Appendix 1: Supplementary tables A-E

Table A: Design features of the 21 randomized trials with individual patient-level data

Publication (1st author & year)	sample size (in dataset) and outcomes	Sirolimus arm(s)	Comparators	Other Immunosuppression in all arms	Induction in all arms	Timing of sirolimus-based therapy (*de novo* versus conversion to sirolimus)	Study Duration and Median Follow-up	Population (donor type, history of cancer)
Barsoum 2007[1]	113 Cancer = 1 Deaths = 6	Sirolimus load 9 mg then 2 mg/d with dose adjusted to maintain trough levels of 5-10 ng/mL until 12 weeks then 10-15 ng/ml thereafter. Cyclosporine dose adjusted to maintain C2 level of 600 ng/ml until 12 weeks then discontinued	Cyclosporine dose adjusted to maintain C2 level of 1600 ng/ml until 24 weeks, 1200 ng/ml until 52 weeks the 1000 ng/ml thereafter	Corticosteroids; mycophenolate mofetil	No induction	De novo sirolimus and cyclosporine followed by cyclosporine elimination at 3 months	24 months Follow-up = 20.1 months	Primary or secondary living donors. History of previous cancer not reported
Blydt-Hansen 2010[2]	22 (2/22 patients enrolled withdrew after 1 month and were excluded from trialists' analyses; however, they are eligible for our modified-ITT analysis) Cancer = 0 Deaths = 0	Sirolimus: 1 mg/m2/d with dose adjusted to maintain trough level of 8-12 ng/ml	Mycophenolate mofetil 1200 mg/m2/d with dose adjusted to maintain trough MPA level of >2.0 µg/ml	Corticosteroids; tacrolimus dose adjusted to maintain trough level of 3-5 ng/ml	ATG or IL-2 receptor blocker at time of initial transplant	Conversion from mycophenolate mofetil to sirolimus at anytime beyond 12 months post-transplant	24 months Follow-up = 24 months	Excluded if history of post-transplant lymphoproliferative disorder
ampbell 2012[3]	86 Cancer = 39 Deaths = 2	Load: 6-12 mg then 2-4 mg/d to maintain a trough level of 5-15 ng/ml	calcineurin inhibitor – tacrolimus or cyclosporine – could be adjusted at the investigators discretion	Corticosteroids; Mycophenolate mofetil, mycophenolate sodium or azathioprine could be decreased or discontinued at investigators discretion	Neither reported in publication nor identified in the database	Conversion from calcineurin inhibitor to sirolimus at anytime beyond 12 months post-transplant	13 months Follow-up = 13 months	Primary or secondary deceased or living donor. Must have history of SCC or BCC of the skin within 3 years of enrollment. Excluded if any other malignancy, >20 lesions in preceding year or metastatic disease
Ekberg 2007[4] [Symphony]	1589 Cancer = 20 Deaths = 43	Sirolimus load 9 mg/d x 3 d then 3 mg/d with dose adjusted to maintain trough level of 4-8 ng/mL	Group A: Standard dose cyclosporine with dose adjusted to maintain trough level of 150-300 ng/mL until 12 weeks then 100-200 ng/mL thereafter. Group B: Low dose cyclosporine with dose adjusted to maintain trough level of 50-100 ng/mL. Group C: Low dose tacrolimus with dose adjusted to maintain trough level of 3-7 ng/ml	Corticosteroids; mycophenolate mofetil	Daclizumab (5 doses) in all groups but Group A	De novo in all arms	12 months Follow-up = 12 months	Primary or secondary deceased or living donor. Exclusion: history of malignancy excepted treated non-melanoma skin cancer
Flechner 2011[5] [ORION]	443	Group A: Sirolimus load 15 mg then 5 mg/d to	Tacrolimus given to maintain trough level of 8-	Corticosteroids	Daclizumab (2 doses)	De novo sirolimus and tacrolimus followed by	24 months	Primary or secondary deceased or living donor.

Publication (1st author & year)	sample size (in dataset) and outcomes	Sirolimus arm(s)	Comparators	Other Immunosuppression in all arms	Induction in all arms	Timing of sirolimus-based therapy (*de novo* versus conversion to sirolimus)	Study Duration and Median Follow-up	Population (donor type, history of cancer)
	Cancer = 14 Deaths = 20	maintain trough level of 8-15 ng/ml until week 13 then 12-20 ng/ml after tacrolimus elimination; Tacrolimus given to maintain trough level of 6-15 ng/ml until week 13 then dose decreased 25%/wk until eliminated. Group B: Sirolimus load 15 mg then 5 mg/d to maintain trough level of 10-15 ng/ml until week 26 then 8-15 ng/ml thereafter; Mycophenolate mofetil 2g/d	15 ng/ml until week 26 then 5-15 ng/ml thereafter; Mycophenolate mofetil 2g/d			tacrolimus elimination starting week 13 in Group A	Follow-up = 22.8 months	Exclusion: malignancy within 5 years before enrollment except treated BCC or SCC of skin
Flechner 2013[6] [PROTECT]	475 Cancer = 4 Deaths = 10	Load 15 mg/d x 2 days then 10 mg/d with dose adjusted to maintain trough level 10-15 ng/mL until week 26 then 8-15 thereafter	Cyclosporine dose adjusted to maintain trough levels of 150-300 ng/mL until week 13, 50-200 ng/mL until week 26 then 50-150 thereafter	Mycophenolate mofetil. Corticosteroids	Basiliximab (2 doses)	De novo in all arms	12 months Follow-up = 6 months	Primary deceased or living donor. Exclusion: malignancy within 5 years before enrollment except treated BCC or SCC of skin
Gallon 2006[7]	82 Cancer = 0 Deaths = 2	Sirolimus 3 mg/d with dose adjusted to maintain trough levels of 7-10 ng/mL	Mycophenolate mofetil (1 g BID)	Tacrolimus dose adjusted to maintain trough levels of 8-10 ng/mL until 12 weeks, 7-9 ng/mL until 24 weeks then 6-8 ng/mL thereafter. Methylprednisolone for 3 days only	Basiliximab (2 doses)	De novo in all arms	36 months Follow-up = 36 months	Primary or secondary deceased or living donor. History of previous cancer not reported
Gelens 2006[8]	54 Cancer = 0 Deaths = 1	Group A: Sirolimus load 3 mg then 1 mg/d to maintain trough level of 10-15 µg/l until week 24, 5-10 µg/l thereafter; Same tacrolimus dosing as comparator arm. Group B: Sirolimus load 15 mg then 5 mg/d to maintain trough level of 10-15 µg/l until week 24, 5-10 µg/l thereafter; Mycophenolate mofetil 2g/d	Tacrolimus given to maintain trough level of 15-20µg/l until week 2, 10-15µg/l until week 4, 5-8µg/l thereafter; Mycophenolate mofetil 2g/d	Methylprednisolone on Days 1 and 2 only	Daclizumab (2 doses) in group B only	De novo in all arms	12 months Follow-up = 12 months	Primary or secondary deceased or living donor. History of previous cancer not reported.
Glotz 2010[9]	141 Cancer = 3 Deaths = 5	Load 15 mg/d x 2 d then 10 mg/d x 5 d then dose adjusted to maintain trough level of 12-20 ng/ml	Tacrolimus dose adjusted to maintain trough level of 8-12 ng/ml until 12 weeks then 5-9 ng/ml thereafter	Corticosteroids; Mycophenolate mofetil	ATG to a maximum of 6 mg/kg in the sirolimus group only	De novo in all arms	12 months Follow-up = 11.8 months	Primary or secondary deceased donor. History of previous cancer not reported
Groth 1999[10]	83 Cancer = 1 Deaths = 0	Load: 16-24 mg/m2. Then: 8-12 mg/m2/d. After Day 7-10: Dose adjusted to obtain trough	Cyclosporine Initial dose: 10 mg/kg/d. Then, dose adjusted to obtain trough levels of 200-400 ng/ml	Corticosteroids. Azathioprine	No induction	De novo in all arms	12 months Follow-up = 12 months	Primary deceased donor. Excluded if history of any malignancy.

