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A comparison of mycophenolate mofetil and calcineurin inhibitor as maintenance immunosuppression for kidney transplant recipients: A meta-analysis of randomized controlled trials

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Background/aim: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the comparison and its timing between mycophenolate mofetil (MMF) and calcineurin inhibitor (CNI) as maintenance immunosuppression for kidney transplant recipients.

Materials and methods: The RCTs of MMF versus CNI as maintenance immunosuppression for kidney transplant recipients were searched from PubMed, Embase, Cochrane Central Register of Controlled Trials (CCRCT), and ClinicalTrials.gov. After screening relevant RCTs, two authors independently assessed the quality of included studies and performed a meta-analysis using RevMan5.3. Relative risk (RR) was used to report dichotomous data, while mean difference (MD) with 95% confidence interval (CI) was used to report continuous outcomes. The analysis was conducted using the random-effect model due to the expected heterogeneity among different studies. Four subgroups were allocated to compare MMF with CNI as maintenance immunosuppression: (1) after 3 months of CNI-based therapy, (2) after 6 months of CNI-based therapy, (3) after 12 months of CNI-based therapy, and (4) in recipients with allograft dysfunction.

Results: Twelve RCTs with 950 renal transplant recipients were included. This meta-analysis presented the following results upon comparison between MMF and CNI as maintenance immunosuppression for kidney transplant recipients: (1) MMF significantly improved the glomerular filtration rate (GFR) not only in the comparison performed after 3, 6, or 12 months of CNI-based therapy but also in the comparison of recipients with allograft dysfunction, (2) MMF may increase the risk of acute rejection in the comparison performed after 3 months of CNI-based therapy, but no increase was noted in the comparison performed after 6 or 12 months of CNIbased therapy.

Conclusion: Our present meta-analysis suggested that MMF followed at least 6 months of CNI-based therapy is an effective maintenance immunosuppressive regimen for kidney transplant recipients to improve renal function but not increase rejection.

Key words: Kidney transplantation, mycophenolate mofetil, calcineurin inhibitor, meta-analysis

1. Introduction

End-stage renal disease (ESRD) is a chronic, irreversible decline in kidney function that severely and deleteriously affects the duration and quality of life of patients. Approximately 1.9 million patients receiver enalreplacement therapy (RRT) worldwide [1]. RRT, which includes kidney transplantation (KT), hemodialysis (HD), and peritoneal dialysis (PD), is the only option for individuals with ESRD to survive at present. Compared to dialysis, KT prolongs the life-span, improves renal function and quality of life, and is more cost-effective [2-5]. Nevertheless, a suitable and effective immunosuppressive regimen that minimizes acute rejection (AR) and limits adverse events (AEs) is paramount for KT success. Regarding immunosuppressive therapy, calcineurin inhibitors (CNIs), such as cyclosporine A (CsA) or tacrolimus (TAC), have served as fundamental therapies for renal allograft recipients since CsA became available in the early 1980s. However, significant AEs, such as hypertension, dyslipidemia, new-onset diabetes transplantation (NODAT), and particularly after nephrotoxicity of CNI, have been noted and they serve as major causes of later graft loss [6]. Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid (MPA), which inhibits T and B lymphocyte proliferation, has been shown to reduce the risk of acute allograft rejection and lack nephrotoxicity [7,8]. Moreover, a meta-analysis demonstrated the positive effect of CNI sparing with MMF as solo adjunctive immunosuppressive agents after KT [9].



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Several randomized controlled trials (RCTs) compared the outcomes after MMF or CNI withdrawal in renal transplant recipients [10–12]. However, to date, meta-analysis data are not available to compare the efficacy and safety of MMF with CNI as maintenance immunosuppression for kidney transplant recipients. In addition, given the correlation between the duration of CNI and its therapeutic efficacy and side effects, we conducted a systematic review and meta-analysis of RCTs to evaluate the comparison and its timing between MMF and CNI as maintenance immunosuppression for kidney transplant recipients.

2. Materials and methods

2.1. Search strategy

PubMed, Embase, Cochrane Central Register of Controlled Trials (CCRCT), and ClinicalTrials.gov were searched without language restrictions using the following mesh terms and entry terms: kidney transplantation, renal transplantations, kidney grafting, mycophenolate mofetil, mycophenolate sodium, cellcept, calcineurin inhibitors, protein phosphatase-2b inhibitors, calcineurin antagonists, cyclosporine, cyclosporine a, tacrolimus, and FK506 (all to September 2019). We retrieved the reference lists of all relevant trials and consulted experts in the field to identify potentially relevant studies.

2.2. Inclusion criteria

For inclusion in this meta-analysis, studies had to meet the following criteria: (1) Only RCTs were considered, (2) Patients received renal transplant from a living or deceased donor, (3) Studies compared the outcomes of the use of MMF to CNI as maintenance immunosuppression for kidney transplant recipients, (4) Trials analyzed primary outcomes, including renal function, acute rejection, graft survival, or patient survival. Studies with complete CNI avoidance in de novo patients or multiple organ transplant recipients were excluded. The studies were subsequently allocated to four subgroups to compare MMF and CNI as maintenance immunosuppression: (1) after 3 months of CNI-based therapy, (2) after 6 months of CNI-based therapy, (3) after 12 months of CNI-based therapy; and (4) in recipients with allograft dysfunction.

2.3. Study selection

Two authors separately examined the titles and/or abstracts of each study and excluded irrelevant trials. Subsequently, the full text of all articles was scanned and evaluated independently by two authors strictly according to the inclusion criteria. All disagreements regarding study eligibility for inclusion were discussed to achieve a consensus.

2.4. Data extraction

Two authors independently extracted data on the baseline demographic characteristics of participants, study design,

intervention and control treatment, and outcome data of studies. We contacted the trial authors or sponsors directly to obtain the required information if data were unavailable. When disagreements occurred, the third author provided an opinion to resolve the issue.

2.5. Study quality assessment

Two authors independently evaluated the quality of the included studies. Disagreements were resolved by consensus. The quality of included studies was evaluated by the Cochrane Handbook [13]. The risk of bias comprised a description and judgment for the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other source of bias. Each criterion was judged 'low risk of bias', 'unclear risk of bias', or 'high risk of bias'.

2.6. Statistical analysis

Outcomes were analyzed using Cochrane Review Manager Software (RevMan5.3, Copenhagen, Denmark: the Nordic Cochrane Centre, the Cochrane Collaboration). Continuous variables are expressed as the mean difference (MD) and 95% confidence interval (CI). The risk ratio (RR) and 95%CI were calculated for dichotomous data. If there are no events in one arm or two arms, the data also will be filled truthfully in the forest figures. The I²statistic and Chi-squared test were used to assess the heterogeneity of the included studies (I²>50% and p<0.1 indicated significant heterogeneity)[14]. If significant heterogeneity was present among trials, the random-effect model was used. Otherwise, the fixed-effect model was used. Publication bias was evaluated using a funnel plot.

