Conversion From Calcineurin Inhibitors to Sirolimus for Chronic Renal Allograft Dysfunction: A Systematic Review of the Evidence

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Background. Conversion from a calcineurin inhibitor to sirolimus has been used as a strategy to improve deteriorating renal allograft function but the efficacy and safety of this intervention is unknown.
Methods. We performed a systematic review of studies that involved conversion from a calcineurin inhibitor to sirolimus in kidney transplantation. The search yielded five randomized trials (n=1,040 patients) and 25 nonrandomized studies (n=977 patients).
Results. In the randomized trials, conversion to sirolimus improved short-term creatinine clearance (weighted mean difference 6.4 mL/min; 95% CI 1.9 to 11.0) compared to controls. In the nonrandomized studies, renal function improved or stabilized in 66% (95% CI 61% to 72%), creatinine clearance improved (weighted mean change 5.7 mL/min; 95% CI 1.4 to 10.1), cholesterol increased (weighted mean change 20.8 mg/dL; 95% CI 11.2 to 30.4) and triglycerides increased (weighted mean change 40.1 mg/dL; 95% CI 18.6 to 61.7). Sirolimus was discontinued by 28% of patients (95% CI 0 to 59%) in the randomized trials and 17% (95% CI 12 to 22%) in the nonrandomized trials.
Conclusion. Conversion to sirolimus is associated with an improvement in short-term renal function. However, given the discontinuation rate and potential side effects, adequately powered randomized trials with longer follow-up of hard outcomes are needed to determine whether this strategy leads to a lasting benefit in the clinical care of transplant recipients.

Keywords: Kidney transplantation, Chronic allograft nephropathy, Calcineurin inhibitor, Sirolimus, Systematic review, Meta-analysis.

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Since 1980, the incidence and prevalence of end-stage renal disease has grown each year in most countries throughout the world (*1*). Kidney transplantation is the treatment of choice for end-stage renal disease as it prolongs survival (*2*), improves quality of life (*3*) and is less costly when compared to dialysis (*3*). However, we are not realizing the full potential of this treatment because many renal transplants fail prematurely. Over 50% of kidney transplants fail because of progressive chronic allograft nephropathy or premature patient death with a functioning transplant (*1*, *4*, *5*). Although patients can return to dialysis after transplant failure, loss of a functioning transplant is associated with a threefold increased risk of death (*6*, *7*), a substantial decrease in quality of life for those who survive (*3*) and a fourfold increase in cost (*1*, *3*). In the United States alone, approximately 5,000 patients each year return to dialysis after kidney transplant failure (*8*). From the perspective of both the patient and the health care system, it is essential to maximize the number of patients who remain alive with functioning renal transplants.

Chronic allograft nephropathy, the main cause of late allograft failure, is characterized by impaired renal function along with the pathological changes of tubular atrophy, interstitial fibrosis, fibrous intimal thickening in the arteries with variable glomerular lesions (*9*). Despite the use of potent immunosuppression, the prevalence of chronic allograft nephropathy may be as high as 94% by one year (*10*, *11*). The pathogenesis of chronic allograft nephropathy is uncertain, but both immune as well as nonimmune factors are involved (*12*). Because calcineurin inhibitor toxicity is thought to contribute to the pathogenesis of chronic allograft nephropathy (*4*, *13–15*), several investigators have attempted to replace calcineurin inhibitors with other immunosuppressive medications. Calcineurin inhibitor withdrawal with addition or continuation of mycophenolate mofetil in patients with established chronic allograft nephropathy has been associated with improved graft survival (*16*). A recent randomized trial showed that calcineurin inhibitor withdrawal with the addition of mycophenolate mofetil was associated with an improvement in renal function compared to addition of mycophenolate mofetil with continued calcineurin inhibitor use (*17*).

Because sirolimus is an immunosuppressive agent that is considered largely free of nephrotoxicity (*18*, *19*), it is increasingly being used to replace calcineurin inhibitors in patients with chronic allograft nephropathy (*20*, *21*). However, the potential risks and benefits of this conversion strategy are not known. Accordingly, the aim of this study was to systematically review all clinical studies that evaluated calcineurin inhibitor conversion to sirolimus in patients with chronic allograft nephropathy. The endpoints of the study involved both efficacy measures (change in renal function, proportion of patients that improved/stabilized) and safety measures (proteinuria, discontinuation rate, serum lipids).

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MATERIALS AND METHODS

Search Strategy

A systematic literature search strategy was conducted on Medline (1966 to November 2005), Embase (1980 to November 2005) and Cochrane Central register of Clinical Trials (4th quarter, 2005) by combining MeSH term "Kidney Transplantation" with (sirolimus or rapamycin or Rapamune or everolimus). We did not restrict the search by language, age or, publication type. In addition, we hand-searched the table of contents of two key transplantation journals (*Transplantation* and the *American Journal of Transplantation*) from January 2003 to November 2005 for relevant publications. Abstracts presented at the American Transplant Congress between 2002 and 2005 were also hand-searched to identify relevant studies. Bibliographies of eligible trials were examined for additional trials. As suggested by experts in the field, a recently published trial (*22*) and abstracts of a large trial submitted for the meetings of American Society of Nephrology 2005 (*23*) and European Society for Organ Transplantation 2005 (*24*) were also included.

Study Selection

Two investigators (A.M., R.S.) assessed all citations for potentially eligible studies. Full publications of all potentially eligible studies were retrieved and were evaluated by two investigators (A.M., R.S.), independently, to decide eligibility. Disagreements were resolved by consensus or by consulting a third reviewer (G.K.). To be eligible, the following inclusion criteria had to be met: (a) patients were recipients of a solitary kidney transplant (e.g., multiorgan transplants excluded); (b) initial immunosuppression consisted of a calcineurin inhibitor but not sirolimus or everolimus; (c) patients were converted from calcineurin inhibitor to sirolimus or everolimus followed by *complete stoppage* of calcineurin inhibitor; and (d) indication for conversion was either *histological* confirmation of chronic allograft nephropathy and/or chronic calcineurin inhibitor toxicity or decreased renal function that was clinically presumed to be due to chronic allograft nephropathy and/or chronic calcineurin inhibitor toxicity. When studies reported patients who were converted to sirolimus for different indications, they were included if chronic allograft nephropathy was the indication for conversion in >50% of the patients or data from the subgroup converted for chronic allograft nephropathy was reported separately. In order to have a uniform study population and minimize heterogeneity, we excluded studies that reported conversion from calcineurin inhibitor to sirolimus for thrombotic microangiopathy, acute calcineurin inhibitor toxicity, malignancy, viral disease, or other individual adverse effects (e.g., hirsutism).

Data Abstraction

Data were abstracted from eligible studies using a standardized data abstraction form. When a study included patients who were converted to sirolimus for different indications, an attempt was made to extract data only from patients with chronic allograft nephropathy and/or chronic calcineurin inhibitor toxicity. The following data were abstracted: patient demographics, reason for conversion, time posttransplant at the time of conversion, renal function, proteinuria, total cholesterol, triglyceride level, dose and target sirolimus levels, patient survival, and graft survival.

