A Comparison Between Tacrolimus and Cyclosporine As Immunosuppression after Renal Transplantation in Children, A Meta-Analysis and Systematic Review

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Introduction. There are some randomized trials which have already evaluated different calcineurin inhibitors (CNIs), especially comparing Tacrolimus and Cyclosporine, as immunosuppressant agents in children. However, their findings have been occasionally conflicting and thus debatable. Therefore, the evidence on safety and efficacy of immunosuppressive therapy after kidney transplantation in children has been inconclusive and argued to date. This study was aimed to compare the benefits and disadvantages of tacrolimus versus cyclosporine as the primary immunosuppression after renal transplantation in children.

Methods. A systematic review and meta-analysis was done. An electronic literature review was conducted to identify appropriate studies. The outcomes were presented as relative risk, with 95% confidence intervals.

Results. Five qualified randomized controlled trials were included in this systematic review. Tacrolimus was insignificantly superior to cyclosporine considering the total effect size of graft loss (RR = 0.67, 95% CI: 0.40 - 1.11; $P > .05$) and acute rejection (RR = 0.79, 95% CI: 0.59 – 1.05; $P > .05$). On the contrary, cyclosporine seemed to be insignificantly superior to tacrolimus regarding mortality rate (RR = 1.06, 95% CI: 0.59 - 1.90; $P > .05$).

Conclusion. Admitting the study limitations mainly because of the nature and case study size of the included trials, it can be concluded from our systematic review results that Tacrolimus seems insignificantly superior to Cyclosporine respecting graft loss and acute rejection. However, Cyclosporine was shown to be insignificantly superior regarding mortality rate. However additional studies with a larger sample size are highly recommended.

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Original Paper

INTRODUCTION

FDA (United States Food and Drug Administration) approved two calcineurin inhibitors (CNIs), Cyclosporine A (CsA) and tacrolimus (TAC), respectively in 1983 and 1997, to be used in kidney transplantation for prevention of acute rejection.[1] To date, only a few studies have evaluated and compared the efficacy and safety of different calcineurin inhibitors in pediatric population. In contrast, there are several large-scale multicenter randomized trials in adults, which compared the clinical efficacy and safety of TAC and CsA on renal transplant recipients. The outcomes were not however consistent.[2] Only some clinical trials

in kidney transplantation have reported improved kidney allograft survival using TAC versus CsA as a part of the maintenance immunosuppression protocol, both in adult and pediatric kidney transplant recipients.[1] As the findings of different trials have been conflicting and the evidence on efficacy and safety of immunosuppressive therapy for kidney transplant is inconclusive, we decided to conduct this study to compare the efficacy of TAC and CyA as immunosuppressive therapy after renal transplantation in children.

MATERIALS AND METHODS

A systematic literature review on PubMed, Cochrane Library, Science Direct, Scopus, and Web of Science was conducted. The search terms were devised using a combination of free-text title and abstract search terms and Medical Subject Heading (MeSH) terms. We tried to identify parallel-group randomized controlled trials comparing all formulations of tacrolimus with ciclosporin as the immunosuppressive regimen used after first kidney transplantation in children. The search terms were *(Cyclosporin* or CyA or Neoral* or Sandimmun*) and (Tacrolimus or FK506 or FK506 or Prograf) and "kidney transplantation" and (random* or blind* or placebo* or meta-analysis)*. A search was performed to identify studies which have been published in peer-reviewed journals between January 1st 2000 and July 1st 2018. We scanned bibliographies in relevant articles and conference proceedings, and studies by the same author were checked for possible overlapping participant groups. If the study was reported as a duplicate, only the most recent or complete one was included. The following selection criteria were applied: We included all randomized trials comparing Tacrolimus with Cyclosporine as initial immunosuppressive therapy, with any combination of additional immunosuppressive treatments in the intervention and control arms. Trials in which participants received another solid organ in addition to a kidney transplant (such as kidney with pancreas) and studies that failed to meet the inclusion criteria were excluded. No protocol for this analysis was registered before manuscript submission.

