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.
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Electronic database searched:
Pubmed: n=49
Web of Science: n=99
Cochrane library: n=16

164 records
160 records excluded because of duplicates (n=65)
99 records
91 records excluded because of irrelevant topics and various reasons (n=91)

Research included (n=8)

Figure 1. Flow chart of study selection process.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Sex boys/girls</th>
<th>Age (years)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM Yang [16]</td>
<td>2016</td>
<td>Korea</td>
<td>Prospective, open-label,</td>
<td>54/23</td>
<td>Average age 9.9</td>
<td>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.</td>
</tr>
<tr>
<td>Isabel Roberti [15]</td>
<td>2010</td>
<td>USA</td>
<td>Retrospective, single-center,</td>
<td>8/11</td>
<td>1.6-18 (median:</td>
<td>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.</td>
</tr>
<tr>
<td>Kim Loeffler [13]</td>
<td>2004</td>
<td>Canada</td>
<td>Retrospective study</td>
<td>12/4</td>
<td>Average age 11.4</td>
<td>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.</td>
</tr>
<tr>
<td>Sanjeev Gulati [14]</td>
<td>2008</td>
<td>India</td>
<td>Prospective study</td>
<td>20/2</td>
<td>7.33 ± 5.9</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Group</th>
<th>Case</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aditi Sinha [19]</td>
<td>2017</td>
<td>India</td>
<td>Open-label, one-to-one random-</td>
<td>TAC vs MMF</td>
<td>31</td>
<td>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.</td>
</tr>
<tr>
<td>Ashima Gulati [18]</td>
<td>2012</td>
<td>India</td>
<td>A multicenter, randomized,</td>
<td>TAC vs CTX</td>
<td>63</td>
<td>The dose of tacrolimus and cyclophosphamide was 0.12 ± 0.03 mg/kg/day and 554.1 ± 98.2 mg/m²/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).</td>
</tr>
<tr>
<td>Swati Choudhry [17]</td>
<td>2009</td>
<td>India</td>
<td>Randomized, controlled trial,</td>
<td>TAC vs CsA</td>
<td>21</td>
<td>Tacrolimus (0.1 to 0.2 mg/kg/d) or CsA (5 to 6 mg/kg/d). Cotreatment with alternate day prednisolone and enalapril.</td>
</tr>
<tr>
<td>Wenjing Wang [20]</td>
<td>2012</td>
<td>China</td>
<td>Comparative cohort study</td>
<td>TAC vs CsA</td>
<td>26</td>
<td>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.</td>
</tr>
</tbody>
</table>
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In the 4 self-controlled studies, TAC treatment has significantly reduced urine protein to creatinine ratio (mean difference = -5.78, 95% CI = -8.00 to -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 to 2.07, P = 0.09; and mean difference = -8.95, 95% CI = -29.92 to 12.01, P = 0.40, respectively; Figure 2B and 2C).

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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 to 2.90, P = 0.02 and risk ratio = 3.07, 95% CI = 1.78 to 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 to 3.40, P = 0.57; Figure 4); However, TAC signifi-
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Significantly 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
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 synthetase [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
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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 hypertrichosin 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 non-consistent 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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