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Short Review Article

Comparison of Tacrolimus and Cyclosporine for Immunosuppression after Renal Transplantation: An Updated Systematic Review and Meta-Analysis

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ABSTRACT. Kidney transplantation is usually followed by immunosuppressive therapy to prevent early rejection and prolong graft survival. The calcineurin inhibitors (CNIs) represent the most commonly used agents. However, available evidence suggests the poor outcome over the long term, maybe be due to the potential nephrotoxicity associated with CNIs. Several randomized trials have compared tacrolimus (TAC) with cyclosporine, to find the optimal agent for renal transplantation; however, studies have shown conflicting results. The aim of this study was to systematically review and update the evidence for the benefits and harm of TAC versus cyclosporine as the primary immunosuppression after renal transplantation. The study was a systematic review and meta-analysis. An electronic literature search was conducted to identify appropriated trial studies. The outcomes were presented as relative risk (RR), with 95% confidence intervals (CI). Statistical analysis used was meta-analysis. Twenty-one eligible randomized controlled trials were included in this systematic review. TAC was significantly superior to cyclosporine considering the total effect size of graft loss (RR 0.089; 95% CI0.057–0.122, *P* <0.001), acute rejection (RR 0.638; 95% CI 0.571–0.713, *P* <0.001) and hypercholesterolemia (RR 0.634; 95% CI, 0.539–0.746, *P* <0.001). On the contrary, cyclosporine seemed to be significantly superior to TAC with regard

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to diabetes (RR 1.891; 95% CI 1.522–2.350, *P* <0.001). However, no significant differences between the two CNIs were found with regard to mortality, infection, and hypertension. The review indicates that TAC is significantly superior to cyclosporine regarding graft loss, acute rejection, and hypercholesterolemia, but cyclosporine seems to be significantly superior to TAC regarding diabetes. However, further large randomized trials are suggested.

Introduction

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD), which is also called chronic renal failure.[1] For patients with ESRD, renal transplantation can improve survival and quality of life, and cause cost reduction in healthcare.[2] At present, the reported one-year patient and graft survival rates are 94% and 82%, respectively.[3] At the time of transplantation, cyclosporine A (CyA) and tacrolimus (TAC), as calcineurin inhibitors, are used to achieve adequate immunosuppression and to prevent acute rejection episodes.[3] CyA was discovered in 1971, and in 1983, this drug was approved for prevention of organ transplant rejection.[4] TAC (Prograf) was discovered in the early 1980s and from 1989, used for the prevention of liver transplant rejection. After that, the usage of this drug developed rapidly for the transplantation of other organs.[4]

Some randomized trials have compared TAC with CyA in transplant recipients. However, the results have been conflicting, and hence the immunosuppressive therapy for kidney transplant continues to be debated,[4] and the evidence on its efficacy and safety is inconclusive.[2] Therefore, the aim of this study was to compare the efficacy of TAC and CyA for immunosuppressive therapy after renal transplantation.

Subjects and Methods

We searched PubMed, The Cochrane Library, Science Direct, Scopus, and Web of Science (updated up to January 2017). Search term was (c*closporin* or CyA or Neoral* or Sandimmun*) and (TAC or FK506 or FK506 or Prograf) and "kidney transplantation" and (random* or blind* or placebo* or meta-analysis). We scanned bibliographies in relevant articles and conference proceedings. Studies by the same author were checked for possible overlapping participant groups. If the study was reported as duplicate, only the most recent or complete study was included in this study. The following selection criteria were applied: we included all randomized trials comparing TAC with CyA as initial immunosuppressive therapy, with combination of any additional immunosuppressive treatments in the intervention and control arms. We excluded trials in which participants received another solid organ in addition to a kidney transplant (such as kidney with pancreas). Studies that failed to meet the inclusion criteria were excluded from the study.

