

## Calcineurin inhibitor sparing strategies in renal transplantation, part one: Late sparing strategies

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### Abstract

Kidney transplantation improves quality of life and reduces the risk of mortality. A majority of the success of kidney transplantation is attributable to the calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, and their ability to reduce acute rejection rates. However, long-term graft survival rates have not improved over time, and although controversial, evidence does suggest a role of chronic CNI toxicity in this failure to improve outcomes. Consequently, there is interest in reducing or removing CNIs from immunosuppressive regimens in an attempt to improve outcomes. Several strategies exist to spare calcineurin inhibitors, including use of agents such as mycophenolate mofetil (MMF), mycophenolate sodium (MPS), sirolimus, everolimus or belatacept to facilitate late calcineurin inhibitor withdrawal, beyond 6 mo post-transplant; or using these agents to plan early withdrawal within 6 mo; or to avoid the CNIs all together using CNI-free regimens. Although numerous reviews have been written on this topic, practice varies significantly between centers. This review organizes the

data based on patient characteristics (*i.e.*, the baseline immunosuppressive regimen) as a means to aid the practicing clinician in caring for their patients, by matching up their situation with the relevant literature. The current review, the first in a series of two, examines the potential of immunosuppressive agents to facilitate late CNI withdrawal beyond 6 mo post-transplant, and has demonstrated that the strongest evidence resides with MMF/MPS. MMF or MPS can be successfully introduced/maintained to facilitate late CNI withdrawal and improve renal function in the setting of graft deterioration, albeit with an increased risk of acute rejection and infection. Additional benefits may include improved blood pressure, lipid profile and serum glucose. Sirolimus has less data directly comparing CNI withdrawal to an active CNI-containing regimen, but modest improvement in short-term renal function is possible, with an increased risk of proteinuria, especially in the setting of baseline renal dysfunction and/or proteinuria. Renal outcomes may be improved when sirolimus is used in combination with MMF. Although data with everolimus is less robust, results appear similar to those observed with sirolimus.

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**Key words:** Kidney transplantation; Calcineurin inhibitor; Withdrawal; Sparing; Cyclosporine; Tacrolimus; Renal function; Graft survival

**Core tip:** Mycophenolic acid derivatives have been used successfully to facilitate late calcineurin inhibitor withdrawal to improve short-term renal function in kidney transplantation. The benefit carries an increased risk of acute cellular rejection. Sirolimus and everolimus are also options, but have comparatively less evidence and carry an increased risk of proteinuria, which is dependent on baseline renal function.

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## INTRODUCTION

Compared with hemodialysis, kidney transplantation improves quality of life and reduces of mortality risk<sup>[1-3]</sup>. The survival benefit of kidney transplantation over hemodialysis applies even to the use of marginal donor kidneys<sup>[4]</sup>. Much of this success has been attributed to calcineurin inhibitors, cyclosporine and tacrolimus, and their ability to reduce acute rejection rates. However, despite dramatic reductions in acute rejection rates over time, long-term graft survival rates have not improved to an appreciable extent<sup>[5,6]</sup>. A number of factors have been postulated that contribute to the lack of improvement in graft survival, including donor factors, recipient factors, human leukocyte antigen matching, death with a functioning allograft, delayed graft function, calcineurin inhibitor toxicity, chronic allograft nephropathy, and infectious nephropathy (BK virus)<sup>[6]</sup>.

Calcineurin inhibitor nephrotoxicity was recognized early after the use of cyclosporine began, and it comes in many forms<sup>[7]</sup>. Calcineurin inhibitors cause acute and chronic nephrotoxicity. The acute forms include arteriopathy, tubular vacuolization and thrombotic microangiopathy. Chronic forms of nephrotoxicity include interstitial fibrosis and tubular atrophy, medial arteriolar hyalinosis, glomerular capsular fibrosis, global glomerulosclerosis, focal segmental glomerulosclerosis, juxtaglomerular apparatus hyperplasia, and tubular microcalcifications, many of which can be caused by other factors and tend to be nonspecific findings on post-transplant biopsy<sup>[7]</sup>. Because of the known contribution of calcineurin inhibitors to nephrotoxicity, there has been much interest in finding the optimal agent and/or regimen<sup>[8-14]</sup>. While many studies demonstrated improved renal function with reduced dose calcineurin inhibitor use, or an early benefit on renal function with tacrolimus use when compared to cyclosporine, improvements in long-term graft function were not demonstrated<sup>[9-14]</sup>. Additionally, there are numerous differences in the adverse event profile of cyclosporine and tacrolimus. Many outside factors differentiate the calcineurin inhibitors and influence their contribution to nephrotoxicity, including therapeutic drug monitoring strategy, dosing strategy, drug-drug interaction, pharmacogenetics, and non-adherence<sup>[15-20]</sup>. These medication-related variables make nephrotoxicity and decline in allograft function very difficult to predict in practice. The lack of surveillance biopsies also makes differentiation of outcomes related to calcineurin inhibitor use and non-medication related factors difficult in practice<sup>[21-25]</sup>.

A long-term biopsy study helped determine the true consequence of calcineurin inhibitors on chronic allograft nephropathy and graft failure<sup>[26]</sup>. In a well-

designed study, Nankivell *et al*<sup>[26]</sup> demonstrated the natural history of chronic allograft nephropathy in 120 type 1 diabetics who underwent kidney-pancreas transplant followed by routine biopsies over a 10-year period. The initial phase (year 1) in the development of chronic allograft nephropathy was characterized by early tubulointerstitial damage from ischemic injury, prior severe rejection, and subclinical rejection, where these findings were present in 94.2% of patients. Beyond year 1, chronic allograft nephropathy was characterized by microvascular and glomerular injury and chronic rejection, defined as subclinical rejection for two or more years, and was uncommon (5.8%). Progressive high-grade arteriolar hyalinosis with luminal narrowing, increasing glomerulosclerosis, and tubulointerstitial damage were linked to the calcineurin inhibitors, and were irreversible. Despite dose reductions of both cyclosporine and tacrolimus, calcineurin inhibitor nephrotoxicity was nearly universal by 10 years, and was found to be the chief cause of late injury and renal function decline<sup>[26]</sup>.

The data from Nankivell *et al*<sup>[26]</sup> suggested that chronic allograft nephropathy was primarily a function of calcineurin inhibitor nephrotoxicity. This has been interpreted with controversy, but the data surrounding the definition and pathophysiology of chronic allograft nephropathy have always been controversial, due to varied definitions utilized in both practice and research<sup>[27,28]</sup>. In addition, many believe that calcineurin inhibitor nephrotoxicity is a non-specific finding<sup>[7,22]</sup>. Still, the evidence from Nankivell *et al*<sup>[26]</sup> is the among the most robust long-term evidence available on calcineurin inhibitors. It should also be mentioned that objective assessment is superior to clinical assessment, to determine the presence of chronic allograft nephropathy and calcineurin inhibitor nephrotoxicity, because clinicians underestimate the chronic renal toxicity<sup>[29,30]</sup>. Despite underestimation, clinicians have many ways of dealing with perceived medication toxicity. Commonly, when adverse effects are noted, adjustments are made in the regimen of the individual patient<sup>[31]</sup>. This may result in unintended consequences, such as acute rejection and graft loss<sup>[32-34]</sup>.

Collectively, protocols have been developed to assess the conversion between calcineurin inhibitors, or to select a preferable one, in order to avoid certain toxicities, or promote renal function improvements or short-term graft survival<sup>[9-14,35]</sup>. However, in a paired kidney analysis from a database with 5-year follow-up, no difference could be determined between cyclosporine and tacrolimus with respect to allograft survival, despite superior renal function in the tacrolimus group<sup>[36]</sup>. These results were similar in a prospective study with mean 2.8 years follow-up, and supported a 5-year histologic study that determined similar development of moderate to severe arteriolar hyalinosis with cyclosporine or tacrolimus<sup>[37,38]</sup>. When patients are switched between the two calcineurin inhibitors, or one is used in preference to the other, the basic tenet that calcineurin inhibitors are the primary contributors to graft decline is ignored<sup>[30]</sup>. In addition, the graft decline appears to occur primarily between 5 and 10

years post transplant<sup>[26]</sup>. It must also be emphasized that switching agents off-protocol in an uncontrolled way may have harmful effects, and is inconsistent with evidence-based practice<sup>[32]</sup>.

In recent years, various schools of thought have emerged with the introduction of newer agents and experience gained through research. The main strategies are based on personalization, corticosteroid minimization, and calcineurin inhibitor sparing<sup>[39,40]</sup>. It is too soon for personalized medicine, although the foundation has been laid<sup>[17-19,39]</sup>. Steroid avoidance strategies have been generally disappointing. They focus on minimizing adverse effects, and usually require calcineurin inhibitor persistence for successful outcome<sup>[40-47]</sup>. Calcineurin inhibitor sparing strategies also aim to reduce adverse effects, but also seek to improve graft survival<sup>[43-66]</sup>. Understanding the different treatment options may lead to improvement in long-term care.

Although the calcineurin inhibitor sparing strategies have been extensively reviewed, we aim to provide a unique approach to the issue. Since many transplant centers have set protocols for their specific populations, and clinical trial results or experiences of other centers may not be generalizable, we aim to review the literature according to general age groups (adult and pediatric) and therapeutic approaches (de novo, early or late) based on the specific baseline regimens used. We will analyze calcineurin inhibitor withdrawal and avoidance, and only touch on minimization when directly compared since exposure appears to lead to chronic toxicity and follow-up was usually inadequate to determine the true consequence on chronic allograft nephropathy<sup>[26,54]</sup>.

Due to the expanse of the issue, we will divide the topic into two manuscripts. The first, herein, will cover late calcineurin inhibitor withdrawal, beyond 6 mo post-transplant, and the second will cover early withdrawal and de novo avoidance. We will focus primarily on renal function and graft survival as the main outcomes of interest, and make recommendations based on the available evidence for each clinical subgroup since data on predicting or monitoring the outcome of changes in immunosuppression are still lacking<sup>[67-78]</sup>. The intent of the article is to aid the practicing clinician in identifying studies relevant to their practice to assist in clinical decision making. The clinician may have to refer the cited articles to find more specific information, such as the countries where the analysis was performed, ethnic breakdown of the population, transplant characteristics, *etc.*

## STRATEGIES

Three basic strategies are available for calcineurin-sparing, “Avoidance”, and “Early” and “Late” reduction or withdrawal. Late, defined as calcineurin inhibitor reduction withdrawal or elimination beyond 6 mo ( $> 6$  mo) after the kidney transplant, is a strategy that has been frequently used when patients are faced with diminishing renal function, possibly related to established toxicity, and is the focus of this manuscript. Early, defined as calci-

neurin inhibitor withdrawal or reduction within the first 6 mo ( $\leq 6$  mo) after the kidney transplant, is generally done to prevent anticipated calcineurin inhibitor toxicity or in response to early evidence of diminished renal function. Calcineurin inhibitor avoidance or calcineurin inhibitor-free regimens are typically a proactive strategy in response to the concerns about the potential toxicity of the calcineurin inhibitors and their failure to promote long-term graft survival, despite dramatic reduction in the risk of acute cellular rejection. Early and de novo are the focus of a second manuscript in this series.