Data Extraction and Quality ASSESSMENT

Two independent reviewers extracted data from the articles according to the selection criteria. Disagreements were resolved by discussion between two reviewers considering the opinion of a third reviewer. The following information was obtained from each included study: first author and year of publication, design of study, sample size, gender of patients, intervention regimen, follow-up duration, concomitant treatment, and outcome measures. All the analyses were based on previously published studies; thus, no ethical approval or patient consent was required.

Quantitative Data Synthesis and Data Analysis

We extracted data and then used comprehensive meta-analysis to pool them for summary estimation. We expressed the results as relative risk with 95% confidence intervals and checked heterogeneity among studies by the Chi-square-based Cochran's Q and I^2 statistics to measure the proportion of total variation due to heterogeneity beyond chance. If $I^2 > 50\%$, heterogeneity was considered statistically significant, and data were analyzed using a random effect model. Otherwise, the fixed-effect model was applied as the preferred method. In the whole study, $P < .05$ was considered as statistically significant.

RESULTS

Search Results and Characteristics

The literature review and reference mining yielded 77 potentially relevant articles. We removed 32 articles because of duplication. We also excluded 26 articles after reviewing the titles and abstracts because they were books, book sections, review papers and therefore not relevant. Subsequently, we reviewed the full text of the selected articles and removed 14 studies because topics were not relevant to the subject. Eventually, five studies were enrolled in the systematic review (all of them were clinical trials or retrospective studies).[1, 4-7] The flow diagram of study selection is shown in Figure 1. Characteristics and details of the studies are summarized in Table 1.

Outcome

Summary of outcomes, comparing two groups (Tacrolimus (tac) and Cyclosporine (cycl)), is provided in Table 2.

Quantitative Synthesis

Mortality. Six trials reported mortality rate, and between Tacrolimus versus Cyclosporine, no

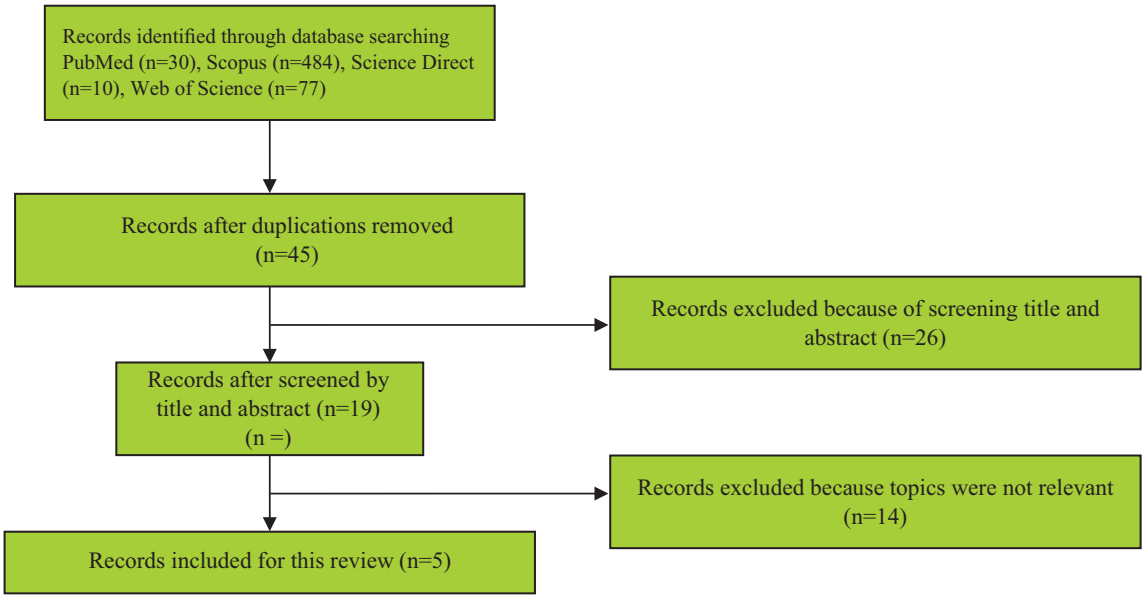

Figure 1. The flow diagram of study selection is shown in this figure.

significant difference was found regarding mortality rate, as sketched in Figure 2 (RR = 1.06, 95% CI: 0.59 - 1.90; $P > .05$).

