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

Karpe KM, Talaulikar GS, Walters GD

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[Intervention Review]

Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients

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ABSTRACT

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 or 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.

PLAIN LANGUAGE SUMMARY

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.

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 participants (studies)	Quality of the evidence (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			

	(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
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	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}
	58 per 1,000	44 per 1,000 (32 to 60)			Sensitivity analysis after excluding 1 study which also involved steroid withdrawal; significant reduction in graft loss in the low dose regimen
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 participants (studies)	Quality of the evidence (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
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	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 participants (studies)	Quality of the evidence (GRADE)
	Risk with standard dose CNI	Risk with CNI avoidance and withdrawal + 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).

RESULTS

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

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; Bertonni 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; Grimbirt 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; Grimbirt 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; Baczowska 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; $I^2 = 65\%$) but not in AZA studies ([Analysis 2.1.2](#) (5 studies, 556 participants): RR 1.81, 95% CI 0.78 to 4.19; $I^2 = 72\%$).

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; $I^2 = 71\%$), TAC ([Analysis 3.1.2](#) (2 studies, 88 participants): RR 5.65, 95% CI 1.96 to 16.27; $I^2 = 0\%$), 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; $I^2 = 0\%$; 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; $I^2 = 0\%$; moderate certainty) and graft loss ([Analysis 4.4](#) (15 studies, 3286 participants): RR 0.75, 95% CI 0.55 to 1.02; $I^2 = 0\%$; 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; $I^2 = 16\%$; moderate certainty). Low dose CNI regimen probably slightly lowers SCr ([Analysis 4.5](#) (6 studies, 742 participants): MD -4.28 $\mu\text{mol/L}$, 95% CI -14.65 to 6.10; $I^2 = 37\%$; low certainty).

Hypertension was probably reduced ([Analysis 4.7.1](#) (5 studies, 1877 participants): RR 0.84, 95% CI 0.70 to 1.00; $I^2 = 0\%$; 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; $I^2 = 12\%$), CMV infection ([Analysis 4.7.3](#) (6 studies, 1948 participants): RR 1.23, 95% CI 0.94 to 1.62; $I^2 = 10\%$; moderate certainty), diabetes mellitus ([Analysis 4.7.4](#) (5 studies, 1292 participants): RR 0.82, 95% CI 0.50 to 1.34; $I^2 = 53\%$), malignancy ([Analysis 4.7.5](#) (5 studies, 1637 participants): RR 0.90, 95% CI 0.41 to 1.97; $I^2 = 0\%$; low certainty), and total infections ([Analysis 4.7.6](#) (9 studies, 1437 participants): RR 0.95, 95% CI 0.84 to 1.07; $I^2 = 0\%$).

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; $I^2 = 0\%$) and graft loss ([Analysis 4.10.1](#) (11

studies, 2800 participants): RR 0.75, 95% CI 0.55 to 1.03; $I^2 = 0\%$), and GFR improved ([Analysis 4.9.1](#) (9 studies, 2200 participants): MD 3.09 mL/min, 95% CI 0.95 to 5.23; $I^2 = 4\%$) 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; $I^2 = 21\%$) or graft loss ([Analysis 4.10.2](#) (3 studies, 306 participants): RR 0.95, 95% CI 0.12 to 7.56; $I^2 = 0\%$) however GFR was higher ([Analysis 4.9.2](#) (3 studies, 243 participants): MD 8.81 mL/min, 95% CI 3.79 to 13.83; $I^2 = 0\%$).

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; $I^2 = 0\%$) 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; $I^2 = 0\%$) 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; $I^2 = 0\%$; moderate certainty) and graft loss ([Analysis 6.4](#) (25 studies, 5446 participants): RR 0.94, 95% CI 0.75 to 1.19; $I^2 = 0\%$; 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; $I^2 = 52\%$; 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; $I^2 = 90\%$). SCr was lower at one year in the CNI withdrawal with mTOR-I group ([Analysis 6.5](#) (12 studies, 1702 participants): MD -17.10 $\mu\text{mol/L}$, 95% CI -26.95 to -7.25; $I^2 = 76\%$).

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; $I^2 = 49\%$). 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; $I^2 = 79\%$), diabetes mellitus ([Analysis 6.7.4](#) (11 studies, 2833 participants): RR 1.27, 95% CI 0.97 to 1.66; $I^2 = 0\%$), and infections ([Analysis 6.7.6](#) (9 studies, 1624 participants): RR 0.99, 95% CI 0.92 to 1.07; $I^2 = 0\%$) 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 μ mol/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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abramowicz 2002

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: 5 years from 1997 to 2002 Duration of follow-up: 5 years
Participants	<ul style="list-style-type: none"> 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 10⁹/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	<p>Treatment group</p> <ul style="list-style-type: none"> Gradual withdrawal of CsA over a 3 month period in the treatment group <ul style="list-style-type: none"> * 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 <p>Control group</p> <ul style="list-style-type: none"> Continued on triple drug therapy of CsA, MMF and steroids <ul style="list-style-type: none"> * 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 <p>Baseline immunosuppression</p> <ul style="list-style-type: none"> At randomisation all patients were on triple immunosuppression of MMF, CsA and corticosteroids for at least 3 months
Outcomes	<ul style="list-style-type: none"> SCr CrCl Patient survival Graft survival AR episodes Malignancies
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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	<p>Treatment group 1</p> <ul style="list-style-type: none"> 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) <p>Treatment group 2</p> <ul style="list-style-type: none"> CsA: 15 mg/kg/d; CsA level trough 300 to 800 ng/mL PRED: 0.5 mg/kg/d
Outcomes	<ul style="list-style-type: none"> Patient survival Graft survival AR
Notes	<ul style="list-style-type: none"> Funding source: not reported Abstract-only publications

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

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	<ul style="list-style-type: none"> Study design: 3 arm, parallel RCT Study duration: recruitment March 2002 to March 2003 Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group 1</p> <ul style="list-style-type: none"> Low dose early CsA <ul style="list-style-type: none"> * 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) <p>Treatment group 2</p> <ul style="list-style-type: none"> Normal dose early CsA <ul style="list-style-type: none"> * 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	<ul style="list-style-type: none"> • Graft loss • Death • GFR • AR • Infection
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: November 2005 to March 2009
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APOLLO Study 2015 (Continued)

	<ul style="list-style-type: none"> Duration of follow-up: 5 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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 $\geq$ II, recurrent AR, or steroid-resistant rejection in the preceding 6 months; proteinuria > 1 g/d, platelets < 100,000 cells/mm³; leukocytes < 4000/mm³; Hb < 8 g/dL; evidence of severe liver disease
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> Treatment regimen continued unchanged <ul style="list-style-type: none"> CsA trough levels: 80 to 150 ng/mL TAC trough levels: 5 to 10 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> Received EC-MPS and steroids if administered at study entry
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment February 2002 to 2004 Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Norway de novo kidney transplant recipients Number: treatment group (27); control group (27) Mean age $\pm$ 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 $< 2.5 \times 10^9/L$ (IU); platelet count $< 100 \times 10^{12}/L$ (IU); Hb < 6 g/dL
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> 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 <p>Both groups</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> GFR AR Graft failure Patient survival Post-transplant diabetes mellitus

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

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 $\pm$ SD (years): treatment group 1 (49.4 $\pm$ 11.8); treatment group 2 (49.7 $\pm$ 13.0); control group (48.2 $\pm$ 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 $\geq$ 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	<ul style="list-style-type: none"> • GFR at 24 months • Patient survival • Graft survival • BPAR • Hypertension • Hyperlipidaemia • Diabetes
Notes	<ul style="list-style-type: none"> • 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

Baczowska 2003

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 3 years
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Poland Low rejection-risk primary kidney transplant recipients Number: treatment group (16); control group (16) Mean age $\pm$ SD (both groups): 42.6 $\pm$ 10.8 years Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p> <ul style="list-style-type: none"> MMF: 2.0 g/d PRED: standard dose
Outcomes	<ul style="list-style-type: none"> AR Kidney function SCr Graft loss
Notes	<ul style="list-style-type: none"> 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

Baczowska 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment March 2011 to December 2012 Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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 $\text{SCr} \leq 1.2$ 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; $\text{WCC} < 3000$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Funding source: Biocon Nephrology, India.