Our search strategy involved PubMed database for all years until August 2013 for articles involving kidney or renal transplantation with the search terms calcineurin inhibitor “reduction”, “withdrawal”, “elimination”, “avoidance”, “minimization”, “sparing” and “free”. References of identified articles were reviewed to identify additional articles of interest. Articles were separated according to the post-transplant time period when the intervention took place, according to the three categories (avoidance, early, and late), and then arranged according to population and baseline regimen. Based on the assumption that most long-term calcineurin inhibitor nephrotoxicity is irreversible and progressive, and minimization articles were only included if they directly compared with avoidance or withdrawal/elimination regimens. The remainder of the article will summarize the available evidence by patient type, intervention and baseline regimen.

## ADULT PATIENTS AT VARIABLE TIME POST-TRANSPLANT

### *Regimens utilizing older agents to eliminate calcineurin inhibitors*

**Baseline calcineurin inhibitor and corticosteroid with or without azathioprine:** A meta-analysis by Kasiske *et al.*<sup>[79]</sup> evaluated early studies of calcineurin inhibitor withdrawal in patients on a baseline regimen of azathioprine, cyclosporine and corticosteroid, and compared calcineurin inhibitor withdrawal with continuation (part 1), and calcineurin inhibitor withdrawal with patients who never received calcineurin inhibition (part 2)<sup>[79]</sup>. In part 1 of the meta-analysis, 17 studies were included, with 9 of them including patients withdrawn during the first 6 mo after the transplant. The mean duration of follow-up of the studies was  $26.6 \pm 7.5$  mo. It should be noted that the meta-analysis included mixed populations, containing patients withdrawn due to toxicity of cyclosporine (3 studies), patients with stable renal function and/or without recent rejection (10 studies), recipients of living donor kidneys (6 studies), and patients with first transplant (4 studies). In part 1, there was a higher rate of acute rejection episodes per patient in the cyclosporine withdrawal group (0.126; 95%CI: 0.085-0.167;  $P < 0.001$ ), but no difference in graft loss per patient per year (-0.009; 95%CI: -0.022-0.004,  $P = 0.19$ ) or deaths per patient per year (-0.005; 95%CI: -0.016-0.006,  $P = 0.4$ ). The authors noted a trend toward higher serum creatinine in the con-

trol group who continued cyclosporine relative to those who discontinued the agent ( $1.84 \pm 0.29$  mg/dL *vs*  $1.63 \pm 0.28$  mg/dL;  $P = 0.17$ ). In part 2 of the meta-analysis, consisting of 6 studies, 3 included stable patients, none involved withdrawal due to toxicity, 3 studies included living donor kidneys, and 2 studies included only the first allograft, and 5 were performed in the first 6 mo after the transplant. The mean duration of follow-up was  $28.8 \pm 11.6$  mo. When the six studies were analyzed together, the rate of graft loss per patient per years was similar ( $-0.02$ ; 95%CI:  $-0.022-0.003$ ,  $P = 0.08$ ), but when only the 3 randomized trials were considered, graft survival was better among those withdrawn from cyclosporine (0.0382; 95%CI:  $0.0002-0.0762$ ,  $P = 0.049$ ). The deaths per patient per year were similar (0.001; 95%CI:  $-0.006-0.008$ ,  $P = 0.87$ ) and the serum creatinine was non significantly higher in the group who never received calcineurin inhibitors ( $1.71 \pm 0.36$  *vs*  $1.50 \pm 0.18$  mg/dL;  $P = 0.2$ ). The authors noted that none of the outcomes were affected by the timing (before or after 6 mo) or method (slow or rapid taper) of cyclosporine withdrawal<sup>[79]</sup>.

This meta-analysis demonstrated that cyclosporine withdrawal resulted in an early increase in the risk of acute cellular rejection, but similar graft function, graft survival and patient survival at about 2-year follow-up to patients retained on cyclosporine or who never received cyclosporine<sup>[79]</sup>. Despite promising results, azathioprine as an antiproliferative has been largely replaced in practice with newer agents that are considered more potent immunosuppressants. Another study evaluated withdrawal of cyclosporine using azathioprine versus mycophenolate mofetil in patients 1 year post-transplant. The primary endpoint was development of donor-specific antibodies (DSAs), measured by complement-dependent cytotoxicity assay, enzyme-linked immunosorbent assay (ELISA) and flow-cytometry crossmatch with donor spleen cells. DSAs, by three methods were not detected during cyclosporine treatment or during acute rejection treatment while on cyclosporine, but after conversion to azathioprine, 3 of 8 (37.5%) had DSAs in the presence of acute rejection, while none (0 of 6) of the mycophenolate mofetil patients had DSAs during rejection. These results highlight the potential benefits of mycophenolic acid over azathioprine, which have been described previously<sup>[80-82]</sup>.

## ADULT PATIENTS 6 OR MORE MONTHS POST-TRANSPLANT

### *Regimens utilizing mycophenolic acid to eliminate calcineurin inhibitors*

**Baseline calcineurin inhibitor and corticosteroid:** At least two studies<sup>[83,84]</sup> evaluated patients withdrawn late from a calcineurin inhibitor with a baseline regimen of calcineurin inhibitor and corticosteroid (Table 1)<sup>[83-93]</sup>. One study was designed to prospectively evaluate arterial distensibility and endothelial function before and after removal of cyclosporine in a population with biopsy-

proven CAN and deteriorating renal function. MMF was introduced at 500 mg per day and increased to a target dose of 2000 mg per day over 4 wk. The mean daily dose of MMF was 1700 mg at the end of the trial. Half the patients were randomized to withdrawal (tapered to off over 4 wk) and half to cyclosporine continuation. At 6 mo, serum creatinine increased slightly in both groups, but to a numerically greater extent on the control group who remained on cyclosporine. Though blood pressure improved from baseline in the intervention group, but not in the control group, there was no significant effect on brachial artery endothelial-dependent vasodilation. Acute rejection was not reported<sup>[83]</sup>. Another study performed by the same investigators also evaluated patients with biopsy-proven CAN, serum creatinine less than 4 mg/dL, and deteriorating renal function. That study introduced MMF more aggressively, at 1 g/d, and titrated to 2 g/d over 3 wk, and then patients were randomized to withdrawal or continuation of the calcineurin inhibitor. In patients randomized to withdrawal, the calcineurin inhibitor was reduced by 33% every 2 wk. The primary endpoint of slope of reciprocal serum creatinine per month at week 35 was positive and higher ( $0.00585 \pm 0.01122$ ) in the dual therapy group than the triple therapy group ( $-0.00728 \pm 0.01105$ ). Additional findings were the degree of proteinuria ( $P = 0.01$ ), diastolic blood pressure ( $P = 0.04$ ) and mean arterial pressure ( $P = 0.04$ ), which were lower in the dual therapy group at follow-up. No episodes of acute rejection were reported<sup>[84]</sup>. These results provide modest evidence that late withdrawal of calcineurin inhibitor with replacement by MMF may improve renal function, or at least reduce the rate of deterioration of renal function, and improve blood pressure relative to calcineurin inhibitor continuation.

**Baseline calcineurin inhibitor, corticosteroid and azathioprine:** A prospective, single-center randomized trial randomized patients on cyclosporine, azathioprine and corticosteroid, with biopsy-proven CAN and deteriorating renal function to MMF or tacrolimus. In patients randomized to cyclosporine, it was discontinued 24 h before tacrolimus was initiated. In patients randomized to MMF, MMF was introduced at 500 mg twice daily and then titrated up over 2-4 wk to 2 g/d. After 6 wk, cyclosporine was incrementally reduced to achieve withdrawal by 14 wk. Azathioprine was discontinued at conversion. At 6-mo, measured glomerular filtration rate (GFR) and serum creatinine were not improved in the tacrolimus group, but in the MMF group, GFR ( $P < 0.001$ ) and serum creatinine ( $P < 0.001$ ) were improved. In contrast, total cholesterol and triglycerides improved from baseline in the tacrolimus group, but not in the MMF group, and systolic and diastolic blood pressure improved in the MMF group, but not the tacrolimus. There were no reported rejection episodes<sup>[85]</sup>. Another study evaluated consecutive patients converted from cyclosporine, azathioprine and corticosteroid to MMF plus corticosteroid for CAN. Azathioprine was immediately stopped and MMF was introduced over 1 wk, with target dose of

**Table 1** renal transplant studies utilizing mycophenolic acid to withdraw calcineurin inhibitor beyond 6 mo post-transplant ("Late")<sup>[83-93]</sup>

Ref.	Design	Population (n)	Baseline Regimen	n	Strategy	Follow-up	Renal function	Acute rejection	Graft survival	Patient survival
Kosch <i>et al</i> <sup>[83]</sup>	Prospective, randomized, single-center	6-mo of deteriorating renal function, BP-CAN	CsA, Prednisolone	12	MMF added, target 2 g per day; CsA withdrawn over 4 wk	6 mo	SCr + 0.03 mg/dL vs baseline (P = NS)	NA	NA	NA
				12	MMF added, target 2 g; CsA continued		SCr + 0.07 mg/dL vs baseline (P = NS)	NA	NA	NA
Suwelack <i>et al</i> <sup>[84]</sup>	Prospective, randomized, single-center	> 1-yr post transplant, SCr < 4 mg/dL, BP-CAN, deteriorating renal function	CsA or TAC, Prednisolone	18	MMF added, target 2 g; CsA withdrawn over 6 wk	35 wk	Slope 1/SCr 0.00585 ± 0.01122; 67% responders; Proteinuria 0.5 ± 0.55 g/24 h	0%	100%	NA
				20	MMF added, target 2 g; CsA continued		Slope 1/SCr -0.00728 ± 0.01105 (P = 0.0018); 25% responders (P = 0.021); Proteinuria 1.5 ± 0.48 g/24 h (P = 0.01)	0%	85%	NA
McGrath <i>et al</i> <sup>[85]</sup>	Prospective, randomized, single-center	> 1-yr post transplant, BP-CAN, deteriorating renal function	CsA, azathioprine, prednisolone	15	MMF added, target 2 g; CsA withdrawn by 14 wk	6 mo	SCr - 58 µmol/L vs baseline (P < 0.001); isotope GFR + 8.5 mL/min vs baseline (P < 0.01)	0%	NA	NA
				15	CsA switch to TAC		SCr + 15 µmol/L vs baseline (P = NS); isotope GFR -2.1 mL/min vs baseline (P = NS)	0%	NA	NA
Hanvesakul <i>et al</i> <sup>[86]</sup>	Retrospective, consecutive patients, single-center	> 1-yr post transplant, CAN	CsA or TAC, azathioprine, prednisolone	30	MMF added, target 1.5-2 g; azathioprine stopped; CNI withdrawn over 4 wk	1 yr	eGFR + 2 mL/min vs baseline	3.30%	86.70%	96.70%
Dudley <i>et al</i> <sup>[87]</sup>	Randomized, open, multicenter	> 6-mo post transplant, deteriorating renal function, no recent ACR	CsA monotherapy, or CsA/corticosteroid, or CsA/azathioprine/corticosteroids	73	MMF added, target 2 g; azathioprine discontinued, if applicable; CsA withdrawn over 6 wk, if needed corticosteroid added	1 yr	Response rate (6 mo): 58% stabilized or reduced SCr; Response rate (1 yr): 48%; Least squares mean SCr -24.9 µmol/L; Least squares mean CrCL +5 mL/min	0%	93.20%	95.90%
				70	Continued regimen		Response rate (6 mo): 32% stabilized or reduced SCr (P = 0.006); Response rate (1 yr): 35% (P = 0.1885); Least squares mean SCr +22.2 µmol/L (P < 0.01); Least squares mean CrCL -0.7 mL/min (P < 0.01)	0%	94.3%	100%

