Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients (Review)

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Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients

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A B S T R A C T

Background

Calcineurin inhibitors (CNI) can reduce acute transplant rejection and immediate graft loss but are associated with significant adverse effects such as hypertension and nephrotoxicity which may contribute to chronic rejection. CNI toxicity has led to numerous studies investigating CNI withdrawal and tapering strategies. Despite this, uncertainty remains about minimisation or withdrawal of CNI.

Objectives

This review aimed to look at the benefits and harms of CNI tapering or withdrawal in terms of graft function and loss, incidence of acute rejection episodes, treatment-related side effects (hypertension, hyperlipidaemia) and death.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 11 October 2016 through contact with the Information Specialist using search terms relevant to this review. Studies contained in the Specialised Register are identified through search strategies specifically designed for CENTRAL, MEDLINE, and EMBASE; handsearching conference proceedings; and searching the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

All randomised controlled trials (RCTs) where drug regimens containing CNI were compared to alternative drug regimens (CNI withdrawal, tapering or low dose) in the post-transplant period were included, without age or dosage restriction.

Data collection and analysis

Two authors independently assessed studies for eligibility, risk of bias, and extracted data. Results were expressed as risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CI).

Main results

We included 83 studies that involved 16,156 participants. Most were open-label studies; less than 30% of studies reported randomisation method and allocation concealment. Studies were analysed as intent-to-treat in 60% and all pre-specified outcomes were reported in 54 studies. The attrition and reporting bias were unclear in the remainder of the studies as factors used to judge bias were reported inconsistently. We also noted that 50% (47 studies) of studies were funded by the pharmaceutical industry.

We classified studies into four groups: CNI withdrawal or avoidance with or without substitution with mammalian target of rapamycin inhibitors (mTOR-I); and low dose CNI with or without mTOR-I. The withdrawal groups were further stratified as avoidance and withdrawal subgroups for major outcomes.

CNI withdrawal may lead to rejection (RR 2.54, 95% CI 1.56 to 4.12; moderate certainty evidence), may make little or no difference to death (RR 1.09, 95% CI 0.96 to 1.24; moderate certainty), and probably slightly reduces graft loss (RR 0.85, 95% CI 0.74 to 0.98; low quality evidence). Hypertension was probably reduced in the CNI withdrawal group (RR 0.82, 95% CI 0.71 to 0.95; low certainty), while CNI withdrawal may make little or no difference to malignancy (RR 1.10, 95% CI 0.93 to 1.30; low certainty), and probably makes little or no difference to cytomegalovirus (CMV) (RR 0.87, 95% CI 0.52 to 1.45; low certainty)

CNI avoidance may result in increased acute rejection (RR 2.16, 95% CI 0.85 to 5.49; low certainty) but little or no difference in graft loss (RR 0.96, 95% CI 0.79 to 1.16; low certainty). Late CNI withdrawal increased acute rejection (RR 3.21, 95% CI 1.59 to 6.48; moderate certainty) but probably reduced graft loss (RR 0.84, 95% CI 0.72 to 0.97, low certainty).

Results were similar when CNI avoidance or withdrawal was combined with the introduction of mTOR-I; acute rejection was probably increased (RR 1.43; 95% CI 1.15 to 1.78; moderate certainty) and there was probably little or no difference in death (RR 0.96; 95% CI 0.69 to 1.36, moderate certainty). mTOR-I substitution may make little or no difference to graft loss (RR 0.94, 95% CI 0.75 to 1.19; low certainty), probably makes little of no difference to hypertension (RR 0.86, 95% CI 0.64 to 1.15; moderate), and probably reduced the risk of cytomegalovirus (CMV) (RR 0.60, 95% CI 0.44 to 0.82; moderate certainty) and malignancy (RR 0.69, 95% CI 0.47 to 1.00; low certainty). Lymphoceles were increased with mTOR-I substitution (RR 1.45, 95% CI 0.95 to 2.21; low certainty).

Low dose CNI combined with mTOR-I probably increased glomerular filtration rate (GFR) (MD 6.24 mL/min, 95% CI 3.28 to 9.119; moderate certainty), reduced graft loss (RR 0.75, 95% CI 0.55 to 1.02; moderate certainty), and made little or no difference to acute rejection (RR 1.13 ; 95% CI 0.91 to 1.40; moderate certainty). Hypertension was decreased (RR 0.98, 95% CI 0.80 to 1.20; low certainty) as was CMV (RR 0.41, 95% CI 0.16 to 1.06; low certainty). Low dose CNI plus mTOR-I makes probably makes little of no difference to malignancy (RR 1.22, 95% CI 0.42 to 3.53; low certainty) and may make little of no difference to death (RR 1.16, 95% CI 0.71 to 1.90; moderate certainty).

Authors' conclusions

CNI avoidance increased acute rejection and CNI withdrawal increases acute rejection but reduced graft loss at least over the short-term. Low dose CNI with induction regimens reduced acute rejection and graft loss with no major adverse events, also in the short-term. The use of mTOR-I reduced CMV infections but increased the risk of acute rejection. These conclusions must be tempered by the lack of long-term data in most of the studies, particularly with regards to chronic antibody-mediated rejection, and the suboptimal methodological quality of the included studies.

P L A I N   L A N G U A G E   S U M M A R Y

Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients

What is the issue?

Calcineurin inhibitors (CNI, cyclosporin and tacrolimus) are an important part of treatment to suppress the immune system to prevent rejection of transplanted kidneys. However, CNI can cause high blood pressure and kidney scarring which contribute to worsening of risk factors for heart attack, stroke, and loss of the transplanted organ over time.

There are conflicting data on the results of withdrawing these drugs from kidney transplant recipients; some studies suggest improved kidney function but others report a moderate risk of developing rejection. Because of this uncertainty, we assessed the benefits and harms of CNI withdrawal or tapering in kidney transplant recipients to identify which approach was more beneficial.

What did we do?
We included 83 studies that involved more than 16,000 people in our review. Studies which compared standard dose CNI regimens with withdrawal, tapering or low dose CNI in the post-transplant period were analysed.

What did we find?
Although withdrawing CNI treatment resulted in more rejections in the short term, there was no clear change in transplanted organ failure, death, development of cancer, or infections. Replacing CNI with another group of drugs - the mTOR inhibitors - did not significantly change outcomes, except for fewer cytomegalovirus (CMV) infections. Lower CNI dose was associated with fewer episodes of kidney transplant rejection and loss, but only in the first year to up to five years after the transplant.

Conclusions
We found that the long-term outcomes for stopping or gradually reducing CNI therapy were not clear, and that mTOR inhibitors can reduce CMV infections with a higher risk of acute rejection. There were insufficient studies with long term follow-up to clearly determine which treatment is better for people who receive kidney transplants.

Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients (Review)

SUMMARY OF FINDINGS

Summary of findings for the main comparison.   Calcineurin inhibitor (CNI) withdrawal versus standard dose CNI for kidney transplant recipients

CNI withdrawal versus standard dose CNI for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: CNI withdrawal
Comparison: standard dose CNI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (studies)	Quality of the evi-dence (GRADE)
	Risk with standard dose CNI	**Risk with CNI withdrawal**			
Death Follow-up: range 9 months to 20 years	Study population		RR 1.09 (0.96 to 1.24)	2010 (14)	⊕⊕⊕⊖ MODERATE [1][2][3][4]
	225 per 1,000	245 per 1,000 (216 to 279)			
Acute rejection Follow-up: range 9 months to 15 years	Study population		RR 2.54 (1.56 to 4.12)	1666 (15)	⊕⊕⊕⊖ MODERATE [2][4][5][6]
	137 per 1,000	348 per 1,000 (214 to 564)			
GFR Follow-up: range 1 to 15 years	The mean GFR in the intervention group was 3.56 mL/min more (1.13 less to 8.25 more) than the control group		-	910 (8)	⊕⊕⊖⊖ LOW [7][8]
Graft loss Follow-up: range 9 months to 20 years	Study population		RR 0.85 (0.74 to 0.98)	2090 (16)	⊕⊕⊖⊖ LOW [1][2][9][10][11][12]
	236 per 1,000	201 per 1,000 (175 to 231)			
Adverse events: hypertension Follow-up: range 1 to 15 years	Study population		RR 0.82 (0.71 to 0.95)	950 (5)	⊕⊕⊖⊖ LOW [2][10]
	555 per 1,000	455 per 1,000 (394 to 527)			
Adverse events: CMV infection Follow-up: range 9 months to 15 years	Study population		RR 0.87 (0.52 to 1.45)	608 (7)	⊕⊕⊖⊖ LOW [1][2][10]
	98 per 1,000	86 per 1,000			

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	(51 to 143)				
Adverse events: malignancy Follow-up: range 1 to 15 years	Study population		RR 1.10 (0.93 to 1.30)	1079 (6)	⊕⊕⊖⊖ LOW [1][2][4][10]
	257 per 1,000	282 per 1,000 (239 to 334)			

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] despite different follow up times, heterogeneity not noted on analysis
[2] Most studies were ITT analysis, some small studies did not specify randomisation and allocation concealment
[3] Larger studies closer to pooled estimate on funnel plot
[4] Some studies were small with large confidence intervals, CI fails to exclude benefit or harm
[5] Heterogeneity low when biopsy-proven rejections were analysed in subgroup
[6] Smaller studies not distributed around point estimate
[7] Significant heterogeneity noted despite separating time periods of reporting GFR
[8] Only few studies reported GFR with possible attrition bias
[9] 2 large studies had more than 2 comparison groups
[10] Very few studies reported the outcome
[11] Symmetric distribution studies around estimate of effect
[12] 2 studies with high event rates skew the effect

Summary of findings 2.   Low dose calcineurin inhibitors (CNI) versus to standard dose CNI for kidney transplant recipients

Low dose CNI versus standard dose CNI for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: low dose CNI
Comparison: standard dose CNI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments

	Risk with standard dose CNI	Risk with low dose CNI				
Death Follow-up: range 6 months to 2 years	Study population		RR 0.79 (0.50 to 1.27)	3462 (15)	⊕⊕⊕⊝ MODERATE [1] [2] [3]	
	23 per 1,000	19 per 1,000 (12 to 30)				
Acute rejection Follow-up: range 6 months to 2 years	Study population		RR 0.87 (0.76 to 1.00)	3757 (19)	⊕⊕⊕⊝ MODERATE [1] [2] [4]	
	183 per 1,000	159 per 1,000 (139 to 183)				
GFR Follow-up: range 6 months to 2 years	The mean GFR in the intervention group was 4.1 mL/min more (2.07 more to 6.12 more) than the control group		-	2623 (13)	⊕⊕⊕⊝ MODERATE [5] [6] [7]	
Graft loss Follow-up: range 6 months to 2 years	Study population		RR 0.75 (0.55 to 1.02)	3286 (15)	⊕⊕⊕⊝ MODERATE [1] [2] [3] [6]	Sensitivity analysis after excluding 1 study which also involved steroid withdrawal; significant reduction in graft loss in the low dose regimen
	58 per 1,000	44 per 1,000 (32 to 60)				
Adverse events: hypertension Follow-up: range 6 months to 2 years	Study population		RR 0.84 (0.70 to 1.00)	1877 (5)	⊕⊕⊝⊝ LOW [2] [7] [8] [9]	
	218 per 1,000	184 per 1,000 (153 to 218)				
Adverse events: CMV infection Follow-up: range 6 months to 2 years	Study population		RR 1.23 (0.94 to 1.62)	1948 (6)	⊕⊕⊕⊝ MODERATE [2] [8] [10]	
	101 per 1,000	124 per 1,000 (95 to 163)				
Adverse events: malignancy Follow-up: range 6 months to 2 years	Study population		RR 0.90 (0.41 to 1.97)	1637 (5)	⊕⊕⊝⊝ LOW [2] [3] [9]	
	15 per 1,000	14 per 1,000 (6 to 30)				

*The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Most studies with ITT analysis, randomisation procedure and allocation concealment not clear from most publications
[2] Minimal heterogeneity noted on analysis
[3] Several small studies with wide confidence intervals
[4] Despite studies with or without induction, sensitivity analysis made no difference to outcome
[5] Heterogeneity noted only between subgroups
[6] Only 2/15 studies had more than 2 comparison groups
[7] Industry sponsored
[8] 1/6 studies did not report some outcomes due to high dropout
[9] Only 5 studies reported the outcome and had wide CI
[10] Few studies reported the outcome

Summary of findings 3.   Calcineurin inhibitor (CNI) withdrawal + mammalian target of rapamycin inhibitor (mTORi) versus standard dose CNI for kidney transplant recipients

CNI withdrawal + mTORi versus standard dose CNI for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: CNI withdrawal + mTORi
Comparison: standard dose CNI

Outcomes	Anticipated absolute effects[*] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard dose CNI	**Risk with CNI withdrawal + mTOR**			
Death Follow-up: range 6 months to 5 years	Study population		RR 0.99 (0.69 to 1.40)	5427 (23)	⊕⊕⊕⊝ MODERATE [1][2][3][4]
	26 per 1,000	26 per 1,000 (18 to 36)			
Acute rejection Follow-up: range 6 months to 5 years	Study population		RR 1.43 (1.15 to 1.78)	5903 (30)	⊕⊕⊕⊝ MODERATE [1][3][4][5]

	134 per 1,000	191 per 1,000 (154 to 238)			
Graft loss Follow-up: range 1 to 5 years	Study population		RR 0.94 (0.75 to 1.19)	5446 (25)	⊕⊕⊝⊝ LOW [2][4][6]
	53 per 1,000	50 per 1,000 (40 to 64)			
Adverse events: hypertension Follow-up: range 6 months to 5 years	Study population		RR 0.86 (0.64 to 1.15)	2207 (7)	⊕⊕⊝⊝ LOW [7][8]
	218 per 1,000	187 per 1,000 (139 to 250)			
Adverse events: CMV Infection follow-up: range 6 months to 5 years	Study population		RR 0.60 (0.44 to 0.82)	2503 (13)	⊕⊕⊕⊝ MODERATE [9][10]
	150 per 1,000	90 per 1,000 (66 to 123)			
Adverse events: malignancy Follow-up: range 6 months to 5 years	Study population		RR 0.69 (0.47 to 1.00)	3699 (14)	⊕⊕⊝⊝ LOW [2][4][10]
	54 per 1,000	38 per 1,000 (26 to 54)			
Adverse events: lymphocele Follow-up: range 6 months to 5 years	Study population		RR 1.45 (0.95 to 2.21)	1926 (8)	⊕⊕⊝⊝ LOW [6][8][11]
	100 per 1,000	144 per 1,000 (95 to 220)			

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Randomisation method and allocation concealment performed in most studies
[2] No significant heterogeneity noted in analysis
[3] Only 2 studies had more than 2 comparison arms
[4] Many studies with small events and wide CI

5 Significant heterogeneity in studies in biopsy-proven acute rejection
6 Funnel plot skewed
7 Significant heterogeneity noted
8 Few studies reported this outcome
9 Moderate heterogeneity but follow-up times are variable
10 Not all studies reported the outcome
11 Heterogeneity is not significant when 1 long-term study was excluded

Summary of findings 4.   Low dose CNI calcineurin inhibitor (CNI) + mammalian target of rapamycin inhibitor (mTORi) versus standard dose CNI for kidney transplant recipients

Low dose CNI + mTORi versus standard dose CNI for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: low dose CNI + mTORi
Comparison: standard dose CNI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (studies)	Quality of the evi-dence (GRADE)
	Risk with standard dose CNI	Risk with low dose CNI + mTORi			
Death Follow-up: range 6 months to 3 years	Study population		RR 1.16 (0.71 to 1.90)	2750 (11)	⊕⊕⊕⊝ MODERATE [1 2 3 4]
	22 per 1,000	26 per 1,000 (16 to 42)			
Acute rejection Follow-up: range 6 months to 3 years	Study population		RR 1.13 (0.91 to 1.40)	3300 (16)	⊕⊕⊕⊝ MODERATE [2 4]
	132 per 1,000	149 per 1,000 (120 to 185)			
GFR Follow-up: range 6 months to 2 years	The mean GFR in the intervention group was 6.24 mL/min more (3.28 more to 9.19 more) than the control group		-	1749 (11)	⊕⊕⊕⊝ MODERATE [5]
Graft loss Follow-up: range 6 months to 3 years	Study population		RR 0.67 (0.45 to 1.01)	3304 (16)	⊕⊕⊕⊝ MODERATE [2 6]
	38 per 1,000	25 per 1,000 (17 to 38)			
Adverse events: hypertension Follow-up: range 6 months to 2 years	Study population		RR 0.98 (0.80 to 1.20)	1421 (5)	⊕⊕⊝⊝ LOW [7 8]
	203 per 1,000	199 per 1,000			

		(162 to 243)			
Adverse events: CMV infection Follow-up: range 1 to 3 years	Study population		RR 0.41 (0.16 to 1.06)	1250 (5)	⊕⊕⊝⊝ LOW [5][7][9]
	105 per 1,000	43 per 1,000 (17 to 111)			
Adverse events: malignancy Follow-up: range 1 to 3 years	Study population		RR 1.22 (0.42 to 3.52)	1074 (5)	⊕⊕⊝⊝ LOW [2][4][7]
	11 per 1,000	14 per 1,000 (5 to 40)			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio

__GRADE Working Group grades of evidence__
__High quality:__ We are very confident that the true effect lies close to that of the estimate of the effect
__Moderate quality:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
__Low quality:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
__Very low quality:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Randomisation and allocation process not clear in some studies
[2] No significant heterogeneity
[3] Only 2 of the studies had more than 2 comparisons
[4] Some small studies with wide CI
[5] Substantial heterogeneity noted due to recording at different time periods
[6] Small number of events and some small studies with wide CI
[7] Only few studies reported this outcome
[8] 95% CI fails to exclude benefit or harm
[9] Heterogeneity present but when abstract only studies are removed, heterogeneity is zero

Summary of findings 5. Calcineurin inhibitor (CNI) avoidance and late CNI withdrawal versus standard dose CNI

Subgroup analysis: CNI avoidance and late withdrawal versus standard dose CNI for kidney transplant recipients

__Patient or population:__ kidney transplant recipients
__Intervention:__ CNI avoidance and late withdrawal
__Comparison:__ standard dose CNI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants	Quality of the evidence

	Risk with standard dose CNI	Risk with CNI avoidance and withdrawal		(studies)	(GRADE)
Acute rejection: avoidance Follow-up: range 1 to 12 years	Study population		RR 2.16 (0.85 to 5.49)	238 (3)	⊕⊕⊖⊖ LOW [1] [2]
	344 per 1,000	744 per 1,000 (293 to 1,000)			
Acute rejection: late withdrawal	Study population		RR 3.21 (1.59 to 6.48)	1428 (12)	⊕⊕⊕⊖ MODERATE [3]
	102 per 1,000	328 per 1,000 (162 to 661)			
GFR: avoidance	The mean GFR for avoidance studies in the intervention group was 2.22 mL/min lower (14.84 less to 10.4 more) than the control group		-	242 (3)	⊕⊖⊖⊖ VERY LOW [1] [2] [4]
GFR: late withdrawal	The mean GFR for late withdrawal studies in the intervention group was 5.54 mL/min more (1.66 more to 9.43 more) than the control group		-	668 (5)	⊕⊕⊖⊖ LOW [5] [6]
Graft loss: avoidance	Study population		RR 0.96 (0.79 to 1.16)	566 (4)	⊕⊕⊖⊖ LOW [7] [8]
	355 per 1,000	341 per 1,000 (281 to 412)			
Graft loss: late withdrawal	Study population		RR 0.84 (0.72 to 0.97)	1831 (13)	⊕⊕⊕⊖ MODERATE [3] [9] [10]
	260 per 1,000	219 per 1,000 (187 to 252)			

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] 3 small studies with one study including a non-randomised arm
[2] Significant heterogeneity
[3] Several small studies with wide confidence intervals

[4] Small numbers to make a judgement of difference
[5] Skewed funnel plot
[6] Substantial heterogeneity
[7] 2/4 are small studies with wide CI
[8] 4 studies included with one study with high event rate
[9] No heterogeneity identified on analysis
[10] Larger studies are not industry sponsored

Summary of findings 6. Calcineurin inhibitor (CNI) avoidance and late withdrawal with mammalian target of rapamycin inhibitor (mTORi) versus standard dose CNI

Subgroup analysis: CNI avoidance and late withdrawal + mTORi versus standard dose CNI for kidney transplant recipients

Patient or population: kidney transplant recipients
Intervention: CNI avoidance and late withdrawal + mTORi
Comparison: standard dose CNI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (studies)	Quality of the evi-dence (GRADE)
	Risk with standard dose CNI	**Risk with CNI avoidance and with-drawal + mTORi**			
Acute rejection: avoidance Follow-up: range 6 months to 3 years	Study population		RR 1.27 (0.98 to 1.65)	1844 (11)	⊕⊕⊕⊖ MODERATE [1]
	234 per 1,000	297 per 1,000 (229 to 386)			
Acute rejection: late withdrawal Follow-up: range 6 months to 5 years	Study population		RR 1.90 (1.44 to 2.51)	3636 (17)	⊕⊕⊕⊖ MODERATE [1]
	65 per 1,000	124 per 1,000 (94 to 163)			
GFR: avoidance Follow-up: range 6 months to 3 years	The mean GFR for avoidance studies in the intervention group was 6.45 mL/min higher (1.33 higher to 11.58 higher) than the control group		-	1748 (9)	⊕⊕⊖⊖ LOW [1] [2]
GFR: late withdrawal Follow-up: range 6 months to 5 years	The mean GFR for late withdrawal studies in the intervention group was MD 4.55 higher (0.26 higher to 8.85 higher) than for control group		-	2679 (14)	⊕⊕⊖⊖ LOW [1] [2]
Graft loss: avoidance	Study population		RR 1.03 (0.72 to 1.48)	1420 (8)	⊕⊕⊕⊖ MODERATE [1]
	74 per 1,000	76 per 1,000			

	(53 to 110)			
Graft loss: late withdrawal	Study population		RR 0.92 (0.65 to 1.30)	4026 (17)	⊕⊕⊕⊖ MODERATE [1] [2]
	46 per 1,000	42 per 1,000 (30 to 59)			

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Several smaller studies with wide CI
[2] Significant heterogeneity

BACKGROUND

Description of the condition

Standard immunosuppressive protocols to prevent acute graft rejection in kidney transplantation involve three major groups of drugs - calcineurin inhibitor(s) (CNI), antimetabolites and steroids. CNI have been an important part of primary immunosuppression therapy together with adjunctive agents such as mycophenolate mofetil (MMF), azathioprine (AZA) and steroids in kidney transplant recipients (Hariharan 2000).

CNI inhibit the calcium-dependent enzyme serine phosphatase calcineurin. This process prevents the dephosphorylation of nuclear factors of activated T lymphocytes (NFAT), which is essential for translocation into the nucleus leading to reduced activation of cytokine genes for interleukin-2 (IL2) production. Cyclosporin (CsA) and tacrolimus (TAC) are CNI used for kidney transplant recipients (Melk 2003).

Description of the intervention

CNI have dramatically reduced the incidence of acute transplant rejection and decreased early graft loss (Ahsan 2001). However, CNI have been associated with significant adverse effects such as nephrotoxicity (Bennett 1996) causing decreased glomerular filtration rate (GFR), hypertension, hyperlipidaemia and a significant contribution to chronic allograft nephropathy. These effects could lead to subsequent graft loss and contribute directly or indirectly to patient morbidity and mortality by affecting the cardiovascular risk factors (Kasiske 1996). The immunological causes of graft loss have to be however considered. The potential risks of CNI use should be balanced against the risks of acute rejection and chronic antibody-mediated rejection, especially in patients with a high immunological risk.

How the intervention might work

The significant toxicity profile of CNI have prompted many studies investigating CNI withdrawal and tapering strategies. However, some highlighted an increase in acute rejection following withdrawal (Abramowicz 2002) and others showed no effect on graft survival and a short term improvement in creatinine values (Gonwa 2002).

Why it is important to do this review

Despite the large number of studies conducted, uncertainty remains about tapering or withdrawing CNI. These strategies must be balanced with the significant benefits conferred by CNI in preventing early graft rejection. In the absence of a clear clinical consensus, this review aimed to assess the benefits and harms of CNI withdrawal or tapering for kidney transplant recipients.

OBJECTIVES

This review aimed to look at the benefits and harms of CNI tapering or withdrawal in terms of graft function and loss, incidence of acute rejection episodes, treatment-related side effects (hypertension, hyperlipidaemia) and death.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) where standard dose CNI regimens were compared with CNI withdrawal or tapering for kidney transplant recipients were included. The first period of randomised cross-over studies were also included.

Types of participants

Inclusion criteria

Patients with end-stage kidney disease (ESKD), irrespective of age or gender, who received a first or subsequent cadaveric or living donor kidney transplant and received CNI (CsA or TAC) as the primary immunosuppression, were included.

Exclusion criteria

Recipients who received another solid organ in addition to a kidney transplant (e.g. pancreas) were excluded.

Types of interventions

- Transplant recipients who received CNI (CsA or TAC) as the primary immunosuppression which was subsequently tapered or withdrawn completely were included.
- All studies where tapering or withdrawal was compared with controls were included irrespective of the duration of treatment prior to the intervention. In cases of significant heterogeneity, subgroup analysis was performed.
- All definitions of tapering mentioned in the studies were included irrespective of the duration of tapering; sensitivity analysis was used to differentiate between the tapering groups.
- Studies that defined low dose either by exposure to CsA and TAC calculated using 12-hour post-dose nadir (trough; C0) blood levels, or studies which employed fixed doses (mg/kg) were included.

Specific comparisons were made between:

- Standard dose CNI versus CNI withdrawal
- Low dose CNI versus standard dose CNI
- CNI withdrawal with conversion to mammalian target of rapamycin inhibitor (mTOR-I) versus standard dose CNI
- Low dose CNI with conversion to mTOR-I versus normal dose CNI.

In case of significant heterogeneity among interventions, subgroup analysis was carried out in:

- Duration of tapering or withdrawal
- AZA and MMF groups.

Types of outcome measures

- Graft loss (censored and not censored for death)
- All-cause mortality
- Acute rejection episodes: both clinical and biopsy-proven acute rejection (BPAR) were included

- Graft kidney function at six months and at one, two and five years measured by serum creatinine (SCr), calculated GFR or creatinine clearance (CrCl)
- Treatment-related side effects (e.g. hyperlipidaemia, hypertension)
- Rates of malignancy
- Incidence of infections.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register to 11 October 2016 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that were relevant to the review. Titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however, studies and reviews that included relevant data or information on trials were retained initially. The same two authors independently assessed retrieved abstracts, and if necessary, the full text of studies which satisfied the inclusion criteria. Studies reported in non-English language journals were translated before assessment. Discrepancies were resolved by discussion with a third author.

Data extraction and management

Data extraction was carried out independently by the same authors using standard data extraction forms. Where more than one

publication of one study existed, reports were grouped together and the most recent or most complete data set were used. Any discrepancies between published versions were highlighted.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Results for dichotomous outcomes (e.g. incidence of acute rejections, graft loss, death) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. blood pressure, SCr, GFR), the mean difference (MD) was used, or the standardised mean difference (SMD) if different scales were used.

Dealing with missing data

Further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review.

Assessment of heterogeneity

Heterogeneity was analysed using a Cochran Q test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). In case of significant heterogeneity, subgroup analysis was considered.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity (e.g. interventions and study quality). Heterogeneity among participants could be related to age and renal pathology. Heterogeneity in treatments could be related to prior agent(s) used, the agent (CsA/TAC) and duration of therapy prior to withdrawal or tapering. Adverse effects are tabulated and assessed with descriptive techniques, as they are likely to be different for the various agents used.

Sensitivity analysis

Sensitivity analysis was used to differentiate between tapering groups.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Death
- Graft loss
- Acute rejection
- GFR
- Adverse events (e.g. hypertension, CMV infection, malignancy).

R E S U L T S

Description of studies

Results of the search

Our search identified 2398 records. After title and abstract review we excluded 1605 records. The remaining 793 records were for 159 studies. We included only studies that compared standard dose CNI with tapering or withdrawal with or without mTOR-I substitution which resulted in 83 studies (583 reports) being included in the analyses. We excluded 72 studies (202 records). Four studies (8 records) are ongoing (David-Neto 2014; ERIC Study 2010; ISRCTN63298320; TRANSFORM Study 2013) and will be assessed in a future update of this review. See Figure 1.

Figure 1. Flow chart showing number of studies identified

MEDLINE & EMBASE (1485); Specialised Register (913)

Records identified: 2398

Excluded after title and abstract assessment: 1605
(not RCTs, wrong population or intervention)

Full-text records screened: 793

Records excluded: 202 (72 studies)
Wrong population (2); wrong intervention (62); wrong outcomes (4); other (4)

Studies identified: 87 (591 records)

Ongoing studies: 4 (8 records)

Included studies: 83 (583 records; 16,156 participants)

Studies by outcome

- Graft loss/survival: 68
- Mortality/patient survival: 59
- Acute rejection: 75
- Biopsy-proven acute rejection: 56
- Kidney function (GFR): 52
- Malignancy: 29
- CMV infection: 30

Included studies

See Characteristics of included studies.

The 83 studies included 16,156 randomised participants. Of these, 13 studies were available only in abstract form (2345 participants) (Alsina 1987; Bertoni 2007; Cockfield 2002; El-Agroudy 2014; Heering 1993; HERAKLES Study 2012; Holm 2008; Kreis 2003; MODIFY Study 2012; Pacheco-Silva 2013; Qazi 2014; Rossini 2007; Salvadori 2007).

CNI withdrawal or avoidance versus standard dose CNI regimens

We found 17 studies (81 reports, 1939 participants) that compared CNI withdrawal or avoidance with standard dose CNI regimens; four studies compared avoidance with standard dose CNI regimens (Asberg 2006; Garcia 2007; Grimbert 2002; Kosch 2003a), and one study with three arms and compared avoidance and withdrawal with standard dose CNI (Hall 1988). The remainder compared CNI withdrawal with standard dose CNI regimen.

Garcia 2007 and CTOT-09 Study 2015 investigated TAC; two studies involved patients on either CsA or TAC (Pascual 2008; Suwelack 2002), and the remainder were CsA-based studies (Abramowicz

2002; Asberg 2006; Dudley 2005; Grimbert 2002; Hall 1988; Hazzan 2005; Heering 1993; Hollander 1995; Isoniemi 1990; Kosch 2003a; MacPhee 1998; Pedersen 1991; Smak Gregoor 1999).

Standard versus low dose CNI

We included 18 studies (89 reports, 2904 participants) that compared standard dose CNI with low dose CNI. Of these, 15 were CsA-based studies (Alsina 1987; Andres 2009; Baczkowska 2003; Budde 2007; Cai 2014; Chadban 2013; Cibrik 2007; de Sevaux 2001; DICAM Study 2010, Fangmann 2010; Ferguson 2006; Kreis 2003; Pascual 2003; REFERENCE Study 2006; Salvadori 2007); two investigated TAC (Chan 2012; MODIFY Study 2012); and OPTICEPT Study 2009 included either TAC or CsA. Of these, 12 studies involved introduction of low dose CNI regimen early in the post-transplant period and six introduced low dose CNI later in the post-transplant period (Cibrik 2007; DICAM Study 2010; Kreis 2003; MODIFY Study 2012; Pascual 2003; REFERENCE Study 2006).

Standard dose CNI versus CNI withdrawal or avoidance with mTOR-I substitution

There were 29 studies (252 reports, 5012 participants) that compared standard dose CNI with CNI withdrawal or avoidance combined with mTOR-I substitution (APOLLO Study 2015; Bansal 2013; Barsoum 2007; CALFREE Study 2010; CENTRAL Study 2012; CERTITEM Study 2015; Chhabra 2013; CONCEPT Study 2009; CONVERT Trial 2009; El-Agroudy 2014; Flechner-318 Study 2002; Grinyo 2004; Holm 2008; Martinez-Mier 2006; Nafar 2012; ORION Study 2011; Pacheco-Silva 2013; Pontrelli 2008; Rivelli 2015; RMR Study 2001; Rossini 2007; Schaefer 2006; SMART TX Study 2010; Spare-the-Nephron Study 2011; Stallone 2003; Stallone 2004; Stegall 2003; Watson 2005; ZEUS Study 2011). Of these, nine compared CNI avoidance with mTOR-I substitution versus conventional CNI regimen (CENTRAL Study 2012; Nafar 2012; Stegall 2003; Schaefer 2006; Barsoum 2007; CALFREE Study 2010; Flechner-318 Study 2002; Martinez-Mier 2006, SMART TX Study 2010). The rest looked at delayed CNI withdrawal with mTOR-I substitution.

We included only five studies that investigated everolimus (APOLLO Study 2015; CENTRAL Study 2012; CERTITEM Study 2015; Pacheco-Silva 2013; ZEUS Study 2011); the remainder investigated sirolimus. The CNI studied were:

- TAC (eight studies: Chhabra 2013; El-Agroudy 2014; Grinyo 2004; ORION Study 2011; Pacheco-Silva 2013; Rivelli 2015; Schaefer 2006; Stegall 2003)
- CsA (13 studies: Barsoum 2007; CALFREE Study 2010; CERTITEM Study 2015; CONCEPT Study 2009; Flechner-318 Study 2002; Holm 2008; Martinez-Mier 2006; CENTRAL Study 2012; Nafar 2012; RMR Study 2001; SMART TX Study 2010; Stallone 2003; ZEUS Study 2011)
- TAC or CsA (seven studies: APOLLO Study 2015; Bansal 2013; CONVERT Trial 2009; Holm 2008; Spare-the-Nephron Study 2011; Rossini 2007; Stallone 2004; Watson 2005).

Standard dose CNI versus low dose CNI and mTOR-I

We identified 14 studies (80 reports, 3110 participants) that compared standard dose CNI with combination of low dose CNI

and mTOR-I; (Bechstein-193 2013; Bertoni 2007; Bertoni 2011; Chan 2008; Cockfield 2002; Muhlbacher 2014; Nashan 2004; Oh 2012; Paoletti 2012; Qazi 2014; Russ 2003; Takahashi 2013a; Tedesco-Silva 2010; Velosa-212 Study 2001). Interventions were administered immediately post-transplant in all studies.

There were nine studies that investigated everolimus as the mTOR-I (Bertoni 2007; Bertoni 2011; Chan 2008; Nashan 2004; Oh 2012; Paoletti 2012; Qazi 2014; Takahashi 2013a; Tedesco-Silva 2010); the remainder looked at sirolimus. TAC (CNI) was studied in five studies (Bechstein-193 2013; Chan 2008; Cockfield 2002; Qazi 2014; Russ 2003) and the rest of the studies used CsA.

Low versus normal dose CNI with or without mTOR-I (mixed studies)

Five studies (83 reports, 3191 participants) had more than two arms and compared low dose versus normal dose CNI with or without mTOR-I (ASCERTAIN Study 2011; CAESAR Study 2007; HERAKLES Study 2012; MECANO Study 2009; SYMPHONY Study 2007). Each were split to form two studies comparing low dose or withdrawal with or without mTOR-I.

Reporting of outcomes was variable, and definitions of outcomes were unclear in most studies. Acute rejection episodes were reported as biopsy proven (56 studies) or unspecified/mixed (19 studies). Most reported graft loss or failure (68 studies) and GFR (52 studies). Methods used to determine GFR varied: 15 studies applied the Nankivell formula; 17 used Cockcroft-Gault; 12 used MDRD; six used nuclear GFR (iothalamate or Cr EDTA); and four did not state the method used. CMV infection rates were reported in 30 studies and malignancy rates were reported in 29 studies.

Excluded studies

We excluded 72 studies following full text assessment: two studies included populations that did not match our inclusion criteria; 62 investigated interventions that were not relevant to this review; four measured outcomes not relevant to this review; two were incomplete studies that stopped early; one was only published as an abstract 35 years ago; and one study converted patients from TAC to sirolimus, however 40% we converted back to TAC. See Characteristics of excluded studies.

This review excluded studies involving Belatacept as the intervention assessed efficacy of the new biologic agent rather than CNI withdrawal. The Belatacept studies has been analysed and published recently (Mason 2014).

Risk of bias in included studies

Study methodology reporting was incomplete in most studies. Randomisation methods and allocation concealment were clearly described in fewer than 50% of studies. Most were open-label studies. Intention-to-treat (ITT) analysis was either not reported or did not contain adequate information in 20% of studies to assess reporting bias. Seven studies did not report all possible outcomes due to early termination. Details are summarised below and in Figure 2.

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

Allocation

Random sequence generation

Randomisation methods were reported in detail in 27 studies (APOLLO Study 2015; ASCERTAIN Study 2011; Bansal 2013; CAESAR Study 2007; Cai 2014; CENTRAL Study 2012; Chan 2012; Cibrik 2007; CONCEPT Study 2009; CONVERT Trial 2009; DICAM Study 2010; Dudley 2005; Fangmann 2010; Flechner-318 Study 2002; Grinyo 2004; Hall 1988; MacPhee 1998; MECANO Study 2009; Paoletti 2012; REFERENCE Study 2006; Rivelli 2015; SMART TX Study 2010; Spare-the-Nephron Study 2011; SYMPHONY Study 2007; Takahashi 2013a; Watson 2005; ZEUS Study 2011). Three studies were judged to be at high risk of bias; Pedersen 1991 randomised alternate participants to intervention and control groups, and Garcia 2007 and Schaefer 2006 included a third non-randomised arm to the studies. The remaining 53 studies did not report randomisation methods.

Allocation concealment

Methods of allocation concealment were adequate in 25 studies (Abramowicz 2002; APOLLO Study 2015; Bansal 2013; CAESAR Study 2007; CENTRAL Study 2012; Chan 2008; Cibrik 2007; CONVERT Trial 2009; de Sevaux 2001; DICAM Study 2010; Dudley 2005; Fangmann 2010; Hall 1988; Isoniemi 1990; MacPhee 1998; MECANO Study 2009; Paoletti 2012; REFERENCE Study 2006; Smak Gregoor 1999; SMART TX Study 2010; Spare-the-Nephron Study 2011; SYMPHONY Study 2007; Tedesco-Silva 2010; Watson 2005; ZEUS Study 2011). Five studies were judged to be at high risk of bias (Barsoum 2007; Garcia 2007; Grinyo 2004; OPTICEPT Study 2009; Schaefer 2006) and the method of allocation concealment was not reported or unclear in 53 studies.

Blinding

Almost all studies were open-label. Ferguson 2006 reported blinding of investigators and participants in one part of the study, and four studies (Cibrik 2007; DICAM Study 2010; Oh 2012; Rivelli 2015) reported blinding of outcome investigators.

Incomplete outcome data

Outcome data was reported or analysed as Intention- to-treat in (ITT) in 55 studies (Abramowicz 2002; Andres 2009; APOLLO Study 2015; ASCERTAIN Study 2011; Bansal 2013; Barsoum 2007; Bertoni 2011; Budde 2007; CAESAR Study 2007; Cai 2014; CALFREE Study 2010; CENTRAL Study 2012; Chadban 2013; Chan 2008; Chhabra 2013; Cibrik 2007; CONCEPT Study 2009; CTOT-09 Study 2015; de Sevaux 2001; DICAM Study 2010; El-Agroudy 2014; Fangmann 2010; Ferguson 2006; Flechner-318 Study 2002; Garcia 2007; Grimbert 2002; Hall 1988; Hazzan 2005; HERAKLES Study 2012; Hollander 1995; Isoniemi 1990; Kosch 2003a; MacPhee 1998; Martinez-Mier 2006; MODIFY Study 2012; Oh 2012; Paoletti 2012; Pascual 2003; Pontrelli 2008; Qazi 2014; REFERENCE Study 2006; Rivelli 2015; RMR Study 2001; Salvadori 2007; Smak Gregoor 1999; SMART TX Study 2010; Spare-the-Nephron Study 2011; Stallone 2003; Stegall 2003; Suwelack 2002; SYMPHONY Study 2007; Takahashi 2013a; Tedesco-Silva 2010; Velosa-212 Study 2001; Watson 2005; ZEUS Study 2011).

There was missing outcome data in seven studies (CENTRAL Study 2012; Cockfield 2002; Holm 2008; Heering 1993; Muhlbacher 2014; OPTICEPT Study 2009).

Attrition bias was judged to be unclear for the remaining 21 studies.

Selective reporting

There were 54 studies that reported prespecified outcomes (Abramowicz 2002; Andres 2009; APOLLO Study 2015; ASCERTAIN Study 2011; Bansal 2013; Barsoum 2007; Bertoni 2007; Bertoni 2011; Budde 2007; CAESAR Study 2007; Cai 2014; CENTRAL Study 2012; Chadban 2013; Chan 2008; Chan 2012; Chhabra 2013; Cibrik 2007; CONCEPT Study 2009; CONVERT Trial 2009; de Sevaux 2001; DICAM Study 2010; Dudley 2005; Fangmann 2010; Ferguson 2006; Flechner-318 Study 2002; Garcia 2007; Grinyo 2004; Hall 1988; HERAKLES Study 2012; Isoniemi 1990; Kosch 2003a; MacPhee 1998; MODIFY Study 2012; Nashan 2004; Oh 2012; Pacheco-Silva 2013; Pascual 2003; Pascual 2008; Qazi 2014; Pontrelli 2008; RMR Study 2001; Russ 2003; Salvadori 2007; Smak Gregoor 1999; SMART TX Study 2010; Spare-the-Nephron Study 2011; Stallone 2003;

Stallone 2004; Pontrelli 2008; Suwelack 2002; SYMPHONY Study 2007; Takahashi 2013a; Tedesco-Silva 2010; Watson 2005; ZEUS Study 2011).

Eight studies were judged to be at high risk of reporting bias. Three studies did not report all possible outcomes due to early termination (CTOT-09 Study 2015; MECANO Study 2009; ORION Study 2011). Cockfield 2002 and CERTITEM Study 2015 did not report all prespecified outcomes. Full-text publications had not been identified for three studies 10 years after the abstracts were first published (Holm 2008; Rossini 2007; Salvadori 2007).

Twenty four studies had insufficient information to ascertain reporting bias.

Other potential sources of bias

Of the 83 included studies, 49 received pharmaceutical industry funding, which is a potential source for bias (Abramowicz 2002; Andres 2009; APOLLO Study 2015; Asberg 2006; ASCERTAIN Study 2011; Bansal 2013; Bechstein-193 2013; Budde 2007; CAESAR Study 2007; Cai 2014; CALFREE Study 2010; CENTRAL Study 2012; CERTITEM Study 2015; Chadban 2013; Chan 2008; Chan 2012; Chhabra 2013; Cibrik 2007; CONCEPT Study 2009; CONVERT Trial 2009; de Sevaux 2001; Dudley 2005; Ferguson 2006; Flechner-318 Study 2002; Grinyo 2004; Hall 1988; MECANO Study 2009; Muhlbacher 2014; Nashan 2004; Oh 2012; OPTICEPT Study 2009; ORION Study 2011; Pascual 2003; Pascual 2008; Qazi 2014; REFERENCE Study 2006; RMR Study 2001; Russ 2003; Smak Gregoor 1999; SMART TX Study 2010; Spare-the-Nephron Study 2011; Stegall 2003; Suwelack 2002; SYMPHONY Study 2007; Takahashi 2013a; Tedesco-Silva 2010; Velosa-212 Study 2001; Watson 2005; ZEUS Study 2011).

In two studies, one study arm was terminated due to increased rates of acute rejection (MECANO Study 2009; ORION Study 2011) and in Heering 1993 and CTOT-09 Study 2015 the studies were stopped due to increased acute rejections in the CNI withdrawal group.

Garcia 2007 included a third group of non-randomised patients after the interim analysis of randomised patients.

Only preliminary data were reported in Cockfield 2002 and Muhlbacher 2014.

There was a high drop-out rate in four studies (Grinyo 2004; OPTICEPT Study 2009, Stegall 2003, Tedesco-Silva 2010) which resulted in protocol amendment in Grinyo 2004.

Effects of interventions

See: **Summary of findings for the main comparison** Calcineurin inhibitor (CNI) withdrawal versus standard dose CNI for kidney transplant recipients; **Summary of findings 2** Low dose calcineurin inhibitors (CNI) versus to standard dose CNI for kidney transplant recipients; **Summary of findings 3** Calcineurin inhibitor (CNI) withdrawal + mammalian target of rapamycin inhibitor (mTORi) versus standard dose CNI for kidney transplant recipients; **Summary of findings 4** Low dose CNI calcineurin inhibitor (CNI) + mammalian target of rapamycin inhibitor (mTORi) versus standard dose CNI for kidney transplant recipients; **Summary of findings 5** Calcineurin inhibitor (CNI) avoidance and late CNI withdrawal versus standard dose CNI; **Summary of findings 6** Calcineurin inhibitor (CNI) avoidance and late withdrawal with mammalian target of rapamycin inhibitor (mTORi) versus standard dose CNI

CNI withdrawal (avoidance or late withdrawal) versus standard dose CNI

There was little or no difference in patient death between CNI withdrawal and standard dose CNI regimens (Analysis 1.1 (14 studies 2010 participants): RR 1.09, 95% CI 0.96 to 1.24; $I^2 = 0\%$; moderate certainty evidence).

Acute rejection episodes were higher with CNI withdrawal whether diagnosed by biopsy or clinically (Analysis 1.2 (15 studies, 1666 participants): RR 2.54, 95% CI 1.56 to 4.12; $I^2 = 70\%$; moderate certainty). However GFR increased (Analysis 1.3 (8 studies, 910 participants): MD 3.56 mL/min, 95% CI -1.25 to 8.25; $I^2 = 66\%$; low certainty) and graft loss decreased (Analysis 1.4 (16 studies, 2090 participants): RR 0.85, 95% CI 0.74 to 0.98; $I^2 = 0\%$; low certainty) with CNI withdrawal.

There was 18% reduction in hypertension noted with CNI withdrawal (Analysis 1.6.1 (5 studies, 950 participants): RR 0.82, 95% CI 0.71 to 0.95; $I^2 = 36\%$; low certainty). There was no differences in incidences of hyperlipidaemia (Analysis 1.6.2 (3 studies, 562 participants): RR 0.88, 95% CI 0.63 to 1.21; $I^2 = 2\%$), CMV infection (Analysis 1.6.3 (7 studies, 608 participants): RR 0.87, 95% CI 0.52 to 1.45; $I^2 = 0\%$; low certainty), diabetes mellitus (Analysis 1.6.4 (6 studies, 810 participants): RR 0.85, 95% CI 0.94 to 1.42; $I^2 = 0\%$), malignancy (Analysis 1.6.5 (6 studies, 1079 participants): RR 1.10, 95% CI 0.936 to 1.30; $I^2 = 0\%$; low certainty), or total infections (Analysis 1.6.6 (6 studies, 724 participants): RR 0.96, 95% CI 0.61 to 1.51; $I^2 = 46\%$) between the groups.

Subgroup analyses

CNI avoidance versus standard dose CNI

There was more acute rejection episodes in CNI avoidance compared with standard dose CNI (Analysis 1.7.1 (3 studies, 238 participants): RR 2.16, 95% CI 0.85 to 5.49; $I^2 = 84\%$, low certainty). However, there was no difference in death (Analysis 1.1.1 (4 studies, 566 participants): RR 1.11, 95% CI 0.94 to 1.32; $I^2 = 0\%$), GFR (Analysis 1.8.1 (3 studies, 242 participant): MD -2.22 mL/min, 95% CI -14.84 to 10.40; $I^2 = 84\%$, very low certainty), and graft loss (Analysis 1.9.1 (4 studies, 566 participants): RR 0.96, 95% CI 0.79 to 1.16; $I^2 = 0\%$, low certainty).

Late withdrawal versus standard dose CNI

Analysis of late withdrawal studies indicated that there was no difference in death (Analysis 1.1.2 (10 studies, 1444 participants): RR 1.06, 95% CI 0.88 to 1.29; $I^2 = 0\%$), however acute rejection episodes were higher in CNI withdrawal group (Analysis 1.7.2 (12 studies, 1428 participants): RR 3.21, 95% CI 1.59 to 6.48; $I^2 = 66\%$, moderate certainty). GFR was higher (Analysis 1.8.2 (5 studies, 668 participants): MD 5.54 mL/min, 95% CI 1.66 to 9.43; $I^2 = 29\%$, low certainty) and there was less graft loss (Analysis 1.9.2 (13 studies, 1848 participants): RR 0.84, 95% CI 0.72 to 0.97; $I^2 = 0\%$, low certainty) in the CNI withdrawal group.

Type of antimetabolite (MMF/MPA or AZA)

Subgroup analysis on antimetabolites found a higher acute rejection episodes associated with CNI withdrawal compared with

standard dose CNI in the MMF/MPA studies (Analysis 2.1.1 (10 studies, 1110 participants): RR 3.51, 95% CI 1.79 to 6.88; I² = 65%) but not in AZA studies (Analysis 2.1.2 (5 studies, 556 participants): RR 1.81, 95% CI 0.78 to 4.19; I² = 72%).

Type of CNI (CsA or TAC)

When classified by CNI type, acute rejection episodes increased in the withdrawal arm of CsA studies (Analysis 3.1.1 (11 studies, 1500 participants): RR 2.13, 95% CI 1.31 to 3.48; I² = 71%), TAC (Analysis 3.1.2 (2 studies, 88 participants): RR 5.65, 95% CI 1.96 to 16.27; I² = 0%), and in studies that investigated either CsA or TAC (Analysis 3.1.3 (2 studies, 78 participants): RR 9.00, 95% CI 0.52 to 156.9) compared with standard dose CNI.

Sensitivity analyses

On sensitivity analyses stratified for steroid-free regimens the effects were not different from steroid regimens for death, acute rejection and GFR. When stratified for time of follow-up, the reduction in graft loss observed in the CNI withdrawal group was not significant when the long-term studies were excluded in the analysis (RR 1.07, 95% CI 0.72 to 1.57; forest plot not shown).

Low dose CNI versus standard dose CNI

There was little or no difference in patient death between low dose and standard dose CNI regimens (Analysis 4.1 (15 studies, 3462 participants): RR 0.79, 95% CI 0.50 to 1.27; I² = 0%; moderate certainty).

There was a lower incidence of acute rejection (Analysis 4.2 (19 studies, 3757 participants): RR 0.87, 95% CI 0.76 to 1.00; I² = 0%; moderate certainty) and graft loss (Analysis 4.4 (15 studies, 3286 participants): RR 0.75, 95% CI 0.55 to 1.02; I² = 0%; moderate certainty) in the low dose CNI group.

Patients treated with low dose CNI had higher GFR (Analysis 4.3 (13 studies, 2623 participants): MD 4.10, 95% CI 2.07 to 6.12; I² = 16%; moderate certainty). Low dose CNI regimen probably slightly lowers SCr (Analysis 4.5 (6 studies, 742 participants): MD -4.28 µmol/L, 95% CI -14.65 to 6.10; I² = 37%; low certainty).

Hypertension was probably reduced (Analysis 4.7.1 (5 studies, 1877 participants): RR 0.84, 95% CI 0.70 to 1.00; I² = 0%; low certainty) in the low dose CNI group. There was no difference in hyperlipidaemia (Analysis 4.7.2 (3 studies, 1443 participants): RR 1.04, 95% CI 0.90 to 1.19; I² = 12%), CMV infection (Analysis 4.7.3 (6 studies, 1948 participants): RR 1.23, 95% CI 0.94 to 1.62; I² = 10%; moderate certainty), diabetes mellitus (Analysis 4.7.4 (5 studies, 1292 participants): RR 0.82, 95% CI 0.50 to 1.34; I² = 53%), malignancy (Analysis 4.7.5 (5 studies, 1637 participants): RR 0.90, 95% CI 0.41 to 1.97; I² = 0%; low certainty), and total infections (Analysis 4.7.6 (9 studies, 1437 participants): RR 0.95, 95% CI 0.84 to 1.07; I² = 0%).

Subgroup analyses

Low dose CNI immediately post-transplant versus standard dose CNI

For studies which compared low dose CNI immediately post-transplant with standard dose CNI regimens, there were less acute rejection episodes (Analysis 4.8.1 (12 studies, 2209 participants): RR 0.82, 95% CI 0.67 to 1.00; I² = 0%) and graft loss (Analysis 4.10.1 (11

studies, 2800 participants): RR 0.75, 95% CI 0.55 to 1.03; I² = 0%), and GFR improved (Analysis 4.9.1 (9 studies, 2200 participants): MD 3.09 mL/min, 95% CI 0.95 to 5.23; I² = 4%) with the low dose regimen.

Late intervention with low dose CNI versus standard dose CNI

For studies which compared late intervention with low dose CNI, there was no difference acute rejection (Analysis 4.8.2 (6 studies, 759 participants): RR 1.05, 95% CI 0.61 to 1.81; I² = 21%) or graft loss (Analysis 4.10.2 (3 studies, 306 participants): RR 0.95, 95% CI 0.12 to 7.56; I² = 0%) however GFR was higher (Analysis 4.9.2 (3 studies, 243 participants): MD 8.81 mL/min, 95% CI 3.79 to 13.83; I² = 0%).

Type of CNI (CsA or TAC)

When studies were classified on the type of CNI, there was less acute rejection in the low dose CsA (Analysis 5.1.1 (16 studies, 2906 participants): RR 0.87, 95% CI 0.76 to 1.01; I² = 0%) compared to standard dose CsA but the results were not significant for low dose TAC (Analysis 5.1.2 (2 studies, 371 participants): RR 1.53, 95% CI 0.61 to 3.83; I² = 0%) and for studies which used either CsA or TAC (Analysis 5.1.3 (1 study, 480 participants): RR 0.64, 95% CI 0.34 to 1.19).

Sensitivity analysis

When stratified for steroid-free regimens, the reduction in graft loss was significant when the study using a steroid-free regimen was excluded from the analysis (RR 0.72, 95% CI 0.52 to 0.98; forest plot not shown).

When stratified for induction treatment with IL2RA or anti-lymphocyte serum or globulin, the incidence of acute rejection was similar between the groups (12 studies: RR 0.84, 95% CI 0.66 to 1.07; forest plot not shown).

CNI withdrawal (avoidance or withdrawal) with mTOR-I substitution versus standard dose CNI

There was little or no difference in death (Analysis 6.1 (23 studies, 5427 participants): RR 0.96, 95% CI 0.68 to 1.36; I² = 0%; moderate certainty) and graft loss (Analysis 6.4 (25 studies, 5446 participants): RR 0.94, 95% CI 0.75 to 1.19; I² = 0%; low certainty) between the CNI withdrawal with mTOR-I and standard dose CNI regimens.

There was an increase in acute rejection episodes (Analysis 6.2 (30 studies, 5903 participants): RR 1.43, 95% CI 1.15 to 1.78; I² = 52%; moderate certainty) in the mTOR-I group. Patients in the CNI withdrawal with mTOR-I group had a higher GFR compared to standard dose CNI regimen (Analysis 6.3 (23 studies, 4427 participants): MD 5.29, 95% CI 2.08 to 8.51; I² = 90%). SCr was lower at one year in the CNI withdrawal with mTOR-I group (Analysis 6.5 (12 studies, 1702 participants): MD -17.10 µmol/L, 95% CI -26.95 to -7.25; I² = 76%).

CNI withdrawal with mTOR-I group had a higher incidence of hyperlipidaemia (Analysis 6.7.2 (13 studies 3494 participants): RR 1.76, 95% CI 1.40 to 2.20; I² = 49%). There was little or no difference in hypertension Analysis 6.7.1 (7 studies, 2207 participants): RR 0.86, 95% CI 0.64 to 1.15; I² = 79%), diabetes mellitus (Analysis 6.7.4 (11 studies, 2833 participants): RR 1.27, 95% CI 0.97 to 1.66; I² = 0%), and infections (Analysis 6.7.6 (9 studies, 1624 participants): RR 0.99, 95% CI 0.92 to 1.07; I² = 0%) between the two groups. There

was a reduction in malignancy (Analysis 6.7.5 (14 studies, 3699 participants): RR 0.69, 95% CI 0.47 to 1.00; I^2 = 19%; low certainty) and CMV infection (Analysis 6.7.3 (13 studies, 2503 participants): RR 0.60, 95% CI 0.44 to 0.82; I^2 = 43%; moderate certainty) in the mTOR-I group compared to those treated with standard dose CNI regimen. There was an increase in lymphoceles in the CNI withdrawal, mTOR-I group (Analysis 6.7.7 (8 studies, 1926 participants): RR 1.45, 95% CI 0.95, 2.21; I^2 = 56%; low certainty).

Subgroup analysis

CNI avoidance with mTOR-I substitution versus standard dose CNI

There was an increase acute rejection episodes (Analysis 6.8.1 (11 studies, 1844 participants): RR 1.27, 95% CI 0.98 to 1.65; I^2 = 31%), while GFR was better (Analysis 6.9.1 (9 studies, 1748 participants): MD 6.45 mL/min, 95% CI 1.33 to 11.58; I^2 = 86%) in the CNI avoidance with mTOR-I regimen. Graft loss (Analysis 6.10.1 (8 studies, 1420 participants): RR 1.03, 95% CI 0.72 to 1.48; I^2 = 0%) was similar in the two groups.

Late CNI withdrawal with mTOR-I substitution versus standard dose CNI

Acute rejection episodes were higher in the late CNI withdrawal with mTOR-I substitution group (Analysis 6.8.2 (17 studies, 3636 participants): RR 1.90, 95% CI 1.44 to 2.51; I^2 = 23%). GFR was not significantly higher (Analysis 6.9.2 (14 studies, 2679 participants): MD 4.55 mL/min, 95% CI 0.26 to 8.85; I^2 = 92%) and there was no difference in graft loss (Analysis 6.10.2 (17 studies, 4026 participants): RR 0.92, 95% CI 0.65 to 1.30; I^2 = 13%) in the late CNI withdrawal with mTOR-I group.

Type of CNI (CsA or TAC)

There were more acute rejection episodes in the late CNI withdrawal with mTOR-I group compared to standard dose CsA (Analysis 7.1.1 (18 studies, 5903 participants): RR 1.42, 95% CI 1.15 to 1.76; I^2 = 37%) and standard dose TAC (Analysis 7.1.2 (7 studies, 753 participants): RR 2.23, 95% CI 1.43 to 3.49; I^2 = 15%), however in studies which used either CsA or TAC (Analysis 7.1.3 (5 studies, 1687 participants): RR 0.97, 95% CI 0.40 to 2.33; I^2 = 64%) there were no differences in acute rejection episodes.

Sensitivity analyses

On sensitivity analyses stratified for steroid-free regimens the effects were not different from steroid regimens for death, acute rejection, and GFR.

Low dose CNI with mTOR-I versus standard dose CNI

There was little or no difference in patient deaths (Analysis 8.1 (11 studies, 2750 participants): RR 1.16, 95% CI 0.71 to 1.90; I^2 = 0%; moderate certainty), acute rejection episodes (Analysis 8.2 (16 studies, 3300 participants): RR 1.13, 95% CI 0.91 to 1.40; I^2 = 22%; moderate certainty), and graft loss (Analysis 8.4 (16 studies, 3304 participants): RR 0.67, 95% CI 0.45 to 1.01; I^2 = 0%; moderate certainty) when low dose CNI with mTOR-I was compared to standard dose CNI.

Patients treated with low dose CNI in combination with mTOR-I had a higher GFR compared with standard dose CNI regimens (Analysis 8.3 (11 studies, 1749 participants): MD 6.24 mL/min, 95% CI 3.28 to 9.19; I^2 = 56%; moderate certainty), and a lower SCr at one year

(Analysis 8.5 (6 studies, 1320 participants): MD -14.14 μmol/L, 95% CI -22.55 to -5.72; I^2 = 17%).

Hypertension (Analysis 8.7.1 (5 studies, 1421 participants): RR 0.98, 95% CI 0.80 to 1.20; I^2 = 0%, low certainty), hyperlipidaemia (Analysis 8.7.2 (8 studies, 1793 participants): RR 1.07, 95% CI 0.89 to 1.28; I^2 = 30%), and diabetes mellitus (Analysis 8.7.4 (5 studies, 686 participants): RR 1.36, 95% CI 0.81 to 2.27; I^2 = 0%) were noted to be similar in patients treated with either low dose CNI in combination with mTOR-I or standard dose CNI regimens. There was no reduction in malignancy in the low CNI in combination with mTOR-I group compared to those treated with standard dose CNI regimens (Analysis 8.7.5 (5 studies, 1074 participants): RR 1.22, 95% CI 0.42 to 3.52; I^2 = 0%, low certainty). There was little or no difference in total Infections (Analysis 8.7.6 (5 studies, 1271 participants): RR 0.95, 95% CI 0.83 to 1.08; I^2 = 28%) and CMV infection (Analysis 8.7.3 (5 studies, 1250 participants): RR 0.41, 95% CI 0.16 to 1.06; I^2 = 74%; low certainty) between the two groups.

Subgroup analysis

CNI and mTOR-I combination with standard dose CNI regimen in the immediate post-transplant period

GFR was higher in the low dose CNI with mTOR-I group (Analysis 8.9.1 (10 studies, 1537 participants): MD 6.91 mL/min, 95% CI 3.86 to 9.96; I^2 = 53%), however acute rejection (Analysis 8.10.1 (14 studies, 2736 participants): RR 1.09, 95% CI 0.86 to 1.39; I^2 = 27%) and graft loss (Analysis 8.8.1 (14 studies, 2736 participants): RR 0.75, 95% CI 0.48 to 1.18; I^2 = 0%) were similar in the two groups.

Late introduction of low dose CNI regimen with mTOR-I substitution

Incidence of acute rejection was higher in the low dose CNI with mTOR-I group (Analysis 8.10.2 (2 studies, 564 participants): RR 1.38, 95% CI 0.82 to 2.31; I^2 = 0%), there was no difference in graft loss (Analysis 8.8.2 (2 studies, 568 participants): RR 0.40, 95% CI 0.15 to 1.04; I^2 = 0%) and one study reported no difference in GFR in the late withdrawal group (Analysis 8.9.2 (1 study, 212 participants): MD 0.58 mL/min, 95% CI -5.00 to 6.16).

Type of CNI (CsA or TAC)

There was no difference in acute rejection in the low dose CsA with mTOR-I compared to standard dose CsA (Analysis 9.1.1 (11 studies, 2232 participants): RR 0.97, 95% CI 0.78 to 1.22; I^2 = 7%), however acute rejection was higher when low dose TAC with mTOR-I was compared to standard dose TAC (Analysis 9.1.2 (5 studies, 1068 participants): RR 1.58, 95% CI 1.16 to 2.13; I^2 = 0%).

Sensitivity analysis

On sensitivity analyses stratified for steroid free regimens the effects were not different from steroid regimens for death, acute rejection, or GFR.

DISCUSSION

Summary of main results

This review describes CNI withdrawal or tapering classified according to: CNI withdrawal, low dose CNI, CNI withdrawal with mTOR-I substitution and low dose CNI with mTOR-I compared to standard dose CNI regimens. The four groups were further stratified into CNI avoidance and withdrawal studies for major outcomes.

In the CNI withdrawal comparison with standard regimens, there was an increase in both clinical acute rejection and BPAR. GFR was higher in the withdrawal group especially over longer time periods. Death, diabetes mellitus, hyperlipidaemia, total and CMV infections were not significantly different between the groups. Standard dose CNI regimens were more likely to be associated with hypertension when compared to CNI withdrawal patients. Graft loss was lower in the CNI withdrawal group; however, when stratified for avoidance studies, there was no difference in graft loss between the groups. These protocols (late withdrawal or avoidance) resulted in an increase in acute rejection with no clear benefit in terms of reduced graft loss. There was also no difference in the type of CNI (TAC or CsA) used or steroid-free regimens in causing acute rejection. The beneficial effects of CNI withdrawal in reducing graft loss were lost when studies with long-term outcomes were excluded.

In the low dose CNI comparison with standard dose regimens, there was a reduction in acute rejection, however when studies which administered induction treatment (IL2RA or anti-lymphocyte serum or globulin) were excluded from the analysis, acute rejection was similar in the low dose CNI and standard dose CNI regimens, both in the immediate and late introduction groups. GFR was higher in the low dose CNI group at both one and five years. There were no significant differences in death, diabetes mellitus, hyperlipidaemia, and CMV infection between the groups. Low dose CNI regimens had a marginal reduction in hypertension and total infections. Graft loss was reduced in the low dose CNI regimen, however when stratified for early and late intervention (taper), the effect was limited to the early intervention studies.

In the CNI avoidance or tapering with mTOR-I substitution compared to standard dose CNI regimens, there was no difference in death between the two groups. The mTOR-I substitution regimen however had more acute rejections (clinical and biopsy-proven) and had more hyperlipidaemia. CMV infection and malignancy were significantly lower in the mTOR-I substitution group. GFR was higher in the CNI avoidance with mTOR-I subgroup but not in the late intervention subgroup. There was no difference in other outcomes when stratified for early or late intervention. Overall these protocols (avoidance or tapering) showed no major change compared to CNI alone except for the increase in acute rejection when compared with either CNI (CsA or TAC). The major benefit of mTOR-I substitution is seen in the reduction in malignancies and CMV infections over time.

When low dose CNI was combined with mTOR-I and compared to standard dose CNI regimens, there were no differences in death, graft loss or acute rejection. Adverse events including malignancy were not significantly different between the groups. GFR and SCr at one year favoured the low dose CNI with mTOR-I regimen. However when stratified for early and late intervention there was increased acute rejection in the low dose CNI with mTOR-I regimens.

This review investigated a large number of studies comparing different CNI regimens. Many studies and reports were published in multiple journals at various time points and were presented as abstracts at scientific meetings without acknowledging previous publications. The same studies were also published under different authors and this review combined these reports under a single study and reported outcomes systematically. The methodology was robust and the studies were also assessed for study quality and heterogeneity explored by subgroup and stratified analysis.

The review classified interventions into four groups which reduced multiple comparisons due to several different regimens.

Overall completeness and applicability of evidence

Short time scales of most studies restrict the external validity of this review. Moving away from CNI may have multiple adverse long-term effects that will not be measured by these studies. The studies also do not mention of antibody-mediated rejection and pretransplant donor specific antibodies which could impact on short- and long-term graft survival. Removal of CNI may remove one long-term problem (CNI toxicity) but potentially cause worsening of other immunological issues which may in turn limit the duration of the graft. Low dose CNI seem the best option and mTOR-I benefits appear to be limited to a reduction in the risks of malignancy and CMV infection, though these benefits are uncertain and are not the case when combined with CNI.

Quality of the evidence

The overall quality of the evidence was poor, with unclear risks of bias due to poor reporting (Figure 2); only 30% reported randomisation method and allocation concealment. Almost all studies were open-label however for study outcomes such as death and graft loss they were not downgraded on GRADE assessment. Studies were analysed as intent to treat in 60% and all pre specified outcomes were reported in 54 studies. Almost half the studies received pharmaceutical funding which were classified as a high risk of bias.

The studies also used variable outcome measures and induction immunosuppression regimens. There is also variability in dosing, drug monitoring and time intervals of reporting outcomes. Most studies did not indicate baseline SCr or GFR to assess for changes due to the intervention. The follow-up duration in majority of the included studies was between six months and three years which is a major limitation for concluding long-term outcomes such as patient and graft survival.

Potential biases in the review process

There are multiple limitations of this review. The quality of data reporting was variable in terms of outcome and adverse effects. Most studies did not indicate the baseline creatinine or GFR to assess for changes due to the intervention. The standard deviation or confidence intervals were not noted when recording outcomes such as GFR and creatinine. Adverse effects were prevalent rather than incident cases which may affect outcomes such as diabetes mellitus, hyperlipidaemia and hypertension. The number of patients affected by individual outcomes were not indicated but mentioned as being significant with or without P values. Outcome reporting was not defined in cases of CMV, hypertension, hyperlipidaemia (total or low-density lipoprotein) or diabetes mellitus. Different studies used different targets for CNI monitoring and also used either trough (C0) or two hour (C2) levels; some studies based the dose on mg/kg body weight and this review used the study author definitions to classify low dose and standard dose regimens. This may have some limitation in external validity of these recommendations. However we have tried to minimise this by subclassification into four groups and analyse them further into early and late interventions. Most studies were short-term and did not capture long-term hard outcomes such as graft survival, patient survival or adverse effects (such as cardiovascular outcomes) and malignancy. The duration of

the majority of studies was between six months and three years with only three studies of up to five years duration. This raises the concern of how outcomes might be different after that time, particularly with regards to antibody-mediated rejection which can be a complication of reduced immune suppression. The only studies that included more than 10 years of follow-up tended to be much older studies, and compared immunosuppression such as azathioprine which is now largely obsolete or in very little use. The data from these studies is therefore limited by era effect. Studies with longer follow-up are required to confirm the potential benefits of CNI reduction or risks of long-term antibody-mediated rejection, most studies also do not differentiate between patients with high versus low immunological risk.

Agreements and disagreements with other studies or reviews

This is the first review which sub classified studies into four different intervention groups and analysed them as low dose calcineurin inhibitor or CNI withdrawal with or without mTOR-I substitution. The classification analysed the possible advantages noted in various studies with additional immunosuppressive agent such as mTOR-I or continuation of CNI at a low dose.

Sharif 2011 (56 studies, 11,337 participants) showed a similar increase in acute rejection without affecting graft survival, infection, and patient survival, it also concluded an increase in graft failure when mTOR-I was used. The review however did not classify studies into low dose or withdrawal as in our review but performed a pooled analysis which resulted in significant heterogeneity. In contrast to the conclusions of this review, Sharif 2011 reported lower NODAT in the CNI-sparing group. Moore 2009 included only CNI-sparing with MMF. The results were not stratified for mTOR-I; however the studies were classified into those who had de novo CNI minimisation and elective minimisation or elimination of CNI. The results in the withdrawal group were similar to our review but the lower dose of CNI was not beneficial in reduction of acute rejection as we report. A systematic review by Lim 2014 (29 studies, 2350 participants) analysed conversion to an mTOR-I based immunosuppression from CNI based therapy. They review reported short-term improvements in GFR with mTOR-I but increased acute rejections; there were no differences in graft loss or death. The conclusions of Lim 2014 are similar to our analysis of CNI withdrawal with mTOR-I, however our review also analysed low dose CNI and mTOR-I substitution.

AUTHORS' CONCLUSIONS

Implications for practice

CNI avoidance increased acute rejection and CNI withdrawal increases acute rejection but reduced graft loss at least over the short-term. Low dose CNI with induction regimens reduced acute rejection and graft loss with no major adverse events, also in the short-term. The use of mTOR-I reduced CMV infections but increased the risk of acute rejection. These conclusions must be tempered by the lack of long-term data in most of the studies, particularly with regards to chronic antibody-mediated rejection, and the suboptimal methodological quality of the included studies.

Implications for research

Despite a large number of randomised multicentre studies, significant issues remain unanswered. Most study data highlighted short-term outcomes due to the short follow-up. Longer follow-up will highlight hard end points such as cardiovascular outcomes, long-term graft survival and effects on malignancy. Cost benefit analysis and quality of life surveys to assess the effect of lower immunosuppression may also be of significant benefit. Carefully structured longer term studies into immunosuppression of kidney transplant patients need to delineate patient death, malignancy risk in protocols with or without CNI, immunological risk will need to include acute rejection, donor-specific antibodies and antibody-mediated rejection.

ACKNOWLEDGEMENTS

REFERENCES

References to studies included in this review

Abramowicz 2002 *{published data only}*

Abramowicz D, Del Carmen Rial M, Vitko S, del Castillo D, Manas D, Lao M, et al. Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: results of a five-year, prospective, randomized study. *Journal of the American Society of Nephrology* 2005;**16**(7):2234-40. [MEDLINE: 15917338]

Abramowicz D, Manas D, Lao M, Vanrenterghem Y, Del Castillo D, Wijngaard P, et al. Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen in stable kidney transplant recipients: a randomized, controlled study. *Transplantation* 2002;**74**(12):1725-34. [MEDLINE: 12499889]

del Castillo D, Abramowicz D, Manas D, Lao M, Vanrenterghem Y, Barker D, et al. Benefits of cyclosporine (CsA) withdrawal in stable renal transplant recipients, receiving mycophenolate mofetil (MMF) and steroids (S): a multicenter, randomised, controlled study [abstract no: A3674]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):726A. [CENTRAL: CN-00550730]

Alsina 1987 *{published data only}*

Alsina J, Grino JM, Castelao AM, Sabate I, Mestre M, Gil-Vernet S, et al. Low dose cyclosporine (CsA), ALG and steroids in first cadaveric renal transplants [abstract]. 10th International Congress of Nephrology; 1987 Jul 26-31; London, UK. 1987:606. [CENTRAL: CN-00583779]

Grino JM, Castelao AM, Sabate I, Mestre M, Gil-Vernet S, Andres E, et al. Low dose cyclosporine (CyA), ALG and steroids in first cadaveric renal transplants [abstract]. *Kidney International* 1988;**34**(2):301. [CENTRAL: CN-00644138]

Grino JM, Castelao AM, Sabate I, Mestre M, Gil-Vernet S, Andres E, et al. Low-dose cyclosporin (CsA), ALG and steroids in first cadaveric renal transplants [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(1):99-100.

Andres 2009 *{published data only}*

Andres A, Marcen R, Sanchez J, Valdes F, Errasti P, Sola R, et al. Comparative study of three different patterns of immunosuppression based on induction with basiliximab and low initial doses or delayed initiation of neoral in kidney transplant recipients at high risk of delayed graft function [abstract no: 1629]. *American Journal of Transplantation* 2005;**5**(Suppl 11):570. [CENTRAL: CN-00644164]

Andres A, Marcen R, Valdes F, Plumed JS, Sola R, Errasti P, et al. A randomized trial of basiliximab with three different patterns of cyclosporin A initiation in renal transplant from expanded criteria donors and at high risk of delayed graft function. *Clinical Transplantation* 2009;**23**(1):23-32. [MEDLINE: 18798851]

Marcen R, Andres A, Sanchez-Plumed J, Valdes F, Errasti P, Sola R, et al. A randomized study to compare immunosuppression based on basiliximab induction and low initial doses or delayed neoral in kidney transplant recipients

at high risk for delayed graft function [abstract no: PO-266]. *Transplant International* 2005;**18**(Suppl 1):114.

APOLLO Study 2015 *{published data only}*

Arns W, Rath T, Sommerer C, Reinke P, Haller H, Suwelack B, et al. Outcome on renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 5 year data of the APOLLO trial [abstract]. *Transplantation* 2014;**98**(Suppl 1):145. [EMBASE: 71543988]

Budde K, Rath T, Sommerer C, Haller H, Reinke P, Witzke O, et al. Renal, efficacy and safety outcomes following late conversion of kidney transplant patients from calcineurin inhibitor therapy to everolimus: the randomized APOLLO study. *Clinical Nephrology* 2015;**83**(1):11-21. [MEDLINE: 25512099]

Budde K, Sommerer C, Haller H, Suwelack B, May C, Paulus E, et al. Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 3 year data of the APOLLO trial [abstract no: 928]. *American Journal of Transplantation* 2012;**12**(Suppl S3):298. [EMBASE: 70746881]

Budde K, Sommerer C, Rath T, Reinke P, Haller H, Witzke O, et al. Renal function to 5 years after late conversion of kidney transplant patients to everolimus: a randomized trial. *Journal of Nephrology* 2015;**28**(1):115-23. [MEDLINE: 25192833]

Budde K, Sommerer C, Reinke P, Haller H, Arns W, Witzke O, et al. Outcome on renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 4 year data of the APOLLO Trial [abstract no: B396]. *American Journal of Transplantation* 2013;**13**(Suppl S5):311-2. [EMBASE: 71057512]

Budde K, Zeier M, Haller H, Arns W, Kramer S, Vogel EM, et al. Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients [abstract no: 1639]. *American Journal of Transplantation* 2010;**10**(Suppl 4):504. [EMBASE: 70465014]

Haller H, Rath T, Zeier M, Arns W, Kramer S, Vogel E, et al. Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients [abstract no: Sa645]. *NDT Plus* 2010;**3**(Suppl 3):iii259. [EMBASE: 70484111]

Rath T, Budde K, Sommerer C, Haller H, Suwelack B, May C, et al. Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 3 year data of the APOLLO trial [abstract no: 1684]. *Transplantation* 2012;**94**:994. [EMBASE: 71251767]

Rath T, Sommerer C, Suwelack B, Arns W, Haller H, Reinke P, et al. Outcome on renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 5 year data of the APOLLO trial [abstract]. *Transplantation International* 2014;**98**:50. [EMBASE: 71664130]

Reinke P, Haller H, Rath T, Arns W, Paulus E, Scheidf S, et al. Two year data of the APOLLO trial: Renal function of an

everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients [abstract no: P141]. *Transplant International* 2011;**24**:50. [EMBASE: 70537441]

Rhat T, Sommerer C, Haller H, Reinke P, Witzke O, Suwelack B, et al. Outcome on renal function of everolimus conversion in maintenance KTX patients: 4 years APOLLO trial [abstract no: P271]. *Transplant International* 2013;**26**(Suppl 2):240. [EMBASE: 71359891]

Sommerer C, Rath T, Budde K, Haller H, Arns W, Scheidl S, et al. Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 2 year follow-up data of the APOLLO trial [abstract no: RO-185]. *Transplant International* 2011;**24**(Suppl 2):180. [EMBASE: 70527714]

Sommerer C, Rath T, Haller H, Arns W, Suwelack B, Reinke P, et al. 4 year data of the APOLLO trial: outcome on renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients [abstract no: V79]. *Transplant International* 2013;**26**(Suppl 1):21. [EMBASE: 71356263]

Asberg 2006 {*published data only*}

Asberg A, Midtvedt K, Line PD, Narverud J, Holdaas H, Jenssen T, et al. Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006;**82**(1):62-8. [MEDLINE: 16861943]

Asberg A, Midtvedt K, Line PD, Narverud J, Holdaas H, Jenssen T, et al. Calcineurin inhibitor-avoidance with daclizumab, mycophenolate mofetil and prednisolone in DR matched de novo kidney transplant recipients [abstract no: SP737]. *Nephrology Dialysis Transplantation* 2006;**21**(Suppl 4):iv264.