Bansal 2013 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done with the help of a computer generated Bernoulli random number table
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved by opaque sequentially numbered 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	Unclear risk	Insufficient information to permit judgement, ITT not specified
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	Funded by Biocon Nephrology, India

Barsoum 2007

Methods	<ul style="list-style-type: none"> Study design: parallel RCT (2:1) Study duration: recruitment July 2002 to July 2006 Duration of follow-up: 2 years
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Egypt Live donor recipients (84% unrelated), randomised immediate post-transplant Number: treatment group (76); control group (37) Mean age $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> SRL + MMF + PRED after 3 months of CsA (C2 levels 600 mg/mL) * SRL: level 5 to 10 ng/mL after 3 months <p>Control group</p> <ul style="list-style-type: none"> CsA + MMF + PRED * CSA C2 level: 1600 ng/mL (6 months), thereafter 1200 ng/mL
Outcomes	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (47.9 $\pm$ 13.3); control group (44.6 $\pm$ 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 $\leq$ 3000/mm³ or platelet count $\leq$ 100,000/mm³; 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, pimozone, 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> BPAR Patient survival Graft survival SCr CrCl Infection Malignancy
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Single centre RCT Study duration: not reported Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Italy Kidney transplant recipients Number: 52 Mean age $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Basiliximab induction CsA: standard dose MMF Steroids <p>Control group</p> <ul style="list-style-type: none"> Basiliximab induction CsA: reduced dose (to obtain predefined levels) EVL: trough levels 3 to 8 ng/mL Steroids
Outcomes	<ul style="list-style-type: none"> DGF Graft survival Patient survival BPAR Triglycerides Need for hospitalisation
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> Setting: single centre country: Italy Kidney transplant recipients Number: treatment group (56); control group (50) Mean age $\pm$ SD (years): treatment group (45.70 ± 12.77); control group (49.75 ± 12.06) Sex (M/F): not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> EVL trough levels: 8 to 12 ng/mL CsA C2 levels: 250 to 300 ng/mL Steroids <p>Control group</p> <ul style="list-style-type: none"> EC-MPS: 1,440 mg/d CsA C2 levels: 500 to 700 ng/mL Steroids <p>Both groups</p> <ul style="list-style-type: none"> Basiliximab induction
Outcomes	<ul style="list-style-type: none"> BPAR CrCl Graft survival at 12 months Patient survival at 12 months CMV
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (45.5 $\pm$ 14.9); control group (48.7 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<p>Treatment group 1</p> <ul style="list-style-type: none"> 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 <p>Treatment group 2</p>

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

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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment April 2009 to April 2012 Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> Low-dose CsA Short-term intensified EC-MPS dosing 2160 mg/d to week 6, 1440 mg/d thereafter Steroids <p>Control group</p> <ul style="list-style-type: none"> standard-dose CsA EC-MPS 1440 mg/d Steroids
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment January 2001 to July 2004 Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> SRL trough levels: 10 to 20 ng/mL (months 1 to 3), 8 to 15 ng/mL (months 4 to 6) MMF PRED <p>Control group</p> <ul style="list-style-type: none"> CsA trough levels: 250 to 350 ng/mL (for 3 months), thereafter 200 to 250 ng/mL MMF PRED
Outcomes	<ul style="list-style-type: none"> SCr levels Patient survival Graft survival Number of rejections Evidence of kidney damage assessed using glomerular and tubular urine biomarker levels
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 $\pm$ 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 $\leq 2.5 \times 10^9$/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	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p>

CENTRAL Study 2012 (Continued)

	<ul style="list-style-type: none"> • Basiliximab induction therapy • Steroids: 10 mg/d PRED until 10 to 12 weeks then as per local practice
Outcomes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 $\pm$ SD (years): treatment group (48.2 $\pm$ 12.3); control group (50.4 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> • 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 <p>Control group</p> <ul style="list-style-type: none"> • CsA: dose was tapered over time • EC-MPS: continued unchanged (1440 mg/d) <p>Both groups</p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 (re-reporting bias)	High risk	All prespecified outcomes not reported
Other bias	High risk	Funded by Novartis Pharma

Chadban 2013

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: 2002 to 2004 Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> Low-dose CsA C2 levels: 700 to 1000 ng/mL (months 4 to 6), 550 to 700 ng/mL (months 7 to 12) <p>Control group</p> <ul style="list-style-type: none"> Normal dose CsA C2 levels: 1000 to 1300 ng/mL (months 4 to 6), 850 to 1000 ng/mL (months 7 to 12) <p>Both groups</p> <ul style="list-style-type: none"> EC-MPS Basiliximab induction Corticosteroids
Outcomes	<ul style="list-style-type: none"> CrCl BPAR Patient survival Graft survival
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Setting: multicentre (18 centres) country: USA De novo kidney transplant patients Immediately post-transplant Number: treatment group (49); control group (43) Mean age $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> Low-dose TAC trough levels: 4 to 7 ng/mL (months 0 to 3), 3 to 6 ng/mL (months 4 to 6) <p>Control group</p> <ul style="list-style-type: none"> Standard-dose TAC trough levels: 8 to 11 ng/mL (months 0 to 3), 7 to 10 ng/mL (months 4 to 6) <p>Both groups</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT (1:1) Study period: September 2005 to March 2007 Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (47.7 $\pm$ 12.6); control group (45.3 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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
	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Kidney function at 6 months Incidence of BPAR Graft loss Death NODAT
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT (2:1) Study duration: recruitment between June 2007 and May 2011 Duration of follow-up: 24 months
Participants	<ul style="list-style-type: none"> Setting: single centre Country: USA De novo kidney transplant recipients; > 18 years Number: treatment group (123); control group (64) Mean age $\pm$ SD (years): treatment group (49.2 $\pm$ 11.9); control group (49.1 $\pm$ 12.8)

Chhabra 2013 (Continued)

- 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/mm³, WCC < 2000/mm³; history of malignancy during the post-transplant period