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Weir <i>et al</i> <sup>[88]</sup>	Prospective, non-randomized, single-center	Mean 853.3 d post transplant, BP-CAN, deteriorating renal function, no ACR	CsA or TAC, prednisone, azathioprine or MMF	18	Azathioprine stopped; MMF added, target 2 g; CNI withdrawn	Mean 651 d	Response rate: 91.7% improved or lack of deterioration in renal function using least squares method slope 1/SCr ( $P = 0.038$ )	NCR	100%	NA
			CsA, prednisone, azathioprine or MMF	67	CsA dose reduced approximately 50%; azathioprine withdrawn; MMF added, target 2 g		Response rate: 51.7% improved or lack of deterioration	NCR	100%	NA
			TAC, prednisone, azathioprine or MMF	33	TAC dose reduced approximately 50%; azathioprine withdrawn; MMF added, target 2 g		Response rate: 59.3% improved or lack of deterioration	NCR	100%	NA
Weir <i>et al</i> <sup>[89]</sup>	Continuation of above trial			13	CNI withdrawn	76 mo	2.7 ± 0.2 mg/dL	7.7%	92.3%	100%
				64	CsA dose reduced	54 mo	3 ± 0.1 mg/dL	4.7%	62.5%	92.2%
Abramowicz <i>et al</i> <sup>[90]</sup>	Randomized, controlled, multicenter	No recent ACR, ≤ 1 ACR overall, 12 to 30 mo post-transplant, stable renal function	CsA, prednisone, ± azathioprine or MMF	28	TAC dose reduced	42 mo	3 ± 0.2 mg/dL	7.1%	67.8%	100%
				85	MMF added over 3 mo, target 2 g; CsA withdrawn over 3 mo	12 mo	CrCL improved 10% in 46%; SCr -1 μmol/L; CrCL + 4.5 mL/min vs control group ( $P = 0.16$ ), eGFR + 2.3 mL/min vs control group ( $P = 0.24$ )	10.6%	100%	NA
Abramowicz <i>et al</i> <sup>[91]</sup>	Continuation of above trial			85	MMF added over 3 mo, target 2 g; continued triple therapy		SCr + 4 μmol/L	2.4% ( $P = 0.03$ )	100%	
				74	CsA withdrawn	60 mo	CrCL 67.4 mL/min	10%	88%	93%
Heeg <i>et al</i> <sup>[92]</sup>	Retrospective	BP-CNI toxicity, deteriorating renal function, mean 11.2 mo post-transplant	CsA or TAC, Prednisolone, ± MMF or MPS	17	MPS added; CNI withdrawn; MMF withdrawn	48 mo	All vs Baseline. SCr at 6 mo -0.5 mg/dL ( $P < 0.05$ ); eGFR at 6 mo + 11 mL/min; SCr at 36 mo -0.5 mg/dL ( $P = 0.063$ ); eGFR at 36 mo +11 mL/min $P = 0.022$ ; SCr at 48 mo + 0.6 mg/dL ( $P = 0.27$ ); eGFR at 48 mo +1 mL/min ( $P = 0.91$ )	NA	NA	NA
				77	Triple therapy		CrCL 61.7 mL/min ( $P = 0.05$ )	1% ( $P = 0.028$ )	92%	95%
Mourer <i>et al</i> <sup>[93]</sup>	Prospective, randomized, single-center	No recent ACR, ≤ 2 ACR overall, at least 12 mo post-transplant, stable renal function	CsA or TAC, Prednisone, MMF	79	CNI withdrawn, MMF concentration controlled	36 mo	eGFR 59.5 ± 2.1 mL/min	5.1%	98.7%	94.9%
				79	MMF withdrawn, CNI concentration controlled		eGFR 51.1 ± 2.1 mL/min ( $P = 0.006$ )	2.5%	98.7%	92.4%

ACR: Acute cellular rejection; BP-CAN: Biopsy-proven chronic allograft nephropathy; CAN: Chronic allograft nephropathy; CNI: Calcineurin inhibitor; CsA: Cyclosporine; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; MMF: Mycophenolate mofetil; MPS: Mycophenolate sodium; NA: not assessed/applicable; NCR: Not clearly reported by group; NS: Not significant; SCr: Serum creatinine; TAC: Tacrolimus.

1500 to 2000 mg per day. Calcineurin inhibitor was withdrawn over 4 wk by 25% reduction. Estimated GFR improved from the time of conversion to 1-year follow-up

by 2 mL/min, but the authors cautioned that there was a dramatic increase in the risk of infection in the patients converted to MMF<sup>[86]</sup>.

**Baseline calcineurin inhibitor monotherapy, calcineurin inhibitor with corticosteroid, calcineurin inhibitor with azathioprine, or calcineurin inhibitor, corticosteroid and azathioprine:** The “Creeping Creatinine” study<sup>[87]</sup> evaluated patients on various calcineurin inhibitor-based regimen who did not receive MMF at baseline. In the open, randomized, multicentered trial, patients had a negative slope of reciprocal serum creatinine, baseline serum creatinine of 100 to 400  $\mu\text{mol/L}$  and a calculated creatinine clearance of at least 20 mL/min. A biopsy had to show absence of transplant glomerulopathy, recurrent renal disease, de novo renal disease, obstruction, renal artery stenosis, acute rejection, or acute rejection within 3 mo. Patients were randomized to MMF or maintenance of cyclosporine according to normal practice. Those randomized to MMF had the drug introduced incrementally over 4 wk to a target dose of 2 g/d, and corticosteroids were introduced if not previously used. Cyclosporine was reduced in three steps over 6 wk to off. Patients randomized to maintain cyclosporine were continued as per usual practice with a permitted reduction of cyclosporine to a trough not less than 80 ng/mL. Baseline biopsies documented CAN in 78% of the MMF group and 77% of the cyclosporine group. A responder, defined as an improvement in the slope of 1/SCr with no change in the randomized treatment and no graft loss occurred in 58% of the MMF group and 32% of the control group ( $P = 0.006$ ) at 6 mo and 48% of the MMF group and 35% of the control group ( $P = 0.1185$ ) at 1 year. At 12-mo the least squares mean (LSM) creatinine clearance was +5 mL/min in the MMF group and -0.7 mL/min in the cyclosporine group ( $P < 0.01$ ). LSM serum creatinine and serum cholesterol were lower in the MMF group at follow-up, and platelet count was higher, but triglycerides, hemoglobin, white blood cell count, systolic blood pressure and diastolic blood pressure were not significantly different. There were no acute rejection episodes in either group. The incidence of diarrhea, abdominal pain and opportunistic infections were numerically higher in the MMF group<sup>[87]</sup>.

**Baseline calcineurin inhibitor and corticosteroid with or without azathioprine or MMF:** A study evaluated patients on calcineurin inhibitor and corticosteroid, with or without azathioprine or MMF, in a prospective non-randomized, single-centered fashion where decision to reduce or withdrawal CNI was arbitrary<sup>[88]</sup>. Patients with deteriorating renal function and CAN on biopsy were started on MMF (target 2 g/d) if it was not previously given, and azathioprine was stopped. Patients were analyzed in three groups, those who had CNI withdrawn ( $n = 18$ ), those with a 50% reduction in cyclosporine after MMF introduction ( $n = 67$ ), and those with 50% reduction in tacrolimus after MMF was introduced ( $n = 33$ ). At mean 651 d follow-up, 91.7% of the withdrawal group, 51.7% of the reduced dose cyclosporine group, and 59.3% of the reduced dose tacrolimus group had improved or lack of deterioration in the LS 1/SCr ( $P = 0.038$ ). The withdrawal group also had lower serum

glucose ( $P < 0.05$ ) and total cholesterol ( $P < 0.05$ ), but not systolic or diastolic blood pressure. It should be noted that patients selected for CNI withdrawal had a lower incidence of acute rejection prior to the intervention, but the nadir serum creatinine was similar in all three groups<sup>[88]</sup>. A continuation of the trial, out to 76 mo demonstrated that about one third of the CNI reduction patients and only 7.7% of the withdrawal group lost their graft during follow-up ( $P = 0.05$ ). The serum creatinine at follow-up was 2.7 mg/dL in the withdrawal group and 3 mg/dL in the CNI reduction groups<sup>[89]</sup>. A randomized, controlled, multicenter trial also evaluated patients on cyclosporine and corticosteroid, with or without azathioprine or MMF. Patients were selected if they had a first or second cadaveric or living transplant, were between 12-30 mo post-transplant and maintained on a cyclosporine-based regimen. Patients had to have had no more than one acute rejection episode, with none in the last 3 mo, and a SCr less than 300  $\mu\text{mol/L}$  for at least 3 mo. All patients had MMF introduced to a target of 2 g/d over 3 mo. Patients randomized to cyclosporine withdrawal had it tapered over 3 mo ( $n = 85$ ) and those randomized to remain on cyclosporine ( $n = 85$ ), continued on triple-drug therapy. Creatinine clearance improved by 10% in 46% of the withdrawal group, and the creatinine clearance difference was 4.5 mL/min higher in the withdrawal group 9 mo after randomization ( $P = 0.16$ ). Serum creatinine improved by decreasing 1  $\mu\text{mol/L}$  in the withdrawal group, and increased 4  $\mu\text{mol/L}$  in the continuation group, creating a net effect of 5  $\mu\text{mol/L}$  in favor of the withdrawal group ( $P = 0.34$ ). Withdrawal improved the total ( $P = 0.02$ ) and low density lipoprotein (LDL) cholesterol ( $P = 0.015$ ), but blood pressure did not differ significantly. Acute rejection (10.6% vs 2.4%;  $P = 0.03$ ) and diarrhea were more common in the withdrawal group<sup>[90]</sup>. A five-year follow-up publication demonstrated a creatinine clearance of 67.4 mL/min in the withdrawal group and 61.7 mL/min ( $P = 0.05$ ) in the continuation group, but graft loss due to chronic rejection occurred in 12% of the withdrawal group and 8% of the continuation group, due to a respective acute rejection rate of 10% and 1% ( $P = 0.028$ )<sup>[91]</sup>.