3. Results

3.1. Literature selection

The literature search is presented in Figure 1. A total of 2350 articles were retrieved, and 2324 studies were excluded after examining the titles and abstracts. After reading the full text of the remaining 26 trials, we identified 12 eligible studies for inclusion in the meta-analysis that strictly fulfilled the inclusion and exclusion criteria. Three trials investigated comparison after 3 months of CNI-based therapy [12,15,16], two trials investigated comparison after12 months of CNI-based therapy [10,18,19], and four trials that investigated comparison in recipients with allograft dysfunction [20–23].

3.2. Study characteristics and quality assessment

A total of 950 eligible renal transplant recipients were included in the meta-analysis, of whom 497 were treated with MMF, and 453 were treated with CNI. All studies reported randomization. Six studies reported random

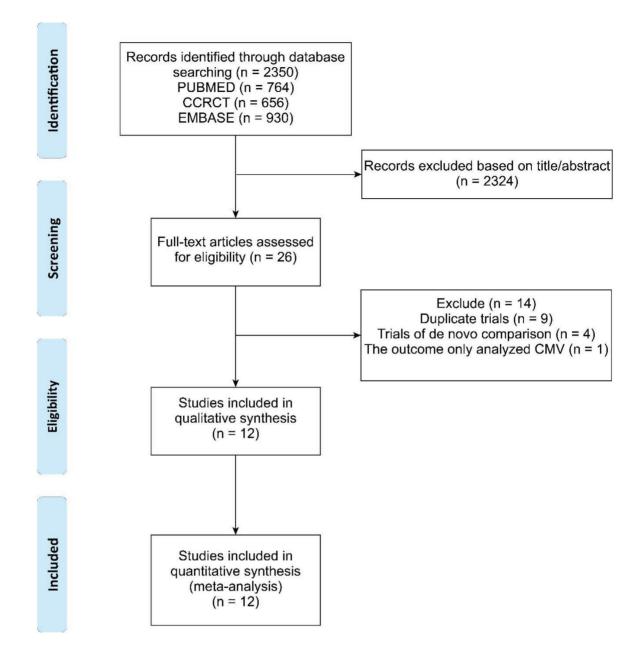


Figure 1. Flow chart of literature selection.

sequence generation and allocation concealment [11,17,18,20,21,23]; however, no studies referred to double-blinding. The baseline characteristics of the included studies are summarized in Table 1, and the risk of bias are showed in Figure 2.

3.3. Glomerular filtration rate

Nine studies that reported changes of the GFR were included in the meta-analysis. Compared to CNI, MMF significantly improved the GFR after CNI-based therapy (MD 8.47, 95%CI (7.79, 9.14), p < 0.00001) (Figure 3). Subgroup analysis showed similar effects in comparison after 3, 6, or 12 months of CNI-based therapy (3 months: MD 10.11, 95%CI (5.77, 14.46), p < 0.00001; 6 months: MD 8.40, 95%CI (7.71, 9.09), p < 0.00001 or 12 months: MD 19.00, 95%CI (5.02, 32.98), p = 0.008) (Figure 3). Furthermore, MMF also significantly improved the GFR in comparison of recipients with allograft dysfunction compared with CNI (MD 7.20, 95%CI (4.09, 10.32), p < 0.00001) (Figure 3).

Subgroup Study		N	Mean age (year	rs)*	Sex	Intervention	Duration	
Subgroup	Study	N	Recipient	donor	(M/F)	Intervention	(M)	
Comparison	Hoerning 2012	T: 6 C: 8	T: 46 ± 9.8 C: 60 ±11.5	_	T: 2/4 C: 3/5	MPA +CsA +Bas+ CS for 3 mo, then T: EVL+ CS+ MPA (0.72g b.i.d); C: EVL+CS+ Low-CsA (target level:50– 75ng/mL)	12	
months of CNI-based therapy	CNI-based Hazzan 2005		T: 45.1 ± 11.2 C: 42.5 ± 12.1	T: 40.0 ± 14.0 C: 36.7 ± 13.1	T: 32/22 C: 36/18	MMF+ CsA + ATG+ CS for 3 mo, then T: CS+ MMF (2g q.d); C: CS+ CsA (target level:100–300ng/mL)	12	
	Schnulle 2002	T: 44 C: 40	T: 44.7 ± 13.3 C: 51.3 ± 11.5	T: 40.7 ± 15.3 C: 47.7 ± 15.4	T: 32/12 C: 22/18	MMF+ CsA + CS for 3 mo, then T: CS+ MMF (1g b.i.d); C: CS+ CsA (target level:100–250ng/mL)	12	
Comparison after 6	Stevens 2014	T:90 C:88	T:47.9 ± 12.1 C:46.5 ± 11.6	T: 39.3 ± 13.1 C: 42.6 ± 12.1	T: 62/28 C: 59/29	TAC+ SRL+ATG+ CS for 6 mo, then T: SRL+ MMF (1g b.i.d); C: SRL+ TAC (target level:2–4ng/mL)	24	
months of CNI-based therapy	Mourer 2012	T: 79 C: 79	T: 52.5 ± 10.8 C: 52.7 ± 13.0	B T: 43.3 ± 16.6 T: 56/23 T: CS+ MMF (. C: 42.5 ± 14.4 C: 54/25 CS+ CsA (AUC)		MMF+ CsA or TAC + CS for 6 mo, then T: CS+ MMF (AUC:75ug.hr/ml); C: CS+ CsA (AUC3250ng.hr/ml) or TAC (AUC120ng.hr/mL)	36	
	Asberg 2013	T: 20 C: 19	T: 63.0 ± 11.2 C: 56.4 ± 13.4	_	T: 12/8 C: 14/5	MMF+ CsA+ CS for 12 mo, then T: CS+ MMF (2g q.d); C: CS+ CsA (target level:75–125ng/mL)	12	
Comparison after 12 months of CNI-based therapy	Albano 2012	T:15 C:15	T:58.8 ± 7.6 C:62.3 ± 9.5	T: 64.7 ± 12.0 C: 62.9 ± 9.8	T: 13/2 C: 11/4	CsA +EVL+ CS for 12 mo, then T: EVL+ CS+ MMF (0.72g b.i.d); C: EVL+ CS+ CsA (target level:200–450ng/ mL)	12	
шстару	Cransberg 2007	T: 18 C: 18	T: 11.9ª C: 10.9ª	_	T: 8/10 C: 14/4	MMF+ CsA+ CS for 12 mo, then T: CS+ MMF (0.6g b.i.d); C: CS+ CsA (target level:150–200ng/mL)	24	
	Frimat 2006	T:70 C: 31	T:43.8 ± 10.6 C:44.7 ± 11.1	_	T:55/15 C:27/4	T: MMF (2g q.d) +half dose of CsA (target level: not available) C: CsA standard- dose (target level:>80ng/mL)	24	
Comparison in allograft	Dudley 2005	T: 73 C: 70	T:43(18-63) ^b C:43(18-63) ^b	T:43.8(13-72) ^b C:34.8(10-65) ^b	T: 45/28 C: 44/26	T:CS+ MMF (2g q.d) C: CsA-based standard therapy (target level:>80ng/mL)	14	
dysfunction recipients	Stoves 2004	T: 13 C: 16	_	_	_	T: MMF (1g b.i.d) + reduced dose of CsA (target level:75–100ng/mL) C: CsA standard- dose (target level: unit standard)	6	
	Mcgrath 2001	T: 15 C: 15	T: 50.4 ± 8.3 C: 42.6 ± 3.1	T: 41.8 ± 5.0 C: 40.9 ± 2.7	T: 10/5 C: 10/5	T: MMF+ CS (2g q.d) C: AZA+ CS+ TAC (target level:8–12ng/ mL)	8	

MMF, mycophenolate mofetil; CNIs, calcineurin inhibitors; CsA, cyclosporine A; TAC, tacrolimus; TAC-Elim, TAC-elimination; SRL, sirolimus; ATG, antithymocyte globulin; Bas, basiliximab; Dac, daclizumab; EVL, everolimus; AZA, azathioprine; MPA, mycophenolate sodium; CS, corticosteroids; KT: kidney transplantation. *Data are represented as mean ± standard deviation (SD); — means data deficiency; T, treatment group; C, control group; N, number; ^a Values were expressed as mean; ^b Values were mean (range); AUC, area under the time-blood concentration curve.

