KDIGO CLINICAL PRACTICE GUIDELINE FOR THE CARE OF KIDNEY TRANSPLANT RECIPIENTS

SUPPORTING TABLES

November 2009

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National Kidney Foundation®

Supporting Table 1. Evidence Profile Topic 1.2.1: Induction: IL-2 antibody vs. placebo[a,b]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Mortality	5 RCTs (High) 2 SRs (17/8 trials)	584 (300) 2786/1858	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 3 years	Critical
Graft loss	5 RCTs (High) 2 SRs (17/8 trials)	584 (300) 2786/1858	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 3 years	Critical
CVD events	0 RCTs								Critical
Cancer	4 RCTs (High) 2 SRs (17/8 trials)	476 (248) 2786/1858	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 3 years	Critical
Acute rejection	5 RCTs (High) 2 SRs (17/8 trials)	584 (300) 2786/1858	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	The incidence of acute rejection as well as the incidence of severe acute rejection is reduced in patients treated with IL-2 antibody compared to no induction/placebo in the first year after transplantation (but very limited evidence for children).	High
CAN	2 RCTs (High)	292 (149)	Some limitations (–1)	Important inconsistencies (–1)	Some uncertainty (–1)	Sparse data (–1)	Very low	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 5 years	High
NODAT	2 RCTs (High)	292 (149)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very low	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 12 months	High

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Infection	4 RCTs (High) 2 SRs (17/8 trials)	476 (248) 2786/1858	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 3 years, especially there is no evidence about differences in CMV-infection	High
Delayed graft function	4 RCTs (High) 1 SR (17 trials)	484 (250) 2786	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between induction with IL-2 antibody compared to no induction/placebo	Moderate
Kidney function	5 RCTs (High)	584 (300)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between induction with IL-2 antibody compared to no induction/placebo for up to 12 months	Moderate
Proteinuria	1 RCT (High)	100 (50)	Serious limitations (–2)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very low	No difference between induction with IL-2 antibody compared to no induction/placebo	Moderate
Blood pressure	1 RCT (High)	100 (50)	Serious limitations (–2)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very low	No difference between induction with IL-2 antibody compared to no induction/placebo	Moderate
Adverse events	1 RCT (High)	192 (99)						There is no clear evidence that induction therapy with an IL-2 antibody is causing more adverse events than placebo.	Depends on outcome
Balance of potential benefits and harm: Net benefits Treatment with IL-2 antibody is better than placebo for prevention of acute rejection							Quality of overall evidence: Low (Moderate for acute rejection)		

CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CNI, Calcineurin inhibitors; CVD, Cardiovascular disease; IL-2, Interleukin-2; N, Number; NODAT, New onset diabetes after transplant; QOL, Quality of life; RCT, Randomized controlled trials; SR, Systematic review.

Annotations:

a. Overlap with topic 2.5 (steroid avoidance vs. steroid maintenance) and topic 3.1 (CNI low vs. standard dose).

b. References: [1-7]

Supporting Table 2. Summary Table Topic 1.2.1: Induction: IL-2 antibody vs. placebo[a] (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
6 mo	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	0%	0%	NS	fair
12 mo	Lawen, 2003,[2]US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	0%	0%	NS	good
5 y	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	0%	4%	NS	poor
12 mo	Parrott, 2005,[4]UK	12 mo	52 (52)	56 (56)	Basiliximab	Placebo	CsA-ME	46	88	<2004	2%	4%	NS	poor
12 mo	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	2%	0%	NS	good
Graft loss														
6 mo	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	5%	5%	NS	fair
12 mo	Lawen, 2003,[2] US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	5%	8%	NS	good
5 y	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	14%	12%	NS	poor
12 mo	Parrott, 2005,[4] UK	12 mo	52 (52)	56 (56)	Basiliximab	Placebo	CsA-ME	46	88	<2004	12%	12%	NS	poor
12 mo	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	4%	0%	NS	good
Cancer														
Without PTLD	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	0%	0%	NS	fair
PTLD											0%	2%	NS	fair
Without PTLD	Lawen, 2003,[2] US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	0%	0%	NS	good
PTLD											0%	0%	NS	good
Kaposi sarcoma	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	2%	4%	NS	poor
PTLD	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	0%	0%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Acute rejection														
Biopsy-proven	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	19%	20%	NS	fair
Severity of AR, Banff II or higher											4%	9%	nd	fair
Steroid-resistant											3%	3%	NS	fair
Time to AR, days											41	43	NS	fair
Biopsy-proven 6 mo	Lawen, 2003,[2] US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	15%	27%	NS	good
Severity of AR, Banff II or higher 6 mo											5%	19%	nd	good
Steroid-resistant 6 mo											5%	16%	NS	good
Time to AR, days 4 wk/6 mo											nd	nd	<0.01 <0.05	fair
Acute rejection 1 y/5 y	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	36% 54%	62% 72%	<0.01 NS	poor
Severity of AR, Banff II or higher 1 y/5 y											4% 6%	20% 22%	<0.01 <0.05	poor
Total	Parrott, 2005,[4] UK	12 mo	52 (52)	56 (56)	Basiliximab	Placebo	CsA-ME	46	88	<2004	29%	43%	NS	poor
Total	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	14%	20%	nd	fair
Biopsy-proven											14%	16%	nd	good
Chronic allograft nephropathy and proteinuria														
'Toxic nephropathy	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	14%	4%	<0.05	fair
CAN	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	14%	14%	NS	poor
CNI-toxicity											6%	8%	NS	poor
Proteinuria >1 g/24 h											2%	6%	NS	poor
NODAT														
NODAT	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	5%	2%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
DM	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	8%	14%	NS	poor
Infection														
Bacterial	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	32%	32%	NS	poor
Viral											15%	16%	NS	poor
UTI											19%	28%	nd	fair
CMV											7%	2%	NS	fair
All	Lawen, 2003,[2] US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	63%	70%	nd	fair
Infection											14%	19%	nd	good
UTI	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	6%	10%	NS	poor
CMV											6%	8%	NS	poor
All 6 mo	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	20%	16%	nd	good
CMV 6 mo/12 mo											8% 18%	0% 0%	nd	good
Delayed graft function														
6 mo	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	11%	5%	NS	fair
12 mo	Lawen, 2003,[2] US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	15%	23%	NS	good
12 mo	Parrott, 2005,[4] UK	12 mo	52 (52)	56 (56)	Basiliximab	Placebo	CsA-ME	46	88	<2004	19%	38%	<0.05	poor
12 mo	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	12%	12%	NS	good
Kidney function														
S_{cr}, µmol/L	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	91	86	NS	fair
eGFR, mL/min											78	78	NS	fair
CrCl, mL/min 2 wk/4 wk	Lawen, 2003,[2] US, EU	12 mo	59 (59)	64 (64)	Basiliximab	Placebo	CsA-ME/MMF/ Steroids	45	73	1998-99	55 nd	43 nd	<0.05 NS	fair poor
S_{cr}, µmol/L 1 y/5 y	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	126 152	128 151	NS	poor
CrCl, mL/min 1 y/5 y											75 73	72 72	NS	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
S_{cr}, µmol/L 6 mo	Pescovitz, 2003,[5] US	12 mo	40 (50)	21 (25)	Daclizumab	Placebo	CsA-ME/MMF/ Steroids	46	68	<2002	133	159	NS	good
Hypertension														
Hypertension	Sheashaa, 2005,[3] Egypt	5 y	50 (50)	50 (50)	Basiliximab	No Basiliximab	CsA/AZA/ Steroids	33	0	1998-99	74%	86%	NS	poor
Blood pressure, mm Hg											125/82	125/82	NS	poor
Adverse events														
Anemia	Grenda, 2006,[1] EU	6 mo	99 (99)	93 (93)	Basiliximab	No Basiliximab	Tac/AZA/ Steroids	12	79	2001-04	15%	12%	NS	fair

AE, Adverse events; AR, Acute rejection; AZA, Azathioprine; CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CNI, Calcineurin inhibitors; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; DM, Diabetes mellitus; eGFR, Estimated glomerular filtration rate; EU, Europe; GFR, Glomerular filtration rate; IL-2, Interleukin-2; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; Tac, Tacrolimus; UK, United Kingdom; US, United States; UTI, Urinary tract infection.

Annotations:

a. Induction: IL-2 antibody vs. Placebo: similar intervention, but categorized in different topics: (A) Topic 2.5 “Steroid avoidance” Rostaing 2005[8] and terMeulen 2004 [9]; (B) Topic 3.1 “CNI low vs. standard dose” Ekberg 2007,[10] “ELITE Symphony” and Ekberg 2007,[11] “CAESAR”

Supporting Table 3. Summary Table Topic 1.2.1: Induction: IL-2 antibody vs. placebo[a] (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
S_{cr}, µmol/L 6 mo/12 mo	Parrott, 2005,[4] UK	12 mo	52 (52)	56 (56)	Basiliximab	Placebo	CsA-ME	46	88	<2004	150 (234)	+9/–9 (–60/–70)	nd	poor

CsA-ME, Cyclosporine microemulsion; IL-2, Interleukin-2; nd, Not documented; S_{Cr}, Serum creatinine; UK, United Kingdom.

Annotations:

a. Induction: IL-2 antibody vs. Placebo: similar intervention, but categorized in different topics: (A) Topic 2.5 "Steroid avoidance" Rostaing 2005[8] and terMeulen 2004[9]; (B) Topic 3.1 "CNI low vs. standard dose" Ekberg 2007,[10] "ELITE Symphony" and Ekberg 2007,[11] "CAESAR"

Supporting Table 4. Summary Table Topic 1.2.1: Induction—Depleting antibody vs. placebo (categorical outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant Medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Am 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
6 mo	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	2%	3%	NS	fair
Graft loss														
6 mo	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	5%	7%	NS	fair
Cancer														
All	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	1%	0.5%	nd	fair
Lymphoma											0.5%	0%	NS	fair
Acute rejection														
Total	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	23%	33%	<0.01	fair
Biopsy-proven											15%	25%	<0.01	fair
Severity of AR, Banff II or higher											5%	11%	NS	fair
Steroid-resistant											5%	7%	NS	fair
Time to AR, days											20	12	NS	fair
NODAT														
6 mo	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	7%	4%	NS	fair
Infection														
All	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	68%	58%	<0.01	fair
UTI											27%	27%	NS	fair
CMV											24%	16%	<0.05	fair
Delayed graft function														
6 mo	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	20%	26%	NS	fair
Kidney function														
S_{cr}, µmol/L	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	133	132	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant Medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Am 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Lipids														
Hypercholesteremia	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	3%	2%	NS	poor
Hypertension														
Hypertension	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	18%	18%	NS	poor
Adverse events														
Serum sickness	Charpentier 2003,[12] EU	6 mo	186 (186)	185 (185)	ATG	No ATG	Tac/AZA/ Steroids	45	100	<2003	16%	0%	<0.001	fair
Anemia											31%	25%	NS	fair
Leukopenia											39%	9%	0.001	fair
Thrombocytopenia											12%	3%	0.007	fair

AR, Acute rejection; ATG, Antithymocyte globulin; AZA, Azathioprine; CMV, Cytomegalovirus; EU, Europe; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; Tac, Tacrolimus; UTI, Urinary tract infection.

Annotations:

a. Overlap with topic 2.2 “early vs. delayed introduction of CNI”.

Supporting Table 5. Evidence Profile Topic 1.2.2: Induction—IL-2 antibody vs. depleting antibody

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Mortality	3 RCTs (High)	449 (225)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Moderate	No difference between induction with IL-2 antibody compared to induction with a depleting antibody for up to 5 years	Critical
	1 SR (15 trials)	1264	Some limitations (–1)				Low		
Graft loss	3 RCTs (High)	449 (225)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Moderate	No difference between induction with IL-2 antibody compared to induction with a depleting antibody for up to 5 years	Critical
	1 SR (15 trials)	1264	Some limitations (–1)				Low		
CVD events	0 RCTs								Critical
Cancer	2 RCTs (High)	389 (195)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Moderate	No difference between induction with IL-2 antibody compared to induction with a depleting antibody for up to 12 months	Critical
	1 SR (15 trials)	1264	Some limitations (–1)				Low		
Acute rejection	3 RCTs (High)	449 (225)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Moderate	There is no clear evidence that induction with a depleting antibody is superior in reducing the incidence of acute rejection to induction therapy with an IL-2 antibody.	High
	1 SR (15 trials)	1264	Some limitations (–1)	No important inconsistencies (0)					
NODAT	2 RCTs (High)	171 (88)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse date (–1)	Low	No difference between induction with IL-2 antibody compared to induction with a depleting antibody for up to 12 months	High
Infection	3 RCTs (High)	449 (225)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	Based on the systematic review there is no significant difference between induction therapy with an IL-2 antibody vs. a depleting antibody. However, the largest trial of good quality showed lower incidence of infections (except CMV) in IL-2 treated patients.	High
	1 SR (15 trials)	1264	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low		

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Delayed graft function	3 RCTs (High)	449 (225)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Moderate	Based mainly on the results from the systematic review, there is evidence that induction therapy with a depleting antibody might reduce the incidence of delayed graft function when compared to induction therapy with an IL-2 antibody.	Moderate
	1 SR (15 trials)	1264	Some limitations (–1)	No important inconsistencies (0)					
Kidney function	3 RCTs (High)	449 (225)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between Induction with IL-2 antibody compared to induction with a depleting antibody	Moderate
Adverse events	1 RCT (High)	278 (137)							Depends on outcome
Balance of potential benefits and harm: Tradeoffs Treatment with a depleting antibody is superior over IL-2 antibody in the prevention of acute rejection, but is associated with a higher number of infections.							Quality of overall evidence: Moderate		

CMV, Cytomegalovirus; CVD, Cardiovascular disease; IL-2, Interleukin-2; N, Number; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials; SR, Systematic review; vs, versus

Annotations:

a. References: [6,13-15]

Supporting Table 6. Summary Table Topic 1.2.2: Induction—IL-2 antibody vs. depleting antibody (categorical outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
12 mo	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	4%	4%	NS	good
5 y	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	3%	8%	NS	good
12 mo	Ciancio, 2005,[13], US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	12%	8%	NS	poor
Graft loss														
12 mo	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	10%	9%	NS	good
5 y	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	3%	9%	nd	good
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	12%	12%	NS	poor
Cancer														
All	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	1%	4%	NS	good
PTLD											0%	3%	NS	good
All 12 mo	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	0%	4%	NS	good
Acute rejection														
Biopsy-proven	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	26%	16%	<0.05	good
Severe AR, antibody treated											8%	1%	<0.01	fair
5 y	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	12%	11%	NS	good
Median time to AR, days											46	13	NS	good
Biopsy-proven	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	17%	17%	NS	poor
Severity of AR, Banff II or higher											3%	10%	NS	poor
NODAT														
12 mo	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	9%	4%	nd	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	14%	23%	NS	poor
Infection														
All	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	75%	86%	<0.05	good
UTI											27%	39%	<0.05	good
CMV											18%	8%	<0.05	good
Viral other than CMV											12%	21%	<0.05	good
CMV 12 mo	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	16%	17%	NS	good
UTI 12 mo											12%	1.9%	nd	good
UTI	Ciancio, 2005,[13], US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	0%	3%	NS	poor
CMV											0%	3%	NS	poor
Polyoma											0%	0%	NS	poor
Delayed graft function														
12 mo	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	45%	40%	NS	good
5 y	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	24%	6%	0.025	good
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	7%	13%	NS	poor
Kidney function														
S_{cr}, µmol/L	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	159	177	NS	good
CrCl, mL/min	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	63	73	NS	good
Adverse events														
Leukopenia	Brennan, 2006,[14] US, EU	12 mo	137 (137)	141 (141)	Basiliximab	ATG	CsA-ME/MMF/ Steroids	51	100	2000-02	15%	33%	<0.001	good
Thrombocytopenia											6%	11%	NS	good

AR, Acute rejection; ATG, Antithymocyte globulin; AZA, Azathioprine; CMV, Cytomegalovirus; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; EU, Europe; IL-2, Interleukin-2; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; Ster, Steroids; Tac, Tacrolimus; UTI, Urinary tract infection; US, United States.

Annotations:

a. Overlap with topic 2.2 early vs. delayed introduction of CNI.

b. Kyllonen, 2007[15] has a third arm of CsA+ AZA without induction.

c. Ciancio 2005[13]: three arm study split: (A) Topic 1.2.2 Induction: IL-2 vs. depleting antibody; (B) Topic 2.5 Steroid avoidance.

Supporting Table 7. Summary Table Topic 1.2.2: Induction—IL-2 antibody vs. depleting antibody (continuous outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
S_{cr}, µmol/L 12 mo	Kyllonen, 2007,[15] Finland[b]	5 y	58 (58)	53 (53)	Basiliximab	ATG	CsA/AZA	47	100	1999-2001	129 (148)	-8 (-30)	<0.05	good
S_{cr}, µmol/L	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Daclizumab	Thymo	Tac/MMF/ Steroids	50	100	2002-04	108 (111)	-4 (+5)	NS	poor
CrCl, mL/min											73 (75)	+8 (+5)	NS	poor

ATG, Antithymocyte globulin; AZA, Azathioprine; CrCl, Creatinine clearance; CsA, Cyclosporine; IL-2, Interleukin-2; MMF, Mycophenolate mofetil; NS, Not significant; S_{Cr}, Serum creatinine; Ster, Steroids; Tac, Tacrolimus; Thymo, Thymoglobulin; US, United States.

Annotations:

a. Overlap with topic 2.2 early vs. delayed introduction of CNI.

b. Kyllonen, 2007[15] has a third arm of CsA+ AZA without induction.

c. Ciancio 2005[13]: three arm study split: (A) Topic 1.2.2 Induction: IL-2 vs. depleting antibody; (B) Topic 2.5 Steroid avoidance

Supporting Table 8. Evidence Profile Topic 2.2: Tac vs. CsA[a,b]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	11 RCTs (High)	3548 (1820)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Limited duration of follow-up (–1)	Moderate	No difference between Tac and CsA/CsA-ME	Critical
	1 SR (14 RCTs)	2604	No limitations (0)						
Graft loss	11 RCTs (High)	3548 (1820)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	Tac is not significantly better in prolonging graft survival when compared mainly to CsA-ME.	Critical
	1 SR (14 RCTs)	2604	No limitations (0)	No important inconsistencies (0)			High	Tac is better than CsA/CsA-ME in graft survival outcomes.	
CVD events	0 RCTs								Critical
Cancer	5 RCTs (High)	1843 (964)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Limited duration of follow-up (–1)	Moderate	No difference between Tac and CsA/CsA-ME	Critical
	1 SR (7 RCTs)	1765	No limitations (0)						
Acute rejection	11 RCTs (High)	3548 (1820)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Tac is better than CsA/CsA-ME in the prevention of acute rejection.	High
	1 SR (14 RCTs)	2751	No limitations (0)				High		
CAN	3 RCTs (High)	328 (163)	Serious limitations (–2)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Low	No difference between Tac and CsA-ME	High
	1 SR (3 RCTs)	914	No limitations (0)				High	Tac is better than CsA/CsA-ME in the prevention of CAN.	
NODAT	11 RCTs (High)	3548 (1820)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	NODAT is more common in Tac-treated patients compared to CsA/CsA-ME	High
	1 SR (11 RCTs)	1956	No limitations (0)						

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Infection	8 RCTs (High)	3072 (1583)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference in the incidence of bacterial and viral infections (especially CMV) between Tac and CsA/CsA-ME (limited data on BK, but there is no clear evidence for differences between Tac and CsA)	High
	1 SR (5 RCTs)	1422	No limitations (0)						
Delayed graft function	9 RCTs (High)	3174 (1633)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between Tac and CsA/CsA-ME	Moderate
Kidney function	11 RCTs (High)	3223 (1668)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Moderate	There is some evidence that kidney function in Tac treated patients is better then in CsA/CsA-ME treated patients however, this effect seems to be apparent particularly in the first 12 months.	Moderate
	1 SR (8 RCTs)	1216	No limitations (0)						
Proteinuria	4 RCTs (High)	924 (465)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	There is some evidence that treatment with Tac is causing less proteinuria when compared to CsA/CsA-ME.	Moderate
Lipids	11 RCTs (High)	3223 (1668)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Total cholesterol levels as well as LDL-C levels are higher in CsA/CsA-ME treated patients compared to Tac treated patients, whereas there is no difference in the effect on HDL-C levels.	Moderate
	1 SR (3 RCTs)	722	No limitations (0)				High		
Blood pressure	8 RCTs (High)	2749 (1421)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No clear difference between Tac and CsA/CsA-ME	Moderate
	1 SR (8 RCTs)	1216	No limitations (0)				High		
Adverse events	5 RCTs (High) 1SR (7 RCTs)	2556 (1288) 2152						Tac: more tremor and diarrhea (due to higher MPA levels while on the same MMF dose?) CsA/CsA-ME: more hirsutism, hypertrichosis, gingival hyperplasia	Depends on outcome
Balance of potential benefits and harm: Net benefit Tac is superior to CsA/CsA-ME in the prevention of acute rejection and kidney function. Adverse event profiles vary with impaired lipid metabolism in CsA/CsA-ME and a higher incidence of NODAT in Tac-treated patients.							Quality of overall evidence: High		

BK, BK virus; CAN, Chronic Allograft Nephropathy; CMV, Cytomegalovirus; CsA, Cyclosporine A; CsA-ME, Cyclosporine A microemulsion; CVD, Cardiovascular disease; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MMF, Mycophenolate mofetil; MPA, Mycophenolate acid; N, Number; NODAT, New onset diabetes after transplant; QOL, Quality of life; RCT, Randomized controlled trials; SR, Systematic review; Tac, Tacrolimus.

Annotations:

a. Systematic review about Tac vs. CsA largely balanced between CsA original formulation and CsA microemulsion (CsA-ME), more recent RCTs mainly about CsA-ME.

b. References: [10,16-32]