Publication (1st author & year)	sample size (in dataset) and outcomes	Sirolimus arm(s)	Comparators	Other Immunosuppression in all arms	Induction in all arms	Timing of sirolimus-based therapy (*de novo* versus conversion to sirolimus)	Study Duration and Median Follow-up	Population (donor type, history of cancer)
		levels of 30 ng/ml until week 8 then 15 ng/ml thereafter	until week 8 then 100-200 ng/ml thereafter					
Guba 2010[11] [SMART]	140 Cancer = 4 Deaths = 2	Load 0.1 mg/kg then 2-4 mg/d with dose adjusted to maintain trough level of 8-12 ng/ml until 12 weeks then 5-10 ng/ml thereafter. Mycophenolate mofetil reduced to 1.5 g/d when sirolimus started. SRL Conversion Group: Target blood level6-8 ng/mL	Cyclosporine dose adjusted to maintain trough level of 200-250 ng/ml until week 3 then 150-200 ng/ml until week 16 then 100-150 ng/ml thereafter. Mycophenolate mofetil 2 g/d. Control Group: AZA (11 pts), Cyclosporine (1 pt), TAC (1 pt), Mycophenolate (6 pts)	Corticosteroids	ATG	Conversion from cyclosporine to sirolimus at 10-24 days post-transplant	12 months Follow-up = 11.5 months	Primary or secondary deceased or living donor. History of malignancy excluded unless successfully treated
Kahan 1999[12]	149 Cancer = 2 Deaths = 9	Group A: 1 mg/m2/d; Group B: 3 mg/m2/d; Group C: 1 mg/m2/d; Group D: 3 mg/m2/d; Group E: 5 mg/m2/d	Placebo	Corticosteroids. Cyclosporine full dose for placebo group, group A and B; reduced dose for groups C, D and E. Full dose adjusted for trough levels of 200-350 ng/ml until 4 weeks, 200-300 ng/ml until week 12 then 150-250 ng/ml thereafter. Reduced dose adjusted for trough levels of 100-175 ng/ml until 4 weeks, 100-150 ng/ml until week 12 then 75-125 ng/ml thereafter.	No induction	De novo in all arms	12 months Follow-up = 12 months	Primary living or deceased donor. History of previous cancer not reported.
Kahan 2000[13]	719 Cancer = 33 Deaths = 19	Group A: 2 mg/d Group B: 5 mg/d	Azathioprine (2-3 mg/kg/d)	Cyclosporine. Corticosteroids.	No induction	De novo in all arms	24 months Follow-up = 23.9 months	Primary living or deceased donor. Exclusion: malignancy within 10 years before enrollment except treated BCC or SCC of skin.
Kreis 2000[14]	78 Cancer = 0 Deaths = 3	Load: 24 mg/m2. Then: 24 mg/m2/d x 2d. Thereafter: 12 mg/m2/d with dose adjusted to obtain trough levels of 30 ng/ml until week 8 then 15 ng/ml	Cyclosporine: dose adjusted to obtain trough levels of 200-400 ng/ml until week 8 then 100-200 ng/ml thereafter	Corticosteroids. Mycophenolate mofetil	No induction	De novo in all arms	12 months Follow-up = 12 months	Primary deceased donor. Previous cancer status not reported.
MacDonald 2001[15]	575 (1/576 patients enrolled died before being transplanted) Cancer = 31 Deaths = 36	Group A: 2 mg/d Group B: 5 mg/d	Placebo	Cyclosporine. Corticosteroids.	No induction	De novo in all arms	24 months Follow-up = 24 months	Primary living or deceased donor. Exclusion: malignancy within 10 years before enrollment except treated BCC or SCC of skin.
Machado 2004[16] [Rapa002]	70	SRL + CsA: SRL dose 2 mg/day ; CsA dose 8-10	AZA + CsA: AZA dose 2 mg/kg; CsA dose 8-10	Cyclosporine and prednisone	No induction	De novo in all arms	12 months	Primary living donor. Exclusion: history of

Publication (1st author & year)	sample size (in dataset) and outcomes	Sirolimus arm(s)	Comparators	Other Immunosuppression in all arms	Induction in all arms	Timing of sirolimus-based therapy (*de novo* versus conversion to sirolimus)	Study Duration and Median Follow-up	Population (donor type, history of cancer)
	Cancer = 0 Deaths = 2	mg/kg twice daily	mg/kg twice daily				Follow-up = 12 months	malignancy within 10 yr of enrollment into the study
Salgo 2010[17]	44 Cancer = 8 Deaths = 0	SRL Conversion Group: Target blood level6-8 ng/mL	Control Group: AZA (11 pts), Cyclosporine (1 pt), TAC (1 pt), Mycophenolate (6 pts)	Prednisone	Neither reported in publication nor identified in the database	Conversion to sirolimus from AZA, Cyclosporine, TAC or Mycophenolate with an overlap interval of 2-4 weeks	12 months Follow-up = 12 months	Primary or secondary graft. Inclusion: existence of keratotic dysplasia such as history of NMSC, AK, verruca vulgaris or lesions sharing clinical aspects of both
Sampaio 2008[18] [FK-Local]	98 (data for 2/100 patients enrolled were not retrieved in data custodian's records) Cancer = 0 Deaths = 3	Oral tablets;(TAC + SRL) SRL: one loading dose of 15 mg, 5 mg/d till 7 and 2 mg/d thereafter; TAC dose: 0.10-0.15 mg/kg twice daily	(TAC+MMF) MMF dose: 2 g/d daily; TAC dose: 0.10-0.15 mg/kg twice daily	Tacrolimus, corticosteroids (methlyprednisolone, prednisone)	No induction	De novo in all arms	12 months Follow-up = 12 months	Primary living or deceased donor. No specification about previous malignancy.
Schena 2009[19] [CONVERT]	829 (1/830 patients enrolled died before receiving any dose of study drug) Cancer = 79 Deaths = 39	Load: 12-20 mg. Then 4-8 mg/d with dose adjusted to maintain trough level of 8 to 20 ng/mL	Cyclosporine dose adjusted to maintain trough level of 50-250 ng/ml; Tacrolimus dose adjusted to maintain trough level of 4-10 ng/ml;	Corticosteroids, mycophenolate mofetil or azathioprine initially but could be discontinued at discretion of physician	Neither reported in publication nor identified in the database	Conversion from calcineurin inhibitor to sirolimus at 6 to 120 months post-transplant	49 months Follow-up = 47.8 months	Primary or secondary deceased or living donor. Exclusion: known or suspected malignancy within 5 years before enrollment into the study (exception of adequately treated basal cell or squamous cell carcinomas of the skin)
Vitko 2006[20] [TERRA]	48 (out of 977 enrolled in all study sites) Cancer = 0 Deaths = 0	Group A: Load 1.5 mg then 0.5 mg/d. Group B: Load 6 mg then 2 mg/d	Mycophenolate mofetil (1 g BID)	Tacrolimus dose adjusted to maintain trough level of 8-16 ng/ml for 2 weeks then 5-15 ng/ml thereafter; corticosteroids	No induction	De novo in all arms	6 months Follow-up = 5.9 months	Primary or secondary deceased or living donor. Exclusion: any malignancy
Watson 2005[21]	38 Cancer events = 4 Deaths = 0	Sirolimus load 8 mg then 4 mg/d with dose adjusted to maintain trough level of 5-15 ng/ml. If already on mycophenolate mofetil dose reduced to 1 g/d	Calcineurin inhibitor-cyclosporine or tacrolimus – continued as previously but no drug levels specified	Azathioprine, mycophenolate mofetil and corticosteroids permitted but not mandated	12 patients had Simulect or placebo, 5 Alemtuzumab, 1 anti-thymocyte globulin, 20 no induction (from dataset, not in publication)	Conversion from calcineurin inhibitor to sirolimus at 6 to 96 months post-transplant	12 months Follow-up = 12 months	Primary or secondary deceased or living donor. Exclusion: malignancy within 5 years before enrollment except treated BCC or SCC of skin

Table B: Cochrane Risk of Bias Assessment for the 21 randomized trials with individual patient-level data