**Baseline calcineurin inhibitor with or without corticosteroid and with or without MMF or mycophenolate sodium:** One retrospective study analyzed 17 patients approximately 11 years post-transplant for 4 years before and after conversion to mycophenolate sodium (MPS) for biopsy-proven CNI toxicity ( $n = 7$ ) or clinical deterioration of GFR and exclusion for other reasons for graft dysfunction. Patients on CNI and corticosteroid were converted to MPS and prednisolone, patients on CNI monotherapy were converted to MPS alone, and patients on triple therapy were converted to MPS with prednisolone. At conversion, GFR was  $43 \pm 15$  mL/min. After conversion, graft function, as determined by GFR, improved within one month, and peaked at  $55.7 \pm 21.7$  mL/min at one year ( $P = 0.00362$ ), but then declined to near-baseline ( $44 \pm 27$  mL/min;  $P = 0.91$ ) by four years,

indicating a slowing of progression. However, the overall slope of the regression line for GFR did not change significantly ( $P = 0.116$ ). Three patients discontinued MPS due to infection ( $n = 2$ ) and lost to follow-up ( $n = 1$ )<sup>[92]</sup>. A randomized trial compared CNI withdrawal ( $n = 79$ ) with MMF withdrawal ( $n = 79$ ) in patients who were on CNI/MMF/corticosteroid triple therapy. This trial used concentration controlled area-under-the-curve (AUC) monitoring for the CNIs (3250 ng/mL per hour for cyclosporine, 120 ng/mL per hour for tacrolimus) and MMF (75 µg/mL per hour). Estimated GFR was significantly better in the CNI withdrawal group at 6 wk ( $63.1 \pm 1.9$  mL/min *vs*  $55.2 \pm 1.9$  mL/min;  $P = 0.004$ ), 1-year ( $61.1 \pm 1.8$  mL/min *vs*  $52.9 \pm 1.8$  mL/min;  $P = 0.002$ ), and 3-year ( $59.5 \pm 2.1$  mL/min *vs*  $51.1 \pm 2.1$  mL/min;  $P = 0.006$ ). By 6 mo, 1.3% of the MMF withdrawal group and 3.8% of the CNI withdrawal group had biopsy-proven acute rejection. None were high immunologic risk. Three year graft survival did not differ. Blood pressure, lipid values, proteinuria and infections did not differ between the groups. Anemia was more frequent in the CNI withdrawal group<sup>[93]</sup>.

#### Summary of MMF and mycophenolic acid studies:

These studies suggest that MMF or MPS can be introduced or maintained to facilitate late (beyond 6-mo post-transplant) CNI withdrawal after kidney transplantation in the setting of graft deterioration and BP-CAN. Withdrawal of CNI using MMF or MPS appears to improve serum creatinine and creatinine clearance/GFR in a majority of patients, without an increased risk of proteinuria. The studies also demonstrate a potential for this strategy to improve blood pressure, lipid profile and serum glucose<sup>[94]</sup>. Benefits of mycophenolic acid derivatives may be offset by an increased risk of acute rejection and infection, so patients should be carefully selected. It appears that concentration-controlling the administration may limit the occurrence of these adverse events and possibly explain differences in adverse effects, such as diarrhea<sup>[93,95-97]</sup>. Taken individually, these studies were too small and too limited in follow-up to determine an improvement in graft survival, but a meta-analysis did demonstrate a trend toward improvement in graft survival (OR = 0.72, 95%CI: 0.52-1.01,  $P = 0.06$ ) with CNI withdrawal using MMF in a mixed population that was not limited to late withdrawal<sup>[98]</sup>. Generally speaking, our findings are in line with other recent reviews and meta-analyses, and support a potential role of late CNI elimination with mycophenolic acid derivatives<sup>[98-101]</sup>.

#### Regimens utilizing sirolimus to eliminate calcineurin inhibitors

**Baseline regimen not specified:** The mammalian target of rapamycin inhibitor (mTOR), sirolimus, has also been used to eliminate CNIs. A study<sup>[102]</sup> evaluated patients more than one year post-transplant with chronic allograft dysfunction according to baseline proteinuria stratification in 3 groups, and either withdrew CNI with addition of sirolimus or reduced the dose of CNI with addition

of sirolimus as shown in Table 2<sup>[102-118]</sup>. As shown, the patients who had sirolimus added demonstrated a statistically significant increase in proteinuria when CNI was withdrawn, but not when CNI was reduced. The post-conversion increase in proteinuria was greater, when the baseline proteinuria value was higher. In addition, when analyzed overall (both withdrawal and continuation combined based on baseline proteinuria) the group with negative baseline proteinuria had a mean 10.4 mL/min ( $P = 0.05$ ) improvement in CrCL over about 2 years, while the group with baseline proteinuria 0.3-0.8 g/d had a mean 7 mL/min ( $P = \text{NS}$ ) improvement in CrCL, and the group with baseline proteinuria > 0.8 g/d had a 5.5 mL/min ( $P = 0.05$ ) decline in CrCL. Taken together these results suggested that use of sirolimus to facilitate CNI withdrawal beyond 1 year had the potential for an adverse impact on renal function that was dependent on the baseline level of proteinuria. Another retrospective study<sup>[103]</sup> examined 30 patients with unspecified baseline regimen and with about 2 years of follow-up based on indication for switching from CNI to sirolimus, as shown in Table 2. They concluded that sirolimus was associated with an improvement in CrCL and an increase in proteinuria, but that the benefits were achieved only when the conversion occurred within the first year after the transplant<sup>[103]</sup>.

#### Baseline corticosteroid and either azathioprine or calcineurin inhibitor:

A cohort study evaluated 19 patients who had sirolimus added and CNI withdrawn by 3 mo for progressive CAN. At 6-mo follow-up, 36% demonstrated improvement in renal function, 21% exhibited stabilization, and 43% resulted in continued worsening. Patients who demonstrated improvement in renal function had lower baseline SCr ( $2.6 \pm 0.9$  mg/dL *vs*  $3.3 \pm 0.7$  mg/dL)<sup>[104]</sup>.

#### Baseline calcineurin inhibitor and corticosteroid with or without mycophenolate mofetil:

A retrospective study<sup>[105]</sup> of patients more than 1 year post-transplant with CAN examined 32 patients for 8.5 mo who had sirolimus added to their regimen and CNI reduced. Only 3 patients had improved SCr (9.4%) and 13 (40.6%) had stable SCr, suggesting that 50% of the population achieved a benefit from the strategy of CNI dose reduction with sirolimus introduction. The authors suggested that the benefit was greater when the baseline SCr was less than 3 mg/dL.

#### Baseline tacrolimus and mycophenolate mofetil with or without corticosteroids:

A prospective, randomized study of 200 patients more than 1 year post-transplant, with about 3.5 years follow-up, examined sirolimus addition with trough target 5-8 ng/mL and tacrolimus withdrawal by week 2 ( $n = 123$ ) or continuation of the current regimen with target tacrolimus trough of 6-8 ng/mL. As shown in Table 2, the GFR decreased, and proteinuria increased to a similar degree in both groups during follow-up, with similar acute cellular rejection (ACR) and graft survival, suggesting no tangible benefit to the late switch<sup>[106]</sup>. In contrast, a cohort study analyzed



Table 2 Renal transplant studies utilizing sirolimus to withdraw calcineurin inhibitor beyond 6 mo post-transplant

Ref.	Design	Population (n)	Baseline regimen	n	Strategy	Follow-up	Renal function	Acute rejection	Graft survival	Patient survival
Gutierrez <i>et al</i> <sup>[102]</sup>	Cohort	> 1-yr post transplant, chronic allograft dysfunction, no proteinuria	Not specified	8	SRL added, CNI dose reduced 50%	24.6 mo	Proteinuria = +0.56 g/d <i>vs</i> baseline (P = NS)	NA	90.50%	85.70%
				13	SRL added, CNI withdrawn		Proteinuria = + 0.67 g/d <i>vs</i> baseline (P = 0.02)			
		> 1-yr post transplant, chronic allograft dysfunction, proteinuria = 0.3-0.8 g/d		10	SRL added, CNI dose reduced 50%	23.2 mo	Proteinuria = +0.5 g/d <i>vs</i> baseline (P = NS)	NA	83.30%	94.40%
				8	SRL added, CNI withdrawn		Proteinuria = +1.1 g/d <i>vs</i> baseline (P = 0.05)			
				14	SRL added, CNI dose reduced 50%	25.9 mo	Proteinuria = -0.1 g/d <i>vs</i> baseline (NS)	NA	79.20%	87.50%
Maharaj <i>et al</i> <sup>[103]</sup>	Retrospective cohort	> 1-yr post transplant, CsA-induced biochemical toxicity	Not specified	6	SRL added, CNI withdrawn	25 mo	Proteinuria = +0.06 g/d <i>vs</i> baseline eGFR = +12.2 mL/min <i>vs</i> baseline	NA	NA	NA
		> 1-yr post transplant, CAN		6			Proteinuria = +0.85 g/d <i>vs</i> baseline eGFR = -9.7 mL/min <i>vs</i> baseline	NA	NA	NA
		> 1-yr post transplant, Severe gum hypertrophy		9			Proteinuria = +0.99 g/d <i>vs</i> baseline eGFR = -1.0 mL/min <i>vs</i> baseline	NA	NA	NA
		4.5 mo post transplant, Posttransplant diabetes		4			Proteinuria = -0.22 g/d <i>vs</i> baseline eGFR = +13.3 mL/min <i>vs</i> baseline	NA	NA	NA
		5.5 mo post transplant, CNI induced histological nephrotoxicity		2			Proteinuria = +0.63 g/d <i>vs</i> baseline eGFR = -10.0 mL/min <i>vs</i> baseline	NA	NA	NA
		> 1-yr post transplant, CNI associated malignancy		3			Proteinuria = +0.09 g/d <i>vs</i> baseline eGFR = +7.0 mL/min <i>vs</i> baseline	NA	NA	NA
Citterlo <i>et al</i> <sup>[104]</sup>	Cohort	> 6-mo post transplant, deteriorating renal function, sCr 2-4.5 mg/dL, proteinuria > 500 mg/d, biopsy confirmed fibrosis, tubular atrophy and intimal hyperplasia	CsA or TAC or azathioprine with corticosteroid	19	SRL added to target trough 8-12 ng/mL, CNI withdrawn by 3 mo	6 mo	Response rate: 57% improved or lacked deterioration in renal function	0%	NA	100%