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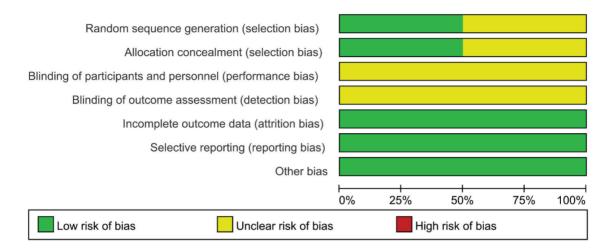


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.4. Graft loss

No significant difference in graft loss (including death) was observed between the MMF group and the CNI group after CNI-based therapy (RR 1.01, 95%CI (0.62, 1.67), p = 0.95). Subgroup analysis showed similar effects in comparison after 3, 6, or 12 months of CNI-based therapy (3 months: RR 2.73, 95%CI (0.11, 65.24), p = 0.53; 6 months: RR 0.68, 95%CI (0.32, 1.42), p = 0.30 or 12 months: RR 1.60, 95%CI (0.80, 3.23), p = 0.19). Similar effect was also seen in comparison of recipients with allograft dysfunction (RR 0.91, 95%CI (0.36, 2.33), p = 0.84). The fixed-effect model was used for the meta-analysis given that no heterogeneity was noted among the included studies. One study was excluded for analysis due to the absence of graft loss data [15]. The results are presented in Figure 4.

3.5. Mortality

Eleven included studies reported mortality data. There were no significant differences in mortality between the MMF and CNI groups after CNI-based therapy (RR 0.71, 95%CI (0.37, 1.35), p = 0.30). Subgroup analysis showed similar effects in comparison after 3, 6, or 12 months of CNI-based therapy (3 months: could not be estimated; 6 months: RR 0.63, 95%CI (0.25, 1.58), p = 0.33 or 12 months: RR 0.82, 95%CI (0.34, 2.01), p = 0.67). Moreover, there was also no significant difference in mortality between the MMF and CNI groups in comparison of recipients with allograft dysfunction (RR 6.72, 95%CI (0.35, 127.71), p = 0.21). The fixed-effect model was used given the lack of heterogeneity among the studies. The results are presented in Figure 5.

3.6. Acute rejection

MMF was associated with increased episodes of acute rejection (biopsy proven) compared with CNI after CNIbased therapy (RR 2.05, 95%CI (1.27, 3.32), p = 0.003). Similar effect was seen in comparison after 3 months of CNI-based therapy (RR 2.90, 95%CI (1.10, 7.64), p = 0.03) when subgroup analysis was performed. However, no significant differences in acute rejection were found between the MMF and CNI groups for comparison after 6 or 12 months of CNI-based therapy (6 months: RR 1.59, 95%CI (0.83, 3.02), p = 0.16 or 12 months: RR 2.51, 95%CI (0.81, 7.72), p = 0.11). No acute rejection episodes occurred in recipients with allograft dysfunction. The fixed-effect model was used given the lack of heterogeneity among the studies. The results are presented in Figure 6.

3.7. Adverse events

A comparison of adverse events in the MMF and CNI groups is shown in Table 2. The random-effect model was used if significant heterogeneity (I²>50% and p < 0.1) was presented among studies. Otherwise, the fixed-effect model was used instead. The results indicated that MMF reduced the occurrence rate of proteinuria (RR 0.63, 95%CI (0.43, 0.92), p = 0.02), although the opposite effects were presented for anemia (RR 2.36, 95%CI (1.46, 3.81), p = 0.0005) and diarrhea (RR 5.36, 95%CI (2.66, 10.80), p = 0.00001). The incidence rates of infection, NODAT, malignancies, and hypertension were similar between the MMF and CNI groups.

3.8. Publication bias

A funnel plot of acute rejection was examined to evaluate publication bias. As shown in Figure 7, no publication bias was observed.

4. Discussion

Kidney transplantation, which is a form of RRT, is an efficient and preferable option for ESRD patients [3]. However, acute rejection and graft loss represent the

