CHAPTER 5

Long-term renal function after late complete calcineurin inhibitor withdrawal with mycophenolate mofetil

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ABSTRACT

Background. Prolonged calcineurin inhibitor (CNI) use is associated with nephrotoxicity. Early CNI withdrawal has not become routine practice, because of the risk of acute rejection. We assessed the safety of late CNI withdrawal and intermediate- to long-term impact on renal function in renal transplant recipients, including those with declining function.

Methods. 139 renal transplant recipients (age: 51±13 yrs, 65% male, median time post-transplantation: 4.8 yrs (IQR 1.8-7.8 yrs), eGFR: 44±17 mL/min/1.73 m^2), converted from a CNI-based regime to dual therapy with mycophenolate mofetil (MMF), were identified. Eighty-three patients (60%) were converted because of reasons unrelated to renal function (group 1) and 56 (40%) because of deteriorating renal function (group 2). Renal function was evaluated with a median follow-up of 3.4 yrs (IQR 2.9-5.1 yrs).

Results. In both groups eGFR improved immediately after CNI withdrawal (group 1: 4.9±2.4 mL/min/1.73 m^2, p=0.04; group 2: 5.4±1.8 mL/min/1.73 m^2, p=0.004). Group 1 had a stable eGFR before and after conversion (slopes: before: 0.11±0.09 mL/min/1.73 m^2/month; after: 0.04±0.06 mL/min/1.73 m^2/month, p=0.52). Group 2 had a declining eGFR slope (-0.34±0.07 mL/min/1.73 m^2/month), that stabilized after conversion (0.01±0.05 mL/min/1.73 m^2/month, p<0.001). One patient in each group experienced acute rejection.

Conclusion. Late CNI elimination to dual therapy with MMF was safe and improved renal function on the intermediate- to long-term, also in recipients with already deteriorating renal function.

INTRODUCTION

The introduction of calcineurin inhibitors (CNIs) in renal transplantation significantly reduced acute rejection rates, but to date long-term graft outcome has not improved accordingly [1-3]. Prolonged CNI use is associated with more hypertension, diabetes mellitus and hyperlipidemia; all factors known to contribute to the observed excess cardiovascular morbidity and mortality. In addition, CNI-related nephrotoxicity is a significant predictor of chronic allograft nephropathy (CAN), currently defined by interstitial fibrosis and tubular atrophy (IF/TA), the dominant cause of progressive graft dysfunction and late renal allograft loss [4-5].

A meta-analysis including 15 randomized, controlled, trials evaluating early CNI sparing regimens, either minimization or elimination, in stable kidney transplant recipients receiving mycophenolate mofetil (MMF), found that CNI sparing was associated with significantly better renal function and a tendency towards prolonged graft survival [6]. There was however an increased risk of acute rejection after CNI elimination, favoring CNI minimization to preserve renal function [7]. The largest multicenter study with cyclosporine reported a 50% increase in the incidence of acute rejection after early CNI withdrawal and no difference in renal function at one year [8]. Posthoc analysis showed that the risk of rejection was highest in patients with low mycophenolic acid (MPA) exposure, and that the optimal range of MPA exposure was close to 60 µg·h/mL [8-9]. Late elective complete CNI withdrawal (beyond month 12) also resulted in better renal function with a modest increase of acute rejection [10]. Long-term results, however, indicated a higher incidence of late rejection, probably explained by underdosing of steroids or MMF [11]. Therefore, early CNI minimization with MMF has become the preferred strategy, providing adequate protection against rejection and better renal function with reduced tacrolimus exposure. Disappointingly, follow-up failed to demonstrate a significant difference in graft function between the different treatment groups three years after transplantation [12].

Late CNI withdrawal in stable renal transplant patients with prospective therapeutic drug monitoring resulted in significantly better renal function compared to MMF withdrawal with only a low risk of acute rejection [13]. In accordance with the results after late conversion to mammalian target of rapamycin (mTOR) inhibitors [14-15], a limited benefit for patients with preserved renal function was found [13] . However, in contrast to the experience with mTOR inhibitors, the subgroup of patients with an estimated glomerular filtration rate (eGFR)<50 mL/min/1.73 m^2, but still ≥30 mL/min/1.73 m^2, benefitted most from late CNI elimination with MMF [13]. Two prospective studies, examining late CNI withdrawal in renal transplant recipients with deteriorating graft function and biopsy-confirmed CAN, observed an improvement in the course of renal function without the risk of acute rejection. Follow-up time of these trials was however limited with

only 6 months [16], while the other showed very promising results, but had to be stopped prematurely after 32 weeks for ethical reasons [17]. Therefore, we initiated an explorative study to assess our experience from daily clinical practice concerning the safety and the long-term impact on renal function of late complete CNI withdrawal with MMF and steroids in renal transplant recipients, including those with deteriorating renal function.

