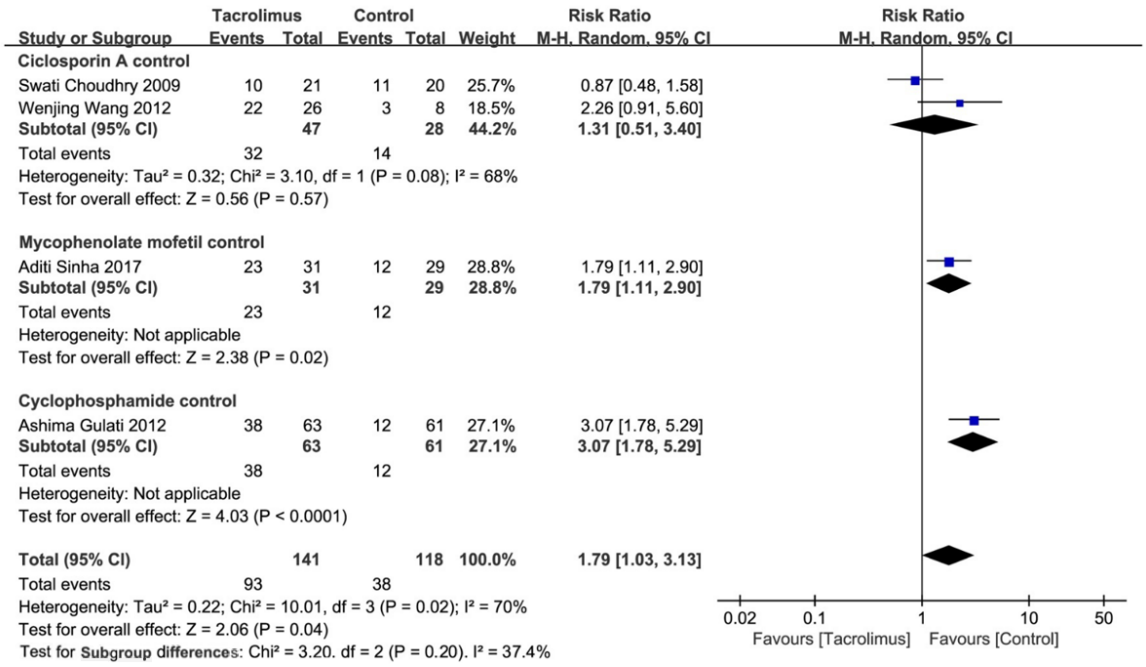


**Figure 4.** Forest plot showing a meta-analysis for tacrolimus versus other immunosuppressive control treatment on complete remission rate.

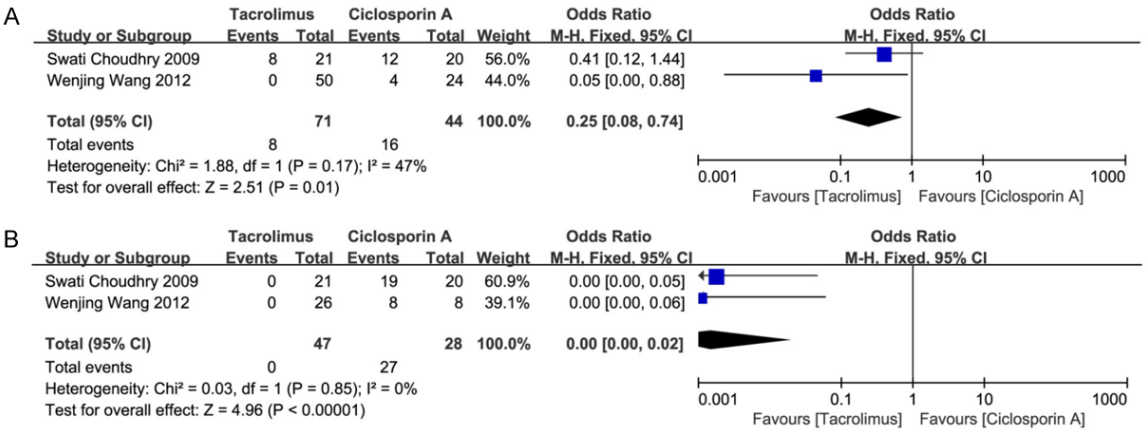


**Figure 5.** Forest plot showing a meta-analysis for tacrolimus versus ciclosporin A treatment on adverse drug reaction. A: Nephrotoxicity. B: Hypertrichosis.

cantly reduced adverse events of nephrotoxicity and hypertrichosis (odds ratio = 0.25, 95% CI = 0.08-0.74, $P$ = 0.01, and odds ratio = 0.00, 95% CI = 0.00-0.02, $P$ < 0.00001, respectively; **Figure 5A** and **5B**).