tazzan 2005 64.7 18.7 54 56.5 18 54 1.0% 8.20 $[1.28, 15.12]$ toerning 2012 54.8 14.4 6 42.9 19.7 8 0.1% 11.90 $[-5.96, 29.76]$ Acure2012 59.5 2.1 71 51.1 2.1 73 97.3% 8.40 $[7.71, 9.09]$ Schnulle 2002 73.2 14.9 41 61.9 11.8 39 1.3% 11.30 $[5.42, 17.18]$ teterogeneity: Chi ² = 3.26, df = 4 (P = 0.52); P = 0% test for overall effect: Z = 24.52 (P < 0.00001) 1.1.2 Comparison after 3 mo of CNI-based therapy tazzan 2005 64.7 18.7 54 56.5 18 54 39.4% 8.20 $[1.28, 15.12]$ toerning 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 $[-5.96, 29.76]$ toibubtat $[95\% CI)$ 101 101 101 100.0% 10.11 $[5.77, 14.46]$ teterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); P = 0% test for overall effect: Z = 4.56 (P < 0.00001) 1.3 Comparison after 6 mo of CNI-based therapy toubtat $[95\% CI)$ 101 101 100.0% 8.40 $[7.71, 9.09]$ valubtat $[95\% CI)$ 71 7 73 100.0% 8.40 $[7.71, 9.09]$ teterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); P = 0% test for overall effect: Z = 4.00 (P < 0.00001) 1.3 Comparison after 6 mo of CNI-based therapy toucre2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 $[7.71, 9.09]$ teterogeneity: Not applicable test for overall effect: Z = 24.00 (P < 0.00001) 1.4 101 100 19.00 $[5.02, 32.98]$ teterogeneity: Not applicable test for overall effect: Z = 2.66 (P = 0.008) 1.5 Comparison for allograft dysfunction Dudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 $[1.49, 9.51]$ trimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 $[3.72, 19.28]$ towes 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 $[-8.91, 14.51]$			MMF			CNI			Mean Difference	Mean Difference
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Advers2012 59.5 2.1 71 61.1 2.1 73 97.3% 8.40 [7.71, 9.09] Charles 2002 73.2 14.9 41 61.9 11.8 39 1.3% 11.30 [5.42, 17.18] Heterogeneity: Chi ² = 3.26, df = 4 (P = 0.52); P = 0% rest for overall effect: $Z = 24.52$ (P < 0.00001) 1.1.2 Comparison after 3 mo of CNI-based therapy Hazzan 2005 64.7 18.7 54 56.5 18 54 39.4% 8.20 [1.28, 15.12] Hoerning 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 [-5.96, 29.76] Schnulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] Hotoral gives Chi ² = 0.49, df = 2 (P = 0.78); P = 0% rest for overall effect: $Z = 4.56$ (P < 0.00001) 101 101 100.0% 10.11 [5.77, 14.46] Heterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); P = 0% rest for overall effect: $Z = 4.56$ (P < 0.00001) 1.1.2 Comparison after 6 mo of CNI-based therapy Hourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] Heterogeneity: Not applicable rest for overall effect: $Z = 24.00$ (P < 0.00001) 1.4 Comparison after 12 mo of CNI-based therapy Habao 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] Heterogeneity: Not applicable rest for overall effect: $Z = 2.66$ (P = 0.008) 1.5 Comparison for rallograft dysfunction Nucley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] rimat 2006 56.2 16.6 53 45.1 16.4 27 166.% 11.10 [3.77, 18.73] Hoy 2005 56.2 16.6 53 45.1 16.4 27 166.% 11.10 [3.77, 18.73] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.30); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Heteroge	Hazzan 2005	64.7	18.7	54	56.5	18	54	1.0%	8.20 [1.28, 15.12]	
Schnulle 2002 73.2 14.9 41 61.9 11.8 39 1.3% 11.30 [5.42, 17.18] Jubtotal (95% Cl) 186 187 100.0% 8.47 [7.79, 9.14] Heterogeneity: Chi ² = 3.26, df = 4 (P = 0.52); P = 0% Test for overall effect: Z = 24.52 (P < 0.00001) 1.1.2 Comparison after 3 mo of CNI-based therapy Hazzan 2005 64.7 18.7 54 56.5 18 54 39.4% 8.20 [1.28, 15.12] Jobrahig 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 [5.96, 27.76] Schnulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] Jubtotal (95% Cl) 101 101 100.0% 10.11 [5.77, 14.46] Heterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); P = 0% Test for overall effect: Z = 4.56 (P < 0.00001) 1.3 Comparison after 6 mo of CNI-based therapy Hourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] Heterogeneity: Not applicable Test for overall effect: Z = 24.00 (P < 0.00001) 1.4 Comparison after 12 mo of CNI-based therapy Heterogeneity: Not applicable Test for overall effect: Z = 2.66 (P = 0.008) 1.5 Comparison for allograft dysfunction Judley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] Trimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.00 [3.72, 19.28] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Test for overall effect: Z = 4.53 (P < 0.00001) Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); P = 12% Test for overall effect: Z = 4.53 (P < 0.00001)	Hoerning 2012	54.8	14.4	6	42.9	19.7	8	0.1%	11.90 [-5.96, 29.76]	
hubtotal (95% Cl) 186 187 100.0% 8.47 [7.79, 9.14] leterogeneity: Chi ² = 3.26, df = 4 (P = 0.52); P = 0% 187 100.0% 8.47 [7.79, 9.14] iest for overall effect: Z = 24.52 (P < 0.00001)	Mourer2012	59.5	2.1	71	51.1	2.1	73	97.3%	8.40 [7.71, 9.09]	
teterogeneity: $Ch^2 = 3.26$, $df = 4$ (P = 0.52); $l^2 = 0\%$ test for overall effect: $Z = 24.52$ (P < 0.00001) 1.1.2 Comparison after 3 mo of CNI-based therapy tazzan 2005 64.7 18.7 54 56.5 18 54 39.4% 8.20 [1.28, 15.12] toeming 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 [5.96, 29.76] Schnulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] tubtotal (95% CI) 101 101 101 100.0% 10.11 [5.77, 14.46] teterogeneity: $Ch^2 = 0.49$, $df = 2$ (P = 0.78); $l^2 = 0\%$ test for overall effect: $Z = 4.56$ (P < 0.00001) 1.3 Comparison after 6 mo of CNI-based therapy Mourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] tubtotal (95% CI) 71 71 73 100.0% 8.40 [7.71, 9.09] teterogeneity: Not applicable test for overall effect: $Z = 24.00$ (P < 0.00001) 1.4 Comparison after 12 mo of CNI-based therapy Nubano 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] teterogeneity: Not applicable test for overall effect: $Z = 2.66$ (P = 0.008) 1.5 Comparison for allograft dysfunction hudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] rimmat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.72, 19.28] Koves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [8.9.1, 14.51] tubtotal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] teterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% test for overall effect: $Z = 4.53$ (P < 0.00001)	Schnulle 2002	73.2	14.9	41	61.9	11.8	39	1.3%	11.30 [5.42, 17.18]	
The st for overall effect: $Z = 24.52$ ($P < 0.00001$) 1.1.2 Comparison after 3 mo of CNI-based therapy tazzan 2005 64.7 18.7 54 56.5 18 54 39.4% 8.20 [1.28, 15.12] toerning 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 [5.62, 29.76] technulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] tubtotal (95% CI) 101 101 101 10.0% 10.11 [5.77, 14.46] telerogeneity: Chi ² = 0.49, df = 2 ($P = 0.78$); $P = 0\%$ test for overall effect: $Z = 4.56$ ($P < 0.00001$) 1.1.3 Comparison after 6 mo of CNI-based therapy tourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] teterogeneity: Not applicable test for overall effect: $Z = 24.00$ ($P < 0.00001$) 1.1.4 Comparison after 12 mo of CNI-based therapy tbatotal (95% CI) 71 73 100.0% 19.00 [5.02, 32.98] teterogeneity: Not applicable test for overall effect: $Z = 2.66$ ($P = 0.008$) 1.5 Comparison for allograft dysfunction budley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] rimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] tograth 2001 34.7 12.8 15 23.2 8.5 15 160.% 11.50 [3.72, 19.28] toterageneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$ teterogeneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$ teterogeneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$ teterogeneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$ teterogeneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$ teterogeneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$	Subtotal (95% CI)			186			187	100.0%	8.47 [7.79, 9.14]	•
$\begin{array}{c} \textbf{.1.2 Comparison after 3 mo of CNI-based therapy \\ fazzan 2005 & 64.7 & 18.7 & 54 & 56.5 & 18 & 54 & 39.4\% & 8.20 [1.28, 15.12] \\ iderning 2012 & 54.8 & 14.4 & 6 & 42.9 & 19.7 & 8 & 5.9\% & 11.90 [-5.96, 29.76] \\ ischnulle 2002 & 73.2 & 14.9 & 41 & 61.9 & 11.8 & 39 & 54.7\% & 11.30 [5.42, 17.18] \\ idubtotal (95% CI) & 101 & 101 & 100.0\% & 10.11 [5.77, 14.46] \\ idetrogeneity: Chi2 = 0.49, df = 2 (P = 0.78); i2 = 0\% \\ iest for overall effect: Z = 4.56 (P < 0.00001) \\ \textbf{.1.3 Comparison after 6 mo of CNI-based therapy \\ idourer2012 & 59.5 & 2.1 & 71 & 51.1 & 2.1 & 73 & 100.0\% & 8.40 [7.71, 9.09] \\ idubtotal (95% CI) & 71 & 73 & 100.0\% & 8.40 [7.71, 9.09] \\ idetrogeneity: Not applicable \\ iest for overall effect: Z = 24.00 (P < 0.00001) \\ \textbf{.1.4 Comparison after 12 mo of CNI-based therapy \\ ubbtotal (95% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtotal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtal (95\% CI) & 14 & 13 & 100.0\% & 19.00 [5.02, 32.98] \\ idubtal (95\% CI) & 14 & 13 & 100.0\% & 7.20 [4.09, 10.32] \\ idubtal (95\% CI) & 140 & 113 & 100.0\% & 7.20 [4.09, 10.32] \\ idubtal (95\% CI) & 140 & 113 & 100.0\% & 7.20 [4.09, 10.32] \\ idubtal (95\% CI) & 140 & 113 & 100.0\% & 7.20 [4.09, 10.32] \\ idubtal (95\% CI) & 140 & 113 & 100.0\% & 7.20 [4.09, 10.32] \\ idubtal (95\% CI) & 140 & (9.33); i2 = 12\% \\ iest for overall effect: Z = 4.53 (P < 0.00001) \\ \end{array}$	Heterogeneity: Chi ² = 3	3.26, df	= 4 (P	= 0.52);	$ ^2 = 0\%$	6				