Primary efficacy endpoints were change in renal function (serum creatinine or creatinine clearance) and proportion of patients whose renal function either improved or stabilized after conversion to sirolimus. Safety endpoints included serum cholesterol, serum triglyceride level and discontinuation of sirolimus due to adverse events.

Methodological quality of randomized controlled trials was assessed using the Jadad scale, which measures blinding, randomization, withdrawals and dropouts (*25*). A maximum score of five represents the highest quality trial. A score of three or higher is considered good quality (*25*). We did not use any formal scale to assess the methodological quality of single-arm, nonrandomized studies, as no validated scale is available to evaluate this type of study.

Analysis

The randomized trials were analyzed separately from the non-randomized studies. Results of the intention-to-treat analysis were used when provided, although this was clearly stated in only one trial (*26*). Patients in the conversion arm of nonrandomized controlled trials were analyzed along with single-arm nonrandomized studies. For continuous outcomes in the randomized trials, the difference in mean change between baseline and end of treatment value was calculated for individual trials. When variance of change from baseline to end of study value was unavailable, it was assumed to be the same as the variance of the values at the end of the study. Pooled weighted mean differences with 95% confidence intervals were calculated. To analyze continuous outcomes of nonrandomized studies, we calculated mean change from baseline to end of treatment value for individual studies and used weighted means with 95% confidence intervals to combine the results. Heterogeneity was formally tested using the Q-statistic with $P<0.1$ considered significant (*27*). In the absence of significant heterogeneity, individual study effects were pooled using a fixed effects model by inverse variance method (*27*). If there was evidence of heterogeneity, the outcomes were pooled using the random effects model of DerSimonian and Laird (*27*).

For dichotomous outcome (proportion of patients whose renal function either improved or stabilized), two sided 95% confidence intervals were calculated using Watson's score method (*28*) and the single proportions were combined using a general estimating equation based random effects model (*29*). All reported P values are two sided and $P<0.05$ was considered statistically significant. We used an Excel spreadsheet and Cochrane Collaboration's RevMan 4.2 software to perform the analyses.

RESULTS

The search strategy resulted in 662 citations from Medline, 1,228 from Embase, 256 from Cochrane Central Register of Clinical Trials, 19 from the hand-search, and three from experts in the field. (Fig. 1). Of 2,168 citations, 58 were considered potentially eligible. Full-text evaluation identified 31 publications of 30 eligible studies (*20–24*, *26*, *30–54*) (Fig. 1). The primary reviewers disagreed on the eligibility of one study (*55*) that was excluded after consulting a third reviewer.

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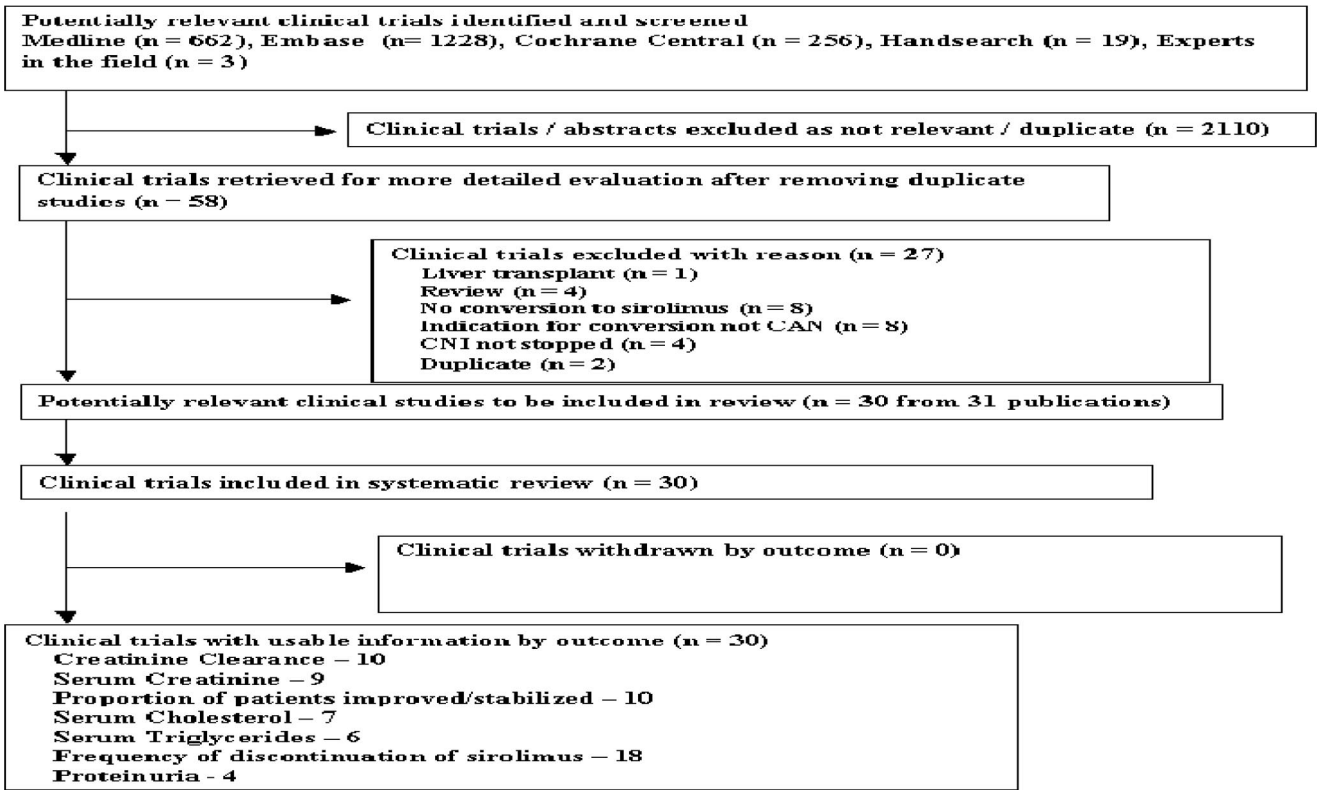

FIGURE 1. Search results and selection of trials for analysis.

Trial Characteristics

We identified five randomized controlled trials involving 1,040 patients, two nonrandomized controlled trials and 23 single-arm, nonrandomized studies. The control arm of the nonrandomized trials was ignored and the conversion arm was combined with the single-arm studies. In all, 977 patients underwent conversion to sirolimus in nonrandomized studies (Table 1). None of the identified studies involved everolimus. Of the five randomized trials, one (*46*) was stopped prematurely due to adverse events in the conversion arm. Two of the other four randomized trials (*22*, *26*) were published as full journal article and the other two studies (*23*, *24*, *32*) were presented in abstract form. Patients included in the largest randomized trial (CONVERT Trial; n=830) (*23*) were stratified according to baseline renal function. Sample size of randomized trials ranged from 31 to 830 and the follow-up time ranged from six to 24 months. None of the randomized trials was blinded and renal biopsy was necessary for inclusion in only one study (*22*). Dose of calcineurin inhibitor was reduced by 40% in the control group in one trial (*22*), whereas it was unchanged in the other studies. The quality score on the Jadad scale was less than three for four of the five trials (*22–24*, *32*, *46*) indicating poor quality.