*Publication bias*

Publication bias was evaluated with Galbraith graph. The shapes of the plots did not reveal any obvious asymmetry in the 4 self-controlled studies (**Figure 6A**), the 3 RCTs, and the comparative cohort study (**Figure 6B**). Also, Harbord's modified test was used to provide statistical evidence of plot symmetry. These results implied no publication bias (t = 0.37, $P$ = 0.745; t = -0.27, $P$ = 0.809, respectively).

## Discussion

PRNS patients experience repeated and prolonged steroid therapy, which increases the

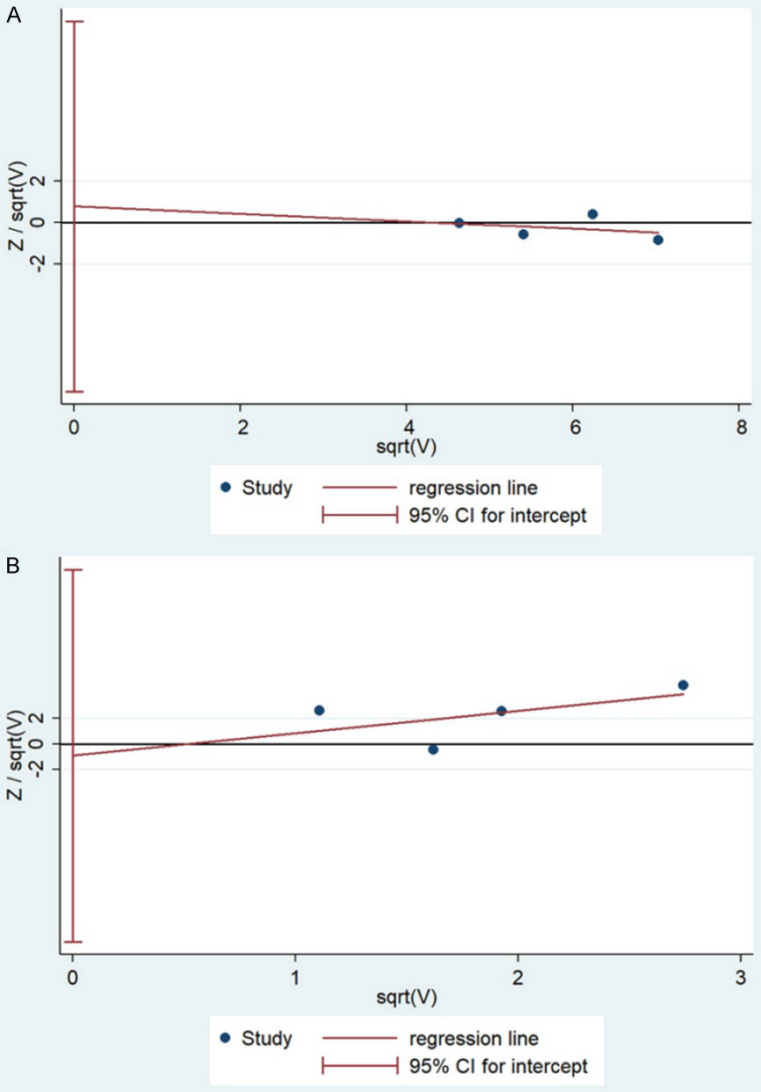


**Figure 6.** Publication bias. A: Urine protein to creatinine ratios. B: Complete remission rate.

danger of obesity, cushingoid appearance, hypertension, growth retardation, osteoporosis, infections, and psychological problems. With the result that all kinds of steroid sparing agents such as cyclophosphamide [21], cyclosporine A [22, 23] and mycophenolate mofetil [24-28] have been applied to treat patients with PRNS to improve the responses with reduced adversary effects of steroid therapy. Among these immunosuppressant agents, cyclosporine A appears as a first-line treatment for PRNS after alkylating agents or mycophenolate mofetil in patients with relapses or who are contraindicated for steroid therapy due to severe adverse reactions [29, 30]. However, cyclosporine A treatment has also been confronted with relapses, nephrotoxicity and hypertrichosis etc [31, 32].

TAC, a calcineurin inhibitor, presents much higher potency in cytokine suppression compared to cyclosporine A [33]. Nevertheless, the mechanism of action of TAC in treating PRNS is not clearly elucidated. Some studies have stated calcineurin inhibitors function via binding to protein called immunophilin. 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 synthatase [33]. 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. Thus, TAC affects the growth and differentiation of T- and B-lymphocytes, thereby, inhibiting immunity [34-36].