tazzan 2005 64.7 18.7 54 56.5 18 54 39.4% 8.20 [1.28, 15.12] toeming 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 [-5.96, 29.76] schnulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] tubtotal (95% Cl) 101 101 100.0% 10.11 [5.77, 14.46] teterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); l ² = 0% rest for overall effect: Z = 4.56 (P < 0.00001) .1.3 Comparison after 6 mo of CNI-based therapy <i>Acurer2012</i> 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] tubtotal (95% Cl) 71 73 100.0% 8.40 [7.71, 9.09] teterogeneity: Not applicable rest for overall effect: Z = 24.00 (P < 0.00001) .1.4 Comparison after 12 mo of CNI-based therapy <i>Wano</i> 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] teterogeneity: Not applicable rest for overall effect: Z = 2.66 (P = 0.008) .1.5 Comparison for allograft dysfunction Dudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] rimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] <i>Acgrath</i> 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] teterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% rest for overall effect: Z = 4.53 (P < 0.00001)	Test for overall effect:	Z = 24.5	2 (P <	0.0000	1)					
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toerning 2012 54.8 14.4 6 42.9 19.7 8 5.9% 11.90 [-5.96, 29.76] chnulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] subtotal (95% CI) 101 101 100.0% 10.11 [5.77, 14.46] teterogeneity: Chi ² = 0.49, df = 2 ($P = 0.78$); $P = 0\%$ rest for overall effect: Z = 4.56 ($P < 0.00001$) 1.3 Comparison after 6 mo of CNI-based therapy hourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] subtotal (95% CI) 71 73 100.0% 8.40 [7.71, 9.09] teterogeneity: Not applicable rest for overall effect: Z = 24.00 ($P < 0.00001$) 1.4 Comparison after 12 mo of CNI-based therapy houres 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] teterogeneity: Not applicable rest for overall effect: Z = 2.66 ($P = 0.008$) 1.5 Comparison for allograft dysfunction budley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] rimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] Acgrath 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] totves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] bubtotal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] teterogeneity: Chi ² = 3.41, df = 3 ($P = 0.33$); $P = 12\%$ rest for overall effect: Z = 4.53 ($P < 0.00001$)	Hazzan 2005	64.7	18.7	54	56.5	18	54	39.4%	8.20 [1.28, 15.12]	
Schnulle 2002 73.2 14.9 41 61.9 11.8 39 54.7% 11.30 [5.42, 17.18] Subtotal (95% CI) 101 101 100.0% 10.11 [5.77, 14.46] Heterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); l ² = 0% rest for overall effect: Z = 4.56 (P < 0.00001) .1.3 Comparison after 6 mo of CNI-based therapy Acurer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] Heterogeneity: Not applicable rest for overall effect: Z = 24.00 (P < 0.00001) .1.4 Comparison after 12 mo of CNI-based therapy Abano 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] Heterogeneity: Not applicable rest for overall effect: Z = 2.66 (P = 0.008) .1.5 Comparison for allograft dysfunction Dudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] rimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] Acgrath 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] Nototal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% rest for overall effect: Z = 4.53 (P < 0.00001)	Hoerning 2012									
Subtotal (95% Cl) 101 101 101 101 101 101 100.0% 10.11 [5.77, 14.46] Heterogeneity: Chi ² = 0.49, df = 2 (P = 0.78); I ² = 0% iest for overall effect: Z = 4.56 (P < 0.00001)	Schnulle 2002	73.2	14.9	41	61.9	11.8	39			
The set for overall effect: $Z = 4.56 (P < 0.00001)$ 1.3 Comparison after 6 mo of CNI-based therapy Mourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] Mourer2012 59.5 2.1 71 51.1 2.1 73 100.0% 8.40 [7.71, 9.09] Heterogeneity: Not applicable Test for overall effect: $Z = 24.00 (P < 0.00001)$ 1.4 Comparison after 12 mo of CNI-based therapy Ubano 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] Heterogeneity: Not applicable Test for overall effect: $Z = 2.66 (P = 0.008)$ 1.5 Comparison for allograft dysfunction Dudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] Trimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] Acgraft 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] Stoves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] Subtotal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% Test for overall effect: $Z = 4.53 (P < 0.00001)$	Subtotal (95% CI)			101			101	100.0%		•
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$\begin{array}{c} \textbf{i} \textbf{teterogeneity: Not applicable} \\ \hline \textbf{rest for overall effect: } Z = 24.00 (P < 0.0001) \\ \textbf{.1.4 Comparison after 12 mo of CNI-based therapy} \\ \textbf{whano 2012} & 55 & 18 & 14 & 36 & 19 & 13 & 100.0\% & 19.00 & [5.02, 32.98] \\ \textbf{subtotal (95\% CI)} & 14 & 13 & 100.0\% & 19.00 & [5.02, 32.98] \\ \textbf{teterogeneity: Not applicable} \\ \hline \textbf{rest for overall effect: } Z = 2.66 (P = 0.008) \\ \textbf{.1.5 Comparison for allograft dysfunction} \\ \textbf{Dudley 2005} & 41.7 & 10.9 & 61 & 36.2 & 11.1 & 55 & 60.3\% & 5.50 & [1.49, 9.51] \\ \hline \textbf{rimat 2006} & 56.2 & 16.6 & 53 & 45.1 & 16.4 & 27 & 16.6\% & 11.10 & [3.47, 18.73] \\ \hline \textbf{Acgrath 2001} & 34.7 & 12.8 & 15 & 23.2 & 8.5 & 15 & 16.0\% & 11.50 & [3.72, 19.28] \\ \hline \textbf{stoves 2004} & 32.2 & 15.3 & 11 & 29.4 & 15.2 & 16 & 7.1\% & 2.80 & [-8.91, 14.51] \\ \hline \textbf{subtotal (95\% CI)} & 140 & 113 & 100.0\% & 7.20 & [4.09, 10.32] \\ \hline \textbf{teterogeneity: Chi^2 = 3.41, df = 3 (P = 0.33); ^2 = 12\% \\ \hline \textbf{rest for overall effect: } Z = 4.53 (P < 0.00001) \\ \end{array}$		59.5	2.1		51.1	2.1				
The set for overall effect: $Z = 24.00 (P < 0.00001)$.1.4 Comparison after 12 mo of CNI-based therapy Name 2012 55 18 14 36 19 13 100.0% 19.00 [5.02, 32.98] Subtotal (95% CI) 14 13 100.0% 19.00 [5.02, 32.98] Heterogeneity: Not applicable Test for overall effect: $Z = 2.66 (P = 0.008)$.1.5 Comparison for allograft dysfunction Dudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] Frimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] Mograth 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] Stoves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] Subtotal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% Test for overall effect: $Z = 4.53 (P < 0.0001)$				71			73	100.0%	8.40 [7.71, 9.09]	•
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The set for overall effect: $Z = 2.66$ (P = 0.008) .1.5 Comparison for allograft dysfunction Dudley 2005 41.7 10.9 61 36.2 11.1 55 60.3% 5.50 [1.49, 9.51] Frimat 2006 56.2 16.6 53 45.1 16.4 27 16.6% 11.10 [3.47, 18.73] Acgrath 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] Stoves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] Subtotal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% Test for overall effect: Z = 4.53 (P < 0.00001)	Subtotal (95% CI)			14			13	100.0%	19.00 [5.02, 32.98]	
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Acgrath 2001 34.7 12.8 15 23.2 8.5 15 16.0% 11.50 [3.72, 19.28] Stoves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] Subtotal (95% Cl) 140 113 100.0% 7.20 [4.09, 10.32] Heterogeneity: Chi² = 3.41, df = 3 (P = 0.33); l² = 12% est for overall effect: Z = 4.53 (P < 0.00001)	Frimat 2006									
Stoves 2004 32.2 15.3 11 29.4 15.2 16 7.1% 2.80 [-8.91, 14.51] Subtotal (95% CI) 140 113 100.0% 7.20 [4.09, 10.32] Heterogeneity: Chi ² = 3.41, df = 3 (P = 0.33); l ² = 12% 'est for overall effect: Z = 4.53 (P < 0.00001)	Mcgrath 2001									
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Test for overall effect: Z = 4.53 (P < 0.00001)	Subtotal (95% CI)									•
Test for overall effect: Z = 4.53 (P < 0.00001)		3.41, df	= 3 (P	= 0.33)	² = 12	2%				
			•	,						
-20 -10 0 10 20										
-20 -10 0 10 20										
CNI MMF										