Of the nonrandomized studies, 11 were published as full journal articles (*20*, *21*, *31*, *33*, *35–37*, *43*, *48*, *53*, *54*) and the other 14 were presented in abstract form (*30*, *34*, *38–42*, *44*, *45*, *47*, *49–52*) (Table 1). Sample size of individual studies ranged from 10 to 107 and the follow-up time ranged from six to 36 months. Median time from transplantation to conversion ranged from 15.6 to 104 months. Conversion to sirolimus was undertaken on clinical criteria alone in eight studies (*30*, *33*, *39*, *40*, *42*, *43*, *48*, *53*) while the rest used histological information in addition to clinical parameters.

Change in Renal Function

Three randomized trials (*22*, *26*, *32*) reported creatinine clearance at baseline and at the end of follow-up. In the CONVERT Trial (*23*), the stratum of patients with creatinine clearance 20 to 40 ml/min (n=90) could not be included in meta-analysis because data were not provided. As change in creatinine clearance from baseline was available in the stratum with baseline creatinine clearance greater than 40 ml/min (n=740), this stratum was included in this analysis. In all four studies, the change from baseline in creatinine clearance was positive in the sirolimus conversion group, whereas it was negative in the control arm remaining on calcineurin inhibitor (Fig. 2A). The studies were heterogeneous (Q=9.6, P=0.02) and the weighted mean difference in change from baseline was 6.4 mL/min (95% confidence interval 1.9 to 11.0 ml/min; P=0.006; Fig. 2A). Six nonrandomized studies (*42*, *43*, *47*, *49*, *51*, *54*) reported creatinine clearance at baseline and at the study end. Mean change in creatinine clearance from baseline to study end was heterogeneous across the studies (Q=18.0, P=0.003). Pooled estimate showed that mean creatinine clearance improved significantly after sirolimus conversion (weighted mean change 5.7 ml/min; 95% confidence interval 1.4 to 10.1 mL/min; P=0.003; Fig. 2B). Ten nonrandomized studies (*21*, *34*, *35*, *37*, *39*, *41*, *43*, *49*, *50*, *54*) reported mean creatinine at baseline and at study end, of which one (*41*) could not be included in analysis as variance was not reported. The studies were homogeneous (Q=12.2, P=0.14) and the pooled estimate showed a significant decrease in creati-

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TABLE 1. Characteristics of included studies[a]

Study	Year	Design	Published or abstract	Sample size	Time since transplantation	Follow-up (months)	Reason for conversion	Efficacy outcomes
Baboolal (*32*)	2004	RCT	Abstract	30/25	6–120 (Range)	6	CrCl >20 and <70 mL/min	CrCl
Watson (*26*)	2005	RCT	Published	19/19	>6 mo	12	S. Cr >120 and <400 μmol/L	GFR
van Gelder (*46*)	2003	RCT	Published	15/18	12	NR	12 months post-Tx on steroid-free protocol	None
Schena (*23*, *24*)	2005	RCT	Abstract	555/275	36 (25.2)/38.4 (24)	12	6–120 months post-Tx	CrCl
Stallone (*22*)	2005	RCT	Published	34/50	21 (9)/24 (7)	24	12–36 months post-Tx, S.Cr >1 and <3 mg/dl, CAN on biopsy	CrCl
Egidi (*37*)	2003	Single arm	Published	36	15.6 (21.6)	6	Bx: CAN or CNI toxicity (n=21), CrCl >30 or creatinine <2.8	Creatinine
Letavernier (*40*)	2004	Single arm	Abstract	68	55 (52)	24	Deteriorating graft function	Proteinuria
Lord (*41*)	2004	Single arm	Abstract	48	51.9 (57.5)	12	Bx: CAN or CNI toxicity (n=33)	Creatinine
Guasch (*38*)	2004	Single arm	Abstract	30	NR	12	Bx: CAN and deteriorating graft function	Progression
Sankaranarayanan (*44*)	2004	Single arm	Abstract	31	NR	12	Bx: CAN	CrCl
Thaunat (*45*)	2005	Single arm	Abstract	46	NR	24 (27.5) weeks	Bx: CAN	None
Hadaya (*39*)	2004	Single arm	Abstract	23	21.9 (median)	4.1	CAN (n=18)	Creatinine
Citterlo (*33*)	2003	Single arm	Published	19	104 (73)	6	Declining graft function, creatinine >2 and <4.5 mg/dl or proteinuria >500 vmg/d	Progression
Diekmann (*35*)	2001	Single arm	Published	22	94.5 (63)	6	Bx: CNI toxicity	Creatinine
Wyzgal (*21*)	2002	Single arm	Published	13	6–60 (Range)	6	Bx: CNI toxicity, creatinine >1.6 and <4 mg/dl, no proteinuria	Creatinine
Sundberg (*48*)	2004	Single arm	Published	12	23	NR	CAN	Progression
Renders (*31*)	2004	Single arm	Published	13	76.4 (50.4)	11.3 (5.6)	Bx: CAN, declining graft function	Creatinine and progression
Dominguez (*20*)	2000	Single arm	Published	12	38	20	Bx: CNI toxicity, >20% increase in creatinine × 6 mo	Progression
Diekmann (*36*)	2004	Single arm	Published	59	88 (7.2)	12	Bx: CNI toxicity with declining graft function	Creatinine
Paczek (*42*)	2003	Single arm	Abstract	54	NR	6	Mild to moderate renal dysfunction	GFR
Peddi (*43*)	2004	Single arm	Published	60	61	12	GFR >30 and <70 mL/min	CrCl, creatinine
Amm (*30*)	2003	Single arm	Abstract	57	NR	6–12 (Range)	Clinical CAN	Progression
Wali (*47*)	2003	Single arm	Abstract	107	NR	17.7 (7.6)	Bx: CAN, increased creatinine	CrCl and progression
Moneim (*49*)	2005	Single arm	Abstract	43	19.1	36.6	Renal dysfunction, CNI toxicity	CrCl, Creatinine
Lacha (*50*)	2005	Single arm	Abstract	34	NR	12	CNI toxicity	Creatinine
Hoecker (*51*)	2005	Non-random controlled	Abstract	10/9	51 (9.9)/56.3 (19.9)	12	CNI toxicity	CrCl
Ruiz (*52*)	2005	Single arm	Abstract	94	NR	6	CAN	None
Wu (*53*)	2005	Non-random controlled	Published	16/16	84 (54)	6	>24 months post-Tx, worsening renal function	Progression
Bumbea (*54*)	2005	Single arm	Published	43	54	27 (1.5)	CAN or CNI toxicity	CrCl, creatinine
Crowley (*34*)	2003	Single arm	Abstract	45	60 (48)	10.5 (7.2)	Bx: CAN/CNI toxicity or increased creatinine (n=38)	Creatinine

[a] Time since transplant is average number of months with standard deviation in brackets unless otherwise stated.