However, a few researches have investigated TAC therapies in PRNS, and the sample size is limited. As a result, this survey aims to evaluate the efficacy and safety of TAC in PRNS. Our meta-analysis included 4 self-controlled studies [13-16], 3 RCTs [17-19] and 1 comparative cohort study [20] involving 393 patients. The 4

self-controlled studies including EM Yang [16], Isabel Roberti [15], Kim Loeffler [13], and Sanjeev Gulati [14], confirmed that treatment of TAC significantly reduced urine protein to creatinine ratio and improved kidney function.

Additionally, the 3 RCTs and 1 comparative cohort study were used to prove the efficacy and safety of TAC comparing with other immunosuppressive therapies in PRNS. Compared with mycophenolate mofetil and cyclophosphamide, TAC achieved higher rates of complete remission, indicating that TAC is a better agent in PRNS than mycophenolate mofetil and cyclophosphamide. But when compared to cyclosporine A, TAC showed no significant difference in complete remission rate.

Nephrotoxicity is a common side effect of calcineurin inhibitors. The outcome of persistent drug induced nephrotoxicity is extremely serious for patients. Interestingly, the meta-analysis found that TAC significantly reduced the adverse events of nephrotoxicity and hypertrichosisin comparison with ciclosporin A. Curative effect of TAC is not superior to ciclosporin A, but it has better safety than ciclosporin A.

This paper also has some limitations that should be pointed out. First, our meta-analysis included 4 self-controlled studies [13-16], 3 RCTs [17-19] and 1 comparative cohort study [20], whose clinical evidence was not strong. Second, our study included patients with nonconsistent basic characteristics such as different pathological types. All of the variations could introduce heterogeneity to some extent in the results. But, no obvious evidence of publication bias was found, according to the statistical analysis and Galbraith graph. Third, owing to the limited information, the relapse rates were not assessed in our study. Fourth, 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 PRNS because it can reduce urine protein to creatinine ratio, increase the complete remission rate, and decrease adverse reaction. However, the long-term effects and cost-effectiveness of TAC therapy have not fully been evaluated. Consequently, further well-designed large studies are urgently needed.

## Disclosure of conflict of interest

None.