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Threats to Validity
Campbell 2012[3]	Yes	Yes	Yes (not blinded but primary outcome was biopsy-confirmed NMSC and pathologist was blinded)	Yes (imbalanced but ITT analysis and follow-up continued in both groups)	Yes	Yes
Blydt-Hansen 2010[2]	Yes	Yes	Yes (outcome assessor was blinded)	Yes	Yes	Yes
Guba 2010[11]	Yes	Yes	Yes (not blinded but objective outcome measure)	Unclear (unbalanced treatment discontinuation between groups; did not state number of missing values; used last observation carried forward to impute for ITT analysis)	Yes	Yes
Flechner 2011[5]	Unclear	Unclear	Yes (not blinded but objective outcome measure)	Unclear (unbalanced treatment discontinuation between groups; did not state number of missing values; used last observation carried forward to impute for ITT analysis)	Yes	Yes
Glotz 2010[9]	Unclear	Unclear	Yes (not blinded but objective outcome measure)	Unclear (unbalanced treatment discontinuation between groups, did not state number of missing	Yes	Yes

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Threats to Validity
				values or how they were dealt with)		
Salgo 2010[17]	Unclear	Unclear	Yes (outcome assessor was blinded)	No (unbalanced treatment discontinuation likely related to intervention, primary outcome not analyzed by ITT and missing may have had different outcomes)	Yes	Yes
Schena 2009[19]	Yes	Yes	Yes (not blinded but objective outcome measure)	Unclear (unbalanced treatment discontinuation between groups at time of primary outcome assessment, did not state number of missing values)	Yes	Yes
Sampaio 2008[18]	Yes	Unclear	No (not blinded; part of primary endpoint is biopsy-confirmed acute rejection; medical team was not blinded and pathologist not blinded)	Yes (missing data was similar between groups, analyzed by ITT)	Yes	Yes
Ekberg 2007[4]	Yes	Yes	Yes (not blinded but objective outcome measure)	No (unbalanced missing values likely related to intervention, method of replacing missing values may have affected outcome)	Yes	Yes
Barsoum 2007[1]	Unclear	Unclear	Yes (not blinded but objective	Unclear (unbalanced treatment	Yes	Yes

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Threats to Validity
			outcome measure)	discontinuation between groups at time of primary outcome assessment, did not state number of missing values, stated that primary analysis was ITT but did not state how missing values were handled)		
Gallon 2006[7]	Unclear	Unclear	Yes (not blinded but objective outcome measure)	No (unbalanced treatment discontinuation likely related to intervention, primary outcome only analyzed PP and missing may have had different outcomes)	Yes	Yes
Gelens 2006[8]	Unclear	Unclear	Yes (blinded pathologist)	Yes	No (the primary outcome as stated in the paper is not reported)	Yes
Watson 2005[21]	Yes	Yes	Yes (not blinded but objective outcome measure)	No (missing outcome data is imbalanced between groups and is excluded from primary analysis)	Yes	Yes
Machado 2004[16]	Unclear	Unclear	No	Yes	Yes	Yes

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Threats to Validity
			(not blinded; part of primary endpoint is biopsy-confirmed acute rejection - medical team was not blinded and pathologist not blinded)	(all patients included in analysis of primary endpoint)		
Kahan 1999[12]	Unclear	Unclear	No (medical team not blinded; primary endpoint is biopsy and pathologist not blinded)	Unclear (unbalanced treatment discontinuation between groups due to lack of efficacy, did not state number of missing values for primary outcome)	Yes	Yes
MacDonald 2001[15]	Yes	Unclear	Yes	Yes	Yes	Yes
Kahan 2000[13]	Yes	Yes	Yes	Yes	Yes	Yes
Groth 1999[10]	Yes	Yes	No (not blinded; part of primary endpoint is biopsy-confirmed acute rejection - medical team was not blinded and pathologist not blinded)	Yes	Yes	Yes
Kreis 2000[14]	Unclear	Unclear	No (not blinded; primary endpoint is biopsy-confirmed acute rejection and it is unclear what criteria were used to decide to go to biopsy - medical team was not blinded and pathologist not blinded)	Yes	Yes	Yes

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Threats to Validity
Vitko 2006[20]	Unclear	Unclear	No (not blinded; primary endpoint is biopsy-confirmed acute rejection and it does not state what criteria were used to decide to go to biopsy - no mention of pathologist being blinded)	Yes	Yes	Yes
Flechner 2013[6]	Yes	Unclear	Yes (not blinded but objective outcome measure - GFR)	No (discontinuations were unbalanced between groups)	No (planned primary outcome not reported because study was stopped early)	Yes

Table C: Causes of cancer in sirolimus and control group patients*

	Control (n=2600)	Sirolimus (n=3276)
Squamous cell carcinoma	51 (2.0%)	41 (1.3%)
Basal cell carcinoma	36 (1.4%)	26 (0.79%)
Other carcinoma	27 (1.0%)	36 (1.1%)
Leukemia/Lymphoma	5 (0.19%)	21 (0.64%)
Melanoma	3 (0.12%)	7 (0.21%)

*Patients may have reported more than one cancer type.
*The distribution of the causes of cancer were significantly different between the two treatment groups (P=0.004).

Table D: Cause of death in sirolimus and control group patients*

	Control (n=2600)	**Sirolimus (n=3276)**	**All (N=5876)**
unknown	43 (1.7%)	43 (1.3%)	86 (1.5%)
cardiovascular	14 (0.54%)	42 (1.3%)	56 (0.95%)
infection	4 (0.15%)	19 (0.58%)	23 (0.39%)
cancer	5 (0.19%)	7 (0.21%)	12 (0.2%)
respiratory	2 (0.08%)	5 (0.15%)	7 (0.12%)
gastrointestinal	0 (0%)	4 (0.12%)	4 (0.07%)
sudden death	0 (0%)	3 (0.09%)	3 (0.05%)
other	1 (0.04%)	10 (0.31%)	11 (0.19%)
TOTAL	**69 (2.7%)**	**133 (4.1%)**	**202 (3.4%)**

*The distribution of the causes of death were significantly different between the two treatment groups (P=0.002).

Table E: Design features of the 35 randomized trials with aggregate data only

Publication (1st author & year)	sample size	Sirolimus arm(s)	Comparators	Other Immunosuppression in all arms	Induction in all arms	Timing of sirolimus-based therapy (*de novo* versus conversion to sirolimus)	Study Duration	Population (donor type, history of cancer)
Anil Kumar 2005[22]	150	SRL was initiated on day 4 at 2mg per day without a loading dose. The dose was adjusted to maintain trough blood levels of 6 to 10 ng per ml.	MMF was initiated on day 1 at 2 g per day. The dose was adjusted according to patients' tolerance.	TAC was initiated on day 1 at 0.02 mg per kilogram body weight per day and gradually increased to maintain trough blood levels of 12 to 18 ng per ml by day 7.	Induction included two doses of Basiliximab 20 mg intravenous on days 0 and 4 and two doses of methylprednisolone 250 mg on day 0 and 125 mg on day 1.	*De novo* in all arms	24 months	Both living and deceased donors were included. No previous history of cancer reported.
Anil Kumar 2008[23]	200	SRL was initiated on day 4 at 2 mg/day: the dose was then adjusted to maintain trough blood levels of 5 to 10 ng/ml. In the CSA/SRL and TAC/SRL groups, the daily doses of CSA and TAC were adjusted to maintain C2 blood levels of CSA of between 500 and 800 ng/ml and trough levels of TAC of between 5 and 9 ng/ml of blood. We did not use a loading dose of SRL and initiation of SRL was delayed.	TAC or CSA was initiated on day 1. TAC was initiated at 0.02 mg/kg per day and the dose was increased to achieve trough levels of 15-18 ng/ml by day 4; levels were maintained for 1 month. Starting with the 2nd month, the TAC blood levels were gradually reduced to10 ng/ml by the end of 1 year. CSA was initiated at 3 mg/kg body weight per day and the dose was rapidly increased to maintain C2 blood levels (cyclosporine blood levels 2 h after the dose) of 1000-1200 ng/ml at 1 month and then gradually tapered to maintain 700 ng/ml at 1 year. MMF was initiated on day 1 at 2 g/day in divided doses, and trough blood levels of Mycophenolic acid were maintained between 1 and 3 μ/ml.	2 doses of methylprednisolone, 250 mg on day 0 and 125 mg on day 1. Steroid therapy was discontinued completely after the second dose of methylprednisolone	All recipients were given induction therapy with 2 doses of 20 mg Basiliximab on days 0 and 4.	Conversion therapy if necessary, however patients were included in their baseline randomized group for analysis.	60 months	Deceased and living donor kidneys. No information on previous malignancy reported.
Baboolal 2009[24]	190	Single dose of 12 mg of sirolimus followed by 4 mg a day, subsequent doses adjusted to target trough level 8-16 ng/ml.	Not reported	Not reported	Not reported	Conversion from CNI standard regimen (either CsA or TAC)	12 months	Not reported