Supporting Table 9. Summary Table Topic 2.2: Tac vs. CsA (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
12 mo	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	1%	0%	NS	good
6 mo/24 mo	Kramer, 2003, 2005[18,19], Margreiter 2002 [20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	1% 2%	1% 3%	NS <0.05	good fair
12 mo	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	4%	0%	NS	poor
12 mo	Rowshani, 2006,[22] Netherlands[a]	12 mo	63 (63)	63 (63)	Tac (AUC)	CsA (AUC)	MMF/Steroids/ Basiliximab	nd	nd	2000-02	2%	3%	NS	poor
6 mo	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS Steroids/ Basiliximab	47	68	2003-05	2%	2%	NS	good
12 mo	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	1%	2%	NS	fair
12 mo			212 (212)	212 (212)	Tac	CsA-ME					4%	2%	NS	fair
12 mo	Ciancio, 2006, 2004[25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	4%	2%	NS	good
24 mo	Gonwa, 2003,[28] US[d]	36 mo	72 (72)	75 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	6%	12%	NS	good
12 mo	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	3%	2%	NS	good
6 mo	Artz, 2003, 2004[29,30] EU[f]	6 mo 24 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	2%	3%	NS	good
24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	8%	4%	NS	good
Graft loss														
Censored for death	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	5%	0%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
6 mo/24 mo	Kramer, 2003, 2005,[18,19], Margreiter 2002[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	5% 9%	8% 11%	NS NS	good fair
12 mo	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	4%	10%	NS	poor
12 mo	Rowshani, 2006,[22] Netherlands[a]	12 mo	63 (63)	63 (63)	Tac (AUC)	CsA (AUC)	MMF/Steroids/ Basiliximab	nd	nd	2000-02	9%	5%	NS	poor
6 mo	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS Steroids/ Basiliximab	47	68	2003-05	3%	2%	NS	good
12 mo	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	3%	4%	NS	fair
12 mo			212 (212)	212 (212)	Tac	CsA-ME					7%	4%	NS	fair
12 mo	Ciancio, 2006, 2004, [25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	0%	4%	NS	good
36 mo	Gonwa, 2003,[28] US[d]	36 mo	72 (72)	75 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	19%	27%	NS	good
Censored death with a functioning graft	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	4%	6%	NS	good
24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	18%	10%	NS	good
Cancer														
12 mo	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	2%	0%	NS	good
PTLD											0%	0%	NS	good
6 mo/24 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	0.3% 1%	0.7% 1%	NS NS	good fair
PTLD	Rowshani, 2006,[22] Netherlands[a]	12 mo	63 (63)	63 (63)	Tac (AUC)	CsA (AUC)	MMF/Steroids/ Basiliximab	nd	nd	2000-02	nd	2%	nd	poor
12 mo	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	1%	1%	NS	good
PTLD											0%	0%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
All 24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	3%	3%	NS	good
PTLD 24 mo											0%	0%	NS	good
Acute rejection														
12 mo	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	4%	6%	NS	good
Severity of AR, Banff II and higher											2%	5%	nd	good
6 mo/12 mo/24 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	20% 22% 23%	37% 42% 43%	<0.001 <0.001 <0.001	good good fair
Severity of AR, Type II and higher 6 mo/24 mo											12% 14%	25% 27%	nd nd	good fair
Steroid-resistant 6 mo/24 mo											9% 9%	21% 22%	<0.001 <0.001	fair poor
12 mo	Murphy, 2003,[21]UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	35%	36%	NS	poor
Biopsy-proven	Rowshani, 2006,[22] Netherlands[a]	12 mo	63 (63)	63 (63)	Tac (AUC)	CsA (AUC)	MMF/Steroids/ Basiliximab	nd	nd	2000-02	7%	16%	NS	poor
Steroid-resistant											2%	6%	NS	poor
Subclinical rejection, Protocol Bx 6 mo											15%	39%	<0.05	poor
Biopsy-proven	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	7%	10%	NS	good
Severity of AR, Banff II or higher											4%	4%	NS	good
Antibody treated											4%	3%	NS	fair
12 mo	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	18%	21%	NS	fair
Biopsy-proven											5%	7%	NS	fair
Severity of AR, Banff II or higher											4%	4%	NS	fair
12 mo			212 (212)	212 (212)	Tac	CsA-ME					12%	21%	<0.05	fair
Biopsy-proven											4%	7%	NS	fair
Severity of AR, Banff II or higher											2%	4%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
12 mo/36 mo	Ciancio, 2006, 2004, [25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	4% 26%	14% 20%	nd	good
Severity of AR Banff II or higher											6%	6%	nd	good
12 mo/36 mo	Gonwa, 2003,[28] US[d]	36 mo	72 (72)	75 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	11% 17%	20% 25%	NS	good
Steroid-resistant 12 mo/36 mo											6%	12%	0.03	good
12 mo	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	17%	30%	<0.001	fair
Biopsy-proven											12%	24%	<0.001	fair
Steroid-resistant											2%	5%	NS	fair
6 mo	Artz, 2003, 2004,[29,30] EU[f]	6 mo 24 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	0%	0%	NS	fair
Biopsy-proven 24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	16%	14%	NS	good
Banff I+II 24 mo											14%	13%	NS	good
Steroid-resistant 24 mo											6%	6%	NS	good
Chronic allograft nephropathy and proteinuria														
Interstitial extracellular matrix, mm^2	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	16	25	<0.01	poor
CAN 6 mo/12 mo	Rowshani, 2006,[22] Netherlands[a]	12 mo	63 (63)	63 (63)	Tac (AUC)	CsA (AUC)	MMF/Steroids/ Basiliximab	nd	nd	2000-02	57% 65%	51% 61%	NS NS	poor poor
CNI toxicity 12 mo											Total 24%, no differences between groups		NS	poor
Subclinical rejection 6 mo											15%	39%	<0.05	poor
CAN 36 mo	Ciancio, 2006, 2004,[25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	50%	44%	NS	fair
Proteinuria	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[c]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	5%	2%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
NODAT														
12 mo	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	4%	2%	NS	good
6 mo/24 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	5% 4%	2% 2%	NS NS	good fair
12 mo	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	8%	4%	NS	poor
6 mo	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	17%	9%	<0.01	good
Impaired fasting glucose											12%	7%	<0.05	good
Insulin use ≥30 d	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	6%	3%	NS	poor
Oral hypoglycemic use											14%	3%	<0.05	poor
Fasting glucose ≥7.0 mmol/L											56%	53%	NS	poor
Insulin use ≥30 d			212 (212)	212 (212)	Tac	CsA-ME					6%	3%	NS	poor
Oral hypoglycemic use											10%	3%	<0.001	poor
Fasting glucose ≥7.0 mmol/L											64%	53%	NS	poor
36 mo	Ciancio, 2006, 2004, [25-27] US	12 mo 36 mo	41 (50)	45 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	27%	31%	NS	good
36 mo	Gonwa, 2003[28] US[d]	36 mo	46 (72)	46 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	13%	7%	nd	fair
12 mo	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	11%	5%	0.02	fair
6 mo	Artz, 2003, 2004,[29,30] EU[f]	6 mo 24 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	6%	5%	NS	good
24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	27%	16%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Infection														
CMV	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	4%	6%	NS	good
BK-viruria (DNA)											36%	31%	NS	good
BK-viremia (DNA)											12%	11%	NS	good
BK nephropathy (biopsy)											0%	0%	nd	good
CMV 6 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	7%	6%	NS	good
UTI 6 mo											28%	26%	NS	good
CMV	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	6%	12%	<0.01	good
CMV	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	7%	8%	NS	fair
Polyoma											3%	2%	nd	fair
Viral											23%	21%	NS	fair
Bacterial											8%	8%	NS	fair
CMV			212 (212)	212 (212)	Tac	CsA-ME					8%	8%	NS	fair
Polyoma											4%	2%	nd	fair
Viral											26%	21%	NS	fair
Bacterial											12%	8%	NS	fair
12 mo/36 mo	Ciancio, 2006, 2004, [25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	24% 32%	20% 30%	NS	good fair
CMV 36 mo											2%	2%	NS	fair
BK 36 mo											4%	2%	NS	fair
CMV	Gonwa, 2003,[28] US[d]	36 mo	72 (72)	75 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	14%	11%	NS	good
PCP											0%	0%	NS	good
Opportunistic infections	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	4%	7%	NS	fair
CMV											10%	12%	NS	fair
UTI											24%	24%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	45%	46%	NS	good
UTI 24 mo											35%	31%	NS	good
CMV infection/ disease 24 mo											25%/ 11%	20%/ 3.7%	<0.01 NS	good
Delayed graft function														
12 mo	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	5%	5%	NS	good
6 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	20%	27%	nd	good
12 mo	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	35%	40%	NS	poor
6 mo	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	20%	19%	NS	good
12 mo	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	18%	18%	NS	fair
12 mo			212 (212)	212 (212)	Tac	CsA-ME					22%	18%	NS	fair
12 mo	Ciancio, 2006, 2004, [25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	12%	6%	NS	good
36 mo	Gonwa, 2003,[28] US[d]	36 mo	72 (72)	75 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	36%	28%	NS	fair
12 mo	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME[3]	MMF/Steroids/ Daclizumab	46	64	2002-04	36%	32%	NS	good
24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	40%	33%	NS	good
Kidney function														
S_{cr}, µmol/L 6 mo/12 mo	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	115 115	132 141	<0.05 <0.05	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
S_{cr}, µmol/L 6 mo/24 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	139 137	147 162	NS <0.01	good fair
CrCl, mL/min 24 mo											69	62	nd	good fair
S_{cr}, µmol/L	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	157	170	NS	poor
CrCl, mL/min	Rowshani, 2006,[22] Netherlands[a]	12 mo	63 (63)	63 (63)	Tac (AUC)	CsA (AUC)	MMF/Steroids/ Basiliximab	nd	nd	2000-02	65	64	NS	poor
CrCl, mL/min	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	66	64	NS	good
S_{cr}, µmol/L 12/36 mo	Ciancio, 2006, 2004,[25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	124 124	133 141	NS	good
CrCl, mL/min 12/36 mo											73 73	71 62	NS	fair
S_{cr}, µmol/L 36 mo	Gonwa, 2003,[28] US[d]	36 mo	72 (72)	75 (75)	Tac	CsA-ME	MMF/Steroids/ ±OKT3	47	100	<1999	123	141	NS	fair
CrCl, mL/min 36 mo											59	56	NS	fair
CrCl, mL/min	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	65	59	0.001	good
GFR, mL/min											70	65	NS	fair
eGFR, mL/min											54	50	<0.01	good
Lipids														
No. of pts. on lipid-lowering drug 12 mo	Ciancio, 2006, 2004,[25-27] US	12 mo 36 mo	49 (50)	50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	54%	80%	0.001	fair
Hypercholesterol-emia	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	5%	10%	nd	fair
Hyperlipidemia 24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	49%	63%	NS	fair
Hypertension														
Blood pressure, mm Hg 24 mo	Kramer, 2003, 2005[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	136/82	136/81	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
No. of antihypertensive drugs per pt.	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	1.7	1.8	NS	poor
Hypertension	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	13%	12%	nd	fair
Hypertension 24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	40%	36%	NS	fair
Adverse events														
Fractures AND bone disease 24 mo	Kramer, 2003, 2005[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	2%	5%	nd	poor
Diarrhea	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[b]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	28%	16%	<0.001	good
Tremor											22%	15%	<0.05	good
Peripheral edema											15%	23%	<0.01	good
Hirsutism, Hypertrichosis											1%	9%	<0.001	good
Diarrhea	Silva, 2007,[24] US, Canada, Brazil[c]	12 mo	214 (214)	212 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	45%	26%	<0.001	good
Gingival hyperplasia											1%	5%	<0.01	good
Tremor											35%	20%	<0.001	good
Hypertrichosis											0%	3%	<0.01	good
Hirsutism											0%	9%	<0.001	good
Diarrhea			212 (212)	212 (212)	Tac	CsA-ME					44%	26%	<0.001	good
Gingival hyperplasia											0%	5%	<0.01	good
Tremor											34%	20%	<0.01	good
Hypertrichosis											0%	3%	<0.01	good
Hirsutism											0%	9%	<0.001	good
Lymphocele 12 mo	Ciancio, 2006, 2004, Ciancio, 2006[25,26] US	12 mo	41 (50)	45 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	16%	14%	NS	good
Wound infection/ dehiscence 12 mo		36 mo	50 (50)	50 (50)							6%	4%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Diarrhea	Ekberg, 2007,[10] EU, Can, Aus, Brazil, Israel[e]	12 mo	401 (401)	399 (399)	Tac low dose	CsA/ CsA-ME	MMF/Steroids/ Daclizumab	46	64	2002-04	27%	14%	<0.001	good
Lymphocele											4%	7%	NS	good

AE, Adverse events; AR, Acute rejection; ATG, Antithymocyte globulin; AUC, Area under the curve; AZA, Azathioprine; Bx, Biopsy; CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CNI, Calcineurin inhibitors; cont., Continued; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; DNA, Deoxyribonucleic acid; EC-MPS, Enteric-coated mycophenolate sodium; eGFR, Estimated glomerular filtration rate; EU, Europe; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; OKT3, Muromonab; PCP, Pneumoystis pneumonia; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; SRL, Sirolimus; Tac, Tacrolimus; Tac-XL, Tacrolimus extended-release formula; UK, United Kingdom; US, United States; UTI, Urinary tract infection

Annotations:

a. Rowshani, 2006 [22]: Tac and CsA adjusted to AUC within the first 6 weeks, thereafter adjusted to trough levels.
b. Vincenti, 2007 [23]: CsA-ME adjusted to C2-levels.
c. Silva, 2007[24]: three-arm study split within topic 2.3 Tac vs. CsA.
d. Gonwa, 2003[28]: three-arm study split (A) topic 2.3 Tac vs. CsA, (B) topic 2.4 MMF vs. AZA.
e. Ekberg, 2007 [10] "ELITE-Symphony": four-arm study split: (A) topic 2.3 CsA vs. Tac , (B) topic 3.2 CNI sparing/withdrawal.
f. Artz, 2003, 2004 [29,30]: conversion of stable patients 1 year after transplant

Supporting Table 10. Summary Table Topic 2.2: Tac vs. CsA (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
S_{cr}, µmol/L	Silva, 2007,[24] US, Canada, Brazil[a]	12 mo	199 (214)	193 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	144 (148)	-21 (–17)	<0.05	poor
CrCl, mL/min											55 (54)	+3.3 (+1)	<0.01	poor
eGFR, mL/min											53 (52)	+5.4 (+3.5)	<0.05	poor
S_{cr}, µmol/L			202 (212)	193 (212)	Tac	CsA-ME					143 (148)	–17 (–17)	NS	poor
CrCl, mL/min											55 (54)	+2.6 (+1)	<0.05	poor
eGFR, mL/min											54 (52)	+5.6 (+3.5)	<0.01	poor
S_{cr}, µmol/L	Artz, 2003, 2004,[29,30] EU[b]	24 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	137 (143)	+8 (+14)	<0.05	good
CrCl, mL/min											60 (59)	+4 (–10)	<0.01	good
CrCl, mL/min 12 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	71 (69)	+3 (-4)	<0.05	good
CrCl, mL/min 24 mo											71 (69)	–1 (-3)	<0.05	good
eGFR, mL/min/1.73 m² 12 mo											46 (51)	+4 (+5)	<0.05	good
eGFR, mL/min/1.73 m² 24 mo											46 (51)	+4 (+5)	0.06	good
eGFR, mL/min/1.73 m² 12 mo											46 (52)	+16 (+7)	<0.05	good
eGFR, mL/min/1.73 m² 24 mo											46 (52)	+16 (+8)	<0.05	good
Chronic allograft nephropathy														
Chronic injury score 12 mo	Ciancio, 2006, 2004,.[25-27] US	12 mo 36 mo	50/50 (50)	50/50 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	2.1 (1.8)	+1.0 (+1.3)	NS	good
Proteinuria														

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Proteinuria 6 mo	Artz, 2003, 2004,[29,30] EU[b]	6 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	0.2 (0.2)	-0.06 (+0.02)	<0.01	good
Proteinuria, mg/d 24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	266 (280)	-32 (+37)	0.06 at baseline	good
Lipids														
No. of pts. on Lipid-lowering therapy	Hardinger, Brennan, 2005 [16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	40% (67%)	–10% (-32%)	<0.01	fair
Cholesterol, mmol/L 6 mo	Kramer, 2003, 2005[18,19], Margreiter, 2002,[20] EU	6 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	5.5 (5.4)	-0.1 (+0.5)	<0.001	good
Cholesterol, mmol/L 24 mo		24 mo									5.5 (5.4)	-0.3 (+0.1)	<0.01	fair
Cholesterol, mmol/L	Murphy, 2003,[21] UK	12 mo	50 (50)	52 (52)	Tac	CsA-ME	±AZA/Steroids	45	84	<2002	5.5 (5.5)	±0 (+0.5)	<0.05	poor
LDL, mmol/L											3.2 (3.5)	±0 (+0.5)	<0.05	poor
Cholesterol, mmol/L	Vincenti, 2007,[23]US, Can, EU, Aus, Japan[c]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids/ Basiliximab	47	68	2003-05	4.5 (4.6)	+0.3 (+0.7)	<0.01	good
LDL, mmol/L											2.4 (2.5)	+0.2 (+0.5)	<0.01	good
No. of pts. on Lipid-lowering therapy											24% (20%)	+23% (+30%)	NS	fair
Cholesterol, mmol/L	Silva, 2007,[24] US, Canada, Brazil[a]	12 mo	180 (214)	178 (212)	Tac XL	CsA-ME	MMF/Steroids/ Basiliximab	48	52	<2006	3.7 (3.7)	+1.2 (+1.5)	<0.05	fair
HDL, mmol/L											1.1 (1.1)	+0.2 (+0.2)	NS	fair
LDL, mmol/L											2.1 (2.1)	+0.6 (+0.9)	<0.05	fair
Cholesterol, mmol/L			182 (212)	178 (212)	Tac	CsA-ME					3.7 (3.7)	+1.0 (+1.5)	<0.05	fair
HDL, mmol/L											1.2 (1.1)	+0.2 (+0.2)	NS	fair
LDL, mmol/L											2.1 (2.1)	+0.4 (+0.9)	<0.05	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Cholesterol, mmol/L 12 mo	Ciancio, 2006, 2004,[25-27] US	12 mo 36 mo	47 (50)	44 (50)	Tac	CsA-ME	SRL/Steroids/ Daclizumab	47	80	2000-01	4.7 (4.6)	+0.5 (+0.6)	NS	fair
Triglycerides, mmol/L 12 mo											2.0 (2.1)	-0.2 (-0.1)	NS	fair
Cholesterol, mmol/L 6 mo	Gonwa, 2003,[28] US[d]	36 mo	46 (72)	46 (75)	Tac	CsA-ME	MMF/Steroids/ ± OKT3	47	100	<1999	5.2 (5.9)	+0.6 (+1.5)	<0.05	good
LDL, mmol/L 6 mo											2.9 (3.7)	+0.1 (+1.1)	<0.05	good
No. of pts. on Lipid-lowering therapy 6 mo											7% (5%)	+6% (+21%)	<0.01	good
Cholesterol, mmol/L	Artz, 2003, 2004,[29,30] EU[b]	24 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	5.8 (5.9)	-0.6 (-0.06)	<0.001	fair
LDL, mmol/L											3.5 (3.6)	-0.4 (-0.08)	<0.001	fair
HDL, mmol/L											1.4 (1.4)	-0.06 (-0.03)	NS	fair
Triglycerides, mmol/L											2.1 (1.9)	-0.4 (0.17)	<0.01	fair
Total cholesterol, mmol/L 24 mo	Hernandez, 2007,[31] Spain	24 mo	80 (80)	80 (80)	Tac low dose	CsA low dose	MMF/Steroids/ Basiliximab	47	100	1999-2004	5.5 (5.8)	-0.5 (-0.7)	NS	good
LDL cholesterol, mmol/L 24 mo											3.1 (3.6)	-0.2 (-0.4)	0.04 at baseline	good
HDL cholesterol, mmol/L 24 mo											1.7 (1.6)	-0.2 (0)	NS	good
Triglycerides, mmol/L 24 mo											1.6 (1.7)	0 (0)	NS	good
Hypertension														
No. of pts. on antihypertensive drugs	Hardinger, Brennan, 2005,[16,17] US	12 mo	134 (134)	66 (66)	Tac	CsA-ME	AZA or MMF/ Steroids/ATG	45	58	2000-02	21% (24%)	+11% (+8%)	NS	fair
Hypertension 6 mo	Kramer, 2003, 2005, Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	78% (75%)	62% (52%)	<0.05	fair
Hypertension 24 mo											78% (75%)	+1% (-3%)	NS	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
SBP, mm Hg	Vincenti, 2007,[23] US, Can, EU, Aus, Japan[c]	6 mo	346 (346)	336 (336)	Tac	CsA-ME (C2)	MMF or EC-MPS, Steroids / Basiliximab	47	68	2003-05	140 (140)	–10 (–10)	NS	good
DBP, mm Hg											80 (85)	±0 (-5)	NS	good
No. of pts. on antihypertensive medication											14% (12%)	+23% (+31%)	NS	fair
No. of antihypertensive drugs	Artz, 2003, 2004,[29,30] EU[b]	24 mo	64 (64)	60 (60)	Tac	CsA-cont.	nd	50	nd	<1999	2.1 (1.9)	+0.2 (+0.4)	NS	good
SBP, mm Hg											144 (140)	-7 (+1)	<0.01	fair
DBP, mm Hg											84 (83)	-4 (+1)	<0.01	fair
Other outcomes														
10 y CAD-risk in males, median 6 mo	Kramer, 2003, 2005,[18,19], Margreiter, 2002,[20] EU	6 mo 24 mo	286/237 (286)	271/222 (271)	Tac	CsA-ME	AZA/Steroids	43	97	<2002	13% (12%)	-3% (+3%)	<0.01	good
10 y CAD-risk in females, median 6 mo											7% (8%)	-2% (-2%)	NS	good

ATG, Antithymocyte globulin; AZA, Azathioprine; CAD, Coronary artery disease; cont., Continued; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; d, Day; DBP, Diastolic blood pressure; EC-MPS, Enteric-coated mycophenolate sodium; eGFR, Estimated glomerular filtration rate; EU, Europe; HDL, High density lipoprotein; LDL, Low-density lipoprotein; MMF, Mycophenolate mofetil; NS, Not significant; OKT3, Muromonab; pt, Patient; SBP, Systolic blood pressure; S_{Cr}, Serum creatinine; SRL, Sirolimus; Tac, Tacrolimus; Tac-XL, Tacrolimus extended-release formula; UK, United Kingdom; US, United States

Annotations:

a. Silva, 2007[24]: three-arm study split within topic 2.3 Tac vs. CsA.

b. Artz, 2003, 2004 [29,30]: conversion of stable patients 1 year after transplant.

c. Vincenti, 2007 [23]: CsA-ME adjusted to C2-levels.

d. Gonwa, 2003[28]: three-arm study split (A) topic 2.3 Tac vs. CsA, (B) topic 2.4 MMF vs. AZA.

Supporting Table 11. Evidence Profile Topic 2.2.1: Early vs. delayed introduction of calcineurin inhibitors[a,b,c]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Mortality	5 RCTs (High)	620 (313)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Not adequately powered for the outcome (–1)	Low	No difference between early vs. delayed introduction of CsA for up to 2 years	Critical
Graft loss	5 RCTs (High)	620 (313)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Not adequately powered for the outcome (–1)	Low	No difference between early vs. delayed introduction of CsA for up to 2 years	Critical
CVD events	0 RCTs								Critical
Cancer	2 RCTs (High)	222 (111)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Not adequately powered for the outcome, limited number of studies (–1)	Low	No difference between early vs. delayed introduction of CsA for up to 2 years	Critical
Acute rejection	5 RCTs (High)	620 (313)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	None (0)	Moderate	No difference between early vs. delayed introduction of CsA for up to 2 years	High
CAN	1 RCT (High)	194 (97)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Limited number of studies (–1)	Low	No difference between early vs. delayed introduction of CsA for up to 2 years	High
Infection	5 RCTs (High)	620 (313)	Some limitations (–1)	Important inconsistencies (–1)	Some uncertainty (–1)	None (0)	Very low	There is no clear evidence that the incidence of infections, in particular CMV, is different between early vs. delayed CsA introduction. Differences in some trials are probably based on the use of a depleting antibody.	High
Delayed graft function	3 RCTs (High)	338 (167)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	None (0)	Moderate	No difference between early vs. delayed CsA introduction	Moderate
Kidney function	5 RCTs (High)	620 (313)	No limitations (0)	Important inconsistencies (–1)	Some uncertainty (–1)	None (0)	Low	There is no clear evidence that kidney function is different between early vs. delayed CsA introduction.	Moderate
Lipids	2 RCTs (High)	294 (147)	No limitations (0)	Important inconsistencies (–1)	Some uncertainty (–1)	Limited number of studies (–1)	Very low	There is no clear evidence that hyperlipidemia is different between early vs. delayed CsA introduction.	Moderate

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Blood pressure	2 RCTs (High)	294 (147)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Limited number of studies (–1)	Very low	No difference between early vs. delayed CsA introduction	Moderate
Adverse events	1 RCT (High)	278 (137)						There is no clear evidence that the incidence of adverse events is different between early vs. delayed CsA introduction. Differences are probably based on the use of a depleting antibody.	Depends on outcome
Balance of potential benefits and harm: No net benefit or harm							Quality of overall evidence: Low (Moderate for CsA-containing regimens)[1]		

CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CNI, Calcineurin inhibitors; CsA, Cyclosporine A; CVD, Cardiovascular disease; EC-MPS, Enteric-coated mycophenolate sodium; IL-2, Interleukin-2; N, Number; RCT, Randomized controlled trials; SR, Systematic review; Tac, Tacrolimus.

Annotations:

a. Evidence limited to CsA containing regimens, no data about Tac.

b. One RCT testing early vs. late CNI introduction in a Basiliximab/EC-MPS/steroids containing regimen, whereas three RCTs are testing early CNI introduction without induction therapy vs. depleting antibody/delayed CNI introduction; one RCT tested IL-2 antibody induction/early CsA vs. depleting antibody/delayed CNI introduction.

c. References: [33-37]

Supporting Table 12. Summary Table Topic 2.2.1: Early vs. delayed introduction of calcineurin inhibitors (categorical outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
24 mo	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	4%	1%	NS	good
90 d	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	10%	2%	NS	good
12/24 mo	Henry, 2001,[35] US[d]	24 mo	49 (49)	55 (55)	Early CsA (day 0)	OKT3/ delayed CsA (S_{Cr} 221-265 µmol/L)	MMF/Steroids	47	73	<2001	4% 6%	4% 5%	NS	poor
32 mo	Slakey, 1993,[36] US[e]	32 mo	60 (60)	61 (61)	Early CsA (day 0)	ALG/ delayed CsA (day 6)	AZA/Steroids	47	100	1988-1990	10%	7%	NS	fair
6 mo	Lebranchu, 2002,[37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250µmol/L)	MMF/Steroids	45	nd	1998-2000	2%	0%	NS	good
Graft loss														
24 mo	Kamar, 2006[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	4%	3%	NS	good
90 d	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	16%	10%	NS	good
12/24 mo	Henry, 2001,[35] US[d]	24 mo	49 (49)	55 (55)	Early CsA (day 0)	OKT 3/ delayed CsA (S_{Cr} 221-265 µmol/L)	MMF/Steroids	47	73	<2001	8% 14%	4% 7%	NS	poor
Death-censored 12/24 mo											4% 6%	0% 2%	NS	poor
24/36/48 mo	Slakey, 1993,[36] US[e]	32 mo	60 (60)	61 (61)	Early CsA (day 0)	ALG/ delayed CsA (day 6)	AZA/Steroids	47	100	1988-1990	20% 22% 27%	12% 20% 20%	NS	fair
6 mo	Lebranchu, 2002,[37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250µmol/L)	MMF/Steroids	45	nd	1998-2000	4%	0%	NS	good
Cancer														
PTLD	Slakey, 1993,[36] US[e]	Mean 32 mo	60 (60)	61 (61)	Early CsA (day 0)	ALG/ delayed CsA (day 6)	AZA/Steroids	47	100	1988-1990	0%	0%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
12 mo	Lebranchu, 2002,[37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250µmol/L)	MMF/Steroids	45	nd	1998-2000	0%	0%	NS	good
PTLD 12 mo											0%	0%	NS	good
Acute rejection														
Biopsy-proven 12 mo	Kamar, 2006,[33]France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	16%	26%	NS	good
Steroid-resistant, antibody treated 12 mo											4%	9%	NS	fair
Biopsy-proven	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	29%	43%	NS	good
Steroid-resistant, antibody treated											10%	14%	NS	fair
24 mo	Henry, 2001,[35] US[d]	24 mo	49 (49)	55 (55)	Early CsA (day 0)	OKT 3/ delayed CsA (SCr 221-265 µmol/L)	MMF/Steroids	47	73	<2001	27%	11%	NS	poor
32 mo	Slakey, 1993,[36] US[e]	32 mo	60 (60)	61 (61)	Early CsA (day 0)	ALG/ delayed CsA (day 6)	AZA/Steroids	47	100	1988-1990	51%	49%	NS	fair
Steroid-resistant, antibody treated											30%	28%	NS	fair
Biopsy-proven 6 mo	Lebranchu, 2002,[37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250µmol/L)	MMF/Steroids	45	nd	1998-2000	8%	8%	NS	good
Steroid-resistant 6 mo											2%	2%	NS	good
Chronic allograft nephropathy														
CAN	Kamar, 2006,[33]France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	11%	13%	NS	good
Infections														
UTI	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	33%	25%	nd	good
CMV														
CMV	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	17%	12%	nd	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
CMV	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	14%	22%	NS	fair
CMV	Henry, 2001,[35] US[d]	24 mo	49 (49)	55 (55)	Early CsA (day 0)	OKT 3/ delayed CsA (SCr 221-265 µmol/L)	MMF/Steroids	47	73	<2001	16%	20%	NS	poor
Non-CMV requiring hospitalization	Slakey, 1993,[36] US[e]	32 mo	60 (60)	61 (61)	Early CsA (day 0)	ALG/ delayed CsA (day 6)	AZA/Steroids	47	100	1988-1990	23%	18%	NS	poor
CMV											7%	20%	<0.05	fair
Any 6 mo	Lebranchu, 2002,[37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250µmol/L)	MMF/Steroids	45	nd	1998-2000	65%	86%	NS	good
CMV 6 mo											12%	38%	<0.01	good
Delayed graft function														
DGF	Kamar, 2006, [33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	27%	23%	NS	good
Slow graft function											31%	28%	NS	good
DGF	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	34%	28%	NS	good
DGF	Lebranchu, 2002 [37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (SCr <250µmol/L)	MMF/Steroids	45	nd	1998-2000	18%	22%	NS	good
Kidney function														
CrCl, mL/min 3 mo	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/ Steroids	48	96	2002-03	51	54	NS	good
S_{cr}, µmol/L	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	194	203	NS	good
Hypertension														
Hypertension	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	18%	25%	nd	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Blood pressure, mm Hg	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	135/79	140/80	NS	good
Hyperlipidemia														
Hypercholesterol-emia	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	6%	13%	nd	fair
Total cholesterol, mmol/L	Kasiske, 1997,[34] US[c]	90 d	50 (50)	50 (50)	Early CsA (day 0)/ Diltiazem	ATG/ delayed CsA (established kidney fct.)	AZA/Steroids	47	42	1994-96	7.1	6.2	<0.01	good
LDL cholesterol, mmol/L											4.5	3.7	<0.01	good
HDL cholesterol, mmol/L											1.6	1.4	NS	good
Triglycerides, mmol/L											2.6	2.5	NS	good
Adverse events														
Anemia	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	33%	27%	nd	fair
Leukopenia											16%	18%	nd	fair
Diarrhea											17%	10%	nd	good
Tremor											15%	14%	nd	good
Anemia	Lebranchu, 2002,[37] France[f]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250 µmol/L)	MMF/Steroids	45	nd	1998-2000	0%	8%	NS	fair
Leukopenia											0%	10%	<0.05	fair

AE, Adverse events; ALG, Antilymphocyte globulin; ATG, Antithymocyte globulin; AZA, Azathioprine; CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CrCl, Creatinine clearance; CsA, Cyclosporine; DGF, Delayed graft function; EC-MPS, EC-MPS, Enteric-coated mycophenolate sodium; fct, Function; HDL, High density lipoprotein; IL-2 AB, Interleukin-2 antibody; Ktx, Kidney transplant; LDL, Low-density lipoprotein; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; OKT3, Muromonab; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; Thymo, Thymoglobulin; US, United States; UTI, Urinary tract infection.