RCT, randomized controlled trial; Bx, biopsy; GFR, glomerular filtration rate; CAN, chronic allograft nephropathy; CNI, calcineurin inhibitor; CrCl, creatinine clearance; NR, not reported; Bx, biopsy; S Cr, serum creatinine.

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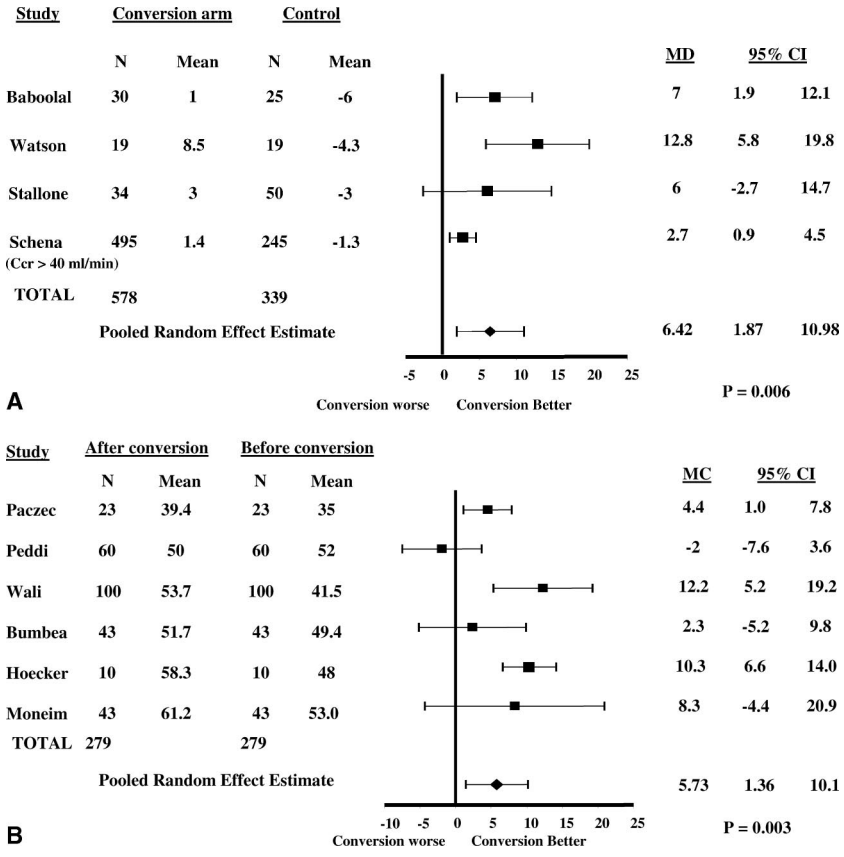

FIGURE 2. Change from baseline in creatinine clearance after conversion to sirolimus. (A) Randomized controlled trials. (B) Nonrandomized studies. CI, confidence interval; MD, mean difference in change in creatinine clearance in ml/min from baseline between conversion and control arm; MC, mean change in creatinine clearance in mL/min from baseline.

nine with sirolimus conversion (weighted mean change −0.19 mg/dl; 95% confidence interval −0.32 to −0.06; $P=0.004$).

The number of patients whose renal function either improved or stabilized was reported by 11 studies (*20*, *30*, *31*, *33*, *35*, *36*, *38*, *47*, *48*, *51*, *53*). One study published in 2001 (*35*) was excluded because the same patients were included in a follow-up study published in 2004 (*36*). The criteria used by individual studies to define improvement or stabilization in renal function are shown in Table 2. The results were homogeneous across studies ($Q=9.8$, $P=0.37$). Pooled estimate showed that renal function either improved or stabilized in 66% (95% confidence interval 61% to 72%) of the patients (Fig. 3).

Serum Lipids

Serum cholesterol and triglycerides increased significantly in the conversion group in one randomized controlled trial (*22*). In another randomized trial (*26*), use of statins significantly increased in the conversion group, although serum lipids did not change significantly. Serum cholesterol level was reported in eight nonrandomized studies (*31*, *33–37*, *43*, *54*). Results from one study (*35*) were not included in

TABLE 2. Criteria used by different single-arm nonrandomized studies to define improvement or stabilization of renal function

Study	Criteria for improvement or stabilization of renal function	Number of patients improved or stabilized (n/N)	Proportion (%)
Guasch (*38*)	Decline in glomerular filtration rate <2 mL/min	18/30	60
Citterlo (*33*)	Not stated	11/19	58
Dominguez (*20*)	<10% increase in serum creatinine	10/12	83
Diekmann (*36*)	<0.3 mg/dL increase in serum creatinine	32/59	54
Amm (*30*)	Not stated	42/57	74
Wali (*47*)	Increase in creatinine clearance >0 mL/min	70/100	70
Sundberg (*48*)	Not stated	9/12	75
Renders (*31*)	Not stated	10/13	77
Wu (*53*)	<10% increase in serum creatinine	10/16	62.5
Hoecker (*51*)	Not stated	7/10	70

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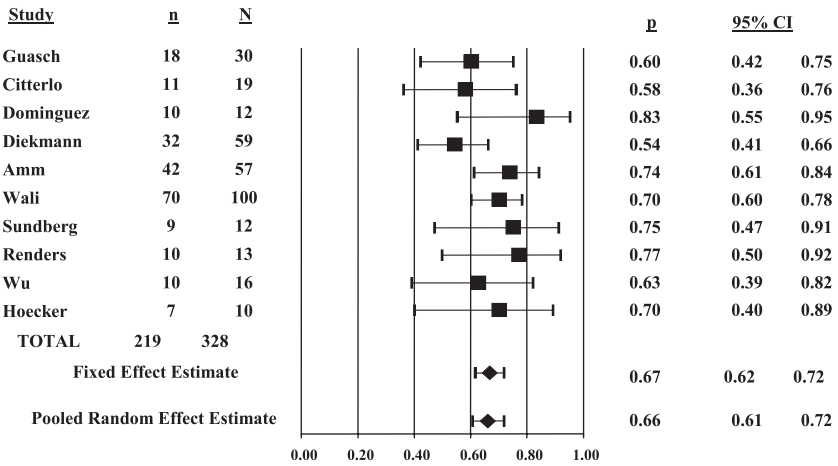

FIGURE 3. Proportion of patients in nonrandomized studies with improved or stabilized renal function after conversion to sirolimus. CI, confidence interval; p, proportion of patients with improved or stabilized renal function.

the meta-analysis as the patients from this study were also included in a larger study (*36*). The change in serum cholesterol from baseline was homogeneous across the studies (Q=2.1, *P*=0.91). Pooled estimate showed that there was significant increase in serum cholesterol after conversion to sirolimus (weighted mean change 20.8 mg/dL; 95% confidence interval 11.2 to 30.4 mg/dL; *P*<0.0001). Serum triglyceride level was reported in seven nonrandomized studies (*31*, *33*, *35–37*, *43*, *54*). Once again, only the larger of the two studies by Diekmann (*36*) was included in the analysis. The results were homogenous (Q=7.2, *P*=0.20). Pooled estimate showed that conversion to sirolimus resulted in significant increase in serum triglyceride level (weighted mean change 40.1 mg/dL; 95% confidence interval 18.6 to 61.7 mg/dL; *P*=0.0003).