Buchler 2007[25]	145	Patients began sirolimus within 48 h after transplantation, with a loading dose of 15 mg for 2 days followed by 10 mg/day, then adapted to maintain trough whole-blood concentrations between 10 and 15 ng/ml.	Patients began CsA within 48 h after transplantation at 6-8 mg/kg/day. During the following 3 months trough whole-blood concentration (C0) were targeted between 150 and 250 ng/ml (monoclonal TDX or equivalent), reducing to between 75 and 150 ng/ml from the 4th month onwards.	All patients received a 5-day course of MMF 2 g/day from day 0 and subsequently adapted according to clinical events and corticosteroids (500 mg of methylprednisolone IV on day 0 then prednisolone 1 mg/kg/day between day 1 and day 7, 0.5 mg/kg/day between day 8 and day 14, followed by a progressive decrease and complete discontinuation at the end of the 5th month).	All patients received a 5-day course of antithymocyte globulin (1.5 mg/kg/day).	*De novo* in all arms	12 months	All kidneys were from deceased donors. No previous history of cancer reported.
Durrbach 2008[26]	69	Patients received two loading doses of SRL for a total of 30 mg within 48 hr of transplantation, followed by a dose of 10 mg per day adjusted to maintain the 24-hr whole blood trough (C0) level between 10 and 20 ng/ml.	Patients randomized to CsA received 6 mg/kg per day from day 6, adjusted to maintain whole-blood C0 or C2 level (range 150–300 to 800–1,200 ng/ml at month 3 and 75–200 to 600–1,000 ng/ml at month 6).	Patients also received mycophenolate mofetil 2 g per day from day 0 adjusted to maintain mycophenolic acid plasma C0 between 1.0 and 3.5 g/ml or according to clinical tolerance.	All patients were given intravenous antithymocyte globulin 1.00 to 1.25 mg/kg per day from day 0 to day 7.	*De novo* in all arms	6 months	First or second ECD kidney allograft recipients. Deceased donor (except after cardiac death). No previous history of cancer reported.
Euvrard 2012[27]	120	Calcineurin inhibitors were discontinued and sirolimus was added to the usual immunosuppressive agents, according to the routine practice of each center (target trough level of sirolimus, 6-12 ng per ml).	Target cyclosporine and tacrolimus blood trough levels, 75 to 125 ng per ml and 4 to 7 ng per ml respectively.	The limits on baseline immunosuppressant doses were as follows: glucocorticoids, 10 mg or less per day; azathioprine, 1 mg or less per kilogram of body weight per day; mycophenolate mofetil, 1.5 g or less per day.	No induction	Patients converted from calcineurin inhibitors to receive sirolimus.	24 months	No information of donors reported. 7 patients had a history of non-cutaneous cancer.
Ferguson 2011[28]	89	SRL was initiated at 5 mg/day orally on day 1 and adjusted to keep pre-dose (C0) levels at 7–12 ng/ml from day 3 through month 6 and 5–10 ng/ml thereafter. Belatacept was administered 10 mg/kg IV on days 1 and 5, then once every 2 weeks through month 3, every 4 weeks through month 6 and 5 mg/kg every 4 weeks from month 7 onward.	Belatacept was administered in the 1st control arm, same way as the SRL arm. MMF was given in both control arms at 1 g twice daily, which could be reduced and/or split into 4 divided doses. TAC was initiated in the 2nd control arm when serum creatinine had improved to ≤4 mg/dL TAC was given orally as 0.1 mg/kg/day in two divided doses and adjusted to keep pre-dose levels at 8–12 ng/ml through day 30 and 5–10 ng/ml thereafter.	All patients received 500, 250, 125 and 60 mg IV methylprednisolone on days 1, 2, 3 and 4, respectively.	Thymoglobulin was given to all arms	*De novo* in all arms	12 months	Primary, first time renal allograft from living or deceased donor. No history of malignancy in previous 5 years (except non-melanoma skin cancer cured by resection)

Flechner 2007[29]	61	5-year mean doses for sirolimus 2.5±0.14 mg, MMF 1.27±0.073 g (divided dosing), and prednisone 6.4 mg daily.	For group II, mean doses were CsA 186.7±10.6 mg (divided dosing), MMF 1.68 (divided dosing), and prednisone 7.1 mg daily.	All groups received MMF and prednisone.	Basiliximab was given to all patients.	*De novo* in all arms	60 months	Both living and deceased donors were included. No previous history of cancer reported.
Franz 2010[30]	127	Patients in the SRL arm received 30 mg of the drug once daily on days 0, 1, and 2, which then was decreased to 16 mg until serum levels were received. Target serum levels were 10-20 ng/ml during months 1-3 and 8-15 ng/ml during months 4-6.	In the CsA arm, patients received 300 mg twice daily until serum levels were received, and then dosage was titrated to serum levels of 250-350 ng/ml during the first 3 months and 200-250 ng/ml thereafter.	Patients in both arms received mycophenolate mofetil, 1,000 mg, twice daily (2 x 750 mg if body weight <50 kg, 2 x 1,500 mg if body weight > 100 kg) starting on the transplant date; and methylprednisolone, 1,000, 500, and 250 mg, intravenously on days 0, 1, and 2, respectively; followed by oral prednisone, 0.5 mg/kg of body weight. Prednisone dose was tapered every other week in 5 mg steps to 15 mg, then in 2.5 mg decrements to 7.5 mg. Mycophenolate mofetil was monitored to keep trough levels >2 mg/ml.	No induction	*De novo* in all arms	6 months	Primary kidney transplant or retransplant. Living or deceased donor.
Guerra 2011[31]	150	The first SRL arm received TAC given at a dose of 0.1 mg/kg twice daily, with an initial target trough level (during the first 2 mo post transplant) of 10 ng/ml, then lowered to 6–10 ng/ml between 3 to 6 mo post-transplant and 4–8 ng/ml thereafter. The second sirolimus arm received CSA given at 5 mg/kg twice daily with an initial target trough level of 200–250 ng/ml, and then lowered to 100–200 ng/ml thereafter. In both SRL arms, a loading dose of 4mg of SRL was given on the evening after surgery, and then daily, with a target trough level 6–10 ng/ml.	Planned MMF dosing was 1 g twice daily, maintained as tolerated and TAC was instituted at a dose of 0.1 mg/kg twice daily, with an initial target trough level (during the first 2 mo post-transplant) of 10 ng/ml, then lowered to 6–10 ng/ml between 3 to 6 mo post-transplant and 4–8 ng/ml thereafter.	All patients received maintenance corticosteroids.	Daclizumab	*De novo* in all arms	96 months	Deceased donor or non-HLA identical living donors were included. No previous history of cancer reported.