Annotations:

a. Overlap with topics 1.2.2 (Induction: IL-2 vs. depleting antibody) and 1.2.1 (depleting antibody vs. placebo).
b. Kamar[33]: CAN: Grade I-III, Banff 97; delayed graft function: ≥1 dialysis session within the first week post KTx; slow graft function: S_{Cr} >264 µmol/L at day 5.
c. Kasiske[34]: DGF: ≥1 dialysis session within the first week post KTx, detailed information, e.g. number of postoperative dialysis sessions, number of dialysis days, transplant renogram (Tc-99).
d. Henry[35]: "poor"-grade because of exclusion of DGF, which represents an outcome of interest for this guideline-topic, and because of only few safety results reported.
e. Slakey[36]: "fair"-grade because of exclusion of DGF, which represents an outcome of interest for this guideline-topic.
f. Lebranchu[37]: Steroid-resistant AR: treated either with antibody or with Tacrolimus; DGF: need for dialysis during first week post KTx and/or S_{Cr} > 250 µmol/L in the absence of dialysis.

Supporting Table 13. Summary Table Topic 2.2.1: Early vs. delayed introduction of calcineurin inhibitors (continuous outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
CrCl, mL/min 12/24 mo	Kamar, 2006,[33] France[b]	12 mo 24 mo	97/73 (97)	97/71 (97)	Early CsA (day 0)	Delayed CsA (day 6)	IL2-AB/EC-MPS/Steroids	48	96	2002-03	51 (54)	+2/ +4 (+2/ +3)	NS	good
S_{cr}, µmol/L 12 mo											178 (162)	-9 (+18)	NS	good
S_{cr}, µmol/L 12 mo	Henry, 2001,[35] US[c]	24 mo	49 (49)	55 (55)	Early CsA (day 0)	OKT 3 / delayed CsA (S_{Cr} 221-265 µmol/L)	MMF/Steroids	47	73	<2001	177 (171)	-20 (–16)	NS	poor
CrCl, mL/min 12 mo	Slakey, 1993,[36] US[d]	Mean 32 mo	60 (60)	61 (61)	Early CsA (day 0)	ALG/ delayed CsA (day 6)	AZA/Steroids	47	100	1988-1990	60 (64)	+4 (+4)	NS	fair
S_{cr}, µmol/L 12 mo											141 (141)	±0 (+18)	NS	fair
CrCl, mL/min 12 mo	Lebranchu, 2002,[37] France[e]	6 mo 12 mo	51 (51)	50 (50)	Basiliximab/ early CsA (day 0)	Thymo/ delayed CsA (S_{Cr} <250µmol/L)	MMF/Steroids	45	nd	1998-2000	64 (54)	+2 (+6)	<0.01	good
S_{cr}, µmol/L 12 mo											134 (151)	–10 (–16)	<0.05	good

ALG, Antilymphocyte globulin; AZA, Azathioprine; CAN, Chronic allograft nephropathy; CrCl, Creatinine clearance; CsA, Cyclosporine; DGF, Delayed graft function; IL-2 AB, Interleukin-2 antibody; Ktx, Kidney transplant; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; OKT3, Muromonab; S_{Cr}, Serum creatinine; Thymo, Thymoglobulin; US, United States.

Annotations:

a. Overlap with topics 1.2.2 (Induction: IL-2 vs. depleting antibody) and 1.2.1b (depleting antibody vs. placebo).
b. Kamar[33]: CAN: Grade I-III, Banff 97; delayed graft function: ≥1 dialysis session within the first week post KTx; slow graft function: S_{Cr} >264 µmol/L at day 5.
c. Henry[35]: "poor"-grade because of exclusion of DGF, which represents an outcome of interest for this guideline-topic, and because of only few safety results reported.
d. Slakey[36]: "fair"-grade because of exclusion of DGF, which represents an outcome of interest for this guideline-topic.
e. Lebranchu[37]: Steroid-resistant AR: treated either with antibody or with Tacrolimus; DGF: need for dialysis during first week post KTx and/or S_{Cr} > 250 µmol/L in the absence of dialysis.

Supporting Table 14. Evidence Profile Topic 2.3: MMF various doses and MMF vs. placebo[a,b]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	5 RCTs (High)	1871 (1233)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (duration of follow-up) (–1)	Low	No difference between various doses of MMF and placebo for up to 36 months	Critical
Graft loss	5 RCTs (High)	1871 (1233)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	Not adequately powered for the outcome (duration of follow-up) (–1)	Very low	No statistical significant evidence graft survival in MMF treated patients is prolonged.	Critical
CVD events	0 RCTs								Critical
Cancer	5 RCTs (High)	1871 (1233)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (duration of follow-up) (–1)	Low	No difference between various doses of MMF and placebo for up to 36 months	Critical
Acute rejection	5 RCTs (High)	1871 (1233)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	MMF (2 g or 3 g, not 1 g) is better than placebo in the prevention of acute rejection for up to 36 months. MMF 2 g is better than MMF 1 g in the prevention of acute rejection for up to 12 months. There is no clear evidence that MMF 3 g is better than MMF 2 g in the prevention of acute rejection for up to 36 months.	High
NODAT	2 RCTs (High)	384 (224)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No statistical significant effect on NODAT between MMF and placebo, but there might be less NODAT in MMF treated patients	High
Infection (disease)	5 RCTs (High)	1871 (1233)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	There is no statistical significant difference between various doses of MMF and placebo in the incidence of infections.	High

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Delayed graft function	2 RCTs (High)	673 (455)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	No difference between various doses of MMF	Moderate
Kidney function	4 RCTs (High)	1552 (1008)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	Kidney function is better in patients treated with various doses of MMF than with placebo. There is no difference between different doses of MMF.	Moderate
Lipids	1 RCT (High)	208 (102)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between various doses of MMF and placebo, respectively	Moderate
Blood pressure	1 RCT (High)	208 (102)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between various doses of MMF and placebo, respectively	Moderate
Bone marrow suppression	4 RCTs (High)	1520 (1119)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Low	MMF is causing more bone marrow suppression than placebo. There is no statistical significant effect between MMF 2 g and MMF 3 g on leucopenia and anemia.	Moderate
Diarrhea	4 RCTs (High)	1520 (1119)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No statistical significant effect on diarrhea between MMF and placebo. There might be evidence that higher doses of MMF cause more diarrhea than lower doses of MMF.	Moderate
Balance of potential benefits and harm: Net benefit MMF (2 g or 3 g, not 1 g) is better than placebo in the prevention of acute rejection							Quality of overall evidence: Low (Moderate for acute rejection)		

AZA, Azathioprine; CVD, Cardiovascular disease; g, grams; MMF, Mycophenolate mofetil; N, Number; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials; SR, Systematic review.
Annotations:
a. Including information of three RCTs comparing MMF 2 g vs. MMF 3 g listed in the summary table about MMF vs. AZA (topic 2.4).
b. References: [38-42]

Supporting Table 15. Summary Table Topic 2.3: MMF various doses and MMF vs. placebo (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)			Intervention/Control			Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results			*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3					Arm 1	Arm 2	Arm 3		
Mortality																	
6 mo/3 y	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	165 (165)	166 (166)	160 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	3% 8%	2% 7%	4% 11%	nd	fair
With functioning graft 3 y													6%	7%	6%	nd	fair
15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	4%	7%	nd	fair
Graft loss																	
6 mo/3 y	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	165 (165)	166 (166)	160 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	6% 19%	4% 15%	9% 22%	nd	fair
Excluding death 3 y													13%	9%	16%	nd	fair
15 mo	Shapiro, 1999,[39], US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	8%	15%	nd	fair
Cancer																	
6 mo/3 y	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	165 (165)	166 (166)	160 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	0% 1%	1% 2%	1% 3%	nd	fair
PTLD 6 mo													0%	0%	0%	nd	fair
PTLD 15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	0%	1%	nd	fair
Acute rejection																	
6 mo	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	165 (165)	166 (166)	160 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	26%	30%	55%	nd	fair
Biopsy-proven 6 mo													14%	17%	46%	nd	fair
Severity of AR, Banff II or higher 6 mo													5%	10%	30%	nd	fair
Steroid-resistant 6 mo													3%	5%	22%	nd	fair
15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	27%	44%	0.014	poor
Steroid-resistant 15 mo													—	3%	8%	NS	fair
Severity of AR, Banff II or higher 15 mo													—	7%	19%	nd	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)			Intervention/Control			Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results			*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3					Arm 1	Arm 2	Arm 3		
NODAT																	
12 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	1%	5%	nd	poor
Infection																	
CMV 3 y	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	165 (165)	166 (166)	160 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	23%	19%	16%	nd	fair
PCP 6 mo													7%	3%	2%	nd	fair
CMV 15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	17%	9%	nd	fair
Kidney function																	
S_{cr}, µmol/L 6 mo	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	108 (165)	126 (166)	114 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	130	126	142	<0.05	poor
S_{cr}, µmol/L 15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	150	141	nd	poor
Lipids																	
Cholesterol, mmol/L 15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	4.97	5.17	nd	fair
Hypertension																	
Pts w/o anti-hypertensive drugs 15 mo	Shapiro, 1999,[39] US	12 mo	—	106 (106)	102 (102)	—	MMF 2 g	No Placebo	Tac/Steroids	51	100	1995-97	—	39%	25%	nd	poor
Adverse events																	
Diarrhea 6 mo/3 y	European MMF study, 1999,[38] EU	6 mo 12 mo 3 y	165 (165)	166 (166)	160 (160)	MMF 3 g	MMF 2 g	Placebo	CsA/Steroids	46	100	1992-95	16% 26%	13% 21%	13% NA	nd	fair
Leucopenia 6 mo/3 y													14% 20%	11% 14%	4% NA	nd	fair
Anemia 6 mo/ 3 y													7% 8%	4% 5%	2% 2%	nd	fair

AE, Adverse events; AR, Acute rejection; CMV, Cytomegalovirus; CsA, Cyclosporine; EU, Europe; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; PCP, Pneumocystis pneumonia; PTLD, Posttransplant lymphoproliferative disease; pt, Patient; S_{Cr}, Serum creatinine; Tac, Tacrolimus; US, United States; w/o, Without.

Supporting Table 16. Evidence Profile Topic 2.3: MMF vs. AZA[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	6 RCTs (High)	2138 (1356)	No limitations for up to 3 years (0) Some limitations for more than 3 years (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (duration of follow-up) (–1)	Moderate (<3 y) Low (>3 y)	No difference between MMF and AZA for up to 6 years	Critical
Graft loss	6 RCTs (High)	2138 (1356)	No limitations for up to 3 years (0) Some limitations for more than 3 years (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (duration of follow-up) (–1)	Moderate (<3 y) Low (>3 y)	No difference between MMF and AZA for up to 6 years	Critical
CVD events	0 RCTs								Critical
Cancer	4 RCTs (High)	1514 (956)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (duration of follow-up) (–1)	Low	No difference between MMF and AZA for up to 6 years	Critical
Acute rejection	6 RCTs (High)	2138 (1356)	No limitations (0)	Important inconsistencies (–1)	Some uncertainty (–1)	Dose response: MMF 2 g better than 1 g (+1)	Moderate	MMF (2 g or 3 g, not 1 g) might be better than AZA in the prevention of acute rejection within the first year after transplantation, one trial showed similar acute rejection rates in a CsA-ME based regimen	High
NODAT	2 RCTs (High)	323 (190)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (limited number of studies) (–1)	Low	No difference between MMF and AZA for up to 3 years	High
Infection (disease)	6 RCTs (High)	2138 (1356)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	No difference between MMF and AZA for up to 6 years, higher incidence of CMV infection in MMF treated patients in 1 trial	High
Delayed graft function	4 RCTs (High)	1162 (695)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between MMF and AZA	Moderate

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Kidney function	5 RCTs (High)	1962 (1230)	No limitations for up to 3 years (0) Some limitations for more than 3 years (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High (<3 y) Moderate (>3 y)	No difference between MMF and AZA for up to 6 years	Moderate
Proteinuria	1 RCT (High)	336 (168)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (limited number of studies) (–1)	Low	No difference between MMF and AZA	Moderate
Lipids	2 RCT (High)	323 (190)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (limited number of studies) (–1)	Low	No difference between MMF and AZA for up to 3 years	Moderate
Bone marrow suppression	5 RCTs (High)	1991 (1276)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	No statistical significant effect on leucopenia and anemia between MMF and AZA	Moderate
Diarrhea	5 RCTs (High)	1991 (1276)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No statistical significant effect on diarrhea between MMF and AZA as reported, but overall more diarrhea in MMF treated patients	Moderate
Balance of potential benefits and harm: Net benefit MMF (2 g or 3 g, not 1 g) might be better than AZA in the prevention of acute rejection within the first year after transplantation, but not other outcomes							Quality of overall evidence: Low (Moderate for acute rejection)		

AZA, Azathioprine, CMV, Cytomegalovirus; CsA-ME, Cyclosporine A microemulsion; CVD, Cardiovascular disease; MMF, Mycophenolate mofetil; N, Number; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials.
Annotations:
a. References: [28,40-47]

Supporting Table 17. Summary Table Topic 2.3: MMF vs. AZA (categorical outcomes)[a,b]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concom-itant medication	Age (mean)	% deceased donor	Dates of trans-plant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
Mortality																				
Including death with functioning graft	Sadek, 2002,[43] Brazil, EU, Canada[b]	12 mo	—	158 (158)	162 (162)	157 (157)	—	MMF 2 g	MMF → AZA[2]	AZA 1-2 mg/kg	CsA-ME/ Ster	44	86	<2001	—	5%	3%	5%	NS	good
6 mo/12 mo/36 mo	Mathew, 1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	2% 4% 9%	1% 4% 5%	—	1% 4% 8%	nd	good
12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/ Ster/ ±OKT3	44	100	1996-98	—	5%	5%	2%	NS	fair
6 mo/36 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/kg	CsA/Ster /±ATG	46	100	1992-93	5% 12%	4% 11%	—	3% 12%	NS	fair
6 mo/72 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/ ±Ster	44	100	1997-2001	—	2% 4%	—	2% 4%	NS	good fair
24 mo	Gonwa, 2003,[28] US[a]	36 mo	—	72 (72)	—	75 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/kg	Tac/Ster/ ±OKT3	47	100	<1999	—	6%	—	4%	NS	good
Graft loss																				
Excluding death 12 mo	Sadek, 2002,[43], Brazil, EU, Canada[b]	12 mo	—	158 (158)	162 (162)	157 (157)	—	MMF 2 g	MMF → AZA[2]	AZA 1-2 mg/kg	CsA-ME/ Ster	44	86	<2001	—	10%	9%	10%	NS	good
6 mo/12 mo/36 mo	Mathew,1998, 1996,[40,44] Can, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	2% 8% 15%	4% 9% 18%	—	3% 11% 20%	nd	good
Excluding death 12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/Ster/ ±OKT3	44	100	1996-98	—	0%	2%	5%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concom-itant medication	Age (mean)	% deceased donor	Dates of trans-plant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
6 mo/36 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/kg	CsA/Ster/ ±ATG	46	100	1992-93	7% 17%	2% 13%	—	9% 17%	NS	fair
6 mo/72 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/ ±Ster	44	100	1997-2001	—	1% 6%	—	1% 7%	NS	good fair
36 mo	Gonwa, 2003,[28] US[a]	36 mo	—	72 (72)	—	75 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/kg	Tac/Ster/ ±OKT3	47	100	<1999	—	19%	—	20%	NS	good
Cancer																				
12 mo/36 mo	Mathew, 1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	8% 12%	11% 15%	—	7% 18%	nd	good
Lymphoma/LPD 36 mo															2%	1%	—	1%	nd	good
PTLD 12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/Steroids /±OKT3	44	100	1996-98	—	0%	0%	0%	NS	fair
PTLD 6 mo/36 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/kg	CsA/Ster/ ±ATG	46	100	1992-93	1% 2%	<1% <1%	—	0% <1%	NS	fair
72 mo	Remuzzi 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/ ±Ster	44	100	1997-2001	—	6%	—	10%	NS	fair
PTLD 72 mo															—	2%	—	2%	NS	fair
Acute rejection																				
12 mo	Sadek, 2002,[43], Brazil, EU, Canada[b]	12 mo	—	158 (158)	162 (162)	157 (157)	—	MMF 2 g	MMF → AZA[2]	AZA 1-2 mg/kg	CsA-ME/ Ster	44	86	<2001	—	21%	23%	33%	<0.05	good
Biopsy-proven															—	17%	17%	27%	<0.05	good
Steroid-resistant															—	7%	6%	15%	<0.05	good
Biopsy-proven 6 mo	Mathew,1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	16%	20%	—	36%	nd	good
Severity of AR, Banff II or higher 6 mo															6%	10%	—	20%	nd	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concom-itant medication	Age (mean)	% deceased donor	Dates of trans-plant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
6 mo/12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/Ster/ ±OKT3	44	100	1996-98	—	7% 9%	29% 32%	29% 32%	<0.01 <0.01	fair
Time to AR, days 6 mo/12 mo															—	98 129	53 79	28 55	nd	fair
Biopsy-proven 6 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/kg	CsA/Ster/ ±ATG	46	100	1992-93	18%	20%	—	38%	nd	good
6 mo															24%	26%	—	46%	nd	good
Steroid-resistant 6 mo															5%	10%	—	19%	nd	good
Severity of AR, Banff II or higher 6 mo															12%	9%	—	20%	nd	good
6 mo/72 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/124 (168)	—	164/124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/ ±Ster	44	100	1997-2001	—	34% 46%	—	35% 52%	NS	good fair
Biopsy-proven 6 mo															—	18%	—	23%	NS	good
Severity of AR, Banff II or higher 6 mo															—	17%	—	23%	NS	good
Steroid-resistant 6 mo															—	5%	—	11%	NS	good
36 mo	Gonwa, 2003,[28] US[a]	36 mo	—	72 (72)	—	75 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/kg	Tac/Ster/ ±OKT3	47	100	<1999	—	17%	—	21%	NS	good
Treated with antibody															—	6%	—	16%	<0.05	good
NODAT																				
12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/Ster/ ±OKT3	44	100	1996-98	—	5%	12%	19%	NS	fair
36 mo	Gonwa, 2003,[28] US[a]	36 mo	—	46 (72)	—	57 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/kg	Tac/Ster/ ±OKT3	47	100	<1999	—	13%	—	19%	nd	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concom-itant medication	Age (mean)	% deceased donor	Dates of trans-plant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
Infections																				
CMV	Sadek, 2002,[43], Brazil, EU, Canada[b]	12 mo	—	158 (158)	162 (162)	157 (157)	—	MMF 2 g	MMF → AZA[2]	AZA 1-2 mg/kg	CsA-ME/Ster	44	86	<2001	—	20%	22%	11%	NS	fair
CMV – viremia + syndrome 36 mo	Mathew, 1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	13%	13%	—	12%	nd	good
Opportunistic infections 12 mo															46%	46%	—	44%	nd	good
CMV 12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/Ster/±OKT3	44	100	1996-98	—	7%	7%	5%	NS	fair
Opportunistic infections 6 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/kg	CsA/Ster/±ATG	46	100	1992-93	47%	45%	—	46%	NS	fair
CMV 6 mo/36 mo															24% 27%	24% 26%	—	21% 22%	NS nd	fair
CMV 6 mo/72 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/124 (168)	—	164/124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/±Ster	44	100	1997-2001	—	26% 32%	—	25% 37%	NS	good fair
CMV	Gonwa, 2003,[28] US[a]	36 mo	—	72 (72)	—	75 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/kg	Tac/Ster/±OKT3	47	100	<1999	—	14%		4%	<0.01	good
PCP															—	0%		1%	NS	good
Delayed graft function																				
6 mo	Mathew, 1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	18%	21%	—	13%	nd	good
6 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/kg	Tac/Ster/±OKT3	44	100	1996-98	—	16%	14%	12%	nd	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concom-itant medication	Age (mean)	% deceased donor	Dates of trans-plant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
6 mo	Remuzzi 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME / ±Ster	44	100	1997-2001	—	31%	—	35%	NS	good
36 mo	Gonwa, 2003,[28] US[a]	36 mo	—	72 (72)	—	75 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/ kg	Tac/Ster/ ±OKT3	47	100	<1999	—	36%	—	33%	NS	fair
Kidney function																				
S_{cr}, µmol/L 14 wk/12 mo	Sadek, 2002,[43], Brazil, EU, Canada[b]	12 mo	—	158 (158)	162 (162)	157 (157)	—	MMF 2 g	MMF → AZA[2]	AZA 1-2 mg/ kg	CsA-ME /Ster	44	86	<2001	—	140 151	144 146	140 130	NS	good
S_{cr}, µmol/L 6 mo/12 mo/36 mo	Mathew, 1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	123 123 141	141 141 158	—	141 141 150	nd	good
S_{cr}, µmol/L 6 mo/36 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/ kg	CsA/Ster /±ATG	46	100	1992-93	150 150	150 150	—	158 158	NS	fair
S_{cr}, µmol/L 6 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME / ±Ster	44	100	1997-2001	—	141	—	132	NS	good
eGFR, mL/min 6 mo/72 mo															— —	62 47	— —	62 50	NS	good fair
S_{cr}, µmol/L	Gonwa, 2003,[28] US[a]	36 mo	—	72 (72)	—	75 (75)	—	MMF 2 g	—	AZA 1.5-2 mg/ kg	Tac/Ster /±OKT3	47	100	<1999	—	123	—	123	NS	fair
CrCl, mL/min															—	59	—	62	NS	fair
Proteinuria																				
Proteinuria, >0.5 g/d 72 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/ ±Ster	44	100	1997-2001	—	27%	—	25%	NS	fair
Lipids																				
Hyperlipid-emia 12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/	Tac/Ster /±OKT3	44	100	1996-98	—	19%	19%	17%	NS	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concom-itant medication	Age (mean)	% decea sed donor	Dates of trans-plant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
Hypercholes-terolemia 12 mo										kg					—	7%	9%	9%	NS	poor
Adverse events																				
Diarrhea 12 mo	Sadek, 2002,[43] Brazil, EU, Canada[b]	12 mo	—	158 (158)	162 (162)	157 (157)	—	MMF 2 g	MMF → AZA[2]	AZA 1-2 mg/ kg	CsA-ME/ Ster	44	86	<2001	—	17%	13%	8%	NS	good
Leucopenia 12 mo															—	19%	20%	19%	NS	good
Anemia 12 mo															—	17%	18%	16%	NS	good
Diarrhea 12 mo/36 mo	Mathew, 1998, 1996,[40,44] Canada, EU, Aus	6 mo 12 mo 36 mo	164 (164)	171 (173)	—	162 (166)	MMF 3 g	MMF 2 g	—	AZA 100-150 mg	CsA/Ster	46	100	1992-93	31% 38%	28% 35%	—	17% 20%	nd	good
Leucopenia 12 mo/36 mo															35% 38%	19% 20%	—	30% 31%	nd	good
Anemia 12 mo/36 mo															9% 12%	15% 16%	—	10% 10%	nd	good
Anemia 12 mo	Miller, 2000,[41] US	6 mo 12 mo	—	59 (59)	59 (59)	58 (58)	—	MMF 2 g	MMF 1 g	AZA 1.5 mg/ kg	Tac/Ster /±OKT3	44	100	1996-98	—	45%	42%	49%	NS	poor
Leukopenia 12 mo															—	36%	32%	22%	<0.05	poor
Diarrhea 12 mo															—	64%	44%	41%	NS	fair
Diarrhea 6 mo/36 mo	Sollinger, 1995, 1999[42] US	6 mo 36 mo	166 (166)	167 (167)	—	166 (166)	MMF 3 g	MMF 2 g	—	AZA 1-2 mg/ kg	CsA/Ster /±ATG	46	100	1992-93	37% 47%	32% 42%	—	24% 33%	nd	fair
Leucopenia 36 mo															37%	29%	—	24%	nd	fair
Anemia 36 mo															47%	44%	—	43%	nd	fair
Diarrhea 6 mo	Remuzzi, 2004, 2007,[47] EU	6 mo 72 mo	—	164/ 124 (168)	—	164/ 124 (168)	—	MMF 2 g	—	AZA 100-150 mg	CsA-ME/ ±Ster	44	100	1997-2001	—	2%	—	1%	NS	good
Leucopenia 6 mo															—	19%	—	13%	NS	good

AE, Adverse events; AR, Acute rejection; Aus, Australia; AZA, Azathioprine; CMV, Cytomegalovirus; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; EU, Europe; LPD, Lymphoproliferative disorders; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; OKT3, Muromonab; PCP, Pneumoystis pneumonia; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; SRL, Sirolimus; Ster, Steroids; Tac, Tacrolimus; US, United States.