Graft Loss. Six trials reported graft loss, and between Tacrolimus and Cyclosporine, no significant difference in graft loss was found, as shown in Figure 3 (RR = 0.67, 95% CI: 0.40 -1.11; $P > .05$). The forest plot for subgroup analysis

Table 1. General Characteristics of Trials Included in This Systematic Review

Author Name	Year	Sample Size (Patient)		Sex (Male)		Follow-up (month)	Co-interventions†	
		Tac	Cyclo	Tac	Cyclo		Tac	Cyclo
Kizilbash	2017	38	58	20 (53%)	34 (59%)	12	Thymo + Prednisone + MMF	Thymo + Prednisone + MMF
Kaabak	2016	36	63	NS	NS	84	Alemtuzumab + MMF	Alemtuzumab + MMF
Filler	2005	103	93	64 (62.1%)	56 (60.2%)	48	Azathioprine + Corticosteroids	Azathioprine + Corticosteroids
Filler	2002	103	93	64 (62.1%)	56 (60.2%)	24	Azathioprine + Corticosteroids	Azathioprine + Corticosteroids
Alicia M	2003	220	766	NS	NS	12	MMF + Steroids	MMF + Steroids
Alicia M	2003	77	391	NS	NS	24	MMF + Steroids	AZA + Steroids
Trompeter	2002	103	93	64 (62.1%)	56 (60.2%)	12	Azathioprine + Corticosteroids	Azathioprine + Corticosteroids

NS, not stated

Table 2. Outcome of Trials

Author Name	Year	Mortality		DCGS		Acute Rejection		Graft Loss	
		Tac	Cyclo	Tac	Cyclo	Tac	Cyclo	Tac	Cyclo
Kizilbash	2017	0	1 (2%)	36 (95%)	56 (97%,)	29 (75%)	45 (77%,)	NS	NS
Kaabak	2016	2 (2.8%)	8 (11.9%)	NS	NS	NS	NS	6 (14.8%)	18 (28.1%)
Filler	2005	5 (6%)	4 (8%)	98 (95.4%)	74 (79.2%)	38 (36.9%) (12 month)	55 (59.1%) (12 month)	15 (14%)	29 (31%)
Filler	2002	3 (2.9%)	4 (4.3%)	NS	NS	NS	NS	10 (9.7%)	19 (20.4%)
Alicia M	2002	NS	NS	NS	NS	NS	NS	5 (2.1%)	25 (3.2%)
Alicia M	2003	4 (5.19%)	4 (1.02%)	NS	NS	24 (31%)	162 (41.5%)	18 (8%)	55 (7.2%)
Trompeter	2002	4 (3.9%)	3 (3.4%)	NS	NS	38 (36.9%)	55 (59.1%)	10 (9.7%)	17 (18.3%)