Heilman 2012[32]	122	The protocol for sirolimus conversion included a loading dose for 3 days, the MMF dose was decreased by 50%, the tacrolimus dose was decreased by 50%, and sirolimus was dosed at 10 mg in single daily dose. Once the sirolimus level was more than 8 ng/ml, the tacrolimus was stopped.	Tacrolimus was started when the serum creatinine dropped by at least 30% or by postoperative day (POD) 4. Trough tacrolimus levels were 10 to 12 ng/ml for the first 30 days, 8 to 10 ng/ml between days 30 to 90 ng/ml, and 5 to 8 ng/ml after 90 days.	MMF was started at 2000 mg/day, in divided doses, and adjusted according to the individual patient's tolerance. The protocol for rapid corticosteroid withdrawal was methylprednisolone 500 mg intravenously intraoperatively, MP 250 mg IV POD 1, MP 125 mg IV on POD 2, prednisone 60 mg orally on POD 3 and prednisone 30 mg orally on POD 4, and no corticosteroids thereafter.	All patients received induction with rabbit antithymocyte globulin for a total dose of 6 mg/kg starting with 1.5 mg/kg on the day of transplant and usually given in four divided doses.	At 1 month post-transplant, patients were converted from tacrolimus to sirolimus.	24 months	Both living and deceased donors were included. No previous history of cancer was reported.
Hendrikx 2009[33]	46	Target trough level at 6 months was 8–12 ng/ml for rapamycin	Target trough level at 6 months was 5–10 ng/ml for tacrolimus and >2 1 g/ml for MMF.	In all arms of treatment, patients also received prednisone for the first month where after prednisone was fully withdrawn.	No induction	All arms initially on TAC and MMF. Conversion to TAC, MMF and SRL monotherapy occurred throughout 3 months after randomization.	6 months	Kidney transplantation patients with living or deceased donor. No previous history of cancer reported.
Kandaswamy 2005[34]	239	Arm 2 (high TAC, low SRL) received 1 mg preoperatively and 2 mg qd of SRL and was adjusted to achieve levels of 3-7 µg/L. TAC was also given at 0.03 mg/bid and adjusted to achieve levels of 8-12 µg/L. In arm 3 (low TAC, high SRL) patients received 1 mg preoperatively and 5 mg qd of SRL and was adjusted to achieve levels of 8-12 µg/L. TAC was also given at 0.015 mg/kg bid and was adjusted to achieve levels of 3-7 µg/L.	Arm 1 patients received 1 g of MMF in operating room and 1 g bid. CsA was also administered at 4 mg/kg bid and was adjusted to achieve levels of 150-200 µg/L.	All recipients received prednisone: 500 mg of methylprednisolone in the operating room, 1 mg/kg on postoperative day 1, and 0.5 mg/kg on postoperative day 2 and 3, and 0.25 mg/kg on postoperative day 4 and 5.	All patients received thymoglobulin (1.25-1.5 mg/kg) for 5 doses; the 1st dose was given in the operating room.	*De novo* in all arms	24 months	Deceased, HLA-identical, and living unrelated donors were included. No previous history of cancer reported.

Kim 2006[35]	59	Sirolimus was administered at a daily dose of 30 mg for 3 days (including preoperative administration on day 1), followed by 16 mg/day for the next 2 days, and then at an adjusted dose according to trough blood concentration. Target trough concentration was 10–20 ng/ml for 3 months post-transplant and then 8–15 ng/ml.	The initial dose of CsA was 300 mg twice daily for 3 days (including one preoperative administration on day 1) and then adjusted according to blood trough concentration. Target trough concentration was 250–350 ng/ml for 3 months and then 150–250 ng/ml.	The initial dose of MMF was 1000 mg twice daily, the target trough concentration above 2 g/ml, and the dose was modified according to trough level. All patients received methylprednisolone for 3 days, and prednisone was started at a dose of 0.5 mg/kg once daily from day 3 post-transplant. Prednisone was tapered to 5 mg/day, and continued till 6 months.	6 patients in SRL and 10 patients in CsA received ATG	*De novo* in all arms	6 months	Both cadaveric donors and living donors were included. No previous history of cancer reported.
Larson 2006[36]	165	Sirolimus (SRL) was started on post-operative day 4. SRL was initially dosed at 10 mg daily for 2 days and 5 mg daily thereafter. The target 24-hour trough levels for sirolimus were 15–20 ng/ml in the first 4 months and 10–15 ng/ml thereafter.	TAC was started on post-operative day 4. TAC was initially dosed at 3 mg twice daily. The target 12-hour trough levels for TAC was 10–12 ng/ml in the first month, 8–10 ng/ml in months 1–4 and 6–8 ng/ml thereafter.	All patients received mycophenolate mofetil at a dose of 750 mg orally twice daily. Patients received 500 mg of methylprednisolone intraoperatively and tapered to a dose of 20 mg of prednisone daily at 1 month. Prednisone doses were further tapered to 5 mg daily at 3 months.	All patients received Thymoglobulin induction (1.5 mg/kg/day) on days 0, 1, 2, 4 and 6	*De novo* in all arms	33 months	Kidney transplant recipients, living or deceased donors.
Lebranchu 2009[37]	192	The SRL dose consisted of a loading dose of 10 mg/day for 2 consecutive days, followed by 6 mg daily adjusted to maintain C0 blood levels between 8 ng/ml and 15 ng/ml from week 12 to week 39, then between 5 ng/ml and 10 ng/ml after week 39.	Cyclosporine adjusted to maintain blood levels 2 h after intake (C2) in the range 1000–1500 ng/ml until the end of month 1 and 800–1200 ng/ml until the end of month 3.	All patients received 2g MMF daily, adjusted according to clinical events. All patients received steroids at an initial dose of 500 mg at day 0, then 0.5 mg/kg/day between days 1 and 7, 0.25 mg/kg/day between days 8 and 14, followed by a progressive decrease to 10 mg/day until month 8. Oral steroids were planned to be completely discontinued at month 8.	Daclizumab delivered at 2 mg/kg on day 0 and 1 mg/kg on day 14.	Randomization at week 12 to either SRL conversion or CsA maintenance.	12 months	First renal allograft recipients with no recent history of malignancy. Only deceased donors were included (donation after cardiac death were excluded)

Martinez-Meir 2006[38]	41	A loading dose of 10 mg orally within 48 hours after surgery and then 3 mg/m^2 body surface area. Doses were adjusted to achieve 24 hour blood trough levels between 10 and 15 ng/ml for 6 months and 5-10 ng/ml thereafter.	CsA was given at 4–8 mg/kg/day in divided doses when creatinine level was 3 mg/dL approximately, dosage adjusted to 12-hr blood trough levels between 150–300 ng/ml for six months and 100–200 ng/ml thereafter.	MMF was given at 1 g two times per day the morning before surgery. Intravenous methylprednisolone was also given at 1 g intraoperatively and tapered to oral prednisone 20 mg/day by day six and 5 mg/day at six months follow-up.	Patients were given Basiliximab 20 mg intravenously at surgery and day four if HLA match was less than three.	*De novo* in all arms	Mean follow up of 15.8 months	First-degree living related kidney allograft recipients. No previous history of cancer reported.
Mendez 2005[39]	361	Patients receiving SRLwere administered an initial oral loading dose of 6 mg up to 48 hr following transplantation. Following the loading dose, SRL was administered at a starting dose of 2 mg given orally, once a day. Both TAC and SRL were administered simultaneously. Dosing was adjusted to achieve levels of 4–12 ng/ml.	Those randomized to treatment with MMF, received 2 g/day orally in two divided doses.	Patients received perioperative corticosteroid therapy (methylprednisolone 500 mg or 7–10 mg/kg/IV). Oral prednisone dosing started at 200 mg/day (or 3 mg/kg/day) with a target of 10 mg/day by 6 months following transplantation. Oral TAC was administered at a starting dose of 0.15– 0.20 mg/kg/day in two divided doses. TAC was dosed to maintain levels in the range of 8–16 ng/ml for 3 months post-transplant followed by 5–15 ng/ml thereafter.	Only patients who developed DGF were eligible to receive antibody induction therapy per institutional protocol.	*De novo* in all arms	12 months	Deceased or non-HLA identical living donors were included.
Morelon 2010[40]	19	Sirolimus was administered at a dose of 15 mg/day on days 0, 1.10 mg/day on day 2, and then 5 mg/day on day 3. Doses were adjusted subsequently to target a trough level of 10-15 ng/ml.	CsA was initiated on day 0 at a dose of 5 mg/kg p.o. adjusted to target a trough level of 125-225 ng/ml.	Methylprednisolone was administered at a dose of 500 mg 0.5-4.0 h before the first infusion of Thymoglobulin. Oral prednisone 1 mg/kg/day was given on days 1-10 and tapered to 0.3 mg/kg/day during days 11-30, 10 mg/day during days 31-60, and 5 mg/day thereafter. MMF 2 g/day was initiated on day 0.	All patients received Thymoglobulin induction	*De novo* in all arms	12 months	Primary kidney transplant from deceased donor only. No previous history of malignancy except from successfully treated basal or squamous cell carcinoma.