SUBJECTS AND METHODS

Study design

This study was conducted at the renal transplant outpatient clinic of the Leiden University Medical Center. All kidney transplant recipients, initially treated with CNI-based therapy and later (between 1997 and 2007) converted by their treating physician to dual therapy with MMF and steroids, were identified. Patients were followed 3 to 4 monthly either in Leiden or by an experienced nephrologist in one of the affiliated dialysis centers. The general policy over the years has been to consider complete CNI elimination in case of an otherwise unexplained gradual deterioration of renal graft function. A renal biopsy was encouraged to exclude recurrent glomerular disease, but not mandatory. The CNI dose was reduced by 50% every 2 weeks and withdrawn after 4 weeks with a temporary increase in steroid dose. Prednisolone was increased to 20 mg for 1 week, 15 mg the next week and returned to the maintenance dose of 7.5 to 10 mg daily. CNI withdrawal with therapeutic drug monitoring of MPA was optional from 2004 and included MPA levels predose and 1, 2 and 3 hours postdose. The MMF dose during and after withdrawal was adjusted to reach a target MPA-area under the concentration-time curve ($AUC_{0\text{-}12}$) of 75 µg·h/mL (range 60-90 µg·h/mL).

The primary outcome parameter of the current study was renal graft function. The eGFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation [18]. Secondary parameters included proteinuria, number of acute rejection episodes and graft loss. Recipient, donor and transplant characteristics, including immunologic risk profile (HLA mismatches, % panel reactive antibodies, rejection history), timing/reason for complete CNI withdrawal, the occurrence of rejection after withdrawal, blood pressure and number of antihypertensive drugs were retrieved from the Leiden Kidney Transplant Data system. The eGFR and degree of proteinuria were collected: (a) 3, 6, 12 and 24 months before CNI withdrawal; (b) at the time of CNI withdrawal; (c) 3, 6, 12, 18, 24, 30 and 36 months after CNI withdrawal; and (d) at the last visit of the patient to the hospital or outpatient clinic. To calculate the eGFR at the time of CNI withdrawal the last serum creatinine before CNI dose reduction was used.

Statistical analysis

Two subpopulations among our patients with CNI elimination were defined before examining the data. Group 1 consisted of a control group of patients switched for reasons not related to renal function (n=83) and group 2 consisted of patients with deteriorating renal function (n=56). All continuous variables are presented as mean±standard deviation or median with interquartile range and categorical variables as numbers and percentages. Continuous numeric variables were compared between the groups by the unpaired two-sample *t* test (parametric) or Mann-Whitney test (nonparametric) and nominal categorical variables by the chi-square test. Changes in renal function in the two groups were assessed using linear mixed models. Briefly, our model assumed that every patient experienced a linear trend in renal function before switching, a rapid increase at the time of CNI withdrawal, followed by again another linear trend after withdrawal. We tested if the rapid increase in renal function was significant and if the slopes (before and after) were different in both groups. Proteinuria measured at the conversion, at the first visit after CNI withdrawal and at the last visit was compared within the groups by a Friedman related samples test. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software version 20.0.

RESULTS

Characteristics of the patient population

Between 1997 and 2007, a total of 139 kidney transplant recipients had been converted to dual maintenance therapy with steroids and MMF after complete CNI withdrawal. Demographics, biometrics and the most relevant transplant-related factors are summarized in Table 1. These patients were transplanted between 1984 and 2005. We compared the most relevant characteristics with the reference population, being all single kidney transplants performed in our center in the same time period (Table 2). In the more recent cohort, there were less recipients of kidneys from deceased donors (69.6% vs. 78.8%, p=0.02) and less retransplants (6.5% vs. 15.8%, p=0.003). There were no differences with respect to the degree of immunization or HLA class II mismatches. Less patients experienced an acute rejection episode (25.9% vs. 47.9%, p<0.001) in more recent eras.