DCGS, death-censored graft survival; NS, not stated

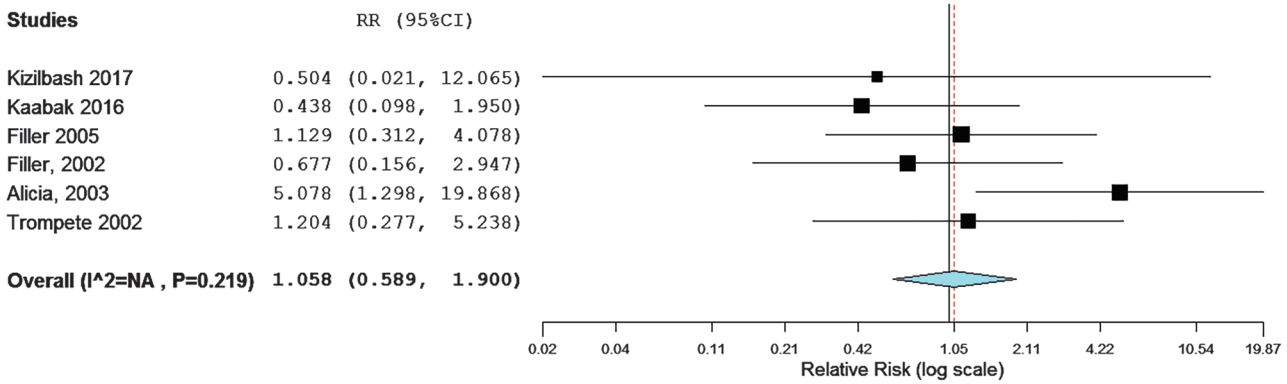

Figure 2. It shows Forest plot of mortality comparing two groups of intervention (tacrolimus vs. cyclosporine).

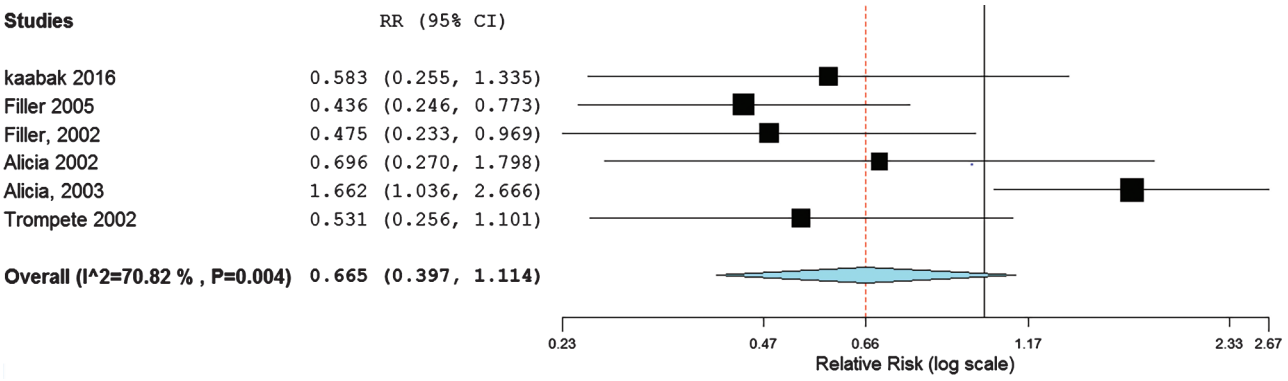

Figure 3. It demonstrates Forest plot of graft loss comparing two groups of Intervention (tacrolimus vs. cyclosporine).

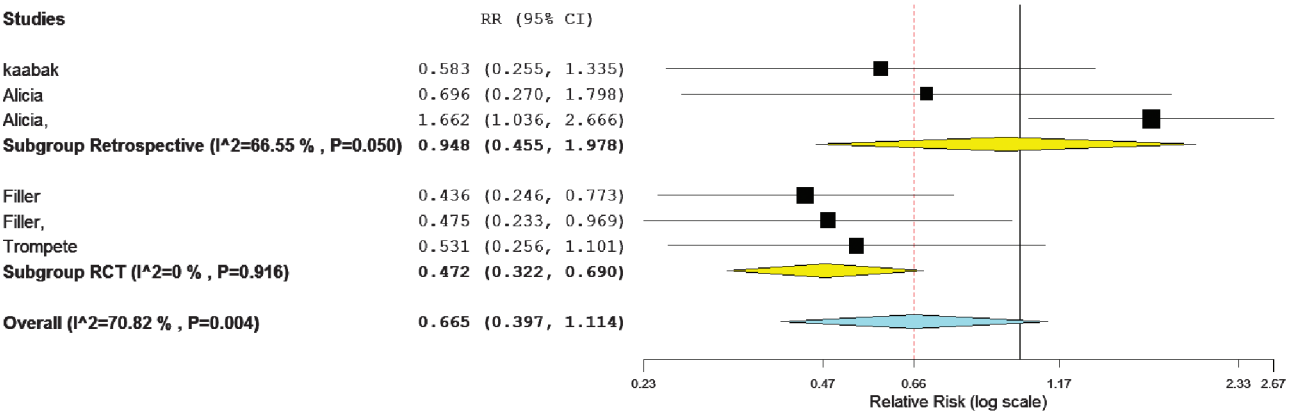

Figure 4. It mentions Forest plot for subgroup analysis based on study type.

based on study type is shown in Figure 4.