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 and where necessary taking the opinion of one-third reviewer. The quality of randomized trials was assessed using the Jaded score system. The following information was abstracted from each included study: first author and year of publication, design of study, sample size, mean age of patients, intervention regime, follow-up duration, concomitant treatment, and outcome measures for each group. 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 estimates. We expressed the results' relative risk (RR), with 95% confidence intervals (CIs). Heterogeneity among our studies was checked 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 was >50%, heterogeneity was considered statistically significant, and data were analyzed using a random effect model. Otherwise, the fixed-effects model was applied as the preferred method; P <0.05 was considered as statistically significant.

Results

Search results and characteristics

The literature search yielded 867 potential relevant articles. We excluded 59 articles because of duplication. We also excluded 775 articles after reviewing the titles and abstracts because they were books, book sections or, review papers and therefore not relevant. We then reviewed full text of selected articles and a total of 21 studies were included in the systematic review (all of them were clinical trials (CT)].[5-25] The flow diagram of study selection is given in Figure 1. Characteristics and the details of the studies are summarized in Table 1.

Outcome

The summary of outcomes of this study, comparing the two groups, TAC and CyA are provided in Table 2.

Quantitative synthesis

Mortality

Sixteen trials reported on mortality, and between TAC and CyA no significant difference was found, as shown in Figure 2 (RR 1.072; 95% CI 0.792–1.452, P = 0.651).

Graft loss

Eighteen trials reported on graft loss. There was a significant difference, and higher graft loss was seen in the CyA group compared with TAC as shown in Figure 3 (RR 0.089; 95% CI 0.057–0.122, P <0.001).

Acute rejection

Eighteen trials reported on acute rejection. There was a lower frequency of acute rejection with TAC therapy (RR 0.638; 95% CI 0.571–0.713, P <0.001; Figure 4).

Diabetes

Eighteen trials reported on diabetes. An insignificant trend toward more diabetes was seen in the TAC group compared with the CyA group (RR 1.891; 95% CI 1.522–2.350, P <0.001; Figure 5).

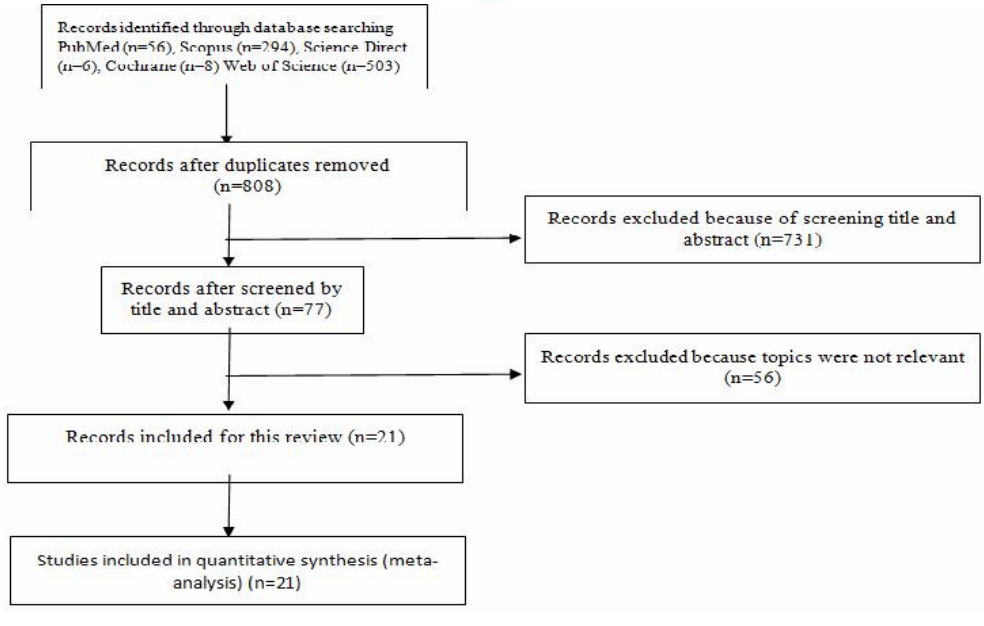

Figure 1. Flowchart of study selection process.