Proteinuria After Conversion to Sirolimus

Two randomized trials reported data on proteinuria (*22*, *26*). In the report by Stallone et al., proteinuria was similar in both groups at baseline (0.75±0.43 vs. 0.83±0.19 g/24-hours). In the other trial, mean values were not provided but it appeared from a figure that most patients had less than 0.5 g/24-hours of proteinuria (*26*). In one randomized trial (*22*), mean daily proteinuria tended to increase after conversion to sirolimus while another randomized trial (*26*) did not show any significant change in mean daily proteinuria. The data could not be pooled because variance was not reported in one study. Five nonrandomized trials (*21*, *40*, *50–52*) reported proteinuria before and after conversion. Four of these studies reported baseline proteinuria in grams/24-hours with a range from 0.39 to 1.9 g/24-hours (*21*, *40*, *50*, *52*). The other study reported a baseline protein excretion of 183 ± 639 mg/m^2/24-hours (*51*). Due to both clinical as well as highly significant statistical heterogeneity, the studies were not pooled.

Discontinuation of Sirolimus Due to Adverse Events

Of the five randomized trials, one was stopped prematurely (*46*) because 9/15 patients in the conversion arm developed painful oral ulcers. The three randomized trials that reported sirolimus discontinuation rate (*26*, *32*, *46*) were heterogeneous for discontinuation rate (Q=14.7, *P*<0.001). In the pooled estimate of randomized trials, 28% (95% confidence interval 0 to 59%) of patients discontinued sirolimus due to adverse effects. Fifteen nonrandomized studies (*20*, *21*, *30*, *31*, *33*, *34*, *36*, *37*, *39*, *40*, *43*, *45*, *47*, *53*, *54*) reported discontinuation rates of sirolimus (Table 3). The studies were heterogeneous for discontinuation rate (Q=59.9, *P*<0.00001). In the pooled estimate of nonrandomized studies, 17% (95% confidence interval 12% to 22%) of patients discontinued sirolimus due to adverse effects. Most common reported causes of discontinuation were proteinuria (n=14), anemia (n=8), pneumonia (n=4), bad taste (n=3), and decreased renal function (n=4).

Acute Rejection After Conversion to Sirolimus

None of the patients in three (*22*, *26*, *32*) of the randomized trials experienced acute rejection after conversion, whereas a fourth trial (*46*) was prematurely stopped due to other reasons. In the CONVERT trial (*23*), rejection rates were not significantly different between the two study arms in patients with baseline creatinine clearance greater than 40 mL/min (2.0% vs. 2.4%, *P*=1.0). Fifteen nonrandomized studies (*20*, *21*, *30*, *31*, *33*, *36*, *37*, *39*, *41–43*, *47*, *48*, *51*, *54*) reported acute rejection rate. Overall, 20 of 593 (3.4%) patients had acute rejection following sirolimus conversion. Of these, only two resulted in graft loss.

DISCUSSION

Our systematic review found that conversion from calcineurin inhibitors to sirolimus in kidney transplant recipients with chronic allograft nephropathy was associated with improved creatinine clearance in the short term. Renal function is improved or stabilized in the majority of the patients. However, this strategy was associated with a high discontinuation rate, as well as an increase in the serum cholesterol and triglyceride concentration.

Studies have shown that withdrawal of calcineurin inhibitor alone is associated with improved creatinine clearance both in stable patients with kidney transplantation (*56*) or patients with chronic allograft nephropathy (*17*). Therefore, improved creatinine clearance seen in this study could simply be due to withdrawal of calcineurin inhibitor rather that due to a beneficial effect of sirolimus. Also, follow up of most of the studies was relatively short, often less than 12 months. Therefore, it is uncertain if the initial increase in creatinine

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TABLE 3. Discontinuation of sirolimus due to adverse effects

Study	No. discontinued (%)	Reasons for discontinuation
Baboolal (*32*) (RCT)	4/30 (13.3)	Not specified
Watson (*26*) (RCT)	2/19 (18.8)	Acneiform rash
van Gelder (*46*) (RCT)	9/15 (60.0)	RCT prematurely stopped because 9/15 patients developed painful oral ulcers
Schena (*15*) (RCT)	Data not available	
Egidi (*37*)	4/62 (6.5)	Leucopenia (1), gastrointestinal intolerance (1), bad taste (2)
Letavernier (*40*)	19/68 (27.9)	Not specified
Hadaya (*39*)	12/23 (52.2)	Nephrotic proteinuria (7), acute rejection (1), pancreatitis (1), hepatitis (1), abscess (1), wound healing (1), stroke (1), high triglyceride (1), increase in creatinine (1)
Citterlo (*33*)	2/19 (10.5)	Eyelid edema (1), pruritus (1)
Wyzgal (*21*)	2/13 (23.1)	Pneumonia (2)
Dominguez (*20*)	4/20 (20)	Pneumonia (2), PTLD (1), oral ulcer (1)
Diekmann (*36*)	4/59 (5.1)	Pneumonia (1), nephrotic proteinuria (1), bad taste (1), diarrhea (1)
Peddi (*43*)	13/60 (21.7)	Hyperlipidemia (55%), diarrhea (37%), rash (31.7%), anemia (26.7%)
Amm (*30*)	4/57 (7.0)	Diarrhea, low white blood cell, low platelet count
Wali (*47*)	7/107 (6.5)	Not specified
Crowley (*34*)	8/45 (17.8)	Increase in creatinine (2), allergic reaction (3), high triglyceride (2), leucopenia (1), fatigue (1)
Renders (*31*)	0/13	None discontinued
Wu (*53*)	3/16 (18.75)	Itching, rash-2, edema-1
Bumbea (*54*)	13/43 (30.2)	Proteinuria (6), low platelets (1), increased s. cholesterol (1), decreased creatinine (1), edema (1)
Thaunat (*45*)	8/46 (17.4)	Anemia (8)

RCT, randomized controlled trial; PTLD, posttransplant lymphoproliferative disease.

clearance will be sustained over longer period of time. Although some studies (*31*, *34*, *44*, *57*) had an initial improvement in renal function followed by decline towards baseline with continued follow-up, all four randomized trials (*22*, *23*, *26*, *32*) showed slower decline in renal function after conversion compared to control arm, which is reassuring. It should be noted, however, that only on-therapy results of the CONVERT trial were available (*23*) and the results of intention-to-treat analysis may well be different. Also, in the CONVERT trial, only the results of the stratum with baseline creatinine clearance greater than 40 mL/min were available. It is unclear if these results apply to the patients with lower baseline renal function. In all, 68% of the patients in Watson trial (*26*) had baseline creatinine clearance <40 ml/min and the trials by Baboolal (*32*) and Stallone (*22*) included patients with wide range of baseline renal function. Despite this, all three of these randomized trials showed improvement in renal function following conversion to sirolimus. The role of baseline renal function could not be explored further due to limited availability of data.