Annotations:

a. Gonwa, 2003[28]: three-arm study split (A) topic 2.3 Tac vs. CsA, (B) topic 2.4 MMF vs. AZA. b. Sadek, 2002[43]: arm 3: MMF 2 g from d0 to d90, thereafter switch to AZA.

Supporting Table 18. Summary Table Topic 2.3: MMF vs. AZA (continuous outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1 (intervention)	Arm 2 (control)					Baseline (Control)	Δ (Control)		
Lipids														
Total cholesterol, mmol/L 6 mo	Gonwa, 2003,[28] US[a]	36 mo	72 (72)	75 (75)	MMF 2 g	AZA 1.5-2 mg/kg	Tac /Ster/ ±OKT3	47	100	<1999	5.79 (5.99)	+0.62 (+0.77)	NS	good
LDL, mmol/L, 6 mo											2.92 (3.54)	+0.02 (+0.55)	NS	good
No. of pts. on lipid-lowering therapy 6 mo											7% (7%)	+6% -1.3%	<0.01	fair

AZA, Azathioprine; LDL, Low-density lipoprotein; MMF, Mycophenolate mofetil; NS, Not significant; OKT3, Muromonab; pt, Patient; Ster, Steroids; Tac, Tacrolimus; US, United States.

Annotations:

a. Gonwa 2003 [619]: three-arm study split (A) topic 2.3 Tac vs. CsA, (B) topic 2.4 MMF vs. AZA.

Supporting Table 19. Evidence Profile Topic 2.4: Steroid avoidance/early withdrawal vs. steroid maintenance[a,b]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Mortality	4 RCTs (High)	1348 (667)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Moderate	No difference between steroid avoidance and steroid maintenance for up to 5 years	Critical
Graft loss	4 RCTs (High)	1348 (667)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Moderate	No difference between steroid avoidance and steroid maintenance for up to 5 years	Critical
CVD events	0 RCTs								Critical
Cancer	3 RCTs (High)	1288 (637)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Moderate	No difference between steroid avoidance and steroid maintenance for up to 5 years	Critical
Acute rejection	4 RCTs (High)	1348 (667)	No limitations (0)	important inconsistencies (–1)	No uncertainty (0)	None (0)	Moderate	Higher rate of steroid sensitive acute rejections in patients treated with induction antibody with early steroid avoidance compared to patients treated with induction antibody maintained on steroids. No difference in acute rejection rates between steroid avoidance with induction antibody and steroid maintenance/withdrawal without induction antibody.	High
NODAT	4 RCTs (High)	1348 (667)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between steroid avoidance and steroid maintenance for up to 5 years	High
Infection (disease)	3 RCTs (High)	984 (481)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between steroid avoidance and steroid maintenance for up to 5 years	High
Bone fractures	3 RCT (High)	750 (377)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	There is no clear evidence that there is a difference between steroid avoidance and steroid maintenance for up 5 years.	High
Delayed graft function	3 RCTs (High)	962 (476)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between steroid avoidance with induction antibody and steroid maintenance/withdrawal without induction antibody	Moderate

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Kidney function	4 RCTs (High)	1348 (667)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between steroid avoidance and steroid maintenance for up to 5 years	Moderate
Proteinuria	1 RCT (High)	364 (186)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	No difference between steroid avoidance with induction antibody and steroid maintenance/withdrawal without induction antibody for up 12 months	Moderate
Lipids	3 RCTs (High)	1288 (637)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Moderate	No significant difference in lipid profiles between steroid avoidance and steroid maintenance	Moderate
Blood pressure	3 RCTs (High)	1288 (637)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	None (0)	High	No difference between steroid avoidance and steroid maintenance for up to 5 years	Moderate
Bone mineral density	2 RCTs (High)	354 (183)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	Sparse data (–1)	Very low	There is no clear evidence that BMD in patients treated without steroids but with induction antibody is higher than in patients with steroids and without induction antibody for up 12 months	Moderate
Bone marrow suppression	2 RCTs (High)	924 (451)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Moderate	No difference between steroid avoidance and steroid maintenance for up to 5 years in the incidence of anemia Leukopenia might be more common in patients without steroid treatment	Moderate
Adverse events	3 RCTs (High)	1288 (637)						Tachycardia and dyspnea might be more frequent in patients treated without steroids but with induction antibody compared to patients maintained on with steroids and without induction antibody	Depends on outcome
Balance of potential benefits and harm: Tradeoffs Steroid avoidance/early withdrawal is associated with a higher incidence of steroid-sensitive acute rejections.							Quality of overall evidence: Moderate		

BMD, Bone mineral density; CVD, Cardiovascular disease; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials.

Annotations:

a. Evidence combined from trials comparing steroid avoidance/early withdrawal vs. steroid maintenance as well as steroid avoidance/early withdrawal with induction therapy vs. steroid maintenance without induction therapy.

b. References: [8,9,13,48,49]

Supporting Table 20. Summary Table Topic 2.4: Steroid avoidance/early withdrawal vs. steroid maintenance (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
6 mo	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroids	Tac/MMF	47	nd	2000-02	2%	1%	NS	good
12 mo	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	5%	6%	NS	good
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Alemtuzumab/ Steroid avoidance	Thymo/Steroids	Tac/MMF	50	100	2002-04	0%	8%	NS	poor
12 mo					Alemtuzumab/ Steroid avoidance	Daclizumab/ Steroids					0%	12%	NS	poor
5 y	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal[4]	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	6%	7%	NS	good
Graft loss														
6 mo	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab/ Steroids	Tac/MMF	47	nd	2000-02	8%	4%	NS	good
12 mo	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	9%	10%	NS	good
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Alemtuzumab/ Steroid avoidance	Thymo/Steroids	Tac/MMF	50	100	2002-04	0%	12%	NS	poor
12 mo					Alemtuzumab/ Steroid avoidance	Daclizumab /Steroids					0%	12%	NS	poor
5 y	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	6%	4%	NS	good
Cancer														
6 mo	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab/ Steroids	Tac/MMF	47	nd	2000-02	0.4%	1%	NS	fair
Excluding PTLD	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	3%	1%	NS	good
PTLD											1%	1%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
5 y	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	11%	11%	NS	good
PTLD											1%	1%	NS	good
Skin cancer, non-melanoma											5%	9%	NS	good
Acute rejection														
Biopsy-proven	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroids	Tac/MMF	47	nd	2000-02	17%	17%	NS	good
Severity of AR, Banff II or higher											6%	7%	NS	good
Time to AR, days											no difference		NS	fair
Steroid-resistant											5%	4%	NS	good
12 mo	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	29%	24%	NS	good
Biopsy-proven											15%	14%	NS	good
Severity of AR, Banff II or higher											10%	8%	NS	good
Time to AR, days											11	18	NS	good
Biopsy-proven	Ciancio, 2005,[13] US	12 mo	30 (30)	30 (30)	Alemtuzumab/ Steroid avoidance	Thymo/Steroids	Tac/MMF	50	100	2002-04	17%	17%	NS	poor
Severity of AR, Banff II or higher											7%	10%	NS	poor
Biopsy-proven					Alemtuzumab/ Steroid avoidance	Daclizumab /Steroids					17%	17%	NS	poor
Severity of AR, Banff II or higher											7%	3%	NS	poor
Biopsy-proven	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	18%	11%	0.04	good
Moderate/severe											8%	6%	NS	good
NODAT														
6 mo	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroids	Tac/MMF	47	nd	2000-02	0.4%	5%	0.001	good
12 mo	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	7%	12%	NS	good
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Alemtuzumab/ Steroid avoidance	Thymo/Steroids	Tac/MMF	50	100	2002-04	11%	23%	NS	poor
12 mo					Alemtuzumab/ Steroid	Daclizumab /Steroids					11%	14%	NS	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
					avoidance									
Impaired fasting glucose, 5 y	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	22%	21%	NS	good
Insulin use, 5 y											4%	12%	NS	good
Infection														
UTI	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab/ Steroids	Tac/MMF	47	nd	2000-02	25%	30%	NS	good
Pneumonia											4%	1%	<0.05	good
UTI	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Alemtuzumab/ Steroid avoidance	Thymo/Steroids	Tac/MMF	50	100	2002-04	3%	3%	NS	poor
CMV											0%	3%	NS	poor
Polyoma BK											0%	0%	NS	poor
UTI					Alemtuzumab/ Steroid avoidance	Daclizumab/ Steroids					3%	0%	NS	poor
CMV											0%	0%	NS	poor
Polyoma BK											0%	0%	NS	poor
5 y	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	39%	44%	NS	good
CMV infection/ Tissue invasive											10% 2%	6% 3%	NS	good
BK nephropathy, Bx confirmed											4%	3%	NS	good
Fungal infections											7%	10%	NS	good
Delayed graft function														
6 mo	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab/ Steroids	Tac/MMF	47	nd	2000-02	32%	28%	NS	good
12 mo	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	24%	22%	NS	good
12 mo	Ciancio, 2005,[13] US[c]	12 mo	30 (30)	30 (30)	Alemtuzumab /Steroid avoidance	Thymo/Steroids	Tac/MMF	50	100	2002-04	7%	13%	NS	poor
12 mo					Alemtuzumab/ Steroid avoidance	Daclizumab/ Steroids					7%	7%	NS	poor
Kidney function														

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
S_{cr}, µmol/L	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab/ Steroids	Tac/MMF	47	nd	2000-02	131	125	NS	good
CrCl, mL/min											52	54	NS	good
CrCl, mL/min	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/S teroid withdrawal	Tac/MMF	49	64	1999-2002	65	62	NS	good
S_{cr}, µmol/L	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	133	133	NS	good
CrCl, mL/min											59	60	NS	good
Proteinuria														
Proteinuria (>1 g/d)	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	5%	8%	NS	good
Lipids														
Patients on Lipid-lowering drug	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	9%	7%	NS	fair
Hypertension														
Hypertension	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroids	Tac/MMF	47	nd	2000-02	16%	15%	NS	fair
Patients on hypertensive drugs											51%	62%	nd	fair
Adverse events														
Leucopenia	Rostaing, 2005,[8] EU[a]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroid[s]	Tac/MMF	47	nd	2000-02	22%	18%	NS	good
Anemia											24%	21%	NS	good
Tachycardia											3%	0.4%	<0.05	good
Dyspnea											2%	0%	<0.05	good
Rib fractures	ter Meulen, 2004,[9,48] Netherlands[b]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	2%	1%	NS	fair
Bone fractures	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	5%	10%	NS	good
Avascular necrosis + bone fractures											5%	11%	0.04	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled) Arm 1	No. analyzed (enrolled) Arm 2	Intervention/Control Arm 1	Intervention/Control Arm 2	Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results Arm 1	Results Arm 2	*P* value	Quality
Anemia											4%	2%	NS	good
Leucopenia											51%	37%	<0.01	good
Hyperkalemia											29%	15%	<0.01	good

AE, Adverse events; AR, Acute rejection; Bx, Biopsy; CMV, Cytomegalovirus; CrCl, Creatinine clearance; EU, Europe; IL-2, Interleukin-2; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; Tac, Tacrolimus; Thymo, Thymoglobulin; US, United States; UTI, Urinary tract infection.

Annotations:

a. Rostaing, 2005[8]: overlap with topic 1 (Induction); both treatment groups received 500 mg Methylprednisolone IV on day 0; Steroid doses in patients without Daclizumab induction therapy were tapered to 5 mg/day until day 43.

b. ter Meulen, 2004[9,48]: overlap with topic 1 (Induction); both treatment groups received 100 mg Methylprednisolone IV per day from day 0 to day 3; Steroid doses in patients without Daclizumab Induction therapy were tapered down and withdrawn by month 4.

c. Ciancio, 2005[13]: three arm study split: (A) Induction: IL-2 vs. depleting antibody; (B) Steroid avoidance/withdrawal; overlap with topic 1 (Induction); only treatment groups Dacluzimab and Thymoglobulin received 500 mg Methylprednisolone IV on day 0 to day 3; Steroid doses were then tapered to 0.15 mg/kg by month 3; Alemtuzumab treated patients did not receive any steroids by protocol.

d. Woodle, 2008[49]: all pts. received unblinded steroids from day 0 to day 7. Thereafter steroids were discontinued (treatment) or tapered to 5 mg/d at day 120 (control). Patients with DGF were excluded.

Supporting Table 21. Summary Table Topic 2.4: Steroid avoidance/early withdrawal vs. steroid maintenance (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
S_{cr}, µmol/L	Ciancio, 2005,[13] US[a]	12 mo	30 (30)	30 (30)	Alemtuzumab /Steroid avoidance	Thymo/ Steroids	Tac/MMF	50	100	2002-04	138 (111)	–16 (+5)	nd	poor
CrCl, mL/min											58 (75)	+15 (+5)	nd	poor
S_{cr}, µmol/L					Alemtuzumab /Steroid avoidance	Daclizumab /Steroids					138 (108)	–16 (–4)	nd	poor
CrCl, mL/min											58 (73)	+15 (+8)	nd	poor
Lipids														
Total cholesterol, mmol/L	Rostaing, 2005,[8]EU[b]	6 mo	260 (260)	278 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroids	Tac/MMF	47	nd	2000-02	5.12 (5.06)	–0.19 (+0.19)	<0.01	good
Total cholesterol, mmol/L	ter Meulen, 2004,[9,48] Netherlands[c]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	4.9 (5.4)	+0.3 (–0.1)	NS	good
LDL, mmol/L											2.99 (3.11)	+0.13 (+0.05)	NS	good
Treatment of hyperlipidemia	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	30.4% (28.7%)	+31.7% (+44.8%)	NS (0.06)	fair
Hypertension														
Mean arterial pressure, mm Hg	ter Meulen, 2004,[9,48] Netherlands[c]	12 mo	186 (186)	178 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	97 (101)	+1 (–2)	NS	good
Number of antihypertensive drugs											0.9 (1.1)	+0.2 (±0)	NS	fair
Blood pressure	Woodle, 2008,[49] US[d]	5 y	191 (191)	195 (195)	Steroid withdrawal	Steroid maintenance	Tac/MMF/IL2 or Thymo	47	43	1999-2002	130/78 (132/79)	+8/+1 (+6/+0)	NS	good
Number of antihypertensive drugs											1.6 (1.9)	+0.5 (+0.2)	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Other outcomes														
BMD, T-score (total femoral region)	Rostaing, 2005,[8] EU[b]	6 mo	48 (260)	45 (278)	Daclizumab/ Steroid avoidance	No Daclizimab /Steroids	Tac/MMF	47	nd	2000-02	nd (nd)	–0.15 (nd)	<0.05	poor
BMD, Z-score (total femoral region)											nd (nd)	–0.13 (nd)	<0.05	poor
BMD, lumbar spine, mg/cm^2	ter Meulen, 2004,[9,48] Netherlands[c]	12 mo	135 (186)	126 (178)	Daclizumab/ Steroid avoidance	No Daclizumab/ Steroid withdrawal	Tac/MMF	49	64	1999-2002	1118 (1091)	+0.9 (+0.1)	NS	fair
BMD, femoral neck, mg/cm^2											821 (816)	–0.6 (–0.9)	NS	fair

BMD, Bone mineral density; CrCl, Creatinine clearance; EU, Europe; IL-2, Interleukin-2; LDL, Low-density lipoprotein; MMF, Mycophenolate mofetil; mmol, Millimole; mo, Month; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; Tac, Tacrolimus; Thymo, Thymoglobulin; US, United States.

Annotations:

a. Ciancio, 2005[13]: three arm study split: (A) Induction: IL-2 vs. depleting antibody; (B) Steroid avoidance/withdrawal; overlap with topic 1 (Induction); only treatment groups Dacluzimab and Thymoglobulin received 500 mg Methylprednisolone IV on day 0 to day 3; Steroid doses were then tapered to 0.15 mg/kg by month 3; Alemtuzumab treated patients did not receive any steroids by protocol.

b. Rostaing, 2005[8]: overlap with topic 1 (Induction); both treatment groups received 500 mg Methylprednisolone IV on day 0; Steroid doses in patients without Daclizumab induction therapy were tapered to 5 mg/day until day 43.

c. ter Meulen, 2004[9,48]: overlap with topic 1 (Induction); both treatment groups received 100 mg Methylprednisolone IV per day from day 0 to day 3; Steroid doses in patients without Daclizumab Induction therapy were tapered down and withdrawn by month 4.

d. Woodle, 2008[49]: all pts. received unblinded steroids from day 0 to day 7. Thereafter steroids were discontinued (treatment) or tapered to 5 mg/d at day 120 (control). Patients with DGF were excluded.

Supporting Table 22. Evidence Profile Topic 2.5: Sirolimus vs. CNI [a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect (notes)	Importance of outcome
Mortality	4 RCTs (High)	1239 (617)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1)	Moderate	Overall no difference between sirolimus and CNI for mortality outcome	Critical
	1 SR (6 trials)	631 (318)	Some limitations (–1)				Low		
Graft loss	4 RCTs (High)	1239 (617)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1)	Moderate	Overall no difference between sirolimus and CNI for graft loss (censored for death)	Critical
	1 SR (6 trials)	631 (318)	Some limitations (–1)				Low		
CVD events (cardiac mortality)	0 RCTs							No difference between sirolimus and CNI for cardiac mortality	Critical
	1 SR (4 trials) (High)	345	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1)	Low		
Cancer	3 RCTs (High)	1392 (694)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1))	Moderate	Overall no difference between sirolimus and CNI	Critical
	1 SR (4 trials)	447 (223)	Some limitations (–1)				Low		
Acute rejection	3 RCTs (High)	1094 (546)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Overall no difference between sirolimus and CNI	High
	1 SR (6 trials)	631 (318)	Some limitations (–1)						
CAN	2 RCTs (High)	932 (466)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	Overall no difference between sirolimus and CNI	High
	1 SR (1 trial)	123 (64)	Some limitations (–1)				Low		
Skin cancer	1 RCT (High)	530 (215)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	Overall no difference between sirolimus and CNI	High
	1 SR (4 trials)	992 (481)	Some limitations (–1)			None (0)			

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect (notes)	Importance of outcome
NODAT	4 RCTs (High) 1 SR (3 trials)	1239 (617) 244 (111)	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Overall no difference between sirolimus and CNI	High
Infection (disease)	4 RCTs (High) 1 SR (5 trials)	1239 (617) 508 (254)	Some limitations (–1) Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	Statistically significant higher number of CMV infections in the Tac group compared with sirolimus (Consistent)	High
QOL	1 RCT (High)	428 (214)	Serious limitations (–2)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Very low	Significant improvements in some components of QoL with CsA withdrawal	High
Delayed graft function	2 RCTs (High)	932 (466)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	Sparse data (–1)	Low	Overall no difference between sirolimus and CNI	Moderate
Kidney function	5 RCTs (High) 1 SR (4 trials)	1656 (822) 255	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Improved kidney function in the sirolimus (CNI withdrawal) arm reported in the majority of trials	Moderate
Lipids	3 RCTs (High) 1 SR (2 trials)	439 (218) 161 (81)	No limitations (0) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate Low	Statistically higher proportion of patients in the sirolimus group had hyperlipidemia than CNI. There were statistically significant increased mean levels of hypercholesterolemia in the sirolimus arm.	Moderate
Blood pressure	2 RCTs (High 1 SR (2 trials)	962 (479) 161 (80)	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	Overall no difference between sirolimus and CNI	Moderate
Bone marrow suppression	1 RCT (High) 1 SR (4 trials)	430 (215) 302 (152)	Some limitations (–1) Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Statistically significant increased risk of bone marrow suppression was reported in the sirolimus arm compared with CNI arm.	Moderate
Adverse events	2 RCT (High) 1 SR (2 trials)	277 (138) 161 (80)						Diarrhea: Inconsistent results, favors neither Higher drug discontinuation reported in sirolimus arm	Depends on outcome

Balance of potential benefits and harm: Net harm

Treatment with sirolimus is associated with no improved graft or patient outcomes but with increased adverse events.
CNI toxicity is potentiated with the combined use of SRL and CNI.

Quality of overall evidence:
Moderate

CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CNI, Calcineurin inhibitors; CsA, Cyclosporine A; CVD, Cardiovascular disease; N, Number; NODAT, New onset diabetes after transplant; QoL, Quality of life; RCT, Randomized controlled trials; SR, Systematic review; SRL, Sirolimus; Tac, Tacrolimus.