Table 1. General characteristics of trials included in this systematic review.

Author name	Year	Sample size (patient)		Age (year)		Follow-up (month)	Co-interventions†	
		TAC	CyA	TAC	CyA		TAC	CyA
Shapiro	1991	28	29	40.5	38.2	12	Steroids	Steroids
Mayer et at	1997	303	145	47	46	12	AZA + steroids	Steroids
Pirsch JD	1997	205	207	43	44	12	AZA + steroids	AZA + steroids
Morris-Stiff	1998	40	40	44	45	36	AZA	AZA
Radermacher	1998	28	13	41.3	47.1	60	Aza + ATG/OKT3	Aza + ATG/OKT3
Raofi, V.	1999	14	21	44 6	46	12	steroids	AZA + steroids
Yang	1999	30	30	45 6	48 6	6	MMF + OKT3	MMF + OKT3
Wang XH	2000	25	32	38.1 6	38.1 6	12	MMF	MMF
White	2000	24	29	43	43		None	None
Ahsan	2001	72	75			24	MMF	MMF
Campos	2002	85	81	40.5	40.9	12	AZA + ATG	AZA + ATG
Charpentier B	2002	186	184	44.5	44.7	6	AZA + ATG + steroids	AZA+ATG+steroids
Margreiter R	2002	286	271	42·4	43·8	6	AZA + steroids	AZA + steroids
Trompeter R	2002	103	93	10.5	10.1	6	AZA + steroids	AZA + steroids
Jarzembowski	2005	14	21	44	46	78	prednisone	Prednisone
Chi YC	2006	33	33	42.4	41.2	34	AZA + steroids	AZA + steroids
Kramer BK	2008	231	217	43	43	36	AZA + steroids	AZA + steroids
Cheung	2009	38	38	41.8	40.2	84		
Lee YJ	2010	63	68	15<	15<		MMF	MMF
Liu LS	2015	36	36	42	43	24	MMF + steroids	MMF + steroids
Kramer BK	2016	286	271	43	43	84	AZA + steroids	AZA + steroids

Tac: Tacrolimus, CyA: Cyclosporine A, AZA: Azathioprine, ATG: Anti-thymocyte globulin, MMF: Mycophenolate mofetil.
†: Additional treatments and therapeutic procedures.

Table 2. Outcome of trials.

Author name	Year	Mortality		Graft loss		Acute rejection		Diabetes		Infection		Hypertension		Hypercholesterolemia	
		Tac	Cyclo	Tac	Cyclo	Tac	Cyclo	Tac	Cyclo	Tac	Cyclo	Tac	Cyclo	Tac	Cyclo
Shapiro	1991	3	2	7	7			4	2			NS	NS		
Mayer	1997	21	9	53	20	73	63	35	3			8	8		
Pirsch JD	1997	9	7	18	25	63	96	39	8			102	108	16	30
Morris-Stiff G	1998			6	0	16	13	3	2	0	4				
Radermacher	1998			15	9	11	8	1		67	16	4	9		
Raofi V	1999			0	0	2	8	3	4						
Yang	1999	3	0	0	1	1	3	1	1	11	5				
Wang XH	2000	0	0	0	2	0	1	5	4	5	4				
White	2000			0	5	6	8	4	2						
Ahsan	2001	4	9	9	10										
Campos	2002			12	9	3	8	10	3	215	207				
Charpentier B	2002	5	3	14	12	22	20	13	2	45	52			5	12
Margreiter R	2002	2	4	16	23	27	57	19	16	101	88	45	63	12	24
Trompeter R	2002	3	3			38	55	3	2	30	31	71	57		
Jarzembowski T	2005	2	1	0	0	3	10	21	19						
Chi YC	2006	2	0	3	2	5	9	3	2	23	24	27	25	4	11
Kramer BK	2008	4	1	3	6	81	114	29	23	9	8	170	176	45	73
Cheung Chi Yuen	2009	4	6			7	16	10	6	13	18	31	32	16	26
Lee YJ	2010	1	1			5	4	12	4	19	17	38	33	16	18
Liu LS	2015	1	0	1	0	4	2	6	4	30	13				
Kramer BK	2016	25	26	46	48			32	26	30	28	154	140	68	84

Tac: Tacrolimus, Cylo: Cyclosporine.