The discontinuation rate of sirolimus is somewhat concerning. However, the pooled estimate of discontinuation should be interpreted with caution, as possible reporting bias cannot be excluded. In addition, the discontinuation rate in this analysis is similar to other new therapies in renal transplantation and may reflect an initial experience of a novel treatment.

Increased proteinuria was the most common serious side effect leading to discontinuation. Increased proteinuria is an increasingly recognized complication after conversion to sirolimus in both adult (*58*) as well as pediatric (*59*) kidney transplant recipients. Proteinuria from native kidneys has been reported in clinical islet transplantation treated with sirolimus, which resolved after discontinuation of sirolimus (*60*). The mechanism of increased proteinuria remains uncertain, although increased glomerular pressure due to removal of afferent arteriolar vasoconstriction secondary to calcineurin inhibitor may contribute (*57*). Recently, Saurina et al. (*61*) have demonstrated that glomerular capillary pressure tends to increase after conversion from calcineurin inhibitor to sirolimus. This finding suggests that blockade of the renin-angiotensin system, which reduces glomerular pressure, might be useful in this setting (*61*). Myers et al. showed that cyclosporin dose reduction or withdrawal in patients with heart transplants and cyclosporin nephropathy of native kidneys, was associated with increase in proteinuria (*62*). In this study, albuminuria increased from approximately 0.23 g/day to 0.79 g/day (*62*). This amount of proteinuria suggests that reduction in the calcineurin inhibitor itself may play a major role in the proteinuria seen with sirolimus conversion. Direct toxicity of sirolimus cannot be ruled out since sirolimus is associated with delayed recovery from delayed graft function (*63*) and acute renal failure in native kidney glomerulonephritis (*64*). Finally, as shown by Watson et al. (*26*), allografts with proteinuria may continue to have worsening proteinuria even in the absence of sirolimus conversion.

Because posttransplantation proteinuria has been shown to adversely affect both graft and patient survival (*65*), we recommend close monitoring of urinary protein excretion in patients who are converted to sirolimus for chronic allo-

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graft nephropathy. Increased proteinuria usually responds to a reduction in dose or withdrawal of sirolimus (*39*, *40*) Calcineurin inhibitor withdrawal is associated with increased risk of acute rejection (*66*). Recent studies of calcineurin inhibitor withdrawal from sirolimus based triple therapy also have shown increased risk of acute rejection after calcineurin inhibitor withdrawal (*67*). The rejection rate seen in this analysis was comparatively small and rarely led to graft loss.

Dyslipidemia is a known complication of sirolimus therapy (*68*). A clinically important increase in both serum cholesterol and triglycerides was found in our analysis, which was homogeneous across all studies. Conflicting data exist on the role of lipids as an independent predictor of graft and patient survival. Booth et al. (*69*) found no independent effect of posttransplant total cholesterol whereas Roodnat et al. (*70*) showed that total cholesterol was an independent predictor of patient and graft survival. Over a 13-year follow-up period, Ponticelli et al. (*71*) found that low-density lipoprotein (LDL) cholesterol was an independent risk factor for graft failure or death. They also found that cardiovascular disease was the most common cause of death and that total cholesterol, LDL and triglycerides were each independent predictors of cardiovascular events (*71*). However, it should be noted that dyslipidemia associated with sirolimus therapy has not been associated with an increase in cardiovascular mortality (*68*). Chueh and Kahan showed that after 48 months, patients receiving cyclosporine/sirolimus had the same incidence of cardiac events as those receiving cyclosporine/prednisone (*68*). In another analysis, Blum used data from two large sirolimus trials to model cardiac events with the Framingham risk model (*72*). This analysis showed that an increase in mean cholesterol of 17 mg/dL would increase the incidence of coronary heart disease by 1.5 cases per 1,000 patient-years and coronary artery disease death by 0.7 events per 1,000 patient-years (*72*). The author concluded that this additional risk was small compared to the baseline risk of patients with kidney transplantation (*72*). Finally, the clinical impact of the dyslipidemia associated with sirolimus will likely be confounded by the increasing use of statins which have been recommended for this population.

Although sirolimus use may adversely effect proteinuria and lipid status, it may have a beneficial effect on malignancies. Kauffman et al. reported that sirolimus use was associated with reduced incidence of posttransplant malignancies (*73*). Because malignancy accounts for approximately 11% of the known causes of patient death with functioning renal allograft (*74*), conversion to sirolimus may improve long-term survival by reducing malignancy-related death.

There are several limitations of our systematic review. Although we found a relatively large number of studies examining the strategy of sirolimus conversion in chronic allograft nephropathy, most of the studies were nonrandomized and had no concurrent control group. In addition, studies used different measures of renal function and different criteria to define improvement or stabilization of renal function. Such studies are limited by possible selection bias as well as measurement bias, which may ultimately affect the study result. Finally, a large proportion of the studies, both randomized and nonrandomized, were in abstract form, including the largest randomized trial. It is not clear whether this preliminary data will ever be published in a peer-reviewed journal and whether the final results may be different then reported currently.

The deteriorating kidney transplant must be approached as a solvable problem (*75*). Few would agree that the status quo is acceptable when a kidney transplant is failing and a search for treatable conditions should be made (*75*). We have found that patients with chronic allograft dysfunction benefit from replacing the calcineurin inhibitor with sirolimus. However, the documented benefit to date, has been a short-term improvement in renal function. Although this finding is encouraging, an adequately powered randomized controlled trial of sufficient duration addressing a clinically meaningful outcome (e.g., composite endpoint of doubling of serum creatinine, return to dialysis, repeat transplantation, or death) is necessary to address whether this strategy leads to a lasting benefit in the clinical care of transplant recipients.