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • SRL: started at 2 mg/d to achieve a 24 h trough levels were 5 and 8 ng/mL <p>Control group</p> <ul style="list-style-type: none"> • 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 <p>Both groups</p> <ul style="list-style-type: none"> • Alemtuzumab and PRED induction, with rapid steroid elimination • MMF: 1 g/d (titrated based on WCC)
Outcomes	<ul style="list-style-type: none"> • BPAR • Patient survival • Graft survival • eGFR • Donor-specific antibody levels • Adverse events: infections, malignancies, proteinuria, haematological abnormalities, hyperlipidaemia
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ (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 ($< 75,000/\text{mm}^3$); neutropenia ($< 1500/\text{mm}^3$); leukopenia ($< 2500/\text{mm}^3$); Hb < 6 g/dL at baseline
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Higher CsA C2 levels: 1300 ng/mL (at month 3), 1100 ng/mL (months 3 to 6), 900 ng/mL (months 7 to 12) <p>Control group</p> <ul style="list-style-type: none"> Lower CsA C2 levels: 1100 ng/mL (at month 3), 900 ng/mL (months 3 to 6), 700 ng/mL (months 7 to 12) <p>Both groups</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> CrCl Incidence of BPAR and treated AR Graft survival Patient survival Incidence of infections and adverse events.
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Reduced dose TAC trough levels: 5 to 10 ng/mL SRL PRED <p>Control group</p> <ul style="list-style-type: none"> Standard TAC trough levels: 8 to 12 ng/mL SRL PRED
Outcomes	<ul style="list-style-type: none"> BPAR CrCl Graft survival Patient survival Malignancy Infection rates
Notes	<ul style="list-style-type: none"> 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

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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment November 2004 to October 2006 Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (46.5 $\pm$ 12.0); control group (47.3 $\pm$ 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 mm³; Hb < 9g/dL
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> SRL trough levels: 8 to 15 ng/mL (weeks 12 to 39), 5 to 10 ng/mL after 39 weeks <p>Control group</p> <ul style="list-style-type: none"> CsA C2 levels: 500 to 800 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> CNI ceased and SRL introduced (trough 8 to 20 ng/mL) <p>Control group</p> <ul style="list-style-type: none"> CNI group: continued CsA or TAC (CsA trough 50 to 250 ng/mL; TAC trough 4 to 10 ng/mL) <p>Both groups</p> <ul style="list-style-type: none"> AZA MMF
Outcomes	<ul style="list-style-type: none"> GFR at 12 months BPAR Graft survival at 12 and 24 months Patient survival at 12 and 24 months
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT; 2:1 randomisation Study duration: November 2010 to May 2015 Duration of follow-up: 24 months
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CTOT-09 Study 2015 (Continued)

Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> TAC trough levels: 5 to 8 ng/mL MMF PRED <p>Initial treatment for 6 months (both groups)</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

CTOT-09 Study 2015 *(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	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

de Sevaux 2001

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: enrolment 1/1/1997 to 31/12/1998 Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> Low dose CsA trough levels: 150 ng/mL for 6 months <p>Control group</p> <p>Conventional CsA trough levels: 300 ng/mL (1st 3 months), 150 ng/mL (3 to 6 months)</p> <p>Both groups</p> <ul style="list-style-type: none"> MMF: 1000 mg twice/d PRED
Outcomes	<ul style="list-style-type: none"> 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

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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment April 2000 to June 2004 • Duration of follow-up:
Participants	<ul style="list-style-type: none"> • 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 $\pm$ SD (years): treatment group (51.7 $\pm$ 12.6); control group (51.1 $\pm$ 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 $\times$ 10³/μL; Hb < 80 g/dL; platelet count < 100 $\times$ 10³/μL;

DICAM Study 2010 (Continued)

severe intestinal disorders; pregnancy; breastfeeding or current immunosuppressive treatment with drugs other than CsA and MMF

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p> <ul style="list-style-type: none"> MMF
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: November 1998 to April 2002 Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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 10⁹/L; Hb < 5 g/dL; use of bile acid sequestrants
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> MMF: 2 g/d Steroids CsA dose tapered and stopped over a 6-week period <p>Control group</p> <ul style="list-style-type: none"> Centre practice (CsA monotherapy, CsA/steroids, or CsA/AZA/steroids) CsA trough levels to be maintained over 80 ng/mL
Outcomes	<ul style="list-style-type: none"> Change in kidney function over the 6 months Graft survival Patient survival AR incidence Calculated CrCl BP Antihypertensive and lipid-lowering medication use
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 3 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years); not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> SRL-based regime: dose not reported <p>Control group</p> <ul style="list-style-type: none"> TAC-based regime: dose not reported <p>Both groups</p> <ul style="list-style-type: none"> MMF: dose not reported PRED: dose not reported
Outcomes	<ul style="list-style-type: none"> Patient survival Graft survival Kidney function by Cockcroft-Gault BPAR Proteinuria
Notes	<ul style="list-style-type: none"> Abstract-only publication Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment December 2000 and February 2003; data collected until February 2006 Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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 $< 2.5 \times 10^9/L$; platelet count $< 100 \times 10^9/L$; Hb < 60 g/L; PRA (current or peak) $> 20\%$
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Daclizumab induction: 5 doses Low-dose CsA: 50% trough levels of the control <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p> <ul style="list-style-type: none"> MMF Steroids
Outcomes	<ul style="list-style-type: none"> Kidney function 12 months after kidney transplantation by CrCl

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

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 $\pm$ 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/mm³); leukopenia (< 2500/mm³); absolute neutrophil count < 1500/mm³, 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	<p>Treatment group 1</p> <ul style="list-style-type: none"> • FTY720: 5 mg • Reduced dose CsA: 2 to 3 mg/kg <p>Treatment group 2</p> <ul style="list-style-type: none"> • FTY720: 2.5 mg • Reduced dose CsA: 2 to 3 mg/kg <p>Treatment group 3</p> <ul style="list-style-type: none"> • FTY720: 2.5 mg • Full-dose CsA: 8 to 10 mg/kg <p>Control group</p> <ul style="list-style-type: none"> • Full-dose CsA: 8 to 10 mg/kg • MMF <p>C2 levels difference 50 to 70% between reduced and full dose group.</p>
Outcomes	<ul style="list-style-type: none"> • BPAR • GFR at 1 year • death • Graft loss
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment March 2000 to June 2001 Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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/mm³; platelets < 75,000/mm³
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> CsA: 6 to 8 mg/kg to maintain trough levels of 200 to 250 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> MMF PRED
Outcomes	<ul style="list-style-type: none"> Patient survival Graft survival BPAR Mean SCr Calculated CrCl
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Setting: single centre Country: Brazil Recipients of one-haplotype living-related allografts Number: group 1 (92); group 2 (38); group 3 (21) Mean age $\pm$ 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 3 (12/9) Exclusion criteria: evidence of systemic infection; history of clinically significant cardiac abnormalities; malignancy with 10 years
Interventions	<p>Group 1</p> <ul style="list-style-type: none"> 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 <p>Group 2</p> <ul style="list-style-type: none"> Daclizumab induction: 3 doses MMF PRED <p>Enrolment was interrupted in 2002 and a 3rd group of patients were enrolled in a non-randomised fashion</p> <p>Group 3</p> <ul style="list-style-type: none"> Daclizumab induction MMF SRL: 6 mg loading and 2 mg daily PRED

Garcia 2007 (Continued)

Outcomes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment between December 1986 to January 1989 • Duration of follow-up: 12 years
Participants	<ul style="list-style-type: none"> • 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> • PRED: tapered to 15 mg/d after 1st month • AZA: 2 to 3 mg/kg/d over 12 years <p>Control group</p> <ul style="list-style-type: none"> • CsA: introduced on day 14 at 6 to 8 mg/kg * 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 <p>Both groups (immediately post-transplant)</p> <ul style="list-style-type: none"> • ALG induction: 5 mg/kg/d for 14 days • AZA: 1.5 mg/kg/d • Steroids: 1 mg/kg/d for 1st month
Outcomes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel pilot RCT Study duration: recruitment December 2000 to January 2002 Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (45.2 $\pm$ 13.5); control group (47.4 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> SRL trough levels: 8 to 16 ng/mL TAC trough levels: 3 to 8 ng/mL with elimination from month 3 onwards <p>Control group</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> GFR at 12 months BPAR at 12 months BP
Notes	<ul style="list-style-type: none"> 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