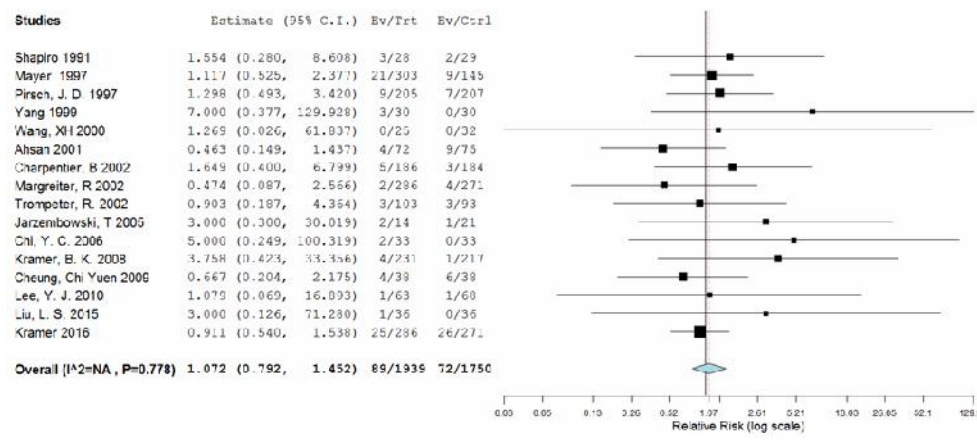

Figure 2. Forest plot of mortality comparing two groups of intervention; tacrolimus versus cyclosporine.

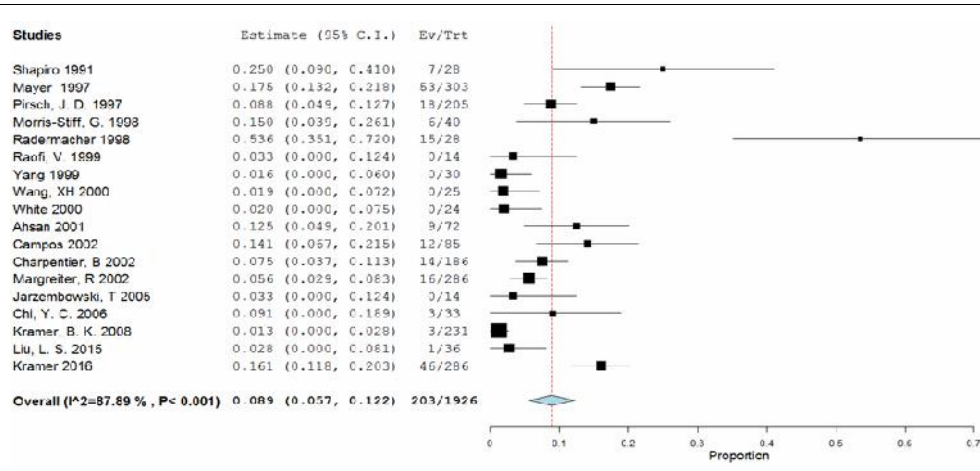

Figure 3. Forest plot of graft loss comparing two groups of intervention; tacrolimus versus cyclosporine.