Figure 3. Forest plot of glomerular filtration rate.

clinical concerns after kidney transplantation (KT). Thus, safe and effective immunosuppressive therapy is needed to reduce graft failure caused by acute rejection and CNI-related nephrotoxicity in the most prevalent CNI-based immunosuppressive regimes [24, 25]. As a nonnephrotoxic immunosuppressive drug, MMF improves renal function without acute rejection after CNI withdrawal [26–28]. Moreover, two studies reported that MMF could have nephroprotective properties [29,30]. Recently, a meta-analysis suggested that CNI sparing strategies with adjunctive MMF after KT can improve renal function, possibly reduce graft loss, and increase rejection rates only after elective CNI elimination [9]. Thus, MMF may enhance renal function but not increase rejection and

nephrotoxicity, consequently improving patient and graft survival.

This is the first meta-analysis to evaluate the comparison and its timing between MMF and CNI as maintenance immunosuppression for kidney transplant recipients. We analyzed the data of 12 studies that compared the use of MMF and CNI as maintenance immunosuppression for kidney transplant recipients. The results of our present meta-analysis indicate that MMF significantly improved the GFR not only in the comparison performed after 3, 6, or 12 months of CNI-based therapy but also in the comparison of recipients with allograft dysfunction. This result suggested the ongoing benefits of using MMF instead of CNI not only in patients with deteriorating renal