Annotations:

a. References: [10,50-60]

Supporting Table 23. Summary Table Topic 2.5: CNI avoidance in sirolimus-based regimens (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
At 1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (399)	401 (401)	No Tac (SRL)	Tac[a]	MMF 2 g, Ster, Daclizumab	46	64	2002-04	3%	3%	NS	good
At 2 y	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	0%	3%	NS	good
>1 y	Larson, 2006,[51] US	<3 y	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	6%	9%	NS	fair
At 1 y											2%	4%	NS	fair
1 y	Buchler, 2007,[52] (SPIESSER), France	12 mo	71 (71)	74 (74)	SRL	CsA	MMF 2 g/d, Ster, ATG	45	100	2002-03	3%	3%	NS	fair
Graft loss														
At 1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	8%	4%	<0.01	good
At 2 y	Hamdy, 2005,[50]Egypt	2 y	65 (65)	67 (67)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	5%	9%	NS	good
At 1 y	Larson, 2006,[51] US	<3 y	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	6%	8%	NS	fair
At 12 mo	Buchler, 2007[52] (SPIESSER), France	12 mo	71 (71)	74 (74)	SRL	CsA	MMF 2 g/d, Ster, ATG	45	100	2002-03	10%	7%	NS	fair
Death-censored at 12 mo											7%	4%	NS	fair
Cancer														
Any cancer	Ekberg, 2007,[10] EU, Canada	12 mo	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	2%	2%	NS	good
PTLD											0.3%	0%	NS	good
PTLD	Larson, 2006,[51] US	12 mo mean 33 mo	80 (80)	82 (82)	SRL	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	3%	1%	NS	fair
Patients. with any non–skin cancer	Campistol, 2006, Mota 2004, Johnson 2001,[53-55] EU, Canada, Australia	5 y	215 (215)	215 (215)	No CsA-ME	CsA-ME	SRL, Ster	45	89	1998-99	4%	8%	<0.01	good
Any skin cancer											7%	9%	NS	good
BCC											5%	7%	NS	good
SCC											3%	3%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Skin cancer, mean annualized rate (events/1000 pts per y)											35.8	107.7	<0.01	good
No. of BCC, mean annualized rate (events/1000 pts. per y)											18.2	49.0	<0.01	good
No. of SCC, mean annualized rate (events/1000 pts. per y)											14.87	41.20	<0.01	good
Time to skin cancer											1126 d	491 d	<0.01	good
Time to BCC											1126 d	275 d	<0.01	good
Time to SCC											896 d	641 d	NS	good
Time to any skin cancer											775 d	668 d	NS	good
Acute rejection														
Any at 2 y	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	14%	19%	NS	good
Any at 1 y	Larson, 2006,[51] US	<3 y	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	19%	14%	NS	fair
Clinical rejection episodes at 1 y											10	8	NS	fair
Subclinical rejection episodes at 1 y											6	6	NS	fair
Any at 1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	44%	17%	<0.01	fair
Biopsy-proven at 1 y											37%	12%	<0.01	fair
Biopsy-proven at 6 mo											35%	11%	<0.01	fair
Chronic allograft nephropathy and Proteinuria														
% with proteinuria ≥1 g	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	30%	14%	0.03	good
% with proteinuria	Ekberg, 2007,[10] EU, Canada	12 mo	399 (399)	401 (401)	Tac-low dose	SRL-low dose	MMF 2 g, Ster, Daclizumab	46	64	2002-04	5%	5%	nd	fair
NODAT														
1 y	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	19%	28%	NS	good
1 y	Ekberg, 2007,[10] EU, Canada	12 mo	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	8%	11%	0.02	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
1 y	Larson, 2006,[51] US	1 y mean 33 mo	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	8%	10%	NS	poor
1 y[c]	Buchler, 2007[52] (SPIESSER), France	12 mo	71 (71)	74 (74)	SRL	CsA	MMF 2 g/d, Ster, ATG	45	100	2002-03	13%	4%	0.07	poor
Infection														
UTI	Ekberg, 2007,[10] EU, Canada	1 y	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	23%	24%	nd	good
CMV											7%	10%	<0.01	fair
UTI 1 y	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	34%	22%	0.01	fair
CMV 1 y	Larson, 2006,[51] US	<3 y	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	3%	12%	0.02	poor
CMV	Buchler, 2007[52] (SPIESSER), France	12 mo	71 (71)	74 (74)	SRL	CsA	MMF 2 g/d, Ster, ATG	45	100	2002-03	6%	23%	0.004	fair
QOL														
KTQ	Russ, 2007[56] EU, Australia, Canada	3 y	163 (~214)	151 (~214)	CsA w/dal at 3 mo	CsA	SRL, Ster	45	88	≥1998	Physical symptoms	Favors Neither	NS (treatment x time = NS)	poor
											Fatigue	Favors CsA w/dal	NS (treatment x time = 0.0005)	
											Uncertainty-fear	Favors Neither	NS (treatment x time = NS)	
											Appearance	Favors CsA w/dal	0.03 (treatment x time = 0.006)	
											Emotions	Favors CsA w/dal	0.03 (treatment x time = 0.03)	

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
SF-36											Physical functioning	Favors Neither	NS (treatment x time = NS)	poor
											Role-physical	Favors CsA w/dal	NS (treatment x time = 0.049)	
											Bodily pain	Favors Neither	NS (treatment x time = NS)	
											General health	Favors CsA w/dal	NS (treatment x time = 0.01)	
											Vitality	Favors CsA w/dal	NS (treatment x time = 0.0001)	
											Social functioning	Favors CsA w/dal	NS (treatment x time = 0.02)	
											Role-emotional	Favors Neither	NS (treatment x time = NS)	
											Mental health	Favors Neither	NS (treatment x time = NS)	
Delayed graft function														
2 y	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	0%	2%	NS	good
1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	21%	36%	<0.01	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Lipids														
% with hypercholesterolemia	Ekberg, 2007,[10] EU, Canada	12 mo	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	12%	13%	nd	fair
% with hyperlipidemia at 1 y	Hamdy, 2005,[50] Egypt	24 mo	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	79%	58%	0.01	fair
% on lipid therapy at 1 y	Larson, 2006,[51] US	12 mo mean 33 mo	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	78%	36%	<0.01	poor
Hypertension														
% with HTN	Ekberg, 2007,[10] EU, Canada	12 mo	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	10%	5%	nd	fair
% on one or more anti-HTN meds	Larson, 2006,[51] US	12 mo mean 33 mo	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	79%	66%	NS	poor
Adverse events														
Anemia, % mild/moderate/severe 1 y	Campistol 2006, Mota 2004, Friend 2007 [53,54,57] EU, Canada, Australia	5 y	163 (215)	184 (215)	SRL+Ster	CsA+SRL+ Ster	nd	45	89	1998-99	4.0/13/80 (4.7/12/81)	19/11/20 (18/16/17)	NS	fair
Anemia, % mild/moderate/severe 2 y											4.0/13/80 (4.7/12/81)	16/10/8.5 (20/13/17)	<0.01[d]	fair
Diarrhea 1 y	Hamdy, 2005,[50] Egypt	24 mo	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[b], Ster, Basiliximab	32	0	2001-03	6%	18%	0.03	fair
Drug withdrawal 2° AE	Buchler, 2007[52] (SPIESSER), France	12 mo	71 (71)	74 (74)	SRL	CsA	MMF 2 g/d, Ster, ATG	45	100	2002-03	16%	7%	NS	fair
Diarrhea 1 y											25%	5%	0.01	fair
Discontinuation of drug 1 y	Larson, 2006,[51] US	12 mo mean 33 mo	80 (80)	82 (82)	SRL	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	38%	16%	nd	poor

2°, Secondary; AE, Adverse events; ATG, Antithymocyte globulin; BCC, Basal cell carcinoma; CMV, Cytomegalovirus; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; EU, Europe; GFR, Glomerular filtration rate; HTN, Hypertension; KTQ, Kidney Transplant Questionnaire; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; PTLD, Posttransplant lymphoproliferative disease; QOL, Quality of life; SCC, Squamous cell carcinoma; SF-36, 36-item Medical outcomes Study Short Form Health Survey; SRL, Sirolimus; Ster, Steroids; Tac, Tacrolimus; Thymo, Thymoglobulin; US, United States; UTI, Urinary tract infection; vs, Versus; w/dal, Withdrawal.

Annotations:

a. Low-dose tacrolimus was used for maintenance.
b. Dose was slightly different between groups with regard to target trough level.
c. Not explicitly stated to be new onset after transplant.
d. Consistent statistically significant difference favoring CsA withdrawal in mild, moderate, and severe anemia rates at 3, 4, and 5 years.

Supporting Table 24. Summary Table Topic 2.5: CNI avoidance in sirolimus-based regimens (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Chronic allograft nephropathy														
CADI score 1 y	Campistol 2006, Mota 2004,[53,54] EU, Canada, Australia	5 y	215 (215)	215 (215)	No CsA-ME	CsA-ME	SRL, Ster	45	89	1998-99	1.23 (1.27)	+2.22 (2.29)	NS	poor
CADI score 3 y											1.23 (1.27)	+2.36 (3.12)	NS	poor
CADI score	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[a], Ster Basiliximab	32	0	2001-03	nd	2.69 (2.41)	NS	good
Kidney function														
CrCl, mL/min 1 y	Hamdy, 2005,[50] Egypt	24 mo	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[a], Ster Basiliximab	32	0	2001-03	nd	93 (89)	NS	good
CrCl, mL/min 2 y											nd	95 (80)	<0.01	good
S_{cr} μmol/L 1 y											nd	104.3 (110.5)	NS	good
GFR, mL/min 3 y	Campistol 2006, Mota 2004,[53,54] EU, Canada, Australia	5 y	215 (215)	215 (215)	No CsA-ME	CsA-ME	SRL, Ster	45	89	1998-99	56 (57)	+3 (–10)	<0.01	fair
eGFR, mL/min	Ekberg, 2007,[10] EU, Can	12 mo	399 (399)	401 (401)	No Tac (SRL)	Tac	MMF 2 g, Ster, Daclizumab	46	64	2002-04	nd	56.7 (65.4)	<0.01	good
GFR (measured), mL/min[3]											nd	64.4 (69.6)	0.04	fair
GFR, mL/min 1 y	Larson, 2006,[51] US	12 mo mean 33 mo	70 (80)	79 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001–04	62 (56)	-7 (0)	NS	poor
eGFR (ITT), mL/min	Buchler, 2007[52] (SPIESSER), France	12 mo	71	74	SRL	CsA	MMF 2 g/d, Ster, ATG	45	100	2002-03	nd	60 (57)	NS	fair
eGFR (completers), mL/min											nd	69 (60)	0.01	fair
$S_{cr,}$ μmol/L 1 y	Hamdy, 2005,[50] Egypt	2 y	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[a], Ster Basiliximab	32	0	2001-03	nd	104.3 (10.5)	NS	good
$S_{cr,}$ μmol/L 2 y											nd	110.5 (126.3)	0.02	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Lipids														
Total cholesterol mmol/L 1 y	Hamdy, 2005,[50] Egypt	24 mo	67 (67)	65 (65)	No Tac (MMF 2 g)	Tac	SRL[a], Ster Basiliximab	32	0	2001-03	4.16 (4.14)	+1.01 (+1.5)	0.04	good
Total cholesterol mmol/L 1 y	Larson, 2006,[51] US	12 mo mean 33 mo	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	4.63 (4.73)	+0.78 (+0.44)	0.02	fair
Total cholesterol, mmol/L	Buchler, 2007,[52] (SPIESSER), France	12 mo	71	74	SRL	CsA	MMF 2 g/d, Steroids, ATG	45	100	2002-03	nd	5.7 (5.1)	0.3	fair
Triglycerides, mmol/L											nd	2.3 (1.7)	NS	fair
HDL, mmol/L											nd	1.4 (1.4)	NS	fair
LDL, mmol/L											nd	3.3 (3.0)	NS	fair
Hypertension														
1 y	Larson, 2006,[51] US	12 mo mean 33 mo	80 (80)	82 (82)	No Tac (SRL)	Tac	MMF 1.5 g, Ster, Thymo	49	17	2001-04	137/74 (130/73)	+0/-3 (+5/+3)	NS	fair

ATG, Antithymocyte globulin; CADI, Chronic allograft damage index; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; eGFR, Estimated glomerular filtration rate; EU, Europe; GFR, Glomerular filtration rate; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; SRL, Sirolimus; Ster, Steroids; Tac, Tacrolimus; Thymo, Thymoglobulin; US, United States.

Annotations:

a. References: [10,50-57]

Supporting Table 25. Summary Table Topic 2 (Rationale): MMF vs. EC-MPS (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
12 mo	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	1%	2%	NS	good
12 mo	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	1%	2%	NS	good
Graft loss														
12 mo	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	2%	3%	NS	good
12 mo	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	0.6%	nd	nd	poor
Chronic allograft nephropathy														
Chronic rejection, Biopsy-proven	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	3%	6%	NS	good
Chronic rejection, Biopsy-proven	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	4%	5%	NS	good
Cancer														
12 mo	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	2%	2%	NS	good
Lymphoma											1%	1%	NS	good
Lymphoma	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	1%	nd	nd	poor
Acute rejection														
Biopsy-proven	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	23%	24%	NS	good
Severity of AR, Banff III											2%	10%	NS	good
Total	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	1%	4%	NS	good
Biopsy-proven											1%	3%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Infection														
All	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	70%	72%	NS	fair
CMV											22%	21%	NS	good
All	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	59%	59%	NS	fair
CMV											2%	2%	NS	good
Delayed graft function														
12 mo	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	18%	17%	NS	good
Adverse events														
GI disorders	Salvadori, 2003,[61] US, Canada, EU[a]	12 mo	213 (213)	210 (210)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ Steroids/ ±Induction	47	83	<2002	81%	80%	NS	good
Leukopenia											1%	3%	NS	good
GI disorders 3 mo/12 mo	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	26% 30%	21% 25%	NS	good
Neutropenia 3 mo											1%	3%	NS	good

AE, Adverse events; AR, Acute rejection; CMV, Cytomegalovirus; CsA-ME, Cyclosporine microemulsion; EC-MPS, Enteric-coated mycophenolate sodium; EU, Europe; GI, Gastrointestinal; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; US, United States.

Annotations:

a. Salvadori, 2003 [61]: primary immunosuppressive regimen; Budde 2003[62]: change in immunosuppressive regimen in stable patients.

Supporting Table 26. Summary Table Topic 2 (Rationale): MMF vs. EC-MPS (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
S_{cr}, µmol/L	Budde, 2003,[62] US, Canada, EU[a]	12 mo	159 (159)	163 (163)	EC-MPS 1.44 g	MMF 2 g	CsA-ME/ ±Steroids	48	nd	<2002	141 (138)	–2 (0)	NS	good

CsA-ME, Cyclosporine microemulsion; EC-MPS, Enteric-coated mycophenolate sodium; EU, Europe; MMF, Mycophenolate mofetil; NS, Not significant; S_{Cr}, Serum creatinine; US, United States

Annotations:

a. Salvadori, 2003[61]: primary immunosuppressive regimen; Budde 2003[62]: change in immunosuppressive regimen in stable patients

Supporting Table 27. Evidence Profile Topic 3.1: CsA low dose vs. CsA standard dose[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	4 RCTs (High)	1584 (799)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1)	Low	No difference between CsA low dose vs. CsA standard dose	Critical
Graft loss	3 RCTs (High)	1473 (746)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1)	Low	No difference between CsA low dose vs. CsA standard dose	Critical
CVD events	0 RCTs								Critical
Cancer	3 RCTs (High)	1256 (635)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA low dose vs. CsA standard dose	Critical
Acute rejection	4 RCTs (High)	1584 (799)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA low dose vs. CsA standard dose	High
CAN	1 RCT (High)	111 (53)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA low dose vs. CsA standard dose	High
NODAT	1 RCT (High)	789 (399)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA low dose vs. CsA standard dose	High
Infection (disease)	4 RCTs (High)	1584 (799)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA low dose vs. CsA standard dose	High
Delayed graft function	3 RCTs (High)	1473 (746)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA low dose vs. CsA standard dose	Moderate
Kidney function	4 RCTs (High)	1584 (799)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	Kidney function is better in the CsA low dose than CsA standard dose in 2 of 3 trials and statistically significantly better in 2 trials.	Moderate
Proteinuria	1 RCT (High)	789 (399)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA low dose vs. CsA standard dose	Moderate
Lipids	2 RCTs (High)	1145 (582)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA low dose vs. CsA standard dose	Moderate
Blood pressure	2 RCTs (High)	1145 (582)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA low dose vs. CsA standard dose	Moderate

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Adverse events	1 RCT (High)	328 (164)						There is no evidence for differences in adverse event profiles between CsA low dose vs. CsA standard dose	Depends on outcome
Balance of potential benefits and harm: No net benefit or harm							Quality of overall evidence: Low		

CAN, Chronic allograft nephropathy; CsA, Cyclosporine A; CVD, Cardiovascular disease; N, Number; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials.

Annotations:

a. References: [10,11,63,64]

Supporting Table 28. Summary Table Topic 3.1: CsA low dose vs. CsA standard dose (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	2%	4%	NS	good
3 y	Nashan, 2004,[63] US, EU	36 mo	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	3%	9%	nd	fair
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	2%	3%	NS	fair
1 y	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	0%	1%	NS	poor
Graft loss														
Graft loss, censored death w/ functioning graft	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	6%	8%	NS	good
Censored for patient death	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	3%	5%	NS	fair
Graft loss 1 y	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	2%	1%	NS	poor
Cancer														
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	3%	1%	NS	fair
Cancer over 3 y	Nashan, 2004,[63] US, EU	3 y	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	5%	4%	nd	fair
PTLD	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	0%	0%	NS	good
Acute rejection (all)														
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	30%	35%	NS	fair
1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	30%	33%	NS	fair
AB treated											5%	6%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
1 y	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	24%	15%	NS	poor
Severity of AR, Banff I+II 1 y											24%	15%	NS	poor
Acute rejection (Biopsy-proven)														
1 y	Ekberg, 2007,[11] EU US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	25%	28%	NS	fair
6 mo											24%	26%	NS	fair
6 mo	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	22%	24%	NS	fair
1 y											24%	26%	NS	fair
At 6 mo	Nashan, 2004,[63] US, EU	3 y	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	3%	15%	NS	fair
At 1 y											7%	17%	NS	fair
At 3 y											12%	19%	NS	fair
Chronic allograft nephropathy														
Biopsy-proven CAN	Nashan, 2004,[63] US, EU	3 y	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	12%	21%	NS	fair
NODAT														
NODAT	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	5%	6%	NS	fair
Infection														
Any over 36 mo	Nashan, 2004,[63] US, EU	3 y	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	85%	87%	nd	fair
CMV											0%	1.9%	nd	fair
PCP											0%	2%	nd	fair
CMV	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	3%	4%	nd	fair
UTI											4%	4%	nd	fair
CMV	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	12%	15%	NS	fair
UTI											24%	28%	nd	good
All 1 y	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	77%	71%	NS	poor
UTI 1 y											32%	12%	<0.01	poor
Delayed graft function														
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	20%	23%	NS	fair
1 y	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	32%	34%	NS	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
2 y	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab/ EC-MPS/ Steroids	48	45	<2006	11%	13%	NS	poor
Kidney function														
S_{cr}, µmol/L	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	141	132	nd	poor
Proteinuria														
Proteinuria	Ekberg, 2007,[10] EU Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	2%	2%	nd	fair
Hypertension														
No requirement of antihypertensive therapy	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	83%	82%	NS	fair
Hypertension	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	12%	14%	NS	fair
Lipids														
Lipid-lowering meds	Ekberg, 2007,[11] EU, US, Australia	1 y	183 (183)	173 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	50%	48%	NS	fair
Hypercholesterol-emia	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	10%	10%	nd	fair
Adverse events														
Anemia 12 mo	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	30%	31%	NS	poor
Leucopenia 12 mo											21%	15%	NS	poor
Hirsutism 12 mo											11%	15%	NS	poor
Nausea 12 mo											40%	59%	<0.05	poor
Diarrhea 12 mo											32%	35%	NS	poor
Composite endpoints														
BPAR, graft loss, death or loss to follow-up 6 mo,	Nashan, 2004,[63] US, EU	3 y	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	3%	15%	0.046	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
BPAR, graft loss, death or loss to follow-up 1 y.											9%	28%	0.021	fair
BPAR, graft loss, death or loss to follow-up 3 y											17%	36%	0.032	fair
Graft loss, death or loss to follow-up 6 mo											2%	2%	nd	fair
Graft loss, death or loss to follow-up 1 y											2%	8%	nd	fair
Graft loss, death or loss to follow-up 3 y											7%	17%	nd	fair
Nonfatal serious AE over 3 y											78%	85%	nd	fair
Coprimary efficacy failure , composite endpoint of death, graft loss and loss to follow-up											7%	19%	NS	fair

AE, Adverse events; AR, Acute rejection; BPAR, Biopsy-proven acute rejection; CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; EC-MPS, Enteric-coated mycophenolate sodium; EU, Europe; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; PCP, Pneumoystis pneumonia; S_{Cr}, Serum creatinine; US, United States; UTI, Urinary tract infection

Annotations:

a. Ekberg, 2007,[10] Europe, Canada the *P*-value was calculated from relative risks.

Supporting Table 29. Summary Table Topic 3.1: CsA low dose vs. CsA standard dose (continuous outcomes)

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
GFR, mL/min	Ekberg, 2007,[11] EU, US, Australia	12 mo	138 (183)	119 (173)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	48	75	2001-02	49.0 (45.4)	+1.9 (+3.2)	NS	poor
CrCl, mL/min 6 mo	Nashan, 2004,[63] US, EU	36 mo	53 (53)	58 (58)	Low dose CsA	Full dose CsA	Basiliximab/ Everolimus/ Steroids	46	77	nd	42 (54)	+17.7 (-2.9)	0.009	fair
CrCl, mL/min 12 mo											42 (54)	+17.1 (–0.5)	0.007	fair
CrCl, mL/min											42 (54)	+14.6 (+2.3)	NS	fair
eGFR, mL/min	Ekberg, 2007,[10] EU, Canada	1 y	399 (413)	390 (410)	Low dose CsA (Daclizumab)	Standard dose CsA	MMF/Steroid	47	64	2002-04	nd	Final 59.4 (57.1)	nd	good
GFR, mL/min											nd	Final 65.3 (63.5)	nd	fair
CrCl, mL/min 12 mo	Cibrik, 2007,[64] Finland	24 mo	66 (total 164)	75 (total 164)	CsA-ME high C2	CsA-ME low C2	Basiliximab /EC-MPS/ Steroids	48	45	<2006	71.0 (79.2)	+6.6 (+9.6)	<0.05	poor
CrCl, mL/min, 24 mo											71.5 (79.4)	+7.1 (+ 9.8)	nd	poor

CrCl, Creatinine clearance; CsA, Cyclosporine; EC-MPS, Enteric-coated mycophenolate sodium; EU, Europe; GFR, Glomerular filtration rate; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; US, United States

Supporting Table 30. Evidence Profile Topic 3.2: CNI withdrawal in the setting of antimetabolite regimens vs. CNI continuation[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	8 RCTs (High)	1891 (1001)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for this outcome (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance with antimetabolite continuation compared to CsA/CsA-ME continuation	Critical
Graft loss	8 RCTs (High)	1891 (1001)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA or CsA-ME withdrawal or avoidance with antimetabolite continuation compared to CsA/CsA-ME continuation	Critical
CVD events	3 RCTs (High)	440 (220)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance with antimetabolite continuation compared to CsA/CsA-ME continuation	Critical
Cancer	5 RCTs (High)	1242 (682)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA or CsA-ME withdrawal or avoidance with antimetabolite continuation compared to CsA/CsA-ME continuation	Critical
Acute rejection	6 RCTs (High)	1547 (839)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	An increased rate of acute rejection in CsA/CsA-ME withdrawn with antimetabolite continuation trials compared to CsA/CsA-ME continuation trials	High
CAN	2 RCTs (High)	433 (217)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	High
Skin cancer	1 RCT (High)	128 (60)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	High
NODAT	2 RCTs (High)	592 (358)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	High
Infection (disease)	5 RCTs (High)	1330 (724)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	High
Delayed graft function	1 RCT (High)	352 (179)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	Moderate
Kidney function	7 RCTs (High)	1456 (784)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Improved kidney function in trials of CsA/CsA-ME withdrawn with antimetabolite continuation compared to CsA/CsA-ME continuation trials	Moderate

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Proteinuria	1 RCT (High)	123 (57)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	Moderate
Lipids	5 RCTs (High)	632 (306)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for this outcome (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	Moderate
Blood pressure	2 RCTs (High)	386 (187)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA or CsA-ME withdrawal or avoidance compared with continuation	Moderate
Adverse events	1 RCT (High)	325 (163)						No difference in drug toxicity between CsA or CsA-ME withdrawal or avoidance compared with continuation at <1 year	Depends on outcome
Balance of potential benefits and harm: Net harm Despite a higher incidence of acute rejections associated with complete CNI withdrawal, kidney function is better. However, there is no improvement in CAN or long-term graft survival							Quality of overall evidence: Moderate		

CAN, Chronic allograft nephropathy; CNI, Calcineurin inhibitors; CsA, Cyclosporine A; CsA-ME, Cyclosporine A microemulsion; CVD, Cardiovascular disease; N, Number; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials
Annotations:
a. References: [11,65-74]