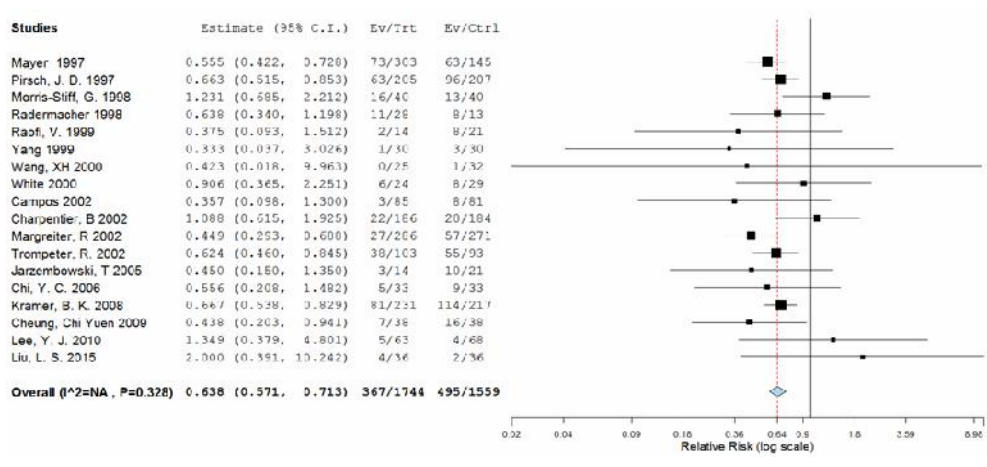

Figure 4. Forest plot of acute rejection comparing two groups of intervention; tacrolimus versus cyclosporine.

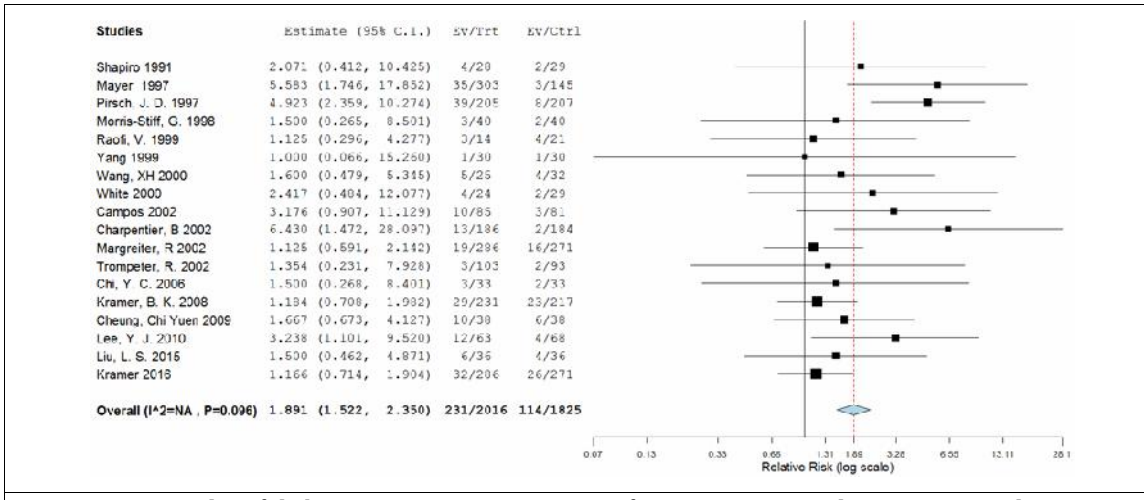

Figure 5. Forest plot of diabetes comparing two groups of intervention; tacrolimus versus cyclosporine.

Infection

The observed frequency and type of infections were similar in the two treatment groups throughout the study (RR 1.053; 95% CI 0.924–1.94, $P = 0.11$, Figure 6).

Hypertension

The incidence of hypertension was reported in 10 studies. No significant difference was found between the TAC and CyA groups in the incidence of hypertension (RR 0.958; 95% CI, 0.849–1.081, $P = 0.489$, Figure 7).

Hypercholesterolemia

Pooled results failed to show statistically significant differences between the TAC and CyA groups in the incidence of hypercholesterolemia (RR 0.634; 95% CI 0.539–0.746, $P < 0.001$ Figure 8).