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Wu <i>et al</i> <sup>[105]</sup>	Retrospective cohort	> 1-yr post transplant, CAN	CsA or TAC/ corticosteroids or CsA or TAC/ corticosteroids/ MMF	32	SRL added with CNI dose reduced	8.5 mo	Response rate: 50% improved or lacked deterioration in renal function	3.10%	87.50%	NA
Chhabra <i>et al</i> <sup>[106]</sup>	Randomized, prospective, open-label, single-center	> 1-yr post transplant	TAC, MMF	123	SRL added to target trough 5-8 ng/mL, TAC withdrawn by week 2	41.1 mo	eGFR = -3.3 mL/min per 1.73 m <sup>2</sup> vs baseline proteinuria > 1 g/d = + 4.7% vs baseline	5.70% (ACR) 4.1% (AHR)	97.60%	97%
				64	Continue TAC to target trough 6-8 ng/mL	40.7 mo	eGFR = -8.7 mL/min per 1.73 m <sup>2</sup> vs baseline, proteinuria > 1 g/d = + 7.4% vs baseline	6.40% (ACR) 3.1% (AHR)	97%	100%
Wali <i>et al</i> <sup>[107]</sup>	Cohort	Renal dysfunction and biopsy confirmed CAN	TAC/MMF or TAC/MMF/ corticosteroids	159	SRL added, target trough 8-10 ng/mL, TAC withdrawn after second dose of SRL	24 mo	sCr = -1.1 mg/dL vs baseline (P < 0.0001) eGFR = +21 mg/dL vs baseline (P < 0.0001)	9.60%	65%	90%
Diekmann <i>et al</i> <sup>[108]</sup>	Cohort	> 1-yr post transplant, biopsy confirmed CNI toxicity	CsA or TAC/ corticosteroids, or CsA or TAC/ corticosteroids/ azathioprine, or CsA or TAC/ corticosteroids/ MMF, or CsA or TAC/ MMF, or TAC/MMF/ corticosteroids CsA or TAC/ azathioprine	22	SRL added, target trough 8-12 ng/mL, CsA or TAC reduced by 50% immediately then further reduced 10%-20% weekly	6 mo	sCr = -0.7 mg/dL vs baseline (% = NS), Response rate: 59.1% improved or lacked deterioration in renal function	NA	86%	100%
Bumbea <i>et al</i> <sup>[109]</sup>	Prospective, single-center cohort	>6-mo post transplant, chronic allograft dysfunction or recurrent cutaneous cancer	CsA or TAC/ corticosteroids, or CsA or TAC/ azathioprine or CsA or TAC/ corticosteroids/ MMF	43	SRL added, target trough = 8-12 ng/mL, CNI withdrawn abruptly or by week 3	27 mo	sCr = -17.8 μmol/L vs baseline (P = NS) CrCL = +2.3 mL/min vs baseline (P = NS) Proteinuria (> 1g/d): 20.6% at 2 yr (P = 0.01)	0%	93%	95.30%
Boratynska <i>et al</i> <sup>[110]</sup>	Cohort	> 1-yr post transplant, biopsy confirmed CAN	CsA, prednisone, azathioprine	5	SRL added, target trough 10-18 ng/mL, CsA withdrawn immediately. After 5 mo, SRL withdrawn and CsA reinitiated	3 mo	sCr = +1.6 mg/dL and proteinuria = +461 mg/dL after 3 mo SRL vs baseline sCr = +1.1 mg/dL and proteinuria = +6 mg/dL 6 mo after reconversion to CsA vs baseline sCr = -0.5 mg/dL and proteinuria = -455 mg/dL after reconversion to CsA vs SRL	0%	40%	100%
Martínez-Mier <i>et al</i> <sup>[111]</sup>	Retrospective cohort	> 6-mo post transplant, > 20% sCr increase in 6 mo or sCr 2-4.5 mg/dL	CsA, prednisone, MMF	15	SRL added, target trough 8-12 ng/mL, CsA withdrawn immediately	6 mo	sCr = -0.78 mg/dL vs baseline (P = 0.003) BUN = - 9.84 mg/dL vs baseline (P = NS)	0%	100%	100%

Kamar <i>et al</i> <sup>[112]</sup>	Prospective, multicenter, noncomparative, open-label cohort	> 1-yr post transplant, moderate renal insufficiency, sCr 160-265 $\mu\text{mol/L}$	CsA or TAC, corticosteroids, MMF	44	SRL added to target trough 6-10 ng/mL, CNI withdrawn	6 mo	GFR = +7.09 mL/min <i>vs</i> baseline ( $P = 0.03$ ) Proteinuria = +0.57 g/d	2.30%	100%	100%
Chen <i>et al</i> <sup>[113]</sup>	Cohort	> 6-mo post transplant, biopsy confirmed CAN	CsA or TAC, prednisone, MMF	16	SRL added, target trough 5-8 ng/mL, CNI withdrawn	12 mo	Response rate: 43.8% improved or lacked deterioration in renal function	0%	88%	100%
Stallone <i>et al</i> <sup>[114]</sup>	Prospective, open-label, single-center	> 1-yr post transplant, Scr 1-3 mg/dL	CsA or TAC, corticosteroids, MMF	50	40% CNI dose reduction	24 mo	sCr = -0.02 mg/dL <i>vs</i> baseline ( $P = \text{NS}$ ) CrCL -3.0 mL/min <i>vs</i> baseline ( $P = \text{NS}$ ) Proteinuria = +0.17 <i>vs</i> baseline ( $P = \text{NS}$ ) Follow-up biopsy: worsened CAN score, increased $\alpha$ -SMA	0%	84%	100%
				34	SRL added, CNI immediately withdrawn		sCr = -0.14 mg/dL <i>vs</i> baseline ( $P = \text{NS}$ ) CrCL = +3.0 mg/dL <i>vs</i> baseline ( $P = \text{NS}$ ) Proteinuria = +0.37 g/d <i>vs</i> baseline ( $P = \text{NS}$ ) Follow-up biopsy: stable CAN score, improved $\alpha$ -SMA	0%	97% ( $P = 0.04$ )	100%
Paoletti <i>et al</i> <sup>[115]</sup>	Cohort	> 6-mo post transplant, biopsy confirmed renal allograft dysfunction	CsA or TAC, corticosteroids, MMF	13	SRL added, target trough 4-8 ng/mL, CNI withdrawn	3 yr	sCr = -0.3 mg/dL <i>vs</i> baseline ( $P = 0.016$ ) eGFR = +5.5 mg/dL <i>vs</i> baseline ( $P = 0.011$ ) Proteinuria = +0.21 g/d <i>vs</i> baseline ( $P = 0.83$ )	8%	100%	100%
		> 6-mo post transplant with stable graft function		26	Continued regimen		sCr = +0.3 mg/dL <i>vs</i> baseline ( $P = 0.016$ ) eGFR = -6.4 mg/dL <i>vs</i> baseline ( $P = 0.011$ ) Proteinuria = +0.17 g/d <i>vs</i> baseline ( $P = 0.83$ )	4%	96%	96%
Alarrayed <i>et al</i> <sup>[116]</sup>	Retrospective, Observational, single-center	> 1-yr post transplant, sCr < 140 $\mu\text{mol/L}$	CsA or TAC, corticosteroids, azathioprine or MMF	45	SRL added to target trough 5-8 ng/mL, CNI withdrawn immediately	72.8 mo	sCr = -6 $\mu\text{mol/L}$ <i>vs</i> baseline ( $P = 0.001$ ) Proteinuria = +0.2 g/d <i>vs</i> baseline ( $P = \text{NS}$ )	0%	100%	NA
		> 1-yr post transplant, sCr $\geq 140$ $\mu\text{mol/L}$		19			sCr = -13 $\mu\text{mol/L}$ <i>vs</i> baseline ( $P = 0.01$ ) Proteinuria = +0.6 g/d <i>vs</i> baseline ( $P = 0.001$ )	36.40%	72.70%	NA

Fischereder <i>et al</i> <sup>[117]</sup>	Prospective cohort	> 1-yr post transplant, deteriorating renal function, Scr 1.8-4 mg/dL	CsA or TAC, corticosteroids, azathioprine or MMF	12	SRL added, target trough = 10-20 ng/mL, CNI withheld by 4 wk	12 mo	sCr = -0.3 mg/dL vs baseline ( <i>P</i> = 0.198) CrCL = +5.8 mL/min ( <i>P</i> = 0.0368) Proteinuria = +735 mg/g creatinine vs baseline ( <i>P</i> = 0.13)	0%	100%	100%
Sчена <i>et al</i> <sup>[118]</sup>	Randomized, prospective, open-label, multicenter, blinded, comparative trial	> 6-mo post transplant, baseline GFR > 40 mL/min	CsA or TAC, corticosteroids, azathioprine or MMF	497	SRL added, target trough 8-20 ng/mL, CNI withdrawn in 1 d, MMF or azathioprine dose reduced or withdrawn	24 mo	GFR = + 1.3 mL/min in patients converted to SRL as compared with patients continued on CNI at 12 mo ( <i>P</i> = NS) GFR = +1.3 mL/min vs baseline, UPr/Cr = -84 vs baseline	7.80%	92.40%	95.60%
		> 6-mo post transplant, baseline GFR 20-40 mL/min		58			GFR = + 3.8 mL/min in patients converted to SRL as compared with patients continued on CNI at 24 mo ( <i>P</i> = NS)	8.60%	65.50%	82.80%
		> 6-mo post transplant, baseline GFR > 40 mL/min		246	Continue regimen		GFR = -1.8 mL/min vs baseline, UPr/Cr = -31 vs baseline	6.50%	93.90%	96.30%
		> 6-mo post transplant, baseline GFR 20-40 mL/min		29			GFR = + 2.6 mL/min in patients continued on CNI as compared with patients converted to SRL at 12 mo ( <i>P</i> = NS)	10.30%	62.10%	89.70%

$\alpha$ -SMA: A-smooth muscle actin; AHR: Acute humoral rejection; CAN: Chronic allograft nephropathy; CNI: Calcineurin inhibitor; CsA: Cyclosporine; GFR: Glomerular filtration rate; MMF: Mycophenolate mofetil; NS: Not significant; SCr: Serum creatinine; TAC: Tacrolimus.

patients on tacrolimus/MMF or tacrolimus/MMF/corticosteroids with biopsy-proven CAN and progressive renal dysfunction when tacrolimus was converted to sirolimus (10 mg per day for 3 d, then 5 mg/d targeting trough levels 8-10 ng/mL<sup>[107]</sup>). Overall, SCr decreased and GFR improved, as shown in Table 2. About 1/3 of the patients were non-responders. Although first ACR was about 10%, it was less than the rate observed prior to the conversion (17%). Follow-up biopsies demonstrated significant improvement in interstitial fibrosis and tubular atrophy relative to baseline. It is important to note that this study only included patients who tolerated 90 d of sirolimus therapy<sup>[107]</sup>.

**Baseline CNI with corticosteroids, or CNI with azathioprine, or CNI with mycophenolate mofetil, or CNI with corticosteroids and azathioprine or mycophenolate mofetil:** Two studies evaluated patients with wide variability in baseline regimens<sup>[108,109]</sup>. One study evaluated patients more than one year post-transplant with biopsy proven CNI toxicity (*n* = 22) and demonstrated a modest decrease in SCr and a 59.1% response rate of improved or lack of progression in renal func-

tion deterioration at 6 mo after CNI conversion to sirolimus<sup>[108]</sup>. The other study evaluated patients more than 6 mo post-transplant with chronic allograft dysfunction or recurrent cancer and demonstrated a modest, non-significant reduction in SCr and increase in CrCL at 27 mo follow-up. However, proteinuria greater than 1 g/d occurred in 20.6% of the population at 2 years<sup>[109]</sup>. Neither study reported any episodes of ACR<sup>[108,109]</sup>.