Asberg A, Midtvedt K, Voytovich MH, Line PD, Narverud J, Reisaeter AV, et al. Calcineurin inhibitor effects on glucose metabolism and endothelial function following renal transplantation. *Clinical Transplantation* 2009;**23**(4):511-8. [MEDLINE: 19210527]

Asberg A, Midtvedt K, Voytovich MH, Line PD, Narverud J, Reisaeter AV, et al. Calcineurin inhibitor effects on glucose metabolism and endothelial function following renal transplantation [abstract no: 529]. *American Journal of Transplantation* 2008;**8**(Suppl 2):319.

ASCERTAIN Study 2011 {*published data only*}

Holdaas H, Midtvedt K, Seron D, O'Connell P, Thiagarajan CM, Fassett R, et al. Everolimus in maintenance renal transplant recipients: the ASCERTAIN Study [abstract no: P-309]. *Transplant International* 2009;**22**(Suppl 2):172.

Holdaas H, Midtvedt K, Seron D, O'Connell P, Thiagrajan C, Fassett R, et al. Assessment of everolimus in maintenance renal transplant recipients: the Ascertain Study [abstract no: 1646]. *Transplantation* 2008;**86**(Suppl 2):546. [CENTRAL: CN-00740482]

Holdaas H, Rostaing L, Midtvedt K, Seron D, Cole E, Chapman J, Fellstrom B, et al. Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study.[Erratum appears in Transplantation. 2011 Nov 27;92(10):e61 Note: multiple investigator names added.]. *Transplantation* 2011;**92**(4):410-8. [MEDLINE: 21697773]

O'Connell P, Fassett R, Pilmore H, Chapman J, Hutchison B, Russ G, et al. Long-term post transplantation switch to an everolimus-based therapy with CNI elimination/minimization does not overall impact graft function: the ASCERTAIN study [abstract no: 8]. Transplantation Society of Australia & New Zealand (TSANZ). 29th Annual Scientific Meeting; 2011 Jun 29-Jul 1; Canberra (ACT). 2011:42.

O'Connell P, Fassett R, Pilmore H, Chapman J, Hutchison B, Russ G, et al. Post-hoc analysis of the ASCERTAIN trial: everolimus based therapy with CNI elimination improves renal function in select populations [abstract no: 7]. Transplantation Society of Australia & New Zealand (TSANZ).29th Annual Scientific Meeting; 2011 Jun 29-Jul 1; Canberra (ACT). 2011:41.

Baczkowska 2003 {*published data only*}

Baczkowska T, Durlik M, Perkowska A, Sadowska A, Cieciura T, Nowacka-Cieciura E, et al. Cytokines and growth factors serum level and renal allograft function (preliminary report) [Cytokiny i czynniki wzrostu w surowicy u biorcow nerki allogenicznej a losy przeszczepu (doniesienie wstepne)]. *Polski Merkuriusz Lekarski* 2003;**15**(88):356-8. [MEDLINE: 14974365]

Baczkowska T, Perkowska A, Cieciura T, Wierzbicki P, Klosowka D, Matlosz B, et al. Daclizumab allows for a protocol with low-dose cyclosporine in low rejection-risk kidney recipients - preliminary data [abstract no: T435]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):309. [CENTRAL: CN-00400168]

Baczkowska T, Perkowska-Francka A, Durlik M, Cieciura T, Nowacka-Cieciura E, Pazik J, et al. The role of the protocol biopsies in renal allograft recipients. *Transplantation Proceedings* 2003;**35**(6):2179-81. [MEDLINE: 14529881]

Baczkowska T, Perkowska-Ptasinska A, Cieciura T, Pazik J, Nowacka-Cieciura E, Lewandowski Z, et al. Untreated subclinical, borderline rejection in 12 and 36-month protocol biopsies is not associated with progressive loss of GFR at 5-year's follow-up [abstract no: 1755]. *Transplantation* 2008;**86**(2 Suppl):581. [CENTRAL: CN-00671803]

Baczkowska T, Perkowska-Ptasinska A, Lewandowski Z, Nowacka-Cieciura E, Cieciura T, Pazik J, et al. Serum TGF-b1 correlates with chronic histopathological lesions in protocol biopsies in kidney allograft recipients [abstract no: P354]. *Transplantation* 2004;**78**(2 Suppl):319. [CENTRAL: CN-00583398]

Baczkowska T, Perkowska-Ptasinska A, Lewandowski Z, Nowacka-Cieciura E, Pazik J, Cieciura T, et al. Increased renal TFG-b protein expression in human allograft specimens correlates with renal allograft function and chronic histopathological changes [abstract no: SaP437]. *Nephrology Dialysis Transplantation* 2007;**22**(Suppl 6):vi382.

Baczkowska T, Perkowska-Ptasinska A, Pazik J, Cieciura T, Nowacka-Cieciura E, Lewandowski Z, et al. The role of the

protocol biopsies in renal allograft recipients: five-years' follow-up [abstract no: P093]. *Transplant International* 2007;**20**(Suppl 2):118.

Baczkowska T, Perkowska-Ptasinska A, Pazik J, Lewandowski Z, Nowacka-Cieciura E, Cieciura T, et al. The role of the protocol biopsies in renal allograft recipients: three-years' follow-up [abstract no: SP736]. *Nephrology Dialysis Transplantation* 2006;**21**(Suppl 4):iv263. [CENTRAL: CN-00602089]

Baczkowska T, Perkowska-Ptasinska A, Sadowska A, Lewandowski Z, Nowacka-Cieciura E, Cieciura T, et al. Serum TGF-beta1 correlates with chronic histopathological lesions in protocol biopsies of kidney allograft recipients. *Transplantation Proceedings* 2005;**37**(2):773-5. [MEDLINE: 15848527]

Baczkowska T, Sadowska A, Perkowska-Ptasinska A, Lewandowski Z, Cieciura T, Pazik J, et al. Optimal mycophenolic acid and mycophenolic acid glucuronide levels at the early period after kidney transplantation are the key contributors to improving long-term outcomes. *Transplantation Proceedings* 2009;**41**(8):3019-23. [MEDLINE: 19857666]

Baczkowska T, Wierzbicki P, Perkowska-Ptasinska A, Klosowska D, Nowaczyk M, Kowalska GK, et al. Pharmacodynamic monitoring in kidney allograft recipients with and without calcineurin inhibitors [abstract no: P-593]. *Transplant International* 2009;**22**(Suppl 2):242.

Bansal 2013 *{published data only}*

Bansal D, Yadav AK, Kumar V, Minz M, Sakhuja V, Jha V. Deferred pre-emptive switch from calcineurin inhibitor to sirolimus leads to improvement in GFR and expansion of t-regulatory cell population: a randomized, controlled trial. *PLoS ONE [Electronic Resource]* 2013;**8**(10):e75591. [MEDLINE: 24146762]

Barsoum 2007 *{published data only}*

Barsoum RS, Morsey AA, Iskander IR, Morgan MM, Fayad TM, Atalla NT, et al. The Cairo Kidney Center protocol for rapamycin-based sequential immunosuppression in kidney transplant recipients: 2-year outcomes. *Experimental & Clinical Transplantation* 2007;**5**(2):649-57. [MEDLINE: 18194116]

Bechstein-193 2013 *{published data only}*

Bechstein W, Paczek L. A phase II, open-label, concentration-controlled, randomized 6-month study of standard-dose tacrolimus + sirolimus + corticosteroids compared to reduced-dose tacrolimus + sirolimus + corticosteroids in renal allograft recipients [abstract]. *American Journal of Transplantation* 2002;**2**(Suppl 3):471. [CENTRAL: CN-00415252]

Bechstein WO, Paczek L, Wramner L, Squifflet JP, European Sirolimus-Tacrolimus Study Group. An open-label, concentration-controlled, randomised 6-month study of standard-dose tacrolimus + sirolimus + steroids compared to reduced-dose tacrolimus + sirolimus + steroids in renal allograft recipients [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):785. [CENTRAL: CN-00444369]

Bechstein WO, Paczek L, Wramner L, Squifflet JP, Zygmunt AJ, European Rapamune Tacrolimus Study Group. A comparative, randomized trial of concentration-controlled sirolimus combined with reduced-dose tacrolimus or standard-dose

tacrolimus in renal allograft recipients. *Transplantation Proceedings* 2013;**45**(6):2133-40. [MEDLINE: 23953523]

Paczek L, Bechstein W, Wramner L, Squifflet JP. A phase II, open-label, concentration-controlled, randomized 6-month study of standard-dose tacrolimus + sirolimus + corticosteroids compared to reduced-dose tacrolimus + sirolimus + corticosteroids in renal allograft recipients [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002.

Paczek L, Bechstein WO, Wramner L, Squifflet JP, European Sirolimus-Tacrolimus Study Group. An open-label, concentration-controlled, randomised 6-month study of standard-dose tacrolimus + sirolimus +steroids compared to reduced-dose tacrolimus + sirolimus + steroids in renal allograft recipients [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):464.

Whelchel J, Paczek L, Bechstein WO, Russ G. A regimen of sirolimus and reduced-dose tacrolimus results in improved renal allograft function: combined analysis of the North American target, European and Australian sirolimus-tacrolimus trials [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):464. [CENTRAL: CN-00448351]

Bertoni 2007 *{published data only}*

Bertoni E, Becherelli P, Salvadori M. Triple therapy with neoral, steroids and enteric-coated mycophenolate acid vs everolimus: efficacy, side effects and pharmaco-economic aspects. A monocentric experience [abstract no: F-PO614]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):234A. [CENTRAL: CN-00716078]

Rosati A, Bertoni E, Rosso G, Larti A, Mehmetaj A, Salvadori M. Triple therapy with Neoral, steroids and enteric coated mycophenolic acid vs everolimus: efficacy, side effects and pharmaco-economic aspects. A monocentric experience [abstract no: SaP477]. *Nephrology Dialysis Transplantation* 2007;**22**(Suppl 6):vi396. [CENTRAL: CN-00725011]

Bertoni 2011 *{published data only}*

Bertoni E, Larti A, Farsetti S, Rosso G, Di Maria L, Zanazzi M. Cyclosporine (CyA) very low dose with everolimus (E) high dose is associated with better outcomes in renal transplant patients with respect to standard treatment with EC-MPS (M) [abstract]. *Transplant International* 2009;**22**(Suppl 2):91.

Bertoni E, Larti A, Rosso G, Zanazzi M, Di Maria L, Salvadori M. Good outcomes with cyclosporine very low exposure with everolimus high exposure in renal transplant patients. *Journal of Nephrology* 2011;**24**(5):613-8. [MEDLINE: 21240873]

Budde 2007 *{published data only}*

Budde K, Bosmans J, Zeier M, Sennesael J, Hopt U, Fischer WH, et al. Safety and efficacy of reduced or full dose of cyclosporine (neoral®) in combination with mycophenolate sodium (Myfortic®), basiliximab (Simulect®), and steroids in de novo kidney transplant recipients [abstract]. *Transplantation* 2004;**78**(2 Suppl):83. [CENTRAL: CN-00527096]

Budde K, Bosmans JL, Sennesael J, Zeier M, Hopt U, Fischer W, et al. Reduced cyclosporine exposure is safe and efficacious in

combination with basiliximab, enteric-coated mycophenolate-sodium, and steroids [abstract no: 1195]. *American Journal of Transplantation* 2005;**5**(Suppl 11):461. [CENTRAL: CN-00644165]

Budde K, Bosmans JL, Sennesael J, Zeier M, Pisarski P, Schutz M, et al. Reduced-exposure cyclosporine is safe and efficacious in de novo renal transplant recipients treated with enteric-coated mycophenolic acid and basiliximab. *Clinical Nephrology* 2007;**67**(3):164-75. [MEDLINE: 17390741]

Budde K, Zeier M, Bosmans JL, Sennesael J, Glander P, Fischer W, et al. Reduced-exposure cyclosporine is safe and efficacious in de novo renal transplant recipients treated with enteric-coated mycophenolic acid and basiliximab [abstract no: F-PO1088]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):565A. [CENTRAL: CN-00644166]

Budde K, Zeier M, Cohen D, Kirchherr B, MyProms Study Group. How much exposure is needed in the first week in patients receiving induction with basiliximab and enteric coated mycophenolate sodium? [abstract no: 1206]. *American Journal of Transplantation* 2005;**5**(Suppl 11):464. [CENTRAL: CN-00602063]

Legendre C, Cohen D, Zeier M, Rostaing L, Budde K. Efficacy and safety of enteric-coated mycophenolate sodium in de novo renal transplant recipients: pooled data from three 12-month multicenter, open-label, prospective studies. *Transplantation Proceedings* 2007;**39**(5):1386-91. [MEDLINE: 17580145]

Legendre CH, Rostaing L, Kirchherr B, MyProms Study Group. Tolerability of enteric coated mycophenolate sodium (EC-MPS) in combination with neoral and steroids in de novo kidney transplant recipients: a 12 months prospective trial [abstract no: 1209]. *American Journal of Transplantation* 2005;**5**(Suppl 11):464-5. [CENTRAL: CN-00602066]

Pietruck F, Budde K, Salvadori M, Sollinger H, Bourbigot B, Gentil MA, et al. Efficacy and safety of enteric-coated mycophenolate sodium in renal transplant patients with diabetes mellitus: post hoc analyses from three clinical trials. *Clinical Transplantation* 2007;**21**(1):117-25. [MEDLINE: 17302600]

Rostaing L, Legendre CH, Cohen D, Budde K, Zeier M, Kirchherr B, et al. Safety and tolerability of enteric coated mycophenolate sodium in combination with neoral and steroids in de novo kidney transplant recipients: 12 months analysis of a prospective trial [abstract no: T-PO50030]. *Nephrology* 2005;**10**(Suppl 1):A215. [CENTRAL: CN-00644301]

CAESAR Study 2007 {*published data only*}

Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, CAESAR Study Group. Low-dose cyclosporine in conjunction with daclizumab, mycophenolate mofetil and corticosteroids is safe and effective in contrast to early cyclosporine withdrawal [abstract]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego (CA). 2004. [CENTRAL: CN-00550672]

Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, Calleja E, et al. The use of daclizumab and mycophenolate mofetil in combination with corticosteroids and cyclosporine (low dose versus low dose followed by withdrawal) to optimize

renal function in recipients of renal allografts [abstract]. *Transplantation* 2004;**78**(2 Suppl):458. [CENTRAL: CN-00509171]

Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. *American Journal of Transplantation* 2007;**7**(3):560-70. [MEDLINE: 17229079]

Grinyo J, Vanrenterghem Y, Nashan B, Vincenti F, Ekberg H, Spleiss O, et al. Association of three polymorphisms with acute rejection after kidney transplantation: an exploratory pharmacogenetic analysis of a randomized multicenter clinical trial (the CAESAR study) [abstract no: 1020]. *American Journal of Transplantation* 2006;**6**(Suppl 2):410. [CENTRAL: CN-00678972]

Kuypers DR, Ekberg H, Grinyo J, Nashan B, Vincenti F, Snell P, et al. Mycophenolic acid exposure after administration of mycophenolate mofetil in the presence and absence of cyclosporin in renal transplant recipients. *Clinical Pharmacokinetics* 2009;**48**(5):329-41. [MEDLINE: 19566116]

Vincenti F, Vanrenterghem Y, Nashan B, Grinyo J, Ekberg H, Nasmyth-Miller C, et al. The use of mycophenolate mofetil, daclizumab and corticosteroids with cyclosporine (low dose, low dose/withdrawal and standard dose) to optimize renal function in renal allograft recipients - 18 month results [abstract no: 1507]. *American Journal of Transplantation* 2005;**5**(Suppl 11):539. [CENTRAL: CN-00644286]

Cai 2014 {*published data only*}

Cai L, Zeng F, Liu B, Wei L, Chen Z, Jiang J. A single-centre, open-label, prospective study of an initially short-term intensified dosing regimen of enteric-coated mycophenolate sodium with reduced cyclosporine A exposure in Chinese live-donor kidney transplant recipients. *International Journal of Clinical Practice. Supplement* 2014;**68**(181):23-30. [MEDLINE: 24673716]

CALFREE Study 2010 {*published data only*}

Franz S, Regeniter A, Hopfer H, Mihatsch M, Dickenmann M. Tubular toxicity in sirolimus- and cyclosporine-based transplant immunosuppression strategies: an ancillary study from a randomized controlled trial. *American Journal of Kidney Diseases* 2010;**55**(2):335-43. [MEDLINE: 19926370]

Giannini O, Dickenmann M, Kim MJ, Franz S, Mayr M, Mihatsch MJ, et al. The CALFREE Study - an open, prospective, randomized single center study to investigate calcineurin free immunosuppression in 100 de novo, normal risk renal transplant recipients: preliminary results [abstract no: P04.02]. *Kidney & Blood Pressure Research* 2004;**27**(5-6):329. [CENTRAL: CN-00615861]

CENTRAL Study 2012 {*published data only*}

Mjornstedt L, Schwartz Sorensen S, von Zur Muhlen B, Jespersen B, Hansen JM, Bistrup C, et al. Renal function three years after early conversion from a calcineurin inhibitor to everolimus: results from a randomized trial in kidney transplantation. *Transplant International* 2015;**28**(1):42-51. [MEDLINE: 25176389]

Mjornstedt L, Sorensen SS, von Zur Muhlen B, Jespersen B, Hansen JM, Bistrup C, et al. Improved renal function after

early conversion from a calcineurin inhibitor to everolimus: a randomized trial in kidney transplantation. *American Journal of Transplantation* 2012;**12**(10):2744-53. [MEDLINE: 22812414]

Murbraech K, Holdaas H, Massey R, Undset LH, Aakhus S. Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients: An echocardiographic substudy of the randomized controlled CENTRAL trial. *Transplantation* 2014;**97**(2):184-7. [MEDLINE: 24092385]

Murbraech K, Massey R, Undset LH, Midtvedt K, Holdaas H, Aakhus S. Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients - a three-yr serial echocardiographic substudy of the randomized controlled CENTRAL trial. *Clinical Transplantation* 2015;**29**(8):678-84. [MEDLINE: 25982053]

CERTITEM Study 2015 *{published data only}*

Hertig A, Kamar N, Albano L, Anglicheau D, Durrbach A, Vuiblet V, et al. Epithelial to mesenchymal transition markers in kidney transplant recipients: The CERTITEM trial [abstract]. *Transplantation* 2014;**98**:81. [EMBASE: 71543793]

Hertig A, Kamar N, Anglicheau D, Moulin B, Hazzan M, Hurault De Ligny B, et al. Epithelial to mesenchymal transition markers in kidney transplant recipients: The CERTITEM trial [abstract no: O5]. *Transplant International* 2013;**26**(Suppl 3):2. [EMBASE: 71356080]

Hertig A, Kamar N, Anglicheau D, Moulin B, Hazzan M, Ligny BH, et al. Epithelial to mesenchymal transition markers in kidney transplant recipients: The CERTITEM trial [abstract no: P081]. *Transplant International* 2013;**26**(Suppl 2):201. [EMBASE: 71359712]

Rostaing L, Hertig A, Albano L, Anglicheau D, Durrbach A, Vuiblet V, et al. Fibrosis progression according to epithelial-mesenchymal transition profile: a randomized trial of everolimus versus CsA. *American Journal of Transplantation* 2015;**15**(5):1303-12. [MEDLINE: 25808994]

Chadban 2013 *{published data only}*

Chadban S, Campbell S, Russ G, Walker R, Chapman J, Pussell B, et al. A one-year, randomised, open label, parallel group study to investigate the safety and efficacy of enteric-coated mycophenolate sodium (EC-MPS) in combination with full dose or reduced dose cyclosporine microemulsion (CSA-ME), basiliximab and steroids in de novo kidney transplantation [abstract no: 32]. 24th Annual Scientific Meeting. Transplantation Society of Australia & New Zealand (TSANZ); 2006 Mar 29-31; Canberra, Australia. 2006:51. [CENTRAL: CN-00583470]

Chadban S, Eris J, Russ G, Campbell S, Chapman J, Pussell B, et al. Enteric-coated mycophenolate sodium in combination with full dose or reduced dose cyclosporine, basiliximab and corticosteroids in Australian de novo kidney transplant patients. *Nephrology* 2013;**18**(1):63-70. [MEDLINE: 23110508]

Chan 2008 *{published data only}*

Chan L, Greenstein S, Hardy MA, Hartmann E, Bunnapradist S, Cibrik D, et al. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. *Transplantation* 2008;**85**(6):821-6. [MEDLINE: 18360262]

Chan L, Hartmann E, Cibrik D, Cooper M, Shaw LM. Everolimus (RAD001) concentration is associated with risk reduction for acute rejection in de novo renal transplant recipients [abstract no: SA-PO2529]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):678A. [CENTRAL: CN-00716072]

Chan L, Hartmann E, Cibrik D, Cooper M, Shaw LM. Optimal everolimus concentration is associated with risk reduction for acute rejection in de novo renal transplant recipients. *Transplantation* 2010;**90**(1):31-7. [MEDLINE: 20517177]

Chan 2012 *{published data only}*

Asderakis A, Chan L. Renal function with enteric-coated mycophenolate sodium in combination with reduced and standard tacrolimus levels: results of a 6-month study in de novo renal transplant recipients [abstract no: O111]. British Transplantation Society (BTS).12th Annual Congress; 2009 Apr 21-24; Liverpool, UK. 2009.

Chan L, Andres A, Bunnapradist S, Gugliuzza K, Parasuraman R, Peddi VR, et al. Renal function and NODM in de novo renal transplant recipients treated with standard and reduced levels of tacrolimus in combination with EC-MPS. *Journal of Transplantation* 2012;**2012**:941640. [MEDLINE: 23227307]

Chan L, Hart M, Andres A, Gugliuzza K, Bunnapradist S, Parasumaran R. Renal function and incidence of NODM with enteric-coated mycophenolate sodium in combination with reduced and standard tacrolimus levels: results of a 6-month comparative study in de novo renal transplant recipients [abstract no: 718]. *Transplantation* 2008;**86**(2S):251.

Nicholson ML, Chan L. Incidence of new onset diabetes mellitus in de novo renal transplant recipients treated with enteric-coated mycophenolate sodium in combination with reduced or standard tacrolimus target levels: results of a 6-month randomized study [abstract no: P266]. British Transplantation Society (BTS).12th Annual Congress; 2009 Apr 21-24; Liverpool, UK. 2009.

Chhabra 2013 *{published data only}*

Alvarado A, Chhabra D, Wang E, Najafian N, Friedewald J, Ho B, et al. Prospective randomized study to evaluate the feasability of CNI elimination with conversion to sirolimus in prednisone-free immunosuppressive regimen [abstract no: 53]. *American Journal of Transplantation* 2012;**12**(Suppl S3):42. [EMBASE: 70746000]

Alvarado A, Shetty A, Traitanon O, Leventhal J, Mas V, Chhabra D, et al. Calcineurin-inhibitor conversion to mTOR inhibitor in renal transplant recipients leads to worse long term clinical outcomes [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953109]

Chhabra D, Alvarado A, Dalal P, Leventhal J, Wang C, Sustento-Reodica N, et al. Impact of calcineurin-inhibitor conversion to mTOR inhibitor on renal allograft function in a prednisone-free regimen. *American Journal of Transplantation* 2013;**13**(11):2902-11. [MEDLINE: 24007570]

Gallon L, Traitanon O, Sustento-Reodica N, Leventhal J, Ansari MJ, Gehrau RC, et al. Cellular and molecular immune profiles in renal transplant recipients after conversion from tacrolimus to sirolimus. *Kidney International* 2014;**87**(4):828-38. [MEDLINE: 25354238]

Shah G, Xu L, Dalal P, Chhabran D, Friedewald J, Ho B, et al. Conversion from CNI to SRL in a pred-free immunosuppressive regimen: interim report of a prospective randomized study [abstract no: 1641]. *American Journal of Transplantation* 2010;**10**(Suppl 4):504.

Cibrik 2007 *{published data only}*

Bresnahan B, Cibrik D, Jensik S, Whelchel J, Klintmalm G, Cohen D, et al. Treatment of high-risk renal transplant recipients with EC-MPS (Myfortic®) is safe and efficacious [abstract no: PUB216]. *Journal of the American Society of Nephrology* 2005;**16**:829A. [CENTRAL: CN-00644277]

Budde K, Zeier M, Cohen D, Kirchherr B, MyProms Study Group. How much exposure is needed in the first week in patients receiving induction with basiliximab and enteric coated mycophenolate sodium? [abstract no: 1206]. *American Journal of Transplantation* 2005;**5**(Suppl 11):464. [CENTRAL: CN-00602063]

Cibrik D, Jensik S, Bresnahan B, Whelchel J, Klintmalm G, ERL2405-US01 Study Group. Safety and efficacy of EC-MPS in combination with simulect and neoral in de novo renal transplant high-risk recipients [abstract no: 135]. *American Journal of Transplantation* 2005;**5**(Suppl 11):190. [CENTRAL: CN-00644170]

Cibrik D, Jensik S, Meier-Kriesche H, Bresnahan B, Lieberman B, Myfortic US01 Renal Transplant Group. Enteric-coated mycophenolate sodium in combination with optimized neoral dosing, basiliximab, and steroids results in good efficacy and renal function in renal transplant recipients in the first six months [abstract no: 220]. *American Journal of Transplantation* 2004;**4**(Suppl 8):218. [CENTRAL: CN-00644278]

Cibrik D, Meier-Kriesche HU, Bresnahan B, Wu YM, Klintmalm G, Kew CE, et al. Renal function with cyclosporine C2 monitoring, enteric-coated mycophenolate sodium and basiliximab: a 12-month randomized trial in renal transplant recipients. *Clinical Transplantation* 2007;**21**(2):192-201. [MEDLINE: 17425744]

Legendre C, Cohen D, Zeier M, Rostaing L, Budde K. Efficacy and safety of enteric-coated mycophenolate sodium in de novo renal transplant recipients: pooled data from three 12-month multicenter, open-label, prospective studies. *Transplantation Proceedings* 2007;**39**(5):1386-91. [MEDLINE: 17580145]

Legendre CH, Rostaing L, Kirchherr B, MyProms Study Group. Tolerability of enteric coated mycophenolate sodium (EC-MPS) in combination with neoral and steroids in de novo kidney transplant recipients: a 12 months prospective trial [abstract no: 1209]. *American Journal of Transplantation* 2005;**5**(Suppl 11):464-5. [CENTRAL: CN-00602066]

Meier-Kriesche H, Cibrik D, Bresnahan B, Cohen D, Lieberman B. Optimized Neoral C2 monitoring in combination with enteric-coated mycophenolic acid, basiliximab and steroids is

effective, safe and tolerable: 12-month results of a multicenter, randomized, prospective trial [abstract no: F-PO1068]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):299A. [CENTRAL: CN-00583408]

Pietruck F, Budde K, Salvadori M, Sollinger H, Bourbigot B, Gentil MA, et al. Efficacy and safety of enteric-coated mycophenolate sodium in renal transplant patients with diabetes mellitus: post hoc analyses from three clinical trials. *Clinical Transplantation* 2007;**21**(1):117-25. [MEDLINE: 17302600]

Rostaing L, Legendre CH, Cohen D, Budde K, Zeier M, Kirchherr B, et al. Safety and tolerability of enteric coated mycophenolate sodium in combination with neoral and steroids in de novo kidney transplant recipients: 12 months analysis of a prospective trial [abstract no: T-PO50030]. *Nephrology* 2005;**10**(Suppl 1):A215. [CENTRAL: CN-00644301]

Cockfield 2002 *{published data only}*

Cockfield S, Whelchel J, MacDonald A. An open-label, concentration-controlled, randomized, 6-month study of standard-dose tacrolimus + sirolimus + corticosteroids compared to reduced-dose tacrolimus + sirolimus + corticosteroids in renal allograft recipients [abstract no: 1021]. *American Journal of Transplantation* 2002;**2**(Suppl 3):395. [MEDLINE: CN-00420821]

Daloze P, Whelchel J, Cockfield S, MacDonald A. A 6-month multicenter randomized concentration-controlled study of reduced-dose tacrolimus (TAC)+sirolimus(SRL)+corticosteroids(CS) compared to standard-dose TAC+SRL+CS in clinical kidney transplantation [abstract no: 0555]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415490]

CONCEPT Study 2009 *{published data only}*

Chun DX, Alexandre H, Sandrine GS, Olivier T, Isabelle E, Christophe L, et al. The phenotype of tubular epithelial cells does not recover after a conversion from cyclosporine A to siroliumus [abstract]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii517. [EMBASE: 70766851]

Joannides R, Monteil C, De Ligny BH, Westeel PF, Iacob M, Thervet E, et al. Immunosuppressant regimen based on sirolimus decreases aortic stiffness in renal transplant recipients in comparison to cyclosporine. *American Journal of Transplantation* 2011;**11**(11):2414-22. [MEDLINE: 21929645]

Lebranchu Y, Etienne I, Touchard G, Thervet E, Westell P, Toupance O, et al. Comparison of efficacy and safety of cyclosporine (CsA) discontinuation with introduction of sirolimus (SRL) at week 12 to standard strategy in renal transplant recipients receiving mycophenolate mofetil (MMF) [abstract no: 53]. *American Journal of Transplantation* 2007;**7**(Suppl 2):160. [CENTRAL: CN-00724873]

Lebranchu Y, Thierry A, Thervet E, Buchler M, Etienne I, Westeel PF, et al. Efficacy and safety of early cyclosporine conversion to sirolimus with continued MMF-four-year results of the Postconcept study. *American Journal of Transplantation* 2011;**11**(8):1665-75. [MEDLINE: 21797975]

Lebranchu Y, Thierry A, Toupance O, Westeel PF, Etienne I, Thervet E, et al. Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: Concept study. *American Journal of Transplantation* 2009;**9**(5):1115-23. [MEDLINE: 19422337]

Lebranchu Y, Toupance O, Touchard G, Thervet E, Etienne I, Mazouz H, et al. Impact on renal function of early conversion at 3 months from cyclosporine (CSA) to sirolimus (SRL) in association with mycophenolate mofetil (MMF) in kidney transplantation: 30 months follow up of a multicenter randomized controlled trial: The CONCEPT Study [abstract no: Sa706]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009. [CENTRAL: CN-00765353]

Lebranchu Y, Toupance O, Touchard G, Thervet E, Etienne I, Mazouz H, et al. Impact on renal function of early conversion at 3 months from cyclosporine (CsA) to sirolimus (SRL) in association with mycophenolate mofetil (MMF) in kidney transplantation: 30-months follow up of a multicenter randomized controlled trial: the Concept Study [abstract no: 241]. *American Journal of Transplantation* 2009;**9**(Suppl 2):260. [EMBASE: 70010114]

Lebranchu Y, Toupance O, Touchard G, Thervet E, Etienne I, Westeel PF, et al. Impact of early conversion at 3 months from cyclosporine (CSA) to sirolimus (SRL) in association with mycophenolate mofetil (MMF) on renal function - "results at 48 months of follow up of a multicenter randomized controlled trial: The Concept Study" [abstract no: 376]. *American Journal of Transplantation* 2010;**10**(Suppl 4):151. [EMBASE: 70463737]

Servais A, Meas-Yedid V, Lebranchu Y, Etienne I, Touchard G, Legendre C, et al. Comparison at one year of interstitial fibrosis (IF) by automatic quantification in renal transplant recipients with cyclosporine (CsA) discontinuation and sirolimus (SRL) introduction [abstract no: 527]. *American Journal of Transplantation* 2008;**8**(Suppl 2):319. [CENTRAL: CN-00716068]

Servais A, Meas-Yedid V, Lebranchu Y, Etienne I, Touchard G, Westeel PF, et al. Comparison of interstitial fibrosis (IF) by automatic quantification at one year in renal transplant recipients with cyclosporine (CsA) discontinuation and sirolimus (SRL) introduction [abstract no: TH-FC040]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):10A. [CENTRAL: CN-00716074]

Servais A, Meas-Yedid V, Toupance O, Lebranchu Y, Thierry A, Moulin B, et al. Interstitial fibrosis quantification in renal transplant recipients randomized to continue cyclosporine or convert to sirolimus. *American Journal of Transplantation* 2009;**9**(11):2552-60. [MEDLINE: 19843033]

Servais A, Meas-Yedid V, Toupance O, Lebranchu Y, Touchard G, Westeel PF, et al. Impact of interstitial fibrosis (IF) by automatic quantification at one year on the evolution of renal function in transplant recipients with cyclosporine discontinuation and sirolimus introduction [abstract no: 1103]. *American Journal of Transplantation* 2009;**9**(Suppl 2):502. [CENTRAL: CN-00775138]

Thervet E, Servais A, Meas-Yedid V, Lebranchu Y, Etienne I, Touchard G, et al. Comparison at one year of interstitial fibrosis (IF) by automatic quantification in renal transplant

recipients (RTR) with cyclosporine (CSA) discontinuation and sirolimus (SRL) introduction [abstract no: 450]. *Transplantation* 2008;**86**(Suppl 2):159. [CENTRAL: CN-00740483]

Thierry A, Lebranchu Y, Toupance O, Westeel PF, Etienne E, Thervet E, et al. Impact of inflammatory subclinical lesions (ISCL) at M12 on renal function at M48: results from Post-Concept Study [abstract no: 1648]. *American Journal of Transplantation* 2010;**10**(Suppl 4):506.

Thierry A, Thervet E, Vuiblet V, Goujon JM, Machet MC, Noel LH, et al. Long-term impact of subclinical inflammation diagnosed by protocol biopsy one year after renal transplantation. *American Journal of Transplantation* 2011;**11**(10):2153-61. [MEDLINE: 21883902]

Vuiblet V, Birembaut P, Francois A, Cordonnier C, Noel LH, Goujon JM, et al. Sirolimus-based regimen is associated with decreased expression of glomerular vascular endothelial growth factor. *Nephrology Dialysis Transplantation* 2012;**27**(1):411-6. [MEDLINE: 21617191]

Vuiblet V, Birembaut P, Francois A, Jaureguy M, Thierry A, Thervet E, et al. Sirolimus-based regimen is associated with decreased expression of vascular endothelial growth factor in kidneys: ancillary study of the CONCEPT Study [abstract no: 1652]. *American Journal of Transplantation* 2010;**10**(Suppl 4):507.

Xu-Dubois YC, Hertig A, Lebranchu Y, Hurault de Ligny B, Thervet E, Jaureguy M, et al. Progression of pulse pressure in kidney recipients durably exposed to CsA is a risk factor for epithelial phenotypic changes: an ancillary study of the CONCEPT trial. *Transplant International* 2014;**27**(4):344-52. [MEDLINE: 24279707]

Xu-Dubois YC, Lebranchu Y, Hurault de Ligny B, Thervet E, Mazouz H, Lepogamp P, et al. Conversion from cyclosporine to sirolimus at M3 after renal transplantation does not reduce the score of epithelial to mesenchymal transition at M12: ancillary study of the CONCEPT Study [abstract no: 1664]. *American Journal of Transplantation* 2010;**10**(Suppl 4):510.

CONVERT Trial 2009 *{published data only}*

Alberu J, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, Polinsky M, et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation* 2011;**92**(3):303-10. [MEDLINE: 21792049]

Alberu J, Schena FP, Wali R, Pascoe M, Del Carmen Rial M, The Sirolimus CONVERT Trial Study Group. Lower malignancy rates in renal allograft recipients converted to sirolimus (SRL)-based, calcineurin inhibitor-free immunotherapy: 24 month results from the CONVERT trial [abstract no: TH-FC082]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):18A. [CENTRAL: CN-00601954]

Brennan D, Schena FP, Wali R, The Sirolimus CONVERT Trial Study Group. Factors contributing to the development of proteinuria after conversion from calcineurin inhibitors to sirolimus: results from the multicenter CONVERT trial [abstract

no: TH-FC083]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):18A. [CENTRAL: CN-00601955]

Chapman J, Campistol JM, Grinyo JM, Morales JM, Mota A, Schena FP. Results from a long-term extension study in renal allograft recipients show that sirolimus-based therapy without cyclosporine is a safe alternative to sirolimus plus cyclosporine therapy. [abstract no: F-PO1050]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):295A. [CENTRAL: CN-00583164]

Oberbauer R, Schena FP, Wali R, Pascoe M, Alberu J, Del Carmen Rial M, et al. Conversion from calcineurin inhibitors to sirolimus compared with continued use of calcineurin inhibitors in renal allograft recipients: 24-month safety and efficacy results from the CONVERT trial [abstract no: F-FC154]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):69A. [CENTRAL: CN-00601952]

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Brown F, et al. A randomised, open-label, comparative evaluation of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients [abstract no: PS71]. *Nephrology* 2005;**10**(Suppl 3):A397. [CENTRAL: CN-00644366]

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Kanellis J, et al. Conversion from calcineurin inhibitors to sirolimus compared with continued use of calcineurin inhibitors in renal allograft recipients: 24-month safety and efficacy results from the CONVERT trial study group [abstract]. *Immunology & Cell Biology* 2007;**85**(4):A27-8.

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Kanellis J, et al. Conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: 18-month efficacy and safety results from a large, randomized, open-label, comparative trial [abstract no: 106]. 24th Annual Scientific Meeting. Transplantation Society of Australia & New Zealand [TSANZ]; 2006 Mar 29-31; Canberra, Australia. 2006:91. [CENTRAL: CN-00644368]

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Kanellis J, et al. Efficacy and safety of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: results of the CONVERT trial [abstract no: 2006]. *Nephrology* 2006;**11**(Suppl 2):A35. [CENTRAL: CN-00583835]

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Kanellis J, et al. Factors contributing to the development of urinary protein excretion after conversion from calcineurin inhibitors to sirolimus: results from the multicenter CONVERT trial [abstract]. *Immunology & Cell Biology* 2007;**85**(4):A21.

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Kanellis J, et al. Reduced incidence of malignancy in renal transplant recipients converted from calcineurin inhibitors (CNIS) to sirolimus (SRL) compared with those who continued CNI therapy [abstract no: 1582]. *Nephrology* 2006;**11**(Suppl 2):A24. [CENTRAL: CN-00583837]

Pussell B, Russ G, Walker R, Campbell S, O'Connell P, et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24 month results from the CONVERT Trial [abstract]. *Immunology & Cell Biology* 2007;**85**(4):A20.

Pussell B, Russ G, Walker R, O'Connell P, Kanellis J. Determinants of proteinuria after conversion from a calcineurin inhibitor to sirolimus-based immunosuppressive regimen: results from the CONVERT Trial [abstract no: 1572]. *Nephrology* 2006;**11**(Suppl 2):A21. [CENTRAL: CN-00583834]

Russ G, Pussell B, Walker R, Campbell S, O'Connell P, Kanellis J, et al. Analysis of the incidence of anaemia and its treatment after sirolimus conversion versus calcineurin inhibitor continuation in renal allograft recipients: 2-year results from the ongoing CONVERT trial [abstract]. *Immunology & Cell Biology* 2007;**85**(4):A20.

Russ G, Schena FP, Oberbauer R, The Sirolimus CONVERT Trial Study Group. Incidence and treatment of anemia after conversion to sirolimus vs. continuation of calcineurin inhibitors in renal allograft recipients: 2-year results from the CONVERT Trial [abstract no: TH-FC081]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):18A. [CENTRAL: CN-00601953]

Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 2009;**87**(2):233-42. [MEDLINE: 19155978]

Schena FP, Wali RK, Pascoe MD, Alberu J, Del Carmen Rial M. A randomized, open-label, comparative evaluation of the safety and efficacy of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients [abstract no: PO-456]. *Transplant International* 2005;**18**(Suppl 1).

Schena FP, Wali RK, Pascoe MD, Alberu J, Del Carmen Rial M, The Sirolimus CONVERT Trial Study Group. Efficacy and safety of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: 12-month results from a large, randomized, open-label, comparative trial [abstract no: TH-FC155]. *Journal of the American Society of Nephrology* 2005;**16**:33A. [CENTRAL: CN-00601956]

Schena FP, Wali RK, Pascoe MD, Alberu J, Del Carmen Rial M, The Sirolimus Renal Conversion Trial Study Group. A randomized, open-label, comparative evaluation of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients [abstract no: 1008]. *American Journal of Transplantation* 2005;**5**(Suppl 11):413. [CENTRAL: CN-00689212]

Schena FP, Wali RK, Pascoe MD, Alberu J, Del Carmen Rial M, The Sirolimus Renal Conversion Trial Study Group. Conversion to sirolimus in kidney transplant patients receiving maintenance calcineurin inhibitor immunosuppression: a randomized, open-label, comparative clinical trial [abstract no: SP440]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):v165. [CENTRAL: CN-00689740]

Steinberg S, Schena FP, Wali R, The Sirolimus CONVERT Trial Study Group. Multivariate and univariate analyses of factors influencing renal allograft function after conversion to sirolimus (SRL)-based immunotherapy from calcineurin inhibitors (CI) [abstract no: TH-PO582]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):231A. [CENTRAL: CN-00601958]

Vathsala A, Schena F, Wali RK, Pascoe MD, Alberu J, Del Carmen Rial M, et al. Conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: a randomized, open-label, comparative trial [abstract no: T-PO50036]. *Nephrology* 2005;**10**(Suppl 1):A217. [CENTRAL: CN-00601967]

CTOT-09 Study 2015 *{published data only}*

Formica R, Nickerson P, Poggio E, Tinckam K, Rush D, Gibson I, et al. Immune monitoring and tacrolimus (TAC) withdrawal in low risk recipients of kidney transplants-results of CTOT09 [abstract]. *Transplantation* 2014;**98**(Suppl 1):225. [EMBASE: 71544207]

* Hricik DE, Formica RN, Nickerson P, Rush D, Fairchild RL, Poggio ED, et al. Adverse outcomes of tacrolimus withdrawal in immune-quiescent kidney transplant recipients. *Journal of the American Society of Nephrology* 2015;**26**(12):3114-22. [MEDLINE: 25925687]

Nickerson P, Wiebe C, Formica R, Tinckam K, Poggio E, Bunnapradist S, et al. Epitope mismatch predicts de novo DSA after CNI withdrawal in low-risk kidney transplant recipients [abstract]. *Transplantation* 2014;**98**(Suppl 1):137. [EMBASE: 71543963]

de Sevaux 2001 *{published data only}*

Smak Gregoor PJ, de Sevaux RG, Hene RJ, Hilbrands LB, van Gelder T, Hoitsma AJ, et al. The cyclosporine sparing effect of mycophenolate mofetil, a randomized study [abstract]. *Journal of the American Society of Nephrology* 1998;**9**(Program & Abstracts):699A. [CENTRAL: CN-00447776]

de Sevaux RG, Gregoor PJ, Hene RJ, Hoitsma AJ, Vos P, Weimar W, et al. A controlled trial comparing two doses of cyclosporine in conjunction with mycophenolate mofetil and corticosteroids. *Journal of the American Society of Nephrology* 2001;**12**(8):1750-7. [MEDLINE: 11461949]

de Sevaux RG, Smak Gregoor PJ, Hene RJ, Hoitsma AJ, Vos P, et al. Addition of mycophenolate mofetil to cyclosporine and prednisone allows for a lower dose of cyclosporine after renal transplantation [abstract]. XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sept 1; Rome, Italy. 2000. [CENTRAL: CN-00583239]

de Sévaux RG, Smak Gregoor PJ, Hené RJ, Weimar W, Hoitsma AJ, Van Gelder T, et al. A randomised study of conventional vs low dose cyclosporine in renal transplant recipients treated with cyclosporine, mycophenolate mofetil and prednisone [abstract no: 418]. *Transplantation* 1998;**65**(12):S107. [CENTRAL: CN-00583548]

DICAM Study 2010 *{published data only}*

Etienne I, Toupance O, Benichou J, Thierry A, Al Najjar A, Hurault dL, et al. A 50% reduction in cyclosporine exposure in stable renal transplant recipients: renal function benefits. *Nephrology Dialysis Transplantation* 2010;**25**(9):3096-106. [MEDLINE: 20299336]

Dudley 2005 *{published data only}*

Dudley C, Pohanka E, Riad H, Dedochova J, Wijngaard P, Marshall S, et al. MMF substitution for CSA in chronic allograft dysfunction: 2 year follow-up of a multi-center randomized controlled study [abstract no: 1513]. *American Journal of Transplantation* 2005;**5**(Suppl 11):541.

Dudley C, Pohanka E, Riad H, Dedochova J, Wijngaard P, Sutter C, et al. Mycophenolate mofetil substitution for cyclosporine a in renal transplant recipients with chronic progressive allograft dysfunction: the "creeping creatinine" study. *Transplantation* 2005;**79**(4):466-75. [MEDLINE: 15729174]

Dudley CR, MMF 'Creeping Creatinine' Study Group. MMF substitution for CSA is an effective and safe treatment of chronic allograft dysfunction; results of a multi-center randomized controlled study [abstract no: 41]. *American Journal of Transplantation* 2002;**2**(Suppl 3):148.

Tedesco de Silva H. MMF replacing CSA reverses the "creeping creatinine" of renal transplant recipients of a multi-center randomized controlled study [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416751]

El-Agroudy 2014 *{published data only}*

El-Agroudy A, Alarrayed S, Ghareeb S, Farid E, Alhellow H, Abdulla S. Long-term outcome of a prospective randomized trial of conversion from tacrolimus to sirolimus treatment after renal transplantation [abstract no: B964]. *Transplantation* 2014;**98**(Suppl 1):539. [EMBASE: 71545346]

Fangmann 2010 *{published data only}*

Fangmann J, Arns W, Marti H, Budde K, Beckurts T, Hauss J. Low dose cyclosporine regimen with daclizumab induction and mycophenolate mofetil after kidney transplantation - impact on renal function and rejection episodes [abstract no: 113]. *American Journal of Transplantation* 2005;**5**(Suppl 11):185. [CENTRAL: CN-00644197]

Fangmann J, Arns W, Marti H, Budde K, Neumayer H, Beckurts T, et al. Impact of daclizumab and low dose cyclosporine in combination with mycophenolate mofetil and steroids on renal function after kidney transplantation [abstract no: 715]. *American Journal of Transplantation* 2004;**4**(Suppl 8):353. [CENTRAL: CN-00509182]

Fangmann J, Arns W, Marti H, Budde K, Neumayer H, Beckurts T, et al. Impact of daclizumab and low dose cyclosporine in combination with mycophenolate mofetil and steroids on renal function after kidney transplantation [abstract no: P249]. *Transplantation* 2004;**78**(2 Suppl):280.

Fangmann J, Arns W, Marti HP, Hauss J, Ketteler M, Beckurts T, et al. Impact of daclizumab, low-dose cyclosporine, mycophenolate mofetil and steroids on renal function after kidney transplantation. *Nephrology Dialysis Transplantation* 2010;**25**(1):283-92. [MEDLINE: 19773417]

Ferguson 2006 *{published data only}*

Ferguson R, Mulgaonkar S, Tedesco Silva H, Oppenheimer F, Walker R, et al. FTY720 with reduced-exposure (R-E) cyclosporine [neoral] (CsA): acute rejection prophylaxis in de novo renal transplant (Tx) recipients [abstract]. Transplantation Society of Australia and New Zealand. 21st Annual Meeting; 2003 Apr 9-11; Canberra (ACT). 2003:63. [CENTRAL: CN-00445317]

Ferguson RM, Mulgaonkar S, Tedesco H, Oppenheimer F, Walker R, Kunzendor U, et al. FTY720 with reduced-exposure neoral provides adequate rejection prophylaxis in de novo renal transplant recipients. Interim results [abstract no: 0049]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415638]

Ferguson RM, Mulgaonkar S, Tedesco H, Oppenheimer F, Walker R, Russ G, et al. High efficacy of FTY720 with reduced cyclosporine dose in preventing rejection in renal transplantation: 12-month preliminary results [abstract no: 624]. *American Journal of Transplantation* 2003;**3**(Suppl 5):311. [CENTRAL: CN-00445316]

Mulgaonkar S, Tedesco H, Oppenheimer F, Walker R, Kunzendorf U, Russ G, et al. FTY720/cyclosporine regimens in de novo renal transplantation: a 1-year dose-finding study. [Erratum appears in Am J Transplant. 2006 Dec;6(12):3044]. *American Journal of Transplantation* 2006;**6**(8):1848-57. [MEDLINE: 16771816]

Russ G, Ferguson RM, Mulgaonkar S, Tedesco-Silva H, Oppenheimer F, Walker R, et al. FTY720 with reduced dose Neoral (RDN) may offer a safety/tolerability profile advantage over conventional immunosuppressive therapies [abstract no: 1000]. *American Journal of Transplantation* 2004;**4**(Suppl 8):432. [CENTRAL: CN-00509451]

Flechner-318 Study 2002 *{published data only}*

Flechner SM, Burke JT, Cook DJ, Mastroianni B, Savas K, Goldfarb D, et al. A randomized prospective trial of sirolimus vs cyclosporine in kidney transplantation: renal function and histology at two years [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):450. [CENTRAL: CN-00445351]

Flechner SM, Cook DJ, Goldfarb D, Modlin C, Mastroianni B, Savas K, et al. A randomized trial of sirolimus vs cyclosporine in kidney transplantation: impact on blood cells, lymphocyte subsets, and flow crossmatches [abstract no: 1317]. *American Journal of Transplantation* 2002;**2**(Suppl 3):470.

Flechner SM, Cook DJ, Goldfarb D, Modlin C, Mastroianni B, Savas K, et al. A randomized trial of sirolimus vs cyclosporine in kidney transplantation: impact on blood cells, lymphocyte subsets, and flow crossmatches [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415657]

Flechner SM, Goldfarb D, Modlin C, Feng J, Krishnamurthi V, Mastroianni B, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. *Transplantation* 2002;**74**(8):1070-6. [MEDLINE: 12438948]

Flechner SM, Goldfarb D, Solez K, Modlin CS, Mastroianni B, Savas K, et al. Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-year results of a randomized prospective trial compared to calcineurin inhibitor drugs. *Transplantation* 2007;**83**(7):883-92. [MEDLINE: 17460558]

Flechner SM, Kurian S, Solez K, Cook DJ, Burke JT, Rollin H, et al. Kidney transplantation with sirolimus and mycophenolate mofetil based immunosuppression preserves renal structure and function at two years compared to calcineurin inhibitor drugs [abstract no: O361]. *Transplantation* 2004;**78**(2 Suppl):141. [CENTRAL: CN-00509193]

Flechner SM, Kurian SM, Solez K, Cook DJ, Burke JT, Rollin H, et al. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *American Journal of Transplantation* 2004;**4**(11):1776-85. [MEDLINE: 15476476]

Flechner SM, Solez K, Cook DJ, Burke JT, Rollin H, Mastoianni B, et al. Kidney transplantation with sirolimus and mycophenolate mofetil based immunosuppression preserves renal structure and function compared to calcineurin inhibitor (CNI) drugs [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):296. [CENTRAL: CN-00509194]

Garcia 2007 *{published data only}*

Garcia R, Hanzawa NM, Machado PG, Moreira SR, Prismich G, Felipe CR, et al. A calcineurin inhibitor-free regimen for low risk kidney transplant recipients [abstract no: 2379]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00520337]

Garcia R, Machado PG, Felipe CR, Park SI, Spinelli GA, Franco MF, et al. Exploratory calcineurin inhibitor-free regimens in living-related kidney transplant recipients. *Brazilian Journal of Medical & Biological Research* 2007;**40**(4):457-65. [MEDLINE: 17401488]

Grimbert 2002 *{published data only}*

Grimbert P, Baron C, Fruchaud G, Hemery F, Desvaux D, Buisson C, et al. Long-term results of a prospective randomized study comparing two immunosuppressive regimens, one with and one without CsA, in low-risk renal transplant recipients. *Transplant International* 2002;**15**(11):550-5. [MEDLINE: 12461659]

Grinyo 2004 *{published data only}*

Campistol JM, Grinyo JM, Paul J, Garcia J, Arias M, Morales JM, et al. Sirolimus, TAC and corticosteroids in the postoperative period. Preliminary results [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002.

Grinyo JM, Campistol JM, Paul J, Garcia J, Arias M, Morales JM, et al. A randomised, open, multicenter, trial comparing tacrolimus (TAC) withdrawal with TAC dose reduction in de novo renal transplants, receiving sirolimus (SIR), TAC and steroids in the postoperative time. Initial results [abstract no: SA-PO0491]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):363A. [CENTRAL: CN-00445561]

Grinyo JM, Campistol JM, Paul J, Garcia J, Arias M, Morales JM, et al. A randomised, open-label, pilot study to compare the safety and efficacy of tacrolimus (TAC) elimination with tac dose reduction in de novo renal allograft recipients, receiving sirolimus, tac and corticosteroids in the postoperative period. Preliminary results [abstract]. *American Journal of Transplantation* 2002;**2**(Suppl 3):394.

* Grinyo JM, Campistol JM, Paul J, Garcia-Martinez J, Morales JM, Prats D, et al. Pilot randomized study of early tacrolimus withdrawal from a regimen with sirolimus plus tacrolimus in kidney transplantation. *American Journal of Transplantation* 2004;**4**(8):1308-14. [MEDLINE: 15268733]

Morales JM, Grinyo JM, Campistol JM, Garcia J, Arias M, Paul J, et al. FK-506 withdrawal from a regimen of sirolimus plus FK-506 results at 2 years in an improvement in renal function, blood pressure and proteinuria in ongoing kidney recipients [abstract no: 1192]. *American Journal of Transplantation* 2005;**5**(Suppl 11):460. [CENTRAL: CN-00724880]

Morales JM, Grinyo JM, Campistol JM, Garcia-Martinez J, Arias M, Paul J, et al. Improved renal function, with similar proteinuria, after two years of early tacrolimus withdrawal from a regimen of sirolimus plus tacrolimus. *Transplantation* 2008;**86**(4):620-2. [MEDLINE: 18724234]

Paul J, Grinyo JM, Campistol JM, Garcia J, Morales JM, Arias M, et al. A randomised, open-label, pilot study to compare the safety and efficacy of tacrolimus (TAC) elimination with tac dose reduction in de novo renal allograft recipients, receiving sirolimus, TAC and corticosteroids in the postoperative period: preliminary results [abstract]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):18-9. [CENTRAL: CN-00550490]

Hall 1988 *{published data only}*

Gallagher M, Jardine M, Cass A, Perkovic V, Petrie J, McDonald S, et al. 20 year outcomes of the Australian multicentre randomised trial of cyclosporine withdrawal in renal transplantation [abstract no: 1075]. *Nephrology* 2007;**12**(Suppl 2):A19. [CENTRAL: CN-00653709]

Gallagher M, Jardine M, Cass A, Perkovic V, Petrie J, McDonald S, et al. 20 year outcomes of the Australian multicentre randomised trial of cyclosporine withdrawal in renal transplantation [abstract]. *Immunology & Cell Biology* 2007;**85**(4):A19.

* Gallagher M, Jardine M, Perkovic V, Cass A, McDonald S, Petrie J, et al. Cyclosporine withdrawal improves long-term graft survival in renal transplantation. *Transplantation* 2009;**87**(12):1877-83. [MEDLINE: 19543068]

Gallagher M, Webster A, Jardine M, Perkovic V, Cass A, Eris J. Twenty year cancer outcomes of a randomized trial of immunosuppression in kidney transplant recipients: results of the Australian multicentre trial of cyclosporine withdrawal [abstract no: 078]. *Nephrology* 2008;**13**(Suppl 3):A119. [CENTRAL: CN-00758532]

Gallagher MP, Eris JM, Tiller DJ, Hall BM. Long term outcome of Australian multicentre trial of cyclosporin withdrawal in

cadaveric renal transplantation [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415694]

Gallagher MP, Hall B, Craig J, Berry G, Tiller DJ, Eris J, et al. A randomized controlled trial of cyclosporine withdrawal in renal-transplant recipients: 15-year results. *Transplantation* 2004;**78**(11):1653-60. [MEDLINE: 15591955]

Gallagher MP, Kelly PJ, Jardine M, Perkovic V, Cass A, Craig JC, et al. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *Journal of the American Society of Nephrology* 2010;**21**(5):852-8. [MEDLINE: 20431040]

Gallagher MP, Webster AC, Jardine MJ, Perkovic V, Cass A, Eris JM. Twenty year cancer outcomes of a randomized trial of immunosuppression in kidney transplant recipients: results of the Australian multicentre trial of cyclosporine withdrawal [abstract no: 288]. *Transplantation* 2008;**86**(2 Suppl):102.

Hall BM, Tiller DJ, Hardie I, Mahony J, Mathew T, Thatcher G, et al. Comparison of three immunosuppressive regimens in cadaver renal transplantation: long-term cyclosporine, short-term cyclosporine followed by azathioprine and prednisolone, and azathioprine and prednisolone without cyclosporine. *New England Journal of Medicine* 1988;**318**(23):1499-507. [MEDLINE: 3285215]

Hazzan 2005 *{published data only}*

Hazzan M, Buob D, Labalette M, Provot F, Glowacki F, Hoffmann M, et al. Assessment of the risk of chronic allograft dysfunction after renal transplantation in a randomized cyclosporine withdrawal trial. *Transplantation* 2006;**82**(5):657-62. [MEDLINE: 16969289]

Hazzan M, Copin MC, Labalette M, Glowacki F, Provot F, Roumilhac D, et al. Predictive factors of acute rejection after early cyclosporine withdrawal in renal transplant recipients receiving mycophenolate mofetil: results from a prospective, randomized trial [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):197. [CENTRAL: CN-00445673]

Hazzan M, Hertig A, Buob D, Noel C, Copin M, Rondeau E, et al. Cyclosporin induces epithelial to mesenchymal transition in renal grafts [abstract no: 131]. *American Journal of Transplantation* 2008;**8**(Suppl 2):214.

* Hazzan M, Labalette M, Copin MC, Glowacki F, Provot F, Pruv FR, et al. Predictive factors of acute rejection after early cyclosporine withdrawal in renal transplant recipients who receive mycophenolate mofetil: results from a prospective, randomized trial. *Journal of the American Society of Nephrology* 2005;**16**(8):2509-16. [MEDLINE: 15987748]

Heering 1993 *{published data only}*

Heering P, Westhoff A, Ivens K K, Grabensee B. Comparison between the effects of CSA and azathioprine on functional renal parameters in randomized study after renal transplantation [abstract]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):940. [CENTRAL: CN-00484304]

Heering P, Westhoff A, Ivens K, Helmchen U, Grabensee B. Increased risk in conversion of stable renal allografts from

cyclosporin to azathioprine: a randomized controlled study [abstract]. 12th International Congress of Nephrology; 1993 Jun 13-18; Jerusalem, Israel. 1993:194.

Heering P, Westhoff K, Ivens B, Kutkuhn B, Grabensee H. Increased risk in conversion of stable renal allografts from cyclosporin to azathioprine [abstract]. *Nephrology Dialysis Transplantation* 1993;**8**(9):1041. [CENTRAL: CN-00260889]

Ivens K, Heering P, Withold W, Koch M, Reinauer H, Grabensee B. Withdrawal of cyclosporine improves the cardio-vascular risk profile in renal graft recipients [abstract]. *Journal of the American Society of Nephrology* 1994;**5**(3):1013.

HERAKLES Study 2012 *{published data only}*

Arns W, Budde K, Sommerer C, Witzke O, Guba M, Jacobi J, et al. Month 48 follow-up results of HERAKLES trial on three different treatment regimen and switching off behaviour in de novo renal transplant patients [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953873]

Arns W, Neumayer H, Lehner F, Witzke O, Sommerer C, Kliem V, et al. HERAKLES at month 24: follow-up results on efficacy and safety of three different treatment regimens in de novo renal transplant patients demonstrate options for individualized immunosuppression [abstract no: BO148]. *Transplant International* 2013;**26**(Suppl 2):21. [EMBASE: 71356261]

Arns W, Sommerer C, Witzke O, Lehner F, Zeier M, Neumayer HH, et al. Efficacy and safety of three different treatment regimens in de novo renal transplant patients: results of the HERAKLES trial [abstract no: 1722]. *Transplantation* 2012;**94**(10):995. [EMBASE: 71251769]

Budde K, Arns W, Sommerer C, Lehner F, Zeier M, Neumayer H, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/ mycophenolate and low cyclosporine/ everolimus: follow-up of the HERAKLES study at month 36 [abstract no: 716]. *Transplantation* 2014;**98**(Suppl 1):81. [EMBASE: 71543792]

Budde K, Arns W, Sommerer C, Lehner F, Zeier M, Neumayer H, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus: follow-up of the HERAKLES study at month 24 [abstract no: B932]. *American Journal of Transplantation* 2013;**13**(Suppl 5):310-1. [EMBASE: 71057508]

Budde K, Sommerer C, Weithofer P, Witzke O, Guba M, Jacobi J, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus: follow-up of the HERAKLES study at month 48 [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71954274]

Budde K, Witzke O, Lehner F, Zeier M, Neumayer H, Stangl M, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/ mycophenolate and low cyclosporine/everolimus: the

HERAKLES Study [abstract no: 50]. *American Journal of Transplantation* 2012;**12**(Suppl S3):41. [EMBASE: 70745997]

Guba M, Budde K, Sommerer C, Neumayer HH, Lehner F, Reinke P, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus: follow-up of the HERAKLES study at month 36 [abstract no: V62]. *Transplant International* 2014;**27**(Suppl 3):22. [EMBASE: 71664029]

Guba M, Witzke O, Lehner F, Arns W, Sommerer C, Neumayer H, et al. The HERAKLES study at 24 month: Superior renal function in an everolimus-based CNI free regimen [abstract no: O219]. *Transplant International* 2013;**26**(Suppl 2):110. [EMBASE: 71359365]

Hauser IA, Witzke O, Arns W, Reinke P, Sommerer C, Neumayer HH, et al. Efficacy and safety of three different treatment regimens in de novorenal transplant patients: month 36 follow-up results of HERAKLES trial [abstract no: P132]. *Transplant International* 2014;**27**(Suppl 3):51. [EMBASE: 71664135]

Hoerning A, Kohler S, Jun C, Lu J, Fu J, Tebbe B, et al. Cyclosporin but not everolimus inhibits chemokine receptor expression on CD4+ T cell subsets circulating in the peripheral blood of renal transplant recipients. *Clinical & Experimental Immunology* 2012;**168**(2):251-9. [MEDLINE: 22471287]

Lehner F, Guba M, Arns W, Sommerer C, Neumayer HH, Jacobi J, et al. Follow-up data from HERAKLES study at month 24: maintained superior renal function in patients on an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus [abstract no: P04]. *Transplant International* 2013;**26**(Suppl 1):28. [EMBASE: 71356287]

Lehner F, Sommerer C, Witzke O, Arns W, Kliem V, Neumayer HH, et al. HERAKLES at month 24: efficacy and safety of 3 different regimens in de novo renal transplant patients [abstract no: BO148]. *Transplant International* 2013;**26**(Suppl 2):82. [EMBASE: 71359263]

Sommerer C, Budde K, Kliem V, Witzke O, Guba M, Jacobi J, et al. Efficacy and safety of three different treatment regimen in de novo renal transplant patients: month 48 follow-up results of the HERAKLES trial [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953341]

Sommerer C, Lehner F, Arns W, Reinke P, Eisenberger U, Heller K, et al. Post HOC analysis of ZEUS and HERAKLES, two prospective, open-label, multicenter, randomized trials: onset and progression of diabetes in kidney transplant recipients on cyclosporine standard or converted to CNI-free or CNI-low everolimus regimen [abstract no: 2921]. *Transplantation* 2014;**98**(Suppl 1):145-6. [EMBASE: 71543989]

Sommerer C, Lehner F, Budde K, Arns W, Hauser IA, Suwelack B, et al. Post hoc analysis of ZEUS and HERAKLES, two prospective, open-label, multicenter, randomized trials: onset and progression of diabetes in kidney transplant recipients on cyclosporine standard or converted to CNI-free or CNI-

low everolimus regimen [abstract no: P127]. *Transplant International* 2014;**27**(Suppl 3):50. [EMBASE: 71664131]

Sommerer C, Witzke O, Lehner F, Zeier M, Neumayer H, Stangl M, et al. Efficacy and safety of three different treatment regimens in de novo renal transplant patients: results of the HERAKLES Trial [abstract no: 51]. *American Journal of Transplantation* 2012;**12**(Suppl S3):41. [EMBASE: 70745998]

Witzke O, Budde K, Lehner F, Zeier M, Neumayer HH, Stangl M, et al. Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus: the HERAKLES study [abstract no: 1675]. *Transplantation* 2012;**94**(Suppl):993. [EMBASE: 71251766]

Zeier M, Budde K, Arns W, Guba M, Sommerer C, Neumayer H, et al. Efficacy and safety of three different treatment regimens in de novo renal transplant patients: follow-up results of the HERAKLES trial at month 24 [abstract no: 495]. *American Journal of Transplantation* 2013;**13**(Suppl S5):183.

Zeier M, Budde K, Arns W, Guba M, Sommerer C, Neumayer H, et al. Efficacy and safety of three different treatment regimens in de novo renal transplant patients: month 36 follow-up results of HERAKLES trial [abstract no: 718]. *Transplantation* 2014;**98**(Suppl 1):81-2. [EMBASE: 71543794]

Hollander 1995 *{published data only}*

Bakker RC, Hollander AA, Mallat MJ, Bruijn JA, Paul LC, de Fijter JW. Conversion from cyclosporine to azathioprine at three months reduces the incidence of chronic allograft nephropathy. *Kidney International* 2003;**64**(3):1027-34. [MEDLINE: 12911553]

Hollander AA, van Saase JL, Kootte AM, van Dorp WT, van Bockel HJ, van Es LA, et al. Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. *Lancet* 1995;**345**(8950):610-4. [MEDLINE: 7898178]

Holm 2008 *{published data only}*

Holm A, Hernandez M, Camarena A, Perez L, Santos M, Porras MA. Efficacy, tolerability and safety of mycophenolate mofetil (Cellcept) + sirolimus (Rapamune) as maintenance therapy after calcineurin inhibitor withdrawal in LRD and CAD, adults and pediatric renal transplant recipients (experience with 405 patients) [abstract no: 627]. *Transplantation* 2008;**86**(Suppl 2):220. [CENTRAL: CN-00740576]

Isoniemi 1990 *{published data only}*

Isoniemi H. Renal allograft immunosuppression V: glucose intolerance occurring in different immunosuppressive treatments. *Clinical Transplantation* 1991;**5**(3):268-72. [EMBASE: 21188067]

Isoniemi H. Renal allograft immunosuppression. III. Triple therapy versus three different combinations of double drug treatment: two year results in kidney transplant patients. *Transplant International* 1991;**4**(1):31-7. [MEDLINE: 2059298]

* Isoniemi H, Ahonen J, Eklund B, Hockerstedt K, Salmela K, von Willebrand E, et al. Renal allograft immunosuppression. II. A randomized trial of withdrawal of one drug in triple drug immunosuppression. *Transplant International* 1990;**3**(3):121-7. [MEDLINE: 2271083]

Isoniemi H, Ahonen J, Krogerus L, Eklund B, Hockerstedt K, Salmela K, et al. Chronic rejection of renal allografts with four immunosuppressive regimens. *Transplantation Proceedings* 1992;**24**(6):2716-7. [MEDLINE: 1465912]

Isoniemi H, Eklund B, Hockerstedt K, Korsback C, Salmela K, von Willebrand E, et al. Discontinuation of one drug in triple drug treatment of renal allograft patients: 1-year results. *Transplantation Proceedings* 1990;**22**(4):1365-6. [MEDLINE: 2202111]

Isoniemi H, Krogerus L, von Willebrand E, Taskinen E, Gronhagen-Riska C, Ahonen J, et al. Renal allograft immunosuppression. VI. Triple drug therapy versus immunosuppressive double drug combinations: histopathological findings in renal allografts. *Transplant International* 1991;**4**(3):151-6. [MEDLINE: 1958279]

Isoniemi H, Tikkanen M, Hayry P, Eklund B, Hockerstedt K, Salmela K, et al. Lipid profiles with triple drug immunosuppressive therapy and with double drug combinations after renal transplantation and stable graft function. *Transplantation Proceedings* 1991;**23**(1 (Pt 2)):1029-31. [MEDLINE: 1989148]

Isoniemi H, Tikkanen MJ, Ahonen J, Hayry P. Renal allograft immunosuppression. IV. Comparison of lipid and lipoprotein profiles in blood using double and triple immunosuppressive drug combinations. *Transplant International* 1991;**4**(3):130-5. [MEDLINE: 1958276]

Isoniemi H, von Willebrand E, Ahonen J, Eklund B, Hockerstedt K, Krogerus L, et al. Late histopathological findings in renal allografts with four immunosuppressive regimens. *Transplant International* 1992;**5 Suppl 1**:S6-7. [MEDLINE: 14621718]

Isoniemi HM, Ahonen J, Tikkanen MJ, von Willebrand EO, Krogerus L, Eklund BH, et al. Long-term consequences of different immunosuppressive regimens for renal allografts. [Erratum appears in Transplantation 1998 Sep 15;66(5):678]. *Transplantation* 1993;**55**(3):494-9. [MEDLINE: 8456467]

Isoniemi HM, Krogerus L, von Willebrand E, Taskinen E, Ahonen J, Hayry P. Histopathological findings in well-functioning, long-term renal allografts. *Kidney International* 1992;**41**(1):155-60. [MEDLINE: 1593852]

Kosch 2003a *{published data only}*

Hausberg M, Lang D, Levers A, Suwelack B, Kisters K, Tokmak F, et al. Sympathetic nerve activity in renal transplant patients before and after withdrawal of cyclosporine. *Journal of Hypertension* 2006;**24**(5):957-64. [MEDLINE: 16612259]

Hausberg M, Suwelack B, Kosch M, Barenbrock M, Gerhardt U, Hohage H, et al. Effects of calcineurin-inhibitor withdrawal on sympathetic nerve activity and blood pressure in renal transplant recipients [abstract]. *Deutsche Medizinische Wochenschrift* 2001;**126**:S193. [CENTRAL: CN-00383083]

Kosch M, Hausberg M, Suwelack B. Studies on effects of calcineurin inhibitor withdrawal on arterial distensibility and endothelial function in renal transplant recipients. *Transplantation* 2003;**76**(10):1516-9. [MEDLINE: 14657697]

Kosch M, Suwelack B, Barenbrock M, Kobelt V, Hohage H, Rahn KH, et al. Studies on effects of calcineurin-inhibitor withdrawal on arterial distensibility and endothelial function in renal transplant recipients. *Deutsche Medizinische Wochenschrift* 2001;**126**:S185. [CENTRAL: CN-00383367]

Kreis 2003 *{published data only}*

Kreis H, Miloradovich T, Mourad G, Cointault O, Berthoux F, Delahousse M, et al. Daclizumab and mycophenolate mofetil in renal transplant recipients: 2-year outcome after early reduction of cyclosporine [abstract no: 1266]. *American Journal of Transplantation* 2003;**3**(Suppl 5):476. [CENTRAL: CN-00446199]

Kreis H, Miloradovich T, Mourad G, Cointault O, Berthoux F, Delahousse M, et al. Lowering cyclosporine dose is not associated with an increased risk of gastro-intestinal adverse events nor the need for dosage decrease of mycophenolate mofetil [abstract no: P743]. *Transplantation* 2004;**78**(2 Suppl):462. [CENTRAL: CN-00509292]

MacPhee 1998 *{published data only}*

Joss N. Randomised study comparing cyclosporin with azathioprine one year after renal transplantation - 15 year outcome [abstract]. *Scottish Medical Journal* 2005;**50**(2):82. [CENTRAL: CN-00653805]

Joss N, Glasgow Transplant Group. Randomised study comparing cyclosporin with azathioprine one year after renal transplantation - 15 year outcome [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:197. [CENTRAL: CN-00636135]

* Joss N, Rodger RS, McMillan MA, Junor BJ. Randomized study comparing cyclosporine with azathioprine one year after renal transplantation-15-year outcome data. *Transplantation* 2007;**83**(5):582-7. [MEDLINE: 17353778]

MacPhee IA, Bradley JA, Briggs JD, Junor BJ, Macpherson SG, McMillan MA, et al. Long-term outcome of a prospective randomized trial of conversion from cyclosporine to azathioprine treatment one year after renal transplantation. *Transplantation* 1998;**66**(9):1186-92. [MEDLINE: 9825816]

MacPhee IA, Briggs JD, Junor BJ, McMillan MA, Rodger RS, Watson MA. A prospective randomised controlled trial of long-term outcome for renal transplant recipients converted from cyclosporin to azathioprine treatment one year after transplantation [abstract]. *Journal of the American Society of Nephrology* 1996;**7**(9):1915. [CENTRAL: CN-00602085]

Martinez-Mier 2006 *{published data only}*

* Martinez-Mier G, Mendez-Lopez MT, Budar-Fernandez LF, Estrada-Oros J, Franco-Abaroa R, George-Micelli E, et al. Living related kidney transplantation without calcineurin inhibitors: Initial experience in a Mexican center. *Transplantation* 2006;**82**(11):1533-6. [MEDLINE: 17164728]

MECANO Study 2009 *{published data only}*

Baas MC, Gerdes VE, ten Berge IJ, Heutinck KM, Florquin S, Meijers JC, et al. Treatment with everolimus is associated with a procoagulant state. *Thrombosis Research* 2013;**132**(2):307-11. [MEDLINE: 23906938]

Baas MC, Kers J, Florquin S, de Fijter JW, van der Heide JJ, van den Bergh Weerman MA, et al. Cyclosporine versus everolimus: effects on the glomerulus. *Clinical Transplantation* 2013;**27**(4):535-40. [MEDLINE: 23795805]

Baas MC, Struijk GH, Moes DJ, van den Berk IA, Jonkers RE, de Fijter JW, et al. Interstitial pneumonitis caused by everolimus: a case-cohort study in renal transplant recipients. *Transplant International* 2014;**27**(5):428-36. [MEDLINE: 24484452]

* Bemelman FJ, de Maar EF, Press RR, van Kan HJ, ten Berge IJ, Homan van der Heide JJ, et al. Minimization of maintenance immunosuppression early after renal transplantation: an interim analysis. *Transplantation* 2009;**88**(3):421-8. [MEDLINE: 19667948]

Havenith SH, Yong SL, van Donselaar-van der Pant KA, van Lier RA, ten Berge IJ, Bemelman FJ. Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8+ T-cell response compared with cyclosporine- or mycophenolate-treated patients. *Transplantation* 2013;**95**(1):184-91. [MEDLINE: 23222818]

Struijk GH, Minnee RC, Koch SD, Zwinderman AH, van Donselaar-van der Pant KA, Idu MM, et al. Maintenance immunosuppressive therapy with everolimus preserves humoral immune responses. *Kidney International* 2010;**78**(9):934-40. [MEDLINE: 20703211]

Van Dijk M, Van Roon A, Sanders JS. Intima media thickness (IMT) and major adverse cardiac events (MACE) in patients after kidney transplantation [abstract no: P226]. *Transplant International* 2015;**28**(Suppl 4):431. [EMBASE: 72112220]

ten Berge IJ, De Maar E, Press R, van der Heide JH, de Fijter H, Bemelman FJ. Minimization of immunosuppressive drug therapy at 6 months after renal transplantation: everolimus or cyclosporin superior to mycophenolate sodium [abstract no: 532]. *Transplantation* 2008;**86**(Suppl 2):186. [CENTRAL: CN-00740475]

van der Heide JJ, de Fijter JW, de Maar EF, ten Berge I, Bemelman FJ. Low acute rejection rate and superior renal function 2 years after early CsA withdrawal and overnight switch to everolimus [abstract no: 1654]. *American Journal of Transplantation* 2010;**10**(Suppl 4):508.

MODIFY Study 2012 *{published data only}*

David-Neto E, Lemos F, Antonopoulos I, Souza P, Piovesan A, Ventura C, Kanashiro H, et al. Five-year follow-up of the MoDIFY study (modification of doses to improve function through the years) shows benefit of low tacrolimus and regular MMF doses [abstract]. *Journal of Urology* 2011;**185**(4 Suppl 1):e828. [EMBASE: 70378695]

David-Neto E, Lemos FC, de Souza PS, Ventura CG, de Castro MCR\, Agena F, et al. Five-year follow-up of the MoDIFY Study (Modification of Doses to Improve Function through the Years) shows benefit of low tacrolimus and regular MMF doses [abstract no: 1655]. *American Journal of Transplantation* 2010;**10**(Suppl 4):508. [EMBASE: 70465030]

David-Neto E, Pereira LM, Castro MC, Mattos RM, Sumita NM, Mendes E, et al. Interim analysis of the MODIFY study in renal transplantation [abstract]. *Transplantation* 2004;**78**(2 Suppl):278-9. [CENTRAL: CN-00509408]

David-Neto E, Pereira LM, Castro MC, Mattos RM, Sumita NM, Mendes E, et al. Therapeutic levels of mycophenolic acid under fixed doses of MMF on the first two months after kidney transplantation [abstract]. *Transplantation* 2004;**78**(2 Suppl):278.