Discussion

This meta-analysis showed that TAC was significantly superior to CyA in reducing graft loss, acute rejection, and hypercholesterolemia, and CyA was significantly superior regarding diabetes. The results of another meta-analysis regarding TAC versus CyA are different from this review. In that study, TAC was significantly superior to CyA with regard to causing hypertension (RR 0.8; 95% CI 0.69–0.93, $P = 0.003$), and hyperlipidemia (RR 0.57; 95% CI 0.44–0.74, $P < 0.0001$).[4]

Another meta-analysis study showed that TAC

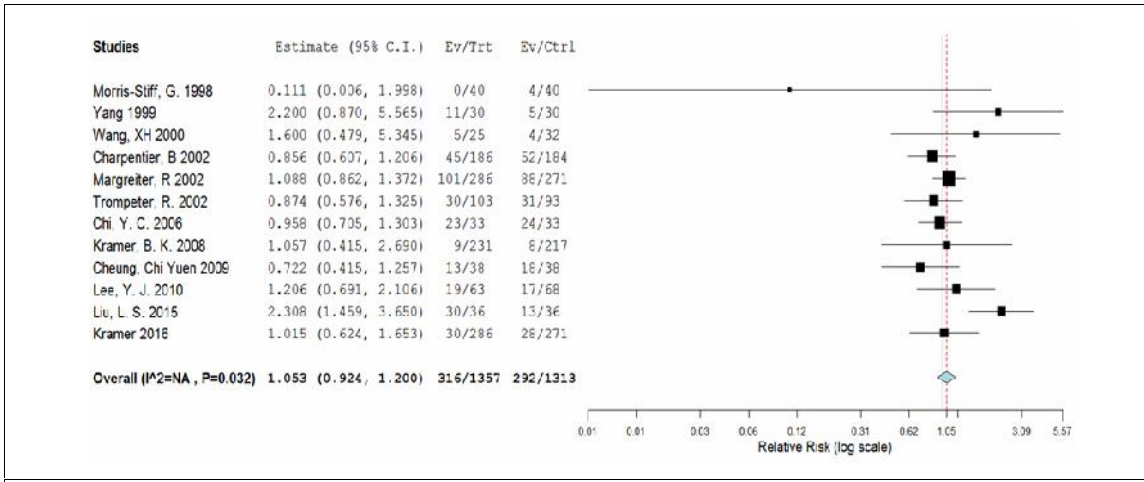

Figure 6. Forest plot of infection comparing two groups of intervention; tacrolimus versus cyclosporine.

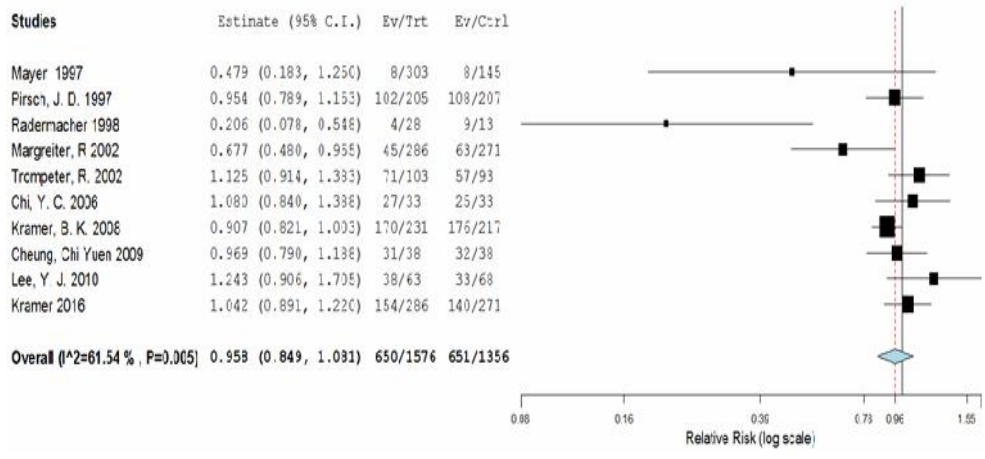

Figure 7. Forest plot of hypertension comparing two groups of intervention; tacrolimus versus cyclosporine.