REFERENCES

1. US Renal data system. US Renal Data System: Excerpts from the USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. *Am J Kidney Dis* 2003; 42: s1–s230.
2. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; 341: 1725.
3. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* 1996; 50: 235.
4. Ojo AO, Hanson JA, Wolfe RA, et al. Long-term survival in renal transplant recipients with graft function. *Kidney Int* 2000; 57: 307.
5. Chapman JR. Longitudinal analysis of chronic allograft nephropathy: clinicopathologic correlations. *Kidney Int* 2005; S108–S112.
6. Kaplan B, Meier-Kriesche HU. Death after graft loss: an important late study endpoint in kidney transplantation. *Am J Transplant* 2002; 2: 970.
7. Knoll G, Muirhead N, Trpeski L, et al. Patient survival following renal transplant failure in Canada. *Am J Transplant* 2005; 5: 1719.
8. USRDS. United States Renal Data System. Accessed February 13, 2006. www.usrds.org
9. Halloran PF, Melk A, Barth C. Rethinking Chronic Allograft Nephropathy: The Concept of Accelerated Senescence. *J Am Soc Nephrol* 1999; 10: 167.
10. Morales JM. Immunosuppressive treatment and progression of histologic lesions in kidney allografts. *Kidney Int Suppl* 2005; S124–S130.
11. Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; 349: 2326.
12. Paul LC. Chronic allograft nephropathy: An update. *Kidney Int* 1999; 56: 783.
13. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease: A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; 108: 2154.
14. de Mattos A, Olyaei A, Bennett W. Nephrotoxicity of immunosuppressive drugs: Long-term consequences and challenges for the future. *Am J Kidney Dis* 2000; 35: 333.
15. Joosten S, van Kooten C, Paul L. Pathogenesis of chronic allograft rejection. *Transplant Int* 2003; 16: 137.
16. Weir MR, Blahut S, Drachenburg C, et al. Late calcineurin inhibitor withdrawal as a strategy to prevent graft loss in patients with suboptimal kidney transplant function. *Am J Nephrol* 2004; 24(4): 379.
17. Suwelack B, Gerhardt U, Hohage H. Withdrawal of Cyclosporine or Tacrolimus After Addition of Mycophenolate Mofetil in Patients With Chronic Allograft Nephropathy. *Am J Transplant* 2004; 4: 655.
18. Morales JM, Andres A, Rengel M, Rodicio JL. Influence of cyclosporin, tacrolimus and rapamycin on renal function and arterial hypertension after renal transplantation. *Nephrol Dial Transplant* 2001; 16: 121.
19. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: A review of the evidence. *Kidney Int* 2001; 59: 3.
20. Dominguez J, Mahalati K, Kiberd B, et al. Conversion to rapamycin immunosuppression in renal transplant recipients: report of an initial experience. *Transplantation* 2000; 70: 1244.
21. Wyzgal J, Paczek L, Senatorski G, et al. Sirolimus rescue treatment in