David-Neto E, Pereira LM, de Castro CR, Mattos RM, Sumita NM, Mendes ME, et al. Interim analysis of the MODIFY study in renal transplantation (Modification of Doses to Improve Function through the Years) [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):234-5. [CENTRAL: CN-00509150]

David-Neto E, Pereira LM, de Castro MC, Mattos RM, Ventura CG, Sumita NM, et al. Therapeutic levels of mycophenolic acid under fixed doses of MMF on the first two months after kidney transplantation [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):255. [CENTRAL: CN-00509409]

David-Neto E, Souza PS, Panajotopoulos N, Rodrigues H, Ventura CG, David DS, et al. The impact of pretransplant donor-specific antibodies on graft outcome in renal transplantation: a six-year follow-up study. *Clinics* 2012;**67**(4):355-61. [MEDLINE: 22522761]

Pereira LM, de Castro MC, Ventura CG, Reis FS, Sumita NM, Saito MI, et al. The MODIFY Study in renal transplantation (Modification of Doses to Improve Function Through the Years) [abstract]. *American Journal of Transplantation* 2005;**5**(Suppl 11):466.

Pereira LM, de Castro MC, Ventura CG, Soares PS, Ferreira GF, Saldanha LB, et al. A prospective, randomized and controlled trial of tacrolimus minimization in renal transplantation: 1-year result of the MODIFY study [abstract no: 53]. *American Journal of Transplantation* 2006;**6**(Suppl 2):84. [CENTRAL: CN-00671794]

Muhlbacher 2014 *{published data only}*

Muehlbacher F, Neumayer HH, del Castillo D, Stefoni S, European Sirolimus CsA Minimisation Study Group. An open-label study to evaluate the efficacy & safety of cyclosporine reduction in de novo renal allograft recipients receiving sirolimus: a dose comparative study [abstract no: 1224]. *American Journal of Transplantation* 2003;**3**(Suppl 5):465. [CENTRAL: CN-00446852]

* Muhlbacher F, Neumayer HH, del Castillo D, Stefoni S, Zygmunt AJ, Budde K, et al. The efficacy and safety of cyclosporine reduction in de novo renal allograft patients receiving sirolimus and corticosteroids: results from an

open-label comparative study. *Transplant International* 2014;**27**(2):176-86. [MEDLINE: 24266855]

Muhlbacher F, Paczek L. An open-label study to evaluate the efficacy & safety of cyclosporine reduction in de novo renal allograft recipients receiving sirolimus: a dose comparative study [abstract no: 399]. *American Journal of Transplantation* 2002;**2**(Suppl 3):238.

Neumayer H, Muhlbacher F, Stefoni S, Del Castillo D, Myfortic Maintenance Renal Transplantation Study Group. An open-label study to evaluate the efficacy & safety of cyclosporine reduction in de novo renal allograft recipients receiving sirolimus: a dose comparative study [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416320]

Neumayer HH, Muehlbacher F, del Castillo D, Stefoni S, European Sirolimus CsA Minimisation Study Group. An open-label study to evaluate the efficacy & safety of cyclosporine reduction in de novo renal allograft recipients receiving sirolimus: a dose comparative study [abstract no: W738]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):785. [CENTRAL: CN-00446926]

Nafar 2012 *{published data only}*

Nafar M, Alipour B, Ahmadpoor P, Pour-Reza-Gholi F, Samadian F, Samavat S, et al. Sirolimus versus calcineurin inhibitor-based immunosuppressive therapy in kidney transplantation: a 4-year follow-up. *Iranian Journal of Kidney Diseases* 2012;**6**(4):300-6. [MEDLINE: 22797101]

Nashan 2004 *{published data only}*

Curtis J, Nashan B, Poniicelli C, Mourad G, Boger R, RAD 156 Study Group. One year result of a multicenter, open-label trial on safety and efficacy of certican (RAD) used in combination with simulect, corticosteroids, and full or reduced dose neoral in renal transplant [abstract no: 1335]. *American Journal of Transplantation* 2001;**1**(Suppl 1):474. [CENTRAL: CN-00444958]

Curtis J, Nashan B, Ponticelli C, Mourad G, Boger R, RAD 156 Study Group. Everolimus (RAD) in combination with reduced dose with reduced dose neoral® maintains effective immunosuppression with improved tolerability compared to full dose neoral [abstract no: A4625]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):884A. [CENTRAL: CN-00550720]

Mourad G, Boger R, Curtis J, Nashan B, Ponticelli C, RAD B 156 Study Group. CERTICAN (TM) (RAD; EVEROLIMUS), the proliferation signal inhibitor, is complementary with a reduced dose NEORAL® based quadruple immunosuppressive regimen [abstract no: 1622]. A Transplant Odyssey; 2001 Aug 20-23; Istanbul, Turkey. 2001. [CENTRAL: CN-00487738]

Nashan B, Curtis J, Ponticelli C, Mourad G, Boger R, RAD B156 Study Group. Certican (RAD; everolimus), the proliferation signal inhibitor, is complementary with a reduced dose neoral based quadruple immunosuppressive regimen [abstract no: 398]. 10th ESOT & 12th ETCO Congress. Bridging the Future; 2001 Oct 6-11; Lisboa, Portugal. 2001. [CENTRAL: CN-00487741]

Nashan B, Mourad G, Boger R, Curtis J, Ponticelli C, Haas T. Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. *Transplantation* 2004;**78**(9):1332-40. [MEDLINE: 15548972]

Ponticelli C, Curtis J, Kovarik JM, Nashan B, Mourad G, Figueiredo J, et al. Everolimus pharmacokinetics are unaltered with full-dose versus reduced-dose cyclosporine [abstract no: 318]. 10th ESOT & 12th ETCO Congress. Bridging the Future; 2001 Oct 6-11; Lisboa, Portugal. 2001. [CENTRAL: CN-00487748]

RADB156 Study Group, Boger R, Frei U, Glotz D, Kahan B, Ponticelli C, et al. CERTICAN(TM) with reduced dose NEORAL® results in a significantly higher GFR in de novo renal transplant recipients over the first 12 Months compared to CERTICAN(TM)-full dose NEORAL® as Assessed by Iohexol Clearance [abstract no:1623]. A Transplant Odyssey; 2001 Aug 20-23; Istanbul, Turkey. 2001. [CENTRAL: CN-00487751]

Oh 2012 *{published data only}*

Oh CK, Ha JW, Kim YH, Kim YL, Kim YS. Safety and efficacy of the early introduction of everolimus (Certican) with low dose of cyclosporine in de novo kidney recipients after 1 month of transplantation (Preliminary results). *Journal of the Korean Society for Transplantation* 2012;**26**(2):83-91. [DOI: 10.4285/jkstn.2012.26.2.83]

* Oh CK, Huh KH, Ha J, Kim YH, Kim YL, Kim YS. Safety and efficacy of the early introduction of everolimus with reduced-exposure cyclosporine a in de novo kidney recipients. *Transplantation* 2015;**99**(1):180-6. [MEDLINE: 24983307]

OPTICEPT Study 2009 *{published data only}*

Bloom R, Kaplan B, Meier-Kriesche H, Shaw L, Shah T, Patel D, et al. Opticept Trial: Efficacy and safety of monitored MMF in combination with CNI in renal transplantation at 1 and 2 years [abstract no: 862]. *Transplantation* 2008;**86**(2 Suppl):301. [CENTRAL: CN-00740509]

Gaston R, Bloom R, Shah T, Cibrik D, Angelis M, Mulgaonkar S, et al. 6-month outcomes of monitored mycophenolate mofetil (MMF) in combination with calcineurin inhibitors (CNI) in renal allograft recipients: an interim analysis of the OPTICEPT trial [abstract no: TH-PO565]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):228A. [CENTRAL: CN-00602020]

Gaston R, Kaplan B, Meier-Kriesche H, Shaw L, Shah T, Patel D, et al. Opticept Trial: efficacy and safety of monitored MMF in combination with CNI in renal transplantation at 12 months [abstract no: 526]. *American Journal of Transplantation* 2008;**8**(Suppl 2):319. [CENTRAL: CN-00653708]

* Gaston RS, Kaplan B, Shah T, Cibrik D, Shaw LM, Angelis M, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the OPTICEPT trial. *American Journal of Transplantation* 2009;**9**(7):1607-19. [MEDLINE: 19459794]

Kaplan B, Gaston R, Meier-Kriesche H, Bloom R, Patel D, Shaw L. Mycophenolate mofetil may require dose modification based on weight: an analysis of MPA exposure in the OptiCept

Trial [abstract no: 787]. *American Journal of Transplantation* 2009;**9**(Suppl 2):419. [CENTRAL: CN-00794654]

Kaplan B, Gaston RS, Meier-Kriesche HU, Bloom RD, Shaw LM. Mycophenolic acid exposure in high- and low-weight renal transplant patients after dosing with mycophenolate mofetil in the Opticept trial. *Therapeutic Drug Monitoring* 2010;**32**(2):224-7. [MEDLINE: 20216117]

Shaw L, Kaplan B, Angelis M, Bloom R, Gaston R, Meier-Kriesche H, et al. Correlation between mycophenolic acid (MPA) trough and abbreviated AUC levels in renal allograft recipients in the Opticept Trial [abstract no: SU-FC128]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):96A-7A. [CENTRAL: CN-00724911]

ORION Study 2011 *{published data only}*

Flechner S, Cockfield S, Grinyo J, Russ G, Wissing KM, Legendre C, et al. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with tacrolimus (TAC)+ mycophenolate mofetil (MMF) in de novo renal allograft recipients: preliminary 2-year safety results from the Orion Trial [abstract no: 444]. *Transplantation* 2008;**86**(Suppl 2):156. [CENTRAL: CN-00740477]

Flechner S, Glyda M, Steinberg S, Harler MB. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with a tacrolimus (Tac) and mycophenolate mofetil (MMF) regimen in de novo renal allograft recipients: renal function results from the ORION study [abstract no: 1141]. *American Journal of Transplantation* 2007;**7**(Suppl 2):440. [CENTRAL: CN-00740477]

Flechner S, Glyda M, Steinberg S, Harler MB. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with a tacrolimus (Tac) and mycophenolate mofetil regimen (MMF) in de novo renal allograft recipients: acute rejection and graft survival results from the ORION study [abstract no: 52]. *American Journal of Transplantation* 2007;**7**(Suppl 2):160. [CENTRAL: CN-00653711]

Flechner S, Glyda M, Steinberg S, Harler MB, ORION Trial Investigators. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with a tacrolimus (TAC) and mycophenolate mofetil regimen (MMF) in de novo renal allograft recipients: acute rejection and graft survival results from The ORION Study [abstract no: P477]. *Transplant International* 2007;**20**(Suppl 2):209.

Flechner SM, Cockfield S, Grinyo J, Russ G, Wissing KM, Legendre C, et al. A randomized, open-label study to compare the efficacy and safety of two different sirolimus (SRL) regimens with tacrolimus (TAC) + mycophenolate mofetil (MMF) in de novo renal allograft recipients: preliminary 2-year efficacy results from the ORION trial [abstract no: 287]. *American Journal of Transplantation* 2008;**8**(Suppl 2):254. [CENTRAL: CN-00653710]

Flechner SM, Cockfield S, Grinyo J, Russ G, Wissing KM, Legendre C, et al. Preliminary two-year efficacy results from a randomized, open-label, comparative study of two different sirolimus (SRL) regimens versus a tacrolimus (TAC) + mycophenolate regimen (MMF) in de novo renal allograft

recipients [abstract no: 531]. *Transplantation* 2008;**86**(Suppl 2):186. [CENTRAL: CN-00740478]

* Flechner SM, Glyda M, Cockfield S, Grinyo J, Legendre C, Russ G, et al. The ORION Study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients.[Erratum appears in Am J Transplant. 2012 Jan;12(1):268]. *American Journal of Transplantation* 2011;**11**(8):1633-44. [MEDLINE: 21668635]

Flechner SM, Glyda M, See Tai S, ORION Trial Investigators. Delayed graft function (DGF) in two sirolimus (SRL)-based regimens compared with tacrolimus (TAC) and mycophenolate mofetil (MMF) in de novo renal allograft recipients [abstract no: 299]. *American Journal of Transplantation* 2009;**9**(Suppl 2):277. [CENTRAL: CN-00774294]

Flechner SM, Glyda M, Steinberg S, Copley JB, ORION Trial Investigators. The efficacy of sirolimus (SRL) and tacrolimus (TAC) withdrawal versus SRL and mycophenolate mofetil (MMF) compared with TAC and MMF in de novo renal allograft recipients: interim results from the Orion Study [abstract no: SU-FC124]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):95A. [CENTRAL: CN-00716077]

Russ G, Flechner SM, Cockfield S, Grinyo J, Wissing KM, Legendre C, et al. Cardiovascular risk profile of renal transplant recipients enrolled in an open-label, randomized study comparing 2 sirolimus (SRL) regimens with a tacrolimus (TAC)+ mycophenolate regimen (MMF): preliminary results from the Orion Trial [abstract no: 445]. *Transplantation* 2008;**86**(Suppl 2):156. [CENTRAL: CN-00740477]

Pacheco-Silva 2013 *{published data only}*

Pacheco-Silva A, Tonato E, Durao M Jr, Requiao-Moura L, Arruda E, Chinen R, et al. A randomized clinical trial of early conversion from tacrolimus to everolimus in deceased donor kidney transplantation [abstract no: P460]. *Transplant International* 2013;**26**(Suppl 2):277-8. [EMBASE: 71360073]

Paoletti 2012 *{published data only}*

Paoletti E, Marsano L, Bellino D, Cassottana P, Cannella G. Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial. *Transplantation* 2012;**93**(5):503-8. [MEDLINE: 22318246]

Pascual 2003 *{published data only}*

* Pascual M, Curtis J, Delmonico FL, Farrell ML, Williams WW, Kalil R, et al. A prospective, randomized clinical trial of cyclosporine reduction in stable patients greater than 12 months after renal transplantation. *Transplantation* 2003;**75**(9):1501-5. [MEDLINE: 12792504]

Wong W, Tolkoff-Rubin N, Delmonico FL, Cardarelli F, Saidman SL, Farrell ML, et al. Analysis of the cardiovascular risk profile in stable kidney transplant recipients after 50% cyclosporine reduction. *Clinical Transplantation* 2004;**18**(4):341-8. [MEDLINE: 15233807]

Wong W, Tolkoff-Rubin N, Delmonico FL, Farell ML, Shih V, Williams W, et al. Analysis of the cardiovascular risk profile in stable renal transplant recipients after 50% cyclosporine reduction [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):213. [CENTRAL: CN-00448411]

Wong W, Tolkoff-Rubin N, Delmonico FL, Farrell ML, Shih V, Cosimi AB, et al. A randomized clinical trial to analyze the effect of 50% cyclosporine reduction on the cardiovascular risk profile in stable kidney transplant recipients [abstract]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):186A. [CENTRAL: CN-00550675]

Pascual 2008 *{published data only}*

Pascual J, Bloom D, Torrealba J, Brahmbhatt R, Chang Z, Sollinger HW, et al. Calcineurin inhibitor withdrawal after renal transplantation with alemtuzumab: clinical outcomes and effect on T-regulatory cells. *American Journal of Transplantation* 2008;**8**(7):1529-36. [MEDLINE: 18510645]

Pedersen 1991 *{published data only}*

Jensen JD, Hansen HE, Pedersen EB. Increased serum erythropoietin level during azathioprine treatment in renal transplant recipients. *Nephron* 1994;**67**(3):297-301. [MEDLINE: 7936019]

* Pedersen EB, Hansen HE, Kornerup HJ, Madsen S, Sorensen AW. Long-term graft survival after conversion from cyclosporin to azathioprine 1 year after renal transplantation. A prospective, randomized study from 1 to 6 years after transplantation. *Nephrology Dialysis Transplantation* 1993;**8**(3):250-4. [MEDLINE: 8385294]

Pedersen EB, Hansen HE, Kornerup HJ, Madsen S, Sorensen AW. Long-term graft survival after conversion from cyclosporin to azathioprine 1 year after renal transplantation: a prospective randomized study from 1 to 6 years after transplantation [abstract]. *Nephrology Dialysis Transplantation* 1993;**8**(9):1047.

Pedersen EB, Hansen HE, Kornerup HJ, Madsen S, Sorensen AW. Long-term graft survival after conversion from cyclosporine to azathioprine one year after renal transplantation. A prospective, randomized study from one to six years after transplantation [abstract]. 12th International Congress of Nephrology; 1993 June 13-18; Jerusalem, Israel. 1993:194. [CENTRAL: CN-00644352]

Pedersen EB, Hansen HE, Olsen S. The effect of cyclosporine and azathioprine on GFR and renal histopathology 12 to 24 months after renal transplantation. *Transplantation Proceedings* 1992;**24**(1):309-10. [MEDLINE: 1539289]

Pedersen EB, Hansen HE, Olsen S, Danielsen H, Eiskjaer AW, Jespersen B, et al. Comparison between the effect of cyclosporin and azathioprine on functional and morphological renal parameters in a randomised study from one to two years after renal transplantation [abstract]. *Nephrology Dialysis Transplantation* 1991;**6**(10):832-3.

Pedersen EB, Hansen HE, Olsen S, Danielsen H, Eiskjaer H, Jespersen B, et al. Comparison between the effects of cyclosporine and azathioprine on functional and morphologic renal parameters in a randomized study from 12 to 24 months after renal transplantation. *Clinical Transplantation* 1991;**5**(6 I):456-66. [EMBASE: 22024462]

Pontrelli 2008 *{published data only}*

  * Pontrelli P, Rossini M, Infante B, Stallone G, Schena A, Loverre A, et al. Rapamycin inhibits PAI-1 expression and reduces interstitial fibrosis and glomerulosclerosis in chronic allograft nephropathy. *Transplantation* 2008;**85**(1):125-34. [MEDLINE: 18192922]

  Rossini M, Pontrelli P, Stallone G, Infante B, Schena A, Loverre A, et al. Regression of glomerulosclerosis in chronic allograft nephropathy (CAN) following calcineurin inhibitors (CNI) withdrawal and conversion to sirolimus (SRL) [abstract no: TH-PO554]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):225A. [CENTRAL: CN-00725009]

  Stallone G, Pontrelli P, Infante B, Schena A, Ursi M, Ranieri E, et al. Rapamycin (RAPA) inhibits PAI-1 expression and reduce interstitial fibrosis in chronic allograft nephropathy (CAN) [abstract no: SO04]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):v4. [CENTRAL: CN-00716118]

Qazi 2014 *{published data only}*

  Peddi V, Qazi Y, Shaffer D, Luan F, Shihab F, Tomlanovich S, et al. Effect of everolimus with low dose tacrolimus vs mycophenolate with standard tacrolimus regimen in African-American de novo renal transplant recipients [abstract no: B955]. *Transplantation* 2014;**98**(Suppl 1):536. [EMBASE: 71545337]

  Qazi Y, Shaffer D, Kaplan B, Kim D, Luan F, Peddi V, et al. Efficacy and safety of everolimus with low-dose tacrolimus in de novo renal transplant recipients: 12-month randomized study [abstract no: 713]. *Transplantation* 2014;**98**(Suppl 1):80. [EMBASE: 71543789]

  Shihab F, Qazi Y, Kaplan B, Kim D, Mulgaonkar S, Peddi V, et al. Everolimus-facilitated tacrolimus minimization preserves renal function in de novo renal transplant recipients [abstract no: B962]. *Transplantation* 2014;**98**(Suppl 1):538-9. [EMBASE: 71545344]

REFERENCE Study 2006 *{published data only}*

  * Frimat L, Cassuto-Viguier E, Charpentier B, Noel C, Provot F, Rostaing L, et al. Impact of cyclosporine reduction with MMF: a randomized trial in chronic allograft dysfunction. The 'REFERENCE' study. *American Journal of Transplantation* 2006;**6**(11):2725-34. [MEDLINE: 17049060]

  Kessler M. Renal function evaluation after half dose reduction of Neoral in combination with Cellcept in renal transplant patients with altered renal function: preliminary 12 months results: randomized, open, multicentric, prospective, controlled study [abstract no: 773]. *American Journal of Transplantation* 2003;**3**(Suppl 5):350. [CENTRAL: CN-00446065]

  Kessler M, Frimat L. Renal function evaluation after half dose reduction of neoral® in combination with Cellcept® in renal transplant patients with altered renal function: preliminary 2 year safety and efficacy results of the MMF-REFERENCE study: a randomised [abstract no: 013]. *Transplantation* 2004;**78**(2 Suppl):5. [CENTRAL: CN-00509272]

  Kessler M, Frimat L, Cassuto-Viguier E, Charpentier B, Djeffal R, Noel C, et al. Impact of cyclosporine reduction with MMF in chronic allograft dysfunction: 4-year results of a multicenter randomized controlled study. The "Reference" study [abstract no: 850]. *American Journal of Transplantation* 2006;**6**(Suppl 2):353. [CENTRAL: CN-00765336]

  Kessler M, Frimat L, Charpentier B, Durrbach A, Noel C, Pruvot F, et al. Renal function evaluation after half dose reduction of neoral® in combination with cellcept® in renal transplant patients with altered renal function: preliminary 2 year safety and efficacy results of the MMF - REFERENCE study: a randomised, open, multicentre, prospective, controlled study [abstract no: 462]. *American Journal of Transplantation* 2004;**4**(Suppl 8):285. [CENTRAL: CN-00602100]

Rivelli 2015 *{published data only}*

  Rivelli RF, Goncalves RT, Leite M Jr, Santos MA, Delgado AG, Cardoso LR, et al. Early withdrawal of calcineurin inhibitor from a sirolimus-based immunosuppression stabilizes fibrosis and the transforming growth factor-beta signalling pathway in kidney transplant. *Nephrology* 2015;**20**(3):168-76. [MEDLINE: 25404086]

RMR Study 2001 *{published data only}*

  Balshaw R, Marra C, Nashan B, Hagenmeyer EG, Keown P. First year cost-implications of early cyclosporine withdrawal in renal transplantation [abstract no: 2378]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415221]

  Campistol JM, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *Journal of the American Society of Nephrology* 2006;**17**(2):581-9. [MEDLINE: 16434506]

  Campistol JM, Kreis H, Oberbauer R, Mota A, Riad H, Chapman J, et al. Sirolimus-based therapy following early cyclosporin withdrawal resulted in superior renal allograft survival at 48 months compared with continuous combined sirolimus and cyclosporine [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):344. [CENTRAL: CN-00509115]

  Campistol JM, Legendre C, Friend P, Riad H, Castagneto M. Evaluating cardiovascular risk factors associated with long-term sirolimus (Rapamune®) immunotherapy used with or without cyclosporine [abstract]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):311. [CENTRAL: CN-00550754]

  Campistol JM, Oberbauer R, Hartmann A, Kreis H, Mota A, Arias M, et al. Long-term graft survival is significantly better in patients receiving sirolimus-based therapy after early cyclosporine withdrawal [abstract no: W736]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):784. [CENTRAL: CN-00444661]

  Campistol JM, Oberbauer R, Kreis H, Brault Y, Burke JT, Rapamune Maintenance Regimen Study Group. Predicting 10-year graft survival with sirolimus used either as base therapy or in association with cyclosporine [abstract no: 1458]. *American Journal of Transplantation* 2003;**3**(Suppl 5):474. [CENTRAL: CN-00444662]

Campistol JM, Oberbauer R, Kreis H, Lawen J, Morales JM, Chapman J, et al. Elimination of cyclosporine with sirolimus-based immunotherapy: 2-year results confirm improved renal function [abstract no: SA-P0489]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):363A. [CENTRAL: CN-00444663]

Chapman J, Johnson RW, Kreis H, Oberbauer R, Vanrenterghem Y, Claesson K, et al. Improved renal function using sirolimus (Rapamune®) maintenance therapy and cyclosporine elimination in renal allograft recipients: 12-month results of the tri-continental trial [abstract no: A4615]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):882A. [CENTRAL: CN-00550709]

Chapman J, Oberbauer R, Campistol JM, Grinyo JM, Morales JM, Mota A, et al. Renal transplant patients receiving sirolimus-based therapy after early cyclosporine withdrawal demonstrate superior renal allograft survival and improved renal function at 48 months after transplantation [abstract no: SU-FC103]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):66A. [CENTRAL: CN-00583160]

Eris J, Grinyo JM, Brault Y, Hutchison B. Sirolimus therapy after early cyclosporine withdrawal in renal transplantation significantly reduces the rate of skin cancer compared with continuous combined therapy with cyclosporine [abstract no: OR-040]. *Transplant International* 2005;**18**(Suppl):10.

Eris J, Russ G, Hutchinson B, Walker R, Chapman J, Pussell B, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk of malignancy at 5 years after renal transplantation [abstract no: 105]. 24th Annual Scientific Meeting. Transplantation Society of Australia & New Zealand (TSANZ); 2006 Mar 29-31; Canberra, Australia. 2006:91. [CENTRAL: CN-00644323]

Eris J, Russ G, Hutchison B, Walker R, Chapman J, Pussell B, et al. Conversion to sirolimus therapy after early cyclosporin withdrawal reduces the risk of malignancy at 5 years post renal transplantation [abstract no: 1581]. *Nephrology* 2006;**11**(Suppl 2):A24. [CENTRAL: CN-00644325]

Friend P, Mota A, Kreis H, Segoloni G, Legendre C, Prats D, et al. Cyclosporine withdrawal followed by sirolimus (Rapamune) maintenance therapy is beneficial to patients regardless of baseline renal function [abstract no: 0553]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415680]

Friend P, Russ G, Oberbauer R, Murgia MG, Tufveson G, Chapman J, et al. Incidence of anemia in sirolimus-treated renal transplant recipients: the importance of preserving renal function. *Transplant International* 2007;**20**(9):754-60. [MEDLINE: 17565578]

Grinyo JM, Vanrentergheim Y, Hutchison B, Segoloni G, Durand D, Sorba G, et al. Sirolimus (Rapamune) in patients receiving kidney from older donors: 2-year results from the Rapamune Maintenance Regimen trial [abstract no: 534]. *American Journal of Transplantation* 2002;**2**(Suppl 3):272. [CENTRAL: CN-00415776]

Grinyo JM, Vanrenterghem Y, Hutchison B, Segoloni G, Durand D, Sorba G, et al. The effects of sirolimus (Rapamune) in patients receiving kidneys from older donors: 2-year results from the Rapamune Maintenance Regimen trial [abstract no: 0435]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00420830]

Hartmann A, Colon J, Pena J, Martinez J, Walker R, Arns W, et al. Favourable cardiovascular risk profile in renal transplant patients receiving sirolimus maintenance therapy following cyclosporine withdrawal: 3 year results of the Rapamune Maintenance Regimen trial [abstract no: W756]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):791-2. [CENTRAL: CN-00445657]

Hartmann A, Mota A, Legendre C, Segoloni G, Grinyo JM, Hutchison B, et al. Patients receiving sirolimus maintenance therapy have better renal function after early cyclosporine withdrawal irrespective of baseline renal function: intent-to-treat results at 3 years [abstract no: W743]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):787. [CENTRAL: CN-00445658]

Hartmann A, Oberbauer R, Kreis H, Johnson RW, Mota A, Schena FP, et al. Long-term results of cyclosporine elimination with sirolimus-based therapy show improved renal function [abstract]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):19. [CENTRAL: CN-00550651]

Hutchison B, Claesson K, Mota A, Eris JM, Kreis H, Oberbauer R, et al. Quality of life in sirolimus-treated kidney transplant patients after cyclosporine elimination: 2-year results [abstract no: 499]. *American Journal of Transplantation* 2002;**2**(Suppl 3):263. [CENTRAL: CN-00415909]

Johnson R, Oberbauer R, Kreis H, Brattstrom B, Claesson K, Eris J, et al. Sirolimus allows early cyclosporine free immunosuppression in renal transplantation: an international trial with the tablet formulation [abstract no: 0429]. XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome, Italy. 2000. [CENTRAL: CN-00445947]

* Johnson RW, Kreis H, Oberbauer R, Brattstrom C, Claesson K, Eris J. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001;**72**(5):777-86. [MEDLINE: 11571437]

Keown P, Chen J, Kreis H, Oberbauer R, Claesson K, Mota A, et al. Improved quality of life after cyclosporine elimination in sirolimus-treated renal transplant patients [abstract no: A4711]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):901A. [CENTRAL: CN-00550607]

Kreis H, Johnson R, Mayer G, Brattstrom C, Claesson K, Eris J, et al. Sirolimus allows early cyclosporine-free immunosuppression in renal transplantation resulting in lower blood pressure and improved renal function [abstract no: A3662]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):696A-7A. [CENTRAL: CN-00550424]

Kreis H, Oberbauer R, Campistol JM, Mathew T, Daloze P, Schena FP, et al. Long-term benefits with sirolimus-based therapy after early cyclosporine withdrawal. *Journal of the*

American Society of Nephrology 2004;**15**(3):809-17. [MEDLINE: 14978184]

Kreis H, Oberbauer R, Claesson K, Mota A, Arias M, Durand D, et al. Quality-of-life assessments in sirolimus-treated renal transplant patients after cyclosporine elimination [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A208. [CENTRAL: CN-00446200]

Kreis H, Oberbauer R, Mota A, Claesson K, Riad H, Campistol JM, et al. Sirolimus-based therapy following early cyclosporine withdrawal results in superior renal allograft survival compared with a continuous combination of sirolimus and cyclosporine [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):460. [CENTRAL: CN-00446201]

Legendre C, Brault Y, Morales JM, Oberbauer R, Altieri P, Riad H, et al. Factors influencing glomerular filtration rate in renal transplantation after cyclosporine withdrawal using sirolimus-based therapy: a multivariate analysis of results at five years. *Clinical Transplantation* 2007;**21**(3):330-6. [MEDLINE: 17488381]

Legendre C, Daloze P, Colon J, Chapman J, Pena J, Martinez J, et al. Sirolimus (Rapamune) used with or without cyclosporine for long term therapy: a comparison of cardiovascular risk factors. [abstract no: 1015]. *American Journal of Transplantation* 2002;**2**(Suppl 3):393. [CENTRAL: CN-00416111]

Legendre C, Mota A, Friend P, Segoloni G, Grinyo JM, Hutchison B, et al. Superior renal function after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function: intent-to-treat results at 3 years [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):466. [CENTRAL: CN-00446313]

Mathew T, Kreis H, Doyen K. Malignancy in renal transplant recipients receiving sirolimus (rapamune) maintenance therapy: 2-year follow up from 5 multicenter studies [abstract no: 58]. *American Journal of Transplantation* 2002;**2**(Suppl 3):152. [CENTRAL: CN-00416243]

Mathew T, Kreis H, Doyen K. Two-year incidence of malignancy in sirolimus (Rapamune)-treated renal transplant recipients: follow-up results from 5 multicenter studies [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416244]

Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clinical Transplantation* 2004;**18**(4):446-9. [MEDLINE: 15233824]

Morales JM, Hartmann A, Walker R, Arns W, Senatorski G, Grinyo JM, et al. Similar lipid profile but improved long-term outcomes with sirolimus after cyclosporine withdrawal compared to sirolimus with continuous cyclosporine. *Transplantation Proceedings* 2009;**41**(6):2339-44. [MEDLINE: 19715914]

Morales JM, Kreis H, Oberbauer R, Campistol JM, Mota A, Henriques AC, et al. 48-month results of sirolimus-based therapy following early cyclosporine withdrawal demonstrate superior renal allograft survival [abstract no: MO05]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:214. [CENTRAL: CN-00509360]

Morales JM, Oberbauer R, Legendre C, Ruiz JC, Mota A, Chapman J, et al. Analysis of risk factors for reduced renal function in renal transplant patients receiving sirolimus maintenance therapy after early cyclosporine withdrawal: 5-year results from the Rapamune Maintenance Regimen (RMR) trial [abstract no: F-FC156]. *Journal of the American Society of Nephrology* 2005;**16**:72A. [CENTRAL: CN-00644316]

Mota A, Arias M, Taskinen EI, Paavonen T, Brault Y, Legendre C, et al. Sirolimus-based therapy following early cyclosporine withdrawal provides significantly improved renal histology and function at 3 years. *American Journal of Transplantation* 2004;**4**(6):953-61. [MEDLINE: 15147430]

Mota A, Arias M, Taskinen EI, Paavonen T, Legendre C, Claesson K, et al. Sirolimus-based therapy after early cyclosporine withdrawal results in significantly better renal histology and function at 3 years following kidney transplantation [abstract no: 1486]. *American Journal of Transplantation* 2004;**4**(Suppl 8):566. [CENTRAL: CN-00509364]

Mota A, Segoloni G, Legendre C, Prats D, Hutchison B, Morales JM, et al. Patients benefit from cyclosporine withdrawal followed by sirolimus (Rapamune) maintenance therapy irrespective of baseline renal function [abstract no: 395]. *American Journal of Transplantation* 2002;**2**(Suppl 3):237. [CENTRAL: CN-00420843]

Oberbauer R, Arias M, Claesson K, Mota A, Eris JM, Hutchison B, et al. Two-year assessment of health-related quality of life in sirolimus-treated kidney transplant patients after cyclosporine elimination [abstract no: 0257]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416378]

Oberbauer R, Hutchison B, Eris J, Arias M, Claesson K, Mota A, et al. Health-related quality-of-life outcomes of sirolimus-treated kidney transplant patients after elimination of cyclosporine A: results of a 2-year randomized clinical trial. *Transplantation* 2003;**75**(8):1277-85. [MEDLINE: 12717216]

Oberbauer R, Hutchison B, Eris J, Arias M, Mota A, the Rapamune Maintenance Regimen Study Group. Health-related quality-of-life assessment in kidney transplant patients receiving sirolimus maintenance therapy with early elimination of cyclosporine: 3-year results [abstract no: W758]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):243. [CENTRAL: CN-00446999]

Oberbauer R, Hutchison B, Eris J, Riad H, Claesson K, Lawen J, et al. Three-year assessment of health-related quality of life in sirolimus-treated kidney transplant patients after cyclosporine elimination [abstract no: 249]. *American Journal of Transplantation* 2003;**3**(Suppl 5):215. [CENTRAL: CN-00447000]

Oberbauer R, Kreis H, Campistol JM, Mota A, Daloze P, Ruiz JC, et al. Renal function improves significantly after early cyclosporine withdrawal in sirolimus-treated renal transplant recipients: 3-year results of the Rapamune Maintenance Regimen (RMR) trial [abstract no: F-FC041]. *Journal of the*

American Society of Nephrology 2003;**14**(Nov):10A. [CENTRAL: CN-00550606]

Oberbauer R, Kreis H, Johnson RW, Mota A, Claesson K, Ruiz JC, et al. Long-term improvement in renal function with sirolimus after early cyclosporine withdrawal in renal transplant recipients: 2-year results of the Rapamune Maintenance Regimen Study. *Transplantation* 2003;**76**(2):364-70. [MEDLINE: 12883194]

Oberbauer R, Kreis H, Johnson RWG, Mota A, Claesson K, Arias M, et al. Long-term improvement in renal function is shown in patients treated with sirolimus (Rapamune) and cyclosporine withdrawal: 2-year results of the Rapamune Maintenance Regimen trial [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416379]

Oberbauer R, Mota A, Prats D, Mathew T, Morales JM, Daloze P, et al. Renal transplant patients with risk factors for reduced renal function benefit from cyclosporine withdrawal and sirolimus maintenance therapy [abstract no: W742]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):786-7. [CENTRAL: CN-00447001]

Oberbauer R, Segoloni G, Campistol JM, Kreis H, Mota A, Lawen J, et al. Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation [abstract no: O80]. *Transplantation* 2004;**78**(2 Suppl):30. [CENTRAL: CN-00653813]

Oberbauer R, Segoloni G, Campistol JM, Kreis H, Mota A, Lawen J, et al. Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation.[erratum appears in Transpl Int. 2005 Mar;18(3):369]. *Transplant International* 2005;**18**(1):22-8. [MEDLINE: 15612979]

Paczek L, Mota A, Schena FP, Johnson RW, Prats D, Mathew T, et al. Renal function benefit from sirolimus maintenance therapy after early cyclosporine withdrawal in the presence of risk factors [abstract no: 180]. *American Journal of Transplantation* 2003;**3**(Suppl 5):197. [CENTRAL: CN-00447075]

Ruiz JC, Campistol JM, Grinyo JM, Mota A, Prats D, Gutierrez JA, et al. Early cyclosporine a withdrawal in kidney-transplant recipients receiving sirolimus prevents progression of chronic pathologic allograft lesions. *Transplantation* 2004;**78**(9):1312-8. [MEDLINE: 15548969]

Ruiz JC, Campistol JM, Mota A, Prats D, Gutierrez JA, Castro A, et al. Early cyclosporine A withdrawal in kidney transplant recipients receiving sirolimus prevents progression of chronic pathologic allograft lesions [abstract no: SU-FC0235]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):48A. [CENTRAL: CN-00447509]

Ruiz JC, Campistol JM, Mota A, Prats D, Gutierrez JA, Castro A, et al. Early elimination of cyclosporine in kidney transplant recipients receiving sirolimus prevents progression of chronic pathologic allograft lesions. *Transplantation Proceedings* 2003;**35**(5):1669-70. [MEDLINE: 12962750]

Ruiz JC, Campistol JM, Sanchez-Fructuoso A, Mota A, Grinyo JM, Paul J, et al. Early sirolimus use with cyclosporine elimination does not induce progressive proteinuria. *Transplantation Proceedings* 2007;**39**(7):2151-2. [MEDLINE: 17889121]

Ruiz JC, Campstol JM, Sanchez-Fructuoso A, Mota A, Grinyo JM, Paul J, et al. The early use of sirolimus with CsA elimination is not associated with progressive proteinuria [abstract no: P113]. *Transplant International* 2007;**20**(Suppl 2):122. [CENTRAL: CN-00740556]

Russ G, Eris J, Hutchison B, Walker R, Chapman J, Pussell B, et al. Anaemia in sirolimus-treated renal transplant recipients: the importance of preserving renal function [abstract no: 2504]. *Nephrology* 2006;**11**(Suppl 2):A37. [CENTRAL: CN-00644362]

Russ G, Eris J, Hutchison B, Walker R, Chapman J, Pussell B, et al. Sirolimus (SRL) maintenance therapy after early cyclosporine (CsA) withdrawal benefits renal transplant recipients with risk factors for reduced renal function: 5-year results [abstract no: 103]. 24th Annual Scientific Meeting. Transplantation Society of Australia & New Zealand (TSANZ); 2006 Mar 29-31; Canberra, Australia. 2006:90. [CENTRAL: CN-00644320]

Russ G, Eris J, Hutchison B, Walker R, Chapman J, Pussell B, et al. Sirolimus-based therapy following early cyclosporine withdrawal resulted in superior renal allograft survival at 48 months compared with continuous combined sirolimus and cyclosporine [abstract no: P150]. *Nephrology* 2004;**9**(Suppl 1):A38. [CENTRAL: CN-00509449]

Russ G, Eris J, Hutchison B, Walker R, Chapman J, Pussell B, et al. Superior outcomes after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function: intent-to-treat results at 4 years [abstract no: 159]. *Nephrology* 2005;**10**(Suppl 3):A422. [CENTRAL: CN-00644317]

Russ G, Jamieson N, Oberbauer R, Arias M, Murgia MG, Blancho G, et al. Three-year health-related quality-of-life outcomes for sirolimus-treated kidney transplant patients after elimination of cyclosporine. *Transplant International* 2007;**20**(10):875-83. [MEDLINE: 17854445]

Russ G, Oberbauer R, Friend P, Campistol JM, Burke JT. The impact of renal function on the incidence of anemia in sirolimus-treated renal transplant recipients [abstract no: TH-PO563]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):227A. [CENTRAL: CN-00615898]

Russ G, Segoloni G, Oberbauer R, Legendre C, Mota A, Eris J, et al. Long-term impact of baseline renal function in kidney transplant patients receiving sirolimus maintenance therapy after early cyclosporine withdrawal [abstract no: FC-50004]. *Nephrology* 2005;**10**(Suppl 1):A2. [CENTRAL: CN-00644319]

Russ G, Segoloni G, Oberbauer R, Legendre C, Mota A, Eris J, et al. Superior outcomes after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function: intent-to-treat results at 4 years [abstract no: 1009]. *American Journal of Transplantation* 2005;**5**(Suppl 11):413.

Russ G, Segoloni G, Oberbauer R, Legendre C, Mota A, Eris J, et al. Superior outcomes in renal transplantation after early cyclosporine withdrawal and sirolimus maintenance

therapy, regardless of baseline renal function. *Transplantation* 2005;**80**(9):1204-11. [MEDLINE: 16314787]

Schena FP, Jamieson N, Colon J, Shoker A, Pena J, Martinez M, et al. Favorable cardiovascular risk profile when sirolimus is used without cyclosporine compared to combination therapy: 3-year results of the Rapamune Maintenance Regimen trial [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):479. [CENTRAL: CN-00447616]

Vanrenterghem Y, Kreis H, Oberbauer R, Mota A, Johnson WG, Sirolimus Tri-contienental Renal Transplant Study Group. Improved renal function in renal allograft recipients with sirolimus (Rapamune) maintenance therapy and early cyclosporine withdrawal: 12-month results [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A209. [CENTRAL: CN-00448163]

Velosa JA, Larson TS, Gloor JM, Stegall MD. Cyclosporine elimination in the presence of TOR inhibitors: effects on renal function, acute rejection, and safety. *American Journal of Kidney Diseases* 2001;**38**(4 Suppl 2):S3-S10. [MEDLINE: 11583938]

Walker R, Russ G, Eris J, Hutchinson B, Chapman J, Pussell B, et al. Treatment of hyperlipidemia in sirolimus (SRL)-treated renal transplant recipients: long-term findings from the Rapamune Maintenance Regimen (RMR) Trial [abstract no 27]. 24th Annual Scientific Meeting. Transplantation Society of Australia & New Zealand [TSANZ]; 2006 Mar 29-31; Canberra, Australia. 2006:49. [CENTRAL: CN-00644318]

Rossini 2007 *{published data only}*

Rossini M, Loverre A, Stallone G, Infante B, Schena A, Maiorano A, et al. Proteinuria and vascular endothelial growth factor (VEGF) expression following calcineurin inhibitors (CNI) withdrawal and conversion to rapamycin [abstract no: 1149]. *American Journal of Transplantation* 2007;**7**(Suppl 2):442. [CENTRAL: CN-00725010]

Rossini M, Stallone G, Infante B, Capobianco C, Loverre A, Schena A, et al. Proteinuria and vascular endothelial growth factor (VEGF) expression following calcineurin inhibitors (CNI) withdrawal and conversion to rapamycin [abstract no: 548]. *Transplant International* 2007;**20**(Suppl 2):226.

Russ 2003 *{published data only}*

Russ G, Campbell S, Chadban S, Eris J, O'Connell P, Pussell B, et al. Comparison of reduced-and standard-target concentration tacrolimus plus sirolimus in renal allograft recipients: preliminary 6-month results [abstract]. Transplantation Society of Australia and New Zealand. 21st Annual Meeting; 2003 Apr 9-11; Canberra, ACT. 2003:64. [CENTRAL: CN-00447521]

Russ G, Campbell S, Chadban S, Eris J, O'Connell P, Pussell B, et al. The safety and efficacy of reduced- and standard-target concentration tacrolimus plus sirolimus in renal allograft recipients: preliminary 6-month results from Australia [abstract no: SA-PO496]. *Journal of the American Society of Nephrology* 2002;**13**(September, Program & Abstracts):364A. [CENTRAL: CN-00447522]

* Russ GR, Campbell S, Chadban S, Eris J, O'Connell P, Pussell B, et al. Reduced and standard target concentration

tacrolimus with sirolimus in renal allograft recipients. *Transplantation Proceedings* 2003;**35**(3 Suppl):115S-7S. [MEDLINE: 12742480]

Whelchel J, Paczek L, Bechstein WO, Russ G. A regimen of sirolimus and reduced-dose tacrolimus results in improved renal allograft function: combined analysis of the North American target, European and Australian sirolimus-tacrolimus trials [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):464. [CENTRAL: CN-00448351]

Salvadori 2007 *{published data only}*

Salvadori M, Scolari MP, Stefoni S, Bertoni E, Sandrini S, Rigotti P, et al. Randomized trial of sodium mycophenolate (MPS) and basiliximab in combination with reduced or standard cyclosporine (CsA) in old recipients of kidney transplant (KTx) [abstract no: O069]. *Transplant International* 2007;**20**(Suppl 2):20.

Salvadori M, Scolari MP, Stefoni S, Bertoni E, Sandrini S, Rigotti P, et al. Randomized trial of sodium mycophenolate and basiliximab in combination with reduced or standard cyclosporine exposure in old recipients of kidney transplants from deceased donors [abstract no: 108]. *Transplantation* 2008;**86**(2 Suppl):39. [CENTRAL: CN-00679020]

Schaefer 2006 *{published data only}*

Schaefer HM, Kizilisik AT, Feurer I, Nylander WA, Langone AJ, Helderman JH, et al. Short-term results under three different immunosuppressive regimens at one center. *Transplantation Proceedings* 2006;**38**(10):3466-7. [MEDLINE: 17175305]

Smak Gregoor 1999 *{published data only}*

Roodnat J, Hilbrands LB, Hene RJ, de Sevaux RG, Gregoor PJ, Kal-van Gestel JA, et al. 15 year follow-up of a multicentre, randomised, calcineurin inhibitor (CNI) withdrawal study in kidney transplantation [abstract no: BO156]. *Transplant International* 2013;**26**(Suppl 2):83-4. [EMBASE: 71359271]

Roodnat JI, Hilbrands LB, Hene RJ, de Sevaux RG, Smak Gregoor PJ, Kal-van Gestel JA, et al. 15-year follow-up of a multicenter, randomized, calcineurin inhibitor withdrawal study in kidney transplantation. *Transplantation* 2014;**98**(1):47-53. [MEDLINE: 24521775]

Smak Gregoor PJ, de Sevaux RG, Hene RJ, Hesse CJ, Hilbrands LB, Vos P, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* 1999;**68**(10):1603-6. [MEDLINE: 10589962]

Smak Gregoor PJ, de Sevaux RG, Ligtenberg G, Hoitsma AJ, Hene RJ, Weimar W, et al. A prospective randomised study of withdrawal of cyclosporine or prednisone in renal transplant recipients treated with mycophenolate mofetil, cyclosporine, and prednisone: 18 months follow-up data [abstract no: 441]. *American Journal of Transplantation* 2001;**1**(Suppl 1):246. [CENTRAL: CN-00763745]

* Smak Gregoor PJ, de Sevaux RG, Ligtenberg G, Hoitsma AJ, Hene RJ, Weimar W, et al. Withdrawal of cyclosporine or prednisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective,

multicenter study. *Journal of the American Society of Nephrology* 2002;**13**(5):1365-73. [MEDLINE: 11961025]

Smak Gregoor PJ, van Gelder T, IJzermans JN, Weimar W. Long-term results of a randomized, prospective study after withdrawal of cyclosporine or prednisone in renal transplant recipients treated with mycophenolate mofetil, cyclosporine, and prednisone [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):217. [CENTRAL: CN-00447777]

Van Gelder T, de Sevaux R, Hene R, Weimar W, Hoitsma A, Ligtenberg G, et al. Discontinuation of cyclosporine or prednisone 6 months after kidney transplantation: a randomized trial [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):920A. [CENTRAL: CN-00583812]

de Sevaux RG, Gregoor P, Smak JH, Hene RJ, Weimar W, Hoitsma AJ, et al. Withdrawal of cyclosporine or prednisone in renal transplant recipients treated with mycophenolate mofetil, cyclosporine, and prednisone: a randomized study [abstract no: 935]. *Transplantation* 1999;**67**(7):S240. [CENTRAL: CN-00767038]

SMART TX Study 2010 *{published data only}*

Guba M, Pratschke J, Hugo C, Kraemer B, Burmeister D, Brockmann J, et al. A randomized multicenter trial of early conversion to sirolimus/mycophenolate/steroids versus cyclosporine/mycophenolate/steroids in renal transplantation: one-year analysis (SMART-Study) [abstract no: 1088]. *American Journal of Transplantation* 2009;**9**(Suppl 2):497. [CENTRAL: CN-00763842]

Guba M, Pratschke J, Hugo C, Kraemer B, Burmeister D, Brockmann J, et al. Comparison of a delayed low-dose sirolimus (Siro)/mycophenolate mofetil (MMF)-based therapy with standard cyclosporine (CsA/MMF-based immunosuppression in patients after kidney transplantation (SMART study) [abstract no: P188]. *Transplant International* 2007;**20**(Suppl 2):141. [CENTRAL: CN-00724890]

Guba M, Pratschke J, Hugo C, Kramer B, Nohr-Westphal C, Brockmann J. Renal function, efficacy and safety of sirolimus and mycophenolate mofetil therapy after early calcineurin-inhibitor withdrawal in de novo renal transplant patients: one-year analysis of a randomized multicenter trial [abstract no: O-296]. *Transplant International* 2009;**22**(Suppl 2):78.

Guba M, Pratschke J, Hugo C, Kramer BK, Pascher A, Pressmar K, et al. Early conversion to a sirolimus-based, calcineurin-inhibitor-free immunosuppression in the SMART trial: observational results at 24 and 36months after transplantation. *Transplant International* 2012;**25**(4):416-23. [MEDLINE: 22320241]

* Guba M, Pratschke J, Hugo C, Krämer BK, Nohr-Westphal C, Brockmann J, et al. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal transplant patients: one-year analysis of a randomized multicenter trial. *Transplantation* 2010;**90**(2):175-83. [MEDLINE: 20463641]

Jauch KW, Pratschke J, Hugo C, Kramer B, Hakenberg O, Brockmann J, et al. Delayed introduction of a calcineurin-inhibitor (CNI)-free, sirolimus (SRL)-based immunosuppression in renal transplantation is safe. Preliminary results of the randomised, multicenter SMART Trial [abstract no: 535]. *Transplantation* 2008;**86**(Suppl 2):187. [CENTRAL: CN-00740484]

Spare-the-Nephron Study 2011 *{published data only}*

Kalil R, Pearson TC, Mulgaonkar S, Patel A, Shidban H, Weir M, et al. Final 1-year outcomes of the spare-the-nephron (STN) trial: mycophenolate mofetil (MMF) - based regimen combined with sirolimus (SRL) to preserve renal function in renal transplantation [abstract no: TH-FC042]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):10A. [CENTRAL: CN-00716075]

Mulgaonkar S, Pearson TC, Patel A, Scandling J, Shidban H, Weir M, et al. Final renal function outcomes from the Spare-the-Nephron (STN) trial: mycophenolate mofetil (MMF)/sirolimus (SRL) maintenance therapy and CNI withdrawal in renal transplant recipients [abstract no: 530]. *American Journal of Transplantation* 2008;**8**(Suppl 2):320. [CENTRAL: CN-00690361]

Patel A, Weir MR, Wali R, Pearson T, Mulgaonkar S, Shidban H, et al. Spare-the-Nephron (STN) Trial: Updated analysis of renal function after one year of mycophenolate mofetil/sirolimus maintenance therapy and calcineurin inhibitor withdrawal in renal transplant recipients [abstract no: 1138]. *American Journal of Transplantation* 2007;**7**(Suppl 2):439. [CENTRAL: CN-00615833]

Pearson T, Mulgaonkar S, Kalil R, Patel A, Scandling J, Patel D, et al. CNI withdrawal in African Americans - 1 year outcomes of African American renal transplant recipients in the Spare-the-Nephron (STN) trial [abstract no: 1083]. *American Journal of Transplantation* 2009;**9**(Suppl 2):496.

Pearson TC, Mulgaonkar S, Patel A, Scandling J, Shidban H, Weir M, et al. Efficacy and safety of mycophenolate mofetil (MMF)/sirolimus (SRL) maintenance therapy after calcineurin inhibitor (CNI) withdrawal in renal transplant recipients: final results of the Spare-the-Nephron (STN) trial [abstract no: 129]. *American Journal of Transplantation* 2008;**8**(Suppl 2):213. [CENTRAL: CN-00690150]

Pearson TC, Patel A, Scandling J, Shidban H, Weir M, Patel D, et al. Final results of the Spare the Nephron trial (CNI withdrawal trial) [abstract no: 629]. *Transplantation* 2008;**86**(2 Suppl):220-1.

Scandling J, Mulgaonkar S, Shidban H, Waid T, Peddi VR, Patel D. Effect of conversion from a calcineurin inhibitor (CNI)-based regimen to sirolimus on proteinuria: 1-year results of the spare-the-nephron trial in renal transplant recipients [abstract no: F-PO594]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):230A. [CENTRAL: CN-00716076]

Wali R, Pearson TC, Shidban H, Patel A, Chan L, Patel D. The Spare-the-Nephron Trial: Evaluating mycophenolate mofetil (MMF)/Sirolimus (SRL) maintenance therapy after calcineurin inhibitor (CNI) withdrawal, 1 year interim results [abstract no: F-PO1087]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):565A. [CENTRAL: CN-00615895]

Weir M, Mulgaonkar S, Pearson T, Patel A, Patel D, Shidban H, et al. Mycophenolate mofetil/sirolimus maintenance therapy after calcineurin inhibitor withdrawal in renal transplant recipients: 2-year outcomes of the SPARE-THE-NEPHRON (STN) trial [abstract no: 33]. *American Journal of Transplantation* 2009;**9**(Suppl 2):200-1.

* Weir MR, Mulgaonkar S, Chan L, Shidban H, Waid TH, Preston D, et al. Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial. *Kidney International* 2011;**79**(8):897-907. [MEDLINE: 21191361]

Weir MR, Pearson TC, Patel A, Peddi VR, Kalil R, Scandling J, et al. Long-term follow-up of kidney transplant recipients in the Spare-the-Nephron-Trial. *Transplantation* 2016;**101**(1):157-65. [MEDLINE: 26950714]

Weir MR, Wali R, Pearson TC, Patel A, Mulgaonkar S, Shidban H, et al. Spare-the-Nephron (STN) Trial: Updated 1 year efficacy and safety of mycophenolate mofetil/Sirolimus maintenance therapy after calcineurin inhibitor withdrawal in renal transplant recipients [abstract no: 51]. *American Journal of Transplantation* 2007;**7**(Suppl 2):439. [CENTRAL: CN-00615832]

Stallone 2003 *{published data only}*

* Stallone G, Di Paola S, Schena A, Infante B, Grandaliano G, Battaglia M, et al. Early withdrawal of cyclosporine A improves 1-year kidney graft structure and function in sirolimus-treated patients. *Transplantation* 2003;**75**(7):998-1003. [MEDLINE: 12698087]

Stallone G, Schena A, Infante B, Grandaliano G, Gesualdo L, Schena PF, et al. Early withdrawal of cyclosporine (CSA) ameliorates 1-year kidney graft function and structure in sirolimus (SRL)-treated patients. [abstract no: 1014]. *American Journal of Transplantation* 2002;**2**(Suppl 3):393. [CENTRAL: CN-00527169]

Stallone 2004 *{published data only}*

* Stallone G, Di Paolo S, Schena A, Infante B, Battaglia M, Ditonno P, et al. Addition of sirolimus to cyclosporine delays the recovery from delayed graft function but does not affect 1-year graft function. *Journal of the American Society of Nephrology* 2004;**15**(1):228-33. [MEDLINE: 14694177]

Stallone G, Infante B, Schena A, Di Paolo S, Gesualdo L, Ditonno P, et al. Sirolimus prolongs delayed graft function in recipients of sub-optimal cadaveric kidney donors [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):563. [CENTRAL: CN-00447829]

Stegall 2003 *{published data only}*

* Dean PG, Grande JP, Sethi S, Park WD, Griffin MD, Cosio FG, et al. Kidney transplant histology after one year of continuous therapy with sirolimus compared with tacrolimus. *Transplantation* 2008;**85**(8):1212-5. [MEDLINE: 18431244]

Dean PG, Larson TS, Rea DJ, Griffin MD, Textor SC, Schwab TR, et al. The effect of immunosuppression on renal function and graft histology: a comparison of tacrolimus and sirolimus [abstract no: 379]. *American Journal of Transplantation* 2005;**5**(Suppl 11):252. [CENTRAL: CN-00725015]

Dean PG, Larson TS, Rea DJ, Griffin MD, Textor SC, Schwab TR, et al. The effects of calcineurin inhibitor avoidance on renal function and graft histology after kidney transplantation: a prospective, randomized comparison of tacrolimus and sirolimus [abstract no: 259]. *Transplantation* 2004;**78**(2 Suppl):89. [CENTRAL: CN-00509154]

Dean PG, Lund WJ, Larson TS, Prieto M, Nyberg SL, Ishitani MB, et al. Wound healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):229.

Dean PG, Lund WJ, Larson TS, Prieto M, Nyberg SL, Ishitani MB, et al. Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation* 2004;**77**(10):1555-61. [MEDLINE: 15239621]

Hamad A, Buehrig CK, Kreps MA, Lager DJ, Fidler ME, Gloor JM, et al. Frequency of polyomavirus-associated nephropathy in a randomized controlled trial of tacrolimus versus sirolimus-based immunosuppression [abstract no: 147]. *American Journal of Transplantation* 2003;**3**(Suppl 5):189. [CENTRAL: CN-00445626]

Kudva YC, Basu A, Larson TS, Stegall MD. Metabolic complications after renal transplantation: a comparison of sirolimus vs tacrolimus-based immunosuppression [abstract no: 256]. *American Journal of Transplantation* 2003;**3**(Suppl 5):217. [CENTRAL: CN-00446214]

Larson TS, Dean PG, Griffin MD, Prieto M, Schwab TR, Cosio FG, et al. Preserving renal function by avoiding calcineurin-inhibitors in renal transplantation: a randomized trial of sirolimus vs. tacrolimus [abstract no: 461]. *American Journal of Transplantation* 2004;**4**(Suppl 8):285. [CENTRAL: CN-00509307]

* Larson TS, Dean PG, Stegall MD, Griffin MD, Textor SC, Schwab TR, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. *American Journal of Transplantation* 2006;**6**(3):514-22. [MEDLINE: 16468960]

Larson TS, Griffin MD, Prieto M, Schwab TR, Lund WJ, Nyberg SL, et al. Avoiding calcineurin-inhibitors in renal transplantation: a randomized trial of sirolimus vs tacrolimus [abstract no: 1261]. *American Journal of Transplantation* 2003;**3**(Suppl 5):475. [CENTRAL: CN-00446279]

Larson TS, Velosa JA, Prieto M, Lund WJ, Griffin MD, Gloor JM, et al. Kidney transplantation without calcineurin-inhibitors: a randomized trial of sirolimus vs tacrolimus [abstract no: 396]. *American Journal of Transplantation* 2002;**2**(Suppl 3):237.

Larson TS, Velosa JA, Prieto M, Lund WJ, Griffin MD, Gloor JM, et al. Kidney transplantation without calcineurin-inhibitors: a randomized trial of sirolimus vs tacrolimus [abstract no: O552]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416102]

Lund WJ, Larson TS, Stegall MD, Prieto M, Kremers WK. Obesity increases wound complications in sirolimus-treated

renal allograft recipients [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):214. [CENTRAL: CN-00446497]

Qian Q, Du H, King BF, Kumar S, Cosio FG, Torres VE. Sirolimus reduces polycystic liver volume in ADPKD patients after renal transplantation [abstract no: SA-PO094]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):365A. [CENTRAL: CN-00716079]

Qian Q, Du H, King BF, Kumar S, Dean PG, Cosio FG, et al. Sirolimus reduces polycystic liver volume in ADPKD patients. *Journal of the American Society of Nephrology* 2008;**19**(3):631-8. [MEDLINE: 18199797]

Stegall MD, Larson TS, Prieto M, Gloor J, Textor S, Nyberg S, et al. Kidney transplantation without calcineurin inhibitors using sirolimus. *Transplantation Proceedings* 2003;**35**(3 Suppl):125S-7S. [MEDLINE: 12742483]

Suwelack 2002 *{published data only}*

Hillebrand U, Suwelack B, Gerhardt U, Kobelt V, Kraemer J, Hohage H. Impact of calcineurin inhibitor withdrawal and mycophenolate mofetil substitution on hematologic toxicity [abstract no: 0014]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415864]

Suwelack B, Diet KH, Kobelt V, Hohage H, Gerhardt U. Impact of calcineurin-inhibitor withdrawal on arterial distensibility and endothelial function in chronic allograft nephropathy [abstract no: 1048]. *American Journal of Transplantation* 2002;**2**(Suppl 3):402. [CENTRAL: CN-00416722]

* Suwelack B, Gerhardt U, Hohage H. Withdrawal of cyclosporine or tacrolimus after addition of mycophenolate mofetil in patients with chronic allograft nephropathy. *American Journal of Transplantation* 2004;**4**(4):655-62. [MEDLINE: 15023160]

Suwelack B, Gerhardt U, Kobelt V, Hillebrand U, Matzkies F, Hohage H. Design and preliminary results of a randomized study on the conversion of treatment with calcineurin inhibitors to mycophenolate mofetil in chronic renal graft failure: effect, on serum cholesterol levels. *Transplantation Proceedings* 2002;**34**(5):1803-5. [MEDLINE: 12176583]

Suwelack B, Hausberg M, Hillebrand U, Rahn KH, Hohage H. Study on effects of calcineurin inhibitor withdrawal on arterial distensibility and endothelial function in renal transplant recipients [abstract no: 0637]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416723]

Suwelack B, Kobelt V, Gerhardt U, Volmer S, Hohage H. Course of intima thickness in long term renal transplant recipients treated with or without calcineurin-inhibitors [abstract no: P04.21]. *Kidney & Blood Pressure Research* 2004;**27**(5-6):335. [CENTRAL: CN-00615862]

Suwelack B, Kobelt V, Hillebrand U, Gerhardt U, Matzkies F, Hohage H. Replacement of calcineurin inhibitors by mycophenolate mofetil: effect on hemoglobine levels. *Transplantation Proceedings* 2002;**34**(5):1808-9. [MEDLINE: 12176585]

Suwelack B, Kobelt V, Hohage H, Gerhardt U. Studies on effects of calcineurin-inhibitor withdrawal on arterial wall structure and intima media thickness in longterm transplant recipients [abstract no: P290]. *Transplantation* 2004;**78**(2 Suppl):295. [CENTRAL: CN-00509495]

Suwelack B, Malyar V, Waldschmidt G, Hohage H. 5 year follow-up of a randomized study on calcineurin-inhibitor-withdrawal with addition of MMF in chronic allograft nephropathy [abstract no: F-PO600]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):231A.

Suwelack BM, Gerhardt UW, Hohage H. Influence of calcineurin-inhibitor free immunosuppression on carotid intima media thickness in chronic allograft nephropathy [abstract no: 659]. *American Journal of Transplantation* 2003;**3**(Suppl 5):320. [CENTRAL: CN-00447914]

SYMPHONY Study 2007 *{published data only}*

Bagul A, Nicholson M, Chavez R, Grinyo J, Frei U, Vanrenterghem Y, et al. Low-dose sirolimus in the first 8 weeks following renal transplantation accompanied by daclizumab induction, MMF and steroids: The experience of the SYMPHONY study [abstract no: P23]. British Transplantation Society (BTS).10th Annual Congress; 2007 Mar 28-30; Manchester, UK. 2007.

Chavez R, Nicholson M, Grinyo J, Frei U, Vanrenterghem Y, Daloze P, et al. SYMPHONY - comparing efficacy of standard immunosuppression to low-dose cyclosporine, tacrolimus or sirolimus in combination with MMF, daclizumab and corticosteroids in renal transplantation. Sub analysis of GFR in cases that completed one year within an intended regime [abstract no: O06]. British Transplantation Society (BTS). 10th Annual Congress; 2007 Mar 28-30; Manchester, UK. 2007.

Claes K, Meier-Kriesche HU, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. *Nephrology Dialysis Transplantation* 2012;**27**(2):850-7. [MEDLINE: 21617197]

Colom H, Fernandez De Troconiz I, Caldes A, Oppenheimer F, Sanchez Plumed J, Gentil MA, et al. Population pharmacokinetics of mycophenolic acid in combination with free or reduced doses of calcineurin inhibitors during the first week in renal transplant: the Symphony Study [abstract no: 105]. *Transplantation* 2008;**86**(2 Suppl):37. [CENTRAL: CN-00678981]

Daloze P, Ekberg H, Vincenti F, Tedesco-Silva H, Pearson T. Low-dose sirolimus in the first 8 weeks following renal transplantation accompanied by daclizumab induction, MMF and steroids: the experience of the SYMPHONY Study [abstract no: F-PO1078]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):563A.

Demirbas A, Hugo C, Grinyo J, Frei U, Gurkan A, Marcen R, et al. Low toxicity regimens in renal transplantation: a country subset analysis of the Symphony study. *Transplant International* 2009;**22**(12):1172-81. [MEDLINE: 19891046]

Demirbas A, Hugo C, Grinyo J, Frei U, Gurkan A, Marcen R, et al. Results of the Symphony Study are applicable across transplant populations; experience from Spain, Turkey and Germany [abstract no: P581]. *Transplant International* 2007;**20**(Suppl 2):234.

Ekberg H, Bernasconi C, Halloran P. CNI minimisation with 2 G mycophenolate mofetil - what have we learned from the Symphony Study [abstract no: 964]. *Transplantation* 2008;**86**(2 Suppl):334. [CENTRAL: CN-00671785]

Ekberg H, Bernasconi C, Noldeke J, Yussim A, Mjornstedt L, Erken U, et al. Cyclosporine, tacrolimus and sirolimus retain their distinct toxicity profiles despite low doses in the Symphony study. *Nephrology Dialysis Transplantation* 2010;**25**(6):2004-10. [MEDLINE: 20106825]

Ekberg H, Bernasconi C, Noldeke J, Yussim A, Mjornstedt L, Erken U, et al. Cyclosporine, tacrolimus and sirolimus retained their distinct toxicity profiles despite low doses in the Symphony Study [abstract no: 55]. *American Journal of Transplantation* 2007;**7**(Suppl 2):160. [CENTRAL: CN-00653721]

Ekberg H, Halloran P, Vanrenterghem Y, Schold J, Meier-Kriesche H. Renal function progression following DGF and early AR is not impaired if function is restored: evidence from the Symphony Study [abstract no: P583]. *Transplant International* 2007;**20**(Suppl 2):235.

Ekberg H, Mamelok R, Bernasconi C, Vincenti F, Tedesco-Silva H, Daloze P, et al. The challenge of meeting target drug concentrations: experience from the Symphony study [abstract no: 58]. *American Journal of Transplantation* 2007;**7**(Suppl 2):161. [CENTRAL: CN-00615834]

Ekberg H, Tedesco-Silva H, Demirbas A, Bitko S, Klempnauer J, Gurkan A, et al. Improved outcomes after de novo renal transplantation: 2-year results from the Symphony Study [abstract no: 531]. *American Journal of Transplantation* 2008;**8**(Suppl 2):320. [CENTRAL: CN-00653754]

Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Klempnauer J, Gurkan A, et al. CNI sparing in de novo renal transplantation: 3-year results from the Symphony Study [abstract no: LB04]. *American Journal of Transplantation* 2008;**8**(Suppl 2):336. [CENTRAL: CN-00653755]

Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Klempnauer J, Gurkan A, et al. CNI sparing with mycophenolate mofetil in de novo renal transplantation: 3-year results from the Symphony Study [abstract no: 623]. *Transplantation* 2008;**86**(2 Suppl):218. [CENTRAL: CN-00676055]

* Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *New England Journal of Medicine* 2007;**357**(25):2562-75. [MEDLINE: 18094377]

Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Symphony - comparing standard immunosuppression to low-dose cyclosporine, tacrolimus or sirolimus in combination with MMF, daclizumab and corticosteroids in renal transplantation [abstract no: 49]. *American Journal of Transplantation* 2006;**6**(Suppl 2):83.

Ekberg H, Vincenti F, Tedesco da Silva H, Daloze P, Pearson T. Low-dose sirolimus in the first 8 weeks following renal transplantation accompanied by daclizumab induction, MMF and steroids: the experience of the Symphony Study [abstract no: 691]. *American Journal of Transplantation* 2006;**6**(Suppl 2):300. [CENTRAL: CN-00602015]

Frei U, Daloze P, Vitko S, Klempnauer J, Reyes-Acevedo R, Titiz I, et al. Acute rejection in low-toxicity regimens: clinical impact and risk factors in the Symphony study. *Clinical Transplantation* 2010;**24**(4):500-9. [MEDLINE: 19758267]

Frei U, Daloze P, Vitko S, Klempnauer J, Reyes-Acevedo R, Titiz I, et al. Characterization of acute rejections and associated relative risk factors in the Symphony Study [abstract no: 245]. *American Journal of Transplantation* 2007;**7**(Suppl 2):210. [CENTRAL: CN-00653713]

Frei U, Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, et al. SYMPHONY - comparing standard immunosuppression to low-dose cyclosporine, tacrolimus or sirolimus in combination with MMF, daclizumab and corticosteroids in renal transplantation [abstract no: F-FC152]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):69A. [CENTRAL: CN-00602018]

Grinyo J, Ekberg H, Oppenheimer F, Gentil MA, Hernandez D, Plumed JS, et al. Pharmacokinetics of total and free mycophenolic acid in renal transplantation receiving standard-dose cyclosporine, low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony PK sub-study [abstract no: P342]. *Transplant International* 2007;**20**(Suppl 2):177. [CENTRAL: CN-00653737]

Grinyo J, Ekberg H, Oppenheimer F, Plumed J, Rodriguez G, Hernandez D, et al. Pharmacokinetics of total and free mycophenolic acid (MPA) when mycophenolate mofetil (MMF) is administered with low-dose tacrolimus, low-dose cyclosporine, low-dose sirolimus or standard-dose cyclosporine in renal transplantation. Results of the Symphony PK substudy [abstract no: 824]. *American Journal of Transplantation* 2006;**6**(Suppl 2):345. [CENTRAL: CN-00602016]

Grinyo J, Ekberg H, Oppenheimer F, Plumed J, Rodriguez G, Hernandez D, et al. Pharmacokinetics of total and free mycophenolic acid in renal transplantation receiving standard-dose cyclosporine, low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony PK sub-study [abstract no: 1151]. *American Journal of Transplantation* 2007;**7**(Suppl 2):443.

Grinyo JM, Ekberg H, Mamelok RD, Oppenheimer F, Sanchez-Plumed J, Gentil MA, et al. The pharmacokinetics of mycophenolate mofetil in renal transplant recipients receiving standard-dose or low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony pharmacokinetic substudy. *Nephrology Dialysis Transplantation* 2009;**24**(7):2269-76. [MEDLINE: 19357111]

Halloran P, Meier-Kriesche HU, Schold J, Vanrenterghem Y. Blood pressure in the first year following renal transplantation is associated with immunosuppressive regimens: evidence from the Symphony study [abstract no: 1137]. *American Journal of Transplantation* 2007;**7**(Suppl 2):439. [CENTRAL: CN-00615835]

Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients (Review)

Hugo C, Frei U, Margreiter R, Peeters P, Ok E, Viebahn R, et al. Elderly kidney transplant recipients are a high-risk group for death, infections and PTx diabetes: evidence from the Symphony study [abstract no: 154]. *American Journal of Transplantation* 2007;**7**(Suppl 2):186. [CENTRAL: CN-00724927]

Hugo C, Frei U, Margreiter R, Peeters P, Toz H, Viebahn R, et al. Marginal donor quality transmits a high risk profile in elderly but not young renal transplant patients - a subgroup analysis of the Symphony Study [abstract no: F-PO1471]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):436A. [CENTRAL: CN-00724891]

Kuypers D, Ekberg H, Oppenheimer F, Plumed J, Rodriguez G, Hernandez D, et al. Pharmacokinetics of total and free mycophenolic acid (MPA) when mycophenolate mofetil (MMF) is administered with low-dose tacrolimus, low-dose cyclosporine, low-dose sirolimus or standard-dose cyclosporine in renal transplantation. Results of the SYMPHONY PK substudy [abstract no: TH-PO564]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):227A.

Llaudo I, Colom H, Gimenez-Bonafe P, Torras J, Caldes A, Sarrias M, et al. Do drug transporter (ABCB1) SNPs and P-glycoprotein function influence cyclosporine and macrolides exposure in renal transplant patients? Results of the pharmacogenomic substudy within the SYMPHONY study. *Transplant International* 2013;**26**(2):177-86. [MEDLINE: 23216707]

Lloberas N, Brunet M, Torras J, Cruzado JM, Oppenheimer F, Sanchez-Plumed J, et al. Influence of MRP2 and UGT1A9 polymorphisms in the MPA pharmacokinetics in renal transplant recipients. Results of the pharmacogenomic substudy within the Symphony Study [abstract no: TH-PO508]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):220A. [CENTRAL: CN-00724892]

Lloberas N, Brunet M, Torras J, Oppenheimer F, Sanchez-Plumed J, Gentil MA, et al. Influence of MRP2 and UGT1A9 polymorphisms in the MPA pharmacokinetics in renal transplant substudy within the Symphony Study [abstract no: 2243]. *Transplantation* 2008;**86**(2 Suppl):733. [CENTRAL: CN-00671787]

Lloberas N, Llaudo I, Torras J, Caldes A, Cruzado JM. Polymorphisms of the MDR1 gene in renal transplant recipients affect the PGP activity. Results of the pharmacogenetic substudy within the Symphony Study [abstract no: 2244]. *Transplantation* 2008;**86**(2 Suppl):734. [CENTRAL: CN-00671786]

Lloberas N, Llaudo I, Torras J, Cruzado JM, Caldes A, Oppenheimer F, et al. Polymorphisms of the MDR1 gene in renal transplant recipients affect the PGP activity. Results of the pharmacogenomic substudy (Symphony Study) [abstract no: TH-PO507]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):220A. [CENTRAL: CN-00724893]

Lloberas N, Torras J, Cruzado JM, Andreu F, Oppenheimer F, Sanchez-Plumed J, et al. Influence of MRP2 on MPA pharmacokinetics in renal transplant recipients-results of the pharmacogenomic substudy within the Symphony Study.

Nephrology Dialysis Transplantation 2011;**26**(11):3784-93. [MEDLINE: 21427078]

Meier-Kriesche H, Halloran P, Vanrenterghem Y, Schold J. Early immunosuppression exposure and incidence of acute rejection and renal function progression: evidence from the Symphony Study [abstract no: 244]. *American Journal of Transplantation* 2007;**7**(Suppl 2):210. [CENTRAL: CN-00724894]

Meier-Kriesche H, Schold J, Vanrenterghem Y, Halloran P, Ekberg H. Factors associated with BMI increases early after renal transplantation: evidence from the Symphony Study [abstract no: P582]. *Transplant International* 2007;**20**(Suppl 2):234.

O'Connell PJ, Walker RG, Ierino F, Eris J, Russ G, Grinyo J, et al. Results of the SYMPHONY trial in renal transplantation - comparing standard immunosuppression to low dose cyclosporine (low-CSA), tacrolimus (low-TAC) or sirolimus (low-SRL with MMF, daclizumab and corticosteroids [abstract]. *Immunology and Cell Biology* 2007;**85**(4):A33.

Oppenheimer F, Rebello P, Grinyo JM, Ortega F, Sanchez-Plumed J, Gonzalez-Molina M, et al. Health-related quality of life of patients receiving low toxicity immunosuppressive regimens. Preliminary results of the quality of life substudy of the Elite Symphony Study [abstract no: TH-PO566]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):228A. [CENTRAL: CN-00747305]

Oppenheimer F, Rebollo P, Grinyo JM, Ortega F, Sanchez J, Gonzalez M, et al. Health care resource consumption (HCRC) of patients receiving low toxicity immunosuppressive regimens. One year follow up results of the quality of life substudy within the Symphony study [abstract no: P108]. *Transplant International* 2007;**20**(Suppl 2):121. [CENTRAL: CN-00724895]

Oppenheimer F, Rebollo P, Grinyo JM, Ortega F, Sanchez-Plumed J, Gonzalez-Molina M, et al. Cost-effectiveness analysis of adverse events in low toxicity immunosuppressive regimens, preliminary results of the quality of life substudy within the Symphony Study [abstract no: 107]. *Transplantation* 2008;**86**(2 Suppl):38. [CENTRAL: CN-00677744]

Oppenheimer F, Rebollo P, Grinyo JM, Ortega F, Sanchez-Plumed J, Gonzalez-Molina M, et al. Health-related quality of life of patients receiving low-toxicity immunosuppressive regimens: a substudy of the Symphony study. *Transplantation* 2009;**87**(8):1210-3. [MEDLINE: 19384168]

Vanrenterghem Y, Meier-Kriesche H, Schold J, Halloran P, Ekberg H. Levels and progression of parameters associated with metabolic syndrome by immunosuppressive regimen: evidence from the Symphony Study [abstract no: P580]. *Transplant International* 2007;**20**(Suppl 2):234.

Takahashi 2013a *{published data only}*

Saito K, Uchida K, Takahara S, Yoshimura N, Teraoka S, Cornu-Artis C, et al. Efficacy of everolimus with reduced cyclosporine in Japanese de novo renal transplant recipients: 24-month, randomized, multicenter study [abstract no: B944]. *American Journal of Transplantation* 2013;**13**(Suppl S5):314. [EMBASE: 71057520]

Takahara S, Uchida K, Yoshimura N, Teraoka S, Kobayashi E, Teshima R, et al. Efficacy and safety of concentration controlled everolimus with reduced dose cyclosporine in Japanese adult de-novo renal transplant patients: 12 month results [abstract no: 935]. *American Journal of Transplantation* 2012;**12**(Suppl S3):300. [EMBASE: 70746888]

* Takahashi K, Uchida K, Yoshimura N, Takahara S, Teraoka S, Teshima R, et al. Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. *Transplantation Research* 2013;**2**(1):14. [MEDLINE: 23866828]

Uchida K, Hoshinaga K, Watarai Y, Goto N, Kusaka M, Sasaki H, et al. Pharmacokinetics of everolimus when combined with cyclosporine in Japanese de novo renal transplant recipients. *Transplantation Proceedings* 2014;**46**(5):1314-8. [MEDLINE: 24935294]

Watarai Y, Akutsu N, Saito K, Nakagawa Y, Kamisawa O, Kenmochi T. Everolimus plus reduced-exposure calcineurin inhibitor versus mycophenolate mofetil plus standard-exposure calcineurin inhibitor: 2-year results in living donor kidney transplant recipients [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953410]

Tedesco-Silva 2010 *{published data only}*

Campbell S, Walker R, Pilmore H, Kanellis J, Russ G, Hutchison B, et al. Wound healing events are dose related: a multicenter, prospective study on everolimus in renal transplantation [abstract no: 43]. Transplantation Society of Australia & New Zealand (TSANZ). 29th Annual Scientific Meeting; 2011 Jun 29-Jul 1; Canberra (ACT). 2011:64.