Hall 1988

Methods	<ul style="list-style-type: none"> Study design: parallel, 3-arm RCT Study duration: recruitment 1983 and 1986 Duration of follow-up: 24 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Group 1</p> <ul style="list-style-type: none"> 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 <p>Group 2</p> <ul style="list-style-type: none"> 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 <p>Group 3</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Death-censored graft survival Patient survival Graft loss Kidney function using MDRD

Hall 1988 (Continued)

- Notes
- Funding sources
 - * 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 2 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (45.1 $\pm$ 11.2); control group (42.5 $\pm$ 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 <ul style="list-style-type: none"> CsA withdrawal: between months 3 and 4 MMF: 2 mg/d

Hazzan 2005 (Continued)

- PRED

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	<ul style="list-style-type: none"> • BPAR • Death • Graft loss • Kidney function • Chronic allograft damage index on graft biopsy at 1 year
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel, 3-arm RCT • Study duration: not reported
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Heering 1993 (Continued)

	<ul style="list-style-type: none"> Duration of follow-up: 24 months
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Germany Adults randomised 6 months post-transplant Number: group 1 (17); group 2 (17); group 3 (18) Mean age $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Group 1</p> <ul style="list-style-type: none"> CsA/AZA/PRED <p>Group 2</p> <ul style="list-style-type: none"> CsA/PRED <p>Group 3</p> <ul style="list-style-type: none"> AZA/PRED <p>Both groups (to 9 months)</p> <ul style="list-style-type: none"> Triple therapy: CsA/AZA/PRED
Outcomes	<ul style="list-style-type: none"> AR Graft survival Graft function (SCR, CrCl)
Notes	<ul style="list-style-type: none"> 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

Heering 1993 (Continued)

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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Setting: multicentre (20 centres) Country: Germany Adults randomised 3 months post-transplant Number: group 1 (159); group 2 (163); group 3 (163) Mean age $\pm$ 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/mm³; leucocytes < 2500/mm³; 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	<p>Group 1</p> <ul style="list-style-type: none"> Standard CsA trough levels: 100 to 180 ng/mL EC-MPS <p>Group 2</p> <ul style="list-style-type: none"> CSA withdrawal EVL trough levels: 5 to 10 ng/mL EC-MPS <p>Group 3</p> <ul style="list-style-type: none"> Low-CsA trough levels: 50 to 75 ng/mL EVL trough levels: 3 to 8 ng/mL <p>Both groups (to 3 months)</p> <ul style="list-style-type: none"> Basiliximab induction CsA EC-MPS steroids
Outcomes	<ul style="list-style-type: none"> Death Graft loss Composite failure: BPAR, death, graft loss, loss to follow-up Premature discontinuation due to adverse effects Kidney function (eGFR)
Notes	<ul style="list-style-type: none"> Abstract-only publications for main study Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
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HERAKLES Study 2012 (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)	Low risk	Prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Hollander 1995

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment 1983 to 1988 Duration of follow-up: 15 years
Participants	<ul style="list-style-type: none"> Setting: single centre Country: the Netherlands Adults randomised 3 months post-transplant Number: treatment group (60); control group (68) Mean age $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> CsA: reduced 5 mg/kg/d adjusted for trough levels (250 to 500 ng/mL) PRED: 10 mg/d <p>Both groups (to 3 months)</p> <ul style="list-style-type: none"> CsA: 16 mg/kg/d reduced to 10 mg/kg/d over 3 months PRED: 20 mg/d tapered to 10 mg/d

Hollander 1995 (Continued)

Outcomes	<ul style="list-style-type: none"> • Patient survival • Graft survival • GFR • Acute and chronic rejection (biopsy proven)
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: not reported • Duration of follow-up: 36 months
Participants	<ul style="list-style-type: none"> • Setting: single centre • Country: Mexico • Adults and children randomised 30 to 1780 days post-transplant • Number: treatment group (220); control group (185) • Mean age $\pm$ SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group <ul style="list-style-type: none"> • 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

Holm 2008 (Continued)

Control group

- MMF: 1 to 2 g/d
- 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	<ul style="list-style-type: none"> • Clinical data of all patients (baseline, 3, 6, 9, 12, 18, 24 and 36 months) • BPAR • Graft loss • Morbidity • Death • Change in GFR
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel, 4-arm study (1:1:1:1) • Study duration: recruitment January 1986 to May 1987 • Duration of follow-up: 1 year
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Isoniemi 1990 (Continued)

Participants	<ul style="list-style-type: none"> Setting: single centre Country: Finland 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 $\pm$ 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	<p>Group 1</p> <ul style="list-style-type: none"> Continued with triple therapy (CsA, AZA, PRED) <ul style="list-style-type: none"> * CsA: maintained at pre-conversion levels * AZA: 1 mg/d * PRED: tapered to 4 to 12 mg/d for the 1st year <p>Group 2</p> <ul style="list-style-type: none"> CsA: maintained at pre-conversion levels AZA: temporarily increased to 2 mg/kg/d then adjusted to WCC PRED: gradually withdrawn over 2 weeks <p>Group 3</p> <ul style="list-style-type: none"> 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 <p>Group 4</p> <ul style="list-style-type: none"> 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 <p>All groups (1st 10 weeks)</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> BPAR Graft survival Patient survival
Notes	<ul style="list-style-type: none"> 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

Isoniemi 1990 (Continued)

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 obvious missing data
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	Unclear risk	Insufficient information to permit judgement

Kosch 2003a

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> CsA withdrawal: CsA tapered over 4 weeks PRED: dose not reported <p>Control group</p> <ul style="list-style-type: none"> Standard CsA trough levels: 75 to 150 μmol/L PRED: dose not reported MMF: 2 g/d during 1st 4 weeks <p>Both groups (to 6 months)</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Carotid and brachial artery distensibility coefficients (baseline and at 6 months) Biochemical data (baseline and at 6 months)

Kosch 2003a (Continued)

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 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: not reported Duration of follow-up: 2 years
Participants	<ul style="list-style-type: none"> Setting: multicentre Country: France 1st or 2nd kidney transplant recipients randomised week 8 post-transplant Number: treatment group (78); control group (80) Mean age $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p>

Kreis 2003 (Continued)

	<ul style="list-style-type: none"> • Daclizumab induction • MMF: 2 g/d • Steroids
Outcomes	<ul style="list-style-type: none"> • SCr • BPAR • Graft survival • Patient survival
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment between 1985 to 1991 • Duration of follow-up: 15 years
Participants	<ul style="list-style-type: none"> • 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)

MacPhee 1998 (Continued)

- Exclusion criteria: AR in preceding 6 months

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • AZA: 3 mg/kg titrated to maintain WCC $> 4 \times 10^6$ • PRED: 10 mg • CsA: stopped after 1 week <p>Control group</p> <ul style="list-style-type: none"> • CsA trough level: 80 to 125 ng/mL at 1 year
Outcomes	<ul style="list-style-type: none"> • Patient survival • Graft survival • Kidney function • Need for anti-hypertensive agents.
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment May 2004 to January 2005 • Duration of follow-up: mean 15.8 months
Participants	<ul style="list-style-type: none"> • Setting: single centre • Country: Mexico