**Baseline calcineurin inhibitor, corticosteroid and azathioprine:** A 5-patient cohort with BP-CAN explored conversion from cyclosporine to sirolimus. After 3 mo, SCr nearly doubled and proteinuria increased, at which time patients were converted back to CNI and proteinuria decreased, but SCr continued to rise, and 3 (60%) patients returned to dialysis<sup>[110]</sup>.

**Baseline calcineurin inhibitor, corticosteroid and azathioprine or mycophenolate mofetil:** A retrospective study of patients more than 6 mo post-transplant, with a 20% increase in SCr in 6 mo or a current SCr 2-4.5 mg/dL were converted to sirolimus with CNI withdrawn immediately. At 6 mo, there was a significant reduction in

SCr versus baseline, and no evidence of ACR, as shown in Table 2<sup>[111]</sup>. A prospective, multicentered study of 44 patients more than one year post-transplant with moderate renal insufficiency demonstrated a 7 mL/min ( $P = 0.03$ ) improvement in GFR with a 0.57 g/d increase in proteinuria ( $P = 0.002$ ). Adverse effects observed included an increase in triglycerides, total cholesterol and LDL cholesterol, and a decrease in hemoglobin levels, and one episode of mild ACR<sup>[112]</sup>. In a cohort of 16 patients with sirolimus added and CNI withdrawn for biopsy proven -chronic allograft nephropathy (BP-CAN), 43.8% demonstrated improved, or lack of deterioration in SCr, without an increased risk of ACR. Patients with SCr at baseline < 2.48 mg/dL were more likely to achieve improvement in SCr after the conversion, and patients with higher SCr or C4d deposition in peritubular capillaries were less likely to achieve success<sup>[113]</sup>.

A prospective open-label single-center study conducted by Stallone and colleagues<sup>[114]</sup> compared a 40% dose reduction in CNI ( $n = 50$ ) with sirolimus addition and CNI elimination ( $n = 34$ ) at greater than 1 year post-transplant<sup>[114]</sup>. Compared with baseline, CNI reduction resulted in no significant change in SCr, CrCL or proteinuria versus baseline at 2 years follow-up. To a similar degree, SCr, CrCL or proteinuria were similar to baseline in the CNI withdrawal group, although graft survival was improved (84% *vs* 97%,  $P = 0.04$ ). On follow-up biopsies, CAN grade and  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) protein expression worsened in the CNI reduction group, and  $\alpha$ -SMA decreased ( $P = 0.005$ ) and CAN grade remained stable in the sirolimus group<sup>[114]</sup>. Another study compared sirolimus addition and CNI elimination ( $n = 13$ ) in patients with BP-CAN versus CNI continuation ( $n = 26$ ) in patients with stable renal function, at least 6 mo post-transplant followed patients for 3 years<sup>[115]</sup>. In that study, sirolimus resulted in an improvement in SCr and GFR, with a statistically significant increase in proteinuria relative to baseline, while CNI continuation resulted in worsening of SCr and GFR and a similar degree of proteinuria. There were more cardiovascular events ( $P = 0.024$ ) in the CNI continuation group, although patient survival was similar. The 3-year change in GFR was the only significant predictor of event-free survival by Cox regression analysis (HR = 0.96, 95%CI: 0.93-0.99,  $P = 0.017$ ), and sirolimus was the strongest predictor of GFR<sup>[115]</sup>.

One retrospective study compared the effects of sirolimus addition and CNI elimination relative to baseline SCr ( $\geq 140 \mu\text{mol/L}$  *vs*  $< 140 \mu\text{mol/L}$ ) and found that patients with more baseline renal dysfunction had a larger decline in SCr relative to baseline, but also developed more proteinuria and had a higher rate of ACR (36.4% *vs* 0%)<sup>[116]</sup>. Another prospective study targeted sirolimus trough 10-20 ng/mL and CNI elimination over 4 wk, in patients more than 1 year post-transplant, and demonstrated a 5.8 mL/min improvement in CrCL along with a non-significant increase in proteinuria at 12 mo<sup>[117]</sup>.

A randomized, prospective, open-label multicentered comparative trial (CONVERT) evaluated sirolimus to facilitate CNI withdrawal in the setting of concurrent

azathioprine or MMF reduction or withdrawal versus continuation of the CNI-based regimen, according to baseline GFR (20-40 mL/min *vs*  $> 40$  mL/min) in patients more than 6 mo post-transplant<sup>[118]</sup>. As shown in Table 2, patients with GFR  $> 40$  mL/min and converted to sirolimus had a non-significant improvement in GFR relative to baseline and relative to CNI continuation at 24 mo. Patients with baseline GFR 20-40 mL/min had a slightly higher, but still non-significant improvement in GFR at 24 mo relative to CNI continuation. Graft survival was poor in all patients with baseline GFR 20-40 mL/min regardless of regimen (62%-66%). A post-hoc analysis revealed that patients with GFR  $> 40$  mL/min who had a baseline urinary protein-to-creatinine ratio ( $U_{Pr/Cr}$ ) less than or equal to 0.11 had more favorable outcome with sirolimus conversion<sup>[118]</sup>.

**Summary of sirolimus studies:** There appears to be less data comparing sirolimus-facilitated late CNI withdrawal to an active CNI-containing regimen than was found for mycophenolic acid (MPA)-facilitated CNI withdrawal. Sirolimus has the potential to support late CNI withdrawal, through a modest improvement in short-term renal function, which has been corroborated in a systematic review<sup>[119]</sup>. However, the benefit of sirolimus is somewhat limited by an increased risk of proteinuria, especially in the setting of baseline renal dysfunction and/or proteinuria and high rate of discontinuation for adverse effects which ranges from 17% in nonrandomized trials to 28% of randomized trials<sup>[119-121]</sup>. Adverse effects of sirolimus on renal function were confirmed in a trial which evaluated late sirolimus withdrawal using MMF and found improvement in the slope 1/SCr in 15 of 17 (88%) patients<sup>[122]</sup>. Renal function results associated with use of sirolimus appear to be improved to a relatively greater degree when sirolimus is used in combination with mycophenolate mofetil<sup>[123]</sup>. This combination may increase the risk of MMF adverse effects, in part due to a drug-drug interaction<sup>[123,124]</sup>. It should also be noted that use of reduced dose CNI in conjunction with sirolimus may also suffer from a pharmacokinetic interaction, which potentiates each's nephrotoxicity<sup>[125]</sup>.

### **Regimens utilizing everolimus to eliminate calcineurin inhibitors**

**Baseline calcineurin inhibitor and unspecified adjunctive agents:** A second mTOR inhibitor, everolimus has also generated evidence on late CNI withdrawal in renal transplantation. As shown in Table 3<sup>[126-135]</sup>, a small case series evaluated 21 Hispanic first renal transplant patients (15 cadaveric), including 5 children, who were undergoing conversion from CNI to everolimus with MPA at a mean 8 mo post-transplant, due to CAN or CNI toxicity. Over 10-mo follow-up there was no mortality or graft loss and a slight mean decline of SCr of 0.2 mg/dL, but ACR rate was 17%<sup>[126]</sup>. Another case series of 78 patients converted CNI to everolimus at a mean 77 mo post-transplant, without manipulation or addition of MPA, and noted a statistically significant mean increase

**Table 3 Renal transplant studies utilizing everolimus to withdraw calcineurin inhibitor beyond 6 mo post-transplant**

Ref.	Design	Population (n)	Baseline regimen	n	Strategy	Follow-up	Renal function	Acute rejection	Graft survival	Patient survival
Giron <i>et al</i> <sup>[126]</sup>	Case series	Conversion due to unspecified reasons in Hispanic renal transplant patients (15 from cadaveric donors), mean conversion 8 mo post-transplant	CsA or TAC, and unspecified regimen	21	Everolimus added with MPS or MMF with complete suspension of CNI	10 mo (range, 2 to 22)	Mean SCr showed a trend to decline: preconversion 1.7 mg/dL; post-conversion 1.5 mg/dL	17%	100%	100%
Sánchez Frutuoso <i>et al</i> <sup>[127]</sup>	Case series, prospective, open	CAN or other reasons, stable renal function, mean 77 mo post-transplant	CNI and unspecified regimen	78	Switched to everolimus with complete and quick elimination of the CNI: An initial dose of 3 mg/d was adequate to obtain the recommended trough levels between 5 and 10 ng/mL	12 mo	Baseline CrCL = 51.9 ± 2.7 mL/min, and 3 mo = 55.7 ± 3.2 (P = 0.02). 12-mo CrCL not stated. Proteinuria = increased at 3 mo (P < 0.001), decreased between 3 to 6 mo (P = 0.001), but remained higher than basal levels (P = 0.002). Everolimus stopped in 13 patients (16.7%)	NA	NA	NA
Ruiz <i>et al</i> <sup>[128]</sup>	Case Series	CAN with deteriorating renal function	CsA or TAC, and unspecified regimen; triple drug (41%), double-drug (52%), monotherapy (7%)	32	Everolimus added, to eliminate CNI	6 mo	Baseline SCr 1.93 ± 0.13 mg/dL vs 1.86 ± 0.14, P = 0.07. Proteinuria = 1.62 ± 0.62 g/d vs 2.11 ± 0.73 (P = 0.11)	NA	NA	NA
Fernández <i>et al</i> <sup>[129]</sup>	Case series	Cadaveric renal transplant patients with CAN, at a mean 123.8 ± 74.2 mo post-transplant	CsA or TAC, ± MMF or azathioprine, corticosteroid not specified	17	Converted to everolimus with complete suspension of CNI	24 mo	Baseline SCr of 1.8 ± 0.4; after a year, 1.62 ± 0.49; and after 2 yr, 1.56 ± 0.49 mg/dL (P < 0.05). Proteinuria was baseline 0.30 ± 0.13 mg/mg, 1 yr = 0.63 ± 0.68 (P < 0.05), and 2 yr = 0.48 ± 0.34. Protein/creatinine quotient was: baseline 0.30 ± 0.13; one year 0.63 ± 0.68; and 2 yr 0.48 ± 0.34. CrCL was baseline 37.1 ± 11.14 mL/min and 2 yr = 46.6 ± 14.6 (P < 0.05)	NA	NA	100%
		Cadaveric renal transplant patients treated with non-CAN diagnosis at a mean 123.8 ± 74.2 mo post-transplant	CsA or TAC, ± MMF or azathioprine, corticosteroid not specified	10	Converted to everolimus with complete suspension of CNI	24 mo	Baseline SCr of 1.1 ± 0.32 mg/dL; 1 yr 0.97 ± 0.15, and 2 yr 0.97 ± 0.15. Proteinuria at baseline 0.12 ± 0.07 mg/mg, 1 yr = 0.46 ± 0.68 (P < 0.05), and 2 yr = 0.32 ± 0.17 (P < 0.05). Protein/creatinine quotient was: baseline 0.2 ± 0.07, 1 yr = 0.73 ± 0.7, and 2 yr = 0.32 ± 0.17. CrCL was baseline 68.81 ± 19 mL/min and 2 yr 74.56 ± 12.3	NA	NA	50%, due to tumors