Carmellini M, Garcia V, Wang Z, Vergara M, Russ G. Efficacy of everolimus with reduced-exposure cyclosporine in de novo kidney transplant patients at increased risk for efficacy events: analysis of a randomized trial. *Journal of Nephrology* 2015;**28**(5):633-9. [MEDLINE: 25708913]

Carmellini M, Garcia V, Wong Z, Vergara M, Escrig C, Russ G. Treatment with everolimus and reduced-exposure cyclosporine is efficacious in de novo renal transplant recipients at increased risk for efficacy failure: Post-Hoc analysis from the A2309 study [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71954404]

Chadban S, Pilmore H, Russ G, Kanellis J, Campbell S, O'Connell P, et al. Everolimus plus reduced-exposure cyclosporin versus mycophenolic acid plus cyclosporin: seven year follow-up of ANZ patients from a randomised controlled trial [abstract no: 079]. *Nephrology* 2015;**30**(Suppl 3):39. [EMBASE: 71995868]

Cibrik D, Johnston T, Kim YS, Walker R, Zibari G, Mange K, et al. Everolimus allows for around 60% reduction in CsA exposure over 12 months: results from a multicenter, prospective study in renal transplantation [abstract no: 1667]. *American Journal of Transplantation* 2010;**10**(Suppl 4):511. [EMBASE: 70465042]

Cibrik D, Johnston T, Kim YS, Walker RG, Zibari G, Cornu-Artis C, et al. Everolimus exposure and relationship to efficacy and safety: results from a multicenter study in renal transplantation using reduced CsA exposure [abstract no: LB25]. *American Journal of Transplantation* 2010;**10**(S4):567-8. [EMBASE: 70465240]

Cibrik D, Kim YS, Johnston T, Walker R, Zibari G, et al. Benefits of everolimus with reduced CsA exposure on renal function: a multicenter, prospective study in renal transplantation [abstract no: 378]. *American Journal of Transplantation* 2010;**10**(Suppl 4):151-2. [EMBASE: 70463739]

Cibrik D, Silva HT, Vathsala A, Lackova E, Cornu-Artis C, Walker RG, et al. Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. *Transplantation* 2013;**95**(7):933-42. [MEDLINE: 23422495]

Colussi G, Vergara M, Wang Z, Roland R. Risk factors associated with efficacy outcomes in kidney transplantation: analysis of a contemporary cohort of patients from the A2309 trial. *Clinical Nephrology* 2015;**83**(6):338-44. [MEDLINE: 25816807]

Kanellis J, Walker R, Pilmore H, Russ G, Hutchison B, Chadban S, et al. Benefits of everolimus with reduced CSA exposure on renal function: a multicenter, prospective study in renal transplantation [abstract no: 6]. Transplantation Society of Australia & New Zealand (TSANZ). 29th Annual Scientific Meeting; 2011 Jun 29-Jul 1; Canberra (ACT). 2011:40.

Kim YS, Tedesco-Silva H, Johnston T, Lee P, Zibari G, Walker R, et al. Lower incidence of cytomegalovirus and BK virus with everolimus versus mycophenolate in de novo renal transplant patients: results from a multicenter, prospective study [abstract no: 1615]. *Transplantation* 2010;**90**(Suppl):256. [EMBASE: 71531587]

Pattison J, Riad H, Yaqoob M, Chan L. Correlation of everolimus exposure with reduced CsA exposure to efficacy and safety outcomes: results from a multicentre study in renal transplantation [abstract no: 19]. British Transplantation Society (BTS). 14th Annual Congress; 2011 Mar 9-11; Bournemouth, UK. 2011.

Pattison J, Riad H, Yaqoob M, Tedesco-Silva H. Preserved efficacy and renal function from 12 to 24 months with everolimus facilitated CsA reduction [abstract no: 47]. British Transplantation Society (BTS). 14th Annual Congress; 2011 Mar 9-11; Bournemouth, UK. 2011.

Pattison J, Riad H, Yaqoob M, Tedesco-Silva H. Renal function in de novo kidney transplant patients receiving everolimus with reduced dose cyclosporin or enteric-coated mycophenolic acid with standard-dose cyclosporin: results from a large-scale, randomised, international trial [abstract no: O36]. British Transplantation Society (BTS). 13th Annual Congress; 2010 Mar 17-19; Kensington, UK. 2010.

Riad H, Pattison J, Yaqoob M, Chan L. 12 month analysis of effects of graft type, donor criteria and gender on improved renal allograft function with everolimus facilitated CNI reduction [abstract no: 21]. British Transplantation Society (BTS). 14th Annual Congress; 2011 Mar 9-11; Bournemouth, UK. 2011.

Riad H, Pattison J, Yaqoob M, Kim YS. Lower incidence of CMV and BK virus with everolimus vs. mycophenolate in de novo renal transplant patients at 12 months [abstract no: 20]. British Transplantation Society (BTS). 14th Annual Congress; 2011 Mar 9-11; Bournemouth, UK. 2011.

Riad H, Pattison J, Yaqoob M, Tedesco-Silva H. Everolimus with reduced-dose cyclosporin as a strategy to optimise long-term renal function: results from a randomised study in 833 de novo kidney transplant recipients [abstract no: P43]. British Transplantation Society (BTS). 13th Annual Congress; 2010 Mar 17-19; Kensington, UK. 2010.

Russ G, Chadban S, Campbell S, Hutchison B, Kanellis J, O'Connell P, et al. Everolimus plus reduced-dose cyclosporine: results from a randomized, phase III study in 833 de-novo renal transplant recipients [abstract no: 70]. *Immunology & Cell Biology* 2010;**88**(6):A22. [EMBASE: 70313681]

Russ G, Walker R, Pilmore H, Kanellis J, Hutchison B, Chadban S, et al. Everolimus plus reduced CSA exposure: efficacy results from a multicenter, randomized prospective study in renal transplantation [abstract no: 1]. Transplantation Society of Australia & New Zealand (TSANZ). 29th Annual Scientific Meeting; 2011 June 29-Jul 1; Canberra, ACT. 2011:36.

Russ G, Walker R, Pilmore H, Kanellis J, Hutchison B, Chadban S, et al. Lower incidence of cytomegalovirus and BK virus with everolimus versus mycophenolate in de novo renal transplant patients: results from a multicenter, prospective study [abstract no: 70]. Transplantation Society of Australia & New Zealand (TSANZ). 29th Annual Scientific Meeting; 2011 June 29-Jul 1; Canberra, ACT. 2011:82.

Shihab F, Cibrik D, Chan L, Kim YS, Carmellini M, Walker R, et al. Exposure-response analysis of everolimus with reduced cyclosporine in renal transplant recipients at 24 months in a randomized trial [abstract no: 929]. *American Journal of Transplantation* 2012;**12**(Suppl S3):298-9. [EMBASE: 70746882]

Shihab F, Cibrik D, Kim YS, Johnston T, Walker R, Roland R, et al. De novo everolimus combined with reduced cyclosporine exposure - analysis of renal function at 12 months in renal transplant recipients [abstract no: 2023]. *Transplantation* 2010;**90**(Suppl 2S):110.

Shihab FS, Cibrik D, Chan L, Kim YS, Carmellini M, Walker R, et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. *Clinical Transplantation* 2013;**27**(2):217-26. [MEDLINE: 23230975]

* Tedesco Silva H Jr, Cibrik D, Johnston T, Lackova E, Mange K, Panis C, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *American Journal of Transplantation* 2010;**10**(6):1401-13. [MEDLINE: 20455882]

Tedesco-Silva H, Johnston TS, Kim Y, Zibari G, Walker R, Mange K, et al. Everolimus-treated renal transplant patients have a lower incidence of CMV and BKV: results from a multicenter, prospective study [abstract: 1659]. *American Journal of Transplantation* 2010;**10**(Suppl 4):509. [EMBASE: 70465034]

Tedesco-Silva H, Kim YS, Johnston T, Walker R, Tufvetson G, Zibari G, et al. Everolimus with reduced exposure of cyclosporine: efficacy results from a randomized prospective study in 833 de novo renal transplant recipients [abstract no: 427]. *Transplantation* 2010;**90**(Suppl):110. [EMBASE: 71531315]

Tedesco-Silva H, Kim YS, Johnston T, Walker R, Zibari G, Mange K, et al. Everolimus plus reduced CsA exposure: efficacy results from a multicenter, randomized prospective study in renal transplantation [abstract no: 374]. *American Journal of Transplantation* 2010;**10**(Suppl 4):150. [EMBASE: 70463735]

Tedesco-Silva H, Kim YS, Lackova E, Johnston T, Zibari G, Panis C, et al. Everolimus with reduced-dose cyclosporine as a strategy for optimizing long-term renal function: results from a randomized study in 833 de-novo renal-transplant recipients [abstract no: P-371]. *Transplant International* 2009;**22**(Suppl 2):186-7.

Vathsala A, Zibari G, Kim YS, Cibrik D, Johnston T, Walker R, et al. Dose related incidences of wound healing events in renal transplant recipients treated with everolimus and cyclosporine [abstract no: 2060]. *Transplantation* 2012;**90**(Suppl):615. [EMBASE: 71532274]

Walker R, Cibrik D, Tedesco-Silva H, Johnston T, Kim YS, Zibari G, et al. Everolimus allows for a 60% reduction in cyclosporine exposure in subject cohorts defined by geography [abstract no: 1616]. *Transplantation* 2010;**90**(Suppl 2S):610. [EMBASE: 71532265]

Wiseman AC, McCague K, Kim Y, Geissler F, Cooper M. The effect of everolimus versus mycophenolate upon proteinuria following kidney transplant and relationship to graft outcomes. *American Journal of Transplantation* 2013;**13**(2):442-9. [MEDLINE: 23205690]

Zibari G, Kim YS, Cibrik D, Johnston T, Walker R, Mange K, et al. Wound healing events are dose related: a multicenter, prospective study on everolimus in renal transplantation [abstract no: 1661]. *American Journal of Transplantation* 2010;**10**(Suppl 4):510. [EMBASE: 70465036]

Velosa-212 Study 2001 *{published data only}*

Campistol JM, Alveranga D, Hricik DE, Velosa J, Grinyo JM, Mourad G, et al. Sirolimus-treated renal transplant recipients experience improved renal function with cyclosporine elimination: one-year results from a phase II trial [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A208. [CENTRAL: CN-00487674]

Gonwa T, Alveranga D, Ancona G, Brinker K, Cambi V, Campistol J, et al. Sirolimus (Rapamune) permits early elimination of cyclosporine in recipients of cadaveric renal allografts [abstract]. *Transplantation* 2000;**69**(8 Suppl):S360. [CENTRAL: CN-00445514]

Gonwa TA. Sirolimus (SRL) treated patients demonstrate improved renal function after withdrawal of cyclosporine (CSA) [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):891A. [CENTRAL: CN-00550647]

* Gonwa TA, Hricik DE, Brinker K, Grinyo JM, Schena FP, Sirolimus Renal Function Study Group. Improved renal function

in sirolimus-treated renal transplant patients after early cyclosporine elimination. *Transplantation* 2002;**74**(11):1560-7. [MEDLINE: 12490789]

Hricik DE, Rapamune Renal Function Study Group. Sirolimus improves renal function without increasing acute rejection after cyclosporine elimination in renal transplant patients [abstract no: 0430]. XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome, Italy. 2000. [CENTRAL: CN-00583304]

Velosa JA, Larson TS, Gloor JM, Stegall MD. Cyclosporine elimination in the presence of TOR inhibitors: effects on renal function, acute rejection, and safety. *American Journal of Kidney Diseases* 2001;**38**(4 Suppl 2):S3-S10. [MEDLINE: 11583938]

Watson 2005 *{published data only}*

Clatworthy M, Bradley V, Wallin E, Camilleri B, Williams P, Bradley JA, et al. Sirolimus conversion post-renal transplantation. 5 year follow up data [abstract no: P246]. British Transplantation Society (BTS).12th Annual Congress; 2009 Apr 21-24; Liverpool, UK. 2009.

Clatworthy MR, Bradley V, Bradley JA, Watson CJ. Sirolimus conversion post-renal transplantation - 5 year follow-up data [abstract no: 1096]. *American Journal of Transplantation* 2009;**9**(Suppl 2):499. [CENTRAL: CN-00766450]

Watson CJ, Firth J, Bradley J, Williams PF, Smith JC, Palmer CR, et al. Superior renal function following conversion to sirolimus after renal transplantation - preliminary results from a randomised trial [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):220-1. [CENTRAL: CN-00509555]

* Watson CJ, Firth J, Williams PF, Bradley JR, Pritchard N, Chaudhry A, et al. A randomized controlled trial of late conversion from CNI-based to sirolimus-based immunosuppression following renal transplantation. *American Journal of Transplantation* 2005;**5**(10):2496-503. [MEDLINE: 16162200]

Willcocks LC, Chaudhry AN, Smith JC, Ojha S, Doffinger R, Watson CJ, et al. The effect of sirolimus therapy on vaccine responses in transplant recipients. *American Journal of Transplantation* 2007;**7**(8):2006-11. [MEDLINE: 17578505]

ZEUS Study 2011 *{published data only}*

Arns W, Becker T, Budde K, Eisenberger U, Fischer W, Kramer S, et al. Conversion to an everolimus/enteric-coated mycophenolate sodium regimen in de novo renal transplant improves 2 year renal function [abstract no: 15]. British Transplantation Society (BTS). 14th Annual Congress; 2011 Mar 9-11; Bournemouth, UK. 2011.

Arns W, Budde K, Becker T, Sommerer C, Reinke P, Eisenberger U, et al. Analysis of renal function in everolimus/ enteric-coated mycophenolate sodium treated de novo renal transplant recipients after calcineurin inhibitor withdrawal: The ZEUS Study [abstract no: SU656]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009. [CENTRAL: CN-00763609]

Becker T, Arns W, Budde K, Eisenberger U, Fischer W, Kramer S, et al. Renal function in everolimus/enteric-coated mycophenolate sodium treated de novo renal transplant recipients after calcineurin inhibitor withdrawal: the Zeus Study [abstract no: O-297]. *Transplant International* 2009;**22**(Suppl 2):78-9.

Becker T, Arns W, Budde K, Pietruck F, Eisenberger U, Fischer W, et al. Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 2 years follow-up of the ZEUS trial [abstract no: 1757]. *Transplantation* 2010;**90**(Suppl 2S):109. [EMBASE: 71531312]

Budde K, Arns W, Sommerer C, Reinke P, Eisenberger U, Fischer W, et al. Improved renal function of an everolimus/ enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 2 years follow-up of the ZEUS trial [abstract no: 1638]. *American Journal of Transplantation* 2010;**10**(Suppl 4):503.

Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Analysis of renal function in everolimus/ enteric-coated mycophenolate sodium treated de novo renal transplant recipients after calcineurin inhibitor withdrawal: the ZEUS Study [abstract no: 237]. *American Journal of Transplantation* 2009;**9**(Suppl 2):259. [EMBASE: 70010110]

* Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial.[Erratum appears in Lancet. 2012 Dec 8;380(9858):1994], [Erratum appears in Lancet. 2011 Jun 11;377(9782):2006 Note: Wuthrich, Rudolf P [added]]. *Lancet* 2011;**377**(9768):837-47. [MEDLINE: 21334736]

Budde K, Klempnauer J, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Multi-center, open-label, prospective, randomized, parallel group study investigating an everolimus-based CNI-free regimen in comparison to a cyclosporine-based standard therapy in de novo renal transplant patients (Zeus Study) [abstract no: 1640]. *Transplantation* 2008;**86**(Suppl 2):544. [CENTRAL: CN-00740480]

Budde K, Klempnauer J, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Renal function, efficacy and safety of everolimus (RAD)/enteric-coated mycophenolate sodium (EC-MPS) therapy after calcineurin inhibitor (CNI) withdrawal in de novo renal transplant patients: final outcomes of the Zeus Study [abstract no: 264]. *Transplantation* 2008;**86**(Suppl 2):93. [CENTRAL: CN-00740481]

Budde K, Lehner F, Arns W, Reinke P, Eisenberger U, Paulus EM, et al. Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 4 years follow-up of the ZEUS trial [abstract no: 927]. *American Journal of Transplantation* 2012;**12**(Suppl S3):298. [EMBASE: 70746880]

Budde K, Lehner F, Sommerer C, Arns W, Reinke P, Eisenberger U, et al. Conversion from cyclosporine to everolimus at 4.5 months posttransplant: 3-year results from the randomized ZEUS study. [Erratum appears in Am

J Transplant. 2012 Nov;12(11):3165]. *American Journal of Transplantation* 2012;**12**(6):1528-40. [MEDLINE: 22642473]

Budde K, Lehner F, Sommerer C, Reinke P, Arns W, Eisenberger U, et al. Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus: the randomized ZEUS study. *American Journal of Transplantation* 2015;**15**(1):119-28. [MEDLINE: 25521535]

Budde K, Witzke O, Sommerer C, Reinke P, Eisenberger U, Paulus E, et al. Improved renal function of an everolimus/ enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 5 years follow-up of the ZEUS trial [abstract no: 18]. *American Journal of Transplantation* 2013;**13**(Suppl S5):35-6. [EMBASE: 71056595]

Eisenberger U, Budde K, Witzke O, Lehner F, Sommerer C, Wuethrich R, et al. Explorative analysis of ZEUS after 5 years: Histological assessment from biopsy analyses [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953380]

Eisenberger U, Pietruck F, Becker T, Arns W, Reinke P, Kramer S, et al. Efficacy and safety of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: results of the ZEUS Study [abstract no: SU667]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009. [CENTRAL: CN-00774728]

Eisenberger U, Pietruck F, Klempnauer J, Arns W, Fehr T, Sommerer C, et al. Everolimus (RAD)/enteric-coated mycophenolate sodium (ECMPS) therapy after calcineurin inhibitor (CNI) withdrawal in de novo renal transplant patients: final outcomes of the ZEUS study [abstract no: 3.1]. *Swiss Medical Weekly* 2008;**138**(Suppl 167):5S.

Eisenberger U, Witzke O, Hauser I, Lehner F, Sommerer C, Wuethrich R, et al. Explorative analysis of ZEUS after 5 years: histological assessment from biopsy analyses [abstract no: O220]. *Transplant International* 2015;**28**(Suppl 4):83. [EMBASE: 72111464]

Lehner F, Arns W, Reinke P, Eisenberger U, Paulus E, Scheidl S, et al. Renal function in everolimus/enteric-coated mycophenolate sodium treated de novo living renal transplant recipients after calcineurin inhibitor withdrawal: subgroup analysis of the ZEUS study [abstract no: P142]. *Transplant International* 2011;**24**(Suppl 3):50-1. [EMBASE: 70537442]

Lehner F, Budde K, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Improved renal function of an everolimus/ enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 3 year follow-up of the ZEUS trial [abstract no: O-199]. *Transplant International* 2011;**24**(Suppl 3):57. [EMBASE: 70527276]

Lehner F, Budde K, Wuethrich R, Reinke P, Arns W, Muehlfeld A, et al. Post Hoc subgroup analysis of ZEUS: Outcome on renal function, efficacy and safety in living-donor kidney transplant recipients after conversion from a calcineurin inhibitor to an everolimus based regimen: 5 year follow-up data [abstract].

American Journal of Transplantation 2015;**15**(Suppl 3). [EMBASE: 71954049]

Lehner F, Budde K, Zeier M, Wuthrich RP, Reinke P, Eisenberger U, et al. Efficacy and safety of conversion from cyclosporine to everolimus in living-donor kidney transplant recipients: an analysis from the ZEUS study. *Transplant International* 2014;**27**(11):1192-204. [MEDLINE: 25070687]

Lehner F, Sommerer C, Arns W, Budde K, Wuethrich R, Reinke P, et al. Outcome on renal function, efficacy and safety in living-donor kidney transplant recipients after conversion from CNI to everolimus-based regimen: 5 year data post hoc analysis from the ZEUS study [abstract no: BO333]. *Transplant International* 2015;**28**(Suppl 4):242-3. [EMBASE: 72111925]

Lehner F, Sommerer C, Arns W, Reinke P, Eisenberger U, Wuthrich R, et al. Post hoc subgroup analysis of ZEUS: Outcome on renal function, efficacy and safety in living-donor kidney transplant recipients after conversion from a calcineurin inhibitor to an everolimus based regimen [abstract]. *Transplantation* 2014;**98**(Suppl 1):613. [EMBASE: 71545612]

Lehner F, Sommerer C, Arns W, Reinke P, Eisenberger U, Wuthrich RP, et al. Post Hoc subgroup analysis from ZEUS: outcome on renal function, efficacy and safety in living-donor kidney transplant recipients after conversion from a calcineurin inhibitor to an everolimus based regimen [abstract no: V22]. *Transplant International* 2013;**26**(Suppl 1):8. [EMBASE: 71356217]

Lehner F, Sommerer C, Reinke P, Arns W, Eisenberger U, Paulus E, et al. 5-year follow-up on the ZEUS KTX trial: everolimus conversion after CNI withdrawal [abstract no: BO142]. *Transplant International* 2013;**26**(Suppl 2):81. [EMBASE: 71359257]

Pietruck F, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Efficacy and safety of an everolimus/ enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: results of the ZEUS trial [abstract no: 1093]. *American Journal of Transplantation* 2009;**9**(Suppl 2):499. [CENTRAL: CN-00774729]

Pietruck F, Budde K, Arns W, Reinke P, Eisenberger U, Fischer W, et al. Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 2 years follow-up of the Zeus-trial [abstract no: OM007]. *NDT Plus* 2010;**3**(Suppl 3):iii553. [EMBASE: 70484927]

Pietruck F, Klempnauer J, Arns W, Sommerer C, Reinke P, Eisenberger U, et al. Everolimus/enteric-coated mycophenolate sodium (EC-MPS) therapy after calcineurin inhibitor withdrawal in de novo renal transplant patients: final outcomes of the ZEUS study [abstract no: TH-FC041]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):10A. [CENTRAL: CN-00716070]

Reinke P, Arns W, Becker T, Eisenberger U, Fischer W, Kramer S, et al. Efficacy and safety of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: results of

the ZEUS trial [abstract no: O-202]. *Transplant International* 2009;**22**(Suppl 2):53.

Reinke P, Lehner F, Witzke O, Sommerer C, Eisenberger U, Arns W, et al. 5 Years follow-up on renal function - ZEUS trial: Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients [abstract no: V76]. *Transplant International* 2013;**26**(Suppl 1):21. [EMBASE: 71356260]

Sommerer C, Lehner F, Arns W, Reinke P, Eisenberger U, Heller K, et al. Post hoc analysis of ZEUS and HERAKLES, two prospective, open-label, multicenter, randomized trials: Onset and progression of diabetes in kidney transplant recipients on cyclosporine standard or converted to CNI-free or CNI-low everolimus regimen [abstract]. *Transplantation* 2014;**98**(Suppl 1):145-6. [EMBASE: 71543989]

Witzke O, Lehner F, Arns W, Reinke P, Eisenberger U, Paulus E, et al. Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 4 years follow-up of the ZEUS trial [abstract no: 1671]. *Transplantation* 2012;**94**(Suppl 10S):993. [EMBASE: 71251765]

van der Giet M, Brakemeier S, Liefeldt L, Glander P, Diekmann F, Hohne M, et al. The impact of everolimus versus CNI-based immunosuppression on cardiovascular function and stiffness after renal transplantation [abstract no: 1646]. *American Journal of Transplantation* 2010;**10**(Suppl 4):506.

References to studies excluded from this review

Abouna 1991 *{published data only}*

Abouna GM, Kumar SM, White AG, Samhan M, Kalawi M, al-Sabawi N. Cyclosporine withdrawal in renal transplant recipients maintained on triple therapy. *Transplantation Proceedings* 1991 Feb;**23**(1 (Pt 2)):1009-10. [MEDLINE: 1989140]

Alexander 2006 *{published data only}*

Alexander JW, Goodman HR, Cardi M, Austin J, Goel S, Safdar S, et al. Simultaneous corticosteroid avoidance and calcineurin inhibitor minimization in renal transplantation. *Transplant International* 2006;**19**(4):295-302. [MEDLINE: 16573545]

Alpay 2013 *{published data only}*

Alpay N. Conversion from calcineurin inhibitors to everolimus resulted in decrease of serum TGF-beta and urinary NGAL in renal transplant recipients [abstract]. *Nephrology Dialysis Transplantation* 2013;**28**(Suppl 1):i500-1. [EMBASE: 71076549]

Alpay N, Ozkok A, Caliskan Y, Akagun T, Cinar S, Deniz G, et al. Conversion from calcineurin inhibitors to everolimus resulted in decrease of serum TGF-beta and urinary NGAL in renal transplant recipients [abstract no: 1744]. *American Journal of Transplantation* 2013;**13**(Suppl 5):545. [EMBASE: 71058320]

Artz 2002 *{published data only}*

Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Hene RJ, et al. Randomized conversion from cyclosporine to tacrolimus in renal transplant patients: improved lipid profile

and unchanged plasma homocysteine levels. *Transplantation Proceedings* 2002;**34**(5):1793-4. [MEDLINE: 12176579]

Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, et al. Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. *American Journal of Transplantation* 2004;**4**(6):937-45. [MEDLINE: 15147428]

Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, et al. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *Journal of the American Society of Nephrology* 2003;**14**(7):1880-8. [MEDLINE: 12819249]

Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, et al. Randomized conversion from cyclosporine to tacrolimus improves renal graft function, the cardiovascular risk profile, and perceived side-effects [abstract]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego (CA). 2004. [CENTRAL: CN-00550511]

Artz MA, Ligtenberg G, Roodnat JI, Christiaans MH, Boots HM, Hene RJ, et al. Randomized conversion from cyclosporine to tacrolimus in renal transplant patients: improved parameters of lipid metabolism and unchanged plasma homocysteine levels [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):876A. [CENTRAL: CN-00433618]

Asberg 2013 *{published data only}*

Asberg A, Apeland T, Reisaeter AV, Foss A, Leivestad T, Heldal K, et al. Long-term outcomes after cyclosporine or mycophenolate withdrawal in kidney transplantation - results from an aborted trial. *Clinical Transplantation* 2013;**27**(2):E151-6. [MEDLINE: 23351013]

Baboolal 2003 *{published data only}*

Baboolal K. A phase III prospective, randomized study to evaluate concentration-controlled sirolimus (Rapamune) with cyclosporine dose minimization or elimination at six months in de novo renal allograft recipients. *Transplantation* 2003;**75**(8):1404-8. [MEDLINE: 12717239]

Baboolal 2004 *{published data only}*

Baboolal K. Six month interim analysis of a phase III prospective, randomized study to compare conversion from calcineurin inhibitors to rapamycin in established renal allograft recipients with mild to moderate renal insufficiency [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):220. [CENTRAL: CN-00509073]

Baboolal K, Zaiac M, Newstead C. Development of early malignant disease in a multicentre, randomised study comparing conversion from calcineurin inhibitors (CNIs) to sirolimus in renal allograft recipients [abstract no: P302]. British Transplantation Society (BTS). 12th Annual Congress; 2009 Apr 21-24; Liverpool, UK. 2009.

Baboolal K, Zaiac M, Zamauskaite A, Newstead C. This multicentre, randomised study comparing conversion from calcineurin inhibitors (CNRs) to sirolimus versus standard therapy in renal allograft recipients showed a lower rate of

development of subsequent malignant disease in the group receiving sirolimus [abstract no: 164]. *American Journal of Transplantation* 2009;**9**(Suppl 2):238. [CENTRAL: CN-00776739]

Baxter 1982 *{published data only}*

Baxter CR, Duggin GG, Willis N, Hall BM, et al. Cyclosporin A in renal transplantation: plasma concentration and nephrotoxicity [abstract]. *Australian & New Zealand Journal of Medicine* 1982;**12**:347-8. [CENTRAL: CN-00319765]

Brady 1990 *{published data only}*

Brady HR, Kamel KS, Harding ME, Cook GT, deVeber GA, Cardella CJ. Low dose ciclosporin from the early postoperative period yields potent immunosuppression after renal transplantation. *Nephron* 1990;**55**(4):394-9. [MEDLINE: 2202920]

Burkhalter 2012 *{published data only}*

Burkhalter F, Oettl T, Descoeudres B, Bachmann A, Guerke L, Mihatsch MJ, et al. High incidence of rejection episodes and poor tolerance of sirolimus in a protocol with early steroid withdrawal and calcineurin inhibitor-free maintenance therapy in renal transplantation: experiences of a randomized prospective single-center study. *Transplantation Proceedings* 2012;**44**(10):2961-5. [MEDLINE: 23195006]

Oettl T, Descoeudres B, Burkhalter F, Bachmann A, Gürke L, Mihatsch MJ, et al. An open, single centre, prospective study to investigate a steroid free immunosuppressive regimen for de novo renal transplant recipients followed by a two arm randomisation to a CNI-sparing and a CNI-free maintenance immunosuppression after 3 months [abstract no: 38]. *Swiss Medical Weekly* 2008;**138**(Suppl 167):15S.

CAMPASIA Study 2005 *{published data only}*

Munoz AS, Cabanayan-Casasola CB, Danguilan RA, Padua FB, Ona ET. Campath-1H (alemtuzumab) as an induction agent for the prevention of graft rejection and preservation of renal function in kidney transplant patients: Philippine 3-year follow-up. *Transplantation Proceedings* 2008;**40**(7):2230-3. [MEDLINE: 18790200]

Vathsala A, CAMPASIA Study Group. One year results of a pilot randomised controlled trial of the effectiveness of alemtuzumab as an induction agent for prevention of graft rejection and preservation of renal function in patients receiving kidney transplants [abstract no: T-PO50029]. *Nephrology* 2005;**10**(Suppl 1):A215. [CENTRAL: CN-00583367]

Vathsala A, CAMPASIA Study Group. Safety and efficacy of campath-1h (mabcampath®) with low dose cyclosprorine monotherapy in patients receiving kidney transplants - 6 month analysis of the pilot randomised controlled [abstract no: O145]. *Transplantation* 2004;**78**(2 Suppl):56. [CENTRAL: CN-00509538]

Vathsala A, Ona ET, Tan S, Suresh S, Chan Y, Lou H, et al. CAMPASIA: a pilot randomised controlled trial of the effectiveness of campath-1h (mabcampath®) as an induction agent for prevention of graft rejection and preservation of renal function in patients receiving kidney transplants. [abstract no: 908]. *American Journal of Transplantation* 2004;**4**(Suppl 8):406. [CENTRAL: CN-00509539]

Vathsala A, Ona ET, Tan SY, Suresh S, Lou HX, Cabanayan Casasola CB, et al. Lymphocyte recovery after depletion by alemtuzumab in renal transplant recipients: impact on outcome [abstract no: 1015]. *American Journal of Transplantation* 2005;**5**(Suppl 11):415. [CENTRAL: CN-00644284]

Vathsala A, Ona ET, Tan SY, Suresh S, Lou HX, Casasola CB, et al. Induction therapy with alemtuzumab together with low dose cyclosporine monotherapy permits steroid-free immunosuppression, mitigates drug-related, non-immune toxicities and improves quality of life [abstract no: TH-PO550]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):224A. [CENTRAL: CN-00644285]

Vathsala A, Ona ET, Tan SY, Suresh S, Lou HX, Casasola CB, et al. Randomized trial of alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation. *Transplantation* 2005;**80**(6):765-74. [MEDLINE: 16210963]

Cattaneo 2005 *{published data only}*

Cattaneo D, Merlini S, Zenoni S, Baldelli S, Gotti E, Remuzzi G, et al. Influence of co-medication with sirolimus or cyclosporine on mycophenolic acid pharmacokinetics in kidney transplantation. *American Journal of Transplantation* 2005;**5**(12):2937-44. [MEDLINE: 16303008]

Cattaneo D, Merlini S, Zenoni S, Baldelli S, Perico N, Gotti E, et al. Effects of sirolimus on the pharmacokinetics of mycophenolic acid in kidney transplantation [abstract no: 650]. *American Journal of Transplantation* 2005;**5**(Suppl 11):322. [CENTRAL: CN-00724878]

Chapman 1985 *{published data only}*

Chapman JR, Griffiths D, Harding NG, Morris PJ. Reversibility of cyclosporin nephrotoxicity after three months' treatment. *Lancet* 1985;**325**(8421):128-30. [MEDLINE: 2857212]

Chapman JR, Marcen R, Arias M, Raine AE, Dunnill MS, Morris PJ. Hypertension after renal transplantation. A comparison of cyclosporine and conventional immunosuppression. *Transplantation* 1987;**43**(6):860-4. [MEDLINE: 3296353]

Higgins RM, Richardson AJ, Endre ZH, Frostick SP, Morris PJ. Hypophosphataemia after renal transplantation: relationship to immunosuppressive drug therapy and effects on muscle detected by 31P nuclear magnetic resonance spectroscopy. *Nephrology Dialysis Transplantation* 1990;**5**(1):62-8. [MEDLINE: 2109286]

Morris PJ, Chapman JR, Allen RD, Ting A, Thompson JF, Dunnill MS, et al. Cyclosporin conversion versus conventional immunosuppression: long-term follow-up and histological evaluation. *Lancet* 1987;**1**(8533):586-91. [MEDLINE: 2881131]

CIS Trial 2014 *{published data only}*

Sommerer C, Schaier M, Morath C, Schwenger V, Rauch G, Giese T, et al. The Calcineurin Inhibitor-Sparing (CIS) Trial - individualised calcineurin-inhibitor treatment by immunomonitoring in renal allograft recipients: protocol for a randomised controlled trial. *Trials [Electronic Resource]* 2014;**15**:489. [MEDLINE: 25494823]

CONCERTO Study 2005 *{published data only}*

Curtis JJ, Thervet E, Vincenti F, Rodriguez A, Soergel M, Barbeito R. Outcomes of 117 cases of delayed graft function from two clinical trials involving early C2 monitored neoral and antibody therapy [abstract]. *Transplantation* 2004;**78**(2 Suppl):5. [CENTRAL: CN-00509145]

Mendez R, Light J, Pearson TC, Wu YM, Curtis J, Vincenti F. Neoral® therapy optimized by C2 monitoring and Simulect® induction can result in low acute rejection rate in renal transplant recipients [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):255. [CENTRAL: CN-00509350]

Vincenti F, Mendez R, Curtis J, Light J, Pearson T, Wu YM, et al. A multicenter, prospective study of C2-monitored cyclosporine microemulsion in a U.S. population of de novo renal transplant recipients. *Transplantation* 2005;**80**(7):910-6. [MEDLINE: 16249738]

David-Neto 2001 *{published data only}*

David-Neto E, Cristiane A, Ianhez L, Nahas W, Zita B. A randomized, open-label, prospective study comparing two different CYA-AUC for the prevention of rejection in renal transplanted patients with and without induction therapy [abstract no: 1398]. A Transplant Odyssey; 2001 Aug 20-23; Istanbul, Turkey. 2001. [CENTRAL: CN-00444997]

de Sandes Freitas 2011 *{published data only}*

de Sandes Freitas TV, Harada KM, Felipe CR, Galante NZ, Sampaio EL, Ikehara E, et al. Steroid or tacrolimus withdrawal in renal transplant recipients using sirolimus. *International Urology & Nephrology* 2011;**43**(4):1221-8. [MEDLINE: 21761129]

de Sevaux 1998 *{published data only}*

de Sevaux RG, Hilbrands LB, Tiggeler RG, Koene RA, Hoitsma AJ. A randomised, prospective study on the conversion from cyclosporine-prednisone to cyclosporine-azathioprine at 6 months after renal transplantation. *Transplant International* 1998;**11 Suppl 1**:S322-4. [MEDLINE: 9665006]

de Sévaux RG, Hoitsma AJ, Hilbrands LB, Tiggeler RG, Koene RA. A randomised study on the effects of conversion of cyslosporine/prednisone to cyclosporine/azathioprine 6 months after kidney transplantation [abstract no: 234]. *Transplantation* 1998;**65**(12):S61. [CENTRAL: CN-00583516]

EVEREST Study 2009 *{published data only}*

Citterio F, Scolari MP, Salvadori M, Castagneto M, Rigotti P, Albertazzi A, et al. A randomized trial comparing standard everolimus plus cyclosporine with higher blood everolimus levels plus very low cyclosporine levels in renal transplant recipients: preliminary results of the Everest Study [abstract no: P118]. *Transplant International* 2007;**20**(Suppl 2):124. [CENTRAL: CN-00724884]

Corbetta G, Salvadori M, Scolari MP, Citterio F, Rigotti P, Cossu M, et al. Exposure to everolimus, and not to cyclosporine, is associated with freedom from acute rejection in de novo renal recipients [abstract no: 447]. *Transplantation* 2008;**86**(Suppl 2):157.

Ponticelli C, Salvadori M, Scolari MP, Citterio F, Rigotti P, Veneziano A, et al. Everolimus and minimization of cyclosporine in renal transplantation: 24-month follow-up of the EVEREST study. *Transplantation* 2011;**91**(10):e72-3. [MEDLINE: 21540717]

Salvadori M, Scolari M, Bertoni E, Citterio F, Rigotti P, Cossu M, et al. Targeting upper everolimus blood levels with very low-dose cyclosporine is effective and safe in de novo renal transplantation [abstract no: 448]. *Transplantation* 2008;**86**(Suppl 2):158. [CENTRAL: CN-00740453]

Salvadori M, Scolari MP, Bertoni E, Citterio F, Rigotti P, Cossu M. Upper everolimus blood levels with very low-dose cyclosporin: 12 months follow up of the Everest Study [abstract no: 1085]. *American Journal of Transplantation* 2009;**9**(Suppl 2):497. [CENTRAL: CN-00776867]

Salvadori M, Scolari MP, Bertoni E, Citterio F, Rigotti P, Cossu M, et al. Everolimus with very low-exposure cyclosporine a in de novo kidney transplantation: a multicenter, randomized, controlled trial. *Transplantation* 2009;**88**(10):1194-202. [MEDLINE: 19935373]

Flechner 2004 *{published data only}*

Flechner SM, Goel M, Feng J, Mastroianni B, Savaas K, Arnovitz J, et al. The effect of 2-gram vs 1-gram concentration controlled mycophenolate mofetil on transplant outcomes using sirolimus based calcineurin inhibitor drug-free immunosuppression [abstract no: 214]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego (CA). 2004. [CENTRAL: CN-00550626]

Fleming 2016 *{published data only}*

Fleming J, Taber D, Pilch N, Meadows H, Mardis C, McGillicuddy J, et al. mTOR-based CNI minimization vs withdrawal in African American kidney transplant recipients [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953883]

Fleming JN, Taber DJ, Pilch NA, McGillicuddy JW, Srinivas TR, Baliga PK, et al. A randomized, prospective comparison of transition to sirolimus-based CNI-minimization or withdrawal in African American kidney transplant recipients. *Clinical Transplantation* 2016;**30**(5):528-33. [MEDLINE: 26914542]

Forwell 1986 *{published data only}*

Forwell MA, Bradley JA. Low-dose cyclosporin or azathioprine one year after renal transplantation [abstract]. *Nephrology Dialysis Transplantation* 1986;**1**(2):138. [CENTRAL: CN-00260295]

Fries 1988 *{published data only}*

Fries D, Hiesse C, Charpentier B, Benoit G. Triple combination of low-dose cyclosporin, azathioprine and steroids in first-cadaver allografts [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(1):96. [CENTRAL: CN-00260361]

Fries D, Hiesse C, Charpentier B, Lantz O, Bensadoun H, Benoit G. A single center experience with "low-dose" cyclosporine in cadaveric renal transplantation. *Clinical Transplants* 1988:115-29. [MEDLINE: 3154465]

Fries D, Hiesse C, Santelli G, Gardin JP, Cantarovich M, Lantz O, et al. Triple therapy with low-dose cyclosporine,

azathioprine, and steroids: long-term results of a randomized study in cadaver donor renal transplantation. *Transplantation Proceedings* 1988;**20**(3 Suppl 3):130-5. [MEDLINE: 3291226]

Fries 1988a *{published data only}*

Fries D. Optimal results in cadaver renal transplantation using prophylactic ALG, cyclosporin (CsA) and prednisone (P) [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(1):95. [CENTRAL: CN-00260355]

Fruchaud 1996 *{published data only}*

Fruchaud G, Buisson C, Abbou C, Desvaux D, Baron C, Benmaadi A, et al. Prospective randomized study of quadruple versus triple therapy in long-term kidney allografts. *Transplantation Proceedings* 1996;**28**(5):2819. [MEDLINE: 8908077]

Gaber 2003 *{published data only}*

Gaber AO, Egidi MF, Lo A, Gaber LW, Shokouh-Amiri MH, Grewal HP, et al. Defining the optimal doses of sirolimus and tacrolimus in high-risk cadaveric renal transplant recipients [abstract no: 541]. *American Journal of Transplantation* 2002;**2**(Suppl 3):274. [CENTRAL: CN-00415690]

Lo A, Egidi MF, Gaber LW, Amiri HS, Vera S, Nezakatgoo N, et al. Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004;**77**(8):1228-35. [MEDLINE: 15114090]

Lo A, Egidi MF, Gaber LW, Gaber AO. Observations on the use of sirolimus and tacrolimus in high-risk renal transplant recipients. *Transplantation Proceedings* 2003;**35**(3 Suppl):105S-8S. [MEDLINE: 12742477]

Lo A, Egidi MF, Gaber LW, Shokouh-Amiri MH, Nazakatgoo N, Fisher JS, et al. Observations regarding the use of sirolimus and tacrolimus in high-risk cadaveric renal transplantation. *Clinical Transplantation* 2004;**18**(1):53-61. [MEDLINE: 15108771]

Gelens 2006 *{published data only}*

Gelens M, Christiaans M, Hooff JV. Calcineurin-free immunosuppression and limited steroid exposure in renal transplantation [abstract no: P-3]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego (CA). 2004. [CENTRAL: CN-00583729]

Gelens M, Christiaans M, Hooff JV. Incidence of post transplant diabetes mellitus during calcineurin-free and calcineurin-based immunosuppression with limited steroid exposure [abstract no: 1210]. *American Journal of Transplantation* 2005;**5**(Suppl 11):465.

Gelens M, Christianns M, Heurn EV, Hooff JV. Calcineurin-free immunosuppression and limited steroid exposure in renal transplantation [abstract no: 865]. *American Journal of Transplantation* 2005;**5**(Suppl 11):376.

Gelens MA, Christiaans MH, van Heurn EL, van den Berg-Loonen EP, Peutz-Kootstra CJ, van Hooff JP. High rejection rate during calcineurin inhibitor-free and early steroid withdrawal immunosuppression in renal transplantation. *Transplantation* 2006;**82**(9):1221-3. [MEDLINE: 17102775]

Ghafari 2007 *{published data only}*

Ghafari A, Makhdoomi K, Ahmadpoor P. Early low dose versus high dose cyclosporine A (CSA) induction protocols in renal transplantation [abstract no: SP742]. *Nephrology Dialysis Transplantation* 2006;**21**(Suppl 4):iv265.

Ghafari A, Makhdoomi K, Ahmadpoor P, Afshari AT, Farshid B, Fallah MM, et al. Mycophenolate mofetil (MMF) plus low dose versus high dose cyclosporine A (CSA) induction protocols in renal transplantation [abstract no: T-PO50034]. *Nephrology* 2005;**10**(Suppl):A216.

Ghafari A, Makhdoomi K, Ahmadpour P, Afshari AT, Fallah MM, Rad PS. Low-dose versus high-dose cyclosporine induction protocols in renal transplantation. *Transplantation Proceedings* 2007;**39**(4):1219-22. [MEDLINE: 17524937]

Gotti 2003 *{published data only}*

Gotti E, Perico N, Perna A, Gaspari F, Cattaneo D, Caruso R, et al. Renal transplantation: can we reduce calcineurin inhibitor/stop steroids? Evidence based on protocol biopsy findings. *Journal of the American Society of Nephrology* 2003;**14**(3):755-66. [MEDLINE: 12595513]

Griffin 1993 *{published data only}*

Griffin PJ, Moore RH, Krishnan H, Fenn N, Salaman JR. Is there an optimal time for the first cyclosporin dose in renal transplantation?. *Transplant International* 1993;**6**(4):223-5. [MEDLINE: 8347269]

Grino 1991 *{published data only}*

Gonzalez C, Grino JM, Castelao AM, Seron D, Gil-Vernet S, Andres E, et al. Pre-transplant ALG, low dose cyclosporine (CsA) and steroids versus pre-transplant OKT3, CsA and steroids in kidney cadaveric transplantation [abstract]. *Kidney International* 1990;**37**(6):1601. [CENTRAL: CN-00601919]

Grino JM, Castelao AM, Gonzalez C, Seron D, Gil-Vernet S, Andres E, et al. Pre-transplant ALG, low dose cyclosporine (CYA) and steroids in kidney cadaveric transplantation [abstract]. 11th International Congress of Nephrology; 1990 Jul 15-20; Tokyo, Japan. 1990:513A. [CENTRAL: CN-00601920]

Grino JM, Castelao AM, Seron D, Gonzalez C, Galceran JM, Gil-Vernet S, et al. Antilymphocyte globulin versus OKT3 induction therapy in cadaveric kidney transplantation: a prospective randomized study. *American Journal of Kidney Diseases* 1992;**20**(6):603-10. [MEDLINE: 1462990]

Grino JM, Castelao AM, Seron D, Gonzalez C, Galceran JM, Gil-Vernet S, et al. Prophylactic OKT3, CyA, and steroids versus antilymphoblast globulin, CyA, and steroids in cadaveric kidney transplantation. *Transplantation Proceedings* 1992;**24**(1):39-41. [MEDLINE: 1539329]

Grino JM, Castelao AM, Seron D, Gonzalez C, Gil-Vernet S, Andres E, et al. Antilymphocyte serum, cyclosporine and corticoids, versus OKT3, cyclosporine, and corticoids in kidney transplantation [Serum anti-lymphocyte, ciclosporine et corticoides, versus OKT3, ciclosporine et corticoides en transplantation renale]. *Presse Medicale* 1991;**20**(40):2039-42. [MEDLINE: 1837121]

Mestre M, Gonzalez C, Grino JM, Valls A, Bonete J, Mane E, et al. Sequential monitoring of immunoregulatory T cell subsets in renal transplantation. *Transplantation Proceedings* 1992;**24**(1):73-5. [MEDLINE: 1539351]

Hamdy 2005 *{published data only}*

Hamdy A, El-Baz M, Bakr M, Ghoneim M. The incidence of chronic allograft nephropathy among live-donor renal transplant recipients primarily treated with sirolimus-based regimens [abstract no: SA734]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009. [CENTRAL: CN-00776624]

Hamdy AF, Bakr MA, Ghoneim MA. Long-term efficacy and safety of a calcineurin inhibitor-free regimen in live-donor renal transplant recipients. *Journal of the American Society of Nephrology* 2008;**19**(6):1225-32. [MEDLINE: 18337483]

Hamdy AF, Bakr MA, Ghoneim MA. Proteinuria among primarily sirolimus treated live-donor renal transplant recipients' long-term experience. *Experimental & Clinical Transplantation: Official Journal of the Middle East Society for Organ Transplantation* 2010;**8**(4):283-91. [MEDLINE: 21143093]

Hamdy AF, El-Agroudy AE, Bakr MA, Mostafa A, El-Baz M, El-Shahawy el-M, et al. Comparison of sirolimus with low-dose tacrolimus versus sirolimus-based calcineurin inhibitor-free regimen in live donor renal transplantation. *American Journal of Transplantation* 2005;**5**(10):2531-8. [MEDLINE: 16162204]

Hariran 2015 *{published data only}*

Haririan A, Klassen D, Keshtkar M, Drachenberg C, Dowling T, Ramos E, et al. Delayed tacrolimus (TAC) to rapamycin (RAPA) conversion in renal transplant recipients with DGF/SGF [abstract]. *American Journal of Transplantation* 2015;**15**(Suppl 3). [EMBASE: 71953312]

Henny 1986 *{published data only}*

Henny FC, Kootte AM, van Bockel JH, Baldwin WM, Hermans J, Bos B, et al. A prospective randomised comparative study on the influence of cyclosporin and azathioprine on renal allograft survival and function. *Nephrology Dialysis Transplantation* 1986;**1**(1):44-9. [MEDLINE: 3110662]

Hollander AA, van Saase JL, Kootte AM, van Dorp WT, van Bockel HJ, Van Es LA, et al. Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. *Lancet* 1995;**345**(8950):610-4. [MEDLINE: 7898178]

Hollander AM, van Saase JL, Kootte AM, van Dorp WT, van Bockel HH, van Es LA, et al. Conversion from cyclosporine (CYA) to azathioprine (AZA) after cadaveric kidney transplantation (KT): in the long run a better renal function, less hypertension and equal graft survival [abstract no: 8P]. *Journal of the American Society of Nephrology* 1993;**4**(Program & Abstracts):941. [CENTRAL: CN-00484382]

Kootte AM, Lensen LM, Van Es LA, Paul LC. Controlled cyclosporine conversion at three months after renal transplantation. Long-term results. *Transplantation* 1988;**46**(5):677-80. [MEDLINE: 3057688]

Kootte AM, Lensen LM, van Bockel JH, Paul LC. A randomized study comparing high- and low-dose regimens of cyclosporine

in renal transplantation. *Transplantation Proceedings* 1988;**20**(3 Suppl 3):136-9. [MEDLINE: 3291227]

Kootte AM, Lensen LM, van Bockel JH, Van Es LA, Paul LC. High and low-dose regimens of cyclosporin in renal transplantation: immunosuppressive efficacy and side-effects. *Nephrology Dialysis Transplantation* 1988;**3**(5):666-70. [MEDLINE: 3146726]

Kootte AM, Lensen LM, van Bockel JH, van Es LA, Paul LC. Long-term results of controlled cyclosporine conversion at 3 months after renal transplantation [abstract]. *Kidney International* 1988;**34**(4):559.

Kootte AM, Van Es LA, Paul LS. Randomised conversion of cyclosporin to conventional therapy at 3 months after renal transplantation: 4-year results [abstract]. *Nephrology Dialysis Transplantation* 1989;**4**(5):505. [CENTRAL: CN-00260455]

Kootte AM, van Es LA, Paul LC. Randomized conversion of cyclosporine to conventional therapy at 3 months after renal transplantation: Four year results. [abstract]. *Kidney International* 1989;**36**(3):512. [CENTRAL: CN-00626040]

van Dorp WT, Kootte AM, van Gemert GW, Van Es LA, Paul LC. Infections in renal transplant patients treated with cyclosporine or azathioprine. *Scandinavian Journal of Infectious Diseases* 1989;**21**(1):75-80. [MEDLINE: 2499036]

Hernandez 2007 *{published data only}*

Hernandez D, Miquel R, Porrini E, Fernandez A, Gonzalez-Posada JM, Hortal L, et al. Randomized controlled study comparing reduced calcineurin inhibitors exposure versus standard cyclosporine-based immunosuppression. *Transplantation* 2007;**84**(6):706-14. [MEDLINE: 17893603]

Hiesse 1991 *{published data only}*

Hiesse C, Neyrat N, Deglise-Favre A, Lantz O, Bensadoun H, Benoit G, et al. Randomized prospective trial of elective cyclosporine withdrawal from triple therapy at 6 months after cadaveric renal transplantation. *Transplantation Proceedings* 1991;**23**(1 (Pt 2)):987-9. [MEDLINE: 1989354]

Hilbrands 1993 *{published data only}*

Hilbrands LB, Demacker PN, Hoitsma AJ. Cyclosporin and serum lipids in renal transplant recipients. *Lancet* 1993;**341**(8847):765-6. [MEDLINE: 8095674]

Hilbrands LB, Demacker PN, Hoitsma AJ, Stalenhoef AF, Koene RA. The effects of cyclosporine and prednisone on serum lipid and (apo)lipoprotein levels in renal transplant recipients. *Journal of the American Society of Nephrology* 1995;**5**(12):2073-81. [MEDLINE: 7579056]

Hilbrands LB, Hoitsma AJ, Koene KA. Randomized, prospective trial of cyclosporine monotherapy versus azathioprine-prednisone from three months after renal transplantation. *Transplantation* 1996;**61**(7):1038-46. [MEDLINE: 8623182]

Hilbrands LB, Hoitsma AJ, Koene RA. Costs of drugs used after renal transplantation. *Transplant International* 1996;**9 Suppl 1**:S399-402. [MEDLINE: 8959872]

Hilbrands LB, Hoitsma AJ, Koene RA. Effect of immunosuppressive therapy on quality of life after renal transplantation [abstract]. *Journal of the American Society of Nephrology* 1994;**5**(3):1011. [CENTRAL: CN-00615875]

Hilbrands LB, Hoitsma AJ, Koene RA. Medication compliance after renal transplantation. *Transplantation* 1995;**60**(9):914-20. [MEDLINE: 7491693]

Hilbrands LB, Hoitsma AJ, Koene RA. The effect of immunosuppressive drugs on quality of life after renal transplantation. *Transplantation* 1995;**59**(9):1263-70. [MEDLINE: 7762059]

Hourmant 1987 *{published data only}*

Hourmant M, Buzelin F, Dubigeon P, Soulillou JP. High long-term graft survival rates in kidney transplantation with the sequential association of antithymocyte globulin and cyclosporine A monotherapy. *Transplantation Proceedings* 1987;**19**(1 (Pt 3)):2113-4. [MEDLINE: 3079073]

Hourmant M, Soulillou JP. Use of delayed cyclosporin A in after administration of anti-lymphocyte serum in kidney transplantation [Utilisation de la cyclosporine A en relais du serum anti-lymphocytaire en transplantation renale]. *Biomedicine & Pharmacotherapy* 1987;**41**(5):247-9. [MEDLINE: 3311191]

Hricik 1990 *{published data only}*

Hricik DE, Mayes JT, Schulak JA. Cyclosporine (CsA) inhibits the generation of antibodies (ABs) to OKT3 [abstract]. *Kidney International* 1990;**37**:607. [CENTRAL: CN-00626073]

Hricik DE, Mayes JT, Schulak JA. Inhibition of anti-OKT3 antibody generation by cyclosporine--results of a prospective randomized trial. *Transplantation* 1990;**50**(2):237-40. [MEDLINE: 2200174]

Infante 2008 *{published data only}*

Infante B, Stallone G, Pontrelli P, Gigante M, Ranieri E, Schena FP, et al. Role of rapamycin in the induction of operational tolerance through up-regulation of ILT3 and ILT4 in kidney transplanted patients [abstract no: F-FC248]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):56A. [CENTRAL: CN-00716071]

Jain 2001 *{published data only}*

Jain S, Metcalfe M, White SA, Furness PN, Nicholson ML. Chronic allograft nephropathy: a prospective randomised trial of cyclosporin reduction with or without mycophenolate mofetil. *Transplantation Proceedings* 2001;**33**(3):2165-6. [MEDLINE: 11377488]

Jain S, Metcalfe M, White SA, Furness PN, Nicholson ML. Randomized trial comparing mycophenolate mofetil and azathioprine to allow cyclosporin reduction in chronic allograft nephropathy [abstract no: PO513W]. XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome, Italy. 2000. [CENTRAL: CN-00445890]

Nicholson ML, Jain S, Metcalfe M, White SA, Furness PN. Chronic allograft nephropathy: a prospective randomised trial of cyclosporin reduction with or without mycophenolate mofetil

[abstract no: 437]. *Transplantation* 2000;**69**(8 Suppl):S227. [CENTRAL: CN-00446949]

Jindal 2002 *{published data only}*

Jardine A. 12 month results of a phase III prospective, randomised study to evaluate concentration controlled Rapamune with cyclosporin dose minimization or elimination in de novo renal allograft recipient [abstract no: 1206]. *American Journal of Transplantation* 2003;**3**(Suppl 5):461. [CENTRAL: CN-00445901]

Jardine A, European and South African Rapamune Study Group. Phase III prospective, randomized study to evaluate the safety and efficacy of concentration controlled Rapamune (sirolimus) with cyclosporine dose minimisation or elimination in de novo renal allograft recipients at 12 months [abstract no: O81]. *Transplantation* 2004;**78**(2 Suppl):31. [CENTRAL: CN-00509251]

Jardine AG. Phase III prospective, randomized study to evaluate the safety and efficacy of concentration controlled Rapamune (sirolimus) with cyclosporin dose minimisation or elimination in de novo renal allograft recipients at 12 months [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):286. [CENTRAL: CN-00520346]

Jindal RM, UK and Ireland Rapamune Study Group. A phase III prospective, randomised study to evaluate concentration controlled rapamune with cyclosporin dose minimization or elimination at six months in de novo renal allograft recipients [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00415940]

John 1999 *{published data only}*

John GT, Dakshinamurthy DS, Jeyaseelan L, Jacob CK. The effect of cyclosporin A on plasma lipids during the first year after renal transplantation. *National Medical Journal of India* 1999;**12**(1):14-7. [MEDLINE: 10326324]

Kamar 2012 *{published data only}*

Kamar N, Mariat C, Albano L, Villemain F, Moal MC, Ladriere M, et al. Improvement in renal function following conversion from low-dose mycophenolate acid to higher-dose enteric-coated mycophenolate sodium (EC-MPS) with concomitant tacrolimus reduction in maintenance kidney transplant recipients [abstract no: O-295]. *Transplant International* 2009;**22**(Suppl 2):78.

Kamar N, Rostaing L, Cassuto E, Villemain F, Moal MC, Ladriere M, et al. A multicenter, randomized trial of increased mycophenolic acid dose using enteric-coated mycophenolate sodium with reduced tacrolimus exposure in maintenance kidney transplant recipients. *Clinical Nephrology* 2012;**77**(2):126-36. [MEDLINE: 22257543]

Kandaswamy 2005 *{published data only}*

Kandaswamy R, Humar A, Dunn T, Gross E, Hughes M, Hill M, et al. Prospective randomized trial of maintenance immunosuppression (IS) in prednisone (P)-free recipients: 5-year results [abstract no: 286]. *American Journal of Transplantation* 2008;**8**(Suppl 2):254. [CENTRAL: CN-00677752]

Kandaswamy R, Humar A, Khwaja K, Asolati M, Harmon J, Gillingham K, et al. A prospective randomized study of

cyclosporine (CSA)/cellcept (MMF) vs. tacrolimus (TAC)/ sirolimus (SIR) with rapid discontinuation of prednisone (P) [abstract]. *American Journal of Transplantation* 2003;**3**(Suppl 5):198. [CENTRAL: CN-00445992]

Kandaswamy R, Humar A, Sturdevant M, Garcia-Roca R, Casingal V, Tan M, et al. Prospective randomized trial of maintenance immunosuppression (IS) in prednisone (P)-free recipients: mixed results [abstract no: 329]. *American Journal of Transplantation* 2006;**6**(Suppl 2):178. [CENTRAL: CN-00766092]

Kandaswamy R, Humar A, Sutherland DE, Gillingham K, Matas A. A prospective, randomized study of cyclosporine (CSA)/mycophenolate mofetil (MMF) versus tacrolimus (TAC)/ sirolimus(SIR) with rapid discontinuation of prednisone (P) [abstract no: 084]. *Transplantation* 2004;**78**(2 Suppl):32. [CENTRAL: CN-00509261]

Kandaswamy R, Melancon JK, Dunn T, Tan M, Casingal V, Humar A, et al. A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients-- an interim analysis. *American Journal of Transplantation* 2005;**5**(6):1529-36. [MEDLINE: 15888064]

Suszynski TM, Gillingham KJ, Matas AJ, Kandaswamy R. Prospective randomized trial of maintenance immunosuppression (IS) with rapid discontinuation of prednisone (RDP) in adult kidney transplantation (KTx): 10-year results [abstract no: 1587]. *American Journal of Transplantation* 2012;**12**(Suppl S3):493. [EMBASE: 70747569]

Suszynski TM, Gillingham KJ, Rizzari MD, Dunn TB, Payne WD, Chinnakotla S, et al. Prospective randomized trial of maintenance immunosuppression with rapid discontinuation of prednisone in adult kidney transplantation. *American Journal of Transplantation* 2013;**13**(4):961-70. [MEDLINE: 23432755]

Keitel 1999 *{published data only}*

Keitel E, Michelon T, Dominguez V, Bittar AE, Santos AF, Goldani JC, et al. Long-term evaluation of two protocols of elective cyclosporine withdrawal in renal transplant recipients. *Transplantation Proceedings* 1999;**31**(7):3013-5. [MEDLINE: 10578370]

Kovarik 2001 *{published data only}*

Kaplan B, Polsky D, Weinfurt K, Fastenau J, Kim J, Ryu S, et al. Quality of life improvement and lower costs associated with simulect based induction therapy [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):733A. [CENTRAL: CN-00401459]

Kovarik JM, Pescovitz MD, Sollinger HW, Kaplan B, Legendre C, Salmela K, et al. Differential influence of azathioprine and mycophenolate mofetil on the disposition of basiliximab in renal transplant patients. *Clinical Transplantation* 2001;**15**(2):123-30. [MEDLINE: 11264639]

Pescovitz M, Kovarik JM, Gerbeau C, Simulect US-O1 Study Group. Pharmacokinetics of basiliximab when coadministered with MMF in kidney transplantation [abstract no: 0112]. XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome, Italy. 2000. [CENTRAL: CN-00402225]

Pescovitz MD, Barbeito R. Effect of "C2" cyclosporine levels and time to initiation of cyclosporine therapy on outcomes in patients receiving neoral and simulect [abstract no: A36]. *Journal of the American Society of Nephrology* 2000;**11**(Sept):703A. [CENTRAL: CN-00433641]

Pescovitz MD, Barbeito R, Simulect US 01 Study Group. Two-hour post-dose cyclosporine level is a better predictor than trough level of acute rejection of renal allografts. *Clinical Transplantation* 2002;**16**(5):378-82. [MEDLINE: 12225436]

Polsky D, Weinfurt KP, Kaplan B, Kim J, Fastenau J, Schulman KA. An economic and quality-of-life assessment of basiliximab vs antithymocyte globulin immunoprophylaxis in renal transplantation. *Nephrology Dialysis Transplantation* 2001;**16**(5):1028-33. [MEDLINE: 11328911]

Sollinger H, Kaplan B, Pescovitz M, Philosophe B, Roza A, Brayman K, et al. A multicenter randomized trial of Simulect with early neoral vs ATGAM with delayed neoral in renal transplantation [abstract no: 0113]. XVIII International Congress of the Transplantation Society; 2000 Aug 27-Sep 1; Rome, Italy. 2000. [CENTRAL: CN-00402698]

Sollinger H, Kaplan B, Pescovitz MD, Philosophe B, Roza A, Brayman K, et al. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. *Transplantation* 2001;**72**(12):1915-9. [MEDLINE: 11773888]

Sollinger H, Pescovitz M, Philosophe B, Roza A, Brayman K, Somberg K. A multicenter, randomized trial of simulect with early neoral vs ATGAM with delayed neoral in renal transplantation. A 6 month interim analysis [abstract no: 580]. *Transplantation* 1999;**67**(7):S151. [CENTRAL: CN-00402699]

Kovarik 2003 *{published data only}*

Kovarik JM, Dantal J, Civati G, Rizzo G, Rouilly M, Bettoni-Ristic O, et al. Influence of delayed initiation of cyclosporine on everolimus pharmacokinetics in de novo renal transplant patients. *American Journal of Transplantation* 2003;**3**(12):1576-80. [MEDLINE: 14629289]

Kovarik-2306 2004 *{published data only}*

Kovarik JM, Tedesco H, Pascual J, Civati G, Bizot MN, Geissler J, et al. Everolimus therapeutic concentration range defined from a prospective trial with reduced-exposure cyclosporine in de novo kidney transplantation. *Therapeutic Drug Monitoring* 2004;**26**(5):499-505. [MEDLINE: 15385832]

Kovarik JM, Tedesco H, Pascual J, Civati G, Schmidli H, Geissler J. Everolimus therapeutic concentration range derived from prospective concentration-controlled trial in de novo kidney transplantation [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):298. [CENTRAL: CN-00509289]

Magee J, Tedesco H, Pascual J, Civati G, Filho G, Garcia V, et al. Efficacy and safety of 2 doses of everolimus combined with reduced dose neoral® in de novo kidney transplant recipients: 12 months analysis [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):296-7. [CENTRAL: CN-00509335]

Pascual J, Cambi V, Dissegna D, Esmeraldo R, Lao M, Durlik M, et al. Efficacy and safety of 2 doses of everolimus combined with reduced dose Neoral® in de novo kidney transplant recipients: 24 months analysis [abstract no: 1010]. *American Journal of Transplantation* 2005;**5**(Suppl 11):414. [CENTRAL: CN-00725012]

Pascual J, Tedesco H, Civati G, Magee J, Haas T, Bernhardt P. Excellent renal function with concentration-controlled everolimus, reduced exposure to neoral, and steroids in de novo kidney transplant recipients: results of a 6 months efficacy and safety analysis [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):786. [CENTRAL: CN-00447112]

Pascual J, Tedesco H, Magee J, Civati G, Mazzali M, Garcia V, et al. 12 month clinical trial results of safety and efficacy of trough-controlled certican® dosing with reduced neoral® exposure in de novo kidney transplant recipients [abstract]. *Transplantation* 2004;**78**(2 Suppl):269. [CENTRAL: CN-00509404]

Tedesco-Silva H Jr, Vitko S, Pascual J, Eris J, Magee JC, Whelchel J, et al. 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in de novo renal transplant recipients. *Transplant International* 2007;**20**(1):27-36. [MEDLINE: 17181650]

Vitko S, Tedesco H, Eris J, Pascual J, Whelchel J, Magee JC, et al. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. *American Journal of Transplantation* 2004;**4**(4):626-35. [MEDLINE: 15023156]

Liu 2002a *{published data only}*

Liu J, Guan D. Chronic allograft nephropathy: a prospective randomized trial of cyclosporin reduction or changing tacrolimus with mycophenolate mofetil [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00416166]

Liu 2007b *{published data only}*

Liu M, Zhang W, Gu M, Yin C, Zhang WY, Lv Q, et al. Protective effects of sirolimus by attenuating connective tissue growth factor expression in human chronic allograft nephropathy. *Transplantation Proceedings* 2007;**39**(5):1410-5. [MEDLINE: 17580150]

Maiorano 2006 *{published data only}*

Maiorano A, Stallone G, Schena A, Infante B, Pontrelli P, Schena FP, et al. Sirolimus interferes with iron homeostasis in renal transplant recipients. *Transplantation* 2006;**82**(7):908-12. [MEDLINE: 17038905]

McGrath 2001 *{published data only}*

McGrath JS, Shehata M. Chronic allograft nephropathy: prospective randomised trial of cyclosporin withdrawal and mycophenolate mofetil or tacrolimus substitution. *Transplantation Proceedings* 2001;**33**(3):2193-5. [MEDLINE: 11377500]

McGrath JS, Shehata M. Complete withdrawal of cyclosporin in chronic allograft nephropathy: a randomised prospective trial of conversion to mycophenolate mofetil or tacrolimus [abstract no: P0539]. XVIII International Congress of the Transplantation

Society; 2000 Aug 27-Sep 1; Rome, Italy. 2000. [CENTRAL: CN-00433636]

McMaster 1983 *{published data only}*

McMaster P, Haynes IG, Michael J. Cyclosporine in cadaveric renal transplantation: a prospective randomized trial. *Transplantation Proceedings* 1983;**15**(4 Suppl 1-2):2523-7. [EMBASE: 14164140]

Meier 2006 *{published data only}*

Fricke L, Meier M, Mueller-Steinhardt M, Ohltmann A, Jabs W, Steinhoff J, et al. Switching from cyclosporine to tacrolimus - beneficial effects in patients with chronic allograft nephropathy over a 3 years period [abstract]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego (CA). 2004.

Meier M, Nitschke M, Weidtmann B, Jabs WJ, Wong W, Suefke S, et al. Slowing the progression of chronic allograft nephropathy by conversion from cyclosporine to tacrolimus: a randomized controlled trial. *Transplantation* 2006;**81**(7):1035-40. [MEDLINE: 16612281]

Messa 2009 *{published data only}*

Messa P, Alberti L, Montagnino G, Cafforio C, Berardinelli L, Rastaldi MP. T-regulatory cell changes after early transition from tacrolimus to sirolimus in renal transplanted patients [abstract no: SU642]. World Congress of Nephrology; 2009 May 22-26; Milan, Italy. 2009. [CENTRAL: CN-00776834]

Metcalfe 2002 *{published data only}*

Brook NR, Metcalf MS, Jain S, Bicknell GR, Nicholson ML, Harper SJ. A randomised trial of mycophenolate mofetil versus azathioprine as calcineurin inhibitor sparing agents in the treatment of chronic allograft nephropathy [abstract no: P-97]. 3rd International Congress on Immunosuppression; 2004 Dec 8-11; San Diego (CA). 2004. [CENTRAL: CN-00550372]

Brook NR, Metcalfe MS, Waller JR, Jain S, Hosgood SA, Nicholson ML. A prospective randomised trial of mycophenolate mofetil and azathioprine after calcineurin reduction in renal allografts with established chronic allograft nephropathy [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):485. [CENTRAL: CN-00509106]

Metcalfe MS, Jain S, Waller JR, Saunders RN, Bicknell GR, Nicholson ML. A randomized trial of mycophenolate mofetil versus azathioprine as calcineurin inhibitor sparing agents in the treatment of chronic allograft nephropathy. *Transplantation Proceedings* 2002;**34**(5):1812-4. [MEDLINE: 12176587]

Miserlis 2008 *{published data only}*

Miserlis G, Papanikolaou V, Vergoulas G, Antoniadis N, Fouzas I, Vrochidis D, et al. Efficacy and safety of everolimus with low dose cyclosporine A compared with mycophenolate mofetil and full dose cyclosporine A in de novo renal transplant recipients [abstract no: 1641]. *Transplantation* 2008;**86**(Suppl 2):544. [CENTRAL: CN-00740580]

Mourad 2004a *{published data only}*

Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving

mycophenolate mofetil and steroids. *Transplantation* 2004;**78**(4):584-90. [MEDLINE: 15446319]

Mourad G, Rostaing L, Legendre C, Lorho R, Therver E, Fares N. Simulect versus thymoglobulin with delayed introduction of neoral in renal transplantation: three month results of a French multicenter randomized trial [abstract no: 0592]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami (FL). 2002. [CENTRAL: CN-00402018]

Mourad GJ, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. A sequential protocol using simulect vs thymoglobulin in low immunological risk renal transplant recipients: six-month results of a French multicenter, randomized trial [abstract no: 1212]. *American Journal of Transplantation* 2003;**3**(Suppl 5):462. [CENTRAL: CN-00446849]

Mourad 2005 *{published data only}*

Budde K, Zeier M, Cohen D, Kirchherr B, MyProms SG. How much exposure is needed in the first week in patients receiving induction with basiliximab and enteric coated mycophenolate sodium? [abstract no: 1206]. *American Journal of Transplantation* 2005;**5**(Suppl 11):464.

Kamar N, Garrigue V, Karras A, Mourad G, Lefrancois N, Charpentier B, et al. Impact of early or delayed cyclosporine on delayed graft function in renal transplant recipients: a randomized, multicenter study. *American Journal of Transplantation* 2006;**6**(5 Pt 1):1042-8. [MEDLINE: 16611342]

Legendre C, Cohen D, Zeier M, Rostaing L, Budde K. Efficacy and safety of enteric-coated mycophenolate sodium in de novo renal transplant recipients: pooled data from three 12-month multicenter, open-label, prospective studies. *Transplantation Proceedings* 2007;**39**(5):1386-91. [MEDLINE: 17580145]

Legendre CH, Rostaing L, Kirchherr B, MyProms SG. Tolerability of enteric coated mycophenolate sodium (EC-MPS) in combination with neoral and steroids in de novo kidney transplant recipients: a 12 months prospective trial [abstract no: 1209]. *American Journal of Transplantation* 2005;**5**(Suppl 11):464-5.

Mourad G, Karras A, Kamar N, Garrigue V, Legendre C, Lefrancois N, et al. Renal function with delayed or immediate cyclosporine microemulsion in combination with enteric-coated mycophenolate sodium and steroids: results of follow up to 30 months post-transplant. *Clinical Transplantation* 2007;**21**(3):295-300. [MEDLINE: 17488375]

Mourad G, Rostaing L, Legendre C. Assessment of two strategies of neoral® administration, early versus delayed, on renal function and efficacy in de novo renal transplant patients receiving myfortic®, steroids and anti-il2r antibodies: 6 months interim results [abstract]. *Transplantation* 2004;**78**(2 Suppl):454. [CENTRAL: CN-00509366]

Mourad G, Rostaing L, Legendre C, Myriade FR. Assessment of two strategies of neoral administration, early versus delayed, on renal function and efficacy in de novo renal transplant patients receiving myfortic, steroids, and anti-IL2R antibodies: 12-month results of a randomized, multicentre, open, prospective

controlled study. *Transplantation Proceedings* 2005;**37**(2):920-2. [MEDLINE: 15848575]

Mourad G, Rostaing, Rostaing L, Legendre C. Assessment of two neoral® administration strategies on renal function and efficacy in de novo renal transplant patients receiving enteric-coated mycophenolate sodium, steroids and anti-IL2r antibodies: 6 months interim analysis of a randomized, multicentre, open, prospective controlled study [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):219. [CENTRAL: CN-00509367]

Pietruck F, Budde K, Salvadori M, Sollinger H, Bourbigot B, Gentil MA, et al. Efficacy and safety of enteric-coated mycophenolate sodium in renal transplant patients with diabetes mellitus: post hoc analyses from three clinical trials. *Clinical Transplantation* 2007;**21**(1):117-25. [MEDLINE: 17302600]

Rostaing L, Legendre CH, Cohen D, Budde K, Zeier M, Kirchherr B, et al. Safety and tolerability of enteric coated mycophenolate sodium in combination with neoral and steroids in de novo kidney transplant recipients: 12 months analysis of a prospective trial [abstract no: T-PO50030]. *Nephrology* 2005;**10**(Suppl 1):A215. [CENTRAL: CN-00644301]

Rostaing L, Mourad G, Kamar N, Garrigue V, Karras A, Lefrancois N, et al. Tolerability of enteric-coated mycophenolate sodium to 1 year in combination with cyclosporine and corticosteroids in renal transplant recipients. *Transplantation Proceedings* 2006;**38**(9):2860-3. [MEDLINE: 17112849]

Rostaing L, Mourad G, Legendre C. Safety and tolerability of enteric-coated mycophenolate sodium in combination with steroids and two regimen of neoral®, in denovo kidney transplant recipients: 6 months interim results. A randomized, multicentre, open, prospective controlled study [abstract]. *American Journal of Transplantation* 2004;**4**(Suppl 8):219. [CENTRAL: CN-00583362]

Rostaing L, Mourad G, Legendre C. Sustainable tolerability effects of myfortic® in combination with neoral® and steroids at 12 months, in de novo kidney transplantation: a randomized, multicentre, open, prospective controlled study [abstract no: 133]. *American Journal of Transplantation* 2005;**5**(Suppl 11):190.

Mourer 2012 *{published data only}*

Mourer JS, Ewe SH, Mallat MJ, Ng AC, Rabelink TJ, Bax JJ, et al. Late calcineurin inhibitor withdrawal prevents progressive left ventricular diastolic dysfunction in renal transplant recipients. [Erratum appears in Transplantation. 2013 Apr 15;95(7):e52]. *Transplantation* 2012;**94**(7):721-8. [MEDLINE: 22955227]

Mourer JS, de Koning EJ, van Zwet EW, Mallat MJ, Rabelink TJ, de Fijter JW. Impact of late calcineurin inhibitor withdrawal on ambulatory blood pressure and carotid intima media thickness in renal transplant recipients. *Transplantation* 2013;**96**(1):49-57. [MEDLINE: 23715049]

Mourer JS, de Koning EJP, Berger SP, Op't Roodt J, Spaans M, Rabelink AJ, et al. Effects of CNI or MMF withdrawal on carotid intima media thickness in renal transplant recipients [abstract no: 528]. *American Journal of Transplantation* 2008;**8**(Suppl 2):319.

Mourer JS, den Hartigh J, Mallat MJ, Berger SP. Estimation of systemic exposure improves safety of withdrawal of either CNI or MMF from triple drug therapy [abstract no: F-PO628]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):237A-8A.