Supporting Table 31. Summary Table Topic 3.2: CNI withdrawal in the setting of antimetabolite regimens vs. CNI continuation (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
15 y	Gallagher 2004, Hall 1988,[65,66] Australia	10-15 y	163 (165)	162 (166)	CsA withdrawn (AZA, steroid)	CsA mono	None	43	100	1983-86	49%	44%	NS	good
9 mo	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85 (85)	85 (85)	CsA-ME withdrawn	CsA-ME continued	MMF/Steroids	45	93	<2001	1%	0%	nd	good
5y			74 (85)	77 (85)							7%	5%	NS	fair
1 y	Hazzan, 2005, 2006 [69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	<2004	0%	0%	NS	good
2 y											0%	0%	NS	good
10 y	MacPhee, 1998,[71] Scotland	Median <8 y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	21%	23%	NS	fair
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	5%	3%	NS	fair
10 y	Bakker, 2003,[72] Netherlands	15 y	60 (60)	68 (68)	CsA withdrawn (AZA)	CsA continued	No Induction/ Steroid	44	nd	1983	27%	28%	NS	fair
15 y											45%	43%	NS	fair
CV mortality											23%	21%	NS	fair
5 y	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	No CsA (AZA)	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	25%	29%	NS	fair
10 y											40%	42%	NS	fair
20 y											65%	60%	NS	fair
1 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	2%	2%	NS	fair
5 y											10%	10%	NS	fair
12 y											17%	25%	NS	fair
Graft loss														
9 mo	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	74 (85)	77 (85)	CsA-ME withdrawn	CsA-ME continued	MMF/Steroids	45	93	<2001	0%	0%	nd	good
5 y			85 (85)	85 (85)							12 %	8 %	nd	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
1 y	Hazzan, 2005, 2006,[69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	<2004	0%	0%	NS	good
2 y											7%	2%	NS	good
15 y	Gallagher 2004, Hall 1988,[65,66] Australia	10 y (up to 15 y)	163 (165)	162 (166)	CsA withdrawn (AZA, steroid)	CsA mono	None	43	100	1983-86	41%	56%	NS (p=0.06)	good
10 y	MacPhee, 1998,[71] Scotland	Median <8 y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	62%	58%	NS	fair
Censored for patient death	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	7%	5%	NS	fair
Graft failure, censored for death with a functioning graft 10 y: ITT Analysis	Bakker, 2003,[72] Netherlands	15 y	60 (60)	68 (68)	CsA withdrawn (AZA)	CsA continued	No induction Steroid	44	nd	1983	15%	25%	NS	fair
Graft failure, censored for death with a functioning graft: ITT Analysis											24%	35%	NS	fair
5 y	Gheith, 2007 [73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	31%	42%	nd	fair
10 y											48%	64%	nd	fair
20 y											74%	76%	NS	fair
1 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	11%	9%	NS	fair
5 y											25%	18%	NS	fair
12 y											44%	41%	NS	fair
CVD														
Median <8 y	MacPhee, 1998,[71] Scotland	Median <8y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	21%	17%	NS	fair
15 y	Bakker, 2003,[72] Netherlands	15 y	60 (60)	68 (68)	CsA withdrawn (AZA)	CsA continued	No Induction Steroid	44	nd	1983	36%	42%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
12 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	12%	14%	NS	fair
Cancer														
Skin cancer	Bakker, 2003,[72] Netherlands	15 y	60 (60)	68 (68)	CsA withdrawn (AZA)	CsA continued	No Induction Steroid	44	nd	1983	16%	15%	NS	fair
Other cancers											18%	10%	NS	fair
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	2%	1%	nd	fair
5 y	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85/74 (85)	85/77 (85)	CsA-ME withdrawn	CsA-ME continued	MMF/Steroids	45	93	nd (<2001)	7%	5%	nd	fair/good
20 y	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	5%	6%	NS	fair
12 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	12%	14%	NS	fair
Acute rejection (all)														
1 y	Hazzan, 2005, 2006 [69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	<2004	19%	6%	<0.05	good
2 y											22%	6%	0.04	good
C4d positivity 1 y											24%	6%	0.007	good
9 mo	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85 (85)	85 (85)	CsA-ME withdrawn	CsA-ME continued	MMF/Steroids	45	93	<2001	2%	11%	nd	good
5 y			74 (85)	77 (85)							1%	16%	<0.01	fair
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	44%	35%	NS	fair
1 y	Gallagher 2004, Hall 1988,[65,66] Australia	10 y (up to 15 y)	163 (165)	162 (166)	CsA withdrawn (AZA, steroid)	CsA mono	None	43	100	1983-86	69%	67%	NS	poor
10 y											33%	24%	<0.01	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Number of episodes	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	23%	37%	<0.001	fair
12 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	56%	52%	NS	fair
Acute rejection (biopsy-proven)														
10 y	MacPhee, 1998,[71] Scotland	Median <8 y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	16%	15%	NS	fair
6 mo	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	25%	26%	NS	fair
1 y											38%	28%	0.04	fair
Time to AR, days post Txp (1 y)	Hazzan, 2005, 2006,[69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	<2004	173 d	149 d	nd	good
Time to AR	MacPhee, 1998,[71] Scotland	Median <8 y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	4 mo (2-22 mo)	7 mo (2-46 mo)	<0.001	fair
Chronic allograft nephropathy														
Proteinuria, >300 mg 1 y	Hazzan, 2005, 2006,[69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	<2004	11%	4%	NS	good
Proteinuria, >300 mg											13%	13%	NS	good
Number of chronic rejection based on numbers of episodes 12 mo	Gallagher 2004, Hall 1988,[65,66] Australia	10 y (up to 15 y)	163 (165)	162 (166)	CsA withdrawn (AZA, steroid)	CsA mono	None	43	100	1983-86	5%	3%	nd	poor
Number of chronic rejection based on numbers of episodes 10 y											36%	34%	nd	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
NODAT														
20 y	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	17%	19%	NS	fair
12 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	3%	4%	NS	fair
Infection														
9 mo	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85 (85)	85 (85)	CsA-ME withdrawn	CsA-ME continued	MMF/Steroids	45	93	<2001	13%	9%	nd	good
Any requiring hospitalization	MacPhee, 1998,[71] Scotland	Median <8 y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	31%	37%	NS	fair
CMV	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	8%	4%	nd	fair
UTI											5%	4%	nd	fair
Bacterial	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	10%	10%	NS	fair
Severe infections requiring hospitalization	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-1989	19%	21%	NS	fair
Delayed graft function														
1 y	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	17%	23%	nd	fair
GFR/Creatinine														
S_{cr} >1.5 µmol/L at 1 y	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	11%	12%	NS	fair
S_{cr} >1.5 µmol/L at last follow-up											41%	58%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Proteinuria														
% with proteinuria ≥1 g/d 1 y	Bakker, 2003,[72] Netherlands	15 y	57 (60)	66 (68)	CsA withdrawn (AZA)	CsA continued	No Induction Steroid	44	nd	1983	14%	11%	NS	fair
% with proteinuria ≥1 g/d 5 y			46 (60)	49 (68)							17%	14%	NS	fair
% with proteinuria ≥1 g/d 10 y			38 (60)	37 (68)							21%	11%	NS	fair
% with proteinuria ≥1 g/d			17 (60)	16 (68)							12%	6%	NS	fair
Lipids														
Lipid-lowering therapy 10/15 y	Bakker, 2003,[72] Netherlands	15 y	60 (60)	68 (68)	CsA withdrawn (AZA)	CsA continued	No Induction Steroid	44	nd	1983	32%	57%	NS	fair
Lipid-lowering therapy 10/15 y											41%	56%	NS	fair
Lipid-lowering meds	Ekberg, 2007,[11] EU, US, Australia	1 y	179 (179)	173 (173)	CsA withdrawn (Daclizumab)	Standard dose CsA	MMF/Steroids	47	74	2001-02	50%	48%	NS	fair
Blood pressure														
No requirement of antihypertensive therapy 1 y	MacPhee, 1998,[71] Scotland	Median <8 y	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	43%	21%	<0.005	fair
No requirement of antihypertensive therapy 1 y											46%	22 %	<0.005	fair
Post-txp hypertension	Gheith, 2007,[73] Egypt	20 y	300 (300)	175 (175)	AZA	CsA	Steroid Antibody induction for high risk patients	33	0 (haploid living KTx)	1983-88	69%	75%	0.02	fair
HTN prevalence	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	70%	74%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant mediation	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Adverse events														
Number of drug toxicity based on numbers of episodes 12 mo/10 y	Gallagher 2004, Hall 1988,[65,66] Australia	10 y (up to 15 y)	163 (165)	162 (166)	CsA withdrawn (AZA, steroid)	CsA mono	None	43	100	1983-86	15% 7%	16% 17%	nd	poor

ALG, Antilymphocyte globulin; AR, Acute rejection; ATG, Antithymocyte globulin, AZA, Azathioprine; CMV, Cytomegalovirus; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; CV, Cardiovascular; CVD, Cardiovascular disease; EU, Europe; HTN, Hypertension; ITT, Intention to treat; KTx, Kidney transplant; MMF, Mycophenolate mofetil; mo, Month; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; S_{Cr}, Serum creatinine; Txp, Transplant; US, United States; UTI, Urinary tract infection.

Supporting Table 32. Summary Table Topic 3.2: CNI withdrawal in the setting of antimetabolite regimens vs. CNI continuation (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (control)	Δ (control)		
Kidney function														
S_{cr}, µmol/L 1 y	MacPhee, 1998,[71] Scotland	Median 93 mo	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	122 (126)	–9 (+3)	<0.05	fair
S_{cr}, µmol/L 7 y			40 (102)	40 (114)							122 (126)	-1 (+25)	<0.05	fair
S_{cr}, µmol/L 1 y	Hazzan, 2005, 2006,[69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	nd (<2004)	114.9 (114.9)	+8.8 (+26.5)	NS	good
eGFR, mL/min 1 y/2 y											nd	Final 49 (46)	<0.05	good
eGFR, mL/min 1 y/2 y											nd	Final 40 (38)	<0.05	good
Measured GFR	Ekberg, 2007,[11] EU, US, Australia	12 mo	128 (179)	119 (173)	CsA withdrawal	Standard dose CsA	MMF Steroids	47	74	2001-02	49.6 (45.4)	+1.3 (+3.2)	NS	poor
CrCl, mL/min 9 mo	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85 (85)	85 (85)	CsA-ME withdrawn	CsA-ME continued	MMF Steroids	45	93	nd (<2001)	nd	Net change 4.5	NS	fair
CrCl, mL/min			74 (85)	77 (85)							nd	Net change 5	0.05	fair
S_{cr}, µmol/L 9 mo			85 (85)	85 (85)							136 (132)	–1 (–2)	NS	good
S_{cr}, µmol/L			74 (85)	77 (85)							136 (132)	–1 (+4)	NS	good
GFR, mL/min 1 y	Bakker, 2003,[72] Netherlands	15 y	57 (60)	66 (68)	CsA withdrawn (AZA)	CsA continued	No Induction Steroid	44	nd	1983	53.5 (56.5)	72.9 (55.7)	<0.05 all times	fair
GFR, mL/min 5 y			46 (60)	50 (68)							53.5 (56.5)	71.0 (56.3)	<0.05 all times	fair
GFR, mL/min 10 y			38 (60)	37 (68)							53.5 (56.5)	71.7 (52.8)	<0.05 all times	fair
GFR, mL/min			17 (60)	15 (68)							53.5 (56.5)	71.7 (56.3)	<0.05 all times	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (control)	Δ (control)		
S_{cr}, µmol/L 12 y	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	nd		NS	poor
CrCl, mL/min											nd		NS	poor
Blood pressure														
Blood pressure 1 y	MacPhee, 1998,[71] Scotland	Median 93 mo	102 (102)	114 (114)	CsA withdrawn (AZA)	CsA	Steroids	41	88	1985-91	135/85 (135/85)	+2/–1 (+3/-1)	NS	fair
Blood pressure 7 y											135/85 (135/85)	–3/–3 (–3/+2)	NS	fair
Blood pressure, SBP/DBP 9 mo/5 y	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85/74 (85)	85/77 (85)	CsA-ME withdrawn	CsA-ME	MMF Steroids	47	91	nd (<2001)	nd	Final 137/ 80 (133/78)	NS	fair
Lipid levels														
Cholesterol total 9 mo	Abramowicz, 2002, 2005,[67,68] EU, South America	5 y	85 (85)	85 (85)	CsA-ME withdrawn	CsA-ME continued	MMF Steroids	45	93	nd (<2001)	nd	nd	0.02	fair
Cholesterol total, mmol/L			74 (85)	77 (85)							nd	Final 5.23 (5.38)	NS	good
Chronic allograft damage index (CADI) 1 y	Hazzan, 2005, 2006,[69,70] France	2 y	54 (54)	54 (54)	CsA-ME withdrawn (MMF)	CsA-ME	Steroids/ATG	44	100	<2004)	3.3	3.5	NS	good
Total Cholesterol, mmol/L 1 y	Bakker, 2003,[72] Netherlands	15 y	49 (60)	60 (68)	CsA withdrawn (AZA)	CsA continued	No Induction Steroid	44	nd	1983	6.70 (6.59)	7.19 (7.29)	NS	fair
Total Cholesterol, mmol/L 5 y			44 (60)	46 (68)							6.70 (6.59)	6.80 (7.01)	NS	fair
Total Cholesterol, mmol/L 10 y			38 (60)	37 (68)							6.70 (6.59)	6.10 (7.45)	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (control)	Δ (control)		
Total Cholesterol, mmol/L 15 y			17 (60)	14 (68)							6.70 (6.59)	5.69 (5.40)	NS	fair
Serum cholesterol, mmol/L	Grimbert, 2002,[74] France	12 y	58 (58)	59 (59)	No CsA	CsA	ALG for induction AZA Steroid	40	nd	1986-89	nd	Final 4.8 (5.4)	NS	poor
Triglyceride levels, mmol/L											nd	Final 1.4 (1.8)	NS	poor

ALG, Antilymphocyte globulin; ATG, Antithymocyte globulin, AZA, Azathioprine; CrCl, Creatinine clearance; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; eGFR, Estimated glomerular filtration rate; EU, Europe; GFR, Glomerular filtration rate; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; Txp, Transplant; US, United States

Supporting Table 33. Evidence Profile Topic 3.3: Steroid withdrawal vs. steroid maintenance in CNI/MMF based regimens[a,b,c]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Description of effect	Importance of outcome
Graft loss	1 SR (6 RCTs) (High)	1519	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Not adequately powered for the outcome (–1)	Low	No difference between steroid withdrawal and steroid maintenance for up to 24 months	Critical
Acute rejection	1 SR (6 RCTs) (High)	1519	No limitations (0)	Important inconsistencies (–1)	Some uncertainty (–1)	None (0)	Low	The incidence of acute rejection is higher in patients withdrawn from steroids compared to patients maintained on steroids.	High
Kidney function	1 SR (6 RCTs) (High)	1519	No limitations (0)	Important inconsistencies (–1)	Some uncertainty (–1)	None (0)	Low	No difference between steroid withdrawal and steroid maintenance for up to 24 months	Moderate
Lipids	1 SR (4 RCTs) (High)	1361	No limitations (0)	No inconsistencies (0)	Some uncertainty (–1)	None (0)	Moderate	Total cholesterol levels are lower in patients withdrawn from steroids compared to patients maintained on steroids.	Moderate
Blood pressure	1 SR (4 RCTs) (High)	1361	No limitations (0)	Important inconsistencies (–1)	Some uncertainty (–1)	None (0)	Low	There is no clear evidence that blood pressure is lower in patients withdrawn from steroids compared to patients maintained on steroids.	Moderate
Adverse events	1 SR (1 RCT)	500	No limitations (0)	N/A	Some uncertainty (–1)	Sparse data (–1)	Low	Steroid withdrawal is beneficial for BMD. No difference in glucose metabolism	
Balance of potential benefits and harm: Net harm Steroid withdrawal in CNI/MMF based regimens is associated with a higher incidence of acute rejections, no significant impact on graft survival. Insufficient evidence on steroid-related adverse effects.							Quality of overall evidence: Low[a]		

BMD, Bone mineral density; CNI, Calcineurin inhibitors; MMF, Mycophenolate mofetil; N, Number; N/A, Not applicable, RCT, Randomized controlled trials; SR, Systematic review; vs, versus.

Annotations:

a. Evidence based on trials comparing steroid withdrawal vs. steroid maintenance only in CNI/MMF-based regimens

b. Reference: [75]

c. This evidence profile is based solely on existing systematic reviews. A de novo systematic review was not conducted.

Supporting Table 34. Evidence Profile Topic 5.1.1: CsA C_2 vs. C_0 [a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 RCT (High)	154 (74)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data, not adequately powered for the outcome (–1)	Very low	No significant difference between CsA C_2 vs. C_0	Critical
Graft loss	2 RCTs (High)	358 (183)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data, not adequately powered for the outcome (–1)	Low	No significant difference between CsA C_2 vs. C_0	Critical
CVD events	0 RCTs								Critical
Cancer	0 RCTs								Critical
Acute rejection	2 RCTs (High)	358 (183)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (limited number of studies) (–1)	Low	No significant difference between CsA C_2 vs. C_0	High
CAN	2 RCTs (High)	240 (109+?)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (limited number of studies) (–1)	Very low	No significant difference between CsA C_2 vs. C_0	High
NODAT	1 RCT (High)	154 (74)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very low	No significant difference between CsA C_2 vs. C_0	High
Infection (disease)	2 RCTs (High)	358 (183)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Low	No significant difference between CsA C_2 vs. C_0	High
Delayed graft function	1 RCT (High)	154 (74)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very low	No significant difference between CsA C_2 vs. C_0	Moderate
Kidney function	2 RCTs (High)	358 (183)	No limitations (0)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Low	No significant difference between CsA C_2 vs. C_0	Moderate
Adverse events	2 RCTs (High)	358 (183)						CsA C_2 might cause more tremor than C_0 monitoring.	Depends on outcome

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Balance of potential benefits and harm: Uncertain								Quality of overall evidence: Very low	

C_0, 12-hour trough; C_2, 2 hour post-dose; CsA, Cyclosporine A; N, Number; RCT, Randomized controlled trials.
Annotations:
a. References: [76,77]

Supporting Table 35. Summary Table Topic 5.1.1: CsA C_2 vs. C_0 (categorical outcomes)[a]

Outcome	Study, year, country	Study duration	No. analyzed (enrolled) Intervention/Control Arm 1	No. analyzed (enrolled) Intervention/Control Arm 2	Intervention/Control Arm 1	Intervention/Control Arm 2	Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results Arm 1	Results Arm 2	*P* value	Quality
Mortality														
12 mo	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	5%	3 %	NS	fair
Graft loss														
12 wk	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	7%	6%	NS	good
12 mo	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	5%	8%	NS	fair
Censored for death											3%	5%	NS	fair
Acute rejection														
12 wk	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	27%	28%	NS	good
Severity of AR, Banff II or higher											14%	29%	NS	good
12 mo	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	11%	8%	NS	fair
Severity of AR, Banff II or higher											0%	3%	nd	fair
Time to AR, days											32	28	NS	fair
Chronic allograft nephropathy and proteinuria														
CsA toxicity or CAN (Bx-proven)	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	9%	5%	NS	good
CsA toxicity	Kyllönen, 2006,[76] Finland	12 mo	36 (160)		CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	0%	0%	NS	poor
NODAT														
12 mo	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	4%	8%	NS	poor
Infection														
12 wk	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	43%	44%	NS	good
CMV											20%	17%	NS	good
Fungal											4%	3%	NS	good
12 mo	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	24%	20%	NS	fair
Delayed graft function														
12 mo	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	31%	31%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Kidney function														
S_{cr} deterioration (increase >30% above baseline)	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	58%	54%	NS	good
Adverse events														
Serious AE (urinary, vascular, hematological)	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	34%	21%	NS	good
Tremor	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	12%	3%	<0.05	fair

AE, Adverse events; AR, Acute rejection; AUC, Area under the curve; CAN, Chronic allograft nephropathy; CMV, Cytomegalovirus; CsA, Cyclosporine; CsA-ME, Cyclosporine microemulsion; EU, Europe; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; S_{Cr}, Serum creatinine.

Annotations:

a. Keown, 2002,[77] for the International Neoral Renal Transplantation Study Group.

Supporting Table 36. Summary Table Topic 5.1.1: C_2 vs. C_0 (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled) Arm 1	No. analyzed (enrolled) Arm 2	Intervention/Control Arm 1	Intervention/Control Arm 2	Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results Baseline (Control)	Results Δ (Control)	*P* value	Quality
Kidney function														
S_{cr}, µmol/L	Keown, 2002,[77] EU, Canada, Argentina[a]	12 wk	109 (109)	95 (95)	CsA-ME AUC (C_0+C_2±C_3)	CsA-ME trough (C_0)	Steroids/ Basiliximab	46	88	<2001	458 (482)	-290 (-315)	NS	good
S_{cr}, µmol/L	Kyllönen, 2006,[76] Finland	12 mo	74 (80)	80 (80)	CsA-ME (C_2)	CsA-ME trough (C_0)	MMF/Steroids	51	100	2001-04	151 (129)	–45 (–29)	nd	fair
CrCl, mL/min											68 (69)	+11 (+10)	nd	fair

AUC, Area under the curve; CrCl, Creatinine clearance; CsA-ME, Cyclosporine microemulsion; EU, Europe; L, Liter; µmol, Micromole; min, Minute; mL, Milliliters; MMF, Mycophenolate mofetil; mo, Month; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; vs, Versus; wk, Week

Annotations:

a. Keown, 2002,[77] for the International Neoral Renal Transplantation Study Group.

Supporting Table 37. Summary Table Topic 5.2: MPA monitoring (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
Mortality																				
12 mo	Le Meur, 2007,[78] France[a]	12 mo	—	65 (65)	—	65 (65)	—	MMF-AUC (40)[b]	—	MMF-fixed (2 g)	CsA/ Steroids/ IL2-AB	49	nd	2003-04	—	2%	—	2%	nd	good
6 mo	Hale, 1998,[79] Netherlands, Belgium[a]	6 mo	51 (51)	47 (47)	52 (52)	—	MMF low AUC (16.1)[b]	MMF med. AUC (32.2)[b]	MMF high AUC (60.6)[b]	—	CsA/ Steroids	48	100	<2001	total group: 1%			—	nd	poor
12 mo	van Gelder, 2008,[80] International	12 mo	—	449 (449)	—	452 (452)	—	MMF AUC (45)[d]	—	MMF fixed (2 g)[d]	CsA or Tac/ Steroids/ Induction	45	74	2003-06	—	3%	—	3%	NS	fair
Graft loss																				
12 mo	Le Meur, 2007,[78] France[a]	12 mo	—	65 (65)	—	65 (65)	—	MMF-AUC (40)[b]	—	MMF-fixed (2 g)	CsA/ Steroids/ IL2-AB	49	nd	2003-04	—	2%	—	0%	nd	good
6 mo	Hale, 1998,[79] Netherlands, Belgium[a]	6 mo	51 (51)	47 (47)	52 (52)	—	MMF low AUC (16.1)[b]	MMF med. AUC (32.2)[b]	MMF high AUC (60.6)[b]	—	CsA/ Steroids	48	100	<2001	4%	2%	2%	—	nd	good
12 mo	van Gelder, 2008,[80] International	12 mo	—	449 (449)	—	452 (452)	—	MMF AUC (45)[d]	—	MMF fixed (2 g)[d]	CsA or Tac/ Steroids/ Induction	45	74	2003-06	—	4%	—	6%	NS	fair
Cancer																				
12 mo	van Gelder, 2008,[80] International	12 mo	—	449 (449)	—	452 (452)	—	MMF AUC (45)[d]	—	MMF fixed (2 g)[d]	CsA or Tac / Steroids / Induction	45	74	2003-06	—	1%	—	2%	NS	fair
Acute rejection																				
Total	Le Meur, 2007,[78] France[a]	12 mo	—	65 (65)	—	65 (65)	—	MMF-AUC (40)[b]	—	MMF-fixed (2 g)	CsA/ Steroids/ IL2-AB	49	nd	2003-04	—	12%	—	31%	0.01	good
Biopsy-proven															—	8%	—	25%	0.01	good
Severity of AR, Banff II or higher															—	3%	—	11%	nd	good
Total	Hale, 1998,[79] Netherlands, Belgium[a]	6 mo	51 (51)	47 (47)	52 (52)	—	MMF low AUC (16.1)[b]	MMF med. AUC (32.2)[b]	MMF high AUC (60.6)[b]	—	CsA/ Steroids	48	100	<2001	31%	17%	13%	—	nd	good
Biopsy-proven															25%	9%	6%	—	nd	good

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)				Intervention/Control				Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results				*P* value	Quality
			Arm 1	Arm 2	Arm 3	Arm 4	Arm 1	Arm 2	Arm 3	Arm 4					Arm 1	Arm 2	Arm 3	Arm 4		
Biopsy-proven	van Gelder, 2008,[80] International	12 mo	—	449 (449)	—	452 (452)	—	MMF AUC (45)[d]	—	MMF fixed (2 g)[d]	CsA or Tac/ Steroids/ Induction	45	74	2003-06	—	15%	—	16%	NS	fair
Mild/Moderate/Severe															—	8/6/1%	—	10/5/0.2%	NS (0.06)	fair
Infections																				
CMV (viremia)	Le Meur, 2007,[78] France[a]	12 mo	—	65 (65)	—	65 (65)	—	MMF-AUC (40)[b]	—	MMF-fixed (2 g)	CsA/ Steroids/ IL2-AB	49	nd	2003-04	—	17%	—	25%	nd	good
CMV (tissue invasive)															—	8%	—	6%	nd	good
Opportunistic infection (at least 1)	van Gelder, 2008,[80] International	12 mo	—	449 (449)	—	452 (452)	—	MMF AUC (45) [d]	—	MMF fixed (2 g)[d]	CsA or Tac/ Steroids/ Induction	45	74	2003-06	—	29%	—	26%	NS	poor[4]
Kidney function																				
S_{cr}, µmol/L	Le Meur, 2007,[78] France[a]	12 mo	—	65 (65)	—	65 (65)	—	MMF-AUC (40)[b]	—	MMF-fixed (2 g)	CsA/ Steroids/ IL2-AB	49	nd	2003-04	—	137	—	150	NS	good
Adverse events																				
GI disorders	Le Meur, 2007,[78] France[a]	12 mo	—	65 (65)	—	65 (65)	—	MMF-AUC (40)[b]	—	MMF-fixed (2 g)	CsA/ Steroids/ IL2-AB	49	nd	2003-04	—	25%	—	20%	nd	good
Leukopenia															—	40%	—	34%	nd	good
Anemia															—	66%	—	61%	nd	good
Proteinuria, mg/d															—	190	—	233	nd	good
Withdrawal due to AE[c]	Hale, 1998,[79] Netherlands, Belgium[a]	6 mo	51 (51)	47 (47)	52 (52)	—	MMF low AUC (16.1)[b]	MMF med. AUC (32.2)[b]	MMF high AUC (60.6)[b]	—	CsA/ Steroids	48	100	<2001	6%	17%	38%	—	nd	fair
Anemia	van Gelder, 2008,[80] International	12 mo	—	449 (449)	—	452 (452)	—	MMF AUC (45)[d]	—	MMF fixed (2 g)[d]	CsA or Tac/ Steroids/ Induction	45	74	2003-06	—	15%	—	14%	NS	fair
Diarrhea															—	25%	—	25%	NS	fair
Leucopenia															—	18%	—	14%	NS	fair
Thrombocytopenia															—	5%	—	6%	NS	fair
Weight loss															—	2%	—	2%	NS	fair

AE, Adverse events; AR, Acute rejection; AUC, Area under the curve; CMV, Cytomegalovirus; CsA, Cyclosporine; GI, Gastrointestinal; IL2-AB, Interleukin-2 antibody; MMF, Mycophenolate mofetil; mo, Month; MPA, Mycophenolate acid; nd, Not documented; NS, Not significant; S_{cr}, Serum creatinine; Tac, Tacrolimus

Annotations:

a. Le Meur, 2007 [78]: MMF AUC versus MMF fixed dose; Hale, 1998 [79]: 3 different MMF-AUC targets.

b. MMF-AUC: numbers in parentheses describe target AUC in µg x h/mL..

c. AE vaguely reported: diarrhea, nausea, leucopenia, CMV, UTI, abdominal pain: "not significantly different".

d. The trial failed to achieve separation of groups (AUC in MMF fixed dose and MMF AUC were similar); the trial failed to achieve the target AUC of 45 mg h/L especially in the early post KTx period.

Supporting Table 38. Evidence Profile Topic 6.3.2 OKT3 vs. other antibody for acute rejection[a,b]

Outcome	No. of studies and study design	Total N	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 SR (3 RCTs) (High)	175	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	No difference between treatment of acute rejection with an OKT3 and other antibodies	Critical
Graft loss	1 SR (3 RCTs) (High)	136	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	No difference between treatment of acute rejection with an OKT3 and other antibodies	Critical
Failure of acute rejection reversal	1 SR (3 RCTs) (High)	136	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None, but some studies with small sample size (0)	Moderate	No difference between treatment of acute rejection with an OKT3 and other antibodies	High
Infection	1 SR (3 RCTs) (High)	175	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between treatment of acute rejection with an OKT3 and other antibodies	High
Kidney function	1 SR (3 RCTs) (High)	120	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between treatment of acute rejection with an OKT3 and other antibodies	Moderate
Fever, chills, malaise following drug administration	1 SR (2 RCTs) (High)	81	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between treatment of acute rejection with an OKT3 and other antibodies	Moderate
			Balance of potential benefits and harm: Uncertain					Quality of overall evidence: Low	

OKT3, Muromonab (anti-T cell antibody); N, Number; RCT, Randomized controlled trials; SR, Systematic review.