was a more cost-effective treatment than CyA for the prevention of adverse events of renal transplant. They concluded that TAC is an effective and safe immunosuppressive agent, and for the primary prevention of graft rejection in renal transplant, it may be more cost-effective than CyA; however, new-onset diabetes should be considered during the medication period.[3] Their results were approximately similar to our results. Another meta-analysis was made on the bioavailability, efficacy and safety of generic immunosuppressive drugs for kidney transplantation.[2] They concluded that all the generic immunosuppressive drugs did not have equivalent relative bioavailability, and it depended on their brands.[2] We did not investigate this issue in our study.

A meta-analysis[4] compared TAC with CyA as primary immunosuppression after heart transplantation and showed that TAC was preferred over CyA considering the increased occurrence of hypertension, hyperlipidemia (similar to our study), gingival hyperplasia, and hirsutism. They suggested more trials with a low risk of bias.[4]

In one study conducted by Liu et al on Chinese *de novo* kidney transplant recipients who were CYP3A5 expressers, CyA-based maintenance therapy was found to be safe with respect to acute rejection, patient, and graft

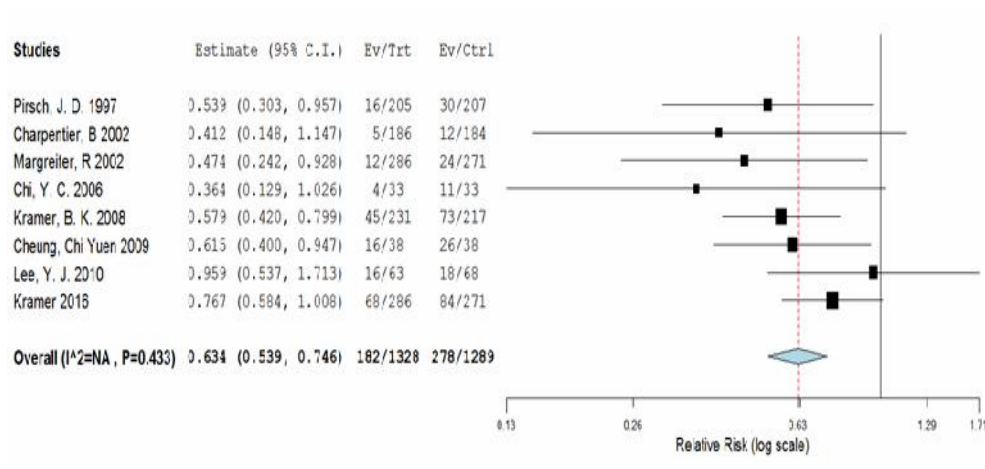

Figure 8. Forest plot of hypercholesterolemia comparing two groups of intervention; tacrolimus vs cyclosporine.

survival.[24] In fact, CyA was a more beneficial agent for this particulr population, meaning that the place of origin of subjects should be taken into account while choosing the optimal drug.

Although CNIs constitute the first-line immunosuppressive agents for maintenance therapy, the optimal maintenance immunosuppressive therapy in renal transplantation is not yet established. Combination therapy regimen in which anti-rejection medications are typically given in combination with antiproliferative agents (e.g., mycophenolate mofetil (MMF), mycophenolate sodium, and azathioprine), has attracted more attention as a new approach to limit CNIs-specific nephrotoxicity.[26] However, despite such therapeutic and interventional strategies that lead to a significant decline of acute rejection in the first year, posttransplant chronic rejection remains an ongoing challenge, and new treatment options with appropriate long-term cases continue to be researched and developed, with the hope of minimizing the risk of rejection and adverse outcomes.

Conclusion

Acknowledging the limitations of the study due to the size and nature of the trials included, our review shows that TAC seems to be significantly superior to CyA regarding graft loss, acute rejection, and hypercholesterolemia, but CyA seems to be significantly superior considering diabetes. However, further large randomized trials are suggested.

Conflict of interest: None declared.

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