Mourer JS, den Hartigh J, van Zwet EW, Mallat MJ, Dubbeld J, de Fijter JW. Randomized trial comparing late concentration-controlled calcineurin inhibitor or mycophenolate mofetil withdrawal. *Transplantation* 2012;**93**(9):887-94. [MEDLINE: 22538450]

Noris 2007 *{published data only}*

Noris M, Casiraghi F, Todeschini M, Cravedi P, Cugini D, Monteferrante G, et al. Regulatory T cells and T cell depletion: role of immunosuppressive drugs. *Journal of the American Society of Nephrology* 2007;**18**(3):1007-18. [MEDLINE: 17287424]

Ruggenenti P, Perico N, Gotti E, Cravedi P, D'Agati V, Gagliardini E, et al. Sirolimus versus cyclosporine therapy increases circulating regulatory T cells, but does not protect renal transplant patients given alemtuzumab induction from chronic allograft injury. *Transplantation* 2007;**84**(8):956-64. [MEDLINE: 17989600]

Todeschini M, Cortinovis M, Perico N, Poli F, Innocente A, Cavinato RA, et al. In kidney transplant patients, alemtuzumab but not basiliximab/low-dose rabbit anti-thymocyte globulin induces B cell depletion and regeneration, which associates with a high incidence of de novo donor-specific anti-HLA antibody development. *Journal of Immunology* 2013;**191**(5):2818-28. [MEDLINE: 23913968]

Novoa 2011 *{published data only}*

Grinyo JM, Paul J, Novoa P, Errasti P, Franco A, Aldana G, et al. Better renal function in renal-transplant recipients treated with everolimus plus CSA elimination compared with CSA reduction [abstract no: P-359]. *Transplant International* 2009;**22**(Suppl 2):183.

Grinyo JM, Paul J, Novoa P, Errasti P, Franco A, Aldana G, et al. Better renal function in renal-transplant recipients treated with everolimus plus cyclosporine elimination compared with cyclosporine minimisation [abstract no: 1636]. *American Journal of Transplantation* 2010;**10**(Suppl 4):503. [EMBASE: 70465011]

Novoa PA, Grinyo JM, Ramos FJ, Errasti P, Franco A, Aldana G, et al. De novo use of everolimus with elimination or minimization of cyclosporine in renal transplant recipients. *Transplantation Proceedings* 2011;**43**(9):3331-9. [MEDLINE: 22099791]

OPTIMA-TX Study 2008 *{published data only}*

Bolin P Jr, Shihab F, Mulloy L, Henning A, Gao J, Bartucci M, et al. Optimizing tacrolimus therapy in maintenance renal allografts: 6 month results [abstract no: 390]. *American Journal of Transplantation* 2006;**6**(Suppl 2):197-8. [CENTRAL: CN-00671805]

Bolin P Jr, Shihab FS, Mulloy L, Henning AK, Gao J, Bartucci M, et al. Optimizing tacrolimus therapy in the maintenance of renal allografts: 12-month results. *Transplantation* 2008;**86**(1):88-95. [MEDLINE: 18622283]

Bolin P, Shihab F, Mulloy L, Gao J, Bartucci M, Holman J, et al. Optimizing tacrolimus therapy in maintenance renal allografts: 6 month results in African Americans (AA) [abstract no: F-PO1077]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):563A. [CENTRAL: CN-00602098]

Pankewycz 2011 *{published data only}*

Pankewycz O, Kohli R, Wallace PK, Said M, Feng L, Patel S, et al. Low dose rabbit anti-thymocyte globulin induction therapy results in prolonged selective CD4 T cell depletion irrespective of maintenance immunosuppression [abstract no: 957]. *American Journal of Transplantation* 2010;**10**(Suppl 4):316-7. [EMBASE: 70464333]

Pankewycz O, Kohli R, Wallace PK, Said M, Feng L, Patel SK, et al. Low dose rabbit anti-thymocyte globulin induction therapy results in prolonged selective CD4 T cell depletion irrespective of maintenance immunosuppression [abstract no: 130]. *Transplantation* 2010;**90**(Suppl S2):62. [EMBASE: 71531221]

Pankewycz O, Leca N, Kohli R, Wallace PK, Said M, Feng L, et al. Low-dose rabbit antithymocyte globulin induction therapy results in prolonged selective lymphocyte depletion irrespective of maintenance immunosuppression. *Transplantation Proceedings* 2011;**43**(2):462-5. [MEDLINE: 21440734]

Pankewycz O, Leca N, Kohli R, Weber-Shrikant E, Said M, Alnimri M, et al. Conversion to low-dose tacrolimus or rapamycin 3 months after kidney transplantation: a prospective, protocol biopsy-guided study. *Transplantation Proceedings* 2011;**43**(2):519-23. [MEDLINE: 21440749]

Pankewycz O, Leca N, Said M, Feng L, Patel S, Kohli R, et al. A protocol biopsy directed randomized trial comparing tacrolimus minimization to sirolimus conversion at 3 months results in an equivalent degree of histological injury at 1 year and equivalent renal function at 2 years [abstract no: 948]. *American Journal of Transplantation* 2012;**12**(Suppl 3):304. [EMBASE: 70746901]

Pankewycz O, Leca N, Said M, Feng L, Patel S, Kohli R, et al. A protocol biopsy directed randomized trial comparing tacrolimus minimization to sirolimus conversion at 3 months results in an equivalent degree of histological injury at 1 year yet equivalent renal function at 2 years [abstract no: 515]. *Transplantation* 2012;**94**(Suppl 10S):967. [EMBASE: 71251715]

Pankewycz O, Leca N, Wallace P, Said M, Feng L, Patel S, et al. Rabbit anti-thymocyte globulin (rATG) induction therapy followed by tacrolimus conversion to sirolimus at 3 months does not increase Treg cells [abstract no: 1436]. *American Journal of Transplantation* 2012;**12**(Suppl 3):448. [EMBASE: 70747403]

Pankewycz O, Said M, Feng L, Patel S, Alnimri M, Kohli R, et al. Conversion to low dose tacrolimus or rapamycin 3 months after kidney transplant: a prospective, protocol biopsy guided study [abstract no: 1657]. *American Journal of Transplantation* 2010;**10**(Suppl 4):509.

Pankewycz O, Said M, Feng L, Patel SK, Alnimri M, Kohli R, et al. Conversion to low dose tacrolimus or rapamycin 3 months after kidney transplant: a prospective, protocol biopsy guided

study [abstract no: 106]. *Transplantation* 2010;**90**(Suppl 2S):294. [EMBASE: 71531658]

Ponticelli 1988 *{published data only}*

Ponticelli C, Tarantino A, et al. Prospective trial of triple therapy in renal transplants [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(1):98. [CENTRAL: CN-00260367]

Rahamimov 2008 *{published data only}*

Rahamimov R, Yusim A, Winkler J, Mashraki T, Gafter U, Mor E. Conversion from tacrolimus to sirolimus-based protocol in renal transplant recipients: a long-term comparative study [abstract no: 1617]. *Transplantation* 2008;**86**(Suppl 2):537. [CENTRAL: CN-00740447]

Ritz 1998 *{published data only}*

Kahn D, Botha JF, Pascoe MD, Pontin AR, Halkett J, Tandon V. Withdrawal of cyclosporine in renal transplant recipients with acute tubular necrosis improves renal function. *Transplant International* 2000;**13**(Suppl 1):S82-3. [MEDLINE: 11111968]

Ritz M, Pascoe MD, Pontin AR, Kahn D. Is cyclosporine toxic to the transplanted kidney with acute tubular necrosis?. *Transplantation Proceedings* 1998;**30**(4):1204. [MEDLINE: 9636488]

Saunders 2003 *{published data only}*

Saunders RN, Bicknell GR, Nicholson ML. The impact of cyclosporine dose reduction with or without the addition of rapamycin on functional, molecular, and histological markers of chronic allograft nephropathy. *Transplantation* 2003;**75**(6):772-80. [MEDLINE: 12660500]

Saunders RN, Carr S, Nicholson ML. Chronic allograft nephropathy: a prospective randomised trial of cyclosporin reduction with or without rapamycin [abstract]. *Transplantation* 2000;**69**(8 Suppl):S226. [CENTRAL: CN-00447600]

Saunders RN, Carr S, Nicholson ML. Chronic allograft nephropathy: a prospective randomized trial of cyclosporin reduction with or without rapamycin [abstract]. *British Journal of Surgery* 2000;**87 Suppl 1**:44.

Saunders RN, Carr S, Nicholson ML. Side-effect profile of rapamycin in patients with chronic allograft nephropathy [abstract]. *British Journal of Surgery* 2000;**87 Suppl 1**:82. [CENTRAL: CN-00339343]

SOCRATES Study 2014 *{published data only}*

Chadban SJ, Eris JM, Kanellis J, Pilmore H, Lee PC, Lim SK, et al. A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. *Transplant International* 2014;**27**(3):302-11. [MEDLINE: 24279685]

Russ G, Eris J, Kanellis J, Hutchison B, Hibberd A, Pilmore H, et al. Multicentre RCT of early switch to everolimus plus steroids or everolimus plus CSA versus CSA, MPA and steroids in de novo kidney transplant recipients: 12 month analysis [abstract no: 93]. Transplantation Society of Australia & New Zealand (TSANZ). 30th Annual Scientific Meeting; 2012 Jun 27-29; Canberra (ACT). 2012:103.

Westhoff 1995 *{published data only}*

Westhoff A, Heering P, Ivens K, Kutkuhn B, Grabensee B. Safe immunosuppression after kidney transplantation even without cyclosporine? A prospective, randomised study following primary triple therapy [Sichere immunsuppression nach nierentransplantation auch ohne ciclosporin? eine prospektive, randomisierte untersuchung nach primarer triple-therapie]. *Transplantationsmedizin - Organ Der Deutschen Transplantationsgesellschaft* 1995;**7**(1):27-32. [EMBASE: 1995161557]

Wu 2007d *{published data only}*

Wu MJ, Shu KH, Cheng CH, Chen CH, Yu DM. Conversion from cyclosporine to sirolimus in stable Taiwanese kidney transplant recipients - one year report [abstract no: P442]. *Transplant International* 2007;**20**(Suppl 2):201.

References to ongoing studies

David-Neto 2014 *{published data only}*

David-Neto E, Galante N, Altona M, Paula F, Triboni A, Ramos F, et al. A randomized, prospective study comparing everolimus/low tacrolimus with regular tacrolimus/MPS for the elderly renal transplant recipients [abstract]. *Transplantation* 2014;**98**(Suppl 1):549. [EMBASE: 71545379]

ERIC Study 2010 *{published data only}*

Sanchez-Fructuoso A, Ruiz JC, Hernandez D, Sanchez-Plumed J, Fernandez A, Pastor Rodriguez A, et al. Early everolimus introduction and calcineurin inhibitor withdrawal in renal transplant patients: a multicenter, randomized, open-label study (the ERIC study) [abstract no: 1647]. *American Journal of Transplantation* 2010;**10**(Suppl 4):506. [EMBASE: 70465022]

ISRCTN63298320 *{published data only}*

Nicholson M. A prospective randomised trial of the use of cellcept to allow early tacrolimus withdrawal in live donor kidney transplantation. www.isrctn.com/ISRCTN63298320 (accessed 6 February 2017).

TRANSFORM Study 2013 *{published data only}*

Chadban S, Hughes P, Campbell S, Irish A, Lim W, O'Connell P, et al. TRANSFORM trial design: a randomized, multicentre, open-label study of everolimus with reduced calcineurin inhibitors in over 20000 de novo renal transplant recipients [abstract no:48]. Transplantation Society of Australia & New Zealand (TSANZ). 32nd Annual Scientific Meeting; 2014 Jun 11-13; Canberra (ACT). 2014:61.

Legendre C, Srinivas T, Pascual J, Chadban S, Citterio F, Henry M, et al. The TRANSFORM trial design: a large randomized, multicenter, open-label study of everolimus with reduced calcineurin inhibitors in de novo renal transplantation [abstract no: P16]. *Transplant International* 2013;**26**(Suppl 3):23-4. [EMBASE: 71356170]

Pascual J, Chadban S, Citterio F, Henry M, Legendre C, Oppenheimer F, et al. TRANSFORM trial design: effect of everolimus on long-term outcomes after kidney transplantation [abstract no: P308]. *Transplant International* 2013;**26**(Suppl 2):247. [EMBASE: 71359928]

Pascual J, Srinivas TR, Chadban S, Citterio F, Henry M, Legendre C, et al. Balancing efficacy and renal function preservation after kidney transplantation with everolimus and reduced calcineurin inhibitors for better graft outcomes: design of the TRANSFORM study [abstract]. *Nephrology Dialysis Transplantation* 2014;**29**(Suppl 3):iii535. [EMBASE: 71493013]

Pascual J, Srinivas TR, Chadban S, Citterio F, Oppenheimer F, Tedesco H, et al. TRANSFORM: a novel study design to evaluate the effect of everolimus on long-term outcomes after kidney transplantation. *Open Access Journal of Clinical Trials* 2013;**6**:45-54. [EMBASE: 605631666]

Additional references

Ahsan 2001

Ahsan N, Johnson C, Gonwa T, Halloran P, Stegall M, Hardy M, et al. Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: results at 2 years. *Transplantation* 2001;**72**(2):245-50. [MEDLINE: 11477347]

Bennett 1996

Bennett WM, DeMattos A, Meyer MM, Andoh T, Barry JM. Chronic cyclosporine nephropathy: the Achilles' heel of immunosuppressive therapy. *Kidney International* 1996;**50**(4):1089-100. [MEDLINE: 8887265]

Gonwa 2002

Gonwa TA, Hricik DE, Brinker K, Grinyo JM, Schena FP, Sirolimus Renal Function Study Group. Improved renal function in sirolimus-treated renal transplant patients after early cyclosporine elimination. *Transplantation* 2002;**74**(11):1560-7. [MEDLINE: 12490789]

GRADE 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

Hariharan 2000

Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *New England Journal of Medicine* 2000;**342**(9):605-12. [MEDLINE: 10699159]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kasiske 1996

Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. *Journal of the American Society of Nephrology* 1996;**7**(1):158-65. [MEDLINE: 8808124]

Lim 2014

Lim W.H, Eris J, Kanellis J, Pussell B, Wild Z, Witcombe D, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *American Journal of Transplantation* 2014;**14**(9):2106-19. [MEDLINE: 25088685]

Mason 2014

Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD010699.pub2]

Melk 2003

Melk A, Halloran P. Immunosuppressive agents used in transplantation. In: Johnson RJ, Feehally J editor(s). Comprehensive Clinical Nephrology. 2nd Edition. Mosby, 2003:1062-4.

Moore 2009

Moore J, Middleton L, Cockwell P, Adu D, Ball S, Little MA, et al. Calcineurin Inhibitor sparing with mycophenolate in kidney transplantation: A systematic review and meta-analysis. *Transplantation* 2009;**87**(4):591-605. [MEDLINE: 19307799]

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Sharif 2011

Sharif A, Shabir S, Chand S, Cockwell P, Ball S, Borrows R. Meta-analysis of calcineurin inhibitor sparing regimens in kidney transplantation. *Journal of the American Society of Nephrology* 2011;**22**(11):2107-18. [MEDLINE: 21949096]

References to other published versions of this review

Karpe 2007

Karpe KM, Talaulikar GS, Walters G. Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abramowicz 2002

Methods	• Study design: parallel RCT • Study duration: 5 years from 1997 to 2002 • Duration of follow-up: 5 years
Participants	• Setting: multicentre (21 centres) • Countries: Europe and South America • Post kidney transplant recipients on triple therapy for at least 3 months with no rejection 3 months • Number(randomised/analysed): treatment group (85/74); control group (85/77) • Age, range (years): treatment group (45, 18 to 69); control group (48, 22 to 69) • Sex (M/F): treatment group (51/34); control group (50/35) • Exclusion criteria: WCC < 2.5 x 10^9/L; Hb < 5 g/dL; severe diarrhoea or severe gastrointestinal disorders that interfere with oral absorption; malignancy or a history of malignancy; PRA > 50% at time of transplant

Interventions	Treatment group
	
	• Gradual withdrawal of CsA over a 3 month period in the treatment group
	  ○ CsA was weaned off over 12 weeks, one 3rd each time
	• MMF was administered 1 g twice daily and steroids were administered based according to the individual centre practice
	
	Control group
	
	• Continued on triple drug therapy of CsA, MMF and steroids
	  ○ CsA was administered to achieve a trough of 100 to 200 ng/ml
	  ○ MMF was administered at 1 g twice daily and steroids according to practice of the individual centre
	
	Baseline immunosuppression
	
	• At randomisation all patents were on triple immunosuppression of MMF, CsA and corticosteroids for at least 3 months

Outcomes	• SCr • CrCl • Patient survival • Graft survival • AR episodes • Malignancies
Notes	• Funding source: Hoffman La-Roche • Contact with study authors for additional information: no • Other: AR included both BPAR and clinical suspicion of rejection without biopsy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed centrally using the minimisation method, with frequency matching for variables

Abramowicz 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation performed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up completed and reported as per ITT
Selective reporting (reporting bias)	Low risk	All relevant outcome data reported
Other bias	High risk	Pharmaceutical industry funded: Hoffman La-Roche

Alsina 1987

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Spain • Kidney transplant recipients randomised immediately post-transplant • Number: treatment group 1 (25); treatment group 2 (25) • Age: not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group 1 • CsA: 8 mg/kg/d; CsA level trough 300 to 600 ng/mL • PRED: 0.25 mg/kg/d • ALG: 10 mg/kg alternate days (6 doses) Treatment group 2 • CsA: 15 mg/kg/d; CsA level trough 300 to 800 ng/mL • PRED: 0.5 mg/kg/d
Outcomes	• Patient survival • Graft survival • AR
Notes	• Funding source: not reported • Abstract-only publications

Risk of bias

Alsina 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome reporting complete; 3/6 of our outcomes of interest reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Abstract-only publications

Andres 2009

Methods	• Study design: 3 arm, parallel RCT • Study duration: recruitment March 2002 to March 2003 • Duration of follow-up: 6 months
Participants	• Setting: multicentre (17 centres) • Country: Spain • Primary and secondary cadaveric transplant recipients randomised within 24 hours post-transplant • Number: treatment group 1 (38); treatment group 2 (40); treatment group 3 (39) • Mean age ± SD (years): treatment group 1 (56.4 ± 9.5); treatment group 2 (55.7 ± 9.5); treatment group 3 (57.7 ± 12.3) • Sex (M/F): treatment group 1 (23/15); treatment group 2 (26/14); treatment group 3 (24/15) • Multiorgan transplantation, previously transplanted with another organ; previous graft loss due to AR in 1st post-transplant year

Interventions	Treatment group 1
	
	• Low dose early CsA
	  ○ CsA: 3 mg/kg administered twice daily to maintain C2 levels of 800 ng/mL (days 2 to 14), 1700 ng/mL (day 15 to month 2), 1500 ng/mL (during month 2), 1300 ng/mL (during month 3), 1100 ng/mL (month 4 to 6)
	
	Treatment group 2
	
	• Normal dose early CsA
	  ○ CsA: 5 mg/kg administered twice daily to maintain C2 levels of 1200 ng/mL (days 2 to 14), 1700 ng/mL (day 15 to month 2), 1500 ng/mL (during month 2), 1300 ng/mL (during month 3), 1100 ng/mL (month 4 to 6)

Andres 2009 *(Continued)*

Treatment group 3

- Normal dose delayed CsA, CsA and MMF were delayed until day 7 to 10
  - CsA: 5 mg/kg administered twice daily to maintain C2 levels of 1200 ng/mL (days 7 to 14), 1700 ng/mL (day 15 to month 2), 1500 ng/mL (during month 2), 1300 ng/mL (during month 3), 1100 ng/mL (month 4 to 6)

All groups

- MMF: initiated on day 0 at 1 g twice/d
- Oral PRED was started from days 1 to 3 at a maximum of 20 mg/d after pulse methyl-PRED at maximum of 500 mg. Oral steroids were dose reduced over time and received at least 5 mg/d for the rest of the study period

Outcomes	- Graft loss - Death - GFR - AR - Infection
Notes	- Funding source: 1st author was an employee of Novartis, funding source not clarified - Contact with study authors for additional information: no - BPAR and clinical assessed AR reported separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported; AR was clinical and BPAR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified ITT analysis
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	First author employee of Novartis; funding source not clarified

APOLLO Study 2015

Methods	- Study design: parallel RCT - Study duration: November 2005 to March 2009

APOLLO Study 2015 *(Continued)*

	• Duration of follow-up: 5 years

Participants	• Setting: multicentre (11 centres) • Country: Germany • Maintenance kidney transplant recipients (> 6 months post-transplant) on CNI therapy (TAC or CsA) • Number: treatment group 1 (46); control group (47) • Mean age ± SD (years): treatment group (51.0 ± 10.3); control group (49.8 ± 11.1) • Sex (M/F): treatment group (29/1); control group (35/12) • Exclusion criteria: received a multiorgan transplant (including kidney-pancreas); more than one previous kidney transplant or any previous non-kidney transplant; rejection of Banff grade ≥ II, recurrent AR, or steroid-resistant rejection in the preceding 6 months; proteinuria > 1 g/d, platelets < 100,000 cells/ mm^3; leukocytes < 4000/mm^3; Hb < 8 g/dL; evidence of severe liver disease

Interventions	Treatment group
	
	• EVL was initiated at a dose of 1.5 mg/d, and the dose of CNI was reduced by 50% on the same day (day 0)
	• One week later (day 7), the dose of EVL was increased to 3.0 mg/d, and CNI therapy was discontinued. From day 7, the dose of EVL was adjusted to target a trough level of 6 to 10 ng/mL
	
	Control group
	
	• Treatment regimen continued unchanged
	  ○ CsA trough levels: 80 to 150 ng/mL
	  ○ TAC trough levels: 5 to 10 ng/mL
	
	Both groups
	
	• Received EC-MPS and steroids if administered at study entry

Outcomes	• eGFR (Nankivell) at 12 months • eGFR (Cockcroft-Gault and abbreviated four-variable MDRD formulae) • SCr slope (1/SCr versus time) from baseline • BPAR • Graft loss • Death • Treatment failure defined as composite endpoint of BPAR, graft loss, death, loss to follow-up, discontinuation due to lack of efficacy or toxicity, or conversion to another regimen
Notes	• Funding source: 3 authors full-time employees of Novartis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a validated, automated, central system
Allocation concealment (selection bias)	Low risk	Investigators notified of the treatment group by fax from central system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	study not feasible to blinded assessment

APOLLO Study 2015 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Pharma funded (Funding source: Novartis), study terminated early, 5 year outcome awaited

Asberg 2006

Methods	• Study design: parallel RCT • Study duration: recruitment February 2002 to 2004 • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: Norway • de novo kidney transplant recipients • Number: treatment group (27); control group (27) • Mean age ± SD (years): treatment group (57.7 ± 14.6); control group (58.2 ± 13.6) • Sex (M/F): treatment group (18/9); control group (20/7) • Exclusion criteria: present or previous multiple organ transplantation; recipients of HLA-identical kidney transplants; PRA positivity (20%) recorded during the last 6 months; active peptic ulcer disease; active infection; disorders which might interfere with their ability to absorb oral medication; treatment with potential interacting drugs; ongoing malignancies other than adequately treated skin carcinoma; pregnancy, nursing mothers; WCC < 2.5 x 10^9/L (IU); platelet count < 100 x 10^{12}/L (IU); Hb < 6 g/dL
Interventions	Treatment group • Daclizumab induction: 1st dose of 2 mg/kg within 24 hr pretransplant, followed by 1mg/kg every 2 weeks for a total of 5 doses • MMF: initially 1.5 g twice daily at the day of transplantation, followed by trough levels of 2 to 6 mg/L with dose restrictions between 1.0 to 4.0 g/d Control group • CSA: 10 mg/kg orally on the day of transplantation followed by C2 levels of 1500 to 2000 g/L (1st month), 1400 to 1600 g/L (2nd month), 1000 to 1200g/L (3rd month) and followed by trough levels of 100 to 200g/L, tapering down to 75 to 125 g/L during the year • MMF: 1.0 g twice daily from the day of transplantation Both groups • IV methyl-PRED at the day of transplantation and the 1st post-transplant day, followed by oral PRED, from the 2nd postoperative day, tapered from 80 to 20 mg/d during the 1st month, 10 mg/d after 2 months and further down to 5 mg/d within the following months
Outcomes	• GFR • AR • Graft failure • Patient survival • Post-transplant diabetes mellitus

Asberg 2006 *(Continued)*

- Infections
- Hypertension

Notes	
	- 58 AR episodes, all except 2 were BPAR
	- Funding source: "Roche Norway AS for supplying a study grant in addition to free daclizumab in this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label RCT
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported
Selective reporting (reporting bias)	Unclear risk	Expected outcomes reported, ITT analysis
Other bias	High risk	Funded by a grant from Roche

ASCERTAIN Study 2011

Methods	
	- Study design: 3-arm, parallel RCT
	- Study duration: February 2005 to October 2011
	- Duration of follow-up: 24 months

Participants	
	- Setting: multicentre
	- Countries: 25 (Europe, Canada, Australia)
	- Maintenance kidney transplant recipients; 1st of 2nd transplant at least 6 months previously from living or cadaveric donor; kidney impairment (GFR 30 to 70 mL/min)
	- Number: treatment group 1 (127); treatment group 2 (144); control group (123)
	- Mean age ± SD (years): treatment group 1 (49.4 ± 11.8); treatment group 2 (49.7 ± 13.0); control group (48.2 ± 12.2)
	- Sex (M/F): treatment group 1 (86/41): treatment group 2 (91/53); control group 82/45)
	- Exclusion criteria: multiorgan transplant; treated AR within the previous 3 months, presence of de novo or recurrent glomerular nephritis or BK polyomavirus nephropathy, and protein:creatinine ratio ≥ 150 mg/mmol

Interventions	Treatment group 1

ASCERTAIN Study 2011 *(Continued)*

- CNI elimination
  - EVL: 2 mg two times/d from day 1 with dose adjustments from week 1 onward to target an EVL trough levels of 8 to 12 ng/mL
  - CNI: dose was reduced by 20% on day 1 and was discontinued when EVL trough level was ≥ 8 ng/mL

Treatment group 2

- CNI withdrawal
  - EVL: 2 mg twice/d from day 1 with dose adjustments from week 1 onward to target an EVL trough levels of 3 to 8 ng/mL
  - CNI: dose was reduced by 20% on day 1 and reduced to 70% to 90% below baseline values when EVL trough levels ≥ 3 ng/mL

Control group

- CNI therapy remained unchanged

All groups

- Baseline doses of MPA, AZA, and corticosteroids, where administered, were continued unaltered

Outcomes	- GFR at 24 months - Patient survival - Graft survival - BPAR - Hypertension - Hyperlipidaemia - Diabetes
Notes	Funding source: Novartis Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation, stratified by centre, was performed using a validated, automated system
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data at 24 weeks was reported as ITT
Selective reporting (reporting bias)	Low risk	Data at 24 weeks was reported as ITT
Other bias	High risk	Funded by Novartis Pharma AG

Baczkowska 2003

Methods	- Study design: parallel RCT - Study duration: not reported - Duration of follow-up: 3 years
Participants	- Setting: single centre - Country: Poland - Low rejection-risk primary kidney transplant recipients - Number: treatment group (16); control group (16) - Mean age ± SD (both groups): 42.6 + 10.8 years - Sex (M/F): not reported - Exclusion criteria: not reported
Interventions	Treatment group - Daclizumab induction: 1 mg/kg before transplant and then at days 14 and 28 - Low dose CsA: initially 5 mg/kg/d followed by dose adjustment to achieve a CsA C2 level of 700 to 900 ng/mL. CsA was slowly tapered and withdrawn at 10 months Control group - Normal dose CsA: initially 10 mg/kg/d, followed by adjusting the dose according to C2 levels of 1500 to 1700 ng/mL (1st 3 months), 900 to 1200 ng/mL (after 4 months) Both groups - MMF: 2.0 g/d - PRED: standard dose
Outcomes	- AR - Kidney function - SCr - Graft loss
Notes	- Funding source: not reported - Follow-up data at 3 months, 12 months and 36 months, all were BPAR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Baczkowska 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Bansal 2013

Methods	• Study design: parallel RCT • Study duration: recruitment March 2011 to December 2012 • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: India • Patients aged 18 to 65 years who had undergone 1st live donor kidney transplantation at least 2 months prior to enrolment and were receiving CNI based triple drug maintenance immunosuppression for 1st 3 months • Number: treatment group (31); control group (29) • Mean age ± SD (years): treatment group (34.71 ± 8.54); control group (30.17 ± 9.06) • Sex (M/F): treatment group (27/4); control group (25/4) • Exclusion criteria: AR; DGF; unable to achieve SCr ≤1.2 mg/dL; active infection in last 30 days; significant liver disease; severe diarrhoea, vomiting, malabsorption or active peptic ulcer disease; investigational drug up to 4 weeks prior to assessment of eligibility; pregnancy or failure to use effective birth control method in women of childbearing age; WCC < 3000 cells/mL; platelets <10,000 cells/mL; fasting total cholesterol ≥ 200 mg/dL and fasting triglyceride ≥ 300 mg/dl with or without treatment; any malignancy
Interventions	Treatment group • SRL: loading dose 6 mg for 2 days followed by 2 mg/d; trough checked at 2 days and trough maintained at 8 to 15 ng/mL • CNI stopped 12 hours prior to initiating SRL Control group • Standard CNI regimen • TAC trough level: 8 to 10 ng/mL (1st 3 months) thereafter 6 to 8 ng/mL • CsA trough level: 200 to 300 ng/mL (1st 3 months), thereafter 150 to 250 ng/mL
Outcomes	• Kidney function assessed at the end of 6 months • Treg population at 6 months • Incidence of BPAR • Patient survival • Graft survival • Incidence of hyperlipidaemia • NODAT • Hypertension • Infection
Notes	• Funding source: Biocon Nephrology, India.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Low risk	Randomisation was done with the help of a computer generated Bernoulli ran-dom number table
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved by opaque sequentially numbered sealed envelopes
Blinding of participants and personnel (perfor-mance bias) All outcomes	High risk	Open-label study
Blinding of outcome as-sessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement, ITT not specified
Selective reporting (re-porting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Biocon Nephrology, India

Barsoum 2007

Methods	• Study design: parallel RCT (2:1) • Study duration: recruitment July 2002 to July 2006 • Duration of follow-up: 2 years
Participants	• Setting: single centre • Country: Egypt • Live donor recipients (84% unrelated), randomised immediate post-transplant • Number: treatment group (76); control group (37) • Mean age ± SD (years): treatment group (45 ± 15.3); control group (44 ± 15.0) • Sex (M/F): treatment group (47/29); control group (27/10) • Exclusion criteria: not reported
Interventions	Treatment group • SRL + MMF + PRED after 3 months of CsA (C2 levels 600 mg/mL) ○ SRL: level 5 to 10 ng/mL after 3 months Control group • CsA + MMF + PRED ○ CSA C2 level: 1600 ng/mL (6 months), thereafter 1200 ng/mL
Outcomes	• Patient survival at 2 years • Graft survival at 2 years • BPAR

Barsoum 2007 *(Continued)*

- Early and late graft function
- Hypertension

Notes	- Funding source: performed exclusively by The Cairo Kidney Center team without technical or financial support by any other institution, firm, or organisation - Rejection episodes: BPAR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Process of generating random numbers not clear
Allocation concealment (selection bias)	High risk	Sequentially randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT performed and outcome reported
Selective reporting (reporting bias)	Low risk	All outcomes reported completely
Other bias	Low risk	Appears free of other biases

Bechstein-193 2013

Methods	- Study design: parallel RCT - Study duration: completed in June 2002 - Duration of follow-up: 6 months
Participants	- Setting: multicentre (13 centres) - Countries: Greece, Italy, Austria, Germany, Belgium - de novo patients receiving primary or secondary kidney allografts from cadaveric or living donors - Number: treatment group (63); control group (65) - Mean age ± SD (years): treatment group (47.9 ± 13.3); control group (44.6 ± 4.8) - Sex (M/F): treatment group (45/18); control group (38/27) - Exclusion criteria: systemic infection; HIV; active HCV or HCV; history of malignancy within the previous 5 years; known hypersensitivity to SRL or TAC or their derivatives; WCC ≤ 3000/mm^3 or platelet count ≤ 100,000/mm^3; use of an investigational drug or treatment within 4 weeks before enrolment or during the 6-month treatment phase; planned use of medications known to interact with SRL; use of terfenadine, cisapride, astemizole, pimozide, or ketoconazole must have been discontinued before receiving SRL; multiple organ transplants; allografts with cold ischaemia times longer than 36 hours;

Bechstein-193 2013 *(Continued)*

allografts obtained from donors after cardiac death; allografts from donors > 65 years; high risk for AR including those with recent PRA > 50%

Interventions	Treatment group • Reduced-dose TAC: 3 to 7 ng/mL • SRL: initial loading dose of 15 mg day 1 then 5 mg/d adjusted to maintain prescribed trough levels • Steroids: standardised tapered regimen Control group • Standard-dose TAC: 8-12 ng/mL • SRL: initial loading dose of 6/mg on day 1, then 2 mg/d adjusted to maintain prescribed trough levels • Steroids: standardised tapered regimen
Outcomes	• BPAR • Patient survival • Graft survival • SCr • CrCl • Infection • Malignancy
Notes	• Initially reported as pooled data from North America, Australia and Europe • Funding source: sponsored by Wyeth Pharmaceuticals; Medical writing support was provided by Wyeth; was funded by Pfizer Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Funded by Wyeth

Bertoni 2007

Methods	• Single centre RCT
	• Study duration: not reported
	• Duration of follow-up: 6 months

Participants	• Setting: single centre
	• Country: Italy
	• Kidney transplant recipients
	• Number: 52
	• Mean age ± SD (years): not reported
	• Sex (M/F): not reported
	• Exclusion criteria: not reported

Interventions	Treatment group
	• Basiliximab induction
	• CsA: standard dose
	• MMF
	• Steroids
	Control group
	• Basiliximab induction
	• CsA: reduced dose (to obtain predefined levels)
	• EVL: trough levels 3 to 8 ng/mL
	• Steroids

Outcomes	• DGF
	• Graft survival
	• Patient survival
	• BPAR
	• Triglycerides
	• Need for hospitalisation

Notes	• Funding source: not reported
	• Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Bertoni 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Bertoni 2011

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 12 months
Participants	• Setting: single centre • country: Italy • Kidney transplant recipients • Number: treatment group (56); control group (50) • Mean age ± SD (years): treatment group (45.70 ± 12.77); control group (49.75 ± 12.06) • Sex (M/F): not reported
Interventions	Treatment group • EVL trough levels: 8 to 12 ng/mL • CsA C2 levels: 250 to 300 ng/mL • Steroids Control group • EC-MPS: 1,440 mg/d • CsA C2 levels: 500 to 700 ng/mL • Steroids Both groups • Basiliximab induction
Outcomes	• BPAR • CrCl • Graft survival at 12 months • Patient survival at 12 months • CMV
Notes	• Funding: "no financial support"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

Bertoni 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Protocol not specified but study reports all possible outcomes
Other bias	Low risk	No other apparent biases

Budde 2007

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 12 months
Participants	• Setting: multicentre (5 centres) • Countries: Germany, Belgium • Primary or secondary kidney transplant from a deceased-donor, living-related or living-unrelated donor randomised 1 month after transplant; aged 18 to 75 years • Number: treatment group (44); control group (45) • Mean age ± SD (years): treatment group (45.5 ± 14.9); control group (48.7 ± 11.7) • Sex (M/F): treatment group (28/16); control group (33/12) • Exclusion criteria: receipt of a multiorgan transplant; PRA > 50%; severe liver disease; thrombocytopenia (< 75,000/mm³); neutropenia (< 1500 mm³); leukopenia (< 2,500 mm³); anaemia (Hb < 6 g/dL); active peptic ulcer disease
Interventions	**Treatment group** • Reduced-dose CsA C2 targets: 1300 to 1700 ng/mL (month 1), 1000 to 1300 ng/mL (months 2 and 3), 700 to 1000 ng/mL (months 4 to 6), 550 to 700 ng/mL (months 7 to 12) **Control group** • Standard-dose CSA C2 targets: 1300 to 1700 ng/mL (months 1 to 3), 1000 to 1300 ng/mL (months 4 to 6), 850 to 1000 ng/mL (months 7 to 12)
Outcomes	• Mean calculated CrCl • Death • Graft survival • BPAR • Adverse events

Budde 2007 *(Continued)*

Notes	• Funding source: supported by Novartis Pharma GmbH (Germany)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	All patient outcome data reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study design may not allow for blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	prespecified outcomes reported
Other bias	High risk	Funded by Novartis

CAESAR Study 2007

Methods	• Study design: 3-arm, parallel RCT (1:1:1) • Study duration: recruitment 12 January 2001 to 24 October 2002 • Duration of follow-up: 1 year
Participants	• Setting: international, multicentre (32 centres) • Countries: Australia, Europe and North America • Patients of low-to-moderate immunologic risk who had received their 1st kidney transplant • Number: treatment group 1 (179); treatment group 2 (184); control group (173) • Mean age, range (years): treatment group 1 (47.2, 19 to 78); treatment group 2 (47.6, 20 to 77); control group (48.7, 21 to 73) • Sex (males): treatment group 1 (60%); treatment group 2 (65%); control group (65%) • Exclusion criteria: HLA-identical living-related donor recipients; patients anticipated to require ALG preparations for DGF
Interventions	Treatment group 1 • Daclizumab induction • MMF: maintenance dose of at least 1.5 g/d • Steroids • CsA withdrawal trough levels: 50 to 100 ng/mL (months 1 to 3), at month 4, CsA decreased by 33% every month, until it was completely withdrawn at month 6 Treatment group 2

CAESAR Study 2007 *(Continued)*

- Daclizumab induction
- MMF
- Steroids
- Low-dose CsA trough levels: 50 to 100 ng/mL for 12 months

Control group

- MMF
- Steroids
- Standard-dose CsA: target trough level 150 to 300 ng/mL from baseline through to month 4 and 100 to 200 ng/mL thereafter

Outcomes	
	• Kidney function at 3 and 12 months (GFR) • Patient survival • Graft survival • Calculated CrCl at 12 months • SCr at 12 months • BPAR at 6 and 12 months
Notes	• Unless medically contraindicated, all rejection episodes were BPAR • Funding source: "Thanks to Elizabeth Calleja of Roche USA for her critique and Iain Bartlett for his editorial assistance... Funding for this study was provided by F. Hoffmann-La Roche Ltd., Basel, Switzerland"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code for the CAESAR study (M67005) was generated in the Oracle Clinical randomisation module, Each site was supplied with a list of unique patient numbers
Allocation concealment (selection bias)	Low risk	Treatment assignment, corresponding to patient number, was provided on a sheet sealed inside a randomisation envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis and had minimal missing data
Selective reporting (reporting bias)	Low risk	The report include all possible outcomes
Other bias	High risk	Funded by Roche, Switzerland

Cai 2014

Methods	• Study design: parallel RCT • Study duration: recruitment April 2009 to April 2012 • Duration of follow-up: 12 months
Participants	• Setting: single centre • Country: China • Primary live-donor kidney transplant recipients; aged 18 to 72 years; PRA < 20% • Number: treatment group (90); control group (90) • Mean age ± SD (years): treatment group (34.3 ± 11.7); control group (32.6 ± 10.5) • Sex (M/F): treatment group (65/25); control group (67/23) • Exclusion criteria: cadaveric kidney transplant recipients; non primary kidney transplant recipients; multi-organ transplant recipients; recipients with marginal donor organs; recipients with daclizumab induction therapy
Interventions	Treatment group • Low-dose CsA • Short-term intensified EC-MPS dosing 2160 mg/d to week 6, 1440 mg/d thereafter • Steroids Control group • standard-dose CsA • EC-MPS 1440 mg/d • Steroids
Outcomes	• BPAR • Graft loss • Death at 12 months • AR during the 12 months after transplant • Graft survival at 12 months • Kidney function and CrCl at 12 months • All adverse drug events
Notes	• Funding source: "Publication of this supplement article was supported as part of an unrestricted educational grant by Novartis. Novartis provided financial support for English-language editorial services."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Cai 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Novartis

CALFREE Study 2010

Methods	• Study design: parallel RCT • Study duration: recruitment January 2001 to July 2004 • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Switzerland • Kidney transplant recipients; living or cadaveric donor; aged 15 to 75 years • Number: treatment group (63); control group (64) • Mean age ± SD (years): treatment group (48 ± 14.4); control group (49.5 ± 14.4) • Sex (M/F): treatment group (44/19); control group (41/23) • Exclusion criteria: low- (HLA-identical graft from related donor) or high-risk (PRA > 25% or lost kidney graft from rejection within the last 3 years) immunologic constellation; positive cross-match; ABO incompatibility; the graft was from an older donor (68 years); long cold ischaemia time (> 36 hours)
Interventions	Treatment group • SRL trough levels: 10 to 20 ng/mL (months 1 to 3), 8 to 15 ng/mL (months 4 to 6) • MMF • PRED Control group • CsA trough levels: 250 to 350 ng/mL (for 3 months), thereafter 200 to 250 ng/mL • MMF • PRED
Outcomes	• SCr levels • Patient survival • Graft survival • Number of rejections • Evidence of kidney damage assessed using glomerular and tubular urine biomarker levels
Notes	• Protocol biopsies on day 90 and 180 + biopsy for indication • Funding source: This study was supported with grants from Wyeth Pharmaceuticals, which markets SRL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

CALFREE Study 2010 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, minimal lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Funded by grants from Wyeth Pharma

CENTRAL Study 2012

Methods	• Study design: parallel RCT • Study duration: recruitment March 2008 to April 2010, with the final patient visit in April 2011. • Duration of follow-up: 3 years
Participants	• Setting: international, multicentre (8 centres) • Countries: Sweden, Norway, Denmark • De novo adult kidney transplant recipients (deceased or living donor) were randomised at week 7 post-transplant with no previous AR • Number: treatment group (102); control group (100) • Mean age ± SD (years): treatment group (55.5 ± 10.9); control group (53.8 ± 12.3) • Sex (M/F): treatment group (70/32); control group (74/26) • Exclusion criteria: multiorgan transplantation or a previous non-kidney transplant; PRA > 30%; HLA-identical sibling donor; Hb < 8.0 g/dL, platelets < 50 × 10^9/L; WCC ≤ 2.5 × 10^9/L; total cholesterol ≥ 9 mmol/L; triglycerides ≥ 6 mmol/L; urinary protein/creatinine ratio ≥ 150 mg/mmol; ongoing wound healing problems or any other severe surgical complication; requirement for dialysis; eGFR < 20 mL/min at week 7 post-transplant
Interventions	Treatment group • EVL: 3 mg in the evening with a 50% reduction in their usual evening dose of CsA, followed the next day by EVL 2 mg in the morning and evening and no CsA; EVL dose was titrated to target a trough concentration of 6 to 10 ng/mL • EC-MPS: 1440 mg/d (minimum 720 mg/d) during the 1st 2 weeks, thereafter reduced to 1080 mg/d (minimum 720 mg/d) Control group • Standard dose CsA: trough level 75 to 200 ng/mL (C2 level 700 to 900 ng/mL) to month 6, thereafter 50 to 150 ng/mL (C2 600 to 800 ng/mL) • EC-MPS: target dose 1440 mg/d (minimum 720 mg/d) Both groups

CENTRAL Study 2012 *(Continued)*

- Basiliximab induction therapy
- Steroids: 10 mg/d PRED until 10 to 12 weeks then as per local practice

Outcomes	• Change in kidney function evaluated by mGFR: 7 weeks, 12 months and 3 years • Composite efficacy endpoint (BPAR, graft loss or death) • Percentage of patients receiving lipid-lowering drugs and antihypertensives
Notes	• CENTRAL was funded by Novartis Scandinavia. The manuscript was drafted with the assistance of a medical writer (Caroline Dunstall) funded by Novartis Scandinavia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally using a validated automated system
Allocation concealment (selection bias)	Low risk	Investigators notified of the randomisation group via the electronic case record form system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals high in the EVL group
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported in 3 year follow-up
Other bias	High risk	Funded by Novartis Scandinavia

CERTITEM Study 2015

Methods	• Study design: parallel RCT; patients were stratified according to epithelial-mesenchymal transition profile based on month 3 protocol biopsies and then randomised 1:1:1:1 (i) EMT+ patients assigned to CNI-free therapy (ii) EMT+ patients assigned to CNI (ii) EMT− patients assigned to CNI-free therapy and (iv) EMT− patients assigned to CNI • Study duration: recruitment September 2009 to June 2012 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (23 centres) • Country: France • Primary or secondary kidney transplant recipients (deceased or living donor) were randomised at 3 months post-transplant after a biopsy • Number: treatment group (96); control group (98) • Mean age ± SD (years): treatment group (48.2 ± 12.3); control group (50.4 ± 11.0) • Sex (M/F): treatment group (62/34); control group (66/32)

CERTITEM Study 2015 *(Continued)*

	• Exclusion criteria: BPAR prior to randomisation; donor specific antibody positive, eGFR < 30 mL/min; proteinuria > 0.8 g/24 h; severe uncontrolled hypercholesterolaemia or hypertriglyceridaemia; elevated liver enzymes
Interventions	**Treatment group** • EVL: starting dose of 1.5 mg twice/d (target concentration 6 to 10 ng/mL) • CsA: dose was reduced by 50% then discontinued when the EVL concentration was in the target range • EC-MPS: dose was reduced immediately to 360 mg twice/d **Control group** • CsA: dose was tapered over time • EC-MPS: continued unchanged (1440 mg/d) **Both groups** • Basiliximab induction (20 mg on day 0 and day 4) • CsA: during the 1st 3 months post-transplant, all patients received CsA at an initial dose of 8 mg/kg/d, adjusted to target pre-specified trough or C2 levels • EC-MPS: 1440 mg/d • Oral steroids: continued to month 12 post-transplant in both treatment arms, dosed according to local practice
Outcomes	• Progression of Interstitial fibrosis and tubular atrophy increase ≥1 between months 3 and 12 post-transplant • Treatment failure: defined as BPAR, graft loss, death or lost to follow-up) • Graft survival • Patient survival • Proteinuria • Adverse events
Notes	• Analysed also as CNI-free and CNI group • Funding source: Novartis Pharma SAS, Rueil-Malmaison, France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Primary outcome comparison of pathology pre and post randomisation not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal lost to follow-up at 2 year period

CERTITEM Study 2015 *(Continued)*

Selective reporting (reporting bias)	High risk	All prespecified outcomes not reported
Other bias	High risk	Funded by Novartis Pharma

Chadban 2013

Methods	• Study design: parallel RCT • Study duration: 2002 to 2004 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (11 centres) • Country: Australia • De novo kidney transplant recipients; living unrelated or living related kidney transplants • Number: treatment group (42); control group (33) • Mean age ± SD (years): treatment group (44.5 ± 13.14); control group (48.1 ± 12.74) • Sex (males): treatment group (74%); control group (48%) • Exclusion criteria: multi-organ transplants or those with previous transplantation with any other organ apart from kidney; recipients of ABO- incompatible transplants; historical or current peak PRA > 50%; existing antibodies against the HLA-type of the donor; evidence of severe liver disease
Interventions	Treatment group • Low-dose CsA C2 levels: 700 to 1000 ng/mL (months 4 to 6), 550 to 700 ng/mL (months 7 to 12) Control group • Normal dose CsA C2 levels: 1000 to 1300 ng/mL (months 4 to 6), 850 to 1000 ng/mL (months 7 to 12) Both groups • EC-MPS • Basiliximab induction • Corticosteroids
Outcomes	• CrCl • BPAR • Patient survival • Graft survival
Notes	• This study was a sub-protocol of the global umbrella MyPROMS study • Funding source: Novartis Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Chadban 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, minimal loss to follow-up
Selective reporting (reporting bias)	Low risk	Reported all prespecified outcomes
Other bias	High risk	Funded by Novartis Australia. Australian sub protocol part of a global trial

Chan 2008

Methods	• Study design: parallel RCT • Study duration: recruitment May 2004 to May 2005, with the last patient visit taking place in November 2005 • Duration of follow-up: 6 months
Participants	• Setting: multicentre (18 centres) • country: USA • De novo kidney transplant patients Immediately post-transplant • Number: treatment group (49); control group (43) • Mean age ± SD (years): treatment group (47 ± 11); control group (47 ± 10) • Sex (M/F): treatment group (27/22); control group (30/13) • Exclusion criteria: multiorgan transplant or an organ from an asystolic or expanded donor criteria donor; ABO-incompatible or T-cell crossmatch positive transplants; PRA > 50%; recipient or donor positive for HCV or HBV
Interventions	Treatment group • Low-dose TAC trough levels: 4 to 7 ng/mL (months 0 to 3), 3 to 6 ng/mL (months 4 to 6) Control group • Standard-dose TAC trough levels: 8 to 11 ng/mL (months 0 to 3), 7 to 10 ng/mL (months 4 to 6) Both groups • Basiliximab induction • EVL was initiated within 24 h of graft reperfusion at an initial dose of 1.5 mg/d, adjusted to maintain EVL trough level 3 ng/mL, a maximum trough level of 12 ng/mL was recommended • TAC was initiated within 24 h of graft reperfusion • Steroids
Outcomes	• Kidney function at 6 months post-transplant • BPAR • Graft loss

Chan 2008 *(Continued)*

Notes	• Funding source: The study was funded and supported by Novartis Pharmaceuticals Corporation. Two authors were employees of Novartis Pharmaceuticals Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Centrally generated sequential sealed treatment allocation cards
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	Data were collected by investigators via a validated electronic system and transferred to an electronic database for analysis
Other bias	High risk	Funded by Novartis, USA

Chan 2012

Methods	• Study design: parallel RCT (1:1) • Study period: September 2005 to March 2007 • Duration of follow-up:6 months
Participants	• Setting: multicentre (32 centres) • Countries: Canada, France, Italy, Poland, Spain, UK, and USA • Patients aged 18 to 70 years of low immunologic risk who had received their 1st kidney transplant allograft randomised within 24 h after transplantation • Number: treatment group (151); control group (141) • Mean age ± SD (years): treatment group (47.7 ± 12.6); control group (45.3 ± 12.9) • Sex (males): treatment group (72.2%); control group (65.2%) • Exclusion criteria: recipients of human leukocyte antigen (HLA)-identical living-related kidney; multiorgan transplant; donation after cardiac death; females of child-bearing potential; donor age > 65 years; cold ischaemia time > 30 h; PRA > 20%;positive test for HBV or HCV of donor or recipient
Interventions	Treatment group • Low-dose TAC trough levels: 5 to 9 ng/mL (1st 3 months), 3 to 6 ng/mL for the next 3 months • Basiliximab induction • EC-MPS: 1440 mg/d • Corticosteroids

Chan 2012 *(Continued)*

Control group

- Standard-dose TAC trough levels: 10 to 15 ng/mL (1st 3 months), 8 to 12 ng/mL for the next 3 months
- Basiliximab induction
- EC-MPS: 1440 mg/d
- Corticosteroids

Outcomes	- Kidney function at 6 months - Incidence of BPAR - Graft loss - Death - NODAT
Notes	Funding source: funded by Novartis Pharma AG, Basel, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated by using a validated automated system
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results stated to be ITT but are different from the randomised number
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Novartis Pharma AG, Basel, Switzerland

Chhabra 2013

Methods	- Study design: parallel RCT (2:1) - Study duration: recruitment between June 2007 and May 2011 - Duration of follow-up: 24 months
Participants	- Setting: single centre - Country: USA - De novo kidney transplant recipients; > 18 years - Number: treatment group (123); control group (64) - Mean age ± SD (years): treatment group (49.2 ± 11.9); control group (49.1 ± 12.8)

- Sex (M/F): treatment group (42/22); control group (65/58)
- Exclusion criteria: ESKD secondary to primary FSGS; severe proteinuria (> 0.5 g/d); eGFR < 40 mL/min; history of more than 2 episodes of ACR post-transplantation or a history of more than grade 1 ACR by Banff classification within 3 months prior to randomisation; any ongoing active infection (HIV/HCV/HBV), pregnant or nursing females, history of severe hyperlipidaemia not controlled with statins; platelet count < 100 000/mm^3, WCC < 2000/mm^3;history of malignancy during the post-transplant period

Interventions	Treatment group
	- SRL: started at 2 mg/d to achieve a 24 h trough levels were 5 and 8 ng/mL
	Control group
	- TAC trough levels: 8 to 10 ng/mL (1st 3 months), 7 to 9 ng/mL (4 to 6 months), thereafter 6 to 8 ng/mL
	Both groups
	- Alemtuzumab and PRED induction, with rapid steroid elimination
	- MMF: 1 g/d (titrated based on WCC)
Outcomes	- BPAR
	- Patient survival
	- Graft survival
	- eGFR
	- Donor-specific antibody levels
	- Adverse events: infections, malignancies, proteinuria, haematological abnormalities, hyperlipidaemia
Notes	- Funding source: supported by Pfizer Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessment not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis reporting complete with minimal loss of follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported as specified in methods
Other bias	High risk	Funded by Pfizer Pharmaceuticals

Cibrik 2007

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 12 months
Participants	• Setting: multicentre (14 centres) • Country: USA • Primary or secondary kidney transplant from a deceased, living-unrelated or living-related donor; aged 18 to 70 years • Number: treatment group (66); control group (75) • Mean age ± (years): Treatment group (49.4 ± 11.6); control group (46.9 ± 11.6) • Sex (M/F): treatment group (42/24); control group (48/27) • Exclusion criteria: received a multi-organ transplant or a kidney from a deceased donor over 60 years; cold ischaemia time > 24 h; PRA > 20%; thrombocytopenia (< 75,000/mm^3); neutropenia (< 1500/mm^3); leukopenia (< 2500/mm^3); Hb < 6 g/dL at baseline
Interventions	Treatment group • Higher CsA C2 levels: 1300 ng/mL (at month 3), 1100 ng/mL (months 3 to 6), 900 ng/mL (months 7 to 12) Control group • Lower CsA C2 levels: 1100 ng/mL (at month 3), 900 ng/mL (months 3 to 6), 700 ng/mL (months 7 to 12) Both groups • EC-MPS • Corticosteroids • Basiliximab induction • CsA: Identical C2 targets were employed in all patients until the end of month 2 (C2 level 1500 ng/mL)
Outcomes	• CrCl • Incidence of BPAR and treated AR • Graft survival • Patient survival • Incidence of infections and adverse events.
Notes	• Funding source: funded by a grant from Novartis Pharma AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally generated randomisation
Allocation concealment (selection bias)	Low risk	Numbers on the outside with concealed information about maintenance group allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators remained blinded but not clear if patients were blinded to treatment
Blinding of outcome assessment (detection bias)	Low risk	Investigators remained blinded until the end of the 2nd month post-transplant

Cibrik 2007 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcomes noted
Selective reporting (reporting bias)	Low risk	Pre specified outcomes reported
Other bias	High risk	Funded by Novartis Pharma

Cockfield 2002

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 6 months
Participants	• Setting: not reported • Country: not reported • Primary or secondary kidney transplant recipients from cadaveric or living donors • Number: treatment group (90); control group (81) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Reduced dose TAC trough levels: 5 to 10 ng/mL • SRL • PRED Control group • Standard TAC trough levels: 8 to 12 ng/mL • SRL • PRED
Outcomes	• BPAR • CrCl • Graft survival • Patient survival • Malignancy • Infection rates
Notes	• Planned antibody induction prohibited • Abstract-only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported

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Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients (Review)

Cockfield 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Preliminary data only
Selective reporting (reporting bias)	High risk	Outcomes not complete and reported as preliminary data
Other bias	High risk	Preliminary data only; no full text publication 15 years after abstracts published

CONCEPT Study 2009

Methods	• Study design: parallel RCT • Study duration: recruitment November 2004 to October 2006 • Duration of follow-up: 1 year
Participants	• Setting: multicentre (16 centres) • Country: France • Patients undergoing 1st kidney transplant; 18 to 75 years; converted to SRL-based treatment 12 weeks after transplantation • Number: treatment group (95); control group (97) • Mean age ± SD (years): treatment group (46.5 + 12.0); control group (47.3 +10.6) • Sex (males): treatment group (70.5%); control group (72.2%) • Exclusion criteria: living and donation after cardiac death; previous kidney transplant; multiple organ transplantation, cold ischaemia time > 36 h; donor age > 65 years; PRA > 30%; active major infection (HBV, HCV, HIV); history of recent malignancy; WCC < 2500 mm^3; Hb < 9g/dL
Interventions	Treatment group • SRL trough levels: 8 to 15 ng/mL (weeks 12 to 39), 5 to 10 ng/mL after 39 weeks Control group • CsA C2 levels: 500 to 800 ng/mL Both groups • Daclizumab induction: 2 mg/kg on day 1 and 1 mg/kg on day 14 • MMF: 2 g/d adjusted according to clinical events • PRED: initial dose of 500 mg at day 0; 0.5 mg/kg/d between days 1 and 7; 0.25 mg/kg/d between days 8 and 14, followed by a progressive decrease to 10 mg/d until month 8. Oral steroids were planned to be completely discontinued at month 8
Outcomes	• CrCl

CONCEPT Study 2009 *(Continued)*

- Patient survival
- BPAR
- eGFR
- Infections
- Cancer

Notes	• Funding source: sponsored by a grant from Roche SAS, Neuilly sur Seine, France

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation at week 12 was centralized and balanced (1:1). Data collections were ensured by an electronic case report form and the centralized randomisation was ensured via Internet
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, minimal withdrawal
Selective reporting (reporting bias)	Low risk	The report included all expected outcomes
Other bias	High risk	Funded by Roche

CONVERT Trial 2009

Methods	• Study design: parallel RCT randomised 2:1; stratified according to baseline GFR • Study duration: recruitment 5 February 2002 to 1 March 2004 • Duration of follow-up: 24 months
Participants	• Setting: multicentre (111 centres) • Countries: Asia, Australia, Europe, the Middle East, Canada, Mexico, United States, South Africa, Argentina, Brazil, Chile • Patients aged ≥ 13 years and recipients of living or deceased donor with functioning graft; received a CNI (CsA or TAC) after transplantation along with corticosteroids, and AZA (50 mg/d) or MMF (500 mg/d) for at least 12 weeks before randomisation kidney transplant 6 to 120 months before randomisation • Number: treatment group (555); control group (275) • Mean age ± SE (years): treatment group (43.7 ± 0.6); control group (42.6 ± 0.82) • Sex (males): treatment group (69.4%); control group (70.5%) • Exclusion criteria: treated for BPAR or clinically diagnosed AR within 12 weeks of enrolment

CONVERT Trial 2009 *(Continued)*

Interventions	Treatment group
	• CNI ceased and SRL introduced (trough 8 to 20 ng/mL)
	Control group
	• CNI group: continued CsA or TAC (CsA trough 50 to 250 ng/mL; TAC trough 4 to 10 ng/mL)
	Both groups
	• AZA
	• MMF

Outcomes	• GFR at 12 months
	• BPAR
	• Graft survival at 12 and 24 months
	• Patient survival at 12 and 24 months

Notes	• Stratified into GFR 20 to 40 mL/min and > 40 mL/min pre randomisation
	• Study included both TAC and CsA
	• Funding source: This study was supported by Wyeth Research, Collegeville, PA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomisation/enrolment system used
Allocation concealment (selection bias)	Low risk	Automatic transtelephonic randomisation was used to assign study treatment groups.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High dropout, however ITT
Selective reporting (reporting bias)	Low risk	Report included all expected outcomes
Other bias	High risk	Funded by Wyeth Research

CTOT-09 Study 2015

Methods	• Study design: parallel RCT; 2:1 randomisation
	• Study duration: November 2010 to May 2015
	• Duration of follow-up: 24 months

CTOT-09 Study 2015 *(Continued)*

Participants	- Setting: multicentre - Country: USA - Non-sensitised primary recipients of living donor kidney transplants; ≥ 18 years; enrolled before transplantation and eligible for randomisation 6 months after transplantation - Number: treatment group (14); control group (7) - Mean age ± SD (years): treatment group (44.1 ± 11.65); control group (47.4 ± 11.12) - Sex (M/F): treatment group (6/8); control group (4/3) - Exclusion criteria: AR in the 1st 6 months; de novo DSA at 6 months, BK polyoma viraemia; MMF dose of < 1500 mg daily; AR (including Banff borderline) on a 6-month protocol biopsy read by the Central Pathology
Interventions	**Treatment group** - TAC: reduced by one 3rd at initiation of taper, reduced by another one 3rd after 1 month, and discontinued no longer than 4 months after randomisation - MMF: ≥1500 mg/d - PRED **Control group** - TAC trough levels: 5 to 8 ng/mL - MMF - PRED **Initial treatment for 6 months (both groups)** - Induction therapy with ATG - MMF: 1000 mg twice/d - PRED - TAC: doses were adjusted to maintain trough levels of 8 to 12 ng/mL for the 1st 3 months and 5 to 8 ng/mL thereafter
Outcomes	- Percentage of subjects in each arm with incremental changes in IF/TA scores, comparing a 24-month protocol biopsy with the preimplantation biopsy - Incidence of AR - eGFR at 6, 12, 18, and 24 months - Graft survival at 6, 12, 18, and 24 months - Patient survival at 6, 12, 18, and 24 months - Percentage of subjects with de novo post-transplant DSA at 6, 12, 18, and 24 months
Notes	- Enrolment was targeted to 300 subjects, with 210 subjects randomised 2:1 to TAC withdrawal: TAC maintenance; both groups received MMF and PRED. Only 47 subjects were enrolled, and 21 subjects were randomised before the study was terminated by safety board - Funding source: The work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number U01-AI063594 (to P.S.H.)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nature of the study does not let for physician blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Prespecified outcomes reported in randomised patients
Selective reporting (reporting bias)	High risk	Study was prematurely stopped and TAC was introduced in more than half of the patients
Other bias	High risk	Only 21 of the planned 210 patients were randomised

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de Sevaux 2001

Methods	- Study design: parallel RCT - Study duration: enrolment 1/1/1997 to 31/12/1998 - Duration of follow-up: 6 months
Participants	- Setting: multicentre (3 centres) - Country: the Netherlands. - Adult recipients of a 1st or 2nd kidney transplant from a living or cadaveric donors - Number: treatment group (152); control group (161) - Mean age ± SD (years): treatment group (49.6 ± 14); control group (48.6 ± 14) - Sex (M/F): treatment group (96/56); control group (98/63) - Exclusion criteria: HLA-identical living related donor or a non–heart beating donor; liver function disturbances, peptic ulcer, diarrhoea, leukocytopenia, or thrombocytopenia; haemolytic uraemic syndrome as original kidney disease; women who were not using adequate contraception, taking immunosuppressive medication other than corticosteroids at the time of transplant
Interventions	Treatment group - Low dose CsA trough levels: 150 ng/mL for 6 months Control group Conventional CsA trough levels: 300 ng/mL (1st 3 months), 150 ng/mL (3 to 6 months) Both groups - MMF: 1000 mg twice/d - PRED
Outcomes	- Incidence of BPAR (Banff grade 1 or higher) during 1st 3 months - CsA nephrotoxicity during the 1st 3 months - Time to 1st AR - Number of AR episodes within the 1st 3 months - Number of biopsies - Incidence and duration of DGF - Graft function at 1 and 3 months

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de Sevaux 2001 *(Continued)*

- Graft survival
- Patient survival

All end points also were assessed at 6 months after transplant

Notes	• BPAR and presumptive AR were classified separately
	• Funding source: Roche Pharmaceuticals, The Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Allocation was carried out by opening a sealed envelope with the lowest available study number
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data noted
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by Roche Pharmaceuticals, The Netherlands

DICAM Study 2010

Methods	• Study design: parallel RCT
	• Study duration: recruitment April 2000 to June 2004
	• Duration of follow-up:

Participants	• Setting: multicentre (7 centres)
	• Country: France
	• Patients aged 18 to 75 years, in their 2nd year post-transplant with stable SCr levels (i.e. < 20% variation for the previous 3 months); all patients were corticosteroid-free for at least 3 months and receiving combination maintenance therapy consisting of CsA and MMF
	• Number: treatment group (106); control group (102)
	• Mean age ± SD (years): treatment group (51.7 ± 12.6); control group (51.1 ± 11.3)
	• Sex (M/F): treatment group (74/32); control group (69/33)
	• Exclusion criteria: patients at either low or high risk of graft dysfunction; evidence of systemic infection or malignancy within the previous 5 years (except adequately treated non-metastatic basal or squamous cell carcinoma of the skin), WCC < 2.5 x 10^3/μL; Hb < 80 g/dL; platelet count < 100 × 10^3/μL;

DICAM Study 2010 *(Continued)*

severe intestinal disorders; pregnancy; breastfeeding or current immunosuppressive treatment with drugs other than CsA and MMF

Interventions	**Treatment group** • Low exposure group: target was 50% of the usual CsA $AUC_{0-12\,h}$ target or 2.2 mg.h/L (range, 2.0 to 2.6 mg.h/L) **Control group** • Standard dose CsA: the CsA $AUC_{0-12\,h}$ target was 4.3 mg.h/L (range, 3.5 to 4.8 mg.h/L) **Both groups** • MMF
Outcomes	• Treatment failure at 24 months, which was a composite of three mutually exclusive outcomes (graft loss, BPAR or a > 15% increase in the mean SCr level from the baseline) • eGFR • BP • Urinary protein • Lipid levels • Infection requiring hospitalisation • Neoplasia or lymphoma • Graft survival • Patient survival
Notes	• Funding source: French Department of Health's National Clinical Research Program

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code was generated and maintained by the Biostatistics Department at the University of Rouen
Allocation concealment (selection bias)	Low risk	"Randomization was performed independently at each centre using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pathologists were blinded for biopsy interpretation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Most patients completed the trial
Selective reporting (reporting bias)	Low risk	All expected outcome data reported
Other bias	Unclear risk	MPA concentration measurements were funded by Roche

Dudley 2005

Methods	• Study design: parallel RCT • Study duration: November 1998 to April 2002 • Duration of follow-up: 1 year
Participants	• Setting: multicentre (24 centres) • Countries: Europe and South America • Patients of at least 6 months post-transplant, on a CsA-based regimen with an SCr in the range of 100 to 400 mol/L and a calculated CrCl > 20 mL/min • Number: treatment group (73); control group (70) • Mean age, range (years): treatment group (43, 18 to 63); control group (45, 20 to 64) • Sex (M/F): treatment group (45/28); control group (44/26) • Exclusion criteria: de novo or recurrent kidney disease; transplant glomerulopathy; AR other causes of graft dysfunction were identified (e.g. obstruction, renal artery stenosis); BPAR within 3 months before study entry; taking MMF, SRL, or TAC before recruitment; pregnancy; history of gastrointestinal disorder; active infection; malignancy (except adequately treated non-metastatic basal or squamous cell carcinoma of the skin); participation in another study; WCC < 2.5 x 10^9/L; Hb < 5 g/dL; use of bile acid sequestrants
Interventions	Treatment group • MMF: 2 g/d • Steroids • CsA dose tapered and stopped over a 6-week period Control group • Centre practice (CsA monotherapy, CsA/steroids, or CsA/AZA/steroids) • CsA trough levels to be maintained over 80 ng/mL
Outcomes	• Change in kidney function over the 6 months • Graft survival • Patient survival • AR incidence • Calculated CrCl • BP • Antihypertensive and lipid-lowering medication use
Notes	• No rejections documented • Funding source: Roche; 2 authors are employees of Hoffmann-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomisation
Allocation concealment (selection bias)	Low risk	Computerized touch-tone system stratified for centre, was used for treatment allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	open label

Dudley 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcome data, analysed ITT
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded and authored (2) by Hoffmann-La Roche

El-Agroudy 2014

Methods	- Study design: parallel RCT - Study duration: not reported - Duration of follow-up: 3 years
Participants	- Setting: single centre - Country: Bahrain - Patients with stable kidney function randomised at 6 months post-transplant - Number: treatment group (29); control group (29) - Mean age ± SD (years); not reported - Sex (M/F): not reported - Exclusion criteria: not reported
Interventions	Treatment group - SRL-based regime: dose not reported Control group - TAC-based regime: dose not reported Both groups - MMF: dose not reported - PRED: dose not reported
Outcomes	- Patient survival - Graft survival - Kidney function by Cockcroft-Gault - BPAR - Proteinuria
Notes	- Abstract-only publication - Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

El-Agroudy 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Fangmann 2010

Methods	• Study design: parallel RCT • Study duration: recruitment December 2000 and February 2003; data collected until February 2006 • Duration of follow-up: 1 year
Participants	• Setting: multicentre (14 centres) • Countries: Germany, Switzerland, Austria • Primary kidney allograft deceased donor recipients, immediate post-transplant • Number: treatment group (75); control group (73) • Mean age ± SD (years): treatment group (52.3 ± 13.8); control group (54.2 ± 12.3) • Sex (M/F): treatment group (47/28); control group (42/31) • Exclusion criteria: cold-ischaemia time > 30 h; combined or prior transplants; grafts from living donors; use of another induction agent; WCC < 2.5 x 10^9/L; platelet count < 100 x 10^9/L; Hb < 60 g/L; PRA (current or peak) > 20%
Interventions	Treatment group • Daclizumab induction: 5 doses • Low-dose CsA: 50% trough levels of the control Control group • Standard dose CsA trough levels: 150 and 250 ng/mL initially (as per centre practice), gradual decrease to 125 to 175 ng/mL (6 months), and 100 to 150 ng/mL (12 months) Both groups • MMF • Steroids
Outcomes	• Kidney function 12 months after kidney transplantation by CrCl

Fangmann 2010 *(Continued)*

- Graft loss
- Death
- Patient survival at 6 and 12 months
- Graft survival at 6 and 12 months
- Incidence of BPAR within the 12-month follow-up
- Infections including CMV, EBV and Herpes zoster

Notes	• All rejections were BPAR • Funding source: none declared, investigator initiated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation lists
Allocation concealment (selection bias)	Low risk	After verification through the central office, centres were notified by fax
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis and all outcomes reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	None identified

Ferguson 2006

Methods	• Study design: parallel, 4-arm RCT, randomised 2:2:2:1 • Study duration: recruitment completed 9 January 2003 • Duration of follow-up: 1 year
Participants	• Setting: multicentre (43 centres) • Countries: five continents (USA, Europe, Australia, Asia and South America) • Aged > 18 years, immediate post-transplant; primary cadaveric or HLA-mismatched living donor (related or unrelated). • Number: treatment group 1 (72); treatment group 2 (74); treatment group 3 (76); control group (39) • Mean age ± SD (years): treatment group 1 (47.4 ± 11.20); treatment group 2 (44.1 ± 12.73); treatment group 3 (43.4 ± 13.35); control group (45.5 ± 10.42) • Sex (M/F): treatment group 1 (49/23); treatment group 2 (49/25); treatment group 3 (43/33); control group (20/19)

Ferguson 2006 *(Continued)*

- Exclusion criteria: allograft cold ischaemia time >30 h, PRA > 50%, or an ABO-incompatible or T-cell crossmatch positive transplant; baseline pulse rate < 50 BPM; significant thrombocytopenia(< 75,000/mm^3); leukopenia (< 2500/mm^3); absolute neutrophil count < 1500/mm^3, Hb < 6 g/dL; severe liver disease; patients in whom antibody induction therapy was planned or those who were treated with other immunosuppressive agents within the preceding 4 weeks

Interventions	**Treatment group 1** • FTY720: 5 mg • Reduced dose CsA: 2 to 3 mg/kg **Treatment group 2** • FTY720: 2.5 mg • Reduced dose CsA: 2 to 3 mg/kg **Treatment group 3** • FTY720: 2.5 mg • Full-dose CsA: 8 to 10 mg/kg **Control group** • Full-dose CsA: 8 to 10 mg/kg • MMF C2 levels difference 50 to 70% between reduced and full dose group.
Outcomes	• BPAR • GFR at 1 year • death • Graft loss
Notes	• Funding source: "This study was funded by Novartis Pharma AG"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Partial blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Ferguson 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Novartis Pharma AG

Flechner-318 Study 2002

Methods	• Study design: parallel RCT • Study duration: recruitment March 2000 to June 2001 • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: USA • Adult, primary kidney-only transplant recipients • Numbers: treatment group (31); control group (30) • Mean age, range (years): treatment group (48.4, 22 to 66); control group (46.7, 21 to 70) • Sex (M/F): treatment group (21/10); control group (19/11) • Exclusion criteria: prior transplantation or exposure to the immunosuppressants used; HLA-identical live donors; treatment for cancer; pregnancy; weight > 105 kg; total cholesterol > 350 mg/dL; triglycerides > 400 mg/dL; WCC < 3000/mm^3; platelets < 75,000/mm^3
Interventions	Treatment group • SRL: 15 mg within 48 hours of transplant, later 5 mg daily to maintain trough levels of 10 to 12 ng/mL (6 months), 5 to 10 ng/mL (6 to 12 months) Control group • CsA: 6 to 8 mg/kg to maintain trough levels of 200 to 250 ng/mL Both groups • MMF • PRED
Outcomes	• Patient survival • Graft survival • BPAR • Mean SCr • Calculated CrCl
Notes	• All BPAR • Funding source: This work was supported in part by a Grant-in-Aid from the Wyeth-Ayerst Pharmaceutical Co., Radnor, PA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised via computer-generated cards
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Flechner-318 Study 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No identifiable missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Funded by Wyeth-Ayerst Pharma

Garcia 2007

Methods	• Study design: parallel RCT, randomised in 1st phase, non-randomised 2nd phase • Study duration: recruitment 6 January 2001 to 16 August 2003 • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: Brazil • Recipients of one-haplotype living-related allografts • Number: group 1 (92); group 2 (38); group 3 (21) • Mean age ± SD (years): group 1 (37.4 ± 11.6); group 2 (33.0 ± 10.0); group 3 (38.2 ± 11.0) • Sex (M/F): group 1 (21/17); group 2 (22/11); group (12/9) • Exclusion criteria: evidence of systemic infection; history of clinically significant cardiac abnormalities; malignancy with 10 years
Interventions	Group 1 • TAC: 0.1 mg/kg twice/d within 24 hours of graft insertion ○ Trough levels: 10 to 20 ng/mL (1st month), 8 to 15 ng/mL (2nd month), 5 to 8 ng/mL thereafter • AZA • PRED Group 2 • Daclizumab induction: 3 doses • MMF • PRED Enrolment was interrupted in 2002 and a 3rd group of patients were enrolled in a non-randomised fashion Group 3 • Daclizumab induction • MMF • SRL: 6 mg loading and 2 mg daily • PRED

Garcia 2007 *(Continued)*

Outcomes	• 1st occurrence of a BPAR • Graft loss • Death • Incidence, time and histological grade of 1st BPAR • Incidence of all treated rejections, antibody-treated rejections and repeated rejections • Patient survival • Graft and functioning (death censored) • Graft survival • Graft function measured by SCr and calculated CrCl • Malignancies • Infections
Notes	• Rejections: BPAR • Funding source: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Study was described as randomised, method of randomisation was not reported; a 3rd group of non-randomised patients included after interim analysis
Allocation concealment (selection bias)	High risk	Process not clarified, also a 3rd group of non-randomised patients included after interim analysis
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	There is no missing outcome data
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	A 3rd group of non-randomised patients included after the interim analysis

Grimbert 2002

Methods	• Study design: parallel RCT • Study duration: recruitment between December 1986 to January 1989 • Duration of follow-up: 12 years
Participants	• Setting: single centre • Country: France • Caucasian adult recipients of a 1st cadaveric kidney allograft • Number: treatment group (58); control group (59)

Grimbert 2002 *(Continued)*

- Mean age ± SD (years): treatment group (40.5 ± 11.6); control group (40.6 ± 10.2)
- Sex (M/F): treatment group (36/22); control group (40/19)
- Exclusion criteria: HLA-immunized; diabetic recipients

Interventions	Treatment group
	- PRED: tapered to 15 mg/d after 1st month
	- AZA: 2 to 3 mg/kg/d over 12 years
	Control group
	- CsA: introduced on day 14 at 6 to 8 mg/kg
	o Trough levels: 200 to 600 ng/mL (6 months), 150 to 400 ng thereafter
	- PRED: tapered to 10 mg/d after 1st month
	- AZA: 1.5 mg/kg/d over 12 years
	Both groups (immediately post-transplant)
	- ALG induction: 5 mg/kg/d for 14 days
	- AZA: 1.5 mg/kg/d
	- Steroids: 1 mg/kg/d for 1st month
Outcomes	- 12-year graft survival
	- Death
	- 1 and 5-year graft survival
	- 12-year patient survival
	- Numbers of AR episodes
	- Numbers of patients switched from their initial regimen to the other regimen
	- Incidence of hypertension and malignancies
	- SCr
	- Calculated CrCl (Cockcroft)
	- Fasting blood glucose
	- Cholesterol and triglyceride levels at 12 years
Notes	- Funding source: none declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias)	Low risk	ITT analysis, no missing outcomes despite long duration

Grimbert 2002 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported
Other bias	Low risk	Study appears free of other biases

Grinyo 2004

Methods	• Study design: parallel pilot RCT • Study duration: recruitment December 2000 to January 2002 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (7 centres) • Country: Spain • Low-risk adult kidney cadaveric allograft; 2nd transplantations were allowed only if the 1st graft was maintained for at least 6 months or if the graft was lost owing to technical surgical causes • Number: treatment group (44); control group (43) • Mean age ± SD (years): treatment group (45.2 ± 13.5); control group (47.4 ± 11.2) • Sex (% M/F): treatment group (70.5/29.5); control group (69.8/30.2) • Exclusion criteria: HIV infection; PRA > 50%; donors younger than 9 or older than 65 years old; cold ischaemic time > 36 h or non-heart beating donors; HCV or HBV with impairment in liver function tests; history of malignancy in the previous 10 years
Interventions	Treatment group • SRL trough levels: 8 to 16 ng/mL • TAC trough levels: 3 to 8 ng/mL with elimination from month 3 onwards Control group • SRL trough levels: 4 to 8 ng/mL • TAC trough levels: 8 to 12 ng/mL (3 months), 5 to 10 ng/mL thereafter
Outcomes	• GFR at 12 months • BPAR at 12 months • BP
Notes	• Funding source: "This study was supported by Wyeth"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	High risk	Envelopes for randomisation prepared by Wyeth
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Grinyo 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	High risk	High drop-out rate resulting in protocol change
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by Wyeth; high drop-out resulting in protocol amendment mid trial