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

calcineurin-inhibitor nephrotoxicity after kidney transplantation. *Transplant Proc* 2002; 34: 3185.
22. 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: 3755.
23. Schena FP, Wali RK, Pascoe MD, et al. Efficacy and safety of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: 12-month results from a large, randomized, open label, comparative trial [Abstract]. Available at: http://www.asn-online.org/home.aspx. Accessed October 12, 2005.
24. Schena FP, Wali RK, Pascoe MD, et al. A Randomized, open label, comparative evaluation of the safety and efficacy of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients [Abstract]. *Transpl Int* 2005; 18 (Suppl 1): 155.
25. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17(1): 1.
26. Watson CJ, 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: 2496.
27. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger MD-SGADG, ed. *Systematic Reviews in Health Care.* BMJ Publishing Group, 2001; 285–312.
28. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998; 17(8): 857.
29. Zhou XH, Brizendine EJ, Pritz MB. Methods for combining rates from several studies. *Stat Med* 1999; 18(5): 557.
30. Amm J, Ramamurthy G, Degala A, et al. Rapamycin substitution for calcineurin inhibitors in renal transplant recipients with chronic allograft nephropathy [Abstract]. *Am J Transplant* 2003; 3 (S5): 211.
31. Renders L, Steinbach R, Valerius T, et al. Low-dose sirolimus in combination with mycophenolate mofetil improves kidney graft function late after renal transplantation and suggests pharmacokinetic interaction of both immunosuppressive drugs. *Kidney Blood Press Res* 2004; 27: 181.
32. Baboolal K. Six month interim analysis of a phase III prospective, randomised study to compare conversion from calcineurin inhibitors to rapamycin in established renal allograft recipients with mild to moderate renal insufficiency [Abstract]. *Am J Transplant* 2004; 4 (S8): 220.
33. Citterlo F, Scata MC, Violi P, et al. Rapid conversion to sirolimus for chronic progressive deterioration of the renal function in kidney allograft recipients. *Transplant Proc* 2003; 35: 1292.
34. Crowley KL, Hardinger KL, Koch M, et al. A single center experience with sirolimus conversion therapy in renal allograft recipients [Abstract]. *Am J Transplant* 2003; 3 (S5): 354.
35. Diekmann F, Waiser J, Fritsche L, et al. Conversion to rapamycin in renal allograft recipients with biopsy-proven calcineurin inhibitor-induced nephrotoxicity. *Transplant Proc* 2001; 33: 3234.
36. Diekmann F, Budde K, Oppenheimer F, et al. Predictors of success in conversion from calcineurin inhibitor to sirolimus in chronic allograft dysfunction. *Am J Transplant* 2004; 4: 1869.
37. Egidi MF, Cowan PA, Naseer A, Gaber AO. Conversion to sirolimus in solid organ transplantation: a single-center experience. *Transplant Proc* 2003; 35: 131S.
38. Guasch A, Near M, Selvaraj S. Determinants of long term preservation of renal function after conversion to sirolimus in patients with chronic allograft nephropathy [Abstract]. *Am J Transplant* 2004; 4(S8): 266.
39. Hadaya K, Wissing M, Broeders N, Abramowicz D. Nephrotic range proteinuria and other severe adverse events after conversion to sirolimus in renal transplantation: Is high exposure to sirolimus responsible? [Abstract]. *Am J Transplant* 2004; 4(S8): 433.
40. Letavernier E, Peraldi M, Kreis H, Legendre C. Proteinuria following switch from calcineurin inhibitors to sirolimus: A retrospective study [Abstract]. *Am J Transplant* 2004; 4(S8): 161.
41. Lord H, Boucher A, Morin M, Dandavino R. Late conversion to sirolimus in a kidney transplant population: Is it worth? [Abstract]. *Am J Transplant* 2004; 4 (S8): 221.
42. Paczek L, Dedochova J, Matl I, Pohanka E. An open non comparative pilot study of renal function after conversion from cyclosporin (CsA) to sirolimus (SRL) in stable renal allograft recipients with mild to moderate renal insufficiency [Abstract]. *Am J Transplant* 2003; 3 (S5): 217.
43. Peddi VR, Jensik S, Pescovitz M, et al. An open-label pilot study evaluating the safety and efficacy of converting from calcineurin inhibitors to sirolimus in established renal allograft recipients with moderate renal insufficiency. *Clin Transplant* 2005; 19: 130.
44. Sankaranarayanan N, Balarezo F, Alleman K, et al. Chronic allograft damage index $(CADI)^2$ scoring at conversion from calcineurin inhibitors (CI) to sirolimus predicts renal outcome in kidney transplant recipients[Abstract]. *Am J Transplant* 2004; 4 (S8): 296.
45. Thaunat O, Lechaton, Mamzer M, et al. Late introduction of sirolimus introduces anemia of inflammatory state in renal transplant recipients. [Abstract]. *Am J Transplant* 2005; 5 (S11): 554.
46. van Gelder T, ter Meulen CG, Hene R, et al. Oral ulcers in kidney transplant recipients treated with sirolimus and mycophenolate mofetil. *Transplantation* 2003; 75: 788.
47. Wali RK, Richards A, Cunningham R, et al. Can we change the progressive decay in graft function after the onset of chronic allograft nephropathy (CAN) in the recipients of kidney allografts? (preliminary results of the ongoing study) [Abstract]. *Am J Transplant* 2003; 3 (S5): 336.
48. Sundberg AK, Rohr MS, Hartmann EL, et al. Conversion to sirolimus-based maintenance immunosuppression using daclizumab bridge therapy in renal transplant recipients. *Clin Transplant* 2004; 18: 61.
49. Moneim HA, Fletchner SM, George P, et al. Conversion to and from sirolimus in renal and hepatic transplant recipients treated with calcineurin inhibitors:Effect on renal function.[Abstract]. *Am J Transplant* 2005; 5(S11): 376.
50. Lacha J, Bartosova K, Matl I, et al. Sirolimus associated proteinuria. Study in kidney (KTx) and heart (HTx) recipients after calcineurin inhibitor (CNI) withdrawal and in KTX with sirolimus de novo immunosuppression [Abstract]. *Am J Transplant* 2005; 5: 414.
51. Hoecker B, Feneberg R, Koepf S, et al. Switch of immunosuppression from calcineurin inhibitors (CNI) to sirolimus (SRL) in pediatric renal transplant recipients with CNI toxicity [Abstract]. *Am J Transplant* 2005; 5(S11): 497.
52. Ruiz JC, Diekmann F, Campistol JM, et al. Evolution of proteinuria after conversion from calcineurin inhibitors (CNI) to sirolimus (SRL) in renal transplant patients. A multicenter study [Abstract]. *Am J Transplant* 2005; 5(S11): 519.
53. Wu M-S, Chang C-T, Hung C-C. Rapamycin in patients with chronic renal allograft dysfunction. *Clin Transplant* 2005; 19: 236.
54. Bumbea V, Kamar N, Ribes D, et al. Long term results in renal transplant patients with allograft dysfunction after switching from calcineurin inhibitors to sirolimus. *Nephrol Dial Transplant* 2005; 20: 2517.
55. Johny KV, Nampoory MR, Hamid MH, et al. Low-dose sirolimus in combination with mycophenolate in calcineurin inhibitor elimination: the Kuwaiti experience. *Transplant Proc* 2003; 35: 2750.
56. Schnuelle P, van der Heide JH, Tegzess A, et al. Open Randomized Trial Comparing Early Withdrawal of either Cyclosporine or Mycophenolate Mofetil in Stable Renal Transplant Recipients Initially Treated with a Triple Drug Regimen. *J Am Soc Nephrol* 2002; 13: 536.
57. Morelon E, Kreis H. Sirolimus therapy without calcineurin inhibitors: Necker Hospital 8-year experience. *Transplant Proc* 2003; 35: 52S.
58. Dittrich E, Schmaldienst S, Soleiman A, et al. Rapamycin-associated post-transplantation glomerulonephritis and its remission after reintroduction of calcineurin-inhibitor therapy. *Transplant Int* 2004; 17: 215.
59. Butani L. Investigation of pediatric renal transplant recipients with heavy proteinuria after sirolimus rescue. *Transplantation* 2004; 78: 1362.
60. Senior PA, Paty BW, Cockfield SM, et al. Proteinuria developing after clinical islet transplantation resolves with sirolimus withdrawal and increased tacrolimus dosing. *Am J Transplant* 2005; 5: 2318.
61. Saurina A, Campistol JM, Piera C, et al. Conversion from calcineurin inhibitors to sirolimus in chronic allograft dysfunction: changes in glomerular haemodynamics and proteinuria. *Nephrol Dial Transplant* 2006; 21: 488.
62. Myers BD, Sibley R, Newton L et al. The long-term course of cyclosporine-associated chronic nephropathy. *Kidney Int* 1988; 33: 590.
63. McTaggart RA, Gottlieb D, Brooks J, et al. Sirolimus Prolongs Recovery from Delayed Graft Function After Cadaveric Renal Transplantation. *Am J Transplant* 2003; 3: 416.
64. Fervenza FC, Fitzpatrick PM, Mertz J, et al. Acute rapamycin nephrotoxicity in native kidneys of patients with chronic glomerulopathies. *Nephrol Dial Transplant* 2004; 19: 1288.

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65. Roodnat JI, Mulder PG, Rischen-Vos J, et al. Proteinuria after renal transplantation affects not only graft survival but also patient survival. *Transplantation* 2001; 72: 438.
66. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A Meta-Analysis of Immunosuppression Withdrawal Trials in Renal Transplantation. *J Am Soc Nephrol* 2000; 11: 1910.
67. Johnson RW, Kreis H, Oberbauer R, et al. Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. *Transplantation* 2001; 72: 777.
68. Chueh SC, Kahan BD. Dyslipidemia in renal transplant recipients treated with a sirolimus and cyclosporine-based immunosuppressive regimen: incidence, risk factors, progression, and prognosis. *Transplantation* 2003; 76: 375.
69. Booth JC, Joseph JT, Jindal RM. Influence of hypercholesterolemia on patient and graft survival in recipients of kidney transplants. *Clinical Transplant* 2003; 17: 101.
70. Roodnat JI, Mulder PG, Zietse R, et al. Cholesterol as an independent predictor of outcome after renal transplantation. *Transplantation* 2000; 69: 1704.
71. Ponticelli C, Villa M, Cesana B, et al. Risk factors for late kidney allograft failure. *Kidney International* 2002; 62: 1848.
72. Blum CB. Effects of sirolimus on lipids in renal allograft recipients: an analysis using the Framingham risk model. *Am J Transplant* 2002; 2: 551.
73. Kauffman HM, Cherikh WS, Cheng Y, et al. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; 80: 883.
74. USRDS Annual Data Report, 2005. Available at http://www.usrds.org/2005/pdf/07_tx_05.pdf. Accessed September 21, 2006.
75. Halloran PF. Call for revolution: A new approach to describing allograft deterioration. *Am J Transplant* 2002; 2: 195.

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