Martinez-Mier 2006 (Continued)

- Adult 1st degree living related kidney allograft recipients
- Number: treatment group (20); control group (21)
- Mean age $\pm$ 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)
- 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 $< 3,000$ mm³; platelets $< 75,000$ mm³

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • SRL: loading dose of 10 mg orally and then 3 mg/m²; dose adjusted to achieve trough levels between 10 and 15 ng/mL for 6 months and 5 to 10 ng/mL thereafter <p>Control group</p> <ul style="list-style-type: none"> • CsA: 4 to 8 mg/kg/d in divided doses, adjusted to trough levels between 150 to 300 ng/mL for six months <p>Both groups</p> <ul style="list-style-type: none"> • Basiliximab induction • MMF: 2g/d • PRED
Outcomes	<ul style="list-style-type: none"> • Patient survival at 1 year • Graft survival at 1 year • Incidence of BPAR
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel, 3-arm RCT (1:1:1) Study duration: recruitment commenced 2005 Duration of follow-up: 24 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group 1</p> <ul style="list-style-type: none"> MPS: target AUC₁₂ 35 mg.h/L or a trough level > 2 mg/L PRED: 10 mg/d <p>Treatment group 2</p> <ul style="list-style-type: none"> EVL: target AUC₁₂ 150 mg.h/L PRED: 10 mg/d <p>Control group</p> <ul style="list-style-type: none"> CsA: Target AUC₁₂ 3250 μg.h/L PRED: 10 mg/d <p>All groups (1st 6 months)</p> <ul style="list-style-type: none"> Basiliximab induction PRED MPS CSA
Outcomes	<ul style="list-style-type: none"> Interstitial graft fibrosis Hyalinosis AR (not defined) Graft survival Patient survival SCr Infections GFR
Notes	<ul style="list-style-type: none"> Funding source: Novartis Pharma
Risk of bias	
Bias	Authors' judgement Support for judgement

MECANO Study 2009 (Continued)

Random sequence generation (selection bias)	Low risk	The randomisation list was generated with “Random Allocation Software” Version 1.0 2004 tripod.com
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	<ul style="list-style-type: none"> • Study design: parallel, 3-arm RCT • Study duration: recruitment 2002 to 2004 • Duration of follow-up: 5 years
Participants	<ul style="list-style-type: none"> • Setting: single centre • Country: Brazil • Adult transplant recipients • Number: group 1 (39); group 2 (40); group 3 (40) • Mean age $\pm$ SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	<p>Group 1</p> <ul style="list-style-type: none"> • Low dose TAC trough levels: 3 to 5 ng/mL • MMF • Steroids <p>Group 2</p> <ul style="list-style-type: none"> • Classic schedule TAC trough levels: 7 to 9 ng/mL • MMF • Steroids <p>Group 3</p> <ul style="list-style-type: none"> • CsA: C2 levels 800 to 1000 ng/mL • MMF

MODIFY Study 2012 (Continued)

- Steroids

Outcomes	<ul style="list-style-type: none"> • Graft loss • Death • Calculated CrCl • BPAR: graft biopsies performed at 6 months and scored according to chronic allograft damage index
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT (1:1) • Study duration: recruitment 2000 to 2002 • Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> • 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 post-transplant • Number: treatment group (178); control group (179) • Mean age $\pm$ SD (years): treatment group (47.4 $\pm$ 13.1); control group (46.1 $\pm$ 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

Muhlbacher 2014 (Continued)

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	<p>Treatment group</p> <ul style="list-style-type: none"> Reduced dose CsA trough levels: 75 to 100 ng/mL SRL trough levels: 4 to 12 ng/mL Steroids <p>Control group</p> <ul style="list-style-type: none"> Full dose CsA trough levels: 150 to 200 ng/mL SRL trough levels: 4 to 12 ng/mL Steroids
Outcomes	<ul style="list-style-type: none"> Patient survival Graft survival BPAR SCr CrCl Infections Hyperlipidaemia
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment 2004 to 2007 Duration of follow-up: 4 years
Participants	<ul style="list-style-type: none"> 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 10⁹/L, platelet count > 100 x 10⁹/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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> CsA trough levels: 150 to 250 ng/mL MMF: 1 to 2 g/d Steroids: 5 mg/d
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

Nafar 2012 (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	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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment not reported Duration of follow-up: 3 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p> <ul style="list-style-type: none"> 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 $\geq$ 5 mg/d during year 1
Outcomes	<ul style="list-style-type: none"> Efficacy failure: defined as BPAR, graft loss, death or loss to follow-up at 6 months Malignancy Infections Kidney function

Nashan 2004 (Continued)

Notes	Funding source: "This study was sponsored by a grant from 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	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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment July 2009 to March 2012 Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (41.9 $\pm$ 11.1); control group (47.0 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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)

Oh 2012 (Continued)

Control group

- Standard dose CsA trough levels: 150 to 250 ng/mL

Both groups

- Basiliximab induction
- CsA
- EC-MPS
- Steroids

Outcomes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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

OPTICEPT Study 2009 (Continued)

- Duration of follow-up: 2 years

Participants	<ul style="list-style-type: none"> • 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 • Number: group 1 (243); group 2 (237); group 3 (240) • Mean age $\pm$ 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	<p>Group 1</p> <ul style="list-style-type: none"> • MMF: controlled concentration <ul style="list-style-type: none"> * CsA group trough levels: $\geq 1.3 \mu\text{g/mL}$ * TAC group trough levels: $\geq 1.9 \mu\text{g/mL}$ • CNI: reduced dose CsA or TAC <ul style="list-style-type: none"> * 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) <p>Group 2</p> <ul style="list-style-type: none"> • MMF: controlled concentration (as for group 1) • CNI: standard dose CsA or TAC <ul style="list-style-type: none"> * 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) <p>Group 3</p> <ul style="list-style-type: none"> • MMF: fixed dose 2 g/d (adults), 600 mg/m² (children) • CNI: standard dose CsA or TAC (as for group 2)
Outcomes	<ul style="list-style-type: none"> • BPAR • Graft loss • Death • Mean percent change in GFR • Adverse events
Notes	<ul style="list-style-type: none"> • 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)	High risk	Open-label study

OPTICEPT Study 2009 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	Not performed
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	<ul style="list-style-type: none"> Study design: parallel, 3-arm RCT (1:1:1) Study duration: recruitment March 2004 to May 2005 Duration of follow-up: 2 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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/m²; WCC ≤ 3000/mm³; platelet count $\leq 100,000$ mm³; fasting triglycerides ≥ 400 mg/dL; fasting total cholesterol ≥ 300 mg/dL; cold ischaemia time > 30 h
Interventions	<p>Group 1</p> <ul style="list-style-type: none"> 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 <p>Group 2</p> <ul style="list-style-type: none"> SRL trough levels: 10 to 15 ng/mL (to week 26), 8 to 15 ng/mL thereafter MMF: 1 to 2 g/d <p>Group 3</p> <ul style="list-style-type: none"> TAC trough levels: 8 to 15 ng/mL (to week 26), 5 to 15 ng/mL thereafter MMF: 1 to 2 g/d
Outcomes	<ul style="list-style-type: none"> Patient survival Graft survival BPAR Time to 1st rejection
Notes	<ul style="list-style-type: none"> Group 2 terminated due to high BPAR rate Funding source: funded by Wyeth; editorial assistance and manuscript preparation funded by Wyeth