Nafar 2012[41]	100	Cyclosporine was changed to MMF from the 4th month on. Sirolimus was administered 6 mg/d as a loading dose and continuing with dosages to reach the trough levels of 8 to 15 ng/ml.	The control group received cyclosporine, MMF, and steroids. Trough levels were maintained at 150 ng/ml to 250 ng/ml for cyclosporine; 1 g/d to 2 g/d for MMF; and 5 mg/d for corticosteroids.	Cyclosporine and steroids	Exclusion criteria: planned antibody induction therapy at the time of transplantation.	*De novo* in all arms	48 months	Exclusion: history of malignancy 5 years before enrollment into the study.
Pescovitz 2007[42]	45	Sirolimus was given once daily as an oral solution at 15 mg/day on days 1–3 following transplantation and was reduced to 10 mg/day (as tablets) beginning on day 4 post-transplant. Sirolimus dosing was adjusted to maintain sirolimus trough concentrations of 10–25 ng/ml until 2 months post-transplant and 8–15 ng/ml thereafter.	Neoral® or bioequivalent CsA was administered according to centre practice.	Enrolled patients received MMF; 1 g twice daily orally was started within 24 h pre- or post-transplant. Intraoperative and maintenance corticosteroids were administered to all patients for the duration of the study according to centre practice.	Daclizumab 1 mg/kg was administered intravenously 24 h before transplant, followed by four additional doses of 1 mg/kg every 2 weeks.	*De novo* in all arms	6 months	Deceased, living related, and living unrelated donors were included in the study. No previous history of cancer reported.
Pussell 2006[43]	830	Not reported	Not reported	Not reported	Not reported	Recipients underwent conversion to SRL-based, CNI-free regimen.	18 months	Not reported
Refaie 2011[44]	21	Sirolimus was given in a dosage of 5 mg/d aiming for a level of 10 to 15 ng/ml.	Tacrolimus was given in a dose of 0.1 mg/kg aiming for a trough level of 4 to 8 ng/ml.	Both groups received a short course of steroids for 5 days post-transplant. Azathioprine (1 mg/kg) was added when the white blood cells > 4000 cells/cm3 which was replaced by mycophenolate mofetil 500 mg twice daily owing to high liver enzymes or the onset of acute rejection.	A single dose of alemtuzumab was diluted in 100 mL of normal saline or glucose and given by IV infusion over 2 hours before transplant.	*De novo* in all arms	48 months	Live donors were included. No previous history of cancer reported.
Ruggenenti 2007[45]	21	Sirolimus was started on day 1 at the oral dose of 4 mg/day in a single administration. The dose was then titrated to blood trough levels of 5–10 ng/ml.	CsA was infused intravenously on day 1 at the dose of 1 to 2 mg/kg/day and then imbricated with oral CsA at the dose of 2 mg/kg twice daily titrated to trough blood concentrations of 120 to 220 ng/ml in the first month post-transplant, and of 70 to 120 ng/ml thereafter.	At surgery, all patients were given methylprednisolone (500 mg intravenously). Methylprednisolone was also infused on days 1 (250 mg) and 2 (125 mg) after transplantation. From postoperative day 1, MMF was introduced at the oral dose of 500 mg twice daily	At surgery, all patients were given a single infusion of alemtuzumab (30 mg).	*De novo*	30 months	Living and deceased donors were included. No previous history of cancer reported.

Saudek 2011[46]	159	Sirolimus maintenance target levels were 5-10 ng/ml	Patients received MMF at a daily dose of 2 g.	Both groups received tacrolimus with maintenance target levels at 5-10 ng/ml	ATG	*De novo* in all arms	36 months	Not reported
Saunders 2003[47]	31	The rapamycin group had a 40% cyclosporine dose reduction with the introduction of rapamycin. This was dispensed as a single loading dose of 6 mg, followed by a daily maintenance dose of 2 mg adjusted to maintain trough levels of 5 to 15 ng/ml. Rapamycin oral suspension was diluted with water or orange juice and taken 4 hr after the first daily dose of Neoral.	The control group received a 40% reduction in cyclosporine dose, adjusted to maintain trough levels at 50 to 75 ng/ml.	Before randomization, patients were receiving 1.8 to 6.5 mg/kg/day of cyclosporine (Neoral, Novartis Pharmaceuticals, East Hanover, NJ) in two equally divided doses, 10 mg of prednisolone on alternate days and 1 to 2 mg/kg/day of azathioprine (n=19). Neoral was taken twice daily with doses administered 12 hr apart in both groups. Prednisolone was continued in at the pre-trial dose and azathioprine was stopped in all patients.	No induction.	Before randomization, patients were receiving cyclosporine, prednisone, and azathioprine. Cyclosporine was reduced when rapamycin was introduced.	6 months	Deceased, non-heart beating, and living donors were included. No previous history of cancer reported.
Smith 2008[48]	51	ECSEL1 patients were switched to SRL at 2 months. TAC was stopped and the next day an 8-mg SRL loading dose was given, followed by 4 mg daily. The target level for SRL was 8–12 ng/ml (5–10 ng/ml after 6 months). ECSEL2 patients started SRL at 4 months with the same initial dosing (target 5–10 ng/ml). Once the SRL target level was obtained, TAC was tapered off gradually over 6 weeks.	The control group continued on TAC/MMF (target 5–10 ng/ml after 3 months).	All patients received TAC at a total daily dose of 0.1 mg/kg/day PO (target 10–15 ng/ml) and MMF 1 g twice daily PO.	Induction was with Basiliximab 20 mg IV (days 0, 4) and methylprednisolone 1 g IV intraoperatively.	ECSEL1 group were converted to SRL at 2 months. ECSEL2 group were converted at 4 months	23 months	Living or deceased donor. No previous history of cancer reported.

Stallone 2003[49]	40	After 3 months, patients were randomly assigned to withdraw CsA, and continue on CS and SRL, trough, 10-15 ng/ml. (500 mg of methylprednisolone intraoperatively, then 200 mg of prednisone daily, tapered to 25 mg by day 8 and to 5 mg by month 6. SRL 2 mg/day with an initial loading dose of 15 mg/day, in the first post-transplant day).	After 3 months, patients were randomly assigned to continue the same treatment (CsA (at the initial dose of 8 mg/kg/day, with dosage adjusted to maintain whole-blood trough levels of 150–250 ng/ml), and SRL 2 mg/day (with an initial loading dose of 15 mg/day, in the first post-transplant day).	All patients were initially treated with corticosteroids (500 mg of methylprednisolone intraoperatively, then 200 mg of prednisone daily, tapered to 25 mg by day 8 and to 5 mg by month 6), CsA (at the initial dose of 8 mg/kg/day, with dosage adjusted to maintain whole-blood trough levels of 150–250 ng/ml), and SRL 2 mg/day (with an initial loading dose of 15 mg/day, in the first post-transplant day).	No induction	*De novo* in all arms	12 months	Deceased donors were included. No previous history of cancer reported.
Stallone 2004[50]	90	Patients of group 1 were treated with SRL (15 mg as loading dose, then 5 mg/d, with dosage adjusted to maintain whole-blood trough levels of 6 to 10 ng/ml)	Patients were treated with CsA (4 to 7 mg/kg per d, resulting in whole-blood C2 levels between 600 and 800 ng/ml). In patients who experienced DGF, CsA dose was reduced to 3 to 5 mg/kg per d, with target C2 levels between 400 and 600 ng/ml). Group 2 patients were treated with CsA (10 mg/kg per d, target C2 levels between 1200 and 1400 ng/ml, reduced to 800 to 1000 in case of DGF) and MMF (2 g/d), without SRL.	All patients were given corticosteroids (500 mg of methylprednisolone intraoperatively, then 250 mg of prednisone daily tapered to 25 mg by day 8 and to 5 mg by month 2).	All patients received Basiliximab in two divided doses of 20 mg each on day 0 and day 4 after transplantation. In both groups, immunosuppressive drugs were administered orally starting from 36 to 48 h after engraftment.	*De novo* in all arms	12 months	Deceased donors were included. No previous history of cancer reported.
Stallone 2005[51]	84	CNI and MMF were withdrawn and rapamycin was introduced with an initial loading dose of 0.10 mg/kg for the first day, then 0.04 to 0.06 mg/kg per day, with dosage adjusted to maintain trough levels at 6 to 10 ng/ml; in all patients, the dose of MMF and prednisone remained the same after randomization.	40 patients received a dose reduction of CsA, adjusted to maintain C2 levels of 400 to 500 ng/ml, and 10 received a dose reduction of tacrolimus adjusted to maintain trough levels at 4 to 6 ng/ml. After randomization, the actual dose of CsA was 1.5 to 2.5 mg/kg per d, and the dose of tacrolimus was 0.05 to 0.14 mg/kg per d.	Before randomization, all patients received 1000 mg/d of MMF and 5 mg/d of prednisone. In all patients, the dose of MMF and prednisone remained the same after randomization.	No induction	60 patients were on CsA and 24 patients were on tacrolimus before randomization. After randomization, CNI and MMF were withdrawn and rapamycin was introduced.	24 months	No information on donors reported