Kamar <i>et al</i> <sup>[130]</sup>	Retrospective case-control	DSA-free kidney transplant patients with CNI toxicity, CAN or other diagnosis	CsA or TAC or belatacept, ± MPA or azathioprine, ± corticosteroids	61	Converted to everolimus-based regimen without CNIs	36 ± 25 mo	SCr (mmol/L) baseline 135 ± 37 to 141 ± 54 ( <i>P</i> = NS). aMDRD GFR (mL/min) 54 ± 18 to 56 ± 22 ( <i>P</i> = NS)	NA	NA	NA
			CsA or TAC, ± MPA or azathioprine, ± corticosteroids	61	Matched control patients on CNI		SCr (mmol/L) baseline 133 ± 51 to 131 ± 45 ( <i>P</i> = NS). aMDRD GFR (mL/min) 65.7 ± 25 to 62 ± 24 ( <i>P</i> = NS)			
Morales <i>et al</i> <sup>[131]</sup>	Case series	1 <sup>st</sup> or 2 <sup>nd</sup> transplant, converted due to CAN, nephrotoxicity or malignancy, mean 5 yr post-transplant	CsA or TAC, ± MMF or azathioprine, ± corticosteroid	8	Everolimus added to replace ( <i>n</i> = 6) or decrease (30% reduction) CNI dose ( <i>n</i> = 2) Antiproliferative dose reduced.	1-16 mo	Mean baseline SCr was 1.96 ± 0.69 mg/dL <i>vs</i> 1.59 ± 0.52. Mean CrCL = 51 ± 34.6 mL/min <i>vs</i> 56.5 ± 25.5. Mean Proteinuria:creatinine ratio = 1.34 ± 2.17 <i>vs</i> 1.28 ± 1.19 mg/g.	NA	NA	NA
Holdaas <i>et al</i> <sup>[132]</sup>	Prospective, randomized, open-label, multi-center. ASCERTAIN study	> 6-mopost transplant, renal impairment, no recent ACR < 3 mo	CsA or TAC, ± MPA or azathioprine, ± corticosteroids	127	Everolimus added, target 8-12 ng/mL; to eliminate CNI	24 mo	Mean measured GFR at month 24, 48 ± 22 mL/min per 1.73 m <sup>2</sup> Difference <i>vs</i> control was 1.12 mL/min per 1.73 m <sup>2</sup> , 95%CI : -3.51-5.76 ( <i>P</i> = 0.63). Urine protein: creatinine (mg/mmol) median increased from baseline 16.6 (3.5-413.7) to 32.6 (4.1-665.9; <i>P</i> = 0.007 <i>vs</i> control)	5.50%	94.50%	97.60%
				144	Everolimus added, target 3-8 ng/mL; to decrease CNI dose		Mean measured GFR at month 24, 46.6 ± 21.1 mL/min per 1.73 m <sup>2</sup> . Difference <i>vs</i> control was 0.59 mL/min per 1.73 m <sup>2</sup> , 95%CI: -3.88-5.07 ( <i>P</i> = 0.79). Urine protein: creatinine (mg/mmol) median increased from baseline 13.5 (2.4-319.4) to 22.4 (5.1-513.5; <i>P</i> = 0.54 <i>vs</i> control)	5.60%	92.40%	97.90%
				123	Controls maintained current CNI-based regimen		Mean measure GFR at month 24 46 ± 20.4 mL/min. Urine protein:creatinine (mg/mmol) median remained stable from baseline 14.3 (3.3-431.9) to 19.3 (3.3-431.9)	2.40%	95.10%	100%
Inza <i>et al</i> <sup>[133]</sup>	Case series	Cadaveric kidney allograft, SCr > 2 mg/dL, proteinuria < 1 g/ 24 h	CsA or TAC, ± MPA or sirolimus, corticosteroids	22	Switched CNI to Everolimus, mean starting dose 1.4 mg/d.	24 mo	Baseline CrCL 29.31 ± 10.15 mL/min to 3-mo 37.99 ± 14.44 ( <i>P</i> = 0.0076). No results specified for 24 mo, but authors stated CrCL trended to decline ( <i>P</i> = 0.6). Proteinuria (mg/24 h) increased from baseline 384 ± 26.13 to one month, 958 ± 1019.38 ( <i>P</i> = 0.05), to month 12, 1295 ± 1200.83 ( <i>P</i> = 0.0106)	4.50%	90.50%	100%

Cataneo-Dávila <i>et al.</i> <sup>[134]</sup>	Prospective, randomized, open pilot	> 6-mo post transplant, stable renal function, Banff grade I or II CAN within 6 mo, without ACR or grade III CAN in last 3 mo	CsA or TAC, MMF or azathioprine, corticosteroids	10	MMF or azathioprine were withdrawn and Everolimus added to decrease CNI dose by 80%.	12 mo	Baseline and end-of-study data were as follows: SCr, 1.27 ± 0.35 mg/dL vs 1.24 ± 0.4 mg/dL; estimated GFR = 72.4 ± 19.86 mL/min vs 76.26 ± 22.69 mL/min ( <i>P</i> = NS); microalbuminuria 0 mg/g (range 0-50) vs 0 (range 0-609; <i>P</i> = NS)	10%	NA	NA
			CsA or TAC, MMF or azathioprine, corticosteroids	10	Everolimus added to eliminate CNI gradually. MMF or azathioprine withdrawn, then re-introduced at CNI elimination		Baseline and end-of-study data were as follows: SCr 1.27 ± 0.36 mg/dL vs 1.25 ± 0.3 mg/dL; estimated GFR 66.2 ± 12.95 mL/min vs 66.2 ± 13.73 mL/min ( <i>P</i> = NS); microalbuminuria 0 mg/g (range 0-60) vs 0 (range 0-34; <i>P</i> = NS)	0%	NA	NA
Albano <i>et al.</i> <sup>[135]</sup>	Prospective, randomized, open-label, multi-center. FOREVER trial	Completion of CALLISTO study of patients at risk for DGF, from transplantation to month 12, with proteinuria < 1 g/24 h at month 12	Low-exposure CsA, everolimus, corticosteroids	15	Switch CsA to mycophenolate sodium 720 mg/d, increase everolimus, target trough goal 6-10 ng/mL	12 mo	Median (range) mGFR was 54 (21-87) mL/min at baseline ( <i>P</i> = 0.053 vs CNI at baseline) vs 56 (18-126) mL/min at month 12 ( <i>P</i> = 0.007 vs CNI continuation; <i>P</i> = 0.3 vs baseline). Difference in mGFR (SE) was +10.3 mL/min (4.8) vs baseline. SCr (SE) = 24 μmol/mL (27). Proteinuria least squares mean change from baseline (SE) = 0.16 g/24 h (0.2)	0%	100%	100%
				15	Continue CsA and everolimus unchanged, trough goal 3-8 ng/mL		Median (range) mGFR was 37 (range 18-69) mL/min at baseline ( <i>P</i> = 0.053) vs 32 (12-63) mL/min at month 12 ( <i>P</i> = 0.007). Difference in mGFR (SE) was -4.1 mL/min (5) vs baseline. Proteinuria least squares mean change from baseline (SE) = 0.08 g/24 h (0.23)	6.67%	100%	93.3%

ACR: Acute cellular rejection; aMDRD: Abbreviated modified diet in renal disease; BP-CAN: Biopsy-proven chronic allograft nephropathy; CAN: Chronic allograft nephropathy; CNI: Calcineurin inhibitor; CsA: Cyclosporine; DGF: Delayed graft function; DSA: Donor specific antibody; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid (includes MMF and MPS); MPS: Mycophenolate sodium; NA: Not assessed/applicable; NCR: Not clearly reported by group; NS: Not significant; SCr: Serum creatinine; TAC: Tacrolimus.

in CrCL of 3.8 mL/min at 3 mo post-conversion, but 12-mo CrCL was not stated. It should be noted that proteinuria increased from baseline at all time points studied, and 16.7% of patients stopped everolimus due to worsening renal function (*n* = 5), dermal eruptions (*n* = 3), or other reasons (*n* = 5)<sup>[127]</sup>. A case series of 32 patients took patients with deteriorating renal function in the face of CAN and added everolimus to eliminate CNI. At 6-mo, SCr decreased slightly, but not significantly (*P* = 0.07), and proteinuria trended toward an increase (*P* = 0.11)<sup>[128]</sup>. Of particular interest, a small study retrospectively com-

pared 17 patients with CAN converted to everolimus with 10 patients being converted to everolimus for other reasons. In the CAN group, SCr was higher and CrCL lower at baseline relative to the non-CAN group. SCr in the CAN group decreased steadily out to 2 years follow-up (*P* < 0.05), and CrCL improved significantly, with 100% patient survival. In contrast, the non-CAN group did not demonstrate a significant improvement in SCr or CrCL, and had a 50% mortality rate due to malignancy present at the time of the switch. An increase in proteinuria was observed in both groups<sup>[129]</sup>.



**Baseline calcineurin inhibitor or belatacept with or without mycophenolic acid or azathioprine or corticosteroids:** A retrospective case-control study evaluated patients on a CNI or belatacept with or without MPA or azathioprine or corticosteroids ( $n = 61$ ) converted to everolimus, and another 61 matched patients maintained on CNI-based regimen to determine if DSAs developed after conversion. At mean 36 mo follow-up there was no changes from baseline or between the groups in SCr or CrCL. None of the patients had DSAs at baseline, but the everolimus group had a follow-up incidence of 9.8% ( $P = 0.03$ ) and the CNI continuation group had an incidence of 5% ( $P = \text{NS}$ ). The only factor independently associated with DSA development was higher age at transplantation, associated with less DSA formation. Overall, 33% of everolimus patients withdrew from everolimus treatment at a mean 32 mo, due to DSA formation ( $n = 5$ ), lymphedema ( $n = 4$ ), proteinuria ( $n = 3$ ), and other reasons. None of the patients switched back to CNI developed DSAs<sup>[130]</sup>. Another case series examined 8 patients converted from CNI to everolimus at approximately 5 years post-transplant for CAN or malignancy. Everolimus replaced the CNI in 6 patients and was used to lower the CNI dose 30% in 2 patients. At 1-16 mo, SCr reduced slightly, CrCL improved slightly, and proteinuria:creatinine ratio decreased slightly. Three of the 8 patients developed serious infections<sup>[131]</sup>. A more robust study, the ASCERTAIN study<sup>[132]</sup>, was a prospective, randomized, open-label, multicenter study with 24 mo follow-up. Patients enrolled were at least 6 mo post-transplant (mean 5.6 years), with renal impairment, and without ACR within 3 mo. The study compared addition of everolimus to eliminate CNI ( $n = 127$ ), addition of everolimus to decreased CNI dose ( $n = 144$ ) and controls maintained on CNI ( $n = 123$ ). Overall, at 24-mo follow-up, ACR rates, graft survival and patient survival were similar. The primary endpoint of the study, CrCL at 24 mo, was not met, because CrCL was similar in all the groups at baseline and at follow-up. Proteinuria increased from baseline and relative to control in the CNI elimination group. Post-hoc analysis showed that patients with a baseline CrCL  $> 50$  mL/min had a larger improvement in CrCL after CNI elimination<sup>[132]</sup>.