ORION Study 2011 (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	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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment no reported Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> EVL: converted during a 3-day overlap with TAC <p>Control group</p> <ul style="list-style-type: none"> TAC: dose not reported <p>Both groups</p> <ul style="list-style-type: none"> Thymoglobulin induction PRED MPS

Pacheco-Silva 2013 (Continued)

Outcomes	<ul style="list-style-type: none"> Incidence of CMV infection Mean SCr at 30 days, 60 days and 1 year AR
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> EVL trough levels: 3 and 8 ng/mL

Paoletti 2012 (Continued)

- 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
- MMF

Both groups

- IL2RA induction
- Steroids

Outcomes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment January 2000 to October 2001 • Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> • 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)

Pascual 2003 (Continued)

- Number: treatment group (32); control group (32)
- Mean age $\pm$ SD (years): treatment group (47 ± 12); control group (45 ± 13)
- Sex (M/F): treatment group (27/5); control group (21/11)
- Exclusion criteria: not reported

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • CsA reduction to 50% over 2 months: initial 25% reduction then further 25% reduction after 2 months if no rejection <p>Control group</p> <ul style="list-style-type: none"> • CsA trough levels: 100 to 300 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> • MMF • PRED • CsA trough at randomisation: 100 to 300 ng/mL
Outcomes	<ul style="list-style-type: none"> • Graft loss • AR • SCr • CrCl • Hypertension
Notes	<ul style="list-style-type: none"> • 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

Methods	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Setting: single centre Country: USA Adults randomised between 2 and 16 months post-transplant Number: treatment group (20); control group (20) Mean age $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> CNI <ul style="list-style-type: none"> CsA trough levels: 100 to 200 ng/mL TAC trough levels: 5 to 10 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> Alemtuzumab induction TAC or CsA MMF/EC-MPS: 500/360 mg every 12 hours at enrolment Low-dose steroids
Outcomes	<ul style="list-style-type: none"> AR Patient survival Graft survival Graft kidney function: GFR, SCr Peripheral Treg levels
Notes	<ul style="list-style-type: none"> 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

Pascual 2008 (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	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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment not reported Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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	<p>Treatment group</p> <ul style="list-style-type: none"> AZA: 2 mg/kg CsA: 150 mg/d for 1st 2 weeks PRED: 5.0 to 7.5 mg/d <p>Control group</p> <ul style="list-style-type: none"> CsA: 3 to 5 mg/kg PRED: 5.0 to 7.5 mg/d <p>Both groups (on entry)</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Graft failure requiring dialysis Adverse effects of the drugs Death
Notes	<ul style="list-style-type: none"> 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

Pedersen 1991 (Continued)

Bias	Authors' judgement	Support for judgement
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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment June 2002 to July 2003 Duration of follow-up: 2 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (37.6 ± 13.8); control group (33.6 ± 9.5) Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> CsA: abruptly discontinued Rapamycin: loading dose of 0.1 mg/kg/d; trough levels 6 to 10 ng/mL <p>Control group</p> <ul style="list-style-type: none"> CsA: maintained at pre-randomisation levels <p>Both groups</p> <ul style="list-style-type: none"> CsA: "At randomization, there was no difference in the dose administered and in the trough levels of cyclosporine between the two groups" MMF AZA

Pontrelli 2008 (Continued)

Outcomes	<ul style="list-style-type: none"> Kidney biopsy at 2 years 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	<ul style="list-style-type: none"> 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'Università 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment January 2010 to March 2013 Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> Setting: multicentre (52 centres) Country: USA, Canada de novo kidney transplant recipients Number: treatment group (309); control group (304) Mean age $\pm$ 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

Qazi 2014 (Continued)

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p> <ul style="list-style-type: none"> Basiliximab or ATG induction Steroids as per local practice
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

REFERENCE Study 2006

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment March 2000 to February 2002 Duration of follow-up: 96 weeks
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (43.8 $\pm$ 10.6); control group (44.7 $\pm$ 11.1) Sex (M/F): treatment group (55/22); control group (27/4) Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> CsA: dose as per local practice (trough levels to be > 100 ng/mL)
Outcomes	<ul style="list-style-type: none"> Change in SCr Graft survival Patient survival BPAR and clinical rejection episodes CrCl Infections
Notes	<ul style="list-style-type: none"> 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)	Low risk	Data accounted for outcomes and analysed as ITT

REFERENCE Study 2006 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes reported
Other bias	High risk	Funded by Roche

Rivelli 2015

Methods	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment over 18 months Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (44.9 $\pm$ 14.2); control group (46.3 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> TAC: stopped at 3 months SRL trough levels: increased to 8 to 15 ng/mL <p>Control group</p> <ul style="list-style-type: none"> TAC trough levels: 3 to 7 ng/mL (after 3 months) <p>Both groups</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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)."

Rivelli 2015 (Continued)

Risk of bias

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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment May 1998 to June 1999 Duration of follow-up: 60 months
Participants	<ul style="list-style-type: none"> Setting: multicentre (57 centres) Country: Europe, Australia, Canada 1st or 2nd kidney transplant recipients aged > 13 years; cadaveric or living donors; WCC $\geq 4000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, fasting triglycerides $\leq 4.6 \text{ mmol/L}$, fasting cholesterol $\leq 7.8 \text{ mmol/L}$, 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	<p>Treatment group</p> <ul style="list-style-type: none"> CsA: gradually decreased and eliminated over 4 to 6 weeks High dose SRL trough levels: 20 to 30 ng/mL Steroids

RMR Study 2001 (Continued)

Control group

- 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	<ul style="list-style-type: none"> • Graft survival at 12, 24 and 36 months • SCr • BPAR • Patient survival • PTLD • Infection
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment not reported • Duration of follow-up: 2 years
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Rossini 2007 (Continued)

Participants	<ul style="list-style-type: none"> Setting: single centre Country: Italy Patients with biopsy-proven CAN and on treatment with CNI Number: treatment group (6); control group (6) Mean age $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Rapamycin: regimen not reported <p>Control group</p> <ul style="list-style-type: none"> CNI-based regimens: regimen not reported
Outcomes	<ul style="list-style-type: none"> Kidney biopsy at 2 years: record vascular endothelial growth factor expression in the glomerulus, total glomerular area on morphometry Urinary protein SCr
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT
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Russ 2003 (Continued)

	<ul style="list-style-type: none"> Study duration: recruitment not reported Duration of follow-up: 6 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> 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) <p>Both groups</p> <ul style="list-style-type: none"> SRL within 48 h of transplant Steroids
Outcomes	<ul style="list-style-type: none"> Graft function Incidence of rejection Patient survival at 6 months Graft survival at 6 months
Notes	<ul style="list-style-type: none"> 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)	Unclear risk	No further data reported after 6 months

Russ 2003 (Continued)