Stegall 2003[52]	85	Patients were randomized at the time of transplant to receive sirolimus (target level 12 to 18 ng/ml in the first month).	Patients were randomized at the time of transplant to receive tacrolimus (target level 12 to 15 ng/ml in the first month).	All patients received mycophenolate mofetil (750 mg BID) and prednisone tapered to 10 mg/d by 3 months.	Thymoglobulin induction in all patients (1.5 mg/kg/d on days 0,1,2,4, and 6).	*De novo* in all arms	4 months	Deceased and living donors were included.
Tedesco 2012[53]	205	SRL	TAC, mycophenolate sodium, and prednisone	Not reported	Not reported	At 3 months patients were converted to SRL from TAC.	12 months	Both living and deceased donors were included. No previous history of cancer was reported.
VanGurp 2010[54]	634	A loading dose of sirolimus 6.0 mg was administered with the postoperative dose of tacrolimus and was followed by maintenance doses of 2.0 mg for 28 days and 1.0mg thereafter.	A loading dose of MMF 1.0 g was administered pre-transplant followed by a daily dose of 2.0 g for the first 14 days and 1.0 g daily thereafter.	TAC was given in both groups at an initial daily dose of 0.2mg/kg (one dose preoperatively and one dose postoperatively). Recommended trough levels for TAC in both groups on days 0 to 14 were 10–15 ng/ml. Trough levels were set at 4–8 ng/ml on days15 to 42 and 4–6 ng/ml on days 43 to 183. Treatment with corticosteroids was given in both regimens using a 100–500 mg bolus dose given perioperatively and a 125 mg bolus on day 1. Steroids were then tapered from 20mg on day 2 to 5mg by day 90 and stopped on day 91.	13 patients in SRL and 5 patients in MMF received antibody induction.	*De novo* in all arms	6 months	Both living and deceased donors were included. A total of 5 patients had reported history of malignancy.
Van Hooff 2003[55]	104	The first SRL dose was administered together with the second dose of TAC within 12 hours after reperfusion. SRL loading doses were three times the maintenance doses (i.e., 1.5 mg, 3 mg, or 6 mg). Subsequent daily maintenance doses were 0.5 mg, 1 mg, or 2 mg and were not to be altered. The appropriate dose was given orally once a day together with the morning dose of TAC.	The control group received both tacrolimus and steroids.	TAC was started at 0.2 mg/kg within 12 hours before graft reperfusion. Subsequent doses were adjusted to maintain whole-blood trough concentrations of 10 to 20 ng/ml for days 0 to 14, 10 to 15 ng/ml for days 15 to 42, and 5 to 15 ng/ml thereafter. Steroid doses were 500 mg on day 0 and 125 mg on day 1. Subsequent daily doses were tapered from 20 mg (up to day 14), 15 mg (up to day 28), and 10 mg (up to day 42) to 5 mg until study end.	No induction.	*De novo* in all arms	6 months	Living and deceased donors were permitted. No previous history of cancer reported.

Weir 2011[56]	305	Patients in the CNI arms were completely withdrawn from CNIs within 72 h of randomization, followed by a 2–10 mg loading dose of SRL at least 2 mg once daily adjusted to maintain whole-blood trough levels of 5–10 ng/ml.	In the CNI maintenance group, the CNI was dosed according to each center's protocol.	All patients continued to receive 1–1.5 g of MMF twice daily, and corticosteroids were administered according to center practice consistently across all study arms.	105 patients received ATG, 80 received Basiliximab, 32 received Daclizumab and 1 received Muromonab-CD3	Randomized 30-180 days post transplant, conversion to SRL within 72h of randomization.	24 months	Primary renal allograft from a living or deceased donor within the preceding 30–180 days. No malignancy within previous 5 years (except successfully treated localized non-melanomatous skin cancer)

REFERENCES

1. Barsoum RS, Morsy AA, Iskander IR et al. The Cairo kidney center protocol for rapamycin-based sequential immunosuppression in kidney transplant recipients: 2-year outcomes. Exp Clin Transplant 2007;5(2):649-657.

2. Blydt-Hansen TD, Gibson IW, Birk PE. Histological progression of chronic renal allograft injury comparing sirolimus and mycophenolate mofetil-based protocols. A single-center, prospective, randomized, controlled study. Pediatr Transplant 2010;14(7):909-918.

3. Campbell S, Walker R, Tai SS, Jiang Q, Russ G. Randomized Controlled Trial of Sirolimus for Renal Transplant Recipients at High Risk for Nonmelanoma Skin Cancer. Am J Transplant 2012;12(5):1146-1156.

4. Ekberg H, Tedesco-Silva H, Demirbas A et al. Reduced exposure to calcineurin inhibitors in renal transplantation. New Engl J Med 2007;357(25):2562-2575.

5. Flechner S, Glyda M, Cockfield S et al. The ORION Study: Comparison of Two Sirolimus-Based Regimens versus Tacrolimus and Mycophenolate Mofetil in Renal Allograft Recipients. Am J Transplant 2011;11(8):1633-1644.

6. Flechner SM, Gurkan A, Hartmann A et al. A Randomized, Open-Label Study of Sirolimus Versus Cyclosporine in Primary De Novo Renal Allograft Recipients. Transplantation 2013;95(10).

7. Gallon L, Perico N, Dimitrov BD et al. Long-term renal allograft function on a tacrolimus-based, pred-free maintenance immunosuppression comparing sirolimus vs. MMF. Am J Transplant 2006;6(7):1617-1623.

8. Gelens MACJ, Christiaans MHL, Van Heurn ELW, Berg-Loonen EPM, Peutz-Kootstra CJ, Van Hooff JP. High rejection rate during calcineurin inhibitor-free and early steroid withdrawal immunosuppression in renal transplantation. Transplantation 2006;82(9):1221-1223.

9. Glotz D, Charpentier B, Abramovicz D et al. Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. Transplantation 2010;89(12):1511-1517.

10. Groth CG, Backman L, Morales JM et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: Similar efficacy and different toxicity compared with cyclosporine. Transplantation 1999;67(7):1036-1042.

11. Guba M, Pratschke J, Hugo C et al. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal transplant patients: One-year analysis of a randomized multicenter trial. Transplantation 2010;90(2):175-183.

12. Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J. Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in caucasian recipients of mismatched primary renal allografts: A phase II trial. Transplantation 1999;68(10):1526-1532.

13. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: A randomised multicentre study. Lancet 2000;356(9225):194-202.

14. Kreis H, Cisterne JM, Land W et al. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation 2000;69(7):1252-1260.

15. MacDonald AS. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 2001;71(2):271-280.

16. Machado PGP, Felipe CR, Hanzawa NM et al. An open-label randomized trial of the safety and efficacy of sirolimus vs. azathioprine in living related renal allograft recipients receiving cyclosporine and prednisone combination. Clin Transplant 2004;18(1):28-38.