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Hall 1988

Methods	• Study design: parallel, 3-arm RCT • Study duration: recruitment 1983 and 1986 • Duration of follow-up: 24 months
Participants	• Setting: multicentre (7 centres) • Country: Australia • Adults receiving 1st cadaveric kidney transplant recipients randomised Immediately post-transplant • Number: group 1 (158); group 2 (166); group 3 (165) • Mean age ± SD (years): group 1 (43.6 ± 14); group 2 (43.1 ± 14); group 3 (43.0 ± 13) • Sex (males): group 1 (55.7%); group 2 (59%); group 3 (56.4%) • Exclusion criteria: insulin-dependent diabetes; abnormal liver function tests; malignancy; malabsorption; active infection; contraindication to AZA
Interventions	Group 1 • AZA: 2 mg/kg/d • PRED: IV methyl-PRED (100 mg pre-op and 500 mg day 1); oral PRED from day 2 with daily tapering to maintenance dose of 10 to 15 mg/d • ATG: induction optional Group 2 • Methyl-PRED induction only: 100 mg pre-op and 500 mg day 1; no maintenance PRED • Long-term CsA: IV CsA (5 mg/kg pre-op and 4 mg/kg day 1); 12.5 mg/kg oral CsA from day 2 tapering to 7.5 mg/kg by 3 months post-transplant Group 3 • Methyl-PRED induction only: 100 mg pre-op and 500 mg day 1 • Short-term CsA: IV CsA (5 mg/kg pre-op and 4 mg/kg day 1); 12.5 mg/kg (day 2) tapering to 7.5 mg/kg by 3 months post-transplant; at 3 months if no evidence of rejection CsA was replaced with AZA and PRED • AZA: 2 mg/kg/d • PRED: 20 mg/d
Outcomes	• Death-censored graft survival • Patient survival • Graft loss • Kidney function using MDRD
Notes	• Funding sources

Hall 1988 *(Continued)*

- Sandoz to 10 years follow-up
- Australian NHMRC research scholarship (MG; AC)
- Australian National Heart Foundation Postdoctoral Fellowship (VP)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation sequence was centrally generated by computer and stratified by centre
Allocation concealment (selection bias)	Low risk	Patient assignment was delivered to each of the centres opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, ITT analysis
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	High risk	Funded by Sandoz to 10 years

Hazzan 2005

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 2 years
Participants	• Setting: single centre • Country: France • First cadaveric kidney transplantation; PRA < 30%; no AR during the 1st 3 months after graft; triple immunosuppressive drug regimen with PRED, MMF (1.5 g/d), and CsA (3 mg/kg/d and trough level 100 ng/mL) at the time of randomisation; stable kidney function SCr < 2.5 mg/dL) • Number: treatment group (54); control group (54) • Mean age ± SD (years): treatment group (45.1 ± 11.2); control group (42.5 ± 12.1) • Sex (M/F): treatment group (36/18); control group (36/22) • Exclusion criteria: AR during the 1st 3 months after graft; non-optimal dosage and/or side effects of immunosuppressive drugs; impaired kidney function; early failure of the graft or death
Interventions	Treatment group • CsA withdrawal: between months 3 and 4 • MMF: 2 mg/d • PRED

Hazzan 2005 *(Continued)*

Control group

- MMF withdrawal: between months 3 and 4
- CsA trough levels: 100 to 300 ng/mL
- PRED

Both groups (1st 3 months)

- ATG: 3 mg/kg/d given for 5 days
- PRED: 1 mg/kg/d for 1st 2 weeks then tapered to 0.10 to 0.15 mg/kg/d by 6 months
- MMF: 2 g/d
- Delayed CsA: 1 day before ATG withdrawal, 4 to 6 mg/kg/d then adjusted to trough levels 100 to 300 ng/mL

Outcomes	- BPAR - Death - Graft loss - Kidney function - Chronic allograft damage index on graft biopsy at 1 year
Notes	- Funding source: "This study was partly supported by Santelys Association (Research Department)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data noted
Selective reporting (reporting bias)	Unclear risk	Not all outcomes reported
Other bias	Low risk	Study appears free of other biases

Heering 1993

Methods	- Study design: parallel, 3-arm RCT - Study duration: not reported - Duration of follow-up: 24 months

Heering 1993 *(Continued)*

Participants	• Setting: single centre • Country: Germany • Adults randomised 6 months post-transplant • Number: group 1 (17); group 2 (17); group 3 (18) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Group 1 • CsA/AZA/PRED Group 2 • CsA/PRED Group 3 • AZA/PRED Both groups (to 9 months) • Triple therapy: CsA/AZA/PRED
Outcomes	• AR • Graft survival • Graft function (SCR, CrCl)
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Study was stopped early due to increased rejection
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Study stopped early due to significant increase in acute rejection in group 3

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HERAKLES Study 2012

Methods	
	• Study design: parallel, 3-arm study (1:1:1) • Study duration: recruitment October 2007 to 2010 • Duration of follow-up: 48 months (planned for 60 months)

Participants	
	• Setting: multicentre (20 centres) • Country: Germany • Adults randomised 3 months post-transplant • Number: group 1 (159); group 2 (163); group 3 (163) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: SCr > 3.0 mg/dL; graft loss during the trial period; alterations in immunosuppressive regimen because of AR events (Banff II), platelets < 75,000/mm^3; leucocytes < 2500/mm^3; Hb < 6 g/dL; proteinuria > 1 g/d; clinically significant infection that required continuous treatment or occurrence of severe side effects caused by the immunosuppressive drugs

Interventions	
	Group 1 • Standard CsA trough levels: 100 to 180 ng/mL • EC-MPS Group 2 • CSA withdrawal • EVL trough levels: 5 to 10 ng/mL • EC-MPS Group 3 • Low-CsA trough levels: 50 to 75 ng/mL • EVL trough levels: 3 to 8 ng/mL Both groups (to 3 months) • Basiliximab induction • CsA • EC-MPS • steroids

Outcomes	
	• Death • Graft loss • Composite failure: BPAR, death, graft loss, loss to follow-up • Premature discontinuation due to adverse effects • Kidney function (eGFR)

Notes	
	• Abstract-only publications for main study • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not report- ed

HERAKLES Study 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Hollander 1995

Methods	• Study design: parallel RCT • Study duration: recruitment 1983 to 1988 • Duration of follow-up: 15 years
Participants	• Setting: single centre • Country: the Netherlands • Adults randomised 3 months post-transplant • Number: treatment group (60); control group (68) • Mean age ± SD (years): treatment group (46.1 ± 10.9); control group (43.1 ± 11.9) • Sex: (M/F): treatment group (35/25); control group (44/24) • Exclusion criteria: not reported
Interventions	Treatment group • CsA withdrawal at 3 months • AZA: dose gradually increase to 2 to 2.5 mg/kg/d (WCC dependent) • PRED: temporarily increased to 40 mg/d for 5 days, reduced to 25 mg/d then tapered over 10 months to 10 mg/d Control group • CsA: reduced 5 mg/kg/d adjusted for tough levels (250 to 500 ng/mL) • PRED: 10 mg/d Both groups (to 3 months) • CsA: 16 mg/kg/d reduced to 10 mg/kg/d over 3 months • PRED: 20 mg/d tapered to 10 mg/d
Outcomes	• Patient survival • Graft survival • GFR

Hollander 1995 *(Continued)*

	• Acute and chronic rejection (biopsy proven)
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Long term follow-up reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Holm 2008

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 36 months
Participants	• Setting: single centre • Country: Mexico • Adults and children randomised 30 to 1780 days post-transplant • Number: treatment group (220); control group (185) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • MMF: 1 to 2.0 g/d • SRL: 2 to 8 mg/d reduced to 1 to 2 mg/d (trough levels 5 to 10 ng/mL) • Steroids: 5 to 10 mg/d for 12 months then discontinued Control group • MMF: 1 to 2 g/d

Holm 2008 *(Continued)*

- CNI: continued on current regimen (dose/trough/CNI type not reported)
- Steroids: 5 to 10 mg/d for 12 months then discontinued

Antibody induction

- Daclizumab: 1 mg/kg, divided in two doses (day 0 and 7) used in high risk living-related and cadaveric recipients

Outcomes	- Clinical data of all patients (baseline, 3, 6, 9, 12, 18, 24 and 36 months) - BPAR - Graft loss - Morbidity - Death - Change in GFR
Notes	- Abstract-only publication; follow-up publication planned - Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up data not published as planned
Selective reporting (reporting bias)	High risk	No full-text publication 10 years after abstract publication
Other bias	Unclear risk	Insufficient information to permit judgement

Isoniemi 1990

Methods	- Study design: parallel, 4-arm study (1:1:1:1) - Study duration: recruitment January 1986 to May 1987 - Duration of follow-up: 1 year
Participants	- Setting: single centre - Country: Finland

Isoniemi 1990 *(Continued)*

- Adults with 1st cadaveric transplant; patients were on triple therapy with CsA, AZA and PRED during the 1st 10 weeks post-transplantation
- Number: group 1 (32); group 2 (32); group 3 (32); group 4 (32)
- Mean age ± SD (years): group 1 (47 ± 11); group 2 (49 ± 13); group 3 (45 ± 12); group 4 (43 ± 13)
- Sex (M/F): group 1 (20/12); group 2 (15/17); group 3 (17/15); group 4 (17/15)
- Exclusion criteria: "exclusions from the study were for medical reasons. mainly on the grounds that triple therapy was not considered suitable for these patients"

Interventions	**Group 1**
	
	• Continued with triple therapy (CsA, AZA, PRED)
	  ○ CsA: maintained at pre-conversion levels
	  ○ AZA: 1 mg/d
	  ○ PRED: tapered to 4 to 12 mg/d for the 1st year
	
	Group 2
	
	• CsA: maintained at pre-conversion levels
	• AZA: temporarily increased to 2 mg/kg/d then adjusted to WCC
	• PRED: gradually withdrawn over 2 weeks
	
	Group 3
	
	• CsA: discontinued abruptly
	• AZA: 2 mg/kg/d
	• PRED: initially increased to 0.5 mg/kg/d then tapered to 4 to 12 mg/d
	
	Group 4
	
	• CsA: maintained at pre-conversion levels
	• AZA: discontinued abruptly
	• PRED: initially increased to 0.5 mg/kg/d then tapered to 4 to 12 mg/d
	
	All groups (1st 10 weeks)
	
	• CsA: single pre-op dose (5 mg/kg) then 10 mg/kg/d adjusted for trough levels (200 to 600 ng/mL to 3 months then 150 to 400 ng/mL after 6 months)
	• AZA: 2 mg/kg/d tapered to 1 mg/kg/d by day 14
	• PRED: 1 mg/kg/d tapered to 0.25 mg/kg/d by day 10

Outcomes	• BPAR • Graft survival • Patient survival
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias)	High risk	Open-label study

Isoniemi 1990 (Continued)

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No obvious missing data
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Kosch 2003a

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 6 months
Participants	• Setting: single centre • Country: Germany • Aged 18 and 60 years, had received a kidney from a cadaveric donor, and showed deterioration in graft function during a period of 6 months as the result of biopsy-proven chronic allograft nephropathy • Number: treatment group (12); control group (12) • Mean age ± SEM (years): treatment group (49 ± 4); control group (47 ± 5) • Sex (M/F): treatment group (10/2); control group 10/2() • Exclusion criteria: heart failure; clinical evidence of atherosclerotic disease; abnormal ECG or exercise treadmill test; diabetes mellitus kidney allograft recipients with unstable graft function and changes in SCr > 0.5 mg/dL within 10 days preceding the study
Interventions	Treatment group • CsA withdrawal: CsA tapered over 4 weeks • PRED: dose not reported Control group • Standard CsA trough levels: 75 to 150 µmol/L • PRED: dose not reported • MMF: 2 g/d during 1st 4 weeks Both groups (to 6 months) • CsA trough levels: 75 to 150 µmol/L • PRED: 5 to 10 mg/d • MMF: upon inclusion into study all patients received 500 mg/d increasing to 2 g/d during 1st 4 weeks; after final MMF dose patients were randomised
Outcomes	• Carotid and brachial artery distensibility coefficients (baseline and at 6 months) • Biochemical data (baseline and at 6 months)
Notes	• Funding source: not reported

Kosch 2003a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Kreis 2003

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 2 years
Participants	• Setting: multicentre • Country: France • 1st or 2nd kidney transplant recipients randomised week 8 post-transplant • Number: treatment group (78); control group (80) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Early CsA reduction trough levels: 100 to 150 ng/mL (week 9 to 12), 75 to 100 ng/mL (week 12 to month 12), 75 ng/mL (months 12 to 24) Control group • CsA reduction after 1 year: 150 to 200 ng/mL (week 9 to month 12) and 100 to 150 ng/mL (months 12 to 24) Both groups • Daclizumab induction • MMF: 2 g/d

Kreis 2003 *(Continued)*

	• Steroids

Outcomes	• SCr • BPAR • Graft survival • Patient survival

Notes	• Funding source: not reported • Abstract-only publications

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

MacPhee 1998

Methods	• Study design: parallel RCT • Study duration: recruitment between 1985 to 1991 • Duration of follow-up: 15 years

Participants	• Setting: single centre • Country: UK • Patients who underwent 1st or 2nd live or cadaveric kidney transplant with stable SCr < 300 µmol/L at 1 year post-transplant • Number: treatment group (102); control group (114) • Median age, range (years): treatment group (41, 18 to 62); control group (39, 18 to 66) • Sex (M/F): treatment group (58/44); control group (70/44) • Exclusion criteria: AR in preceding 6 months

Interventions	Treatment group

MacPhee 1998 *(Continued)*

- AZA: 3 mg/kg titrated to maintain WCC > 4 x 10^6
- PRED: 10 mg
- CsA: stopped after 1 week

Control group

- CsA trough level: 80 to 125 ng/mL at 1 year

Outcomes	
	- Patient survival
	- Graft survival
	- Kidney function
	- Need for anti-hypertensive agents.

Notes	
	- Funding source: "no funding was obtained for this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using a computer-generated list of random numbers"
Allocation concealment (selection bias)	Low risk	"allocation was concealed in opaque numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	Study appears free of other biases

Martinez-Mier 2006

Methods	
	- Study design: parallel RCT
	- Study duration: recruitment May 2004 to January 2005
	- Duration of follow-up: mean 15.8 months

Participants	
	- Setting: single centre
	- Country: Mexico
	- Adult 1st degree living related kidney allograft recipients
	- Number: treatment group (20); control group (21)
	- Mean age ± SD (years): treatment group (29.6 ± 7.6); control group (31.2 ± 9.21)
	- Sex (M/F): treatment group (12/8); control group (12/9)

Martinez-Mier 2006 *(Continued)*

	• Exclusion criteria: systemic infection; HLA-identical donors; prior treatment for cancer; pregnancy; weight > 105 kg; hypersensitivity to macrolide antibiotics; total cholesterol > 300 mg/dL; triglycerides > 400 mg/dL; WCC< 3,000 mm^3; platelets < 75,000 mm^3
Interventions	Treatment group • SRL: loading dose of 10 mg orally and then 3 mg/m^2; dose adjusted to achieve trough levels between 10 and 15 ng/mL for 6 months and 5 to 10 ng/mL thereafter Control group • CsA: 4 to 8 mg/kg/d in divided doses, adjusted to trough levels between 150 to 300 ng/mL for six months Both groups • Basiliximab induction • MMF: 2g/d • PRED
Outcomes	• Patient survival at 1 year • Graft survival at 1 year • Incidence of BPAR
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

MECANO Study 2009

Methods	• Study design: parallel, 3-arm RCT (1:1:1)

MECANO Study 2009 *(Continued)*

- Study duration: recruitment commenced 2005
- Duration of follow-up: 24 months

Participants	- Setting: single centre - Country: Netherlands - Patients aged 18 to 70 years receiving a 1st or 2nd kidney transplant from a deceased or living donor were randomised 6 months post-transplant if biopsy did not reveal rejection - Number: treatment group 1 (36); treatment group 2 (38); control group (39) - Mean age ± SD (years): treatment group 1 (52 ± 12.5); treatment group 2 (49 ± 13.2); control group (55 ± 10.1) - Sex (males): treatment group 1 (61%); treatment group 2 (60%); control group (51%) - Exclusion criteria: HLA-identical sibling donor; a 3rd or 4th transplant; current or historical PRA > 50%, female patients unwilling to use adequate contraception during the study; cholesterol > 8.5 mmol/L despite statin use
Interventions	Treatment group 1 - MPS: target AUC_{12} 35 mg.h/L or a trough level > 2 mg/L - PRED: 10 mg/d Treatment group 2 - EVL: target AUC_{12} 150 mg.h/L - PRED: 10 mg/d Control group - CsA: Target AUC_{12} 3250 µg.h/L - PRED: 10 mg/d All groups (1st 6 months) - Basiliximab induction - PRED - MPS - CSA
Outcomes	- Interstitial graft fibrosis - Hyalinosis - AR (not defined) - Graft survival - Patient survival - SCr - Infections - GFR
Notes	Funding source: Novartis Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation list was generated with "Random Allocation Software" Version 1.0 2004 tripod.com

MECANO Study 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	A sealed opaque envelope was used, containing a sheet with the number of the treatment arm. All patients received an envelope after recruitment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study prematurely terminated after increased rejection in one arm
Selective reporting (reporting bias)	High risk	Study prematurely terminated after increased rejection in one arm
Other bias	High risk	Funded by Novartis Pharma. Early termination of the study

MODIFY Study 2012

Methods	• Study design: parallel, 3-arm RCT • Study duration: recruitment 2002 to 2004 • Duration of follow-up: 5 years
Participants	• Setting: single centre • Country: Brazil • Adult transplant recipients • Number: group 1 (39); group 2 (40); group 3 (40) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Group 1 • Low dose TAC trough levels: 3 to 5 ng/mL • MMF • Steroids Group 2 • Classic schedule TAC trough levels: 7 to 9 ng/mL • MMF • Steroids Group 3 • CsA: C2 levels 800 to 1000 ng/mL • MMF • Steroids
Outcomes	• Graft loss • Death

MODIFY Study 2012 *(Continued)*

	• Calculated CrCl
	• BPAR: graft biopsies performed at 6 months and scored according to chronic allograft damage index

Notes	• Abstract-only publications for main results
	• Funding source: not reported
	• IL2 induction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, no missing outcome data
Selective reporting (reporting bias)	Low risk	ITT analysis, all outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Muhlbacher 2014

Methods	• Study design: parallel RCT (1:1)
	• Study duration: recruitment 2000 to 2002
	• Duration of follow-up: 12 months

Participants	• Setting: multicentre (49 centres)
	• Country: Europe
	• Patients > 18 years with 1st or 2nd kidney allograft recipients (cadaveric, living unrelated or mismatched living-related) randomised 1 month past-transplant
	• Number: treatment group (178); control group (179)
	• Mean age ± SD (years): treatment group (47.4 ± 13.1); control group (46.1 ± 12.8)
	• Sex (M/F): treatment group (116/62); control group (125/54)
	• Exclusion criteria: systemic or localized infection; use of medications known to interact with SRL; multiple organ transplants; patients at high risk of rejection ; use of planned antibody induction therapy within 1 week before or at the time of the current transplant; baseline/screening fasting cholesterol level > 7.8 mmol/L; triglycerides > 4.6 mmol/L; Banff Grade 3 AR between transplantation and randomisation; steroid-resistant rejection in the 1st month after transplantation; patients who were dialysis-dependent; inadequate kidney function to support CsA reduction; SRL trough levels < 4 ng/mL

Interventions	Treatment group
	• Reduced dose CsA trough levels: 75 to 100 ng/mL
	• SRL trough levels: 4 to 12 ng/mL
	• Steroids
	Control group
	• Full dose CsA trough levels: 150 to 200 ng/mL
	• SRL trough levels: 4 to 12 ng/mL
	• Steroids
Outcomes	• Patient survival
	• Graft survival
	• BPAR
	• SCr
	• CrCl
	• Infections
	• Hyperlipidaemia
Notes	• Funding source: Wyeth Pharma
	• Medical writing and editorial support were funded by Pfizer.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Interim analysis only reported
Selective reporting (reporting bias)	Unclear risk	Interim analysis, outcomes reported as prespecified
Other bias	High risk	Funded by Wyeth; interim analysis report

Nafar 2012

Methods	• Study design: parallel RCT
	• Study duration: recruitment 2004 to 2007

Nafar 2012 *(Continued)*

	• Duration of follow-up: 4 years

Participants	• Setting: single centre • Country: Iran • Patients 18 to 70 years with ESKD; receiving a 1st or 2nd kidney allograft from a living-unrelated donor or from a living-related donor, serum triglyceride < 400 mg/dL; serum cholesterol < 300 mg/dL; WCC > 4 x 10^9/L, platelet count > 100 x 10^9/L • Number: treatment group (50); control group (50) • Mean age ± SD (years): treatment group (38.5 ± 12.5); control group (42.5 ± 14.3) • Sex (% M/F): treatment group (58/42); control group (52/48) • Exclusion criteria: active systemic or localized major infection at the time of initiation of SRL administration; history of malignancy within 5 years of enrolment; use of any investigational drug other than the specified in the protocol during the 4 weeks before enrolling in the study; use of planned antibody induction therapy at the time of transplantation; active gastrointestinal disorder that may interfere with drug absorption; high risk of rejection; evidence of infiltration, cavitations, or consolidation on chest radiography obtained during the pre-study screening; multiple organ transplant; known hypersensitivity to SRL, MMF, or CsA or its derivatives;. DGF as surgical complication; use of ATG for DGF
Interventions	**Treatment group** • CsA trough levels: 150 to 250 ng/mL for 3 months then stopped • MMF: 1 to 2 g/d from month 4 • SRL: 6 mg/d as a loading dose then trough levels of 8 to 15 ng/mL • Steroids: 5 mg/d **Control group** • CsA trough levels: 150 to 250 ng/mL • MMF: 1 to 2 g/d • Steroids: 5 mg/d
Outcomes	• BPAR rates at 1 years • Graft loss at 1 year • Death at 1 year • GFR and SCr at 4 years • Anaemia at 1 year • Lymphoproliferative disorder at 1 year • Infections at 1 year
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Nafar 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Adverse effects mentioned only for the initial one year
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned for 1st year but only efficacy subsequently
Other bias	Unclear risk	Safety data limited to the 1st year

Nashan 2004

Methods	• Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 3 years
Participants	• Setting: multicentre (13 centres) • Countries: USA (6); France (3); Italy (2); Germany (2) • Patients aged 16 to 65 years who received a primary cadaveric or living-donor kidney transplant • Number: treatment group (58); control group (53) • Mean age ± SD (years): treatment group (43.9 ± 11.3); control group (45.9 ± 11.9) • Sex (M/F): treatment group (38/20); control group (30/23) • Exclusion criteria: previous transplant; an ABO-incompatible or T-cell cross–match-positive transplant; a kidney from a donor without a beating heart; cold ischaemia time > 36 hours, donor-specific transfusions; current PRA > 80%
Interventions	Treatment group • Reduced dose CsA: initiated at 3 to 4 mg/kg/d then adjusted to achieve trough level of 75 to 125 ng/mL (months 1 and 2), 50 to 100 ng/mL (months 3 to 36) Control group • Full dose CsA: initiated at 6 to 8 mg/kg/d then adjusted to achieve trough level of 150 to 300 ng/mL (months 1 and 2), 125 to 250 ng/mL (months 3 to 36) Both groups • Basiliximab induction • EVL: 3 mg/d • PRED: initiated at 0.35 to 2.0 mg/kg/d and tapered to 20 mg/d by 4 weeks and maintained ≥ 5 mg/d during year 1
Outcomes	• Efficacy failure: defined as BPAR, graft loss, death or loss to follow-up at 6 months • Malignancy • Infections • Kidney function
Notes	• Funding source: "This study was sponsored by a grant from Novartis Pharmaceuticals AG, Basel, Switzerland."

Risk of bias

Nashan 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis for efficacy but not safety data
Selective reporting (reporting bias)	Low risk	Published data included all expected outcomes
Other bias	High risk	Funded by Novartis. High drop-out rates, safety data was not ITT

Oh 2012

Methods	- Study design: parallel RCT - Study duration: recruitment July 2009 to March 2012 - Duration of follow-up: 12 months
Participants	- Setting: multicentre (5 centres) - Country: South Korea - Recipients (aged 18-65 years) of de novo kidney transplantation - Number: treatment group (67); control group (72) - Mean age ± SD (years): treatment group (41.9 ± 11.1); control group (47.0 ± 9.0) - Sex (M/F): treatment group (43/24); control group (40/32) - Exclusion criteria: 2nd transplant; recipients of multiple organ transplants or an organ donated after cardiac death; donors younger than 10 years or older than 65 years; recipients of ABO-incompatible transplants; recipients with antibodies against the HLA of the donor organ; WCC < 2,500/μL or neutrophils < 1,500/μL, or platelets < 100,000/μL; total cholesterol > 350 mg/dL, or triglyceride > 500 mg/dL; evidence of severe liver disease
Interventions	Treatment group - EVL: 0.75 mg twice/d, started the day after the 1-month assessment; trough levels of 3 to 8 ng/mL - CsA trough levels: 75 to 125 ng/mL (to 3 months) after transplantation, 50 to 100 ng/mL (to 5 months), and 25 to 50 ng/mL (to 12 months) Control group - Standard dose CsA trough levels: 150 to 250 ng/mL Both groups

Oh 2012 *(Continued)*

- Basiliximab induction
- CsA
- EC-MPS
- Steroids

Outcomes	• Composite variable of the incidence of efficacy failure: BPAR, graft loss, death, or loss to follow-up to 12 months • Graft function: assessed with eGFR by MDRD formula and 24 h urinary protein excretion at 12 months after transplantation • Incidences of adverse events
Notes	• Of 148 randomised patients, 139 comprised the ITT population; 112 (56 in the investigational group and 56 in the control group) completed the study follow-up and comprised the per-protocol population • Funding source: "Funding for this study was provided by Novartis Pharmaceuticals AG (Basel, Switzerland)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were recorded and entered onto an electronic database and re-evaluated by external monitors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data was handled by ITT analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported in final analysis
Other bias	High risk	Funded by Novartis

OPTICEPT Study 2009

Methods	• Study design: parallel, 3-arm RCT (1:1:1) • Study duration: recruitment June 2004 to September 2007 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (51 centres) • Country: USA • Recipients of a single (1st or 2nd) kidney allograft from living (related or unrelated) or deceased donors entered study within 24 h of transplant

OPTICEPT Study 2009 *(Continued)*

- Number: group 1 (243); group 2 (237); group 3 (240)
- Mean age ± SD (years): group 1 (48.3 ± 12.8); group 2 (48.8 ± 13.6); group 3 (49.6 ± 13.2)
- Sex (M/F): group 1 (163/80); group 2 (159/78); group 3 (163/77)
- Exclusion criteria: Immunosuppressive therapy within previous 28 days for a 1st transplant and 3 months for a 2nd transplant; history of malignancy in last 5 years

Interventions	**Group 1**
	
	 • MMF: controlled concentration
	  ◦ CsA group trough levels: ≥ 1.3 µg/mL
	  ◦ TAC group trough levels: ≥ 1.9 µg/mL
	 • CNI: reduced dose CsA or TAC
	  ◦ CsA trough levels: 250 to 325 ng/mL (days 1 to 30), 125 to 165 ng/mL (31 to 90 days), 95 to 145 ng/mL (day 91 to 2 years)
	  ◦ TAC trough levels: 8 to 12 ng/mL (days 1 to 30), 4 to 6 ng/mL (days 31 to 90), 3 to 5 ng/mL (day 91 to 2 years)
	
	 Group 2
	
	 • MMF: controlled concentration (as for group 1)
	 • CNI: standard dose CsA or TAC
	  ◦ CsA trough levels: 250 to 325 ng/mL (days 1 to 30), 230 to 250 ng/mL (days 31 to 90), 190 to 220 ng/mL (day 91 to 2 years)
	  ◦ TAC trough levels: 8 to 12 ng/mL (days 1 to 30), 8 to 10 ng/mL (days 31 to 90), 6 to 8 ng/mL (day 91 to 2 years)
	
	 Group 3
	
	 • MMF: fixed dose 2 g/d (adults), 600 mg/m^2 (children)
	 • CNI: standard dose CsA or TAC (as for group 2)

Outcomes	• BPAR • Graft loss • Death • Mean percent change in GFR • Adverse events
Notes	• Funding source: "This study was sponsored by Roche."; "D. Patel is an employee of Roche."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	High risk	Allocated sequentially
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed

OPTICEPT Study 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported
Other bias	High risk	Funded by Roche

ORION Study 2011

Methods	• Study design: parallel, 3-arm RCT (1:1:1) • Study duration: recruitment March 2004 to May 2005 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (65 centres) • Country: Canada, USA, Europe, Australia • Patients ≥18 years scheduled to receive a 1st or 2nd kidney allograft from a living donor or deceased donor • Number: group 1 (152); group 2 (152); group 3 (139) • Mean age ± SD (years): group 1 (47.9 ± 13.3); group 2 (50.4 ± 13.0); group 3 (48.4 ± 13.2) • Sex (M/F): group 1 (109/43); group 2 (110/42); group 3 (81/58) • Exclusion criteria: multiple organ transplants; BMI > 32 kg/m^2; WCC ≤ 3000/mm^3; platelet count ≤ 100,000 mm^3; fasting triglycerides ≥ 400 mg/dL; fasting total cholesterol ≥ 300 mg/dL; cold ischaemia time >30 h
Interventions	**Group 1** • SRL trough levels: 8 to 15 ng/mL; increased to 12 to 20 ng/mL once TAC eliminated • TAC trough levels: 6 to 15 ng/mL for 13 weeks and then decreased by 25%/week until eliminated **Group 2** • SRL trough levels: 10 to 15 ng/mL (to week 26), 8 to 15 ng/mL thereafter • MMF: 1 to 2g g/d **Group 3** • TAC trough levels: 8 to 15 ng/mL (to week 26), 5 to 15 ng/mL thereafter • MMF: 1 to 2 g/d
Outcomes	• Patient survival • Graft survival • BPAR • Time to 1st rejection
Notes	• Group 2 terminated due to high BPAR rate • Funding source: funded by Wyeth; editorial assistance and manuscript preparation funded by Wyeth

Risk of bias

Bias	Authors' judgement	Support for judgement

ORION Study 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data accounted by modified ITT analysis
Selective reporting (reporting bias)	High risk	Prespecified outcomes reported however group 2 of the study limbs reported high BPAR and was terminated
Other bias	High risk	Funded by Wyeth; one of the study groups was terminated

Pacheco-Silva 2013

Methods	• Study design: parallel RCT • Study duration: recruitment no reported • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: Brazil • Low risk kidney recipients of deceased donors randomised 2 to 5 weeks post-transplant • Number: treatment group (16); control group (15) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • EVL: converted during a 3-day overlap with TAC Control group • TAC: dose not reported Both groups • Thymoglobulin induction • PRED • MPS
Outcomes	• Incidence of CMV infection • Mean SCr at 30 days, 60 days and 1 year • AR

Pacheco-Silva 2013 *(Continued)*

Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Included prespecified outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Paoletti 2012

Methods	• Study design: parallel RCT • Study duration: recruitment 1 August 2008 to 31 December 2009 • Duration of follow-up: 3 years (only 1 year data presented)
Participants	• Setting: single centre • Country: Italy • Consecutive nondiabetic patients aged 18 to 70 years who received a single kidney graft from a deceased donor • Number: treatment group (10); control group (20) • Mean age, range (years): treatment group (47, 32 to 67); control group (51, 28 to 65) • Sex (M/F): treatment group (7/3); control group (14/6) • Exclusion criteria: diabetes; dual kidney transplant; living-related donor transplant; kidney donated after cardiac death; cardiac valvular abnormalities at the time of enrolment
Interventions	Treatment group • EVL trough levels: 3 and 8 ng/mL • CsA trough levels: 75 and 125 ng/mL(1st 2 months), 50 and 100 ng/mL thereafter Control group • CsA trough levels: 150 to 300 ng/mL (1st 2 months), 125 to 250 ng/mL thereafter

Paoletti 2012 *(Continued)*

- MMF

Both groups

- IL2RA induction
- Steroids

Outcomes	- Change in left ventricular mass index at 1 year - Change in kidney graft function at 1 and 3 years - BPAR at 1 and 3 years
Notes	- Funding source: "authors declare no funding or conflicts of interest"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated block randomisation
Allocation concealment (selection bias)	Low risk	Allocation was implemented using sequentially numbered, opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	3 year data yet to be reported
Other bias	Unclear risk	Study not powered, initially planned for 36 patients, ITT was for 30

Pascual 2003

Methods	- Study design: parallel RCT - Study duration: recruitment January 2000 to October 2001 - Duration of follow-up: 6 months
Participants	- Setting: multicentre (2 centres) - Country: USA - Patients aged ≥ 18 years with stable kidney function randomised at least after 1 year post-transplant (cadaveric, living-related or living-unrelated) - Number: treatment group (32); control group (32) - Mean age ± SD (years): treatment group (47 ± 12); control group (45 ± 13) - Sex (M/F): treatment group (27/5); control group (21/11)

Pascual 2003 *(Continued)*

	• Exclusion criteria: not reported
Interventions	**Treatment group** • CsA reduction to 50% over 2 months: initial 25% reduction then further 25% reduction after 2 months if no rejection **Control group** • CsA trough levels: 100 to 300 ng/mL **Both groups** • MMF • PRED • CsA trough at randomisation: 100 to 300 ng/mL
Outcomes	• Graft loss • AR • SCr • CrCl • Hypertension
Notes	• AR: not qualified if biopsy proven or included clinical + BPAR • Funding source: "This work was supported by an unrestricted grant from Roche Laboratories. Manuel Pascual, MD, was supported by the Helen and George Burr Endowed Research and Educational Fund in Support of Transplantation and by the Yates Fund for Transplant Technology."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data noted
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Funded by Roche Laboratories

Pascual 2008 *(Continued)*

Methods	
Methods	• Study design: parallel, pilot RCT • Study duration: recruitment not reported • Duration of follow-up: planned follow-up 3 years (only 1 year data reported)
Participants	• Setting: single centre • Country: USA • Adults randomised between 2 and 16 months post-transplant • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (55.2 ± 9.5); control group (53.6 ± 9.2) • Sex (males): treatment group (85%); control group (75%) • Exclusion criteria: PRA > 10%; eGFR < 40 mL/min; pre-randomisation antibody-mediated or Banff IA AR

Interventions	**Treatment group**
	
	• CNI: reduced by 25% to 50% on day of randomisation, continued for 7 to 14 days and then stopped
	• MMF/EC-MPS: up to 1000/720 mg every 12 hours
	
	Control group
	
	• CNI
	  ○ CsA trough levels: 100 to 200 ng/mL
	  ○ TAC trough levels: 5 to 10 ng/mL
	
	Both groups
	
	• Alemtuzumab induction
	• TAC or CsA
	• MMF/EC-MPS: 500/360 mg every 12 hours at enrolment
	• Low-dose steroids

Outcomes	• AR • Patient survival • Graft survival • Graft kidney function: GFR, SCr • Peripheral Treg levels
Notes	• All but one rejection episode was biopsy proven • Funding source: "This work was supported by a grant from ILEX, Inc., San Antonio, TX, USA. JP is supported by a grant from the Institute Carlos III-Spanish Health Department (BA06/90020)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 year data not available
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by ILEX Inc, San Antonio (makers of Alemtuzumab).

Pedersen 1991

Methods	• Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: Demark • Patients aged 16 to 70 years who received a kidney transplant 12 months prior and on treatment with CsA and steroids with SCr < 300 µmol/L • Number: treatment group (51); control group (55) • Mean age, range (years): treatment group (46, 23 to 69); control group (45, 17 to 68) • Sex (M/F): treatment group (28/23); control group (28/27) • Exclusion criteria: unwillingness to participate; heart failure; cancer; pregnancy
Interventions	Treatment group • AZA: 2 mg/kg • CsA: 150 mg/d for 1st 2 weeks • PRED: 5.0 to 7.5 mg/d Control group • CsA: 3 to 5 mg/kg • PRED: 5.0 to 7.5 mg/d Both groups (on entry) • CsA (dose; trough levels): treatment group (272 mg/d; 100 to 450 ng/mL); control group (270 mg/d; 150 to 500 ng/mL) • PRED: treatment group (7.3 mg/d); control group (7.4 mg/d)
Outcomes	• Graft failure requiring dialysis • Adverse effects of the drugs • Death
Notes	• Funding source: "This study was supported by the Danish Medical Research Council, Provinsbankens Gavefond, Vilhelm Kiers Fond and Fonden til Laegevidenskabens Fremme"

Risk of bias

Bias	Authors' judgement	Support for judgement

Pedersen 1991 *(Continued)*

Random sequence generation (selection bias)	High risk	Randomised consecutively
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Not all adverse events recorded in outcomes
Other bias	Low risk	Study appears free of biases

Pontrelli 2008

Methods	• Study design: parallel RCT • Study duration: recruitment June 2002 to July 2003 • Duration of follow-up: 2 years
Participants	• Setting: single centre • Country: Italy • Consecutive patients with biopsy-proven CAN, receiving CsA as base immunosuppressive therapy • Number: treatment group (12); control group (6) • Mean age ± SD (years): treatment group (37.6 ± 13.8); control group (33.6 ± 9.5) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • CsA: abruptly discontinued • Rapamycin: loading dose of 0.1 mg/kg/d; trough levels 6 to 10 ng/mL Control group • CsA: maintained at pre-randomisation levels Both groups • CsA: "At randomization, there was no difference in the dose administered and in the trough levels of cyclosporine between the two groups" • MMF • AZA
Outcomes	• Kidney biopsy at 2 years

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Pontrelli 2008 *(Continued)*

- Morphometric analysis was conducted at T0 and at T24. PAI-1 expression was evaluated at T0 and T24 by immunohistochemistry. The effect of rapamycin on PAI-1 gene expression in cultured proximal tubular cells incubated with CD40L or thrombin, two potential chronic allograft nephropathy pathogenic mediators
- SCr
- Proteinuria

Notes	• Funding source: " This study was supported by the Ministero della Salute (ex art 12bis to F.P.S.), the 5th European Framework Quality of Life and Management of Living Resources (QLG1–2002-01215 to G.G.), Ministero dell'Universita` e della Ricerca Scientifica (PRIN 2003 to L.G., PRIN 2004 to F.P.S., and PRIN 2005 to G.G.) and a grant from the Fondazione Cassa di Risparmio di Puglia (to L.G.)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Low risk	Study appears free of other biases

Qazi 2014

Methods	• Study design: parallel RCT • Study duration: recruitment January 2010 to March 2013 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (52 centres) • Country: USA, Canada • de novo kidney transplant recipients • Number: treatment group (309); control group (304) • Mean age ± SD (years): treatment group (50.0 ± 13.34); control group (48.4 ± 12.91) • Sex (M/F): treatment group (205/104); control group (202/102) • Exclusion criteria: not reported
Interventions	Treatment group

Qazi 2014 *(Continued)*

- EVL: from day 5 dose was 0.75 mg twice daily; dose increased if the trough level < 3 ng/mL, or reduced if the trough level > 8 ng/mL
- TAC: initiated according to local practice; trough levels 4 to 7 ng/mL, 3 to 6 ng/mL (months 2 to 6), 2 to 5 ng/mL (from month 6)

Control group

- MMF: 2 g/d
- TAC: dose adjusted from day 3; 8 to 12 ng/mL (day 3 to month 2), 7 to 10 ng/mL (months 2 to 6), 5 to 10 ng/mL (from month 6)

Both groups

- Basiliximab or ATG induction
- Steroids as per local practice

Outcomes	• Composite efficacy failure: (1) BPAR; (2) graft loss; (3) death; (4) loss to follow-up • eGFR • CMV (Viraemia, syndrome and disease) • BKV nephropathy • NODAT • Proteinuria
Notes	• Abstract-only data • Funding source: " Peddi, V.: Grant/Research Support, Novartis, Astellas. Shaffer, D.: Grant/Research Support, Novartis. Shihab, F.: Other, Novartis, Consultant and Speaker, Astellas, Consultant. McCague, K.: Employee, Novartis Pharmaceutical Corporation. Patel, D.: Employee, Novartis Pharmaceutical corporation. Mulgaonkar, S.: Grant/Research Support, Novartis, Other, Novartis, Advisor"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Novartis Pharmaceuticals were sponsors, study directors, and authors

Methods	• Study design: parallel RCT • Study duration: recruitment March 2000 to February 2002 • Duration of follow-up: 96 weeks
Participants	• Setting: multicentre (12 centres) • Country: France • 1st or 2nd transplant cadaveric or live donor recipients aged 18 to 65 years who received CsA for at least 3 months before randomisation (1 to 10 years post-transplant) • Number: treatment group (77); control group (31) • Mean age ± SD (years): treatment group (43.8 ± 10.6); control group (44.7 ± 11.1) • Sex (M/F): treatment group (55/22); control group (27/4) • Exclusion criteria: not reported
Interventions	Treatment group • MMF: progressively increased to 2 g/d by the 4th week • Half dose CsA: reduced every 2 weeks by 25% to reach half dose at 8 weeks Control group • CsA: dose as per local practice (trough levels to be > 100 ng/mL)
Outcomes	• Change in SCr • Graft survival • Patient survival • BPAR and clinical rejection episodes • CrCl • Infections
Notes	• Funding source: "The study sponsor, Roche (Neuilly sur Seine, France), identified the participating centers, funded the making of the central database, the external monitoring, and an independent design office which performed the statistical analysis, and participated to the writing of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was centralised and stratified
Allocation concealment (selection bias)	Low risk	"centralized randomization was ensured via Internet"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data accounted for outcomes and analysed as ITT

Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported
Other bias	High risk	Funded by Roche

Rivelli 2015

Methods	• Study design: parallel RCT • Study duration: recruitment over 18 months • Duration of follow-up: 12months
Participants	• Setting: single centre • Country: Brazil • Kidney transplant recipients (1st living or deceased donor) with low-medium immunologic risk aged 18 to 65 years • Number: treatment group (22); control group (23) • Mean age ± SD (years): treatment group (44.9 ± 14.2); control group (46.3 ± 11.9) • Sex (M/F): treatment group (11/11); control group (14/9) • Exclusion criteria: HIV, HCV and HBV virus; active infection evidence at the time of initial administration of drugs; PRA > 25%; deceased donor age > 60 years old and/or SCr > 1.5 mg/dL; cold ischaemia > 30 h; fasting triglyceride > 300 mg/dL; total cholesterol > 300 mg/dL; use of ARB or ACEi; diabetes mellitus type I or II; at the end of the 3rd month CrCl < 30 mL/min, RA grade III (Banff'07) or proteinuria > 1 g/24 h
Interventions	Treatment group • TAC: stopped at 3 months • SRL trough levels: increased to 8 to 15 ng/mL Control group • TAC trough levels: 3 to 7 ng/mL (after 3 months) Both groups • ATG induction therapy for deceased donor recipients • TAC trough levels: 8 to 15 ng/mL (1st month), 6 to 12 ng/mL (to 3rd month) • SRL trough levels: 6 to 12 ng/mL • PRED: 500 mg IV/d for 3 days then progressively decreased to 5 mg/d
Outcomes	• Characterise the interstitial fibrosis by means of the chronicity index, surface density of myofibroblasts and total collagen • Kidney function: SCr, CrCl • DGF • AR • Subclinical AR • Acute pyelonephritis • Polyomavirus associated nephropathy
Notes	• Funding source: "This study was supported by: The Brazilian Council for Scientific and Technological Development (CNPq), Ministério da Saude (MS), and Fundação Amparo à Pesquisa do Rio de Janeiro (FAPERJ)."

Risk of bias

Rivelli 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assigned to groups by random numbers generated by computer immediately before surgery
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pathologist analysing the biopsies was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing patient data
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	This study was supported by: The Brazilian Council for Scientific and Technological Development

RMR Study 2001

Methods	• Study design: parallel RCT • Study duration: recruitment May 1998 to June 1999 • Duration of follow-up: 60 months
Participants	• Setting: multicentre (57 centres) • Country: Europe, Australia, Canada • 1st or 2nd kidney transplant recipients aged > 13 years; cadaveric or living donors; WCC ≥ 4000/mm^3, platelet count ≥ 100,000/mm^3, fasting triglycerides ≤ 4.6 mmol/L, fasting cholesterol ≤ 7.8 mmol/L, randomised 3 months post-transplant • Number: treatment group (215); control group (215) • Mean age (years): treatment group (44.6); control group (45.8) • Sex (males): treatment group (61.9%); control group (66.5%) • Exclusion criteria: active systemic or localized major infection; chronic antiarrhythmic therapy for ventricular arrhythmia; other cardiac abnormality contraindicating general anaesthesia or surgery; history of malignant disease; investigational drug use in the previous 4 weeks; active gastrointestinal disorders interfering with drug absorption; planned use of antibody induction therapy at the time of transplantation; known hypersensitivity to any study drugs
Interventions	Treatment group • CsA: gradually decreased and eliminated over 4 to 6 weeks • High dose SRL trough levels: 20 to 30 ng/mL • Steroids Control group

RMR Study 2001 *(Continued)*

- CsA trough levels: 75 to 200 ng/mL
- Standard dose SRL: 2 mg/d adjusted to maintain trough levels > 5 ng/mL
- Steroids

Both groups

- SRL: 6 mg loading dose then 2 mg/d adjusted to maintain trough levels > 5 ng/mL
- CsA trough levels: 200 to 400 ng/mL (month 1), 150 to 300 ng/mL (until randomisation)
- Steroids: as per local protocol tapered to 5 to 10 mg/d by month 6

Outcomes	- Graft survival at 12, 24 and 36 months - SCr - BPAR - Patient survival - PTLD - Infection
Notes	Funding source: "This work was supported by a grant from Wyeth-Ayerst Research, Philadelphia, Pennsylvania"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data accounted for outcome reporting
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by Wyeth-Ayerst Research

Rossini 2007

Methods	- Study design: parallel RCT - Study duration: recruitment not reported - Duration of follow-up: 2 years
Participants	Setting: single centre

- Country: Italy
- Patients with biopsy-proven CAN and on treatment with CNI
- Number: treatment group (6); control group (6)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group
	- Rapamycin: regimen not reported
	Control group
	- CNI-based regimens: regimen not reported

Outcomes	- Kidney biopsy at 2 years: record vascular endothelial growth factor expression in the glomerulus, total glomerular area on morphometry - Urinary protein - SCr

Notes	- Abstract-only publication - Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Biopsy documented at 2 years for all 12 patients
Selective reporting (reporting bias)	High risk	All prespecified outcomes noted; no full text publication by 2017
Other bias	Unclear risk	Insufficient information to permit judgement

Russ 2003

Methods	- Study design: parallel RCT - Study duration: recruitment not reported

Russ 2003 *(Continued)*

	• Duration of follow-up: 6 months
Participants	• Setting: multicentre (7 centres) • Country: Australia • Adult recipients of a 1st or 2nd cadaveric or non–HLA identical living donor kidney graft • Number: treatment group (33); control group (31) • Mean age ± SD (years): treatment group (43.9 ± 12.1); control group (46.9 ± 12.2) • Sex (M/F): treatment group (20/13); control group (21/20) • Exclusion criteria: PRA > 50%; recipients of re-grafts who had lost their 1st graft from rejection within the 1st 6 months
Interventions	Treatment group • SRL trough levels: 10 to 20 ng/mL (to week 4), 10 to 15 ng/mL (weeks 5 to 12), 8 to 15 ng/mL (to 6 months) • TAC trough levels: 3 to 7 ng/mL Control group • SRL trough levels: 5 to 10 ng/mL • TAC trough levels: 10 to 15 ng/mL (to week 4), 8 to 12 ng/mL (to 6 months) Both groups • SRL within 48 h of transplant • Steroids
Outcomes	• Graft function • Incidence of rejection • Patient survival at 6 months • Graft survival at 6 months
Notes	• Part of a Global trial published separately • Funding source: Wyeth Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No further data reported after 6 months

Russ 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	6 month data was reported as specified in methods
Other bias	High risk	Funded by Wyeth

Salvadori 2007

Methods	• Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 12 months
Participants	• Setting: single centre • Country: Italy • Patients aged > 55 years • Number: treatment group (49); control group (58) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Reduced dose CsA C2 levels: 900 ng/mL (months 1 and 2), 800 ng/mL (months 3 to 6) Control group • Standard dose CsA C2 levels: 1500 ng/mL (month 1), tapered to 1000 ng/mL (by month 6), 800 ng/mL thereafter Both groups • Basiliximab induction • Steroids: stopped day 8 • EC-MPS: 2160 mg/d for 5 days, then 1440 mg/d thereafter
Outcomes	• Mean CrCl • Graft survival • Patient survival • Infection • BPAR
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	High risk	Prespecified outcomes reported; no full text publication by 2017
Other bias	Unclear risk	Insufficient information to permit judgement

Schaefer 2006

Methods	• Study design: parallel, 3-arm RCT (1:1:1) • Study duration: recruitment not reported • Duration of follow-up: 1 year
Participants	• Setting: single centre • Country: USA • Recipients of primary cadaver or non-HLA identical living donor kidney • Number: treatment group (41); control group (39) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria:
Interventions	Treatment group • SRL trough levels: 8 to 12 ng/mL • PRED • MMF: 2 g/d Control group • TAC trough levels: 8 to 12 ng/mL • PRED • MMF: 2 g/d Both groups • Thymoglobulin induction
Outcomes	• Graft survival • BPAR at 1 year • SCr at 3 months • Hyperlipidaemia
Notes	• Funding source: not reported

Schaefer 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	High risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Reported all outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

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Smak Gregoor 1999

Methods	- Study design: parallel, 3-arm RCT (1:1:1) - Study duration: transplanted January 1997 to January 1999, recruited 6 months later - Duration of follow-up: 15 years
Participants	- Setting: multicentre (3 centres) - Country: Netherlands - Patients randomised from a previous study of CsA sparing effect of MMF, were enrolled and randomised to this new study; stratified for donor type and number of ARs during 1st 6 months post-transplant - Number: group 1 (63); group 2 (76); group 3 (73) - Mean age, range (years): group 1 (52, 20 to 72); group 2 (52, 19 to 68); group 3 (51, 19 to 70) - Sex (M/F): group 1 (42/21); group 2 (52/24); group 3 (46/27) - Exclusion criteria: 2 or more AR episodes during the 1st 6 months after transplantation; biopsy-proven chronic vascular rejection; proteinuria > 3 g/d; unstable graft function
Interventions	**Group 1** - CsA withdrawal: dose reduce by 50% 2 weeks prior to cessation - PRED: increased dose to 0.15 mg/kg/d **Group 2** - CsA trough levels: 125 to 175 ng/mL - PRED: tapered to 0 mg in 10 weeks

Smak Gregoor 1999 *(Continued)*

Group 3

- CsA trough levels: 125 to 175 ng/mL
- PRED: dose not reported

All groups

- MMF: 2 g/d

Outcomes	• AR: most BPAR except for 2 in the CsA group • Chronic rejection • Graft failure • Death • SCr, CrCl • Infection • Malignancy
Notes	• Funding source: Roche Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not report- ed
Allocation concealment (selection bias)	Low risk	Used sealed envelopes with random numbers
Blinding of participants and personnel (perfor- mance bias) All outcomes	High risk	Open-label study
Blinding of outcome as- sessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data noted
Selective reporting (re- porting bias)	Low risk	Prespecified expected outcomes reported
Other bias	High risk	Funded by Roche Pharmaceuticals

SMART TX Study 2010

Methods	• Study design: parallel RCT, randomised 10 to 24 days post-transplant • Study duration: recruitment February 2005 to April 2007 • Duration of follow-up: 12 months
Participants	• Setting: multicentre (6 centres) • Country: Germany

SMART TX Study 2010 *(Continued)*

- Patients aged 8 and 65 years, scheduled to receive a single organ kidney transplant from a living or a deceased donor
- Number: treatment group (69); control group (71)
- Mean age ± SD (years): treatment group (47.0 ± 10.8); control group (47.1 ± 11.1)
- Sex (males): treatment group (65.2%); control group (70.4%)
- Exclusion criteria: current or historic PRA > 30%; positive cross-match; gastrointestinal disorder that might interfere with the ability to absorb oral medication; history of cancer, except successfully treated; receipt of a new investigational drug within the previous 3 months and a BMI > 32 kg/m^2; WCC ≥ 4000 mm^3; platelet count ≥100,000 mm^3; fasting triglycerides ≤ 4.6 mmol/L; fasting cholesterol ≤ 7.8 mmol/L

Interventions	Treatment group
	• SRL: 01 mg/kg (loading dose) then 2 to 4 mg/d; target trough level 8 to 12 ng/mL
	• CsA: reduced to 50% then eliminated by day 3
	• MMF: initially decreased to 1.5 g/d
	Control group
	• CsA trough levels: 150 to 200 ng/mL, then 100 to 150 ng/mL (month 4)
	• MMF: 2 g/d
	Both groups
	• ATG induction (modified after 1st 25 patients)
	• PRED: according to local protocol
	• CsA tough levels: 200 to 250 ng/mL (for 1st 2 to 3 weeks)
Outcomes	• BPAR
	• Graft survival
	• Patient survival
	• Treatment failure
	• Change in graft function
	• Infections
Notes	• Funding source: "This study was supported by Wyeth Pharma (Munster, Germany) and Fresenius Biotech (Munich, Germany)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A permuted block randomisation scheme was used to assign trial participants to one of the treatment groups
Allocation concealment (selection bias)	Low risk	Allocation concealment was secured by a centralized distribution of sequentially numbered, opaque, sealed envelopes, and a confirmatory randomisation fax to the clinical research organization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

SMART TX Study 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All possible outcomes reported as ITT
Selective reporting (reporting bias)	Low risk	Pre specified outcomes reported
Other bias	High risk	Funded by Wyeth and Fresenius

Spare-the-Nephron Study 2011

Methods	• Study design: parallel RCT • Study duration: recruitment August 2003 to November 2008 • Duration of follow-up: 2 years
Participants	• Setting: multicentre (35 centres) • Country: USA • Patients aged 18 to 75 years randomised 30 to 180 days post-transplant; deceased or living donor; maintained on MMF and CNI • Number: treatment group (); control group () • Mean age ± SD (years): treatment group (); control group () • Sex (M/F): treatment group (); control group () • Exclusion criteria: corticosteroid-resistant, BPAR; episode or treatment for AR < 90 days before randomisation; corticosteroid-sensitive AR episode < 30 days before randomisation; > 1 BPAR episode before enrolment; other organ transplants; SCr > 42.5 mg/dL and/or eGFR < 30 mL/min at randomisation; inability to provide urine specimens; allergy to cold iothalamate or iodine; If received SRL: not being treated with corticosteroids, or receiving MMF < 1 g twice daily; severe diarrhoea/other gastrointestinal disorders that might interfere with absorption; active peptic ulcer diseases; diabetic gastroenteropathy; active systemic infection requiring antibiotics; HIV; chronic active hepatitis B or C; malignancy in previous 5 years; Hb < 8 g/dL; WCC < 4000/mm^3; platelet count < 100,000/mm^3; total cholesterol > 300 mg/dL; triglycerides > 350 mg/dL; receiving dialysis at study entry; receiving experimental immunosuppressive agents or necessary treatment with AZA, methotrexate, CPA, EVL, or EC-MPS
Interventions	Treatment group • CNI withdrawal: withdrawn from CNI within 72 h or randomisation • SRL trough levels: 5 to 10 ng/mL Control group • CsA tough level: according to local protocol Both groups • Basiliximab induction • PRED: according to local protocol • MMF: 2 to 3 g/d
Outcomes	• Percent change in GFR 12 months post randomisation • BPAR • Graft loss • Proteinuria
Notes	• Funding source: "This study was sponsored by Roche"; "DP is an employee of Genentech"

Spare-the-Nephron Study 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks, numbers generated by study sponsor
Allocation concealment (selection bias)	Low risk	Accessed through interactive voice response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, ITT analysis
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funding by Roche

Stallone 2003

Methods	• Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 12 months
Participants	• Setting: single centre • Country: Italy • Consecutive kidney transplant recipients from cadaveric donors • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (40 ± 10); control group (47 ± 5) • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • CsA withdrawal • SRL trough levels: 10 to 15 ng/mL • PRED Control group • CsA trough levels: 150 to 250 ng/mL • SRL: 2 mg/d • PRED Both groups (to 3 months)

Stallone 2003 *(Continued)*

- PRED: 200 mg/d then tapered to 25 mg (day 8) and to 5 mg (month 6)
- CsA trough levels: 150 to 250 ng/mL
- SRL: 2 mg/d

Outcomes	• Graft biopsy at 12 months for chronic changes • Incidence of DGF • AR • Graft function • CrCl
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Insufficient information to permit judgement

Stallone 2004

Methods	• Study design: parallel RCT • Study duration: recruitment started January 2000 • Duration of follow-up: 1 years
Participants	• Setting: single centre • Country: Italy • Recipients of a suboptimal cadaveric kidney; > 45 years • Number: treatment group (42); control group (48) • Mean age ± SD (years): treatment group (50.4 ± 7.8).; control group (51.8 ± 6.3) • Sex (M/F): not reported • Exclusion criteria: unclear

Stallone 2004 *(Continued)*

Interventions	**Treatment group**
	• SRL trough levels: 6 to 10 ng/mL (to month 3), 10 to 15 ng/mL (from end of month 3)
	• CsA C2 levels: 600 to 800 ng/mL (to month 3), withdrawn at the end of month 3
	Control group
	• CsA C2 levels: 1200 to 1400 ng/mL
	Both groups
	• Basiliximab induction
	• PRED: 250 mg/d tapered to 25 mg (by day 8) and then to 5 mg (by month 2)
Outcomes	• Incidence and length of DGF
	• Long-term graft function of patients who experience DGF
	• SCr and CrCl
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Stegall 2003

Methods	• Study design: parallel RCT
	• Study duration: recruitment April 2001 to January 2004
	• Duration of follow-up: 36 months
Participants	• Setting: single centre
	• Country: USA

Stegall 2003 *(Continued)*

- Living and deceased donor kidney transplant recipients
- Number: treatment group (81); control group (84)
- Mean age, range (years): treatment group (50, 22 to 73); control group (48, 19 to 80)
- Sex (M/F): treatment group (45/36); control group (44/40)
- Exclusion criteria: multi-organ transplants; children; expected to receive a pancreas-after-kidney transplant; ABO-incompatible or positive crossmatch transplant; pre-transplant fasting serum cholesterol level > 350 mg/dL or fasting serum triglyceride level > 500 mg/dL; pre-transplant WCC < 3000/mm^3; 12 months after enrolment began, recipients with a BMI > 32 kg/m^2 were excluded because of a high incidence of wound complications in obese patients using the SRL protocol

Interventions	**Treatment group** • SRL: 10 mg/d initially for 2 days then 5 mg/d thereafter **Control group** • TAC trough levels: 10 to 12 ng/mL (month 1), 8 to 10 ng/mL (months 1 to 4), thereafter 6 to 8 ng/mL • MMF: 1.5 g/d • PRED: tapered to 5 mg by month 3 **Both groups** • ATG induction • PRED
Outcomes	• Patient survival • Graft survival • BPAR • Kidney function • Complications • Adverse events
Notes	• funding source: " This study was supported in part by research contracts from Wyeth Research, Philadelphia, PA, Genzyme Corporation, Cambridge, MA, and Roche Laboratories Inc., Nutley, NJ."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data, reported ITT

Stegall 2003 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported
Other bias	High risk	Funded by Wyeth, Genzyme, and Roche; high drop-out rate

Suwelack 2002

Methods	• Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 35 weeks
Participants	• Setting: single centre • Country: Germany • Patient at least 1 year post-transplant, with SCr < 4 mg/dL and a biopsy-confirmed diagnosis of CAN • Number: treatment group (18); control group (20) • Mean age ± SD (years): treatment group (47.9 ± 13.1); control group (22.90 ± 0.95) • Sex (M/F): treatment group (12/6); control group (16/4) • Exclusion criteria: received MMF or experienced an AR episode in the previous 6 months; diabetes; severe infections; malignancies; WCC < 3000/µL; Hb < 9 g/dL; gastrointestinal ulcers or other gastrointestinal conditions that could impair absorption of medication

Interventions	Treatment group
	
	• CNI withdrawal from week 4: dose reduced by 33% every 2 weeks until complete withdrawal
	• MMF
	• PRED
	
	Control group
	
	• CNI
	• MMF
	• PRED
	
	Both groups
	
	• CNI (weeks 1 to 3)
	  ○ CsA trough levels: 80 to 120 ng/mL
	  ○ TAC trough levels: 4 to 7 ng/mL
	• MMF

Outcomes	• Kidney function: slope of reciprocal SCr (dL/mg/month) at 8 months • Proteinuria • AR: BPAR and clinical rejection • Infection • Malignancy • Gastrointestinal disorders • BP • Number of antihypertensive medications required • Graft loss
Notes	• Funding source: "Funding for this study was provided by F. Hoffman-La Roche AG, Grenzach-Wyhlen, Germany"

Suwelack 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data noted
Selective reporting (reporting bias)	Low risk	Pre specified outcomes reported
Other bias	High risk	Funded by Hoffman-La Roche

SYMPHONY Study 2007

Methods	• Study design: parallel, 4-arm RCT (1:1:1:1)
	• Study duration: recruitment November 2002 to November 2004
	• Duration of follow-up: 12 months
Participants	• Setting: multicentre (83 centres)
	• Country: 15 countries (Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Germany, Greece, Israel, Mexico, Poland, Spain, Sweden, Turkey, UK)
	• Recipients of deceased or living donor kidneys were enrolled immediately post-transplant; 1st or 2nd transplant; aged 18 to 75 years
	• Number: group 1 (390); group 2 (399); group 3 (401); group 4 (399)
	• Mean age ± SD (years): group 1 (45.9 ± 13.8); group 2 (47.2 ± 13.5); group 3 (45.4 ± 14.7); group 4 (44.9 ± 14.5)
	• Sex (males): group 1 (62.3%); group 2 (66.4%); group 3 (65.8%); group 4 (66.7%)
	• Exclusion criteria: need for treatment with AZA, methotrexate or CPA, polyclonal or monoclonal anti-lymphocyte antibodies, basiliximab, or any investigational drug; current or historic PRA > 20%; positive cross-match; a cold ischaemia time > 30 hours for the allograft; receipt of an allograft from a deceased donor without a heartbeat; a gastrointestinal disorder that might interfere with the ability to absorb oral medication; a history of cancer; active peptic ulcer; evidence of active liver disease; severe anaemia, leukopenia, or thrombocytopenia; the receipt of a new investigational drug within the previous 3 months; and previous treatment with daclizumab or basiliximab
Interventions	Group 1
	• Standard dose CsA trough levels: 150 to 300 ng/mL (to month 3), thereafter 100 to 200 ng/mL

SYMPHONY Study 2007 *(Continued)*

Group 2

- Low dose CsA trough levels: 50 to 100 ng/mL throughout the study
- Daclizumab: 2 mg/kg within 24 h prior to transplant; 1 mg/kg every 2 weeks (up to 2 months)

Group 3

- Low dose TAC trough levels: 3 to 7 ng/mL throughout the study
- Daclizumab: 2 mg/kg within 24 h prior to transplant; 1 mg/kg every 2 weeks (up to 2 months)

Group 4

- Low dose SRL trough levels: 4 to 8 ng/mL throughout the study
- Daclizumab: 2 mg/kg within 24 h prior to transplant; 1 mg/kg every 2 weeks (up to 2 months)

All groups

- MMF: 2 g/d
- PRED: as per local protocol

Outcomes	- Graft loss - Death - eGFR - AR - Malignancy - Opportunistic infections
Notes	- Funding source: "Funding for the study was provided by Hoffmann–La Roche, which had advisory input into the study design, collected the data, monitored the conduct of the study, performed the statistical analyses, and coordinated the writing of the manuscript with all authors"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study was described as randomised and stratified, "A minimization algorithm was used to optimize the balance of characteristics of patients in study groups, overall and across the strata."
Allocation concealment (selection bias)	Low risk	Central randomisation, voice interactive allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes that are of interest reported
Other bias	High risk	Funded by Hoffmann-La Roche

Takahashi 2013a

Methods	• Study design: parallel RCT • Study duration: recruitment February 2008 to August 2010 • Duration of follow-up: 12 months
Participants	• Setting: multicentre • Country: Japan • Patients aged 18 to 65 years undergoing primary kidney transplantation • Number: treatment group (61); control group (61) • Mean age ± SD (years): treatment group (42.5 ± 14.13); control group (38.6 ± 11.36) • Sex (M/F): treatment group (46/15); control group (37/24) • Exclusion criteria: no evidence of graft function within 24 hours of transplantation; cold ischaemia time > 24 h; donor age > 65 years; patients of multiorgan, ABO-incompatible, positive T-cell cross-match or HLA identical living-related-donor transplants; PRA > 20%
Interventions	Treatment group • CsA trough levels: 100 to 200 ng/mL (months 0 to 2), 75 to 150 ng/mL (months 2 and 3), 50 to 100 ng/mL (months 4 and 5), 25 to 50 ng/mL thereafter • EVL trough levels: 3 to 8 ng/mL (from day 5) Control group • CsA trough levels: 200 to 300 ng/mL (months 0 to 2), 100 to 250 ng/mL thereafter • MMF: 2 g/d Both groups • Basiliximab induction • PRED: as per local protocol, minimum dose of 5 mg/d at 12 months
Outcomes	• Efficacy failure: defined as the composite of treated BPAR, graft loss, death or loss to follow-up at 12 months • Composite of graft loss, death or long-term follow-up at 12 months
Notes	• Funding source: "This study was supported by Novartis Pharma K.K. Japan. The authors thank Heike Schwende, PhD, Novartis Pharma AG Switzerland, for organizing the development of the manuscript. They also thank Swati Machwe, PhD, and Raghuraj Puthige, PhD, Novartis Healthcare Pvt. Ltd India for editorial assistance."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent validated system that automated the random assignment of treatment arms
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	Unclear risk	Most outcomes were objective, however there was no blinding of assessment

Takahashi 2013a *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis all patients analysed
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported
Other bias	High risk	Funded by Novartis who also helped in manuscript development

Tedesco-Silva 2010

Methods	• Study design: parallel, 3-arm RCT (1:1:1) • Study duration: recruitment not reported • Duration of follow-up: 24 months
Participants	• Setting: multicentre • Country: Europe, Australia, Singapore, New Zealand, Taiwan, USA, S Africa, Hong Kong, Argentina • Patients aged 18 to 70 years receiving 1st kidney • Number: group 1 (277); group 2 (279); group 2 (277) • Mean age ± SD (years): group 1 (45.7 ± 12.7); group 2 (45.3 ± 13.4); group 2 (47.2 ± 12.7) • Sex (M/F): group 1 (177/100); group 2 (191/88); group 2 (189/88) • Exclusion criteria: kidneys donated after cardiac death or with a cold ischaemia time > 40 h; donor age > 65 years; recipients of a previous organ/tissue transplant or of multiorgan, ABO incompatible, positive T-cell crossmatch, or HLA-identical living related-donor transplants;m ost recent PRA > 20%
Interventions	**Group 1** • EVL: 1.5 mg, trough levels 3 to 8 ng/mL • Low dose CsA trough levels: 25 to 50 ng//mL (6 to 24 months) **Group 2** • EVL: 3 mg, trough levels 6 to 12 ng/mL • Low dose CsA trough levels: 25 to 50 ng//mL (6 to 24 months) **Group 3** • MPA: 1.44 g/d • Standard dose CsA trough levels: 100 to 250 ng//mL (6 to 24 months) **All groups** • Basiliximab induction • PRED
Outcomes	• Composite efficacy failure: BPAR, graft loss, death, kidney function at 12 months
Notes	• Funding source: "This study was funded by Novartis Pharma AG (Basel, Switzerland). Novartis was involved in the design and conduct of the study and provided logistical support during the trial. The statistical analyses were performed by Novartis. The article was prepared by the authors with assistance from Caroline Barnett of Real Science Communications, which was funded by Novartis. Novartis was permitted to review the article and suggest changes, but the final decision on content was exclusively retained by the authors"

Tedesco-Silva 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were assigned a randomisation number but procedure not clarified which was linked to one of the three treatment groups, using an interactive voice-response system. The randomisation scheme was reviewed and approved by the Biostatistics Quality Assurance Group.
Allocation concealment (selection bias)	Low risk	Patient allocation was based on an interactive voice-response system centrally
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data outcome despite high drop-out rates due to ITT analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Novartis; high drop-out rates

Velosa-212 Study 2001

Methods	• Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 1 year
Participants	• Setting: multicentre (17 centres) • Country: Europe and USA • Patients with had good kidney function post operatively • Number: treatment group (100); control group (97) • Mean age ± SD (years): treatment group (45.2 ± 11.6); control group (44.9 ± 12.9) • Sex (M/F): treatment group (58/42); control group (55/42) • Exclusion criteria: evidence of systemic infection before SRL administration; chronic antiarrhythmic therapy for ventricular arrhythmia, or other cardiac abnormality contraindicating general anaesthesia or surgery; history of malignancy within 10 years of enrolment in the study; use of any investigational drug within 4 weeks of SRL administration; current use of immunosuppressive agents, except for low-dose corticosteroids for underlying conditions
Interventions	**Treatment group** • Low-dose/withdrawn of CsA trough levels: 100 to 175 ng/mL (month 1), 100 to 150 ng/mL (month 2); CsA withdrawn if stable kidney function, no AR in previous 3 weeks and SRL levels 10 to 20 ng/mL. 25% dose reduction over 4 weeks • SRL: 20 mg/d (days 1 to 3), 10 mg/d (days 4 to 9), then trough levels 10 to 20 ng/mL (day 10 to month 12)

Velosa-212 Study 2001 *(Continued)*

Control group

- Standard dose CsA trough levels: 200 to 400 ng/mL (month 1), 200 to 250 ng/mL (month 3), 150 to 250 ng/mL (months 4 to 12)
- Fixed dosed SRL: 6 mg loading dose then 2 mg/d

Both groups

- PRED

Outcomes	- AR - GFR - patient survival - Graft survival - Hypertension
Notes	- Funding source: "This work was supported by a grant from Wyeth Research, Collegeville, PA."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	One of the randomised groups did not receive the drug and were in a 3rd group
Other bias	High risk	Funded by Wyeth. Patients with ATN-DGF that resolved later than post-transplantation day 7 were not randomised but were assigned to a 3rd group (non-randomised)

Watson 2005

Methods	- Study design: parallel RCT - Study duration: recruitment May 2002 to January 2004 - Duration of follow-up: 12 months
Participants	- Setting: single centre - Country: UK

Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients (Review)

Watson 2005 *(Continued)*

- Patients with sub-optimal kidney function (SCr between 120 and 400 µmol/L); transplanted between 6 months and 8 years; receiving CNI-based treatment
- Number: treatment group (19); control group (19)
- Mean age ± SD (years): treatment group (46.6 ± 9.9); control group (48.2 ± 10.5)
- Sex (M/F): treatment group (13/6); control group (18/1)
- Exclusion criteria: allergies to macrolide antibiotics; patients experiencing an AR episode within the preceding 2 months; histological evidence of recurrent kidney disease; presence of a non-kidney transplant; untreated symptomatic hyperuricaemia; untreated hypercholesterolaemia or hypertriglyceridaemia; malignancy within the preceding 5 years

Interventions	**Treatment group** • CNI abrupt withdrawal: last dose the evening before SRL conversion • SRL conversion: 8 mg on 1st day and 4 mg on 2nd day; adjusted to trough levels of 5 to 15 ng/mL on days 4, 7 and 14 post conversion **Control group** • CNI: therapy continued **Both groups** • PRED • AZA • MMF
Outcomes	• GFR at 12 months • SCr • Uric acid • Hypercholesterolaemia • Hypertension treatment • Number of AR episodes • Dialysis requirement • Mean 24 h BP
Notes	• Funding source: "This study was supported by Wyeth Laboratories, Taplow, Maidenhead, U.K."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Determined by random numbers generated by a Microsoft Excel Software program
Allocation concealment (selection bias)	Low risk	Sealed envelopes but concealed from the members who were involved in the enrolment of the participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded to clinicians
Incomplete outcome data (attrition bias)	Low risk	ITT analysis complete reporting

Watson 2005 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Wyeth

ZEUS Study 2011

Methods	• Study design: parallel RCT • Study duration: recruitment June 2005 to September 2007 • Duration of follow-up: 5 years
Participants	• Setting: multicentre (32 centres) • Country: Germany and Switzerland • Patients who received de novo kidney transplant aged 18 to 65 years; at 4.5 months post-transplant patients had to have no graft loss, dialysis dependency, or death; maintained on an immunosuppressive regimen with EC-MPS (≥ 720 mg/d), CsA, and corticosteroids; SCr < 265·2 µmol/L; proteinuria of no more than 1 g/d; no previous changes to immunosuppressive regimen due to immunological reasons; no rejections of Banff grade 2 or greater, no recurrent or steroid-resistant AR; counts of leucocytes of at least 2500/µL, neutrophils of at least 1500/µL, platelets of at least 75 000/µL, Hb of at least 60 g/L; no evidence of severe liver disease, intractable immunosuppressant side-effects, or infections • Number: treatment group (155); control group (145) • Mean age ± SD (years): treatment group (46.9 ± 11.7); control group (46.7 ± 11.9) • Sex (M/F): treatment group (102/53); control group (86/49) • Exclusion criteria: 2nd transplant who previously had immunological graft loss within 1 year; recipients of multiple organ transplants or an organ donated after cardiac death; donors < 5 years or > 65 years; recipients of A-B-O-incompatible transplants; a previous peak PRA > 25%; antibodies against the HLA of the donor organ
Interventions	Treatment group • EVL: started at month 4.5 1.5 g/d; target trough level 3 to 7 ng/mL (step 1) and 6 to 10 ng/mL thereafter • CsA withdrawal: stepwise over 4 weeks (50%, 25%, 0%) Control group • CsA trough levels: 120 to 180 ng/mL (months 4.5 to 6), thereafter 100 to 150 ng/mL Both groups • CsA trough levels (to month 4.5): 150 to 220 ng/mL • PRED as per local protocol
Outcomes	• GFR at 12 months • BPAR • Graft loss • Death • Evolution of between 4.5 to 12 months and safety
Notes	• Funding source: "This study was funded by Novartis Pharma...Tim Mitchell and Caroline Barnett from Real Science Communications provided medical writing support on behalf of Novartis"

Risk of bias

ZEUS Study 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned in a 1:1 ratio by use of a central, validated system that automated the random assignment of treatment groups to randomisation numbers (stratified according to living-donor or deceased donor status)
Allocation concealment (selection bias)	Low risk	Central automated random assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported and missing data accounted
Selective reporting (reporting bias)	Low risk	prespecified variables reported
Other bias	High risk	Funded by Novartis

ACEi - angiotensin-converting enzyme inhibitor; ACR - albumin:creatinine ratio; ALG - antilymphocyte globulin; ATG - antithymocyte globulin; ATN - acute tubular necrosis; AR - acute rejection; ARB - angiotensin II receptor blocker; AUC - area under the curve; AZA - azathioprine; BMI - body mass index; BP blood pressure; BPAR - biopsy-proven acute rejection; BPM - beats per minute; C2 - drug concentration 2 hours post ingestion; CAN - chronic allograft nephropathy; CMV - cytomegalovirus; CNI - calcineurin inhibitor; CrCl - creatinine clearance; CsA - cyclosporin A; CPA - cyclophosphamide; DGF - delayed graft function; ECG - electrocardiogram; EC-MPS - encapsulated mycophenolate sodium; ESKD - end-stage kidney disease; EVL - everolimus; FSGS - focal segmental glomerulosclerosis; (e or m)GFR - (estimated or measured) glomerular filtration rate; Hb - haemoglobin; HBV - hepatitis B virus; HCV - hepatitis C virus; HIV - human immunodeficiency virus; HLA - human leukocyte antigen; IL2RA - interleukin 2 receptor antagonist; ITT - intention-to-treat; M/F - male/female; MMF - mycophenolate mofetil; MPS - mycophenolate sodium; MMF - mycophenolate mofetil; MPA - mycophenolic acid; mTOR-I - mammalian target of rapamycin inhibitors; NODAT - new-onset diabetes after transplantation; PRA - panel reactive antibodies; PRED - prednisone/prednisolone; PTLD - post-transplant lymphoproliferative disease; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; SRL - sirolimus; TAC - tacrolimus; Treg - regulatory T cells; WCC - white cell count

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abouna 1991	Wrong intervention: abrupt CNI withdrawal compared to slow withdrawal, no standard dose CNI comparison group
Alexander 2006	Wrong intervention: determined if steroids can be eliminated with early discontinuation of CsA and later discontinuation of MMF
Alpay 2013	Wrong outcomes: study outcomes were effects of switch from CNI to EVL on serum/urinary markers of fibrosis (TGF-beta), inflammation, glomerular and tubular injury. the follow-up data was at 3 months of conversion
Artz 2002	Wrong intervention: conversion from CsA to TAC