All outcomes

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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment not reported Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Italy Patients aged > 55 years Number: treatment group (49); control group (58) Mean age $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Reduced dose CsA C2 levels: 900 ng/mL (months 1 and 2), 800 ng/mL (months 3 to 6) <p>Control group</p> <ul style="list-style-type: none"> Standard dose CsA C2 levels: 1500 ng/mL (month 1), tapered to 1000 ng/mL (by month 6), 800 ng/mL thereafter <p>Both groups</p> <ul style="list-style-type: none"> Basiliximab induction Steroids: stopped day 8 EC-MPS: 2160 mg/d for 5 days, then 1440 mg/d thereafter
Outcomes	<ul style="list-style-type: none"> Mean CrCl Graft survival Patient survival Infection BPAR
Notes	<ul style="list-style-type: none"> 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

Salvadori 2007 (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	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	<ul style="list-style-type: none"> Study design: parallel, 3-arm RCT (1:1:1) Study duration: recruitment not reported Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): not reported Sex (M/F): not reported Exclusion criteria:
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> SRL trough levels: 8 to 12 ng/mL PRED MMF: 2 g/d <p>Control group</p> <ul style="list-style-type: none"> TAC trough levels: 8 to 12 ng/mL PRED MMF: 2 g/d <p>Both groups</p> <ul style="list-style-type: none"> Thymoglobulin induction
Outcomes	<ul style="list-style-type: none"> Graft survival BPAR at 1 year SCr at 3 months Hyperlipidaemia
Notes	<ul style="list-style-type: none"> 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

Smak Gregoor 1999

Methods	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<p>Group 1</p> <ul style="list-style-type: none"> CsA withdrawal: dose reduce by 50% 2 weeks prior to cessation PRED: increased dose to 0.15 mg/kg/d <p>Group 2</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> • AR: most BPAR except for 2 in the CsA group • Chronic rejection • Graft failure • Death • SCr, CrCl • Infection • Malignancy
Notes	<ul style="list-style-type: none"> • Funding source: Roche 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)	Low risk	Used sealed envelopes with random numbers
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 noted
Selective reporting (reporting bias)	Low risk	Prespecified expected outcomes reported
Other bias	High risk	Funded by Roche Pharmaceuticals

SMART TX Study 2010

Methods	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 $\pm$ 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/m²; WCC $\geq$ 4000 mm³; platelet count $\geq$ 100,000 mm³; fasting triglycerides $\leq$ 4.6 mmol/L; fasting cholesterol $\leq$ 7.8 mmol/L

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • 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 <p>Control group</p> <ul style="list-style-type: none"> • CsA trough levels: 150 to 200 ng/mL, then 100 to 150 ng/mL (month 4) • MMF: 2 g/d <p>Both groups</p> <ul style="list-style-type: none"> • ATG induction (modified after 1st 25 patients) • PRED: according to local protocol • CsA trough levels: 200 to 250 ng/mL (for 1st 2 to 3 weeks)
Outcomes	<ul style="list-style-type: none"> • BPAR • Graft survival • Patient survival • Treatment failure • Change in graft function • Infections
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment August 2003 to November 2008 Duration of follow-up: 2 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ 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 iohalamate 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/mm³; platelet count < 100,000/mm³; 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	<p>Treatment group</p> <ul style="list-style-type: none"> CNI withdrawal: withdrawn from CNI within 72 h or randomisation SRL trough levels: 5 to 10 ng/mL <p>Control group</p> <ul style="list-style-type: none"> CsA tough level: according to local protocol <p>Both groups</p> <ul style="list-style-type: none"> Basiliximab induction PRED: according to local protocol MMF: 2 to 3 g/d
Outcomes	<ul style="list-style-type: none"> Percent change in GFR 12 months post randomisation BPAR Graft loss Proteinuria
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment not reported Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> Setting: single centre Country: Italy Consecutive kidney transplant recipients from cadaveric donors Number: treatment group (20); control group (20) Mean age $\pm$ SD (years): treatment group (40 ± 10); control group (47 ± 5) Sex (M/F): not reported Exclusion criteria: not reported
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> CsA withdrawal SRL trough levels: 10 to 15 ng/mL PRED <p>Control group</p> <ul style="list-style-type: none"> CsA trough levels: 150 to 250 ng/mL SRL: 2 mg/d PRED <p>Both groups (to 3 months)</p>

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	<ul style="list-style-type: none"> • Graft biopsy at 12 months for chronic changes • Incidence of DGF • AR • Graft function • CrCl
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment started January 2000 • Duration of follow-up: 1 years
Participants	<ul style="list-style-type: none"> • Setting: single centre • Country: Italy • Recipients of a suboptimal cadaveric kidney; > 45 years • Number: treatment group (42); control group (48) • Mean age $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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 <p>Control group</p> <ul style="list-style-type: none"> CsA C2 levels: 1200 to 1400 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> Basiliximab induction PRED: 250 mg/d tapered to 25 mg (by day 8) and then to 5 mg (by month 2)
Outcomes	<ul style="list-style-type: none"> Incidence and length of DGF Long-term graft function of patients who experience DGF SCr and CrCl
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment April 2001 to January 2004 Duration of follow-up: 36 months
Participants	<ul style="list-style-type: none"> 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/mm³; 12 months after enrolment began, recipients with a BMI > 32 kg/m² were excluded because of a high incidence of wound complications in obese patients using the SRL protocol

Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> • SRL: 10 mg/d initially for 2 days then 5 mg/d thereafter <p>Control group</p> <ul style="list-style-type: none"> • 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 <p>Both groups</p> <ul style="list-style-type: none"> • ATG induction • PRED
Outcomes	<ul style="list-style-type: none"> • Patient survival • Graft survival • BPAR • Kidney function • Complications • Adverse events
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment not reported Duration of follow-up: 35 weeks
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (47.9 $\pm$ 13.1); control group (22.90 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> CNI withdrawal from week 4: dose reduced by 33% every 2 weeks until complete withdrawal MMF PRED <p>Control group</p> <ul style="list-style-type: none"> CNI MMF PRED <p>Both groups</p> <ul style="list-style-type: none"> CNI (weeks 1 to 3) <ul style="list-style-type: none"> * CsA trough levels: 80 to 120 ng/mL * TAC trough levels: 4 to 7 ng/mL MMF
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 $\pm$ SD (years): group 1 (45.9 $\pm$ 13.8); group 2 (47.2 $\pm$ 13.5); group 3 (45.4 $\pm$ 14.7); group 4 (44.9 $\pm$ 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	<p>Group 1</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> • Graft loss • Death • eGFR • AR • Malignancy • Opportunistic infections
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment February 2008 to August 2010 Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> Setting: multicentre Country: Japan Patients aged 18 to 65 years undergoing primary kidney transplantation Number: treatment group (61); control group (61) Mean age $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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) <p>Control group</p> <ul style="list-style-type: none"> CsA trough levels: 200 to 300 ng/mL (months 0 to 2), 100 to 250 ng/mL thereafter MMF: 2 g/d <p>Both groups</p> <ul style="list-style-type: none"> Basiliximab induction PRED: as per local protocol, minimum dose of 5 mg/d at 12 months
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel, 3-arm RCT (1:1:1) Study duration: recruitment not reported Duration of follow-up: 24 months
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): group 1 (45.7 $\pm$ 12.7); group 2 (45.3 $\pm$ 13.4); group 2 (47.2 $\pm$ 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; most recent PRA > 20%
Interventions	<p>Group 1</p> <ul style="list-style-type: none"> 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) <p>Group 2</p> <ul style="list-style-type: none"> EVL: 3 mg, trough levels 6 to 12 ng/mL Low dose CsA trough levels: 25 to 50 ng/mL (6 to 24 months) <p>Group 3</p> <ul style="list-style-type: none"> MPA: 1.44 g/d Standard dose CsA trough levels: 100 to 250 ng/mL (6 to 24 months) <p>All groups</p> <ul style="list-style-type: none"> Basiliximab induction PRED
Outcomes	<ul style="list-style-type: none"> Composite efficacy failure: BPAR, graft loss, death, kidney function at 12 months
Notes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment not reported Duration of follow-up: 1 year
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (45.2 $\pm$ 11.6); control group (44.9 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> • AR • GFR • patient survival • Graft survival • Hypertension
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Study design: parallel RCT • Study duration: recruitment May 2002 to January 2004 • Duration of follow-up: 12 months
Participants	<ul style="list-style-type: none"> • Setting: single centre • Country: UK