	MMF		CNI			Risk Ratio	Risk Ratio
Study or Subgroup				Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
2.1.1 Comparison aft	er CNI-bas	sed the	erapy				
Albano 2012	0	14	0	13		Not estimable	
Asberg 2013	11	20	7	19	29.6%	1.49 [0.73, 3.04]	+- -
Cransberg 2007	1	21	0	23	2.0%	3.27 [0.14, 76.21]	
Hazzan 2005	0	54	0	54		Not estimable	
Mourer2012	5	79	7	79	28.8%	0.71 [0.24, 2.16]	
Schnulle 2002	1	44	0	40	2.2%	2.73 [0.11, 65.24]	
Stevens 2014	6	90	9	88	37.5%	0.65 [0.24, 1.75]	
Subtotal (95% CI)		322		316	100.0%	1.01 [0.62, 1.67]	•
Total events	24		23				
Heterogeneity: Chi ² = 3	3.20, df = 4	4 (P = 0	.53); l² =	0%			
Test for overall effect:	Z = 0.06 (F	P = 0.9	5)				
2.1.2 Comparison aft	er 3 mo of	CNI-b	ased the	rapy			
Hazzan 2005	0	54	0	54		Not estimable	
Schnulle 2002	1	44	0	40	100.0%	2.73 [0.11, 65.24]	
Subtotal (95% CI)		98		94	100.0%	2.73 [0.11, 65.24]	
Total events	1		0				
Heterogeneity: Not app	plicable						
Test for overall effect:		P = 0.5	3)				
2.1.3 Comparison aft	er 6 mo of	CNI-b	ased the	rapy			
Mourer2012	5	79	7	79	43.5%	0.71 [0.24, 2.16]	_ _
Stevens 2014	6	90	9	88	56.5%	0.65 [0.24, 1.75]	
Subtotal (95% CI)	0	169	5	167	100.0%	0.68 [0.32, 1.42]	
Total events	11		16				-
Heterogeneity: Chi ² = (1 (P = 0)		0%			
Test for overall effect:				070			
			,				
2.1.4 Comparison aft	er 12 mo o	of CNI-	hasod th	erapy			
	0	14	0	13		Not estimable	
Asberg 2013		14 20	0 7	13 19	93.8%	Not estimable 1.49 [0.73, 3.04]	
Asberg 2013 Cransberg 2007	0	14 20 21	0	13 19 23	6.2%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21]	
Asberg 2013 Cransberg 2007	0 11	14 20	0 7 0	13 19		1.49 [0.73, 3.04]	 ◆
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events	0 11 1 12	14 20 21 55	0 7 0 7	13 19 23 55	6.2%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21]	 ◆
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (0 11 1 12 0.24, df = 7	14 20 21 55	0 7 0 7 0.63); I ² =	13 19 23 55	6.2%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21]	•
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (0 11 1 12 0.24, df = 7	14 20 21 55	0 7 0 7 0.63); I ² =	13 19 23 55	6.2%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21]	
Albano 2012 Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (Test for overall effect: 2.1.5 Comparison for	0 11 1 2 0.24, df = 7 Z = 1.32 (F	14 20 21 55 1 (P = 0 P = 0.19	0 7 0 9.63); I ² =	13 19 23 55	6.2%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21]	
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (Test for overall effect:	0 11 1 2 0.24, df = 7 Z = 1.32 (F	14 20 21 55 1 (P = 0 P = 0.19	0 7 0 9.63); I ² =	13 19 23 55	6.2%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21]	
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (Test for overall effect: 2.1.5 Comparison for Dudley 2005	0 11 1 0.24, df = ⁻ Z = 1.32 (F	14 20 21 55 1 (P = 0 P = 0.19 dysfur	0 7 0.63); I ² = 9)	13 19 23 55 0%	6.2% 100.0%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21] 1.60 [0.80, 3.23]	
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (Test for overall effect: 2.1.5 Comparison for Dudley 2005 Frimat 2006	0 11 1 0.24, df = ⁻ Z = 1.32 (F allograft 5	14 20 21 55 1 (P = 0 P = 0.19 dysfur 73	0 7 0.63); ² = 9) oction 4	13 19 23 55 0%	6.2% 100.0% 48.5%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21] 1.60 [0.80, 3.23] 1.20 [0.34, 4.28]	
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Test for overall effect: 2.1.5 Comparison for Dudley 2005 Frimat 2006 Mcgrath 2001	0 11 1 0.24, df = 7 Z = 1.32 (F allograft 5 1	14 20 21 55 1 (P = 0 P = 0.19 dysfur 73 70	0 7 0.63); ² = 9) (ction 4 1	13 19 23 55 0% 70 31	6.2% 100.0% 48.5% 16.5%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21] 1.60 [0.80, 3.23] 1.20 [0.34, 4.28] 0.44 [0.03, 6.85]	
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 0 Test for overall effect: 2.1.5 Comparison for Dudley 2005 Frimat 2006 Mcgrath 2001 Stoves 2004	0 11 1 0.24, df = 7 Z = 1.32 (F r allograft 5 1 0	14 20 21 55 1 (P = 0 P = 0.19 dysfur 73 70 15	0 7 0.63); l ² = 9) cction 4 1 2	13 19 23 55 0% 70 31 15 16	6.2% 100.0% 48.5% 16.5% 29.7%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21] 1.60 [0.80, 3.23] 1.20 [0.34, 4.28] 0.44 [0.03, 6.85] 0.20 [0.01, 3.85]	
Asberg 2013 Cransberg 2007 Subtotal (95% CI) Total events Heterogeneity: Chi ² = (Test for overall effect: 2.1.5 Comparison for	0 11 1 0.24, df = 7 Z = 1.32 (F r allograft 5 1 0	14 20 21 55 1 (P = 0 P = 0.19 dysfur 73 70 15 13	0 7 0.63); l ² = 9) cction 4 1 2	13 19 23 55 0% 70 31 15 16	6.2% 100.0% 48.5% 16.5% 29.7% 5.4%	1.49 [0.73, 3.04] 3.27 [0.14, 76.21] 1.60 [0.80, 3.23] 1.20 [0.34, 4.28] 0.44 [0.03, 6.85] 0.20 [0.01, 3.85] 3.64 [0.16, 82.62]	
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function but also in patients with stable renal function after KT regardless of the timing of the alternative. Interestingly, our present meta-analysis also found that MMF may increase the risk of acute rejection in the comparison performed after 3 months of CNI-based therapy, but no increase was noted in the comparison performed after 6 or 12 months of CNI-based therapy. Taken together, the

results of this analysis indicate that MMF offers similar efficiency as CNI after at least 6 months of CNI-based therapy as maintenance immunosuppression for kidney transplant recipients, while MMF appears safer than CNI, as reflected by its protective effects on renal function. However, this finding must be further demonstrated by more large-scale, high-quality, and long-term studies. In

Study or Subgroup Events Total Events Total Weight M-H. Fixed. 95% CI M-H. Fixed. 95		MMF		CNI			Risk Ratio	Risk Ratio
31.1 Comparison after CNI-based therapy Nbano 2012 0 14 1 13 8.3% 0.31 [0.01, 7.02] Steper 2013 6 20 6 19 92.8% 0.95 [0.37, 2.44] Crassberg 2007 0 21 0 23 Not estimable Viscard 2012 4 79 6 79 32.0% 0.57 [0.20, 2.27] Schulle 2002 0 44 0 Not estimable Not estimable Storburk 2020 0 44 0 Not estimable Storburk 2014 3 90 5 88 28.9% 0.59 [0.14, 2.38] Total events 13 18 180.0% 0.71 [0.37, 1.35] 18 Storburk (95% CI) 98 94 Not estimable 95 Storburk (95% CI) 98 94 Not estimable 96 Storburk (95% CI) 98 94 Not estimable 96 Storburk (95% CI) 98 94 Not estimable 92.05 93.72.24 Storburk (95% CI) 169 167 100.0% 0.59 [0	Study or Subaroup		Total		Total	Weight		
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$ \begin{array}{c} \mbox{Cransborg 2007} & 0 & 21 & 0 & 23 \\ \mbox{Lazzan 2005} & 0 & 54 & 0 & 54 \\ \mbox{Lazzan 2005} & 0 & 54 & 0 & 54 \\ \mbox{Lazzan 2005} & 0 & 44 & 0 & 40 \\ \mbox{Lazzan 2005} & 0 & 44 & 0 & 40 \\ \mbox{Lazzan 2012} & 4 & 79 & 6 & 79 & 32.0\% & 0.67 (0.20, 2.27] \\ \mbox{Schulle 2002} & 0 & 44 & 0 & 40 \\ \mbox{Schulle 2002} & 0 & 44 & 0 & 40 \\ \mbox{Schulle 2002} & 0 & 44 & 0 & 58 & 26.9\% \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Lazzan 2005} & 0 & 54 & 0 & 54 \\ \mbox{Lazzan 2005} & 0 & 54 & 0 & 54 \\ \mbox{Lazzan 2005} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 44 & 0 & 40 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 54 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 56 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 56 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 56 \\ \mbox{Schulle 2002} & 0 & 54 & 0 & 56 \\ \mbox{Schulle 2002} & 0 & 56 & 58 & 45.7\% & 0.59 [0.42, 2.38] \\ \mbox{Schulle 2005} & 0 & 7 & 11 \\ \mbox{Schulle 3002} & 0 & 14 & 1 & 13 & 20.1\% & 0.31 [0.01, 7.02] \\ \mbox{Schulle 2013} & 6 & 20 & 6 & 7 \\ \mbox{Schulle 2013} & 6 & 20 & 6 & 7 \\ \mbox{Schulle 2013} & 6 & 7 \\ \mbox{Schull 2013} & 0 & 14 & 12 & 200 \\ \mbox{Schull 2013} & 0 & 15 & 0 \\ \mbox{Schull 2013} & 0 & 15 & 0 \\ \mbox{Schull 2014} & 0 & 15 & 0 & 15 \\ \mbox{Schull 2016} & 0 & 15 & 0 & 15 \\ \mbox{Schull 2016} & 0 & 15 & 0 & 15 \\ \mbox{Schull 2016} & 0 & 15 & 0 & 15 \\ \mbox{Schull 2016} & 0 & 15 & 0 & 15 \\ \mbox{Schull 2016} & 0 & 15 &$								-+-
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Figure 5. Forest plot of mortality.

addition, MMF is associated with a reduced incidence of proteinuria, whereas the opposite effects were noted for anemia and diarrhea compared to CNI.