Annotations:

a. Reference: [81]

b. This evidence profile is based solely on existing systematic reviews. A de novo systematic review was not conducted.

Supporting Table 39. Evidence Profile Topic 6.4: Antibody (OKT3, ATG, ALG) vs. steroid alone for acute rejection[a,b]

Outcome	No. of studies and study design	Total N	Methodological quality of studies per outcome[1]	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 SR (6 RCTs) (High)	318	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	There is no evidence that treatment of acute rejection with an antibody is causing more deaths than treatment with steroids alone.	Critical
Graft loss	1 SR (7 RCTs) (High)	380	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered for the outcome (–1)	Low	Treatment of acute rejection with an antibody is associated with less graft loss than treatment with steroids alone.	Critical
Failure of acute rejection reversal	1 SR (6 RCTs) (High)	334	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None, but some studies with small sample size (0)	Moderate	Treatment with an antibody is better than with steroids alone for treatment of acute rejection.	High
Infection	1 SR (4 RCTs) (High)	206	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	There is no evidence that treatment of acute rejection with an antibody is causing more infections than treatment with steroids alone. Data on CMV are very limited due to small sample size.	High
Fever, chills, malaise following drug administration	1 SR (3 RCTs) (High)	185	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None, but some studies with small sample size (0)	Moderate	Treatment of acute rejection with an antibody is associated with more adverse events than treatment with steroids alone.	Moderate
			Balance of potential benefits and harm: No net benefit or harm					Quality of overall evidence: Low	

ALG, Antilymphocyte globulin ; ATG, Antithymocyte globulin; CMV, Cytomegalovirus; OKT3, Muromonab (anti-T cell antibody);N, Number; RCT, Randomized controlled trials; SR, Systematic review

a. Reference: [81]

b. This evidence profile is based solely on existing systematic reviews. A de novo systematic review was not conducted.

Supporting Table 40. Summary Table Topic 6.5: Change in immunosuppression in the setting of acute rejection (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		P value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
3 y	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	4%	3%	NS	poor
12 mo	MMF Refractory Rejection Group, 1996,[84] US, Canada[b]	12 mo	77 (77)	73 (77)	MMF 3 g	IV–Steroids	CsA/Steroids	39	nd	<1996	3%	1%	NS	poor
Graft loss														
Censored for death	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	6%	12%	NS	poor
12 mo	MMF Refractory Rejection Group, 1996,[84]US, Canada[b]	12 mo	77 (77)	73 (77)	MMF 3 g	IV–Steroids	CsA/Steroids	39	nd	<1996	12%	25%	nd	poor
21 d	Böhmig, 2007,[85] Austria[c]	21 d	5 (5)	5 (5)	Immuno-adsorption (Protein A)	No Immuno-adsorption	Switch to Tac/ MMF Steroids	62/30 (median)	nd	2001-05	0%	80%	<0.05	fair
Cancer														
3 y	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	14%	10%	nd	poor
PTLD											3%	3%	NS	poor
12 mo	MMF Refractory Rejection Group, 1996,[84] US, Canada[b]	12 mo	77 (77)	73 (77)	MMF 3 g	IV–Steroids	CsA/Steroids	39	nd	<1996	4%	1%	NS	poor
PTLD											3%	0%	NS	poor
Acute rejection														
Subsequent AR, total	MMF Rejection Group, 2001,[82,83]US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	39%	66%	nd	poor
Subsequent AR, biopsy-proven, censored for death, graft loss, premature withdrawal											42%	69%	Δ27% (13-40) 95% CI	poor
Antibody –											17%	42%	<0.001	poor

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		P value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
therapy 12 mo														
Subsequent AR, total	MMF Refractory Rejection Group, 1996,[84] US, Canada[b]	12 mo	77 (77)	73 (77)	MMF 3 g	IV-Steroids	CsA/Steroids	39	nd	<1996	17%	27%	nd	poor
Subsequent AR, biopsy-proven											27%	41%	nd	poor
Antibody–therapy											10%	25%	nd	poor
Chronic allograft nephropathy														
Chronic renal allograft dysfunction	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	8%	6%	nd	poor
Infection														
CMV	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	37%	26%	nd	poor
PCP											1%	1%	NS	poor
CMV	MMF Refractory Rejection Group, 1996,[84] US, Canada[b]	12 mo	77 (77)	73 (77)	MMF 3 g	IV–Steroids	CsA/Steroids	39	nd	<1996	14%	15%	NS	poor
PCP											0%	1%	NS	poor
CMV	Böhmig, 2007,[85] Austria[c]	21 d	5 (5)	5 (5)	Immuno-adsorption (Protein A)	No Immuno-adsorption	Switch to Tac/ MMF Steroids	62/30 (median)	nd	2001-05	40%	nd	nd	poor
Kidney function														
CrCl, mL/min	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	73	69	nd	poor
S_{cr}, µmol/L, 6 mo	MMF Refractory Rejection Group, 1996,[84] US, Canada[b]	12 mo	77 (77)	73 (77)	MMF 3 g	IV–Steroids	CsA/Steroids	39	nd	<1996	182	218	NS	poor
Adverse events														
Diarrhea	MMF Rejection Group, 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	50%	39%	nd	poor
Anemia											47%	41%	nd	poor
Leucopenia											39%	37%	nd	poor

AE, Adverse events; AR, Acute rejection; AZA, Azathioprine; CMV, Cytomegalovirus; CrCl, Creatinine clearance; CsA, Cyclosporine; IV, Intravenous; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; PCP, Pneumoystis pneumonia; PTLD, Posttransplant lymphoproliferative disease; S_{Cr}, Serum creatinine; Tac, Tacrolimus; US, United States

Annotations:

a. MMF Rejection Group, 2001[82,83]: treatment of patients with biopsy-proven acute rejection, between day 7 and month 6 after transplantation
b. MMF Refractory Rejection Group, 1996[84]: treatment of patients with biopsy-proven acute rejection, that did NOT respond to treatment with OKT3, ATG or ALG over 7 days or recurred within 7 days.
c. Böhmig, 2007[85]: treatment of patients with acute humoral, C4d positive acute rejection; concomitantly all pts. were switched to Tacrolimus and received treatment for cellular rejection according to Banff histology results (IV Steroids and/or ATG); trial prematurely stopped because of high efficacy in the treatment group.

Supporting Table 41. Summary Table Topic 6.5: Change in immunosuppression in the setting of acute rejection (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medication	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
S_{cr}; µmol/L, 12 mo	MMF Rejection Group 2001,[82,83] US, Canada[a]	3 y	113 (113)	108 (108)	MMF 3 g	AZA	CsA/Steroids	44	nd	1991-94	269 (254)	–125 (–108)	<0.05	poor

AZA, Azathioprine; CsA, Cyclosporine; MMF, Mycophenolate mofetil; nd, Not documented; S_{Cr}, Serum creatinine; US, United States.

Annotations:

a. MMF Rejection Group, 2001[82,83]: treatment of patients with Biopsy-proven acute rejection, between day 7 and month 6 after transplantation.

b. MMF Refractory Rejection Group, 1996[84]: treatment of patients with Biopsy-proven acute rejection, that did NOT respond to treatment with OKT3, ATG or ALG over 7 days or recurred within 7 days.

c. Böhmig, 2007[85]: treatment of patients with acute humoral, C4d positive acute rejection; concomitantly all pts. were switched to Tacrolimus and received treatment for cellular rejection according to Banff histology results (IV Steroids and/or ATG); trial prematurely stopped because of high efficacy in the treatment group.

Supporting Table 42. Evidence Profile Topic 7.2: CsA withdrawal in the setting of biopsy-proven CAN[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCTs (High)	329 (199)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Not adequately powered (–1)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	Critical
Graft loss	2 RCTs (High)	329 (199)	Some limitations (–1)	No important inconsistency (0)	No uncertainty (0)	Data available up to 2 years (–1)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	Critical
CVD events	1 RCT (High)	186 (126)	Some limitations (–1)	No important inconsistency (0)	No uncertainty (0)	Sparse data (–1)	Low	Higher rates of incident CVD events with CsA continuation in biopsy-proven CAN compared to the withdrawn arm	Critical
Cancer	0 RCTs								Critical
Acute rejection	1 RCT (High)	186 (126)	Some limitations (–1)	No important inconsistency (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	High
NODAT	1 RCT (High)	186 (126)	Some limitations (–1)	No important inconsistency (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	High
Infection (disease)	2 RCTs (High)	329 (199)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	High
Kidney function	2 RCTs (High)	329 (199)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Kidney function is better in the CsA withdrawal compared with CsA continuation in biopsy-proven CAN.	Moderate
Lipids	2 RCTs (High)	329 (199)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	None (0)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	Moderate
Blood pressure	1 RCT (High)	186 (126)	Some limitations (–1)	No important inconsistency (0)	No uncertainty (0)	Sparse data (–1)	Low	No difference between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	Moderate
Adverse events	1 RCT (High)	186 (126)						No difference in drug discontinuation rates between CsA withdrawal vs. CsA continuation in biopsy-proven CAN	Depends on outcome
Balance of potential benefits and harm: Uncertain							Quality of overall evidence: Low		

CAN, Chronic allograft nephropathy; CsA, Cyclosporine A; CVD, Cardiovascular disease; N, Number; NODAT, New onset diabetes after transplant; RCT, Randomized controlled trials

Annotations:

a. References: [86,87]

Supporting Table 43. Summary Table Topic 7.2: CsA withdrawal in the setting of biopsy-proven CAN (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant Medications	Age* (Mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
12 mo	Dudley, 2005,[86] EU, US, South America	12 mo	73 (73)	70 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	4%	0%	nd	fair
5 y	Shihab, 2008,[88] US	5 y	126 (126)	60 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	18%	22%	NS	fair
Graft loss														
Graft survival including death with functioning graft	Dudley, 2005,[86] EU, US, South America	12 mo	73 (73)	70 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	93%	94%	nd	fair
5 y	Shihab, 2008,[88] US	5 y	126 (126)	60 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	55%	57%	NS	fair
CVD events														
Incident events	Shihab, 2008,[88] US	5 y	123 (126)	58 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	11%	28%	0.004	fair
Acute rejection														
Biopsy-proven	Shihab, 2008,[88] US	5 y	126 (126)	60 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	9%	8%	NS	fair
Kidney function														
Patients with improved kidney function 6 mo	Dudley, 2005,[86] EU, US, South America	12 mo	73 (73)	70 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	49%	26%	0.006	fair
Patients with improved kidney function			62 (73)	60 (70)							48%	35%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant Medications	Age* (Mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Infection														
UTI	Dudley, 2005,[86] EU, US, South America	12 mo	73 (73)	70 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	14%	7%	nd	fair
12 mo											22%	7%	nd	fair
5 y	Shihab, 2008,[88] US	5 y	110 (126)	50 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	22%	26%	NS	fair
NODAT														
5 y	Shihab, 2008,[88] US	5 y	87 (126)	43 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	13%	14%	NS	poor
Adverse events														
Discontinued treatment	Shihab, 2008,[88] US	5 y	126 (126)	60 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	9%	8%	NS	fair

AZA, Azathioprine; CAN, Chronic allograft nephropathy; CsA, Cyclosporine; CVD, Cardiovascular disease; EU, Europe; MMF, Mycophenolate mofetil; nd, Not documented; NODAT, New onset diabetes after transplantation; NS, Not significant; Tac, Tacrolimus; US, United States; UTI, Urinary tract infection.

Supporting Table 44. Summary Table Topic 7.2: CsA withdrawal in the setting of biopsy-proven CAN (continuous outcomes)[a]

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medications	Age (Mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
CrCl, mL/min 6 mo	Dudley, 2005,[86] EU, US, South America	12 mo	61 (73)	55 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	37 (37)	+4.5 (–0.9)	0.01	poor
CrCl, mL/min			53 (73)	50 (70)							37 (37)	+5.0 (–0.7)	0.01	poor
CrCl, mL/min mean	Shihab, 2008,[88] US	5 y	43 (126)	19 (60)	Tac	CsA	MMF Steroids	45	66	1998-2000	34 (34)	+1.3 (-5.5)	nd	poor
CrCl, mL/min median											nd	+1.2 (-4.1)	0.02	
S_{cr}, µmol/L mean											224 (220)	-15 (+42)	nd	poor
S_{cr}, µmol/L median											nd	-18 (+35)	0.004	
Lipids														
Serum cholesterol, mmol/L 6 mo	Dudley, 2005,[86] EU, US, South America	12 mo	47 (73)	49 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	6.02 (6.02)	–0.66 (0.08)	0.05	poor
Serum cholesterol, mmol/L			40 (73)	41 (70)							6.02 (6.02)	–0.85 (-0.28)	0.01	poor
Serum triglycerides, mmol/L 6 mo			46 (73)	48 (70)							2.18 (2.18)	–0.2 (–0.23)	NS	poor
Serum triglycerides, mmol/L			40 (73)	39 (70)							2.18 (2.18)	–0.33 (–0.12)	NS	poor
Total cholesterol, mmol/L	Waid, 2005,[87] US[a]	2 y	62 (126)	24 (60)	Tac	CsA	MMF Steroids	45	nd	1998-2000	5.59 (5.72)	+1.29 (+0.49)	0.004	fair
HDL cholesterol, mmol/L			55 (126)	19 (60)							1.2 (1.1)	+0.1 (–0.1)	NS	fair
LDL cholesterol, mmol/L			52 (126)	19 (60)							3.18 (3.39)	+1.03 (+0.49)	0.008	fair

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		Concomitant medications	Age (Mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Triglycerides, mmol/L			60 (126)	23 (60)							2.42 (2.34)	+0.68 (–0.15)	NS	fair
Hypertension														
SBP, mm Hg 6 mo	Dudley, 2005,[86] EU, US, South America	12 mo	60 (73)	54 (70)	MMF	CsA	Steroids (AZA for CsA group)	43	77	nd	146.2 (146.2)	–8.1 (–1.7)	NS	poor
SBP, mm Hg			52 (73)	50 (70)							146.2 (146.2)	–6.1 (–0.9)	NS	poor
DBP, mm Hg 6 mo			60 (73)	54 (70)							86.0 (86.0)	–3.5 (–0.2)	NS	poor
DBP, mm Hg			60 (73)	54 (70)							86.0 (86.0)	–3.0 (–1.6)	NS	poor

AZA, Azathioprine; CrCl, Creatinine clearance; CsA, Cyclosporine; DBP, Diastolic blood pressure; EU, Europe; HDL, High density lipoprotein; LDL, Low-density lipoprotein; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; SBP, Systolic blood pressure; S_{Cr}, Serum creatinine; Tac, Tacrolimus; US, United States.

a. The reported 2-year results from the same study as Shihab 2008.

Supporting Table 45. Evidence Profile Topic 9 (Rationale): Protocol biopsy[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCTs	281 (141)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very Low	No difference between the groups	Critical
Graft loss	2 RCTs	281 (141)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very Low	No difference between the groups	Critical
CAN	1 RCT	72 (36)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very Low	Protocol biopsy is better than no protocol biopsy in identifying CsA nephropathy	High
Acute rejection	4 RCTs	454 (229)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	None (0)	Low	No difference between the groups	High
Cancer (others)	1 RCT	61 (30)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very Low	Higher rates of cancers reported in the no protocol group	High
CV events	1 RCT	61 (30)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very Low	Higher rates of CV events reported in the protocol group	High
Kidney function	4 RCT	454 (229)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	None (0)	Low	Kidney function was better in the protocol group in 3 small trials. There was no difference between the groups in 1 moderate sample size trial	Moderate
Infection	1 RCT	103 (52)	Some limitations (–1)	No important inconsistencies (0)	Some uncertainty (–1)	Sparse data (–1)	Very Low	No difference between the groups	Moderate
Balance of potential benefits and harm: Net benefit Benefit of protocol biopsies for patients treated with a combination of CsA and AZA (questionably without induction)							Quality of overall evidence: Very Low		

AZA, Azathioprine; CAN, Chronic allograft nephropathy; CsA, Cyclosporine A; CV, Cardiovascular; N, Number; RCT, Randomized controlled trials

Annotations:

a. References: [89-92].

Supporting Table 46. Summary Table Topic 9 (Rationale): Protocol biopsy (categorical outcomes)

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		IS regimen	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
Mortality														
6 mo	Rush, 2007,[92] Canada, US	6 mo	111 (111)	107 (107)	Biopsy	Control	Tac/MMF/ Steroids	48	nd	2001-04	<1%	0%	nd	fair
36 mo	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	3%	0%	nd	poor
Graft loss														
6 mo	Rush, 2007,[92] Canada, US	6 mo	111 (111)	107 (107)	Biopsy	Control	Tac/MMF/ Steroids	48	nd	2001-04	1%	2%	nd	fair
36 mo	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	3%	3%	nd	poor
CAN														
CSA nephropathy	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	43%	nd	nd	poor
Acute rejection														
6 mo	Rush, 2007,[92] Canada, US	6 mo	111 (111)	107 (107)	Biopsy	Control	Tac/MMF/ Steroids	48	nd	2001-04	9%	7%	NS	fair
Subclinical rejection											9%	6%	NS	fair
Subclinical rejection 6 mo	Rush, 1998,[91] Canada	24 mo	36 (36)	36 (36)	Protocol biopsies 1,2,3,6,12 mo	Biopsy at 6 and 12 mo	CsA/AZA/ Steroids	41	86	1992-95	15%	32%	NS	fair
Incidence of clinical rejection 2-3 mo											41%	69%	0.02	fair
Incidence of clinical rejection 4-6 mo											28%	33%	NS	fair
Incidence of clinical rejection 7-12 mo											11%	33%	0.03	fair

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		IS regimen	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Arm 1	Arm 2		
1 mo	Kurtkoti, 2007,[90] India	12 mo	52 (52)	51 (51)	Protocol biopsy	No biopsy	CsA or Tac/MMF or AZA/ Steroids	31	0	2004-05	6%	4%	nd	fair
36 mo	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	63%	0%	nd	poor
DGF														
6 mo	Rush, 2007,[92] Canada, US	6 mo	111 (111)	107 (107)	Biopsy	Control	Tac/MMF/ Steroids	48	nd	2001-04	15.3%	16.8%	NS	fair
Cancer														
Neoplasia	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	3%	14%	nd	poor
Other outcomes														
CV events	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	13%	3%	nd	poor
Clinical outcome events											Fewer in the steroid withdrawal or CsA reduction (.06)		nd	poor
Infection	Kurtkoti, 2007,[90] India	12 mo	52 (52)	51 (51)	Protocol biopsy	No biopsy	CsA or Tac/MMF or AZA/ Steroids	31	0	2004-05	10%	12%	nd	fair

CAN, Chronic allograft nephropathy; CsA, Cyclosporine; CV, Cardiovascular; DGF, Delayed graft function; IS, Immunosuppression; nd, Not documented; NS, Not significant; US, United States

Supporting Table 47. Summary Table Topic 9 (Rationale): Protocol biopsy (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		IS regimen	Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2					Baseline (Control)	Δ (Control)		
Kidney function														
GFR, mL/min/1.73m^2 6 mo	Kurtkoti, 2007,[90] India	12 mo	52 (52)	51 (51)	Protocol biopsy	No biopsy	CsA or Tac/MMF or AZA/ Steroids	31	0	2004-05	70 (69)	–5 (–10)	<0.01	fair
GFR, mL/min/1.73m^2 12 mo											70 (69)	–1 (–9)	<0.01	fair
S_{cr}, µmol/L 6 mo											104.3 (105.2)	+8.8 (+31.8)	<0.01	fair
S_{cr}, µmol/L 12 mo											104.3 (105.2)	+1.8 (+29.1)	<0.01	fair
GFR, mL/min/1.73m^2	Gotti, 2003,[89] Italy	36 mo	30 (30)	31 (31)	Protocol biopsy	No biopsy	CsA/AZA/ Steroids	43	100	nd	79.3 (72.3)	–3.97 (–13.3)	nd	poor
CrCl, mL/min	Rush, 2007,[92] Canada, US	6 mo	111 (111)	107 (107)	Biopsy	Control	Tac/MMF/ Steroids	48	nd	2001-04	nd	Final 72.9 (68.9)	NS	fair
S_{cr}, µmol/L											nd	Final 119.9 (124.1)	NS	fair
Sum of chronic score (ci + ct) ≤2											nd	Final 1.17 (0.79)	NS	fair
S_{cr}, µmol/L 24 mo	Rush, 1998,[91] Canada	24 mo	36 (36)	36 (36)	Protocol biopsies 1,2,3,6,12 mo	Biopsy at 6 and 12 mo	CsA/AZA/ Steroids	41	86	1992-95	133 (183)	nd	0.05	fair

ci, Interstitial score; CrCl, Creatinine clearance; ct, Tubular score; GFR, Glomerular filtration rate; IS, Immunosuppression; nd, Not documented; NS, Not significant; S_{cr}, Serum creatinine; US, United States.

Supporting Table 48. Evidence Profile Topic 13.2: CMV prophylaxis[a]

Outcome	No. of studies and study design	Total N (N on Prophylaxis)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	2 RCTs (High)	217 (107)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	No difference in mortality	Critical
Graft loss	2 RCTs (High)	193 (97)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	Sparse data (–1)	Very Low	Inconsistent findings between studies of benefit of prophylaxis and of underlying rate of graft loss	Critical
Acute rejection	1 RCT (High)	69 (33)	No limitations (0)	NA	No uncertainty (0)	Sparse data (–1)	Moderate	Less than half the rate of biopsy-proven acute rejection with prophylaxis	High
Infection (disease)	2 RCTs (High)	207 (106)	Some limitations (–1)	Important inconsistencies (–1)	No uncertainty (0)	Sparse data (–1)	Very Low	Lower rate of CMV infection with ganciclovir prophylaxis, but not with valacyclovir prophylaxis	High
Infection (asymptomatic)	2 RCTs (High)	207 (106)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	Significantly lower rates of DNAemia with prophylaxis	Moderate
Delayed graft function	1 RCT (High)	69 (33)	No limitations (0)	NA	No uncertainty (0)	Sparse data (–1)	Moderate	No difference in rate of delayed graft function	Moderate
Adverse events	2 RCTs (High)	217 (107)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Low	In one study, a higher rate of leucopenia, but not neutropenia with prophylaxis. No other differences in adverse event rates.	Moderate
Balance of potential benefits and harm: Net benefits Chemoprophylaxis results in less acute rejection and CMV infection, with no clear evidence of increased adverse events							Quality of overall evidence: Low for KTR (Moderate based on additional trials in patients with solid organ transplant [b])		

CMV, Cytomegalovirus; N, Number; RCT, Randomized controlled trials.

Annotations:

a. References: [93,94]

b. Based on a Cochrane systematic review (Hodson EM, et al. Cochrane Database of Systematic Reviews). (2):CD005129, 2007} of 32 trials (high quality of overall evidence) in patients with any solid organ transplant that chemoprophylaxis significantly reduces all-cause mortality, CMV disease mortality, CMV disease, but not acute rejection or graft loss.

Supporting Table 49. Summary Table Topic 13.2: CMV prophylaxis

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Arm 1	Arm 2		
Mortality													
12 mo	Kliem, 2008,[93] Germany	12 mo	74 (74)	74 (74)	Ganciclovir 1 g 3x/d x 90 d	No prophylaxis	48	nd	2000-02	7%	5%	NS	good
12 mo	Reischig, 2008,[94] Czech Rep.	12 mo	33 (34)	36 (36)	Valacyclovir 2 g 4x/d x 3 mo	No prophylaxis	48	34	2003-06	3%	0%	NS	good
Graft outcomes													
Allograft loss beyond 100 d	Kliem, 2008,[93] Germany	4 y	64 (74)	60 (74)	Ganciclovir 1 g 3x/d x 90 d	No prophylaxis	48	nd	2000-02	8%	22%	0.04	fair
Allograft loss	Reischig, 2008,[94] Czech Rep.	12 mo	33 (34)	36 (36)	Valacyclovir 2 g 4x/d x 3 mo	No prophylaxis	48	34	2003-06	9%	3%	NS	good
Delayed graft function										27%	17%	NS	good
Acute rejection, Biopsy-proven										15%	36%	0.03	good
Infection outcomes													
CMV disease (hospitalization)	Kliem, 2008,[93] Germany	12 mo	73 (74)	65 (74)	Ganciclovir 1 g 3x/d x 90 d	No prophylaxis	48	nd	2000-02	7%	18%	0.04	fair
CMV infection (DNAemia)										18%	51%	<0.0001	good
CMV disease (symptomatic)	Reischig, 2008,[94] Czech Rep.	12 mo	33 (34)	36 (36)	Valacyclovir 2 g 4x/d x 3 mo	No prophylaxis	48	34	2003-06	9%	6%	NS	good
CMV infection (DNAemia)										59%	92%	<0.001	good
Complications													
Serious AE (including CMV-related) [Leukopenia/ Neutropenia]	Kliem, 2008,[93] Germany	12 mo	74 (74)	74 (74)	Ganciclovir 1 g 3x/d x 90 d	No prophylaxis	48	nd	2000-02	57% [15%/1%]	53% [1% / 0%]	NS [0.004/NS]	fair
Overall	Reischig, 2008,[94] Czech Rep.	12 mo	33 (34)	36 (36)	Valacyclovir 2 g 4x/d x 3 mo	No prophylaxis	48	34	2003-06	No significant differences			good

AE, Adverse events; CMV, Cytomegalovirus; nd, Not documented; NS, Not significant.