Acute Rejection. Three trials discussed acute rejection. An insignificant trend towards more acute rejection was seen for Tacrolimus compared with Cyclosporine (RR = 0.79, 95% CI: 0.59 – 1.05, $P > .05$; Figure 5).

DISCUSSION

Our study showed that Tacrolimus seems insignificantly superior to Cyclosporine considering graft loss, acute rejection, but Cyclosporine seems to be insignificantly superior regarding mortality. The meta-analysis in[7] which compared Tacrolimus with Cyclosporine as the primary immunosuppression after heart transplantation, reported that Tacrolimus was preferred over Cyclosporine with respect to hypertension, hyperlipidemia (similar to our study), gingival hyperplasia and hirsutism.[1] They

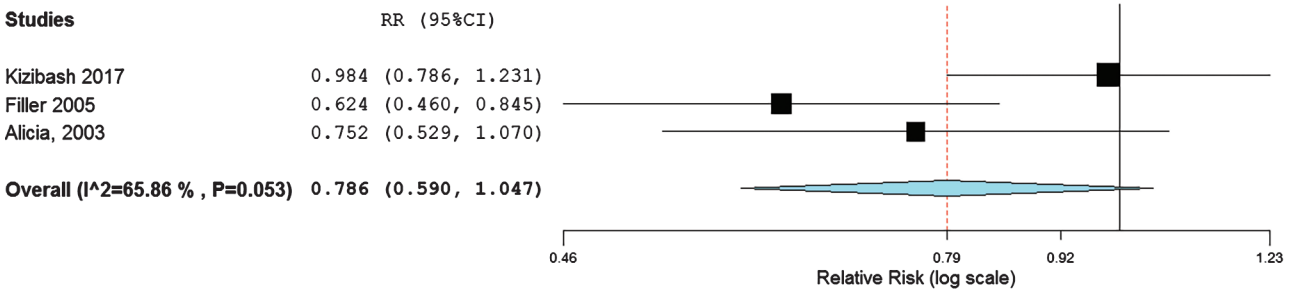

Figure 5. It shows Forest plot of acute rejection comparing two groups of Intervention (tacrolimus vs. cyclosporine).

concluded that Tacrolimus seemed to be superior to microemulsion Cyclosporine considering some outcomes, including death. However, they also suggested larger trials with lower risk of bias. Another meta-analysis conducted at 2018 in Iran, which compared cyclosporine and tacrolimus in adults receiving kidney transplantation, reported no significant differences regarding mortality, infection, and hypertension, but indicated that TAC significantly took precedence to cyclosporine considering graft loss and acute rejection, as what we showed in our meta-analysis among children.[8] Based on the retrospective cohort study by Neu AM in 2003, graft survival and risk of graft failure was not significantly different between patients who received TAC or CsA, similar to our recent findings. However, in Filler study conducted at 2005, they reported significant lower incidence of acute rejection and higher graft survival rate with TAC compared with CsA.[4,6] One of the important differences of the two studies mentioned above is the duration of their follow-up. In the NEO study, patients were followed up for two years while in Filler study, they were monitored for four years. Therefore, graft loss and survival rates might vary due to the difference of follow-up duration as in a longer duration follow up, more graft failure may be observed. The other difference of the two studies was their combination therapy. In Neu study, the patients received Mycophenolate Mofetil (MMF) and steroids, while in Filler study; they were prescribed azathioprine and corticosteroids. Therefore, azathioprine may be preferred to MMF for combination therapy.

CONCLUSION

Admitting the study limitations mainly because of the nature and case study size of the included trials, accompanied by very limited number of qualified studies, our systematic review conveys the conclusion that Tacrolimus seems insignificantly superior to Cyclosporine respecting graft loss and acute rejection. However, Cyclosporine was shown to be insignificantly superior regarding mortality rate. Additional studies with larger sample size are highly recommended.

CONFLICT OF INTEREST

No conflict of interest was declared.

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