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## References

[1] Eddy AA and Symons JM. Nephrotic syndrome in childhood. Lancet 2003; 362: 629-639.
[2] Certikova-Chabova V and Tesar V. Recent insights into the pathogenesis of nephrotic syndrome. Minerva Med 2013; 104: 333-347.
[3] McKinney PA, Feltbower RG, Brocklebank JT and Fitzpatrick MM. Time trends and ethnic patterns of childhood nephrotic syndrome in Yorkshire, UK. Pediatr Nephrol 2001; 16: 1040-1044.
[4] Lombel RM, Gipson DS and Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol 2013; 28: 415-426.
[5] Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. J Am Soc Nephrol 1997; 8: 769-776.
[6] Koskimies O, Vilska J, Rapola J and Hallman N. Long-term outcome of primary nephrotic syndrome. Arch Dis Child 1982; 57: 544-548.
[7] Pravitsitthikul N, Willis NS, Hodson EM and Craig JC. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Database Syst Rev 2013; Cd002290.
[8] Ho S, Clipstone N, Timmermann L, Northrop J, Graef I, Fiorentino D, Nourse J and Crabtree GR. The mechanism of action of cyclosporin A and FK506. Clin Immunol Immunopathol 1996; 80: S40-45.
[9] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
[10] Zhao Z, Liao G, Li Y, Zhou S and Zou H. The efficacy and safety of rituximab in treating childhood refractory nephrotic syndrome: a meta-analysis. Sci Rep 2015; 5: 8219.
[11] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[12] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.
[13] Loeffler K, Gowrishankar M and Yiu V. Tacrolimus therapy in pediatric patients with treatment-resistant nephrotic syndrome. Pediatr Nephrol 2004; 19: 281-287.
[14] Gulati S, Prasad N, Sharma RK, Kumar A, Gupta A and Baburaj VP. Tacrolimus: a new therapy for steroid-resistant nephrotic syndrome in children. Nephrol Dial Transplant 2008; 23: 910-913.
[15] Roberti I and Vyas S. Long-term outcome of children with steroid-resistant nephrotic syndrome treated with tacrolimus. Pediatr Nephrol 2010; 25: 1117-1124.
[16] Yang EM, Lee ST, Choi HJ, Cho HY, Lee JH, Kang HG, Park YS, Cheong HI and Ha IS. Tacrolimus for children with refractory nephrotic syndrome: a one-year prospective, multicenter, and open-label study of Tacrobell(R), a generic formula. World J Pediatr 2016; 12: 60-65.
[17] Choudhry S, Bagga A, Hari P, Sharma S, Kalaivani M and Dinda A. Efficacy and safety of tacrolimus versus cyclosporine in children with steroid-resistant nephrotic syndrome: a randomized controlled trial. Am J Kidney Dis 2009; 53: 760-769.
[18] Gulati A, Sinha A, Gupta A, Kanitkar M, Sreenivas V, Sharma J, Mantan M, Agarwal I, Dinda AK, Hari P and Bagga A. Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. Kidney Int 2012; 82: 1130-1135.
[19] Sinha A, Gupta A, Kalaivani M, Hari P, Dinda AK and Bagga A. Mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome. Kidney Int 2017; 92: 248-257.
[20] Wang W, Xia Y, Mao J, Chen Y, Wang D, Shen H, Fu H, Du L and Liu A. Treatment of tacrolimus or cyclosporine A in children with idiopathic nephrotic syndrome. Pediatr Nephrol 2012; 27: 2073-2079.
[21] Siegel NJ, Gaudio KM, Krassner LS, McDonald BM, Anderson FP and Kashgarian M. Steroid-dependent nephrotic syndrome in children: histopathology and relapses after cyclophosphamide treatment. Kidney Int 1981; 19: 454-459.
[22] Hamasaki Y, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Ishikura K, Yata N, Kaneko T and Honda M. Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2009; 24: 2177-2185.
[23] Shatat IF, Schoeneman M, Flynn JT and Woroniecki RP. Association of steroid and cyclosporin resistance in focal segmental glomerulosclerosis. Pediatr Nephrol 2007; 22: 834-839.
[24] de Mello VR, Rodrigues MT, Mastrocinque TH, Martins SP, de Andrade OV, Guidoni EB, Scheffer DK, Martini Filho D, Toporovski J and Benini V. Mycophenolate mofetil in children with steroid/cyclophosphamide-resistant nephrotic syndrome. Pediatr Nephrol 2010; 25: 453-460.
[25] Afzal K, Bagga A, Menon S, Hari P and Jordan SC. Treatment with mycophenolate mofetil and prednisolone for steroid-dependent nephrotic syndrome. Pediatr Nephrol 2007; 22: 2059-2065.
[26] Moudgil A, Bagga A and Jordan SC. Mycophenolate mofetil therapy in frequently relapsing steroid-dependent and steroid-resistant nephrotic syndrome of childhood: current status and future directions. Pediatr Nephrol 2005; 20: 1376-1381.
[27] Barletta GM, Smoyer WE, Bunchman TE, Flynn JT and Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. Pediatr Nephrol 2003; 18: 833-837.
[28] Bagga A, Hari P, Moudgil A and Jordan SC. Mycophenolate mofetil and prednisolone therapy in children with steroid-dependent nephrotic syndrome. Am J Kidney Dis 2003; 42: 1114-1120.
[29] Cattran DC, Alexopoulos E, Heering P, Hoyer PF, Johnston A, Meyrier A, Ponticelli C, Saito T, Choukroun G, Nachman P, Praga M and Yoshikawa N. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. Kidney Int 2007; 72: 1429-1447.
[30] Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. French Society of Pediatric Nephrology. J Pediatr 1994; 125: 981-986.
[31] Mahmoud I, Basuni F, Sabry A, El-Husseini A, Hassan N, Ahmad NS, Elbaz M, Moustafa F and Sobh M. Single-centre experience with cyclosporin in 106 children with idiopathic focal segmental glomerulosclerosis. Nephrol Dial Transplant 2005; 20: 735-742.
[32] Sairam VK, Kalia A, Rajaraman S and Travis LB. Secondary resistance to cyclosporin A in children with nephrotic syndrome. Pediatr Nephrol 2002; 17: 842-846.
[33] Denton MD, Magee CC and Sayegh MH. Immunosuppressive strategies in transplantation. Lancet 1999; 353: 1083-1091.

[34] Yoshida T, Nakanishi K, Yoshioka T, Tsutsui Y, Maeda A, Kondo H and Sako K. Oral tacrolimus oil formulations for enhanced lymphatic delivery and efficient inhibition of T-cell's interleukin-2 production. Eur J Pharm Biopharm 2016; 100: 58-65.

[35] Maguire O, Tornatore KM, O'Loughlin KL, Venuto RC and Minderman H. Nuclear translocation of nuclear factor of activated T cells (NFAT) as a quantitative pharmacodynamic parameter for tacrolimus. Cytometry A 2013; 83: 1096-1104.

[36] Dong QE, Fu R, Liu CY, Ruan EB, Wang XM, Wang GJ, Qu W, Liu H, Wu YH, Song J, Xing LM, Guan J, Li LJ, Wang HQ and Shao ZH. [Inhibitory effects of tacrolimus on effector T cells from patients with severe aplastic anemia]. Zhonghua Yi Xue Za Zhi 2013; 93: 1541-1545.