17. Salgo R, Gossmann J, Schofer H et al. Switch to a sirolimus-based immunosuppression in long-term renal transplant recipients: Reduced rate of (pre-)malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. Am J Transplant 2010;10(6):1385-1393.

18. Sampaio EL, Pinheiro-machado PG, Garcia R et al. Mycophenolate mofetil vs. sirolimus in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen. Clin Transplant 2008;22(2):141-149.

19. Schena FP, Pascoe MD, Alberu J et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation 2009;87(2):233-242.

20. Vitko S, Wlodarczyk Z, Kyllonen L et al. Tacrolimus combined with two different dosages of sirolimus in kidney transplantation: results of a multicenter study. Am J Transplant 2006;6(3):531-538.

21. Watson CJE, Firth J, Williams PF et al. A randomized controlled trial of late conversion from CNI-based to sirolimus-based immunosuppression following renal transplantation. Am J Transplant 2005;5(10):2496-2503.

22. Anil Kumar MS, Heifets M, Fyfe B, et al. Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy. Transplantation 2005;80(6): 807-814.

23. Anil Kumar MS, Irfan SM, Ranganna K, et al. Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: Five-year outcomes. Transplant Immunol. 2008;20(1):32-42.

24. Baboolal K, Zaiac M, Zamauskaite A, et al. This multicentre, randomised study comparing conversion from calcineurin inhibitors (CNIs) to sirolimus versus standard therapy in renal allograft recipients showed a lower rate of development of subsequent malignant disease in the group receiving sirolimus. Am J Transplant 2009;9:238-238.

25. Buchler M, Caillard S, Barbier S, et al. Sirolimus versus cyclosporine in kidney recipients receiving thymoglobulin, mycophenolate mofetil and a 6-month course of steroids. Am J Transplant 2007;7(11):2522-2531.

26. Durrbach A, Rostaing L, Tricot L, et al. Prospective comparison of the use of sirolimus and cyclosporine in recipients of a kidney from an expanded criteria donor. Transplantation 2008;85(3):486-490.

27. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. New England Journal of Medicine 2012;367(4):329-339.

28. Ferguson R, Grinyo J, Vincenti F, et al. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. Am J Transplant 2011;11(1):66-76.

29. Flechner SM, Goldfarb D, Solez K, et al. Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-Year results of a randomized prospective trial compared to calcineurin inhibitor drugs. Transplantation 2007;83(7):883-892.

30. Franz S, Regeniter A, Hopfer H, et al. Tubular Toxicity in Sirolimus- and Cyclosporine-Based Transplant Immunosuppression Strategies: An Ancillary Study From a Randomized Controlled Trial. Am J Kidney Dis 2010;55(22):335-343.

31. Guerra G, Ciancio G, Gaynor JJ, et al. Randomized trial of immunosuppressive regimens in renal transplantation. Journal of the American Society of Nephrology 2011;22(9):1758-1768.

32. Heilman RL, Cortese C, Geiger XJ, et al. Impact of early conversion from tacrolimus to sirolimus on chronic allograft changes in kidney recipients on rapid steroid withdrawal. Transplantation 2012;93(1):47-53.

33. Hendrikx TK, Velthuis JHL, Klepper M, et al. Monotherapy rapamycin allows an increase of CD4+ CD25 bright+ FoxP3+ T cells in renal recipients. Transplant Int 2009;22(9):884-891.

34. Kandaswamy R, Melancon JK, Dunn T, et al. A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients - An interim analysis. Am J Transplant 2005;5(6):1529-1536.

35. Kim MJ, Mayr M, Pechula M, et al. Marked erythrocyte microcytosis under primary immunosuppression with sirolimus. Transplant international 2006;19(1):12-18.

36. Larson TS, Dean PG, Stegall MD, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. American Journal of Transplantation 2006;6(3):514-522.

37. Lebranchu Y, Thierry A, Toupance O, et al. Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: Concept study. Am J Transplant 2009;9(5):1115-1123.

38. Martinez-Mier G, Mendez-Lopez MT, Budar-Fernandez LF, et al. Living related kidney transplantation without calcineurin inhibitors: Initial experience in a Mexican center. Transplantation 2006;82(11):1533-1536.

39. Mendez R, Gonwa T, Yang HC, et al. A prospective, randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: Results at 1 year. Transplantation 2005;80(3):303-309.

40. Morelon E, Lefrancois N, Besson C, et al. Preferential increase in memory and regulatory subsets during T-lymphocyte immune reconstitution after Thymoglobulin induction therapy with maintenance sirolimus vs cyclosporine. Transplant Immunol 2010;23(1):53-58.

41. Nafar M, Alipour B, Ahmadpoor P, et al. Sirolimus versus calcineurin inhibitor-based immunosuppressive therapy in kidney transplantation: A 4-year follow-up. Iranian Journal of Kidney Diseases 2012;6(4):300-306.

42. Pescovitz MD, Vincenti F, Hart M, et al. Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. Br J Clin Pharmacol 2007;64(6):758-771.

43. Pussell B, Russ G, Walker R, et al. Reduced incidence of malignancy in renal transplant recipients converted from calcineurin inhibitors (CNIS) to sirolimus (SRL) compared with those who continued CNI therapy [abstract no: 1582]. Nephrology 2006;11:A24-A24.

44. Refaie AF, Mahmoud KM, Ismail AM, et al. Alemtuzumab preconditioning allows steroid-calcineurin inhibitor-free regimen in live-donor kidney transplant. Experimental and Clinical Transplantation 2011;9(5):295-301.

45. Ruggenenti P, Perico N, Gotti E, et al. Sirolimus versus cyclosporine therapy increases circulating regulatory T cells, but does not protect renal transplant patients given alemtuzumab induction from chronic allograft injury. Transplantation 2007;84(8):956-964.

46. Saudek F, Girman P, Lipar K, et al. Sirolimus/tacrolimus vs MMF/tacrolimus in simultaneous pancreas and kidney transplantation (SPKTX): A 3 year follow-up in a single center. Transplant International 2011;24:223-224.

47. Saunders RN, Bicknell GR, Nicholson ML. The impact of cyclosporine dose reduction with or without the addition of rapamycin on functional, molecular, and histological markers of chronic allograft nephropathy. Transplantation 2003;75(6):772-780.

48. Smith MP, Newstead CG, Ahmad N, et al. Poor tolerance of sirolimus in a steroid avoidance regimen for renal transplantation. Transplantation 2008;84(4):636-639.

49. Stallone G, Di Paolo S, Schena A, et al. Early withdrawal of cyclosporine A improves 1-year kidney graft structure and function in sirolimus-treated patients. Transplantation 2003;75(7):998-1003.

50. Stallone G, Di Paolo S, Schena A, et al. Addition of sirolimus to cyclosporine delays the recovery from delayed graft function but does not affect 1-year graft function. Journal of the American Society of Nephrology 2004;15(1):228-233.

51. Stallone G, Infante B, Schena A, et al. Rapamycin for treatment of chronic allograft nephropathy in renal transplant patients. J Am Soc Nephrol 2005;16(12):3755-3762.

52. Stegall MD, Larson TS, Prieto M, et al. Kidney transplantation without calcineurin inhibitors using sirolimus. Transplant Proc 2003;35(3):S125-S127.

53. Tedesco H, Garcia V, David-Neto E, et al. Conversion from tacrolimus (TAC) to sirolimus (SRL)-based immunosuppressive regimen in kidney transplant recipients: 1 year results. Transplantation 2012;94(10S):985.

54. Van Gurp E, Bustamante J, Franco A, et al. Comparable Renal Function at 6 Months with Tacrolimus Combined with Fixed-Dose Sirolimus or MMF: Results of a Randomized Multicenter Trial in Renal Transplantation. J Transplant 2010.

55. Van Hooff JP, Squifflet JP, Wlodarczyk Z, et al. A prospective randomized multicenter study of tacrolimus in combination with sirolimus in renal-transplant recipients. Transplantation 2003;75(12):1934-1939.

56. Weir MR, Mulgaonkar S, Chan L, et al. Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: A randomized, controlled Spare-the-Nephron trial. Kidney Int 2011;79(8):897-907.