Study	Reason for exclusion
Asberg 2013	Wrong intervention: CNI withdrawal versus mycophenolate withdrawal
Baboolal 2003	Wrong intervention: CsA elimination versus withdrawal, no standard dose
Baboolal 2004	Wrong intervention: CsA elimination versus withdrawal, no standard dose
Baxter 1982	Other: abstract more than 30 years old; no full text publication
Brady 1990	Wrong intervention: low dose CNI pre-operatively
Burkhalter 2012	Wrong intervention: low dose CNI versus CNI withdrawal, no standard dose comparison
CAMPASIA Study 2005	Wrong intervention: Intervention also included steroid withdrawal
Cattaneo 2005	Wrong intervention: low dose SRL versus low dose CsA; part of a study to evaluate campath and MMF
Chapman 1985	Wrong intervention: CsA withdrawal compared to avoidance, no continuation arm
CIS Trial 2014	Wrong intervention: randomised to either trough CsA monitoring or by residual NFAT-regulated gene expression
CONCERTO Study 2005	Wrong intervention: evaluated C2 monitoring in the context of a quadruple immunosuppressive regimen and planned to assess the efficacy and safety of two C2 targets for patients 3 to 6 months post-transplantation. However, because differences between the groups post-month 2 were not discernible; the secondary endpoints were highlighted as combined outcome
David-Neto 2001	Wrong intervention: compared low versus high dose CsA in presence and absence of antibody induction
de Sandes Freitas 2011	Wrong intervention: steroid withdrawal versus CNI withdrawal
de Sevaux 1998	Wrong intervention: CNI + AZA converted to CNI + PRED
EVEREST Study 2009	Wrong intervention: both arms included low dose CsA, no standard dose arm
Flechner 2004	Wrong intervention: compared 2 doses of MMF
Fleming 2016	Wrong intervention: compared mTOR-I based CNI withdrawal with CNI minimisation, no standard dose CNI for comparison
Forwell 1986	Wrong intervention: compared normal CsA dose with historical controls on azathioprine
Fries 1988	Wrong intervention: CsA with AZA regimen was compared with CsA, antilymphocyte antibody and steroids
Fries 1988a	Wrong intervention: CsA with AZA regimen was compared with CsA, antilymphocyte antibody and steroids
Fruchaud 1996	Wrong intervention: CNI based immunosuppression with and without antilymphocyte antibody compared
Gaber 2003	Wrong intervention: compared CNI sparing with withdrawal
Gelens 2006	Wrong intervention: TAC and SRL versus TAC and SRL versus SRL and MMF intervention

Study	Reason for exclusion
Ghafari 2007	Wrong intervention: compared standard versus high dose which was tapered to standard dose at 3 months, not relevant to this review
Gotti 2003	Wrong population: CNI versus steroid tapering based on biopsy
Griffin 1993	Wrong intervention: Timing of CNI
Grino 1991	Wrong intervention: compared 2 induction regimens (OKT3 and ALG)
Hamdy 2005	Wrong intervention: did not compare low dose/withdrawal to standard dose regimen
Hariran 2015	Other: conversion of TAC based regimen to SRL in DGF; 6/15 randomised patients shifted back to TAC
Henny 1986	Wrong intervention: Study compared very high dose of CsA in the arm with high dose had CsA withdrawal
Hernandez 2007	Wrong intervention: low dose CNI with MMF and normal dose with AZA
Hiesse 1991	Wrong Intervention: multivariate analysis of various doses
Hilbrands 1993	Wrong intervention: CNI versus steroid withdrawal
Hourmant 1987	Wrong intervention: delayed introduction of CNI with monoclonal antibodies
Hricik 1990	Wrong intervention: low dose CNI versus withdrawal, no standard dose comparison
Infante 2008	Wrong intervention: compared withdrawal with low dose CNI, no standard comparison group
Jain 2001	Wrong intervention: no standard CsA group comparison, both arms were low dose
Jindal 2002	Wrong intervention: compared CNI elimination and withdrawal, no standard dose comparison
John 1999	Wrong outcome: compared high and low dose CsA with single outcome (lipid profile)
Kamar 2012	Wrong intervention: compared different doses of MMF
Kandaswamy 2005	Wrong intervention: multiple comparisons not relevant to this review; compared CsA + MMF with high and low dose TAC with variable SRL
Keitel 1999	Wrong intervention: compared early versus late CNI withdrawal, no standard dose comparison
Kovarik 2001	Wrong intervention: early versus delayed CsA
Kovarik 2003	Wrong intervention: compared early versus delayed introduction of CNI
Kovarik-2306 2004	Wrong intervention: did not include standard dose
Liu 2002a	Wrong intervention: compared CNI reduction versus withdrawal with mTOR-I, no standard dose comparison
Liu 2007b	Wrong intervention: compared CNI reduction versus withdrawal with mTOR-I, no standard dose comparison

Study	Reason for exclusion
Maiorano 2006	Wrong intervention: compared CsA reduction with CsA withdrawal and SRL, no standard dose comparison
McGrath 2001	Wrong intervention: CsA withdrawal and substitution with another CNI (TAC) versus mycophenolate
McMaster 1983	Wrong intervention: CsA use alone in one arm
Meier 2006	Wrong intervention: compared two different CNIs (TAC and CsA)
Messa 2009	Wrong outcome: evaluated Treg changes between the SRL and TAC group, not relevant outcomes noted for this review
Metcalfe 2002	Wrong intervention: compared MMF and AZA
Miserlis 2008	Wrong intervention: variable co-intervention (MMF and EVL)
Mourad 2004a	Wrong intervention: Simulect versus ATG
Mourad 2005	Wrong intervention: early versus late introduction of CNI
Mourer 2012	Wrong intervention: mycophenolate withdrawal versus CNI withdrawal
Noris 2007	Wrong intervention: compared low dose SRL with low dose CNI does not satisfy inclusion criteria of this review
Novoa 2011	Wrong intervention: standard dose CNI not part of comparison
OPTIMA-TX Study 2008	Wrong outcomes: reported CsA versus TAC, not relevant to this review
Pankewycz 2011	Wrong intervention: primary intervention to study low dose ATG irrespective of maintenance immunosuppression and included low dose SRL and low dose TAC, no standard dose TAC for comparison
Ponticelli 1988	Wrong intervention: double therapy compared to 3 drug CNI regimen
Rahamimov 2008	Other: incomplete study, stopped prematurely
Ritz 1998	Wrong intervention: CsA was withdrawn with ATG support and reintroduced within a week immediate transplant for ATN
Saunders 2003	Wrong intervention: CNI dose reduction in both arms
SOCRATES Study 2014	Wrong intervention: CNI withdrawal versus steroid withdrawal
Westhoff 1995	Other: study discontinued before conclusion
Wu 2007d	Wrong population: randomisation only if GFR < 40 mL/min

ALG - antilymphocyte globulin; ATG - antithymocyte globulin; ATN - acute tubular necrosis; AZA - azathioprine; CNI - calcineurin inhibitor; CsA - cyclosporin A; C2 - drug dose levels 2 hours after ingestion; EVL - everolimus; GFR - glomerular filtration rate: MMF - mycophenolate mofetil; mTOR - mammalian target of rapamycin; NFAT - nuclear factor of activated T-cells; SRL - sirolimus; TAC - tacrolimus; TGF - transforming growth factor; Treg - regulatory T cells

Characteristics of ongoing studies *[ordered by study ID]*

David-Neto 2014

Trial name or title	A randomized, prospective study comparing everolimus/low tacrolimus with regular tacrolimus/ MPS for the elderly renal transplant recipients
Methods	• Parallel RCT
Participants	• Elderly patients referred for kidney transplantation; 1 month post-transplant
Interventions	Treatment group • Low TAC trough levels: 2 to 4 ng/mL • EVL trough levels: 3 to 8 ng/mL Control group • Regular TAC trough levels: 5 to12 ng/mL • MPS Both groups • Steroids • ATG induction therapy: single dose 2 mg/kg
Outcomes	• AR • DM • Infection • BK virus • CMV infection
Starting date	36 patients have been evaluated of the total 90 planned
Contact information	David-Neto, E
Notes	

ERIC Study 2010

Trial name or title	An appraisal on the convenience of early everolimus introduction and calcineurin inhibitor withdrawal in Kidney recipients: THE ERIC STUDY
Methods	• Multicentre, parallel RCT
Participants	• Kidney transplant recipients treated for the 1st 3 months with TAC, MPS and steroids
Interventions	Treatment group • TAC withdrawal • EVL Control group • TAC • MPS • PRED

ERIC Study 2010 *(Continued)*

Outcomes	• Kidney function eGFR at 12 months • Protocol biopsies were scheduled at 3 months (pre-randomisation) and 27 months • Graft survival • Proteinuria • AR
Starting date	July 2010
Contact information	JC Ruiz
Notes	

ISRCTN63298320

Trial name or title	A prospective randomised trial of the use of cellcept to allow early tacrolimus withdrawal in live donor kidney transplantation
Methods	• Parallel RCT
Participants	• Patients needing kidney transplants
Interventions	• No interventions provided
Outcomes	• Not provided at time of registration
Starting date	01/01/2002
Contact information	M Nicholson, University Hospitals of Leicester c/o Research and Development Office Leicester General Hospital NHS Trust LE1 4PW, Leicester, UK
Notes	Recruitment dates 1/1/2002 to 1/6/2003 - not study results published by February 2017

TRANSFORM Study 2013

Trial name or title	Advancing renal **TRANS**plant e**F**ficacy and safety **O**utcomes with an eve**R**olimus-based regi**M**en (TRANSFORM)
Methods	Multicentre, open-label RCT
Participants	Recipient of a primary (or secondary, if 1st graft is not lost due to immunological reasons) kidney transplant from a deceased heart beating, living-unrelated, living-related non-HLA identical or an expanded criteria donor. Randomised within 24 h of completion of transplant surgery
Interventions	Treatment group • EVL trough level: 3 to 8 ng/mL • Reduced exposure to CNI (CsA or TAC) Control group • MPS or MMF • Standard exposure to CNI (CsA or TAC)

TRANSFORM Study 2013 *(Continued)*

Outcomes	• Incidence of failure on the composite of treated BPAR or eGFR < 50 mL/min/1.73 m^2
	• Incidence of failure on the composite of BPAR, graft loss or death
	• Kidney function: eGFR
	• CMV
	• BK virus
	• NODAT
	• CKD with associated proteinuria
	• CNI-associated adverse events
Starting date	December 2013
Contact information	Novartis Pharmaceuticals
Notes	

AR - acute rejection; ATG - antithymocyte globulin; BPAR - biopsy-proven acute rejection; CKD - chronic kidney disease; CMV - cytomegalovirus; CNI - calcineurin inhibitor; CsA - cyclosporin A; DM - diabetes mellitus; EVL - everolimus; (e)GFR - (estimated) glomerular filtration rate; MMF - mycophenolate mofetil; MPS - mycophenolate sodium; NODAT - new onset diabetes after transplantation; PRED - prednisone/prednisolone; RCT - randomised controlled trial; TAC - tacrolimus

DATA AND ANALYSES

Comparison 1. CNI withdrawal versus standard dose CNI

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death	14	2010	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.93, 1.54]
1.1 Avoidance	4	566	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.85, 2.01]
1.2 Late withdrawal	10	1444	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.83, 1.56]
2 Acute rejection	15	1666	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.56, 4.12]
2.1 Unspecified	7	1066	Risk Ratio (M-H, Random, 95% CI)	1.72 [1.08, 2.75]
2.2 Biopsy-proven	8	600	Risk Ratio (M-H, Random, 95% CI)	4.48 [2.10, 9.55]
3 GFR	8	910	Mean Difference (IV, Random, 95% CI)	3.56 [-1.13, 8.25]
3.1 One year	5	653	Mean Difference (IV, Random, 95% CI)	-0.22 [-5.38, 4.94]
3.2 Two years	1	108	Mean Difference (IV, Random, 95% CI)	7.90 [1.43, 14.37]
3.3 Over 5 years	2	149	Mean Difference (IV, Random, 95% CI)	11.09 [4.81, 17.37]
4 Graft loss	16	2090	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.98]
5 Serum creatinine	4	189	Mean Difference (IV, Random, 95% CI)	19.17 [5.89, 32.44]
5.1 Six months	1	24	Mean Difference (IV, Random, 95% CI)	31.78 [10.58, 52.98]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
5.2 One year	3	165	Mean Difference (IV, Random, 95% CI)	11.04 [-5.99, 28.06]
6 Adverse events	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Hypertension	5	950	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.95]
6.2 Hyperlipidaemia	3	562	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.63, 1.21]
6.3 CMV infection	7	608	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.52, 1.45]
6.4 Diabetes	6	810	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.62, 1.42]
6.5 Malignancy	6	1079	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.93, 1.30]
6.6 Infection	6	724	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.51]
7 Subgroup analysis: acute rejection	15	1666	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.56, 4.12]
7.1 Avoidance	3	238	Risk Ratio (M-H, Random, 95% CI)	2.16 [0.85, 5.49]
7.2 Late withdrawal	12	1428	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.59, 6.48]
8 Subgroup analysis: GFR	8	910	Mean Difference (IV, Random, 95% CI)	3.56 [-1.13, 8.25]
8.1 Avoidance	3	242	Mean Difference (IV, Random, 95% CI)	-2.22 [-14.84, 10.40]
8.2 Late withdrawal	5	668	Mean Difference (IV, Random, 95% CI)	5.54 [1.66, 9.43]
9 Subgroup analysis: graft loss	16	2414	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 0.99]
9.1 Avoidance	4	566	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.16]
9.2 Late withdrawal	13	1848	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.97]

Analysis 1.1.   Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 1 Death.

Study or subgroup	CNI withdrawal	CNI standard dose	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.1.1 Avoidance					
Grimbert 2002	1/58	1/59		0.82%	1.02[0.06,16.66]
Asberg 2006	1/27	2/27		1.05%	0.48[0.04,5.64]
Garcia 2007	2/33	1/38		1.06%	2.39[0.21,27.59]
Hall 1988	103/158	97/166		31.5%	1.33[0.85,2.09]
Subtotal (95% CI)	**276**	**290**		**34.43%**	**1.31[0.85,2.01]**
Total events: 107 (CNI withdrawal), 101 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=0.9, df=3(P=0.82); I²=0%					

Favours CNI withdrawal 0.01 0.1 1 10 100 Favours standard dose CNI

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Study or subgroup	CNI withdrawal	CNI stan-dard dose	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=1.22(P=0.22)					
1.1.2 Late withdrawal					
Pascual 2008	0/20	0/20			Not estimable
Hazzan 2005	0/54	0/54			Not estimable
Dudley 2005	3/73	0/70		0.72%	7[0.36,138.02]
Isoniemi 1990	3/32	4/32		2.54%	0.72[0.15,3.53]
Abramowicz 2002	5/74	4/77		3.47%	1.32[0.34,5.13]
CAESAR Study 2007	8/179	5/173		4.93%	1.57[0.5,4.9]
Pedersen 1991	9/51	6/55		5.15%	1.75[0.58,5.32]
Hollander 1995	27/60	29/68		13.02%	1.1[0.55,2.22]
Smak Gregoor 1999	31/63	31/73		13.88%	1.31[0.67,2.58]
MacPhee 1998	42/102	51/114		21.85%	0.86[0.5,1.48]
Subtotal (95% CI)	**708**	**736**		**65.57%**	**1.14[0.83,1.56]**
Total events: 128 (CNI withdrawal), 130 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=3.85, df=7(P=0.8); I²=0%					
Test for overall effect: Z=0.82(P=0.42)					
Total (95% CI)	**984**	**1026**		**100%**	**1.19[0.93,1.54]**
Total events: 235 (CNI withdrawal), 231 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=5.01, df=11(P=0.93); I²=0%					
Test for overall effect: Z=1.37(P=0.17)					
Test for subgroup differences: Chi²=0.26, df=1 (P=0.61), I²=0%					

Favours CNI withdrawal 0.01 0.1 1 10 100 Favours standard dose CNI

Analysis 1.2. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 2 Acute rejection.

Study or subgroup	CNI withdrawal	CNI stan-dard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.2.1 Unspecified					
Pascual 2008	4/20	0/20		2.45%	9[0.52,156.91]
Abramowicz 2002	7/74	1/77		4.11%	7.28[0.92,57.77]
Smak Gregoor 1999	17/63	1/73		4.37%	19.7[2.7,143.88]
Asberg 2006	19/27	8/27		12.94%	2.38[1.26,4.46]
MacPhee 1998	16/102	17/114		12.96%	1.05[0.56,1.97]
Grimbert 2002	32/58	31/59		15.35%	1.05[0.75,1.47]
CAESAR Study 2007	68/179	48/173		15.55%	1.37[1.01,1.86]
Subtotal (95% CI)	**523**	**543**		**67.74%**	**1.72[1.08,2.75]**
Total events: 163 (CNI withdrawal), 106 (CNI standard dose)					
Heterogeneity: Tau²=0.2; Chi²=19, df=6(P=0); I²=68.43%					
Test for overall effect: Z=2.28(P=0.02)					
1.2.2 Biopsy-proven					
Dudley 2005	0/73	0/70			Not estimable
Suwelack 2002	0/18	0/20			Not estimable
CTOT-09 Study 2015	4/14	0/7		2.55%	4.8[0.29,78.38]
Heering 1993	11/18	0/17		2.6%	21.79[1.38,343.26]
Isoniemi 1990	12/28	1/32		4.41%	13.71[1.9,98.93]

Less with CNI withdrawal 0.002 0.1 1 10 500 Less with standard dose CNI

Study or subgroup	CNI withdrawal	CNI stan-dard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Hollander 1995	3/60	3/68		6.09%	1.13[0.24,5.41]
Hazzan 2005	10/54	3/54		7.99%	3.33[0.97,11.45]
Garcia 2007	15/31	3/36		8.62%	5.81[1.85,18.21]
Subtotal (95% CI)	**296**	**304**		**32.26%**	**4.48[2.1,9.55]**
Total events: 55 (CNI withdrawal), 10 (CNI standard dose)					
Heterogeneity: Tau²=0.17; Chi²=6.2, df=5(P=0.29); I²=19.4%					
Test for overall effect: Z=3.88(P=0)					
Total (95% CI)	**819**	**847**		**100%**	**2.54[1.56,4.12]**
Total events: 218 (CNI withdrawal), 116 (CNI standard dose)					
Heterogeneity: Tau²=0.37; Chi²=40.45, df=12(P<0.0001); I²=70.34%					
Test for overall effect: Z=3.77(P=0)					
Test for subgroup differences: Chi²=4.41, df=1 (P=0.04), I²=77.34%					

Less with CNI withdrawal   0.002   0.1   1   10   500   Less with standard dose CNI

Analysis 1.3. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 3 GFR.

Study or subgroup	CNI withdrawal		CNI standard dose		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.3.1 One year							
Asberg 2006	27	52 (20)	27	69 (29)		7.63%	-17[-30.29,-3.71]
CAESAR Study 2007	179	51 (43)	173	49 (26)		13.23%	2[-5.4,9.4]
Pascual 2008	20	72.1 (11.6)	20	68 (12.1)		13.28%	4.1[-3.25,11.45]
Garcia 2007	33	56.9 (16.4)	38	58.9 (14)		13.52%	-2[-9.15,5.15]
Smak Gregoor 1999	63	66 (17)	73	63 (19)		14.84%	3[-3.05,9.05]
Subtotal ***	**322**		**331**			**62.49%**	**-0.22[-5.38,4.94]**
Heterogeneity: Tau²=18.4; Chi²=8.86, df=4(P=0.06); I²=54.85%							
Test for overall effect: Z=0.08(P=0.93)							
1.3.2 Two years							
Hazzan 2005	54	45.6 (21.6)	54	37.7 (11)		14.34%	7.9[1.43,14.37]
Subtotal ***	**54**		**54**			**14.34%**	**7.9[1.43,14.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.39(P=0.02)							
1.3.3 Over 5 years							
Hollander 1995	17	72 (16)	15	56 (16)		9.36%	16[4.89,27.11]
Grimbert 2002	58	48 (20)	59	39 (18)		13.82%	9[2.1,15.9]
Subtotal ***	**75**		**74**			**23.17%**	**11.09[4.81,17.37]**
Heterogeneity: Tau²=2.24; Chi²=1.1, df=1(P=0.29); I²=9.16%							
Test for overall effect: Z=3.46(P=0)							
Total ***	**451**		**459**			**100%**	**3.56[-1.13,8.25]**
Heterogeneity: Tau²=29.01; Chi²=20.58, df=7(P=0); I²=65.99%							
Test for overall effect: Z=1.49(P=0.14)							
Test for subgroup differences: Chi²=8.29, df=1 (P=0.02), I²=75.88%							

Favours standard dose CNI   -50   -25   0   25   50   Favours CNI withdrawal

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Analysis 1.4.   Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 4 Graft loss.

Study or subgroup	CNI withdrawal n/N	CNI stan-dard dose n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pascual 2008	0/20	0/20			Not estimable
Suwelack 2002	0/18	3/20		0.24%	0.16[0.01,2.86]
Heering 1993	2/18	1/17		0.38%	1.89[0.19,18.97]
Hazzan 2005	4/54	1/54		0.43%	4[0.46,34.64]
Garcia 2007	2/33	2/38		0.56%	1.15[0.17,7.73]
Asberg 2006	3/27	3/27		0.89%	1[0.22,4.52]
Dudley 2005	5/73	4/70		1.25%	1.2[0.34,4.28]
Isoniemi 1990	4/32	6/32		1.48%	0.67[0.21,2.14]
Grimbert 2002	6/58	5/59		1.58%	1.22[0.39,3.78]
Abramowicz 2002	9/74	6/77		2.09%	1.56[0.58,4.17]
CAESAR Study 2007	12/179	9/173		2.87%	1.29[0.56,2.98]
Smak Gregoor 1999	12/63	13/73		4.02%	1.07[0.53,2.17]
Pedersen 1991	14/51	15/55		5.24%	1.01[0.54,1.87]
Hollander 1995	14/60	24/68		6.43%	0.66[0.38,1.16]
MacPhee 1998	52/102	66/114		33.25%	0.88[0.69,1.13]
Hall 1988	68/165	93/166		39.29%	0.74[0.59,0.92]
Total (95% CI)	**1027**	**1063**		**100%**	**0.85[0.74,0.98]**

Total events: 207 (CNI withdrawal), 251 (CNI standard dose)

Heterogeneity: Tau²=0; Chi²=10.38, df=14(P=0.73); I²=0%

Test for overall effect: Z=2.29(P=0.02)

Favours CNI withdrawal 0.005 0.1 1 10 200 Favours Standard dose CNI

Analysis 1.5.   Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 5 Serum creatinine.

Study or subgroup	CNI withdrawal N	Mean(SD)	CNI standard dose N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 Six months							
Kosch 2003a	12	262.5 (26.5)	12	230.7 (26.5)		39.2%	31.78[10.58,52.98]
Subtotal ***	**12**		**12**			**39.2%**	**31.78[10.58,52.98]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=2.94(P=0)							
1.5.2 One year							
Garcia 2007	33	150.3 (70.7)	38	141.4 (61.9)		18.18%	8.88[-22.25,40.01]
Isoniemi 1990	28	152 (59)	26	133 (55)		19.06%	19[-11.41,49.41]
Pascual 2008	20	134.4 (56.5)	20	128.1 (26.5)		23.56%	6.26[-21.09,33.61]
Subtotal ***	**81**		**84**			**60.8%**	**11.04[-5.99,28.06]**
Heterogeneity: Tau²=0; Chi²=0.4, df=2(P=0.82); I²=0%							
Test for overall effect: Z=1.27(P=0.2)							
Total ***	**93**		**96**			**100%**	**19.17[5.89,32.44]**

Heterogeneity: Tau²=0; Chi²=2.63, df=3(P=0.45); I²=0%

Test for overall effect: Z=2.83(P=0)

Test for subgroup differences: Chi²=2.24, df=1 (P=0.13), I²=55.26%

Favours CNI withdrawal -100 -50 0 50 100 Favours Standard dose CNI

Analysis 1.6. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 6 Adverse events.

Study or subgroup	CNI withdrawal	CNI stan-dard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.6.1 Hypertension					
Dudley 2005	5/73	8/70		1.85%	0.6[0.21,1.74]
CAESAR Study 2007	68/179	70/173		20.65%	0.94[0.72,1.22]
Hollander 1995	35/57	53/65		23.28%	0.75[0.59,0.95]
Grimbert 2002	41/58	43/59		24.34%	0.97[0.77,1.22]
MacPhee 1998	59/102	93/114		29.89%	0.71[0.59,0.86]
Subtotal (95% CI)	**469**	**481**		**100%**	**0.82[0.71,0.95]**
Total events: 208 (CNI withdrawal), 267 (CNI standard dose)					
Heterogeneity: Tau²=0.01; Chi²=6.28, df=4(P=0.18); I²=36.32%					
Test for overall effect: Z=2.64(P=0.01)					
1.6.2 Hyperlipidaemia					
ASCERTAIN Study 2011	11/144	6/123		11.02%	1.57[0.6,4.11]
Hollander 1995	12/57	21/68		26.75%	0.68[0.37,1.26]
Abramowicz 2002	29/85	33/85		62.23%	0.88[0.59,1.31]
Subtotal (95% CI)	**286**	**276**		**100%**	**0.88[0.63,1.21]**
Total events: 52 (CNI withdrawal), 60 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=2.04, df=2(P=0.36); I²=2.01%					
Test for overall effect: Z=0.81(P=0.42)					
1.6.3 CMV infection					
Garcia 2007	0/31	2/36		2.95%	0.23[0.01,4.64]
Dudley 2005	1/73	1/70		3.5%	0.96[0.06,15.04]
Smak Gregoor 1999	1/76	2/73		4.69%	0.48[0.04,5.18]
Suwelack 2002	1/18	6/20		6.51%	0.19[0.02,1.39]
Pascual 2008	3/20	2/20		9.42%	1.5[0.28,8.04]
Asberg 2006	6/27	5/27		23.61%	1.2[0.42,3.46]
Grimbert 2002	11/58	12/59		49.32%	0.93[0.45,1.94]
Subtotal (95% CI)	**303**	**305**		**100%**	**0.87[0.52,1.45]**
Total events: 23 (CNI withdrawal), 30 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=4.17, df=6(P=0.65); I²=0%					
Test for overall effect: Z=0.54(P=0.59)					
1.6.4 Diabetes					
Grimbert 2002	1/58	2/59		3.08%	0.51[0.05,5.46]
Garcia 2007	2/31	1/36		3.13%	2.32[0.22,24.4]
Asberg 2006	2/27	5/27		7.21%	0.4[0.08,1.89]
ASCERTAIN Study 2011	7/144	4/123		11.95%	1.49[0.45,4.99]
Abramowicz 2002	8/85	11/85		23.46%	0.73[0.31,1.72]
Smak Gregoor 1999	16/62	18/73		51.16%	1.05[0.58,1.87]
Subtotal (95% CI)	**407**	**403**		**100%**	**0.94[0.62,1.42]**
Total events: 36 (CNI withdrawal), 41 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=3.04, df=5(P=0.69); I²=0%					
Test for overall effect: Z=0.3(P=0.76)					
1.6.5 Malignancy					
Abramowicz 2002	4/74	6/77		1.88%	0.69[0.2,2.36]

Favours CNI withdrawl 0.01 0.1 1 10 100 Favours CNI

Study or subgroup	CNI withdrawal	CNI standard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
MacPhee 1998	8/102	7/114		2.94%	1.28[0.48,3.4]
Grimbert 2002	7/58	8/59		3.14%	0.89[0.35,2.3]
Smak Gregoor 1999	11/63	14/73		5.53%	0.91[0.45,1.86]
Hollander 1995	16/60	22/68		9.59%	0.82[0.48,1.42]
Hall 1988	100/165	86/166		76.92%	1.17[0.97,1.42]
Subtotal (95% CI)	**522**	**557**		**100%**	**1.1[0.93,1.3]**

Total events: 146 (CNI withdrawal), 143 (CNI standard dose)

Heterogeneity: Tau²=0; Chi²=2.72, df=5(P=0.74); I²=0%

Test for overall effect: Z=1.09(P=0.27)

1.6.6 Infection

Study or subgroup	CNI withdrawal	CNI standard dose	Risk Ratio	Weight	Risk Ratio
Suwelack 2002	1/18	6/20		4.47%	0.19[0.02,1.39]
Dudley 2005	16/73	5/70		14.45%	3.07[1.19,7.93]
Pascual 2008	6/20	6/20		14.49%	1[0.39,2.58]
Abramowicz 2002	8/85	11/85		16.3%	0.73[0.31,1.72]
Grimbert 2002	11/58	12/59		19.4%	0.93[0.45,1.94]
MacPhee 1998	31/102	42/114		30.89%	0.82[0.56,1.21]
Subtotal (95% CI)	**356**	**368**		**100%**	**0.96[0.61,1.51]**

Total events: 73 (CNI withdrawal), 82 (CNI standard dose)

Heterogeneity: Tau²=0.14; Chi²=9.27, df=5(P=0.1); I²=46.05%

Test for overall effect: Z=0.17(P=0.87)

Test for subgroup differences: Chi²=6.79, df=1 (P=0.24), I²=26.33%

Favours CNI withdrawl 0.01 0.1 1 10 100 Favours CNI

Analysis 1.7. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 7 Subgroup analysis: acute rejection.

Study or subgroup	CNI withdrawal	CNI standard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.7.1 Avoidance					
Garcia 2007	15/31	3/36		8.62%	5.81[1.85,18.21]
Asberg 2006	19/27	8/27		12.94%	2.38[1.26,4.46]
Grimbert 2002	32/58	31/59		15.35%	1.05[0.75,1.47]
Subtotal (95% CI)	**116**	**122**		**36.92%**	**2.16[0.85,5.49]**

Total events: 66 (CNI withdrawal), 42 (CNI standard dose)

Heterogeneity: Tau²=0.54; Chi²=12.65, df=2(P=0); I²=84.19%

Test for overall effect: Z=1.62(P=0.1)

1.7.2 Late withdrawal

Study or subgroup	CNI withdrawal	CNI standard dose	Risk Ratio	Weight	Risk Ratio
Dudley 2005	0/73	0/70			Not estimable
Suwelack 2002	0/18	0/20			Not estimable
Pascual 2008	4/20	0/20		2.45%	9[0.52,156.91]
CTOT-09 Study 2015	4/14	0/7		2.55%	4.8[0.29,78.38]
Heering 1993	11/18	0/17		2.6%	21.79[1.38,343.26]
Abramowicz 2002	7/74	1/77		4.11%	7.28[0.92,57.77]
Smak Gregoor 1999	17/63	1/73		4.37%	19.7[2.7,143.88]
Isoniemi 1990	12/28	1/32		4.41%	13.71[1.9,98.93]
Hollander 1995	3/60	3/68		6.09%	1.13[0.24,5.41]

Less with CNI withdrawal 0.002 0.1 1 10 500 Less with standard dose CNI

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Study or subgroup	CNI withdrawal	CNI stan-dard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Hazzan 2005	10/54	3/54		7.99%	3.33[0.97,11.45]
MacPhee 1998	16/102	17/114		12.96%	1.05[0.56,1.97]
CAESAR Study 2007	68/179	48/173		15.55%	1.37[1.01,1.86]
Subtotal (95% CI)	703	725		63.08%	3.21[1.59,6.48]
Total events: 152 (CNI withdrawal), 74 (CNI standard dose)					
Heterogeneity: Tau²=0.6; Chi²=26.36, df=9(P=0); I²=65.85%					
Test for overall effect: Z=3.26(P=0)					
Total (95% CI)	819	847		100%	2.54[1.56,4.12]
Total events: 218 (CNI withdrawal), 116 (CNI standard dose)					
Heterogeneity: Tau²=0.37; Chi²=40.45, df=12(P<0.0001); I²=70.34%					
Test for overall effect: Z=3.77(P=0)					
Test for subgroup differences: Chi²=0.44, df=1 (P=0.51), I²=0%					

Less with CNI withdrawal   0.002   0.1   1   10   500   Less with standard dose CNI

Analysis 1.8.   Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 8 Subgroup analysis: GFR.

Study or subgroup	CNI withdrawal		CNI standard dose		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
1.8.1 Avoidance							
Asberg 2006	27	52 (20)	27	69 (29)		7.63%	-17[-30.29,-3.71]
Garcia 2007	33	56.9 (16.4)	38	58.9 (14)		13.52%	-2[-9.15,5.15]
Grimbert 2002	58	48 (20)	59	39 (18)		13.82%	9[2.1,15.9]
Subtotal ***	118		124			34.96%	-2.22[-14.84,10.4]
Heterogeneity: Tau²=102.24; Chi²=12.89, df=2(P=0); I²=84.48%							
Test for overall effect: Z=0.34(P=0.73)							
1.8.2 Late withdrawal							
Hollander 1995	17	72 (16)	15	56 (16)		9.36%	16[4.89,27.11]
CAESAR Study 2007	179	51 (43)	173	49 (26)		13.23%	2[-5.4,9.4]
Pascual 2008	20	72.1 (11.6)	20	68 (12.1)		13.28%	4.1[-3.25,11.45]
Hazzan 2005	54	45.6 (21.6)	54	37.7 (11)		14.34%	7.9[1.43,14.37]
Smak Gregoor 1999	63	66 (17)	73	63 (19)		14.84%	3[-3.05,9.05]
Subtotal ***	333		335			65.04%	5.54[1.66,9.43]
Heterogeneity: Tau²=5.6; Chi²=5.61, df=4(P=0.23); I²=28.66%							
Test for overall effect: Z=2.8(P=0.01)							
Total ***	451		459			100%	3.56[-1.13,8.25]
Heterogeneity: Tau²=29.01; Chi²=20.58, df=7(P=0); I²=65.99%							
Test for overall effect: Z=1.49(P=0.14)							
Test for subgroup differences: Chi²=1.33, df=1 (P=0.25), I²=24.66%							

Favours standard dose CNI   -50   -25   0   25   50   Favours CNI withdrawal

Analysis 1.9. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 9 Subgroup analysis: graft loss.

Study or subgroup	CNI withdrawal	CNI standard dose	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.9.1 Avoidance					
Garcia 2007	2/33	2/38		0.37%	1.15[0.17,7.73]
Asberg 2006	3/27	3/27		0.59%	1[0.22,4.52]
Grimbert 2002	6/58	5/59		1.05%	1.22[0.39,3.78]
Hall 1988	84/158	93/166		33.77%	0.95[0.78,1.16]
Subtotal (95% CI)	**276**	**290**		**35.78%**	**0.96[0.79,1.16]**
Total events: 95 (CNI withdrawal), 103 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=0.23, df=3(P=0.97); I²=0%					
Test for overall effect: Z=0.43(P=0.67)					
1.9.2 Late withdrawal					
Pascual 2008	0/20	0/20			Not estimable
Suwelack 2002	0/18	3/20		0.16%	0.16[0.01,2.86]
Heering 1993	2/18	1/17		0.25%	1.89[0.19,18.97]
Hazzan 2005	4/54	1/54		0.29%	4[0.46,34.64]
Dudley 2005	5/73	4/70		0.82%	1.2[0.34,4.28]
Isoniemi 1990	4/32	6/32		0.98%	0.67[0.21,2.14]
Abramowicz 2002	9/74	6/77		1.39%	1.56[0.58,4.17]
CAESAR Study 2007	12/179	9/173		1.9%	1.29[0.56,2.98]
Smak Gregoor 1999	12/63	13/73		2.66%	1.07[0.53,2.17]
Pedersen 1991	14/51	15/55		3.47%	1.01[0.54,1.87]
Hollander 1995	14/60	24/68		4.26%	0.66[0.38,1.16]
MacPhee 1998	52/102	66/114		22.02%	0.88[0.69,1.13]
Hall 1988	68/165	93/166		26.02%	0.74[0.59,0.92]
Subtotal (95% CI)	**909**	**939**		**64.22%**	**0.84[0.73,0.97]**
Total events: 196 (CNI withdrawal), 241 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=9.78, df=11(P=0.55); I²=0%					
Test for overall effect: Z=2.38(P=0.02)					
Total (95% CI)	**1185**	**1229**		**100%**	**0.88[0.78,0.99]**
Total events: 291 (CNI withdrawal), 344 (CNI standard dose)					
Heterogeneity: Tau²=0; Chi²=11.11, df=15(P=0.74); I²=0%					
Test for overall effect: Z=2.16(P=0.03)					
Test for subgroup differences: Chi²=1.16, df=1 (P=0.28), I²=14.14%					

Favours CNI withdrawal 0.005 0.1 1 10 200 Favours standard dose CNI

Comparison 2. Subgroup analysis (antimetabolite): CNI withdrawal versus standard dose CNI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection	15	1666	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.56, 4.12]
1.1 MMF/MPA	10	1110	Risk Ratio (M-H, Random, 95% CI)	3.51 [1.79, 6.88]
1.2 AZA	5	556	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.78, 4.19]

Analysis 2.1. Comparison 2 Subgroup analysis (antimetabolite): CNI withdrawal versus standard dose CNI, Outcome 1 Acute rejection.

Study or subgroup	CNI withdrawal	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
2.1.1 MMF/MPA					
Suwelack 2002	0/18	0/20			Not estimable
Dudley 2005	0/73	0/70			Not estimable
Pascual 2008	4/20	0/20		2.45%	9[0.52,156.91]
CTOT-09 Study 2015	4/14	0/7		2.55%	4.8[0.29,78.38]
Abramowicz 2002	7/74	1/77		4.11%	7.28[0.92,57.77]
Smak Gregoor 1999	17/63	1/73		4.37%	19.7[2.7,143.88]
Hazzan 2005	10/54	3/54		7.99%	3.33[0.97,11.45]
Garcia 2007	15/31	3/36		8.62%	5.81[1.85,18.21]
Asberg 2006	19/27	8/27		12.94%	2.38[1.26,4.46]
CAESAR Study 2007	68/179	48/173		15.55%	1.37[1.01,1.86]
Subtotal (95% CI)	**553**	**557**		**58.58%**	**3.51[1.79,6.88]**
Total events: 144 (CNI withdrawal), 64 (Standard dose CNI)					
Heterogeneity: Tau²=0.45; Chi²=19.83, df=7(P=0.01); I²=64.71%					
Test for overall effect: Z=3.66(P=0)					
2.1.2 AZA					
Heering 1993	11/18	0/17		2.6%	21.79[1.38,343.26]
Isoniemi 1990	12/28	1/32		4.41%	13.71[1.9,98.93]
Hollander 1995	3/60	3/68		6.09%	1.13[0.24,5.41]
MacPhee 1998	16/102	17/114		12.96%	1.05[0.56,1.97]
Grimbert 2002	32/58	31/59		15.35%	1.05[0.75,1.47]
Subtotal (95% CI)	**266**	**290**		**41.42%**	**1.81[0.78,4.19]**
Total events: 74 (CNI withdrawal), 52 (Standard dose CNI)					
Heterogeneity: Tau²=0.5; Chi²=14.05, df=4(P=0.01); I²=71.53%					
Test for overall effect: Z=1.39(P=0.16)					
Total (95% CI)	**819**	**847**		**100%**	**2.54[1.56,4.12]**
Total events: 218 (CNI withdrawal), 116 (Standard dose CNI)					
Heterogeneity: Tau²=0.37; Chi²=40.45, df=12(P<0.0001); I²=70.34%					
Test for overall effect: Z=3.77(P=0)					
Test for subgroup differences: Chi²=1.46, df=1 (P=0.23), I²=31.45%					

Favours CNI withdrawal 0.002 0.1 1 10 500 Favours standard dose CNI

Comparison 3. Subgroup analysis (CNI type): CNI withdrawal versus standard dose CNI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection	15	1666	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.56, 4.12]
1.1 CSA	11	1500	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.31, 3.48]
1.2 TAC	2	88	Risk Ratio (M-H, Random, 95% CI)	5.65 [1.96, 16.27]
1.3 Either CSA or TAC	2	78	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.52, 156.91]

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Analysis 3.1. Comparison 3 Subgroup analysis (CNI type): CNI withdrawal versus standard dose CNI, Outcome 1 Acute rejection.

Study or subgroup	CNI withdrawal	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
3.1.1 CSA					
Dudley 2005	0/73	0/70			Not estimable
Heering 1993	11/18	0/17		2.6%	21.79[1.38,343.26]
Abramowicz 2002	7/74	1/77		4.11%	7.28[0.92,57.77]
Smak Gregoor 1999	17/63	1/73		4.37%	19.7[2.7,143.88]
Isoniemi 1990	12/28	1/32		4.41%	13.71[1.9,98.93]
Hollander 1995	3/60	3/68		6.09%	1.13[0.24,5.41]
Hazzan 2005	10/54	3/54		7.99%	3.33[0.97,11.45]
Asberg 2006	19/27	8/27		12.94%	2.38[1.26,4.46]
MacPhee 1998	16/102	17/114		12.96%	1.05[0.56,1.97]
Grimbert 2002	32/58	31/59		15.35%	1.05[0.75,1.47]
CAESAR Study 2007	68/179	48/173		15.55%	1.37[1.01,1.86]
Subtotal (95% CI)	**736**	**764**		**86.38%**	**2.13[1.31,3.48]**
Total events: 195 (CNI withdrawal), 113 (Standard dose CNI)					
Heterogeneity: Tau²=0.31; Chi²=31.1, df=9(P=0); I²=71.07%					
Test for overall effect: Z=3.03(P=0)					
3.1.2 TAC					
CTOT-09 Study 2015	4/14	0/7		2.55%	4.8[0.29,78.38]
Garcia 2007	15/31	3/36		8.62%	5.81[1.85,18.21]
Subtotal (95% CI)	**45**	**43**		**11.17%**	**5.65[1.96,16.27]**
Total events: 19 (CNI withdrawal), 3 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.9); I²=0%					
Test for overall effect: Z=3.21(P=0)					
3.1.3 Either CSA or TAC					
Suwelack 2002	0/18	0/20			Not estimable
Pascual 2008	4/20	0/20		2.45%	9[0.52,156.91]
Subtotal (95% CI)	**38**	**40**		**2.45%**	**9[0.52,156.91]**
Total events: 4 (CNI withdrawal), 0 (Standard dose CNI)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.51(P=0.13)					
Total (95% CI)	**819**	**847**		**100%**	**2.54[1.56,4.12]**
Total events: 218 (CNI withdrawal), 116 (Standard dose CNI)					
Heterogeneity: Tau²=0.37; Chi²=40.45, df=12(P<0.0001); I²=70.34%					
Test for overall effect: Z=3.77(P=0)					
Test for subgroup differences: Chi²=3.43, df=1 (P=0.18), I²=41.61%					

Favours CNI withdrawal   0.002   0.1   1   10   500   Favours standard dose CNI

Comparison 4.   Low dose CNI versus standard dose CNI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	15	3462	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.50, 1.27]
1.1 Early intervention	13	3272	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.48, 1.27]
1.2 Late intervention	2	190	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.15, 6.94]
2 Acute rejection	19	3757	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
2.1 Unspecified	8	2028	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.74, 1.03]
2.2 Biopsy-proven	11	1729	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.16]
3 GFR	13	2623	Mean Difference (IV, Random, 95% CI)	4.10 [2.07, 6.12]
3.1 Six months	5	812	Mean Difference (IV, Random, 95% CI)	1.96 [-1.35, 5.28]
3.2 One year	7	1710	Mean Difference (IV, Random, 95% CI)	4.30 [1.78, 6.82]
3.3 Two years	1	101	Mean Difference (IV, Random, 95% CI)	11.10 [4.14, 18.06]
4 Graft loss	15	3286	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.02]
5 Serum creatinine	6	742	Mean Difference (IV, Random, 95% CI)	-4.28 [-14.65, 6.10]
5.1 Six months	4	530	Mean Difference (IV, Random, 95% CI)	-1.46 [-11.25, 8.33]
5.2 One year	2	212	Mean Difference (IV, Random, 95% CI)	-23.18 [-46.12, -0.23]
6 Change in GFR at 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Adverse events	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Hypertension	5	1877	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.00]
7.2 Hyperlipidaemia	3	1443	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.90, 1.19]
7.3 CMV infection	6	1948	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.94, 1.62]
7.4 Diabetes	5	1292	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.50, 1.34]
7.5 Malignancy	5	1637	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.41, 1.97]
7.6 Infection	9	1437	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.07]
8 Subgroup analysis: acute rejection	18	2968	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.02]
8.1 Immediate intervention	12	2209	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.00]
8.2 Late intervention	6	759	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.61, 1.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Subgroup analysis: GFR	12	2443	Mean Difference (IV, Random, 95% CI)	4.21 [1.90, 6.51]
9.1 Immediate intervention	9	2200	Mean Difference (IV, Random, 95% CI)	3.09 [0.95, 5.23]
9.2 Late intervention	3	243	Mean Difference (IV, Random, 95% CI)	8.81 [3.79, 13.83]
10 Subgroup analysis: graft loss	14	3106	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.03]
10.1 Immediate intervention	11	2800	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.03]
10.2 Late intervention	3	306	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.12, 7.56]

Analysis 4.1. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 1 Death.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
4.1.1 Early intervention					
Alsina 1987	0/25	0/25			Not estimable
Chadban 2013	0/42	1/33		2.22%	0.26[0.01,6.27]
Andres 2009	2/38	0/40		2.46%	5.26[0.26,106.06]
Ferguson 2006	1/149	1/78		2.92%	0.52[0.03,8.26]
Cai 2014	1/90	1/90		2.93%	1[0.06,15.74]
Chan 2012	1/151	2/141		3.9%	0.47[0.04,5.09]
Kreis 2003	2/87	1/80		3.92%	1.84[0.17,19.89]
Fangmann 2010	2/75	2/73		5.95%	0.97[0.14,6.73]
Salvadori 2007	2/49	3/68		7.25%	0.93[0.16,5.33]
OPTICEPT Study 2009	4/243	2/237		7.81%	1.95[0.36,10.55]
de Sevaux 2001	3/152	5/161		11.12%	0.64[0.15,2.61]
CAESAR Study 2007	4/183	5/173		13.2%	0.76[0.21,2.77]
SYMPHONY Study 2007	8/399	14/390		30.26%	0.56[0.24,1.32]
Subtotal (95% CI)	**1683**	**1589**		**93.94%**	**0.78[0.48,1.27]**
Total events: 30 (Low dose CNI), 37 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=4.68, df=11(P=0.95); I²=0%					
Test for overall effect: Z=0.99(P=0.32)					
4.1.2 Late intervention					
REFERENCE Study 2006	0/70	0/31			Not estimable
Budde 2007	2/44	2/45		6.06%	1.02[0.15,6.94]
Subtotal (95% CI)	**114**	**76**		**6.06%**	**1.02[0.15,6.94]**
Total events: 2 (Low dose CNI), 2 (Standard dose CNI)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.98)					
Total (95% CI)	**1797**	**1665**		**100%**	**0.79[0.5,1.27]**

Favours low dose CNI 0.005 0.1 1 10 200 Favours standard dose CNI

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI

Total events: 32 (Low dose CNI), 39 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=4.75, df=12(P=0.97); I²=0%

Test for overall effect: Z=0.96(P=0.34)

Test for subgroup differences: Chi²=0.07, df=1 (P=0.79), I²=0%

Favours low dose CNI   0.005   0.1   1   10   200   Favours standard dose CNI

Analysis 4.2.   Comparison 4 Low dose CNI versus standard dose CNI, Outcome 2 Acute rejection.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
4.2.1 Unspecified					
Pascual 2003	0/32	0/32			Not estimable
Baczkowska 2003	3/16	2/16		0.69%	1.5[0.29,7.81]
Andres 2009	2/38	5/40		0.76%	0.42[0.09,2.04]
Alsina 1987	3/25	7/25		1.24%	0.43[0.12,1.47]
Cai 2014	10/90	12/90		3.05%	0.83[0.38,1.83]
OPTICEPT Study 2009	15/243	23/237		4.82%	0.64[0.34,1.19]
CAESAR Study 2007	48/183	47/172		15.92%	0.96[0.68,1.35]
SYMPHONY Study 2007	118/399	128/390		43.76%	0.9[0.73,1.11]
Subtotal (95% CI)	**1026**	**1002**		**70.24%**	**0.88[0.74,1.03]**
Total events: 199 (Low dose CNI), 224 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=3.92, df=6(P=0.69); I²=0%					
Test for overall effect: Z=1.6(P=0.11)					
4.2.2 Biopsy-proven					
REFERENCE Study 2006	0/70	0/31			Not estimable
Chan 2012	2/151	0/141		0.21%	4.67[0.23,96.46]
DICAM Study 2010	6/106	3/101		1.02%	1.91[0.49,7.42]
Kreis 2003	8/87	5/80		1.63%	1.47[0.5,4.31]
Salvadori 2007	5/49	12/68		1.98%	0.58[0.22,1.54]
MODIFY Study 2012	8/39	6/40		2.04%	1.37[0.52,3.58]
Budde 2007	7/44	8/45		2.2%	0.89[0.35,2.26]
Fangmann 2010	6/75	17/73		2.47%	0.34[0.14,0.82]
Cibrik 2007	11/75	16/66		3.93%	0.61[0.3,1.21]
Chadban 2013	15/42	10/33		4.36%	1.18[0.61,2.27]
de Sevaux 2001	29/152	36/161		9.92%	0.85[0.55,1.32]
Subtotal (95% CI)	**890**	**839**		**29.76%**	**0.86[0.64,1.16]**
Total events: 97 (Low dose CNI), 113 (Standard dose CNI)					
Heterogeneity: Tau²=0.04; Chi²=11.13, df=9(P=0.27); I²=19.14%					
Test for overall effect: Z=0.96(P=0.34)					
Total (95% CI)	**1916**	**1841**		**100%**	**0.87[0.76,1]**
Total events: 296 (Low dose CNI), 337 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=15.07, df=16(P=0.52); I²=0%					
Test for overall effect: Z=1.99(P=0.05)					
Test for subgroup differences: Chi²=0, df=1 (P=0.95), I²=0%					

Favours low dose CNI   0.01   0.1   1   10   100   Favours standard dose CNI

Analysis 4.3. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 3 GFR.

Study or subgroup	Low dose CNI		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
4.3.1 Six months							
Pascual 2003	32	64.6 (20)	32	61 (19)		4.13%	3.6[-5.96,13.16]
Chadban 2013	42	63.2 (24.3)	33	60.2 (17.6)		4.18%	3[-6.49,12.49]
Chan 2012	145	63.6 (29.2)	137	61 (29)		7.55%	2.6[-4.2,9.4]
de Sevaux 2001	152	69 (31)	161	65 (28)		8.03%	4[-2.56,10.56]
Andres 2009	38	46.1 (15)	40	47.9 (14)		8.26%	-1.8[-8.25,4.65]
Subtotal ***	**409**		**403**			**32.16%**	**1.96[-1.35,5.28]**
Heterogeneity: Tau²=0; Chi²=1.87, df=4(P=0.76); I²=0%							
Test for overall effect: Z=1.16(P=0.25)							
4.3.2 One year							
Baczkowska 2003	21	73.5 (24)	21	57.5 (14)		2.75%	16[4.12,27.88]
MODIFY Study 2012	39	74 (25)	39	64 (25)		3.13%	10[-1.1,21.1]
CAESAR Study 2007	183	51 (44)	173	49 (46)		4.29%	2[-7.36,11.36]
Fangmann 2010	75	59 (21)	73	52 (22)		7.31%	7[0.07,13.93]
Salvadori 2007	49	50.6 (13.7)	68	47.4 (16.8)		10.59%	3.2[-2.34,8.74]
Cai 2014	90	63 (19)	90	59 (15)		12.39%	4[-1,9]
SYMPHONY Study 2007	399	59.4 (25.1)	390	57.1 (25.1)		20.13%	2.3[-1.2,5.8]
Subtotal ***	**856**		**854**			**60.58%**	**4.3[1.78,6.82]**
Heterogeneity: Tau²=1.57; Chi²=6.92, df=6(P=0.33); I²=13.28%							
Test for overall effect: Z=3.35(P=0)							
4.3.3 Two years							
REFERENCE Study 2006	70	56.2 (16.6)	31	45.1 (16.4)		7.26%	11.1[4.14,18.06]
Subtotal ***	**70**		**31**			**7.26%**	**11.1[4.14,18.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.13(P=0)							
Total ***	**1335**		**1288**			**100%**	**4.1[2.07,6.12]**
Heterogeneity: Tau²=2.11; Chi²=14.23, df=12(P=0.29); I²=15.65%							
Test for overall effect: Z=3.96(P<0.0001)							
Test for subgroup differences: Chi²=5.5, df=1 (P=0.06), I²=63.64%							

Favours standard dose CNI -50 -25 0 25 50 Favours low dose CNI

Analysis 4.4. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 4 Graft loss.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Pascual 2003	0/32	0/32			Not estimable
Cibrik 2007	1/75	0/66		0.94%	2.64[0.11,63.83]
Alsina 1987	0/25	1/25		0.96%	0.33[0.01,7.81]
REFERENCE Study 2006	1/70	1/31		1.27%	0.44[0.03,6.85]
Cai 2014	1/90	2/90		1.67%	0.5[0.05,5.42]
Kreis 2003	3/87	1/80		1.89%	2.76[0.29,25.98]
Chadban 2013	3/42	1/33		1.93%	2.36[0.26,21.63]
Andres 2009	4/38	2/40		3.54%	2.11[0.41,10.83]

Favours low dose CNI 0.01 0.1 1 10 100 Favours standard dose CNI

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Ferguson 2006	5/149	2/78		3.64%	1.31[0.26,6.59]
Salvadori 2007	4/49	3/68		4.51%	1.85[0.43,7.9]
OPTICEPT Study 2009	5/243	4/237		5.6%	1.22[0.33,4.48]
CAESAR Study 2007	6/183	9/173		9.28%	0.63[0.23,1.73]
Fangmann 2010	5/75	15/73		10.32%	0.32[0.12,0.85]
de Sevaux 2001	11/152	19/161		18.92%	0.61[0.3,1.25]
SYMPHONY Study 2007	23/399	32/390		35.52%	0.7[0.42,1.18]
Total (95% CI)	1709	1577		100%	0.75[0.55,1.02]
Total events: 72 (Low dose CNI), 92 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=10.85, df=13(P=0.62); I²=0%					
Test for overall effect: Z=1.84(P=0.07)					

Favours low dose CNI 0.01 0.1 1 10 100 Favours standard dose CNI

Analysis 4.5. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 5 Serum creatinine.

Study or subgroup	Low dose CNI		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
4.5.1 Six months							
Andres 2009	38	179 (77)	40	178 (75)		7.95%	1[-32.76,34.76]
Chadban 2013	42	151.4 (60)	33	130.6 (46.4)		13.55%	20.8[-3.28,44.88]
de Sevaux 2001	152	136 (49)	161	141 (60)		29.79%	-5[-17.11,7.11]
Pascual 2003	32	117.6 (22.5)	32	123.8 (22.1)		32.22%	-6.19[-17.11,4.73]
Subtotal ***	264		266			83.51%	-1.46[-11.25,8.33]
Heterogeneity: Tau²=29.13; Chi²=4.24, df=3(P=0.24); I²=29.16%							
Test for overall effect: Z=0.29(P=0.77)							
4.5.2 One year							
Cai 2014	90	137 (176)	90	142 (118)		5.05%	-5[-48.78,38.78]
Baczkowska 2003	16	106.1 (44.2)	16	136.1 (32.7)		11.44%	-30.06[-57,-3.12]
Subtotal ***	106		106			16.49%	-23.18[-46.12,-0.23]
Heterogeneity: Tau²=0; Chi²=0.91, df=1(P=0.34); I²=0%							
Test for overall effect: Z=1.98(P=0.05)							
Total ***	370		372			100%	-4.28[-14.65,6.1]
Heterogeneity: Tau²=55.9; Chi²=7.89, df=5(P=0.16); I²=36.66%							
Test for overall effect: Z=0.81(P=0.42)							
Test for subgroup differences: Chi²=2.91, df=1 (P=0.09), I²=65.64%							

Favours low dose CNI -100 -50 0 50 100 Favours standard dose CNI

Analysis 4.6. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 6 Change in GFR at 12 months.

Study or subgroup	Low dose CNI		Standard dose CNI		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
OPTICEPT Study 2009	243	12.3 (20.5)	237	5.4 (15.9)		6.9[3.62,10.18]

Favours low dose CNI -20 -10 0 10 20 Favours standard dose CNI

Analysis 4.7. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 7 Adverse events.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
4.7.1 Hypertension					
Andres 2009	7/38	11/40		4.4%	0.67[0.29,1.55]
Cai 2014	10/90	13/90		5.19%	0.77[0.36,1.66]
SYMPHONY Study 2007	47/408	55/384		23.35%	0.8[0.56,1.16]
OPTICEPT Study 2009	54/238	52/233		27.46%	1.02[0.73,1.42]
CAESAR Study 2007	58/183	70/173		39.6%	0.78[0.59,1.04]
Subtotal (95% CI)	**957**	**920**		**100%**	**0.84[0.7,1]**
Total events: 176 (Low dose CNI), 201 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=1.87, df=4(P=0.76); I²=0%					
Test for overall effect: Z=1.94(P=0.05)					
4.7.2 Hyperlipidaemia					
Cai 2014	9/90	7/90		2.27%	1.29[0.5,3.3]
SYMPHONY Study 2007	51/408	57/384		14.79%	0.84[0.59,1.2]
OPTICEPT Study 2009	193/238	177/233		82.94%	1.07[0.97,1.17]
Subtotal (95% CI)	**736**	**707**		**100%**	**1.04[0.9,1.19]**
Total events: 253 (Low dose CNI), 241 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=2.27, df=2(P=0.32); I²=11.99%					
Test for overall effect: Z=0.47(P=0.64)					
4.7.3 CMV infection					
Ferguson 2006	3/74	7/76		4.14%	0.44[0.12,1.64]
Andres 2009	6/38	5/40		5.84%	1.26[0.42,3.8]
OPTICEPT Study 2009	12/238	14/233		12.07%	0.84[0.4,1.78]
Fangmann 2010	19/75	15/73		18.3%	1.23[0.68,2.24]
SYMPHONY Study 2007	47/408	25/380		27.94%	1.75[1.1,2.79]
de Sevaux 2001	35/152	31/161		31.71%	1.2[0.78,1.84]
Subtotal (95% CI)	**985**	**963**		**100%**	**1.23[0.94,1.62]**
Total events: 122 (Low dose CNI), 97 (Standard dose CNI)					
Heterogeneity: Tau²=0.01; Chi²=5.57, df=5(P=0.35); I²=10.3%					
Test for overall effect: Z=1.52(P=0.13)					
4.7.4 Diabetes					
DICAM Study 2010	2/106	7/101		8.09%	0.27[0.06,1.28]
de Sevaux 2001	6/152	6/161		13.29%	1.06[0.35,3.21]
Andres 2009	9/38	10/40		20.15%	0.95[0.43,2.07]
Chan 2012	19/114	33/109		28.96%	0.55[0.33,0.91]
OPTICEPT Study 2009	34/238	25/233		29.51%	1.33[0.82,2.16]
Subtotal (95% CI)	**648**	**644**		**100%**	**0.82[0.5,1.34]**
Total events: 70 (Low dose CNI), 81 (Standard dose CNI)					
Heterogeneity: Tau²=0.15; Chi²=8.51, df=4(P=0.07); I²=53.01%					
Test for overall effect: Z=0.79(P=0.43)					
4.7.5 Malignancy					
Pascual 2003	0/32	0/32			Not estimable
DICAM Study 2010	2/106	2/101		16.22%	0.95[0.14,6.64]
SYMPHONY Study 2007	3/408	2/384		19.2%	1.41[0.24,8.4]

Favours low dose CNI 0.05 0.2 1 5 20 Favours standard dose CNI

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
REFERENCE Study 2006	3/70	2/33		20.17%	0.71[0.12,4.03]
OPTICEPT Study 2009	5/238	6/233		44.41%	0.82[0.25,2.64]
Subtotal (95% CI)	**854**	**783**		**100%**	**0.9[0.41,1.97]**
Total events: 13 (Low dose CNI), 12 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.35, df=3(P=0.95); I²=0%					
Test for overall effect: Z=0.26(P=0.8)					
4.7.6 Infection					
Pascual 2003	0/32	0/32			Not estimable
REFERENCE Study 2006	16/70	3/33		1.04%	2.51[0.79,8.03]
Andres 2009	7/38	7/40		1.56%	1.05[0.41,2.72]
Ferguson 2006	10/74	11/76		2.22%	0.93[0.42,2.07]
DICAM Study 2010	22/106	19/101		4.64%	1.1[0.64,1.91]
OPTICEPT Study 2009	22/238	30/233		5.2%	0.72[0.43,1.21]
Chadban 2013	30/42	26/33		20.66%	0.91[0.7,1.18]
Fangmann 2010	51/75	49/73		28.13%	1.01[0.81,1.27]
Cibrik 2007	53/75	51/66		36.56%	0.91[0.75,1.11]
Subtotal (95% CI)	**750**	**687**		**100%**	**0.95[0.84,1.07]**
Total events: 211 (Low dose CNI), 196 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=4.8, df=7(P=0.68); I²=0%					
Test for overall effect: Z=0.88(P=0.38)					
Test for subgroup differences: Chi²=6.99, df=1 (P=0.22), I²=28.45%					

Favours low dose CNI   0.05   0.2   1   5   20   Favours standard dose CNI

Analysis 4.8. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 8 Subgroup analysis: acute rejection.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
4.8.1 Immediate intervention					
Chan 2012	2/151	0/141		0.37%	4.67[0.23,96.46]
Baczkowska 2003	3/16	2/16		1.23%	1.5[0.29,7.81]
Andres 2009	2/38	5/40		1.35%	0.42[0.09,2.04]
Alsina 1987	3/25	7/25		2.2%	0.43[0.12,1.47]
Salvadori 2007	5/49	12/68		3.52%	0.58[0.22,1.54]
Budde 2007	7/44	8/45		3.92%	0.89[0.35,2.26]
Fangmann 2010	6/75	17/73		4.4%	0.34[0.14,0.82]
Cai 2014	10/90	12/90		5.42%	0.83[0.38,1.83]
Chadban 2013	15/42	10/33		7.75%	1.18[0.61,2.27]
OPTICEPT Study 2009	15/243	23/237		8.57%	0.64[0.34,1.19]
de Sevaux 2001	29/152	36/161		17.64%	0.85[0.55,1.32]
CAESAR Study 2007	48/183	47/172		28.31%	0.96[0.68,1.35]
Subtotal (95% CI)	**1108**	**1101**		**84.68%**	**0.82[0.67,1]**
Total events: 145 (Low dose CNI), 179 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=10.58, df=11(P=0.48); I²=0%					
Test for overall effect: Z=1.93(P=0.05)					
4.8.2 Late intervention					
Pascual 2003	0/32	0/32			Not estimable

Favours low dose CNI   0.01   0.1   1   10   100   Favours standard dose CNI

Study or subgroup	Low dose CNI n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
REFERENCE Study 2006	0/70	0/31			Not estimable
DICAM Study 2010	6/106	3/101		1.82%	1.91[0.49,7.42]
Kreis 2003	8/87	5/80		2.9%	1.47[0.5,4.31]
MODIFY Study 2012	8/39	6/40		3.62%	1.37[0.52,3.58]
Cibrik 2007	11/75	16/66		6.99%	0.61[0.3,1.21]
Subtotal (95% CI)	409	350		15.32%	1.05[0.61,1.81]

Total events: 33 (Low dose CNI), 30 (Standard dose CNI)

Heterogeneity: Tau²=0.07; Chi²=3.8, df=3(P=0.28); I²=21.08%

Test for overall effect: Z=0.17(P=0.86)

| Total (95% CI) | 1517 | 1451 | | 100% | 0.85[0.7,1.02] |

Total events: 178 (Low dose CNI), 209 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=14.87, df=15(P=0.46); I²=0%

Test for overall effect: Z=1.78(P=0.07)

Test for subgroup differences: Chi²=0.68, df=1 (P=0.41), I²=0%

Favours low dose CNI 0.01 0.1 1 10 100 Favours standard dose CNI

Analysis 4.9. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 9 Subgroup analysis: GFR.

Study or subgroup	Low dose CNI N	Low dose CNI Mean(SD)	Standard dose CNI N	Standard dose CNI Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.9.1 Immediate intervention							
Baczkowska 2003	21	73.5 (24)	21	57.5 (14)		3.43%	16[4.12,27.88]
Chadban 2013	42	63.2 (24.3)	33	60.2 (17.6)		5.12%	3[-6.49,12.49]
CAESAR Study 2007	183	51 (44)	173	49 (46)		5.24%	2[-7.36,11.36]
Fangmann 2010	75	59 (21)	73	52 (22)		8.59%	7[0.07,13.93]
Chan 2012	145	63.6 (29.2)	137	61 (29)		8.85%	2.6[-4.2,9.4]
de Sevaux 2001	152	69 (31)	161	65 (28)		9.36%	4[-2.56,10.56]
Andres 2009	38	46.1 (15)	40	47.9 (14)		9.6%	-1.8[-8.25,4.65]
Salvadori 2007	49	50.6 (13.7)	68	47.4 (16.8)		11.96%	3.2[-2.34,8.74]
SYMPHONY Study 2007	399	59.4 (25.1)	390	57.1 (25.1)		20.4%	2.3[-1.2,5.8]
Subtotal ***	1104		1096			82.53%	3.09[0.95,5.23]

Heterogeneity: Tau²=0.42; Chi²=8.31, df=8(P=0.4); I²=3.7%

Test for overall effect: Z=2.83(P=0)

4.9.2 Late intervention							
MODIFY Study 2012	39	74 (25)	39	64 (25)		3.88%	10[-1.1,21.1]
Pascual 2003	32	64.6 (20)	32	61 (19)		5.05%	3.6[-5.96,13.16]
REFERENCE Study 2006	70	56.2 (16.6)	31	45.1 (16.4)		8.54%	11.1[4.14,18.06]
Subtotal ***	141		102			17.47%	8.81[3.79,13.83]

Heterogeneity: Tau²=0; Chi²=1.6, df=2(P=0.45); I²=0%

Test for overall effect: Z=3.44(P=0)

| Total *** | 1245 | | 1198 | | | 100% | 4.21[1.9,6.51] |

Heterogeneity: Tau²=3.58; Chi²=14.22, df=11(P=0.22); I²=22.67%

Test for overall effect: Z=3.58(P=0)

Test for subgroup differences: Chi²=4.22, df=1 (P=0.04), I²=76.33%

Favours standard dose CNI -50 -25 0 25 50 Favours low dose CNI

Analysis 4.10. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 10 Subgroup analysis: graft loss.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
4.10.1 Immediate intervention					
Alsina 1987	0/25	1/25		0.97%	0.33[0.01,7.81]
Kreis 2003	3/87	1/80		1.92%	2.76[0.29,25.98]
Chadban 2013	3/42	1/33		1.97%	2.36[0.26,21.63]
Andres 2009	4/38	2/40		3.6%	2.11[0.41,10.83]
Ferguson 2006	5/149	2/78		3.7%	1.31[0.26,6.59]
Salvadori 2007	4/49	3/68		4.59%	1.85[0.43,7.9]
OPTICEPT Study 2009	5/243	4/237		5.7%	1.22[0.33,4.48]
CAESAR Study 2007	6/183	9/173		9.44%	0.63[0.23,1.73]
Fangmann 2010	5/75	15/73		10.5%	0.32[0.12,0.85]
de Sevaux 2001	11/152	19/161		19.25%	0.61[0.3,1.25]
SYMPHONY Study 2007	23/399	32/390		36.12%	0.7[0.42,1.18]
Subtotal (95% CI)	**1442**	**1358**		**97.76%**	**0.75[0.55,1.03]**
Total events: 69 (Low dose CNI), 89 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=9.99, df=10(P=0.44); I²=0%					
Test for overall effect: Z=1.79(P=0.07)					
4.10.2 Late intervention					
Pascual 2003	0/32	0/32			Not estimable
Cibrik 2007	1/75	0/66		0.95%	2.64[0.11,63.83]
REFERENCE Study 2006	1/70	1/31		1.29%	0.44[0.03,6.85]
Subtotal (95% CI)	**177**	**129**		**2.24%**	**0.95[0.12,7.56]**
Total events: 2 (Low dose CNI), 1 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.71, df=1(P=0.4); I²=0%					
Test for overall effect: Z=0.05(P=0.96)					
Total (95% CI)	**1619**	**1487**		**100%**	**0.75[0.55,1.03]**
Total events: 71 (Low dose CNI), 90 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=10.74, df=12(P=0.55); I²=0%					
Test for overall effect: Z=1.78(P=0.07)					
Test for subgroup differences: Chi²=0.05, df=1 (P=0.83), I²=0%					

Favours low dose CNI 0.01 0.1 1 10 100 Favours standard dose CNI

Comparison 5.   Subgroup analysis (CNI type): low dose CNI versus standard dose CNI

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection	19	3757	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.00]
1.1 CsA	16	2906	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.76, 1.01]
1.2 TAC	2	371	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.61, 3.83]
1.3 Either CsA or TAC	1	480	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.34, 1.19]

Analysis 5.1.   Comparison 5 Subgroup analysis (CNI type): low dose CNI versus standard dose CNI, Outcome 1 Acute rejection.

Study or subgroup	Low dose CNI	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
5.1.1 CsA					
REFERENCE Study 2006	0/70	0/31			Not estimable
Pascual 2003	0/32	0/32			Not estimable
Baczkowska 2003	3/16	2/16		0.69%	1.5[0.29,7.81]
Andres 2009	2/38	5/40		0.76%	0.42[0.09,2.04]
DICAM Study 2010	6/106	3/101		1.02%	1.91[0.49,7.42]
Alsina 1987	3/25	7/25		1.24%	0.43[0.12,1.47]
Kreis 2003	8/87	5/80		1.63%	1.47[0.5,4.31]
Salvadori 2007	5/49	12/68		1.98%	0.58[0.22,1.54]
Budde 2007	7/44	8/45		2.2%	0.89[0.35,2.26]
Fangmann 2010	6/75	17/73		2.47%	0.34[0.14,0.82]
Cai 2014	10/90	12/90		3.05%	0.83[0.38,1.83]
Cibrik 2007	11/75	16/66		3.93%	0.61[0.3,1.21]
Chadban 2013	15/42	10/33		4.36%	1.18[0.61,2.27]
de Sevaux 2001	29/152	36/161		9.92%	0.85[0.55,1.32]
CAESAR Study 2007	48/183	47/172		15.92%	0.96[0.68,1.35]
SYMPHONY Study 2007	118/399	128/390		43.76%	0.9[0.73,1.11]
Subtotal (95% CI)	**1483**	**1423**		**92.94%**	**0.87[0.76,1.01]**
Total events: 271 (Low dose CNI), 308 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=12.08, df=13(P=0.52); I²=0%					
Test for overall effect: Z=1.88(P=0.06)					
5.1.2 TAC					
Chan 2012	2/151	0/141		0.21%	4.67[0.23,96.46]
MODIFY Study 2012	8/39	6/40		2.04%	1.37[0.52,3.58]
Subtotal (95% CI)	**190**	**181**		**2.24%**	**1.53[0.61,3.83]**
Total events: 10 (Low dose CNI), 6 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.59, df=1(P=0.44); I²=0%					
Test for overall effect: Z=0.91(P=0.36)					
5.1.3 Either CsA or TAC					
OPTICEPT Study 2009	15/243	23/237		4.82%	0.64[0.34,1.19]
Subtotal (95% CI)	**243**	**237**		**4.82%**	**0.64[0.34,1.19]**
Total events: 15 (Low dose CNI), 23 (Standard dose CNI)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.42(P=0.16)					
Total (95% CI)	**1916**	**1841**		**100%**	**0.87[0.76,1]**
Total events: 296 (Low dose CNI), 337 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=15.07, df=16(P=0.52); I²=0%					
Test for overall effect: Z=1.99(P=0.05)					
Test for subgroup differences: Chi²=2.42, df=1 (P=0.3), I²=17.44%					

Favours low dose CNI   0.01   0.1   1   10   100   Favours standard dose CNI

Comparison 6.   CNI withdrawal or avoidance + mTOR-I versus standard dose CNI

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Death	23	5427	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.68, 1.36]
1.1 Avoidance	9	1689	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.54, 1.47]
1.2 Withdrawal	14	3738	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.59, 1.76]
2 Acute rejection	30	5903	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.15, 1.78]
2.1 Unspecified	4	937	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.12, 1.60]
2.2 Biopsy-proven	26	4966	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.10, 1.85]
3 GFR	23	4427	Mean Difference (IV, Random, 95% CI)	5.29 [2.08, 8.51]
3.1 Six months	2	187	Mean Difference (IV, Random, 95% CI)	5.22 [-0.02, 10.46]
3.2 One year	16	3144	Mean Difference (IV, Random, 95% CI)	5.02 [0.59, 9.45]
3.3 Two years	4	796	Mean Difference (IV, Random, 95% CI)	6.08 [-0.85, 13.01]
3.4 Five years	1	300	Mean Difference (IV, Random, 95% CI)	6.30 [2.43, 10.17]
4 Graft loss	25	5446	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.19]
5 Serum creatinine at 1 year	12	1702	Mean Difference (IV, Random, 95% CI)	-17.10 [-26.95, -7.25]
6 Change in GFR	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 One year	1	246	Mean Difference (IV, Random, 95% CI)	6.10 [0.01, 12.19]
6.2 Two years	2	521	Mean Difference (IV, Random, 95% CI)	0.28 [-15.00, 15.56]
7 Adverse events	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Hypertension	7	2207	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.15]
7.2 Hyperlipidaemia	13	3494	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.40, 2.20]
7.3 CMV infection	13	2503	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.82]
7.4 Diabetes	11	2833	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.97, 1.66]
7.5 Malignancy	14	3699	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.47, 1.00]
7.6 Infection	9	1624	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.07]
7.7 Lymphocele	8	1926	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.95, 2.21]
8 Subgroup analysis: acute rejection	28	5480	Risk Ratio (M-H, Random, 95% CI)	1.56 [1.27, 1.91]
8.1 Avoidance	11	1844	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.98, 1.65]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.2 Late withdrawal	17	3636	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.44, 2.51]
9 Subgroup analysis: GFR	23	4427	Mean Difference (IV, Random, 95% CI)	5.29 [2.08, 8.51]
9.1 Avoidance	9	1748	Mean Difference (IV, Random, 95% CI)	6.45 [1.33, 11.58]
9.2 Late withdrawal	14	2679	Mean Difference (IV, Random, 95% CI)	4.55 [0.26, 8.85]
10 Subgroup analysis: graft loss	25	5446	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.19]
10.1 Avoidance	8	1420	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.72, 1.48]
10.2 Late withdrawal	17	4026	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.65, 1.30]

Analysis 6.1. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 1 Death.

Study or subgroup	CNI withdraw-al + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Avoidance					
Martinez-Mier 2006	0/20	0/21			Not estimable
Flechner-318 Study 2002	1/31	0/30		1.2%	2.91[0.12,68.66]
Schaefer 2006	2/41	0/39		1.33%	4.76[0.24,96.16]
SMART TX Study 2010	1/69	1/71		1.59%	1.03[0.07,16.13]
CALFREE Study 2010	1/63	2/64		2.13%	0.51[0.05,5.46]
Barsoum 2007	3/76	2/37		3.95%	0.73[0.13,4.18]
CENTRAL Study 2012	3/92	5/90		6.13%	0.59[0.14,2.38]
Stegall 2003	5/81	7/84		9.84%	0.74[0.25,2.24]
SYMPHONY Study 2007	14/390	14/390		22.76%	1[0.48,2.07]
Subtotal (95% CI)	**863**	**826**		**48.94%**	**0.89[0.54,1.47]**
Total events: 30 (CNI withdrawal + mTOR-I), 31 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=2.56, df=7(P=0.92); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
6.1.2 Withdrawal					
CONCEPT Study 2009	0/95	0/97			Not estimable
Spare-the-Nephron Study 2011	0/148	3/151		1.38%	0.15[0.01,2.8]
ASCERTAIN Study 2011	3/127	0/123		1.38%	6.78[0.35,129.94]
El-Agroudy 2014	3/29	0/29		1.41%	7[0.38,129.74]
Chhabra 2013	4/123	0/64		1.43%	4.72[0.26,86.28]
Holm 2008	0/220	5/185		1.44%	0.08[0,1.37]
Rivelli 2015	1/22	2/23		2.22%	0.52[0.05,5.36]
Grinyo 2004	2/25	2/26		3.4%	1.04[0.16,6.83]
APOLLO Study 2015	2/46	4/47		4.43%	0.51[0.1,2.65]
CONVERT Trial 2009	14/555	2/275		5.54%	3.47[0.79,15.15]
HERAKLES Study 2012	3/149	5/154		6.03%	0.62[0.15,2.55]
ZEUS Study 2011	4/155	4/145		6.44%	0.94[0.24,3.67]

Favours CNI withdrawal + mTOR-I 0.002 0.1 1 10 500 Favours standard dose CNI

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
RMR Study 2001	4/215	6/215		7.69%	0.67[0.19,2.33]
ORION Study 2011	7/155	4/140		8.26%	1.58[0.47,5.28]
Subtotal (95% CI)	**2064**	**1674**		**51.06%**	**1.02[0.59,1.76]**
Total events: 47 (CNI withdrawal + mTOR-I), 37 (Standard dose CNI)					
Heterogeneity: Tau²=0.15; Chi²=14.17, df=12(P=0.29); I²=15.29%					
Test for overall effect: Z=0.07(P=0.94)					
Total (95% CI)	**2927**	**2500**		**100%**	**0.96[0.68,1.36]**
Total events: 77 (CNI withdrawal + mTOR-I), 68 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=16.89, df=20(P=0.66); I²=0%					
Test for overall effect: Z=0.24(P=0.81)					
Test for subgroup differences: Chi²=0.12, df=1 (P=0.72), I²=0%					

Favours CNI withdrawal + mTOR-I 0.002 0.1 1 10 500 Favours standard dose CNI

Analysis 6.2. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 2 Acute rejection.