**Baseline calcineurin inhibitor with mycophenolic acid or azathioprine and corticosteroids:** In cadaveric recipients on a CNI with MPA or azathioprine and corticosteroids and a SCr  $> 2$  mg/dL with proteinuria less than 1 g/24 h, everolimus was used to withdraw CNI. CrCL improved from baseline to 3 mo, but no results for 24 mo were presented, although the authors noted a trend toward decline. Proteinuria increased by one month ( $P = 0.05$ ) and more than 3-fold by month 12 ( $P = 0.0106$ ). Two of the 22 patients lost their grafts due to nephrotic syndrome and increasing SCr, and one patient developed ACR<sup>[133]</sup>. Another study compared 10 patients managed with everolimus to facilitate an 80% CNI dose reduction versus 10 patients with gradual complete CNI elimination. MMF or azathioprine were withdrawn when

everolimus was introduced in both groups, but were reintroduced only when the CNI was eliminated. At 12 mo, both groups had similar follow-up SCr, GFR and microalbuminuria, as well as similar changes from baseline. ACR occurred in 10% of the CNI reduction group and none of the CNI elimination group. It is interesting to note that in this study, many of the patients received angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), which could have impacted the degree of proteinuria. Triglycerides and total cholesterol increased due to everolimus<sup>[134]</sup>.

**Baseline calcineurin inhibitor with everolimus and corticosteroids:** The FOREVER trial<sup>[135]</sup> examined patients previously enrolled in another trial of CsA with everolimus who either switched CsA to MPS and increased everolimus ( $n = 15$ ) or continued CsA and everolimus. This study, although prospective and randomized, suffered from differences in baseline GFR between the groups that impacted the interpretation of the results. The median (range) baseline measured GFR was 54 (21-87) mL/min in the CsA withdrawal group, and 37 (18-69) mL/min in the CsA continuation group ( $P = 0.053$ ). The difference at follow-up in GFR was -14.4 mL/min for the CsA continuation group, which did not meet statistical significance. Study drugs were discontinued in 7% of the CNI-free patients and 20% of the CNI-treated patients. Adverse event rates were similar, except aphthous stomatitis and pyrexia were more common in the CNI-free group, and hypertension, proteinuria, acute renal failure and urinary tract infection were more common in the CNI-treated patients<sup>[135]</sup>.

**Summary of everolimus studies:** Although the majority of evidence was from small, low-quality studies, there was clear evidence of an increase in proteinuria with conversion to everolimus from a CNI-based regimen, similar to what has been observed with sirolimus<sup>[119-121,127-129]</sup>. It is interesting to speculate that this may be manageable with ACEI or ARBs<sup>[134]</sup>. As expected, everolimus also had an adverse effect profile similar to sirolimus<sup>[112,122,134,135]</sup>. Here was evidence of a modest short-term improvement in renal function after CNI elimination with use of everolimus, and like sirolimus, combination of the mTOR inhibitor and the CNI resulted in enhanced adverse effect profile<sup>[122,125,135]</sup>. Also, like sirolimus, there was little evidence comparing late CNI withdrawal to an active CNI-containing regimen.

#### **Regimens utilizing other agents to eliminate calcineurin inhibitors**

**Calcineurin inhibitor and variable adjunctive agents:** A randomized, open label phase II trial<sup>[136]</sup> evaluated the T cell costimulation blocker, belatacept for comparison with continued CNI in patients 6-36 mo post-transplant. Patients were randomized to switch to belatacept ( $n = 84$ ) intermittent therapy (5 mg/kg on days 1, 15, 29, 43 and 57, followed by every 28 d thereafter), or to continue the current regimen, which consisted of CNI and the current

regimen (80.7% corticosteroid, 3.4% azathioprine, and 94.3% MMF or MPA). Patients randomized to belatacept underwent a progressive taper to eliminate CNI by day 29. The primary endpoint was renal function over 12 mo as determined by calculated GFR, and the belatacept group improved  $7 \pm 11.99$  mL/min and the CNI group improved  $2.1 \pm 10.34$  mL/min from baseline ( $P = 0.0058$  for comparison at follow-up). Patients in the belatacept group with a baseline CrCL 45-60 mL/min exhibited the greatest numeric improvement ( $10 \pm 13.41$  mL/min). Belatacept patients with baseline CrCL  $< 45$  mL/min improved  $3.7 \pm 11.01$  mL/min and patients with CrCL  $> 60$  mL/min improved  $5.7 \pm 10.17$  mL/min. In contrast, patients remaining on CNI exhibited similar CrCL change according to baseline CrCL stratification, ranging from 1.9-2.8 mL/min. Mild to moderate ACR occurred in 6 patients in the belatacept group, all within the first 6 mo. Four of these patients were on belatacept therapy and 2 had discontinued belatacept. SCr returned to baseline in 4 of the 6 patients. No ACR episodes were reported in the CNI continuation group. Proteinuria occurred in one patient in each group. No grafts were lost in either group in the first 12 mo. One patient in the CNI group died with a functioning graft on day 142. Serious adverse event occurred in 24% of the belatacept group and 19% of the CNI continuation group. The biggest discrepancy in the adverse effects, pyrexia occurred in 4% of the belatacept group and 0% of the CNI group<sup>[136]</sup>. A 2-year follow-up to this study demonstrated 1 additional graft loss in each group, no additional ACR, and a mean change in CrCL from baseline 8.8 mL/min in the belatacept group and 0.3 mL/min in the CNI continuation group. Serious adverse events occurred in 37% of the belatacept group and 33% of the CNI group<sup>[137]</sup>.

## PEDIATRIC PATIENTS 6 OR MORE MONTHS POST-TRANSPLANT

Pediatric renal transplant patients also commonly receive CNIs and are at risk for potential CNI nephrotoxicity. Based on a comparison with adult kidney transplant recipients, pediatric patients have similar graft survival at 10 years ( $P = 0.4325$ ), with similar rates of delayed graft function and SCr levels. However, acute rejections were more common in pediatric patients, and 10-year patient survival tends to be lower in the pediatric transplant group (90.3% *vs* 76.8%;  $P < 0.02$ )<sup>[138]</sup>. Consequently, pediatric patients are at similar or greater risks as adult patients, depending on the endpoint studied, and thus may be considered for immunosuppression changes from CNIs over time<sup>[139]</sup>.

### Regimens using mycophenolic acid or sirolimus to eliminate CNIs

**CNI and variable regimen:** Weintraub and colleagues retrospectively evaluated 17 patients on a baseline regimen of CNI plus either sirolimus, MMF or azathioprine, with or without corticosteroids who were being switched

to sirolimus or MMF for CNI toxicity ( $n = 9$ ), CAN ( $n = 6$ ) or diabetes mellitus ( $n = 2$ ) at a mean 5.9 years post-transplant. Mean CrCL actually decreased from baseline after the switch at 6 mo ( $P = 0.04$ ) and 12 mo ( $P = 0.02$ ), and 41% of patient developed ACR. Risk of ACR was predicted by prior AR history, which was present in 9 of 17 patients, lower sirolimus trough levels, and lower calcineurin inhibitor toxicity scores. Graft loss occurred in 24% of patients and was associated with worse CrCL, proteinuria, and histologic chronicity. Proteinuria increased in a manner unrelated to sirolimus use. Four patients returned to a CNI-base regimen based on adverse effects. The authors suggested that worsened graft function and graft loss after conversion could be minimized by selecting patients with high CNI toxicity scores and low chronicity scores on biopsy, and excluding patients with a history of ACR<sup>[140]</sup>.

### Regimens using mycophenolic acid to eliminate CNIs

**Baseline CNI, corticosteroid and azathioprine :** In another study of patients averaging 40 mo post-transplant, but at least 3 mo post-transplant, conversion from CNI, azathioprine and corticosteroid to MMF plus corticosteroid ( $n = 29$ ) or addition of MMF and elimination of azathioprine, without CNI withdrawal ( $n = 9$ ) resulted in overall patient survival of 100% and graft survival of 94% at approximately 5-year follow-up. There was no significant difference in ACR or proteinuria between the groups. Introduction of MMF resulted in improvement in GFR over 2 year regardless of which group was evaluated, but the patients with CNI withdrawn had a numerically increased GFR<sup>[141]</sup>.

### Regimens using sirolimus and MMF to eliminate CNI

**Baseline calcineurin inhibitor, corticosteroid and azathioprine:** A group retrospectively analyzed addition of sirolimus and MMF to eliminate CNI, and compared the strategy to CNI minimization (39% dose reduction), MMF and corticosteroid. One year after conversion, the sirolimus group had a  $10.3 \pm 3$  mL/min improvement in CrCL ( $P < 0.05$ ) versus baseline, while the CNI minimization group had a  $17.7 \pm 7.1$  mL/min ( $P < 0.05$ ) improvement in CrCL. No patient experienced ACR in either group. The authors concluded that sirolimus and MMF introduction had similar benefit to MMF introduction with CNI minimization<sup>[142]</sup>.

**Summary of pediatric studies:** Data is currently very limited on late CNI withdrawal to improve renal function and further study is required. Patient characteristics may impact the success of selected regimens.

## CONCLUSION

This manuscript presents available evidence on late conversion, beyond 6 mo, from CNIs to alternative regimens as a means to aid practicing clinicians in determining therapeutic options for patients exhibiting CNI toxicity

or CAN. Although recent evidence suggests that CNI toxicity and CAN are non-specific findings, and graft dysfunction may alternatively or additionally be a function of C4d and DSA, it has been shown that 5-year graft survival is not independently predicted by DSA and C4d, suggesting that clinicians will still modify regimens based on the presence of CAN and CNI toxicity on biopsy<sup>[143-146]</sup>. These studies provide moderate-level evidence of a short-term improvement in renal function, that is not without regimen-specific risks, such as increased infection rate with MPA or proteinuria with mTOR inhibitors. There appears to be a “point of no return” after which kidney damage is irreversible and the patient stands to benefit less from withdrawal of CNI<sup>[103-105,132]</sup>. Since the benefit of late withdrawal appears to be modest and dependent on baseline renal function, the second manuscript in this series will evaluate the data surrounding early conversion and de novo CNI avoidance.

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