Several limitations to this meta-analysis should be noted. Above all, most of the included trials had small samples and were not multicenter RCTs. In addition, no studies were double-blinded. Furthermore, data from some studies were unavailable or deficient and could not be obtained from the original authors, which may weaken the evidence of the results. Moreover, given that a few studies in each subgroup and several studies with a short duration, the efficacy and safety of MMF for renal transplant recipients must be proven by further large-scale and long-term studies. Finally, some heterogeneity in clinical features, such as the immunosuppressive therapy and drug dosages, was noted; however, the included studies had similar baseline characteristics. Thus, more large-scale, high-quality, and multicenter RCTs with longer duration

MMFCNIRisk RatioRisk RatioStudy or SubgroupEventsTotalEventsTotalWeightM-H, Fixed, 95% CIM-H, Fixed, 95% CIAlbano 20120141137.0%0.31 [0.01, 7.02]Abberg 20136200192.3%12.38 [0.75, 205.75]Cransberg 20073212238.6%1.64 [0.30, 8.89]Hazzan 2005105435413.5%3.33 [0.97, 11.45]Mourer20124792799.0%2.00 [0.38, 10.61]Schnulle 20025442409.4%2.27 [0.47, 11.07]Stevens 20141790118850.1%1.51 [0.75, 3.04]Subtotal (95% CI)322316100.0%2.05 [1.27, 3.32]Total events4521Heterogeneity: Chi² = 4.39, df = 6 (P = 0.62); l² = 0%Test for overall effect: Z = 2.92 (P = 0.003)4.1.2 Comparison after 3 mo of CNI-based therapyHazzan 20051054354Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); l² = 0%Test for overall effect: Z = 2.15 (P = 0.03)4.1.3 Comparison after 6 mo of CNI-based therapyMourer20124792794.1.3 Comparison after 6 mo of CNI-based therapyMourer20124792794.1.3 Comparison after 6 mo of CNI-based therapyMourer2012479247927915.2% </th <th></th>	
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Subtotal (95% CI) 169 167 100.0% 1.59 [0.83, 3.02] Total events 21 13	
Total events 21 13	
Heterogeneity: $Chi^2 = 0.09$, $df = 1.(P = 0.76)$; $l^2 = 0.%$	
notorogonoity. On = 0.00, u = 1 (1 = 0.70), 1 = 0.0	
Test for overall effect: $Z = 1.40$ (P = 0.16)	
4.1.4 Comparison after 12 mo of CNI-based therapy	
Albano 2012 0 14 1 13 39.1% 0.31 [0.01, 7.02]	
Asberg 2013 6 20 0 19 12.9% 12.38 [0.75, 205.75]	
Cransberg 2007 3 21 2 23 48.1% 1.64 [0.30, 8.89]	
Subtotal (95% Cl) 55 55 100.0% 2.51 [0.81, 7.72]	
Total events 9 3	
Heterogeneity: Chi ² = 3.20, df = 2 (P = 0.20); I ² = 38%	
Test for overall effect: $Z = 1.60$ (P = 0.11)	
4.1.5 Comparison for allograft dysfunction	
Dudley 2005 0 73 0 70 Not estimable	
Frimat 2006 0 70 0 31 Not estimable	
Mcgrath 2001 0 15 0 15 Not estimable	
Stoves 2004 0 13 0 16 Not estimable	
Subtotal (95% CI) 0 0 Not estimable	
Total events 0 0	
Heterogeneity: Not applicable	
Test for overall effect: Not applicable	
	400
0.001 0.1 1 10	100
MMF CNI	

Figure 6. Forest plot of acute rejection (biopsy proven).

times and reduced heterogeneity are required to address the above limitations.

In conclusion, the result of our present meta-analysis is that MMF offers similar efficiency as CNI after at least 6 months of CNI-based therapy as maintenance immunosuppression for kidney transplant recipients, while MMF appears safer than CNI, as reflected by its protective effects on renal function. It is suggested that MMF followed at least 6 months of CNI-based therapy is an effective maintenance immunosuppressive regimen for kidney transplant recipients to improve renal function but not increase rejection. However, these results must be confirmed in future studies.

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Outcome	Studies	MMF group	CNI group	Heterogeneity (P, I ²)	Statistical method	Effect estimate	P value
Infection	7	156/384	117/339	0.006, 66%	Risk ratio (M-H, Random, 95%CI)	1.19(0.83, 1.73)	0.34
Anemia	5	56/250	20/211	0.61, 0%	Risk ratio (M-H, Fixed, 95%CI)	2.36 (1.46, 3.81)	0.0005
Diarrhea	5	54/281	8/235	0.32, 15%	Risk ratio (M-H, Fixed, 95%CI)	5.36 (2.66, 10.80)	0.00001
NODAT	5	25/241	28/238	0.77, 0%	Risk ratio (M-H, Fixed, 95%CI)	0.86 (0.53, 1.42)	0.56
Malignancies	4	12/254	13/198	0.77, 0%	Risk ratio (M-H, Fixed, 95%CI)	0.84 (0.39, 1.84)	0.66
Proteinuria	3	34/139	30/100	0.38,0%	Risk ratio (M-H, Fixed, 95%CI)	0.63 (0.43, 0.92)	0.02
Hypertension	2	5/88	11/85	0.35, 0%	Risk Ratio (M-H, Fixed, 95%CI)	0.46 (0.17, 1.23)	0.12

Table 2. Summary of adverse events of included studies comparing MMF with CNI groups as maintenance immunosuppression after kidney transplantation.

MMF, mycophenolate mofetil; CNI, calcineurin inhibitor; NODAT, new-onset diabetes mellitus after transplantation.

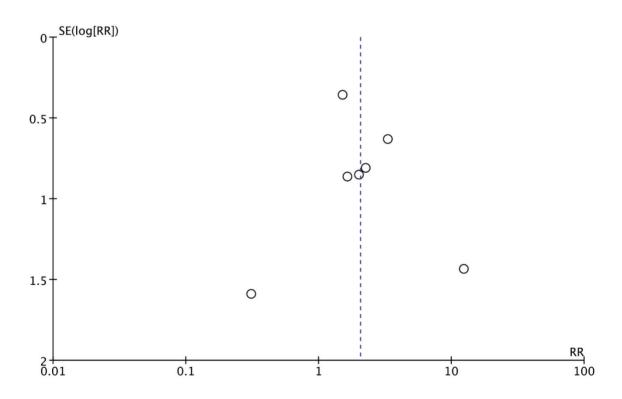


Figure 7. Funnel plot for acute rejection.

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