Supporting Table 50. Evidence Profile Topic 14.1.1: UTI treatment[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	1 RCT (High)	80 (41)	No limitations (0)	Important inconsistencies (–1)	No uncertainty (0)	Sparse data (–1)	Low	No difference between ciprofloxacin vs. placebo	Critical
Graft loss	2 RCTs (High)	183 (92)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference between ciprofloxacin vs. TMP-SMZ or placebo	Critical
Infection (disease)	3 RCTs (High)	315 (159)	Some limitations (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	Antibiotic (ciprofloxacin/TMP-SMZ) prophylaxis is better than no antibiotic. Pneumocystis prevented only in patients on TMP-SMZ	High
Balance of potential benefits and harm: Net benefits Antibiotic prophylaxis exceeds harm. The use of ciprofloxacin alone runs the risk of pneumocystis infection							Quality of overall evidence: Moderate		

N, Number; RCT, Randomized controlled trials; TMP-SMZ, Trimethoprim sulfamethoxazole; UTI, Urinary tract infection.

Annotations:

a. References: [95-97]

Supporting Table 51. Summary Table Topic 14.1.1: UTI Treatment

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Arm 1	Arm 2		
Mortality													
6 mo	Moyses, 1997,[95] Brazil	6 mo	28 (41)	30 (39)	Ciprofloxacin 250 mg twice daily x 10 d 250 mg single dose x 6 mo	Placebo	nd	95	1993-95	7%	8%	nd	fair
Graft outcomes													
Allograft failure	Hibberd, 1992,[95] US	9 mo	51 (51)	52 (52)	Ciprofloxacin 250 mg	TMP-SMZ single strength	44	84	1988-90	8%	2%	NS	fair
Graft loss	Moyses, 1997,[95] Brazil	6 mo	41 (41)	39 (39)	Ciprofloxacin 250 mg twice daily x 10 d 250 mg single dose x 6 mo	Placebo	nd	95	1993-95	15%	8%	nd	fair
Infection outcomes													
UTI at 6 mo	Hibberd, 1992,[95] US	9 mo	51 (51)	52 (52)	Ciprofloxacin 250 mg	TMP-SMZ single strength	44	84	1988-90	0%	8%	0.016	fair
UTI or AE at 9 mo										0%	15%	0.002	fair
PCP										14%	0%	0.006	fair
UTI	Moyses, 1997,[95] Brazil	6 mo	28 (41)	30 (39)	Ciprofloxacin 250 mg twice daily x 10 d 250 mg single dose x 6 mo	Placebo	nd	95	1993-95	15%	49%	<0.05	fair
Overall UTI N of infections	Fox, 1990,[97] US	9 mo	66 (66)	66 (66)	TMP-SMZ	Placebo	38	61	1984-1985	24	54	<0.005	good
Catheter-related UTI										15	18	NS	good
Non–catheter-related UTI										9	36	<0.005	good
PCP										0	1	NS	good

nd, Not documented; NS, Not significant; PCP, Pneumocystis pneumonia; TMP-SMZ, Trimethoprim sulfamethoxazole; US, United States; UTI, Urinary tract infection.

Supporting Table 52. Evidence Profile Topic 18.6: Skin cancer prevention with oral retinoids[a,b]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect*	Importance of outcome
Mortality	0 RCTs						None		Critical
Skin cancer	1 SR (3 RCTs) (High)	93 (74)	No limitations (0)	No important inconsistencies (0)	Some uncertainty[c] (–1)	None (0)	Moderate	Acitretin use resulted in less SCC. No significant difference in the number of SCC lesions on different doses of acitretin	High
Adverse events	1 SR (3 RCTs) (High)	93 (74)	No limitations (0)	No important inconsistencies (0)	Some uncertainty[c] (–1)	None (0)	Moderate	Chelitis, alopecia, HA, myalgia, photosensitivity, dry eyes, epistaxis all common on treatment (with resolution). Drug cessation common.	Moderate
Balance of potential benefits and harm: Tradeoffs Decrease in SCC rates on drug but QoL-related adverse events common							Quality of overall evidence: Moderate		

BCC, Basal cell carcinoma; HA, Headache; N, Number; RCT, Randomized controlled trials; SCC, Squamous cell carcinoma; SR, Systematic review.

Annotations:

a. Reference: [98]

b. This evidence profile is based solely on existing systematic reviews. A de novo systematic review was not conducted.

c. All Caucasian, average 10-15 years after transplant, each with different eligibility criteria (any; ≥10 keratotic lesions on hands/forearms; ≥3 SCC/BCC lesions in past 5 years or ≥10 keratoses at enrollment).

Supporting Table 53. Summary Table Topic 21 (Rationale): Bone outcomes on various immunosuppression regimens

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Interventions		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value (Control)	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Baseline (Control)	Δ (Control)		
Bone mineral density													
18 mo	Aroldi, 1997,[99] Italy	18 mo	27 (13)	30 (20)	CsA alone	CsA + Steroids	38	79	nd	0.966 (0.961)	+0.052 (–0.074)	0.006 (<0.001)	poor
12 mo										0.966 (0.961)	+0.024 (–0.069)	nd	poor
6 mo										0.966 (0.961)	–0.006 (–0.057)	nd	poor
18 mo			27 (13)	32 (20)		CsA + Steroids + AZA				0.966 (0.979)	+0.052 (–0.078)	0.006 (<0.001)	poor
12 mo										0.966 (0.979)	+0.024 (–0.077)	nd	poor
6 mo										0.966 (0.979)	–0.006 (–0.051)	nd	poor
ΔBMD	Farmer, 2006,[100] UK	12 mo	44 (32)	48 (34)	Steroid Withdrawal	Steroids Maintained	44	72	nd	nd	Increased (Reduced)	<0.01 for L1-L4, Femoral Neck; <0.05 for Trochanter, Total Femur	poor
BMD, %Δ Z score lumbar spine	Pelletier, 2006,[101] US[a]	12 mo	39 (39)	35 (35)	Steroid withdrawal	Steroid maintenance	45	64	1997-2002	+6.4%	+0.5%	<0.001	poor
BMD, %Δ Z score femoral neck										+3.1%	–0.3%	<0.001	poor
BMD, %Δ Z score, lumbar spine		36 mo	16 (39)	18 (35)						+7.1%	+1.3%	0.004	poor
BMD, %Δ Z score femoral neck										+1.8%	+0.7%	NS	poor
BMD, %Δ lumbar spine 3 mo	ter Meulen, 2004,[9,48] Netherlands	12 mo	135 (186)	126 (178)	Dac/Tac/ MMF	Tac/MMF/ Steroids (4 mo)	48	64	1999-2002	Δ–2.3%	Δ–1.3%	NS	fair
BMD %Δ femoral neck 3 mo										Δ–1.3%	Δ–1.4%	NS	fair

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Interventions		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value (Control)	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Baseline (Control)	Δ (Control)		
BMD %Δ lumbar spine 12 mo										Δ+0.1%	Δ+0.9%	NS	fair
BMD %Δ femoral neck 12 mo										Δ–0.9%	Δ–0.6%	NS	fair
BMD, L2	Vanrenterghem, 2000,[102] Multiple[b]	12 mo	252 (252)	248 (248)	Low/stop dose steroid	Full standard dose steroid	45	90	nd	nd	(final)100.3 (94.3)	<0.01	poor
BMD, L3										nd	(final)99.5 (94.3)	<0.01	poor
BMD, L4 and femoral neck,										nd	nd	NS	poor
Z-Scores													
Z-Score	Aroldi, 1997,[99] Italy	18 mo	27 (13)	30 (20)	CsA alone	CsA + Steroids	38	79	nd	–1.052 (–1.023)	+0.506 (–0.653)	0.044 (0.02)	poor
Z-Score						CsA + Steroids + AZA				–1.052 (–0.921)	+0.506 (–0.723)	0.044 (0.049)	C
Mean Z-Score (L1-L4)	Farmer, 2006,[100] UK	12 mo	44 (32)	48 (34)	Steroid Withdrawal	Steroids Maintained	44	72	nd	–0.35 (–0.52)	+0.05 (–0.08)	nd	B
Mean Z-Score (Total Hip)										–0.30 (–0.65)	+0.09 (0.00)	nd	B
Fractures													
Rib fractures (12 mo)	ter Meulen, 2004,[9,48] Netherlands	12 mo	135 (186)	126 (178)	Dac/Tac/ MMF	Tac/MMF/ Steroids (4 mo)	48	64	1999-2002	0.8%	1.5%	NS	B

AZA, Azathioprine; BMD, Bone mineral density; CsA, Cyclosporine; Dac, Daclizumab; L1, First lumbar vertebrae; L2, Second lumbar vertebrae; L3, Third lumbar vertebrae; L4, Fourth lumbar vertebrae; MMF, Mycophenolate mofetil; nd, Not documented; NS, Not significant; Tac, Tacrolimus; UK, United Kingdom; US, United States.

Annotations:

a. Z-scores represent percentage changes in Z scores only.

b. No baseline or change was reported; only final values were reported. Unit of measurement not documented.

Supporting Table 54. Summary Table Topic 22.2: Anemia (categorical outcomes)

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Arm 1	Arm 2		
Mortality													
12-18 mo	Linde, 2001,[103] Scandinavian countries	12-18 mo	32 (32)	24 (24)	Normal Hb	Subnormal Hb	52	94	nd	9%	12%	NS	poor
Graft outcomes													
Early kidney graft dysfunction	VanLoo, 1996,[104] Belgium	2 mo	14 (14)	15 (15)	Epoetin beta	Non EPO	47	nd	1993-94	0%	7%	NS	poor
Acute rejection										64%	60%	NS	poor
Acute rejection	Linde, 2001,[103] Scandinavian countries	12-18 mo	32 (32)	24 (24)	Normal Hb	Subnormal Hb	52	94	nd	38%	42%	NS	poor
Topic outcomes													
Correction of anemia	Moore, 1994,[105] US	6 mo	12 (12)	12 (12)	Fe fumarate 66 mg Fe	No treatment	40	76%	1991-92	100%	63%	<0.05	fair
Polycythemia										33%	0%	<0.05	fair
Anemia (Hb <125 g/L)	Van Biesen, 2005,[106] Belgium	3 mo	22 (22)	18 (18)	RhuEPO 100U/kg	Non EPO	44	nd	nd	35%		nd	poor

EPO, Erythropoietin; Fe, Iron; Hb, Hemoglobin; nd, Not documented; NS, Not significant; RhuEPO, Recombinant erythropoietin; S_{Cr} ,Serum creatinine; U, Units; US, United States.

Supporting Table 55. Summary Table Topic 22.2: Anemia (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention used Control used		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Baseline* (Control)	Δ (Control)		
Kidney outcomes													
S_{cr}, µmol/L	Moore, 1994,[105] US	6 mo	12 (12)	12 (12)	Fe fumarate 66 mg Fe	No treatment	40	76	1991-92	327 (389)	–221 (–212)	NS	fair
Topic outcomes													
Hct, L	Moore, 1994,[105] US	6 mo	12 (12)	12 (12)	Fe fumarate 66 mg Fe	No treatment	40	76	1991-92	0.27 (0.25)	+0.17 (+0.11)	<0.05	fair
EPO, mU/mL										88.2 (53.9)	–45.7 (–30.2)	NS	fair
Hb, g/L day 15	Van Biesen, 2005,[105] Belgium	3 mo	22 (22)	18 (18)	RhuEPO 100 U/kg	Non EPO	44	nd	nd	84 (92)	–2 (–7)	NS	poor
Hb, g/L 3 mo										84 (92)	+42 (+29)	NS	poor

EPO, Erythropoietin; Fe, Iron; Hb, Hemoglobin; nd, Not documented; NS, Not significant; RhuEPO, Recombinant erythropoietin S_{Cr} ,Serum creatinine; U, Units; US, United States.

Supporting Table 56. Evidence Profile Topic 22.4: Erythrocytosis treatment

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings		
							Quality of evidence for outcome	Qualitative and quantitative description of effect	Importance of outcome
Mortality	0 RCTs								Critical
Graft loss	0 RCTs								Critical
Kidney function	3 RCTs (High)	66 (39)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	Enalapril better than placebo, but: NS Enalapril vs. losartan: NS Theophylline better than fosinopril, but: NS	Moderate
Hematological outcomes	3 RCTs (High)	66 (39)	No limitations (0)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate	Enalapril better than placebo Enalapril vs. losartan: NS Fosinopril better than theophylline	Moderate
Balance of potential benefits and harm: Net benefit ACE inhibitor better than placebo or theophylline for hematocrit, kidney function unclear							Quality of overall evidence: Low		

N, Number; NS, Not significant; RCT, Randomized controlled trials.

Annotations

a. References: [107-109]

Supporting Table 57. Summary Table Topic 22.4: Erythrocytosis treatment (categorical outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Arm 1	Arm 2		
Topic outcomes													
Hb response (>10 g/L)	Yildiz, 2001,[107] Turkey	2 mo	15 (15)	12 (12)	Enalapril 10 mg	Losartan 50 mg	32	27%	<1996	80%	75%	NS	fair

Hb, Hemoglobin; NS, Not significant.

Supporting Table 58. Summary Table Topic 22.4: Erythrocytosis treatment (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Baseline (Control)	Δ (Control)		
Kidney outcomes													
S_{cr}, µmol/L	Yildiz, 2001,[107] Turkey	2 mo	15 (15)	12 (12)	Enalapril 10 mg	Losartan 50 mg	32	27	<1996	114 (121)	–5 (+5)	NS	fair
GFR, mL/min	Beckingham 1995,[108] England, UK	4 mo	15 (15)	10 (10)	Enalapril 2.5 mg/day	Placebo	nd	nd	nd	59.0 (65.1)	–4.1 (+1.7)	NS	fair
S_{cr}, µmol/L	Trivedi, 2003,[109] US	3 mo	9 (9)	5 (5)	Fosinopril up to 20 mg/d	Theophylline up to 8 mg/kg/d	55	78	nd	141 (124)	0 (+17)	NS	poor
Topic outcomes													
Hb, g/L	Yildiz, 2001,[107] Turkey	2 mo	15 (15)	12 (12)	Enalapril 10 mg	Losartan 50 mg	32	27	<1996	174 (171)	–25 (–12)	NS	fair
Hct, %										54.1 (53.4)	–4.3 (–2.5)	NS	fair
Hb, g/L	Beckingham 1995,[108] England, UK	4 mo	15 (15)	10 (10)	Enalapril 2.5 mg/day	Placebo	nd	nd	nd	163 (167)	–12 (–7)	NS	fair
Hct, %										52.7 (52.4)	–6.6 (–1.3)	0.004	fair
Hct, %	Trivedi, 2003,[109] US	3 mo	9 (9)	5 (5)	Fosinopril up to 20 mg/d	Theophylline up to 8 mg/kg/d	55	78	nd	51.3 (52.4)	–7.6 (–2.3)	nd	poor

GFR, Glomerular filtration rate; Hb, Hemoglobin; Hct, Hematocrit; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; UK, United Kingdom; US, United States

Supporting Table 59. Evidence Profile Topic 24.2: Growth hormone treatment[a]

Outcome	No. of studies and study design	Total N (N on study drug)	Methodological quality of studies per outcome	Consistency across studies	Directness of the evidence generalizability/ applicability	Other considerations	Summary of findings: Quality of evidence for outcome	Summary of findings: Qualitative and quantitative description of effect	Summary of findings: Importance of outcome
Mortality	0								Critical
Graft loss	0								Critical
Graft function	1 SR (9 RCTs) (High)	317 (184)	"Frequently suboptimal" (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)	Moderate	No difference in change in CrCl or SCr	Moderate
	1 RCT (High)	27 (13)	No limitations (0)						
Growth and development	Different doses rhGH 1 SR (4 RCTs) (High)	117 (117)	"Frequently suboptimal" (–1)	No important inconsistencies (0)	No uncertainty (0)	Sparse data (–1)	Moderate (Low for doses)	rhGH much better than placebo (+2.3 cm/y) (95% CI 1.4-3.2)). 28 IU/m²/wk better than 14 IU (3 RCTs) and no different than 56 IU (single RCT)	Moderate
	rhGH vs. placebo 1 SR (9 RCTs) (High)	331 (197)	"Frequently suboptimal" (–1)	No important inconsistencies (0)	No uncertainty (0)	None (0)			
	1 RCT (High)	27 (13)	No limitations (0)						
Adverse events	1 SR (9 RCTs) (High)	433 (287)	"Frequently suboptimal" (–1)	Lack of consistency (–1)	No uncertainty (0)	Inadequate reporting, standardization (–2)	Very Low	No effect on glucose tolerance (3 RCTs) Possible important adverse event included asthma/wheezing (1 RCT)	Moderate
Balance of potential benefits and harm: Net benefit rhGH better than placebo for increasing growth. No evident harm, though data inadequate.							Quality of overall evidence: Moderate		

CI: Confidence interval; CrCl, Creatinine clearance; IU, International units; N, Number; RCT, Randomized controlled trials; rhGH; Recombinant human growth hormone, SCr, Serum creatinine; SR, Systematic reviews.
Annotations:
a. References: [110,111]

Supporting Table 60. Summary Table Topic 24.2: Growth hormone treatment (categorical outcomes)

Outcome	Study, year country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Arm 1	Arm 2		
Acute rejection	Ferraris, 2000,[110] Argentina	12 mo	13 (13)	14 (14)	Deflazacort (mean 0.3 mg/kg/d)	Methylprednisone (mean 0.23 mg/kg/d)	9	0	nd	0%	7%	NS	fair

nd, Not documented; NS, Not significant.

Supporting Table 61. Summary Table Topic 24.2: Growth hormone treatment (continuous outcomes)

Outcome	Study, year, country	Study duration	No. analyzed (enrolled)		Intervention/Control		Age (mean)	% deceased donor	Dates of transplant	Results		*P* value	Quality
			Arm 1	Arm 2	Arm 1	Arm 2				Baseline (Control)	Δ (Control)		
Kidney outcomes													
CrCl, mL/min/1.73 m^2	Ferraris, 2000,[110] Argentina	12 mo	13 (13)	14 (14)	Deflazacort (mean 0.3 mg/kg/d)	Methylprednisone (mean 0.23 mg/kg/d)	9	0	nd	68.6 (66.3)	–3.1 (–8.0)	NS (implied)	fair
S_{cr}, µmol/L										85 (87)	+12 (+19)	NS (implied)	fair
Topic outcomes													
BMC, g/m^2	Ferraris, 2000,[110] Argentina	12 mo	13 (13)	14 (14)	Deflazacort (mean 0.3 mg/kg/d)	Methylprednisone (mean 0.23 mg/kg/d)	9	0	nd	901 (875)	+29 (–48)	<0.05	fair
HDL, mmol/L										1.2 (1.4)	+0.3 (+0.1)	<0.05	fair
Height (SDS)										–2.3 (–2.9)	+0.1 (–0.2)	<0.01	fair
Height Velocity (SDS, unitless)										–3.2 (–2.0)	+2.7 (–1.3)	<0.005	fair
LDL, mmol/L										3.49 (3.54)	–0.1 (+0.44)	<0.025	fair
LS BMD, g/cm^2 per m^2										0.734 (0.749)	–0.0489 (–0.0723)	NS	fair
Tg, mmol/L										1.92 (2.00)	–0.2 (–0.29)	NS	fair
TSk BMD, g/cm^2 per m^2										0.939 (0.976)	–0.018 (–0.067)	NS	fair
Weight/Height (%, exceeded 50th %ile)										22.1 (15.9)	–7.1 (6.6)	<0.005	fair

BMC, Bone mineral content; BMD, Bone mineral density; CrCl, Creatinine clearance; HDL, High density lipoprotein; LDL, Low-density lipoprotein; nd, Not documented; NS, Not significant; S_{Cr}, Serum creatinine; SDS, Standard deviation score; Tg, Triglycerides; TSk BMD, Total skeleton bone mineral density.

Supporting Table 62. The Conference on Guideline Standardization (COGS) Checklist for Reporting Clinical Practice Guidelines[a]

Topic	Description	Discussed in KDIGO Transplant Guideline
1. Overview material	Provide a structured abstract that includes the guideline's release date, status (original, revised, updated), and print and electronic sources.	See *Abstract* and *Appendix: Methods for Guideline Development*.
2. Focus	Describe the primary disease/condition and intervention/service/technology that the guideline addresses. Indicate any alternative preventative, diagnostic, or therapeutic interventions that were considered during development.	This is addressed in the *Guideline Scope* section.
3. Goal	Describe the goal that following the guideline is expected to achieve, including the rationale for development of a guideline on this topic.	This clinical practice guideline is intended to assist the practitioner caring for KTRs in their prevention and treatment of complication that occur after kidney transplantation to improve patient survival and quality of life.
4. User/setting	Describe the intended users of the guideline (e.g., provider types, patients) and the settings in which the guideline is intended to be used.	All Transplant Care Providers: Nurses, coordinators, pharmacists, doctors, and other medical professionals that directly or indirectly care for KTRs. Patients: All KTRs and their relatives and friends. Policy Makers: Those in related health fields.
5. Target population	Describe the patient population eligible for guideline recommendations and list any exclusion criteria.	All KTRs, adult and pediatric.
6. Developer	Identify the organization(s) responsible for guideline development and the names/credentials/potential conflicts of interest of individuals involved in the guideline's development.	Organization: KDIGO. Names/credentials/potential conflicts of interest of individuals involved in the guideline's development are disclosed in section *Biographic and Disclosure Information*.
7. Funding source/sponsor	Identify the funding source/sponsor and describe its role in developing and/or reporting the guideline. Disclose potential conflict of interest.	KDIGO is supported by a consortium of sponsors including Abbott, Amgen, Belo Foundation, Coca-Cola Company, Dole Food Company, Genzyme, Hoffmann-LaRoche, JC Penney, NATCO-The Organization for Transplant Professionals, National Kidney Foundation-Board of Directors, Novartis, Robert and Jane Cizik Foundation, Shire, Transwestern Commercial Services, and Wyeth. No funding is accepted for the development of specific guidelines. Stakeholders could participate in the public review.
8. Evidence collection	Describe the methods used to search the scientific literature, including the range of dates and databases searched, and criteria applied to filter the retrieved evidence.	The MEDLINE, Cochrane Central Registry for trials and Cochrane database of systematic reviews were searched by the ERT to capture all citations relevant to the topic of kidney transplantation including original articles, systematic reviews, and previous guidelines. The Cochrane Renal Group ran parallel searches in their Renal Registry database and these supplemented the primary ERT searches. The search was updated through February 2008 and supplemented by articles identified by Work Group members through November, 2008.

9. Recommendation grading criteria	Describe the criteria used to rate the quality of evidence that supports the recommendations and the system for describing the strength of the recommendations. Recommendation strength communicates the importance if adherence to a recommendation and is based on both the quality of the evidence and the magnitude of anticipated benefits and harm.	Quality of individual studies was graded in a three-tiered grading system (see Table 35 in the *Appendix: Methods for Guideline Development*). Quality of evidence and strength of recommendations were graded following the GRADE approach (Tables 37-41 in the *Appendix: Methods for Guideline Development*). The Work Group could provide general guidance in ungraded statements.
10. Method for synthesizing evidence	Describe how evidence was used to create recommendations, e.g., evidence tables, meta-analysis, decision analysis.	1) Topics were triaged either to a) systematic review, b) systematic search followed by narrative summary, or c) narrative summary. For systematic review topics, summary tables and evidence profiles were generated. 2) For recommendations on treatment interventions, the steps outlined by GRADE were followed.
11. Prerelease review	Describe how the guideline developer reviewed and/or tested the guidelines prior to release.	The guideline will undergo internal and external review.
12. Update plan	State whether or not there is a plan to update the guideline and, if applicable, expiration date for this version of the guideline.	There is no date set yet for updating. The updating of the guideline will depend on the publication of new evidence that would change the quality of the evidence or the estimates for effect sizes. Results from registered ongoing studies and other publications will be reviewed periodically to evaluate their potential to impact on the recommendations in this guideline.
13. Definitions	Define unfamiliar terms and those critical to correct application of the guideline that might be subject to misinterpretation.	See *Abbreviations and Acronyms*.
14. Recommendations and rationale	State the recommended action precisely and the specific circumstances under which to perform it. Justify each recommendation by describing the linkage between the recommendation and its supporting evidence. Indicate the quality of evidence and the recommendation strength, based on the criteria described in 9.	Recommendations are provided in Section I, Immunosuppression; Section II, Graft Monitoring and Infections; Section III, Cardiovascular Disease; Section IV, Malignancy; and Section V, Other Complications. Each recommendation builds on a supporting rationale with evidence tables if available. The strength of the recommendation and the quality of evidence is provided in parenthesis within each recommendation.
15. Potential benefits and harm	Describe anticipated benefits and potential risks associated with implementation of guideline recommendations.	The benefits and harm for each intervention are provided in summary tables and summarized in evidence profiles. The estimated balance between potential benefits and harm was considered when formulating the recommendations.
16. Patient preferences	Describe the role of patient preferences when a recommendation involves a substantial element of personal choice or values.	Level 2 recommendations inherently indicate a greater need to help each patient arrive at a management decision consistent with her or his values and preferences.
17. Algorithm	Provide (when appropriate) a graphical description of the stages and decisions in clinical care described by the guideline.	These were not provided in the guideline, but may be developed later as implementation tools by Kidney Learning Solutions™.
18. Implementation considerations	Describe anticipated barriers to application of the recommendations. Provide reference to any auxiliary documents for providers or patients that are intended to facilitate implementation. Suggest review criteria for measuring changes in care when the guideline is implemented.	These recommendations are global. Review Criteria were not suggested because implementation with prioritization and development of review criteria has to proceed locally. Suggestions were provided for future research.

ERT. Evidence review team; GRADE, Grading of Recommendations Assessment, Development and Evaluation; KDIGO, Kidney Disease Improving Global Outcomes; KTR, Kidney transplant recipients

Annotations:

a. Reference: [112]

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