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
6.2.1 Unspecified					
MECANO Study 2009	0/38	1/39		0.45%	0.34[0.01,8.14]
Martinez-Mier 2006	3/20	1/21		0.9%	3.15[0.36,27.83]
Pacheco-Silva 2013	4/15	2/15		1.65%	2[0.43,9.32]
SYMPHONY Study 2007	174/399	128/390		9.07%	1.33[1.11,1.59]
Subtotal (95% CI)	**472**	**465**		**12.07%**	**1.34[1.12,1.6]**
Total events: 181 (CNI withdrawal + mTOR-I), 132 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=1.57, df=3(P=0.67); I²=0%					
Test for overall effect: Z=3.2(P=0)					
6.2.2 Biopsy-proven					
APOLLO Study 2015	0/46	0/47			Not estimable
Pontrelli 2008	0/12	0/6			Not estimable
Bansal 2013	2/29	0/31		0.5%	5.33[0.27,106.61]
Rivelli 2015	1/22	1/23		0.6%	1.05[0.07,15.7]
Schaefer 2006	5/41	1/39		0.96%	4.76[0.58,38.91]
Stallone 2003	2/20	2/20		1.19%	1[0.16,6.42]
Flechner-318 Study 2002	2/31	5/30		1.61%	0.39[0.08,1.84]
El-Agroudy 2014	4/29	3/29		1.91%	1.33[0.33,5.44]
ASCERTAIN Study 2011	7/127	3/123		2.09%	2.26[0.6,8.54]
Stallone 2004	4/42	5/48		2.3%	0.91[0.26,3.18]
CONVERT Trial 2009	12/555	4/275		2.7%	1.49[0.48,4.57]
Nafar 2012	4/50	9/50		2.74%	0.44[0.15,1.35]
Grinyo 2004	10/44	4/43		2.84%	2.44[0.83,7.2]
CERTITEM Study 2015	26/96	5/98		3.56%	5.31[2.13,13.25]
Barsoum 2007	10/76	7/36		3.73%	0.68[0.28,1.63]
Spare-the-Nephron Study 2011	11/148	9/151		3.89%	1.25[0.53,2.92]
CONCEPT Study 2009	16/95	8/97		4.18%	2.04[0.92,4.55]
SMART TX Study 2010	12/69	11/71		4.5%	1.12[0.53,2.37]

Favours CNI withdrawal + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Stegall 2003	15/80	12/82		4.86%	1.28[0.64,2.56]
ORION Study 2011	47/152	11/139		5.45%	3.91[2.11,7.23]
Holm 2008	14/220	29/185		5.51%	0.41[0.22,0.75]
HERAKLES Study 2012	24/149	19/151		5.9%	1.28[0.73,2.24]
ZEUS Study 2011	36/155	16/145		6.02%	2.1[1.22,3.63]
CENTRAL Study 2012	40/102	21/100		6.83%	1.87[1.19,2.93]
RMR Study 2001	43/215	29/215		7%	1.48[0.96,2.28]
CALFREE Study 2010	29/63	23/64		7.08%	1.28[0.84,1.95]
Subtotal (95% CI)	**2668**	**2298**		**87.93%**	**1.43[1.1,1.85]**
Total events: 376 (CNI withdrawal + mTOR-I), 237 (Standard dose CNI)					
Heterogeneity: Tau²=0.2; Chi²=53.71, df=23(P=0); I²=57.18%					
Test for overall effect: Z=2.65(P=0.01)					
Total (95% CI)	**3140**	**2763**		**100%**	**1.43[1.15,1.78]**
Total events: 557 (CNI withdrawal + mTOR-I), 369 (Standard dose CNI)					
Heterogeneity: Tau²=0.13; Chi²=55.81, df=27(P=0); I²=51.62%					
Test for overall effect: Z=3.23(P=0)					
Test for subgroup differences: Chi²=0.15, df=1 (P=0.69), I²=0%					

Favours CNI withdrawal + mTOR-I   0.005   0.1   1   10   200   Favours standard dose CNI

Analysis 6.3.   Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 3 GFR.

Study or subgroup	CNI withdrawal + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
6.3.1 Six months							
Bansal 2013	31	88.9 (11.8)	29	80.6 (16.5)		4.15%	8.3[1,15.6]
CALFREE Study 2010	63	45.3 (20)	64	42.4 (14.9)		4.43%	2.9[-3.24,9.04]
Subtotal ***	**94**		**93**			**8.57%**	**5.22[-0.02,10.46]**
Heterogeneity: Tau²=2.73; Chi²=1.23, df=1(P=0.27); I²=18.73%							
Test for overall effect: Z=1.95(P=0.05)							
6.3.2 One year							
Stallone 2003	15	60 (20)	15	54 (14)		2.97%	6[-6.35,18.35]
Martinez-Mier 2006	20	73.2 (19.1)	21	67.5 (18.6)		3.14%	5.64[-5.91,17.19]
Flechner-318 Study 2002	31	81.1 (23.9)	30	61.1 (14.6)		3.52%	20[10.1,29.9]
Grinyo 2004	44	71.4 (18.8)	43	64.3 (22.8)		3.78%	7.1[-1.69,15.89]
Nafar 2012	50	82.3 (24.3)	50	73.2 (19.2)		3.83%	9.1[0.52,17.68]
MECANO Study 2009	38	44 (15)	39	55 (20)		4.01%	-11[-18.88,-3.12]
Rivelli 2015	22	68.1 (9.1)	23	57 (16.6)		4.03%	11.1[3.32,18.88]
SMART TX Study 2010	69	55.3 (21.4)	71	46.5 (19.3)		4.28%	8.8[2.04,15.56]
CENTRAL Study 2012	102	68.1 (21.5)	110	69.4 (22.9)		4.46%	-1.3[-7.28,4.68]
Stegall 2003	81	63 (18)	84	61 (19)		4.54%	2[-3.65,7.65]
ORION Study 2011	152	59.3 (24.3)	139	62 (22.1)		4.61%	-2.7[-8.03,2.63]
Stallone 2004	42	61.5 (11.2)	48	60.3 (9.2)		4.83%	1.2[-3.07,5.47]
CONCEPT Study 2009	85	69 (13)	96	64 (13)		4.92%	5[1.21,8.79]
RMR Study 2001	215	62.7 (22)	215	56.6 (17.6)		4.92%	6.1[2.34,9.86]
SYMPHONY Study 2007	399	56.7 (26.9)	390	57.1 (25.1)		4.94%	-0.4[-4.03,3.23]
Holm 2008	220	48.8 (10.2)	185	32.7 (5.4)		5.21%	16.1[14.54,17.66]

Favours standard dose CNI   -50   -25   0   25   50   Favours CNI withdrawal + mTOR-I

Study or subgroup	CNI withdraw-al + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Subtotal ***	1585		1559			67.99%	5.02[0.59,9.45]
Heterogeneity: Tau²=69.08; Chi²=191.28, df=15(P<0.0001); I²=92.16%							
Test for overall effect: Z=2.22(P=0.03)							
6.3.3 Two years							
Chhabra 2013	123	66.7 (21.5)	64	64.2 (22)		4.32%	2.5[-4.09,9.09]
ASCERTAIN Study 2011	94	48 (22)	103	46 (20.4)		4.47%	1.98[-3.96,7.92]
Spare-the-Nephron Study 2011	148	75.5 (19.2)	151	71.2 (23.5)		4.71%	4.3[-0.56,9.16]
Barsoum 2007	76	70.2 (8)	37	55.9 (7.8)		5.03%	14.3[11.21,17.39]
Subtotal ***	441		355			18.53%	6.08[-0.85,13.01]
Heterogeneity: Tau²=42.89; Chi²=23.99, df=3(P<0.0001); I²=87.49%							
Test for overall effect: Z=1.72(P=0.09)							
6.3.4 Five years							
ZEUS Study 2011	155	66.7 (17.4)	145	60.4 (16.8)		4.9%	6.3[2.43,10.17]
Subtotal ***	155		145			4.9%	6.3[2.43,10.17]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.19(P=0)							
Total ***	2275		2152			100%	5.29[2.08,8.51]
Heterogeneity: Tau²=51; Chi²=220.92, df=22(P<0.0001); I²=90.04%							
Test for overall effect: Z=3.23(P=0)							
Test for subgroup differences: Chi²=0.23, df=1 (P=0.97), I²=0%							

Favours standard dose CNI -50 -25 0 25 50 Favours CNI withdrawal + mTOR-I

Analysis 6.4. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 4 Graft loss.

Study or subgroup	CNI withdraw-al + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
CONCEPT Study 2009	0/95	1/97		0.53%	0.34[0.01,8.25]
Bansal 2013	1/29	0/31		0.54%	3.2[0.14,75.55]
Pacheco-Silva 2013	1/15	0/16		0.55%	3.19[0.14,72.69]
El-Agroudy 2014	2/29	0/29		0.6%	5[0.25,99.82]
SMART TX Study 2010	1/69	1/71		0.71%	1.03[0.07,16.13]
Flechner-318 Study 2002	1/31	1/30		0.72%	0.97[0.06,14.78]
Watson 2005	1/19	1/19		0.74%	1[0.07,14.85]
APOLLO Study 2015	3/46	1/47		1.08%	3.07[0.33,28.4]
Schaefer 2006	3/41	1/39		1.09%	2.85[0.31,26.28]
CERTITEM Study 2015	5/96	1/98		1.19%	5.1[0.61,42.89]
Martinez-Mier 2006	2/20	2/21		1.55%	1.05[0.16,6.76]
Chhabra 2013	3/123	2/64		1.73%	0.78[0.13,4.55]
Rivelli 2015	3/22	2/23		1.88%	1.57[0.29,8.51]
Grinyo 2004	3/25	3/26		2.38%	1.04[0.23,4.68]
ZEUS Study 2011	4/155	3/145		2.46%	1.25[0.28,5.48]
Spare-the-Nephron Study 2011	3/148	4/151		2.46%	0.77[0.17,3.36]
Barsoum 2007	6/76	4/37		3.72%	0.73[0.22,2.43]
ASCERTAIN Study 2011	7/127	6/123		4.77%	1.13[0.39,3.27]
RMR Study 2001	6/215	9/215		5.21%	0.67[0.24,1.84]

Favours CNI withdrawal + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

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Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
HERAKLES Study 2012	6/149	9/151		5.29%	0.68[0.25,1.85]
ORION Study 2011	14/155	5/139		5.43%	2.51[0.93,6.79]
Holm 2008	6/220	18/185		6.59%	0.28[0.11,0.69]
Stegall 2003	10/81	10/84		7.96%	1.04[0.46,2.36]
CONVERT Trial 2009	27/555	18/275		16.06%	0.74[0.42,1.33]
SYMPHONY Study 2007	33/399	32/390		24.77%	1.01[0.63,1.61]
Total (95% CI)	2940	2506		100%	0.94[0.75,1.19]

Total events: 151 (CNI withdrawal + mTOR-I), 134 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=20.44, df=24(P=0.67); I²=0%

Test for overall effect: Z=0.51(P=0.61)

Favours CNI withdrawal + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

Analysis 6.5. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 5 Serum creatinine at 1 year.

Study or subgroup	CNI withdrawal + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Rossini 2007	6	137.9 (48.6)	6	206 (166.2)		0.49%	-68.07[-206.62,70.48]
Flechner-318 Study 2002	31	116.7 (29.2)	30	157.4 (67.2)		6.7%	-40.67[-66.81,-14.53]
Stallone 2003	15	114.9 (35.4)	15	176.8 (35.4)		6.9%	-61.9[-87.21,-36.59]
SMART TX Study 2010	69	133.5 (52.2)	70	165.3 (86.6)		7.31%	-31.8[-55.53,-8.07]
Rivelli 2015	22	106.1 (35.4)	23	123.8 (35.4)		8.14%	-17.68[-38.35,2.99]
Spare-the-Nephron Study 2011	148	126.2 (82.8)	151	145 (96.5)		8.22%	-18.8[-39.17,1.57]
Martinez-Mier 2006	20	118.5 (30.9)	21	114.9 (28.3)		8.86%	3.53[-14.64,21.7]
Schaefer 2006	41	114.9 (35.4)	39	132.6 (35.4)		9.65%	-17.7[-33.2,-2.2]
RMR Study 2001	215	158 (61.6)	215	141.6 (77.7)		10.31%	16.4[3.15,29.65]
ZEUS Study 2011	149	127.8 (42.2)	135	143.2 (51.5)		10.95%	-15.4[-26.42,-4.38]
Nafar 2012	50	111.4 (28.3)	50	123.8 (26.5)		11.02%	-12.38[-23.13,-1.63]
CONCEPT Study 2009	85	117.4 (31.5)	96	132.3 (30.6)		11.45%	-14.9[-23.97,-5.83]
Total ***	851		851			100%	-17.1[-26.95,-7.25]

Heterogeneity: Tau²=199.12; Chi²=44.95, df=11(P<0.0001); I²=75.53%

Test for overall effect: Z=3.4(P=0)

Favours CNI withdrawal + mTOR-I -200 -100 0 100 200 Favours standard dose CNI

Analysis 6.6. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 6 Change in GFR.

Study or subgroup	CNI withdrawal + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
6.6.1 One year							
Spare-the-Nephron Study 2011	123	5.2 (25.3)	123	-0.9 (23.4)		100%	6.1[0.01,12.19]
Subtotal ***	123		123			100%	6.1[0.01,12.19]

Favours CNI withdrawal + mTOR-I -20 -10 0 10 20 Favours standard dose CNI

Study or subgroup	CNI withdrawal + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=1.96(P=0.05)							
6.6.2 Two years							
Spare-the-Nephron Study 2011	148	6.5 (28.4)	151	-1.8 (27.3)		48.57%	8.3[1.98,14.62]
ASCERTAIN Study 2011	112	-5.7 (14.7)	110	1.6 (12.8)		51.43%	-7.3[-10.92,-3.68]
Subtotal ***	**260**		**261**			**100%**	**0.28[-15,15.56]**
Heterogeneity: Tau²=114.78; Chi²=17.63, df=1(P<0.0001); I²=94.33%							
Test for overall effect: Z=0.04(P=0.97)							
Test for subgroup differences: Chi²=0.48, df=1 (P=0.49), I²=0%							

Favours CNI withdrawal + mTOR-I −20 −10 0 10 20 Favours standard dose CNI

Analysis 6.7. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 7 Adverse events.

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
6.7.1 Hypertension					
ASCERTAIN Study 2011	13/127	6/123		6.55%	2.1[0.82,5.35]
Spare-the-Nephron Study 2011	25/148	20/151		11.93%	1.28[0.74,2.19]
RMR Study 2001	19/215	46/215		12.73%	0.41[0.25,0.68]
SYMPHONY Study 2007	45/380	55/384		15.41%	0.83[0.57,1.19]
ORION Study 2011	54/152	48/139		16.52%	1.03[0.75,1.41]
Barsoum 2007	40/76	33/37		17.94%	0.59[0.46,0.75]
Bansal 2013	26/29	27/31		18.93%	1.03[0.86,1.24]
Subtotal (95% CI)	**1127**	**1080**		**100%**	**0.86[0.64,1.15]**
Total events: 222 (CNI withdrawal + mTOR-I), 235 (Standard dose CNI)					
Heterogeneity: Tau²=0.11; Chi²=28.33, df=6(P<0.0001); I²=78.82%					
Test for overall effect: Z=1.01(P=0.31)					
6.7.2 Hyperlipidaemia					
Pontrelli 2008	7/12	0/6		0.67%	8.08[0.54,121.54]
Watson 2005	10/19	1/19		1.25%	10[1.42,70.63]
CONCEPT Study 2009	8/96	4/97		3.16%	2.02[0.63,6.49]
SMART TX Study 2010	14/69	5/71		4.3%	2.88[1.1,7.57]
ASCERTAIN Study 2011	18/127	6/123		4.88%	2.91[1.19,7.08]
CENTRAL Study 2012	13/102	9/100		5.67%	1.42[0.63,3.16]
Barsoum 2007	25/76	8/36		6.99%	1.48[0.74,2.95]
ZEUS Study 2011	22/155	15/145		8.06%	1.37[0.74,2.54]
Spare-the-Nephron Study 2011	36/148	16/153		9.29%	2.33[1.35,4.01]
Flechner-318 Study 2002	20/31	16/30		11.77%	1.21[0.79,1.85]
ORION Study 2011	65/152	28/139		12.87%	2.12[1.45,3.1]
SYMPHONY Study 2007	60/380	57/384		14%	1.06[0.76,1.48]
CONVERT Trial 2009	295/551	72/273		17.1%	2.03[1.64,2.51]
Subtotal (95% CI)	**1918**	**1576**		**100%**	**1.76[1.4,2.2]**
Total events: 593 (CNI withdrawal + mTOR-I), 237 (Standard dose CNI)					
Heterogeneity: Tau²=0.07; Chi²=23.32, df=12(P=0.03); I²=48.54%					
Test for overall effect: Z=4.88(P<0.0001)					

Favours CNI withdrawal + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Study or subgroup	CNI withdraw-al + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.7.3 CMV infection					
MECANO Study 2009	0/38	0/39			Not estimable
Martinez-Mier 2006	1/20	0/21		0.94%	3.14[0.14,72.92]
Schaefer 2006	0/41	2/39		1.03%	0.19[0.01,3.85]
Flechner-318 Study 2002	3/31	2/30		2.9%	1.45[0.26,8.09]
Chhabra 2013	7/123	3/64		4.53%	1.21[0.32,4.54]
CONCEPT Study 2009	4/96	6/97		5.05%	0.67[0.2,2.31]
SMART TX Study 2010	5/69	20/71		7.75%	0.26[0.1,0.65]
Spare-the-Nephron Study 2011	7/148	15/153		8.4%	0.48[0.2,1.15]
CENTRAL Study 2012	9/102	13/100		9.26%	0.68[0.3,1.52]
CALFREE Study 2010	7/63	22/64		9.66%	0.32[0.15,0.7]
ZEUS Study 2011	28/155	27/145		15.41%	0.97[0.6,1.56]
SYMPHONY Study 2007	25/380	59/384		16.16%	0.43[0.27,0.67]
Pacheco-Silva 2013	11/15	14/15		18.91%	0.79[0.56,1.1]
Subtotal (95% CI)	**1281**	**1222**		**100%**	**0.6[0.44,0.82]**

Total events: 107 (CNI withdrawal + mTOR-I), 183 (Standard dose CNI)

Heterogeneity: Tau²=0.1; Chi²=19.31, df=11(P=0.06); I²=43.04%

Test for overall effect: Z=3.18(P=0)

Study or subgroup	CNI withdraw-al + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio	Weight	Risk Ratio
6.7.4 Diabetes					
Flechner-318 Study 2002	0/31	2/30		0.82%	0.19[0.01,3.88]
Martinez-Mier 2006	1/20	1/21		1%	1.05[0.07,15.68]
Grinyo 2004	1/44	3/43		1.48%	0.33[0.04,3.01]
CONCEPT Study 2009	3/96	2/97		2.35%	1.52[0.26,8.87]
Barsoum 2007	3/76	3/37		3.05%	0.49[0.1,2.3]
SMART TX Study 2010	5/69	4/71		4.53%	1.29[0.36,4.59]
ASCERTAIN Study 2011	6/127	4/123		4.77%	1.45[0.42,5.02]
Bansal 2013	9/29	7/31		10.21%	1.37[0.59,3.21]
ZEUS Study 2011	20/155	15/145		18.5%	1.25[0.66,2.34]
SYMPHONY Study 2007	25/380	23/384		24.42%	1.1[0.63,1.9]
CONVERT Trial 2009	62/551	18/273		28.86%	1.71[1.03,2.83]
Subtotal (95% CI)	**1578**	**1255**		**100%**	**1.27[0.97,1.66]**

Total events: 135 (CNI withdrawal + mTOR-I), 82 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=6.15, df=10(P=0.8); I²=0%

Test for overall effect: Z=1.72(P=0.09)

Study or subgroup	CNI withdraw-al + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio	Weight	Risk Ratio
6.7.5 Malignancy					
CONCEPT Study 2009	1/96	0/97		1.34%	3.03[0.13,73.49]
APOLLO Study 2015	0/46	1/47		1.35%	0.34[0.01,8.15]
SMART TX Study 2010	0/69	4/71		1.61%	0.11[0.01,2.08]
Barsoum 2007	4/76	0/37		1.62%	4.44[0.25,80.38]
Stegall 2003	1/80	2/82		2.35%	0.51[0.05,5.54]
Chhabra 2013	4/123	1/64		2.79%	2.08[0.24,18.24]
ORION Study 2011	1/152	5/139		2.88%	0.18[0.02,1.55]
Flechner-318 Study 2002	3/26	6/23		7.26%	0.44[0.12,1.57]
SYMPHONY Study 2007	6/380	5/384		8.18%	1.21[0.37,3.94]
Schaefer 2006	6/41	5/39		9.09%	1.14[0.38,3.44]
CENTRAL Study 2012	7/102	7/100		10.4%	0.98[0.36,2.69]
Spare-the-Nephron Study 2011	7/148	10/153		11.59%	0.72[0.28,1.85]
ZEUS Study 2011	14/155	14/145		16.95%	0.94[0.46,1.89]

0.005   0.1   1   10   200

Favours CNI withdrawal + mTOR-I   Favours standard dose CNI

Study or subgroup	CNI withdraw-al + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
CONVERT Trial 2009	21/551	30/273		22.6%	0.35[0.2,0.59]
Subtotal (95% CI)	**2045**	**1654**		**100%**	**0.69[0.47,1]**

Total events: 75 (CNI withdrawal + mTOR-I), 90 (Standard dose CNI)

Heterogeneity: Tau²=0.09; Chi²=15.98, df=13(P=0.25); I²=18.64%

Test for overall effect: Z=1.96(P=0.05)

6.7.6 Infection

Martinez-Mier 2006	1/20	0/20		0.06%	3[0.13,69.52]
Schaefer 2006	0/41	2/39		0.06%	0.19[0.01,3.85]
Barsoum 2007	9/76	4/37		0.45%	1.1[0.36,3.32]
RMR Study 2001	29/215	26/215		2.29%	1.12[0.68,1.83]
Spare-the-Nephron Study 2011	28/148	34/153		2.82%	0.85[0.54,1.33]
APOLLO Study 2015	24/46	20/47		3%	1.23[0.8,1.89]
CALFREE Study 2010	29/63	37/64		4.86%	0.8[0.57,1.12]
SMART TX Study 2010	36/69	43/71		6.5%	0.86[0.64,1.16]
ZEUS Study 2011	137/155	127/145		79.96%	1.01[0.93,1.1]
Subtotal (95% CI)	**833**	**791**		**100%**	**0.99[0.92,1.07]**

Total events: 293 (CNI withdrawal + mTOR-I), 293 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=6.36, df=8(P=0.61); I²=0%

Test for overall effect: Z=0.25(P=0.81)

6.7.7 Lymphocele

Martinez-Mier 2006	0/20	0/21			Not estimable
CALFREE Study 2010	9/63	2/64		6.29%	4.57[1.03,20.33]
Flechner-318 Study 2002	4/31	3/30		6.86%	1.29[0.31,5.29]
CENTRAL Study 2012	7/102	3/100		7.55%	2.29[0.61,8.6]
ORION Study 2011	25/152	12/139		17.25%	1.91[1,3.64]
SMART TX Study 2010	19/69	17/71		19.15%	1.15[0.65,2.02]
SYMPHONY Study 2007	44/380	24/384		21.22%	1.85[1.15,2.98]
ZEUS Study 2011	26/155	34/145		21.68%	0.72[0.45,1.13]
Subtotal (95% CI)	**972**	**954**		**100%**	**1.45[0.95,2.21]**

Total events: 134 (CNI withdrawal + mTOR-I), 95 (Standard dose CNI)

Heterogeneity: Tau²=0.16; Chi²=13.75, df=6(P=0.03); I²=56.37%

Test for overall effect: Z=1.72(P=0.08)

Test for subgroup differences: Chi²=44.44, df=1 (P<0.0001), I²=86.5%

Favours CNI withdrawal + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Analysis 6.8. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 8 Subgroup analysis: acute rejection.

Study or subgroup	CNI withdraw-al + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
6.8.1 Avoidance					
Martinez-Mier 2006	3/20	1/21		0.83%	3.15[0.36,27.83]
Schaefer 2006	5/41	1/39		0.89%	4.76[0.58,38.91]
Flechner-318 Study 2002	2/31	5/30		1.53%	0.39[0.08,1.84]
Pacheco-Silva 2013	4/15	2/15		1.57%	2[0.43,9.32]
Nafar 2012	4/50	9/50		2.73%	0.44[0.15,1.35]

Favours CNI withdrawal + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Study or subgroup	CNI withdrawal + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Barsoum 2007	10/76	7/36		3.89%	0.68[0.28,1.63]
SMART TX Study 2010	12/69	11/71		4.86%	1.12[0.53,2.37]
Stegall 2003	15/80	12/82		5.35%	1.28[0.64,2.56]
CENTRAL Study 2012	28/102	11/100		5.88%	2.5[1.32,4.74]
CALFREE Study 2010	29/63	23/64		8.72%	1.28[0.84,1.95]
SYMPHONY Study 2007	174/399	128/390		12.54%	1.33[1.11,1.59]
Subtotal (95% CI)	**946**	**898**		**48.77%**	**1.27[0.98,1.65]**
Total events: 286 (CNI withdrawal + mTOR-I), 210 (Standard dose CNI)					
Heterogeneity: Tau²=0.05; Chi²=14.59, df=10(P=0.15); I²=31.48%					
Test for overall effect: Z=1.8(P=0.07)					
6.8.2 Late withdrawal					
APOLLO Study 2015	0/46	0/47			Not estimable
MECANO Study 2009	0/38	1/39		0.4%	0.34[0.01,8.14]
Bansal 2013	2/29	0/31		0.45%	5.33[0.27,106.61]
Rivelli 2015	1/22	1/23		0.55%	1.05[0.07,15.7]
Stallone 2003	2/20	2/20		1.11%	1[0.16,6.42]
El-Agroudy 2014	4/29	3/29		1.84%	1.33[0.33,5.44]
ASCERTAIN Study 2011	7/127	3/123		2.02%	2.26[0.6,8.54]
Stallone 2004	4/42	5/48		2.25%	0.91[0.26,3.18]
CONVERT Trial 2009	12/555	4/275		2.68%	1.49[0.48,4.57]
Grinyo 2004	10/44	4/43		2.85%	2.44[0.83,7.2]
ZEUS Study 2011	15/154	5/146		3.28%	2.84[1.06,7.63]
CERTITEM Study 2015	26/96	5/98		3.68%	5.31[2.13,13.25]
Spare-the-Nephron Study 2011	11/148	9/151		4.08%	1.25[0.53,2.92]
CONCEPT Study 2009	16/95	8/97		4.44%	2.04[0.92,4.55]
ORION Study 2011	47/152	11/139		6.16%	3.91[2.11,7.23]
HERAKLES Study 2012	24/149	19/151		6.84%	1.28[0.73,2.24]
RMR Study 2001	43/215	29/215		8.59%	1.48[0.96,2.28]
Subtotal (95% CI)	**1961**	**1675**		**51.23%**	**1.9[1.44,2.51]**
Total events: 224 (CNI withdrawal + mTOR-I), 109 (Standard dose CNI)					
Heterogeneity: Tau²=0.06; Chi²=19.39, df=15(P=0.2); I²=22.64%					
Test for overall effect: Z=4.56(P<0.0001)					
Total (95% CI)	**2907**	**2573**		**100%**	**1.56[1.27,1.91]**
Total events: 510 (CNI withdrawal + mTOR-I), 319 (Standard dose CNI)					
Heterogeneity: Tau²=0.08; Chi²=41.24, df=26(P=0.03); I²=36.95%					
Test for overall effect: Z=4.24(P<0.0001)					
Test for subgroup differences: Chi²=4.35, df=1 (P=0.04), I²=76.99%					

Favours CNI withdrawal + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Analysis 6.9. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 9 Subgroup analysis: GFR.

Study or subgroup	CNI withdrawal + mTOR-I N	Mean(SD)	Standard dose CNI N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.9.1 Avoidance							
Martinez-Mier 2006	20	73.2 (19.1)	21	67.5 (18.6)		3.14%	5.64[-5.91,17.19]

Favours CNI withdrawal + mTOR-I -50 -25 0 25 50 Favours standard dose CNI

Study or subgroup	CNI withdrawal + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Flechner-318 Study 2002	31	81.1 (23.9)	30	61.1 (14.6)		3.52%	20[10.1,29.9]
Nafar 2012	50	82.3 (24.3)	50	73.2 (19.2)		3.83%	9.1[0.52,17.68]
SMART TX Study 2010	69	55.3 (21.4)	71	46.5 (19.3)		4.28%	8.8[2.04,15.56]
CALFREE Study 2010	63	45.3 (20)	64	42.4 (14.9)		4.43%	2.9[-3.24,9.04]
CENTRAL Study 2012	102	68.1 (21.5)	110	69.4 (22.9)		4.46%	-1.3[-7.28,4.68]
Stegall 2003	81	63 (18)	84	61 (19)		4.54%	2[-3.65,7.65]
SYMPHONY Study 2007	399	56.7 (26.9)	390	57.1 (25.1)		4.94%	-0.4[-4.03,3.23]
Barsoum 2007	76	70.2 (8)	37	55.9 (7.8)		5.03%	14.3[11.21,17.39]
Subtotal ***	891		857			38.17%	6.45[1.33,11.58]
Heterogeneity: Tau²=49.2; Chi²=56.58, df=8(P<0.0001); I²=85.86%							
Test for overall effect: Z=2.47(P=0.01)							
6.9.2 Late withdrawal							
Stallone 2003	15	60 (20)	15	54 (14)		2.97%	6[-6.35,18.35]
Grinyo 2004	44	71.4 (18.8)	43	64.3 (22.8)		3.78%	7.1[-1.69,15.89]
MECANO Study 2009	38	44 (15)	39	55 (20)		4.01%	-11[-18.88,-3.12]
Rivelli 2015	22	68.1 (9.1)	23	57 (16.6)		4.03%	11.1[3.32,18.88]
Bansal 2013	31	88.9 (11.8)	29	80.6 (16.5)		4.15%	8.3[1,15.6]
Chhabra 2013	123	66.7 (21.5)	64	64.2 (22)		4.32%	2.5[-4.09,9.09]
ASCERTAIN Study 2011	94	48 (22)	103	46 (20.4)		4.47%	1.98[-3.96,7.92]
ORION Study 2011	152	59.3 (24.3)	139	62 (22.1)		4.61%	-2.7[-8.03,2.63]
Spare-the-Nephron Study 2011	148	75.5 (19.2)	151	71.2 (23.5)		4.71%	4.3[-0.56,9.16]
Stallone 2004	42	61.5 (11.2)	48	60.3 (9.2)		4.83%	1.2[-3.07,5.47]
ZEUS Study 2011	155	66.7 (17.4)	145	60.4 (16.8)		4.9%	6.3[2.43,10.17]
CONCEPT Study 2009	85	69 (13)	96	64 (13)		4.92%	5[1.21,8.79]
RMR Study 2001	215	62.7 (22)	215	56.6 (17.6)		4.92%	6.1[2.34,9.86]
Holm 2008	220	48.8 (10.2)	185	32.7 (5.4)		5.21%	16.1[14.54,17.66]
Subtotal ***	1384		1295			61.83%	4.55[0.26,8.85]
Heterogeneity: Tau²=57.21; Chi²=156.55, df=13(P<0.0001); I²=91.7%							
Test for overall effect: Z=2.08(P=0.04)							
Total ***	2275		2152			100%	5.29[2.08,8.51]
Heterogeneity: Tau²=51; Chi²=220.92, df=22(P<0.0001); I²=90.04%							
Test for overall effect: Z=3.23(P=0)							
Test for subgroup differences: Chi²=0.31, df=1 (P=0.58), I²=0%							

Favours CNI withdrawal + mTOR-I -50 -25 0 25 50 Favours standard dose CNI

Analysis 6.10. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 10 Subgroup analysis: graft loss.

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
6.10.1 Avoidance					
Pacheco-Silva 2013	1/15	0/16		0.55%	3.19[0.14,72.69]
SMART TX Study 2010	1/69	1/71		0.71%	1.03[0.07,16.13]
Flechner-318 Study 2002	1/31	1/30		0.72%	0.97[0.06,14.78]
Schaefer 2006	3/41	1/39		1.09%	2.85[0.31,26.28]
Martinez-Mier 2006	2/20	2/21		1.55%	1.05[0.16,6.76]

Favours CNI withdrawal + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

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Study or subgroup	CNI withdraw-al + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Barsoum 2007	6/76	4/37		3.72%	0.73[0.22,2.43]
Stegall 2003	10/81	10/84		7.96%	1.04[0.46,2.36]
SYMPHONY Study 2007	33/399	32/390		24.77%	1.01[0.63,1.61]
Subtotal (95% CI)	**732**	**688**		**41.08%**	**1.03[0.72,1.48]**
Total events: 57 (CNI withdrawal + mTOR-I), 51 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=1.64, df=7(P=0.98); I²=0%					
Test for overall effect: Z=0.15(P=0.88)					
6.10.2 Late withdrawal					
CONCEPT Study 2009	0/95	1/97		0.53%	0.34[0.01,8.25]
Bansal 2013	1/29	0/31		0.54%	3.2[0.14,75.55]
El-Agroudy 2014	2/29	0/29		0.6%	5[0.25,99.82]
Watson 2005	1/19	1/19		0.74%	1[0.07,14.85]
APOLLO Study 2015	3/46	1/47		1.08%	3.07[0.33,28.4]
CERTITEM Study 2015	5/96	1/98		1.19%	5.1[0.61,42.89]
Chhabra 2013	3/123	2/64		1.73%	0.78[0.13,4.55]
Rivelli 2015	3/22	2/23		1.88%	1.57[0.29,8.51]
Grinyo 2004	3/25	3/26		2.38%	1.04[0.23,4.68]
ZEUS Study 2011	4/155	3/145		2.46%	1.25[0.28,5.48]
Spare-the-Nephron Study 2011	3/148	4/151		2.46%	0.77[0.17,3.36]
ASCERTAIN Study 2011	7/127	6/123		4.77%	1.13[0.39,3.27]
RMR Study 2001	6/215	9/215		5.21%	0.67[0.24,1.84]
HERAKLES Study 2012	6/149	9/151		5.29%	0.68[0.25,1.85]
ORION Study 2011	14/155	5/139		5.43%	2.51[0.93,6.79]
Holm 2008	6/220	18/185		6.59%	0.28[0.11,0.69]
CONVERT Trial 2009	27/555	18/275		16.06%	0.74[0.42,1.33]
Subtotal (95% CI)	**2208**	**1818**		**58.92%**	**0.92[0.65,1.3]**
Total events: 94 (CNI withdrawal + mTOR-I), 83 (Standard dose CNI)					
Heterogeneity: Tau²=0.07; Chi²=18.42, df=16(P=0.3); I²=13.12%					
Test for overall effect: Z=0.46(P=0.64)					
Total (95% CI)	**2940**	**2506**		**100%**	**0.94[0.75,1.19]**
Total events: 151 (CNI withdrawal + mTOR-I), 134 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=20.44, df=24(P=0.67); I²=0%					
Test for overall effect: Z=0.51(P=0.61)					
Test for subgroup differences: Chi²=0.19, df=1 (P=0.67), I²=0%					

Favours CNI withdrawal + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

Comparison 7.   Subgroup analysis (CNI type): CNI withdrawal + mTOR-I versus standard dose CNI

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Acute rejection	30	5903	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.15, 1.78]
1.1 CsA	18	3463	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.15, 1.76]
1.2 TAC	7	753	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.43, 3.49]
1.3 Either CsA or TAC	5	1687	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.40, 2.33]

Analysis 7.1. Comparison 7 Subgroup analysis (CNI type): CNI withdrawal + mTOR-I versus standard dose CNI, Outcome 1 Acute rejection.

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
7.1.1 CsA					
Pontrelli 2008	0/12	0/6			Not estimable
MECANO Study 2009	0/38	1/39		0.45%	0.34[0.01,8.14]
Martinez-Mier 2006	3/20	1/21		0.9%	3.15[0.36,27.83]
Stallone 2003	2/20	2/20		1.19%	1[0.16,6.42]
Flechner-318 Study 2002	2/31	5/30		1.61%	0.39[0.08,1.84]
ASCERTAIN Study 2011	7/127	3/123		2.09%	2.26[0.6,8.54]
Stallone 2004	4/42	5/48		2.3%	0.91[0.26,3.18]
Nafar 2012	4/50	9/50		2.74%	0.44[0.15,1.35]
CERTITEM Study 2015	26/96	5/98		3.56%	5.31[2.13,13.25]
Barsoum 2007	10/76	7/36		3.73%	0.68[0.28,1.63]
CONCEPT Study 2009	16/95	8/97		4.18%	2.04[0.92,4.55]
SMART TX Study 2010	12/69	11/71		4.5%	1.12[0.53,2.37]
HERAKLES Study 2012	24/149	19/151		5.9%	1.28[0.73,2.24]
ZEUS Study 2011	36/155	16/145		6.02%	2.1[1.22,3.63]
CENTRAL Study 2012	40/102	21/100		6.83%	1.87[1.19,2.93]
RMR Study 2001	43/215	29/215		7%	1.48[0.96,2.28]
CALFREE Study 2010	29/63	23/64		7.08%	1.28[0.84,1.95]
SYMPHONY Study 2007	174/399	128/390		9.07%	1.33[1.11,1.59]
Subtotal (95% CI)	**1759**	**1704**		**69.14%**	**1.42[1.15,1.76]**
Total events: 432 (CNI withdrawal + mTOR-I), 293 (Standard dose CNI)					
Heterogeneity: Tau²=0.06; Chi²=25.56, df=16(P=0.06); I²=37.39%					
Test for overall effect: Z=3.29(P=0)					
7.1.2 TAC					
Rivelli 2015	1/22	1/23		0.6%	1.05[0.07,15.7]
Schaefer 2006	5/41	1/39		0.96%	4.76[0.58,38.91]
Pacheco-Silva 2013	4/15	2/15		1.65%	2[0.43,9.32]
El-Agroudy 2014	4/29	3/29		1.91%	1.33[0.33,5.44]
Grinyo 2004	10/44	4/43		2.84%	2.44[0.83,7.2]
Stegall 2003	15/80	12/82		4.86%	1.28[0.64,2.56]
ORION Study 2011	47/152	11/139		5.45%	3.91[2.11,7.23]
Subtotal (95% CI)	**383**	**370**		**18.27%**	**2.23[1.43,3.49]**
Total events: 86 (CNI withdrawal + mTOR-I), 34 (Standard dose CNI)					
Heterogeneity: Tau²=0.06; Chi²=7.1, df=6(P=0.31); I²=15.49%					
Test for overall effect: Z=3.52(P=0)					
7.1.3 Either CsA or TAC					
APOLLO Study 2015	0/46	0/47			Not estimable
Bansal 2013	2/29	0/31		0.5%	5.33[0.27,106.61]
CONVERT Trial 2009	12/555	4/275		2.7%	1.49[0.48,4.57]
Spare-the-Nephron Study 2011	11/148	9/151		3.89%	1.25[0.53,2.92]
Holm 2008	14/220	29/185		5.51%	0.41[0.22,0.75]
Subtotal (95% CI)	**998**	**689**		**12.58%**	**0.97[0.4,2.33]**
Total events: 39 (CNI withdrawal + mTOR-I), 42 (Standard dose CNI)					
Heterogeneity: Tau²=0.46; Chi²=8.36, df=3(P=0.04); I²=64.12%					

0.005 0.1 1 10 200

Favours CNI withdrawal + mTOR-I   Favours standard dose CNI

Study or subgroup	CNI withdrawal + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for overall effect: Z=0.08(P=0.94)					
Total (95% CI)	**3140**	**2763**	♦	**100%**	**1.43[1.15,1.78]**
Total events: 557 (CNI withdrawal + mTOR-I), 369 (Standard dose CNI)					
Heterogeneity: Tau²=0.13; Chi²=55.81, df=27(P=0); I²=51.62%					
Test for overall effect: Z=3.23(P=0)					
Test for subgroup differences: Chi²=4.23, df=1 (P=0.12), I²=52.68%					

Favours CNI withdrawal + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI
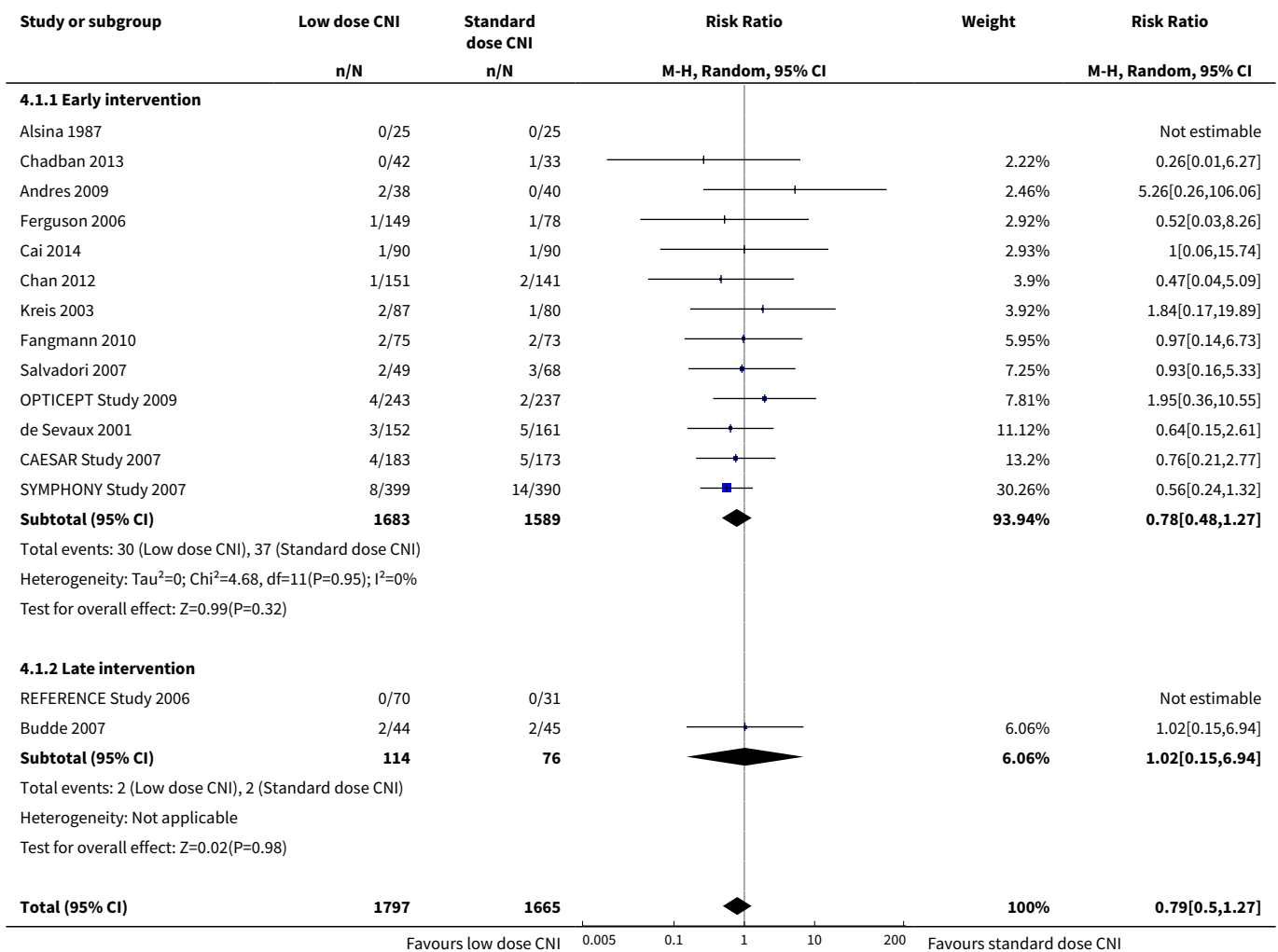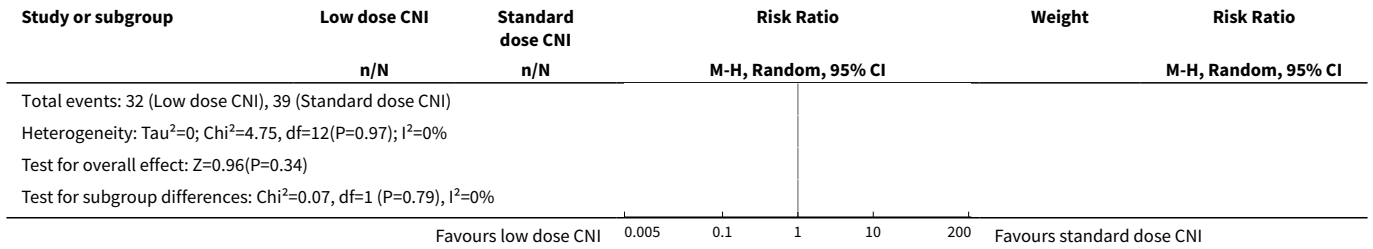
Comparison 8.   Low dose CNI + mTOR-I versus CNI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	11	2750	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.71, 1.90]
1.1 Low dose CNI + immediate mTOR	9	2182	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.62, 1.87]
1.2 low dose CNI + late mTOR	2	568	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.52, 4.59]
2 Acute rejection	16	3300	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.40]
2.1 Unspecified	3	496	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.90, 2.09]
2.2 Biopsy-proven	13	2804	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.83, 1.37]
3 GFR	11	1749	Mean Difference (IV, Random, 95% CI)	6.24 [3.28, 9.19]
3.1 Six months	4	244	Mean Difference (IV, Random, 95% CI)	5.79 [-3.57, 15.15]
3.2 One year	6	1293	Mean Difference (IV, Random, 95% CI)	6.63 [4.11, 9.14]
3.3 Two years	1	212	Mean Difference (IV, Random, 95% CI)	0.58 [-3.00, 6.16]
4 Graft loss	16	3304	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 1.01]
5 Serum creatinine at 1 year	6	1320	Mean Difference (IV, Random, 95% CI)	-14.14 [-22.55, -5.72]
6 Change in GFR at 2 years	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Adverse events	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Hypertension	5	1421	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.80, 1.20]
7.2 Hyperlipidaemia	8	1793	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.89, 1.28]
7.3 CMV infection	5	1250	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.16, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4 Diabetes	5	686	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.81, 2.27]
7.5 Malignancy	5	1074	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.42, 3.52]
7.6 Infection	5	1271	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.08]
8 Subgroup analysis: graft loss	16	3304	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 1.01]
8.1 Immediate mTOR	14	2736	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.48, 1.18]
8.2 Late mTOR	2	568	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.15, 1.04]
9 Subgroup analysis: GFR	11	1749	Mean Difference (IV, Random, 95% CI)	6.24 [3.28, 9.19]
9.1 Immediate mTOR	10	1537	Mean Difference (IV, Random, 95% CI)	6.91 [3.86, 9.96]
9.2 Late mTOR	1	212	Mean Difference (IV, Random, 95% CI)	0.58 [-3.00, 6.16]
10 Subgroup analysis: acute rejection	16	3300	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.40]
10.1 Immediate mTOR	14	2736	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.86, 1.39]
10.2 Late mTOR	2	564	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.82, 2.31]

Analysis 8.1. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 1 Death.

Study or subgroup	Low dose CNI + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 Low dose CNI + immediate mTOR					
Nashan 2004	0/58	2/53		2.68%	0.18[0.01,3.73]
Russ 2003	2/33	0/31		2.71%	4.71[0.23,94.31]
Muhlbacher 2014	0/178	3/179		2.79%	0.14[0.01,2.76]
Bertoni 2007	1/26	1/26		3.3%	1[0.07,15.15]
Bechstein-193 2013	3/63	2/65		7.9%	1.55[0.27,8.95]
Bertoni 2011	3/56	3/50		10.08%	0.89[0.19,4.22]
Velosa-212 Study 2001	4/100	3/97		11.26%	1.29[0.3,5.63]
Qazi 2014	6/309	5/304		17.6%	1.18[0.36,3.83]
Tedesco-Silva 2010	7/277	6/277		20.97%	1.17[0.4,3.43]
Subtotal (95% CI)	**1100**	**1082**		**79.27%**	**1.07[0.62,1.87]**
Total events: 26 (Low dose CNI + mTOR-I), 25 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=4.41, df=8(P=0.82); I²=0%					
Test for overall effect: Z=0.25(P=0.8)					
8.1.2 low dose CNI + late mTOR					
ASCERTAIN Study 2011	3/144	0/123		2.79%	5.99[0.31,114.77]
HERAKLES Study 2012	6/147	5/154		17.94%	1.26[0.39,4.03]

Favours low dose CNI + mTOR-I   0.005   0.1   1   10   200   Favours standard dose CNI

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Subtotal (95% CI)	291	277		20.73%	1.55[0.52,4.59]

Total events: 9 (Low dose CNI + mTOR-I), 5 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=0.97, df=1(P=0.33); I²=0%

Test for overall effect: Z=0.79(P=0.43)

Total (95% CI)	1391	1359		100%	1.16[0.71,1.9]

Total events: 35 (Low dose CNI + mTOR-I), 30 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=5.66, df=10(P=0.84); I²=0%

Test for overall effect: Z=0.58(P=0.56)

Test for subgroup differences: Chi²=0.35, df=1 (P=0.55), I²=0%

Favours low dose CNI + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Analysis 8.2. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 2 Acute rejection.

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
8.2.1 Unspecified					
Bechstein-193 2013	11/63	5/65		3.97%	2.27[0.84,6.16]
Cockfield 2002	12/90	8/81		5.31%	1.35[0.58,3.14]
Velosa-212 Study 2001	22/100	18/97		10.04%	1.19[0.68,2.07]
Subtotal (95% CI)	253	243		19.32%	1.37[0.9,2.09]

Total events: 45 (Low dose CNI + mTOR-I), 31 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=1.25, df=2(P=0.54); I²=0%

Test for overall effect: Z=1.48(P=0.14)

8.2.2 Biopsy-proven					
Paoletti 2012	1/10	2/20		0.85%	1[0.1,9.75]
Bertoni 2007	6/26	1/26		1.04%	6[0.78,46.42]
Takahashi 2013a	3/61	5/61		2.19%	0.6[0.15,2.4]
ASCERTAIN Study 2011	8/144	3/123		2.45%	2.28[0.62,8.4]
Nashan 2004	4/58	9/53		3.25%	0.41[0.13,1.24]
Oh 2012	5/67	8/72		3.53%	0.67[0.23,1.95]
Chan 2008	7/46	6/46		3.89%	1.17[0.42,3.21]
Russ 2003	7/33	6/31		4.15%	1.1[0.41,2.9]
Bertoni 2011	10/56	9/50		5.61%	0.99[0.44,2.24]
HERAKLES Study 2012	23/146	19/151		9.88%	1.25[0.71,2.2]
Muhlbacher 2014	20/178	29/179		10.72%	0.69[0.41,1.18]
Qazi 2014	59/309	34/304		15.44%	1.71[1.15,2.52]
Tedesco-Silva 2010	53/277	54/277		17.69%	0.98[0.7,1.38]
Subtotal (95% CI)	1411	1393		80.68%	1.07[0.83,1.37]

Total events: 206 (Low dose CNI + mTOR-I), 185 (Standard dose CNI)

Heterogeneity: Tau²=0.05; Chi²=16.93, df=12(P=0.15); I²=29.1%

Test for overall effect: Z=0.49(P=0.62)

Total (95% CI)	1664	1636		100%	1.13[0.91,1.4]

Total events: 251 (Low dose CNI + mTOR-I), 216 (Standard dose CNI)

Heterogeneity: Tau²=0.04; Chi²=19.12, df=15(P=0.21); I²=21.55%

Test for overall effect: Z=1.12(P=0.26)

Favours low dose CNI + mTOR-I 0.02 0.1 1 10 50 Favours standard dose CNI

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Test for subgroup differences: Chi²=1.03, df=1 (P=0.31), I²=2.75%					

Favours low dose CNI + mTOR-I 0.02 0.1 1 10 50 Favours standard dose CNI

Analysis 8.3.   Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 3 GFR.

Study or subgroup	Low dose CNI + mTOR-I		Standard dose CNI		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
8.3.1 Six months							
Bertoni 2007	26	59.3 (24.1)	26	69.9 (26.6)		3.65%	-10.67[-24.46,3.12]
Cockfield 2002	22	76.1 (18.9)	17	58.6 (12.3)		5.99%	17.5[7.67,27.33]
Bechstein-193 2013	33	68.4 (16.4)	28	58.2 (15.4)		7.72%	10.2[2.21,18.19]
Chan 2008	49	75.3 (16.6)	43	72.5 (15.2)		9.53%	2.8[-3.7,9.3]
Subtotal ***	**130**		**114**			**26.88%**	**5.79[-3.57,15.15]**
Heterogeneity: Tau²=67.67; Chi²=12.83, df=3(P=0.01); I²=76.62%							
Test for overall effect: Z=1.21(P=0.23)							
8.3.2 One year							
Velosa-212 Study 2001	82	63.2 (31.3)	82	49.1 (30.2)		6.32%	14.08[4.65,23.51]
Muhlbacher 2014	178	57.8 (27)	179	49.5 (39)		8.94%	8.3[1.34,15.26]
Takahashi 2013a	61	62.1 (19)	61	56.3 (15.2)		10.07%	5.75[-0.36,11.86]
Oh 2012	67	69.5 (17.2)	72	61.2 (17.9)		10.47%	8.3[2.46,14.14]
Nashan 2004	58	60.9 (11.3)	53	53.5 (12.1)		12.76%	7.4[3.03,11.77]
Tedesco-Silva 2010	192	65.8 (16.7)	208	62.6 (21.7)		13.71%	3.2[-0.58,6.98]
Subtotal ***	**638**		**655**			**62.27%**	**6.63[4.11,9.14]**
Heterogeneity: Tau²=1.97; Chi²=6.24, df=5(P=0.28); I²=19.92%							
Test for overall effect: Z=5.16(P<0.0001)							
8.3.3 Two years							
ASCERTAIN Study 2011	109	46.6 (21.1)	103	46 (20.4)		10.85%	0.58[-5,6.16]
Subtotal ***	**109**		**103**			**10.85%**	**0.58[-5,6.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.2(P=0.84)							
Total ***	**877**		**872**			**100%**	**6.24[3.28,9.19]**
Heterogeneity: Tau²=12.88; Chi²=22.77, df=10(P=0.01); I²=56.09%							
Test for overall effect: Z=4.13(P<0.0001)							
Test for subgroup differences: Chi²=3.75, df=1 (P=0.15), I²=46.74%							

Favours standard dose CNI -50 -25 0 25 50 Favours low dose CNI + mTOR-I

Analysis 8.4.   Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 4 Graft loss.

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Paoletti 2012	0/10	0/20			Not estimable

Favours low dose CNI + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

Study or subgroup	Low dose CNI + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Takahashi 2013a	0/61	0/61			Not estimable
Oh 2012	0/67	1/72		1.6%	0.36[0.01,8.64]
Chan 2008	0/49	1/43		1.61%	0.29[0.01,7.02]
Bertoni 2007	1/26	1/26		2.2%	1[0.07,15.15]
Muhlbacher 2014	1/179	2/178		2.84%	0.5[0.05,5.43]
Bechstein-193 2013	3/63	1/65		3.25%	3.1[0.33,28.97]
Nashan 2004	1/58	3/53		3.26%	0.3[0.03,2.84]
Russ 2003	3/33	1/31		3.33%	2.82[0.31,25.68]
Cockfield 2002	3/90	3/81		6.57%	0.9[0.19,4.33]
HERAKLES Study 2012	2/147	9/154		7.07%	0.23[0.05,1.06]
Bertoni 2011	3/56	6/50		9.15%	0.45[0.12,1.69]
ASCERTAIN Study 2011	4/144	6/123		10.52%	0.57[0.16,1.97]
Qazi 2014	4/309	12/304		12.93%	0.33[0.11,1.01]
Velosa-212 Study 2001	5/100	7/97		13.1%	0.69[0.23,2.11]
Tedesco-Silva 2010	12/277	9/277		22.57%	1.33[0.57,3.11]
Total (95% CI)	**1669**	**1635**		**100%**	**0.67[0.45,1.01]**

Total events: 42 (Low dose CNI + mTOR-I), 62 (Standard dose CNI)

Heterogeneity: Tau²=0; Chi²=10.99, df=13(P=0.61); I²=0%

Test for overall effect: Z=1.92(P=0.06)

Favours low dose CNI + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

Analysis 8.5. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 5 Serum creatinine at 1 year.

Study or subgroup	Low dose CNI + mTOR-I N	Mean(SD)	Standard dose CNI N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Velosa-212 Study 2001	100	145 (106.1)	97	175.9 (130.6)		6.01%	-30.92[-64.2,2.36]
Muhlbacher 2014	178	158.2 (134)	179	176.8 (89)		11.27%	-18.57[-42.18,5.04]
Cockfield 2002	38	118 (38)	32	145 (42)		16.52%	-27[-45.91,-8.09]
Chan 2008	49	112 (31)	43	127 (50)		19.16%	-15[-32.28,2.28]
Tedesco-Silva 2010	245	142.4 (108.3)	248	142.2 (74.8)		20.74%	0.2[-16.25,16.65]
Nashan 2004	58	151 (34)	53	162 (41)		26.29%	-11[-25.09,3.09]
Total ***	**668**		**652**			**100%**	**-14.14[-22.55,-5.72]**

Heterogeneity: Tau²=18.48; Chi²=6, df=5(P=0.31); I²=16.62%

Test for overall effect: Z=3.29(P=0)

Favours low dose CNI + mTOR-I -100 -50 0 50 100 Favours standard dose CNI

Analysis 8.6. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 6 Change in GFR at 2 years.

Study or subgroup	Low dose CNI + mTOR-I N	Mean(SD)	Standard dose CNI N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
ASCERTAIN Study 2011	124	0.8 (19.5)	112	1.6 (12.8)		-0.73[-4.9,3.44]

Favours low dose CNI + mTOR-I -10 -5 0 5 10 Favours standard dose CNI

Analysis 8.7. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 7 Adverse events.

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
8.7.1 Hypertension					
Bechstein-193 2013	2/63	7/65		1.74%	0.29[0.06,1.37]
ASCERTAIN Study 2011	9/144	6/123		4.04%	1.28[0.47,3.5]
Takahashi 2013a	19/61	21/61		15.74%	0.9[0.54,1.51]
Muhlbacher 2014	28/178	26/179		16.86%	1.08[0.66,1.77]
Tedesco-Silva 2010	81/274	82/273		61.63%	0.98[0.76,1.27]
Subtotal (95% CI)	**720**	**701**		**100%**	**0.98[0.8,1.2]**
Total events: 139 (Low dose CNI + mTOR-I), 142 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=2.89, df=4(P=0.58); I²=0%					
Test for overall effect: Z=0.23(P=0.82)					
8.7.2 Hyperlipidaemia					
ASCERTAIN Study 2011	11/144	6/123		3.34%	1.57[0.6,4.11]
Bechstein-193 2013	17/63	15/65		7.65%	1.17[0.64,2.13]
Takahashi 2013a	28/61	19/61		11.55%	1.47[0.93,2.34]
Nashan 2004	19/58	28/53		12.08%	0.62[0.4,0.97]
Russ 2003	19/33	18/31		13.29%	0.99[0.65,1.51]
Tedesco-Silva 2010	57/274	43/273		16.28%	1.32[0.92,1.89]
Velosa-212 Study 2001	41/100	38/97		17.27%	1.05[0.74,1.47]
Muhlbacher 2014	52/178	53/179		18.55%	0.99[0.72,1.36]
Subtotal (95% CI)	**911**	**882**		**100%**	**1.07[0.89,1.28]**
Total events: 244 (Low dose CNI + mTOR-I), 220 (Standard dose CNI)					
Heterogeneity: Tau²=0.02; Chi²=10, df=7(P=0.19); I²=30.01%					
Test for overall effect: Z=0.68(P=0.5)					
8.7.3 CMV infection					
Nashan 2004	0/58	1/53		7.03%	0.31[0.01,7.33]
Tedesco-Silva 2010	2/277	16/277		18.04%	0.13[0.03,0.54]
Takahashi 2013a	3/61	21/61		21.39%	0.14[0.04,0.45]
Muhlbacher 2014	13/178	14/179		26.37%	0.93[0.45,1.93]
Bertoni 2011	14/56	13/50		27.17%	0.96[0.5,1.84]
Subtotal (95% CI)	**630**	**620**		**100%**	**0.41[0.16,1.06]**
Total events: 32 (Low dose CNI + mTOR-I), 65 (Standard dose CNI)					
Heterogeneity: Tau²=0.77; Chi²=15.18, df=4(P=0); I²=73.65%					
Test for overall effect: Z=1.85(P=0.06)					
8.7.4 Diabetes					
Paoletti 2012	2/10	2/20		8.08%	2[0.33,12.18]
Russ 2003	5/33	4/31		17.72%	1.17[0.35,3.98]
ASCERTAIN Study 2011	7/144	4/123		18.17%	1.49[0.45,4.99]
Velosa-212 Study 2001	8/100	5/97		22.53%	1.55[0.53,4.58]
Bechstein-193 2013	9/63	8/65		33.51%	1.16[0.48,2.82]
Subtotal (95% CI)	**350**	**336**		**100%**	**1.36[0.81,2.27]**
Total events: 31 (Low dose CNI + mTOR-I), 23 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.43, df=4(P=0.98); I²=0%					
Test for overall effect: Z=1.17(P=0.24)					

0.005   0.1   1   10   200

Favours low dose CNI + mTOR-I   Favours standard dose CNI

Study or subgroup	Low dose CNI + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.7.5 Malignancy					
Oh 2012	0/67	1/72		11.15%	0.36[0.01,8.64]
Takahashi 2013a	2/61	0/61		12.42%	5[0.25,102.04]
Bechstein-193 2013	2/184	1/177		19.76%	1.92[0.18,21.03]
Muhlbacher 2014	1/170	2/171		19.77%	0.5[0.05,5.49]
Nashan 2004	3/58	2/53		36.9%	1.37[0.24,7.89]
Subtotal (95% CI)	**540**	**534**		**100%**	**1.22[0.42,3.52]**
Total events: 8 (Low dose CNI + mTOR-I), 6 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=2.1, df=4(P=0.72); I²=0%					
Test for overall effect: Z=0.36(P=0.72)					
8.7.6 Infection					
Cibrik 2007	11/75	16/66		3.54%	0.61[0.3,1.21]
Oh 2012	13/67	20/72		4.45%	0.7[0.38,1.29]
ASCERTAIN Study 2011	40/144	25/123		8.28%	1.37[0.88,2.12]
Nashan 2004	49/58	46/53		38.17%	0.97[0.84,1.13]
Qazi 2014	183/309	195/304		45.55%	0.92[0.81,1.05]
Subtotal (95% CI)	**653**	**618**		**100%**	**0.95[0.83,1.08]**
Total events: 296 (Low dose CNI + mTOR-I), 302 (Standard dose CNI)					
Heterogeneity: Tau²=0.01; Chi²=5.55, df=4(P=0.24); I²=27.92%					
Test for overall effect: Z=0.8(P=0.42)					
Test for subgroup differences: Chi²=6, df=1 (P=0.31), I²=16.7%					

Favours low dose CNI + mTOR-I 0.005 0.1 1 10 200 Favours standard dose CNI

Analysis 8.8. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 8 Subgroup analysis: graft loss.

Study or subgroup	Low dose CNI + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.8.1 Immediate mTOR					
Paoletti 2012	0/10	0/20			Not estimable
Takahashi 2013a	0/61	0/61			Not estimable
Oh 2012	0/67	1/72		1.6%	0.36[0.01,8.64]
Chan 2008	0/49	1/43		1.61%	0.29[0.01,7.02]
Bertoni 2007	1/26	1/26		2.2%	1[0.07,15.15]
Muhlbacher 2014	1/179	2/178		2.84%	0.5[0.05,5.43]
Bechstein-193 2013	3/63	1/65		3.25%	3.1[0.33,28.97]
Nashan 2004	1/58	3/53		3.26%	0.3[0.03,2.84]
Russ 2003	3/33	1/31		3.33%	2.82[0.31,25.68]
Cockfield 2002	3/90	3/81		6.57%	0.9[0.19,4.33]
Bertoni 2011	3/56	6/50		9.15%	0.45[0.12,1.69]
Qazi 2014	4/309	12/304		12.93%	0.33[0.11,1.01]
Velosa-212 Study 2001	5/100	7/97		13.1%	0.69[0.23,2.11]
Tedesco-Silva 2010	12/277	9/277		22.57%	1.33[0.57,3.11]
Subtotal (95% CI)	**1378**	**1358**		**82.41%**	**0.75[0.48,1.18]**
Total events: 36 (Low dose CNI + mTOR-I), 47 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=8.77, df=11(P=0.64); I²=0%					
Test for overall effect: Z=1.24(P=0.21)					

Favours low dose CNI + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

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Study or subgroup	Low dose CNI + mTOR-I n/N	Standard dose CNI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.8.2 Late mTOR					
HERAKLES Study 2012	2/147	9/154		7.07%	0.23[0.05,1.06]
ASCERTAIN Study 2011	4/144	6/123		10.52%	0.57[0.16,1.97]
Subtotal (95% CI)	**291**	**277**		**17.59%**	**0.4[0.15,1.04]**
Total events: 6 (Low dose CNI + mTOR-I), 15 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.81, df=1(P=0.37); I²=0%					
Test for overall effect: Z=1.88(P=0.06)					
Total (95% CI)	**1669**	**1635**		**100%**	**0.67[0.45,1.01]**
Total events: 42 (Low dose CNI + mTOR-I), 62 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=10.99, df=13(P=0.61); I²=0%					
Test for overall effect: Z=1.92(P=0.06)					
Test for subgroup differences: Chi²=1.41, df=1 (P=0.23), I²=29.14%					

Favours low dose CNI + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

Analysis 8.9. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 9 Subgroup analysis: GFR.

Study or subgroup	Low dose CNI + mTOR-I		Standard dose CNI		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
8.9.1 Immediate mTOR							
Bertoni 2007	26	59.3 (24.1)	26	69.9 (26.6)		3.65%	-10.67[-24.46,3.12]
Cockfield 2002	22	76.1 (18.9)	17	58.6 (12.3)		5.99%	17.5[7.67,27.33]
Velosa-212 Study 2001	82	63.2 (31.3)	82	49.1 (30.2)		6.32%	14.08[4.65,23.51]
Bechstein-193 2013	33	68.4 (16.4)	28	58.2 (15.4)		7.72%	10.2[2.21,18.19]
Muhlbacher 2014	178	57.8 (27)	179	49.5 (39)		8.94%	8.3[1.34,15.26]
Chan 2008	49	75.3 (16.6)	43	72.5 (15.2)		9.53%	2.8[-3.7,9.3]
Takahashi 2013a	61	62.1 (19)	61	56.3 (15.2)		10.07%	5.75[-0.36,11.86]
Oh 2012	67	69.5 (17.2)	72	61.2 (17.9)		10.47%	8.3[2.46,14.14]
Nashan 2004	58	60.9 (11.3)	53	53.5 (12.1)		12.76%	7.4[3.03,11.77]
Tedesco-Silva 2010	192	65.8 (16.7)	208	62.6 (21.7)		13.71%	3.2[-0.58,6.98]
Subtotal ***	**768**		**769**			**89.15%**	**6.91[3.86,9.96]**
Heterogeneity: Tau²=11.65; Chi²=19.08, df=9(P=0.02); I²=52.82%							
Test for overall effect: Z=4.45(P<0.0001)							
8.9.2 Late mTOR							
ASCERTAIN Study 2011	109	46.6 (21.1)	103	46 (20.4)		10.85%	0.58[-5,6.16]
Subtotal ***	**109**		**103**			**10.85%**	**0.58[-5,6.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.2(P=0.84)							
Total ***	**877**		**872**			**100%**	**6.24[3.28,9.19]**
Heterogeneity: Tau²=12.88; Chi²=22.77, df=10(P=0.01); I²=56.09%							
Test for overall effect: Z=4.13(P<0.0001)							
Test for subgroup differences: Chi²=3.81, df=1 (P=0.05), I²=73.78%							

Favours standard dose CNI -50 -25 0 25 50 Favours low dose CNI + mTOR-I

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Analysis 8.10.   Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 10 Subgroup analysis: acute rejection.

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
8.10.1 Immediate mTOR					
Paoletti 2012	1/10	2/20		0.85%	1[0.1,9.75]
Bertoni 2007	6/26	1/26		1.04%	6[0.78,46.42]
Takahashi 2013a	3/61	5/61		2.19%	0.6[0.15,2.4]
Nashan 2004	4/58	9/53		3.25%	0.41[0.13,1.24]
Oh 2012	5/67	8/72		3.53%	0.67[0.23,1.95]
Chan 2008	7/46	6/46		3.89%	1.17[0.42,3.21]
Bechstein-193 2013	11/63	5/65		3.97%	2.27[0.84,6.16]
Russ 2003	7/33	6/31		4.15%	1.1[0.41,2.9]
Cockfield 2002	12/90	8/81		5.31%	1.35[0.58,3.14]
Bertoni 2011	10/56	9/50		5.61%	0.99[0.44,2.24]
Velosa-212 Study 2001	22/100	18/97		10.04%	1.19[0.68,2.07]
Muhlbacher 2014	20/178	29/179		10.72%	0.69[0.41,1.18]
Qazi 2014	59/309	34/304		15.44%	1.71[1.15,2.52]
Tedesco-Silva 2010	53/277	54/277		17.69%	0.98[0.7,1.38]
Subtotal (95% CI)	**1374**	**1362**		**87.67%**	**1.09[0.86,1.39]**
Total events: 220 (Low dose CNI + mTOR-I), 194 (Standard dose CNI)					
Heterogeneity: Tau²=0.05; Chi²=17.84, df=13(P=0.16); I²=27.12%					
Test for overall effect: Z=0.72(P=0.47)					
8.10.2 Late mTOR					
ASCERTAIN Study 2011	8/144	3/123		2.45%	2.28[0.62,8.4]
HERAKLES Study 2012	23/146	19/151		9.88%	1.25[0.71,2.2]
Subtotal (95% CI)	**290**	**274**		**12.33%**	**1.38[0.82,2.31]**
Total events: 31 (Low dose CNI + mTOR-I), 22 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=0.69, df=1(P=0.41); I²=0%					
Test for overall effect: Z=1.21(P=0.23)					
Total (95% CI)	**1664**	**1636**		**100%**	**1.13[0.91,1.4]**
Total events: 251 (Low dose CNI + mTOR-I), 216 (Standard dose CNI)					
Heterogeneity: Tau²=0.04; Chi²=19.12, df=15(P=0.21); I²=21.55%					
Test for overall effect: Z=1.12(P=0.26)					
Test for subgroup differences: Chi²=0.63, df=1 (P=0.43), I²=0%					

Favours low dose CNI + mTOR-I 0.01 0.1 1 10 100 Favours standard dose CNI

Comparison 9.   Subgroup analysis (CNI type): low dose CNI + mTOR-I versus standard dose CNI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute rejection	16	3300	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.40]
1.1 CsA	11	2232	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.22]
1.2 TAC	5	1068	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.16, 2.13]

Analysis 9.1. Comparison 9 Subgroup analysis (CNI type): low dose CNI + mTOR-I versus standard dose CNI, Outcome 1 Acute rejection.

Study or subgroup	Low dose CNI + mTOR-I	Standard dose CNI	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
9.1.1 CsA					
Paoletti 2012	1/10	2/20		0.85%	1[0.1,9.75]
Bertoni 2007	6/26	1/26		1.04%	6[0.78,46.42]
Takahashi 2013a	3/61	5/61		2.19%	0.6[0.15,2.4]
ASCERTAIN Study 2011	8/144	3/123		2.45%	2.28[0.62,8.4]
Nashan 2004	4/58	9/53		3.25%	0.41[0.13,1.24]
Oh 2012	5/67	8/72		3.53%	0.67[0.23,1.95]
Bertoni 2011	10/56	9/50		5.61%	0.99[0.44,2.24]
HERAKLES Study 2012	23/146	19/151		9.88%	1.25[0.71,2.2]
Velosa-212 Study 2001	22/100	18/97		10.04%	1.19[0.68,2.07]
Muhlbacher 2014	20/178	29/179		10.72%	0.69[0.41,1.18]
Tedesco-Silva 2010	53/277	54/277		17.69%	0.98[0.7,1.38]
Subtotal (95% CI)	**1123**	**1109**		**67.25%**	**0.97[0.78,1.22]**
Total events: 155 (Low dose CNI + mTOR-I), 157 (Standard dose CNI)					
Heterogeneity: Tau²=0.01; Chi²=10.78, df=10(P=0.37); I²=7.23%					
Test for overall effect: Z=0.24(P=0.81)					
9.1.2 TAC					
Chan 2008	7/46	6/46		3.89%	1.17[0.42,3.21]
Bechstein-193 2013	11/63	5/65		3.97%	2.27[0.84,6.16]
Russ 2003	7/33	6/31		4.15%	1.1[0.41,2.9]
Cockfield 2002	12/90	8/81		5.31%	1.35[0.58,3.14]
Qazi 2014	59/309	34/304		15.44%	1.71[1.15,2.52]
Subtotal (95% CI)	**541**	**527**		**32.75%**	**1.58[1.16,2.13]**
Total events: 96 (Low dose CNI + mTOR-I), 59 (Standard dose CNI)					
Heterogeneity: Tau²=0; Chi²=1.68, df=4(P=0.79); I²=0%					
Test for overall effect: Z=2.95(P=0)					
Total (95% CI)	**1664**	**1636**		**100%**	**1.13[0.91,1.4]**
Total events: 251 (Low dose CNI + mTOR-I), 216 (Standard dose CNI)					
Heterogeneity: Tau²=0.04; Chi²=19.12, df=15(P=0.21); I²=21.55%					
Test for overall effect: Z=1.12(P=0.26)					
Test for subgroup differences: Chi²=6.29, df=1 (P=0.01), I²=84.1%					

Favours low dose CNI + mTOR-I   0.01   0.1   1   10   100   Favours standard dose CNI

A P P E N D I C E S

Appendix 1. Electronic search strategies

DATABASE	Search terms
CENTRAL	1. Kidney Transplantation, MESH term 2. Tacrolimus, MESH 3. (tacrolimus):ti,ab,kw 4. "FK 506" or FK506:ti,ab,kw 5. Cyclosporine, MeSH term

(Continued)

	6. (cyclosporin* or ciclosporin*):ti,ab,kw 7. (csa* or neoral* or cya* or restasis or sandimmun*):ti,ab,kw 8. (calcineurin inhibitor*):ti,ab,kw 9. (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8) 10. (discontinu* or withdraw* or taper* or spar* or avoid* or minim* or remov* or stop* or reduction* or reduc* or free*):ti,ab,kw 11. (9 AND 10) 12. (1 AND 11)
MEDLINE	1. Kidney Transplantation/ 2. Tacrolimus/ 3. tacrolimus.tw. 4. prograf$.tw. 5. ("FK 506" or FK506).tw. 6. fr-900506.tw. 7. fujimycin.tw. 8. protopic.tw. 9. Cyclosporine/ 10. cyclosporin$.tw. 11. ciclosporin$.tw. 12. csa.tw. 13. neoral.tw. 14. cya$.tw. 15. sandimmun$.tw. 16. restasis.tw. 17. calcineurin inhibitor$.tw. 18. or/2-17 19. (discontinu$ or withdraw$ or taper$ or spar$ or avoid$ or minim$ or remov$ or stop$ or reduction or reduc$ or free$).tw. 20. and/18-19 21. and/1,20
EMBASE	1. Kidney Transplantation/ 2. Tsukubaenolide/ 3. tacrolimus.tw. 4. prograf$.tw. 5. ("FK 506" or FK506).tw. 6. fr-900506.tw. 7. fujimycin.tw. 8. protopic.tw. 9. Cyclosporin/ 10. cyclosporin$.tw. 11. ciclosporin$.tw. 12. (csa or neoral or cya).tw. 13. (sandimmun$ or restaisi).tw. 14. Calcineurin Inhibitor/ 15. or/2-14 16. (discontinu$ or withdraw$ or taper$ or spar$ or avoid$ or minim$ or remov$ or stop$ or reduction or reduc$ or free$).tw. 17. and/15-16 18. and/1,17

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias:* No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 7, 2017

Date	Event	Description
9 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review: KK, GW, GT
Screening of titles and abstracts: KK, GW
Assessment for inclusion: KK, GW
Quality assessment: KK, GW
Data extraction: KK, GW
Data entry into RevMan: KK, GW
Data analysis: KK, GW
Disagreement resolution: GT

DECLARATIONS OF INTEREST

- Krishna M Karpe: none known
- Girish S Talaulikar: none known
- Giles Walters: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Cochrane's risk of bias assessment tool has replaced the quality assessment checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

*Graft Survival; *Kidney Transplantation [mortality]; *Withholding Treatment; Acute Disease; Calcineurin Inhibitors [*administration & dosage] [*adverse effects]; Cytomegalovirus Infections [epidemiology] [prevention & control]; Drug Substitution; Graft Rejection [epidemiology] [*etiology] [prevention & control]; Hypertension [epidemiology]; Immunosuppression Therapy [methods]; Immunosuppressive Agents [therapeutic use]; Intention to Treat Analysis; Kidney; Neoplasms [epidemiology]; Randomized Controlled Trials as Topic; TOR Serine-Threonine Kinases [*antagonists & inhibitors]; Time Factors

MeSH check words

Humans