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	<p>Treatment group</p> <ul style="list-style-type: none"> • 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 <p>Control group</p> <ul style="list-style-type: none"> • CNI: therapy continued <p>Both groups</p> <ul style="list-style-type: none"> • PRED • AZA • MMF
Outcomes	<ul style="list-style-type: none"> • GFR at 12 months • SCr • Uric acid • Hypercholesterolaemia • Hypertension treatment • Number of AR episodes • Dialysis requirement • Mean 24 h BP
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> Study design: parallel RCT Study duration: recruitment June 2005 to September 2007 Duration of follow-up: 5 years
Participants	<ul style="list-style-type: none"> 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 $\pm$ SD (years): treatment group (46.9 $\pm$ 11.7); control group (46.7 $\pm$ 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	<p>Treatment group</p> <ul style="list-style-type: none"> 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%) <p>Control group</p> <ul style="list-style-type: none"> CsA trough levels: 120 to 180 ng/mL (months 4.5 to 6), thereafter 100 to 150 ng/mL <p>Both groups</p> <ul style="list-style-type: none"> CsA trough levels (to month 4.5): 150 to 220 ng/mL PRED as per local protocol
Outcomes	<ul style="list-style-type: none"> GFR at 12 months BPAR Graft loss Death Evolution of between 4.5 to 12 months and safety
Notes	<ul style="list-style-type: none"> 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; PTLT - 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
Metcalf 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	<ul style="list-style-type: none"> Parallel RCT
Participants	<ul style="list-style-type: none"> Elderly patients referred for kidney transplantation; 1 month post-transplant
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> Low TAC trough levels: 2 to 4 ng/mL EVL trough levels: 3 to 8 ng/mL <p>Control group</p> <ul style="list-style-type: none"> Regular TAC trough levels: 5 to 12 ng/mL MPS <p>Both groups</p> <ul style="list-style-type: none"> Steroids ATG induction therapy: single dose 2 mg/kg
Outcomes	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Multicentre, parallel RCT
Participants	<ul style="list-style-type: none"> Kidney transplant recipients treated for the 1st 3 months with TAC, MPS and steroids
Interventions	<p>Treatment group</p> <ul style="list-style-type: none"> TAC withdrawal EVL <p>Control group</p> <ul style="list-style-type: none"> TAC MPS PRED

ERIC Study 2010 (Continued)

Outcomes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Parallel RCT
Participants	<ul style="list-style-type: none"> • Patients needing kidney transplants
Interventions	<ul style="list-style-type: none"> • No interventions provided
Outcomes	<ul style="list-style-type: none"> • 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 fficacy 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	<p>Treatment group</p> <ul style="list-style-type: none"> • EVL trough level: 3 to 8 ng/mL • Reduced exposure to CNI (CsA or TAC) <p>Control group</p> <ul style="list-style-type: none"> • MPS or MMF • Standard exposure to CNI (CsA or TAC)

TRANSFORM Study 2013 (Continued)

Outcomes	<ul style="list-style-type: none"> Incidence of failure on the composite of treated BPAR or eGFR < 50 mL/min/1.73 m² 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 participants	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.

Analysis 1.2. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 2 Acute rejection.

Analysis 1.3. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 3 GFR.

Analysis 1.4. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 4 Graft loss. **Analysis 1.5. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 5 Serum creatinine.**

Analysis 1.6. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 6 Adverse events.

Analysis 1.7. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 7 Subgroup analysis: acute rejection.

Analysis 1.8. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 8 Subgroup analysis: GFR.

Analysis 1.9. Comparison 1 CNI withdrawal versus standard dose CNI, Outcome 9 Subgroup analysis: graft loss.

Comparison 2. Subgroup analysis (antimetabolite): CNI withdrawal versus standard dose CNI

Outcome or sub-group 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. **Comparison 3. Subgroup analysis (CNI type): CNI withdrawal versus standard dose CNI**

Outcome or sub-group 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]

Analysis 3.1. Comparison 3 Subgroup analysis (CNI type): CNI withdrawal versus standard dose CNI, Outcome 1 Acute rejection.

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.

Analysis 4.2. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 2 Acute rejection.

Analysis 4.3. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 3 GFR. **Analysis 4.4. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 4 Graft loss.**

Analysis 4.5. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 5 Serum creatinine. **Analysis 4.6. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 6 Change in GFR at 12 months.**

Analysis 4.7. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 7 Adverse events.

Analysis 4.8. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 8 Subgroup analysis: acute rejection.

Analysis 4.9. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 9 Subgroup analysis: GFR.

Analysis 4.10. Comparison 4 Low dose CNI versus standard dose CNI, Outcome 10 Subgroup analysis: graft loss.

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.

Comparison 6. CNI withdrawal or avoidance + mTOR-I versus standard dose CNI

Outcome or sub-group title	No. of studies	No. of participants	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 participants	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.

Analysis 6.2. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 2 Acute rejection.

Analysis 6.3. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 3 GFR.

Analysis 6.4. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 4 Graft loss.

Analysis 6.5. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 5 Serum creatinine at 1 year.

Analysis 6.6. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 6 Change in GFR.

Analysis 6.7. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 7 Adverse events.

Analysis 6.8. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 8 Subgroup analysis: acute rejection.

Analysis 6.9. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 9 Subgroup analysis: GFR.

Analysis 6.10. Comparison 6 CNI withdrawal or avoidance + mTOR-I versus standard dose CNI, Outcome 10 Subgroup analysis: graft loss.

Comparison 7. Subgroup analysis (CNI type): CNI withdrawal + mTOR-I versus standard dose CNI

Outcome or subgroup title	No. of studies	No. of participants	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.

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.

Analysis 8.2. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 2 Acute rejection.

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
Test for subgroup differences: $\chi^2=1.03$, $df=1$ ($P=0.31$), $I^2=2.75\%$					
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.

Analysis 8.4. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 4 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
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

Analysis 8.5. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 5 Serum creatinine at 1 year.

Analysis 8.6. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 6 Change in GFR at 2 years.

Analysis 8.7. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 7 Adverse events.

Analysis 8.8. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 8 Subgroup analysis: graft loss.

Analysis 8.9. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 9 Subgroup analysis: GFR.

Analysis 8.10. Comparison 8 Low dose CNI + mTOR-I versus CNI, Outcome 10 Subgroup analysis: acute rejection.

Comparison 9. Subgroup analysis (CNI type): low dose CNI + mTOR-I versus standard dose CNI

Outcome or sub-group 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.

APPENDICES

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. (discontin* 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. (discontin\$ 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. (discontin\$ 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 [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