Eighty-three patients (59.7%) were converted for reasons not related to renal function: preference of the treating nephrologist or patient (25/83), a HLA-identical transplant (10/83) or adverse effects: gout (18/83), hypertension, diabetes and/or hypercholesterolemia (11/83), gingival hyperplasia (6/83), tremor (2/83), infection (4/83), bone or muscular pain (3/83) or miscellaneous (4/83). As expected, 56 patients (40.3%) converted because of a gradual deterioration of renal function had a significantly lower eGFR (32.1±9.0 vs. 52.0±15.6 mL/min/1.73 m^2, p<0.001), more proteinuria (0.37 g/24 h (IQR 0.15-1.28 g/24 h)

Table 1. Patient and transplant characteristics of study population

Characteristics	All patients N=139	Group 1 Stable renal function N=83	Group 2 Deteriorating renal function N=56	p
At conversion:				
Age (yrs)	50.6±12.6	50.7±12.3	50.5±13.2	0.93
Sex (% male)	65.5	63.9	67.9	0.63
Previous acute rejection (%)	25.9	19.3	35.7	0.03
BMI (kg/m^2)	25.2±4.7	26.3±5.0	23.8±3.6	0.001
eGFR (mL/min/1.73 m^2)	44.0±16.5	52.0±15.6	32.1±9.0	<0.001
Proteinuria (g/24 h)	0.22(0.15-0.46)	0.19(0.13-0.33)	0.37(0.15-1.28)	<0.001
Systolic blood pressure (mm Hg)	144±21	140±21	149±21	0.01
Diastolic blood pressure (mm Hg)	83±11	82±10	85±12	0.06
Time posttransplant (yrs)	4.8 (1.8-7.8)	3.6 (1.0-7.2)	6.0 (4.1-11.5)	<0.001
Immunosuppression: CsA:Tac (%)	85.6/14.4	80.7/19.3	92.9/7.1	0.05
CsA dose (mg/d)	199±81	197±82	200±81	0.75
Tac dose (mg/d)	6.3±4.7	7.1±4.9	3.3±2.2	0.13
MMF dose (mg/d)	1774±486	1786±481	1750±504	0.60
Antihypertensive drugs >2 (%)	43.2	36.1	53.6	0.04
ACE inhibitors (%)	47.8	43.9	53.6	0.26
Angiotensin II receptor blockers (%)	21.0	14.6	30.4	0.03
Diuretics (%)	42.8	37.8	50.0	0.16
At transplantation:				
Primary kidney disease:				
Glomerular disease/glomerulonephritis (%)	38.8	33.7	46.4	0.07
Pyelonephritis/interstitial nephritis (%)	15.1	14.5	16.1	
Hypertension/nephrosclerosis (%)	15.1	21.7	5.4	
APDKD (%)	16.5	14.5	19.6	
Other (%)	14.4	15.7	12.5	
Donor age (yrs)	43.3±12.9	42.5±12.9	44.7±13.0	0.32
Donor sex (% male)	51.8	45.8	60.7	0.08
Deceased donor (%)	69.6	59.8	83.9	0.002
Delayed graft function (%)	27.5	22.9	34.5	0.13
First transplantation (%)	93.5	92.8	94.6	0.74
PRA>5% (%)	53.2	47.0	62.5	0.07

Data are presented as mean±standard deviation, median and interquartile range or percentages.
BMI , body mass index; eGFR, estimated glomerular filtration rate; CsA, cyclosporine; Tac, tacrolimus; MMF, mycophenolate mofetil; ACE, angiotensin converting enzyme; ADPKD, autosomal dominant polycystic kidney disease; PRA, panel reactive antibodies.

Table 2.Transplant characteristics of reference and study population

Variable	Reference population (1984-2005) N = 1415	Study population N = 139	p
Year of transplantation (%):			
1984 – 1994	48.8	28.1	< 0.001
1995 – 1999	19.7	30.2	
2000 – 2005	31.5	41.7	
Acceptor age (yrs)	46.9±13.1	44.9±12.6	0.10
Sex (% male)	62.1	65.5	0.46
Donor age (yrs)	41.5±15.2	43.3±12.9	0.12
Donor sex (% male)	53.3	51.8	0.79
Deceased donor (%)	78.8	69.6	0.02
Retransplantation (%)	15.8	6.5	0.003
Pre-emptive transplantation (%)	5.2	3.6	0.54
Dialysis posttransplantation (%)	31.5	25.7	0.20
PRA>5% (%)	59.8	53.2	0.15
HLA mismatch (%):			
Class I	1.6±1.1	1.3±1.1	0.003
Class II	0.5±0.6	0.4±0.5	0.21
Acute rejection (%)	47.9	25.9	<0.001

Data are presented as mean±standard deviation or percentages.
PRA, panel reactive antibodies; HLA, human leucocyte antigen.

vs. 0.19 g/24 h (IQR 0.13-0.33 g/24 h), p<0.001) and a higher mean systolic (149±21 vs. 140±21 mm Hg, p=0.01) and diastolic blood pressure (85±12 vs. 82±10 mm Hg, p=0.06). A higher proportion of these patients had received a deceased donor kidney (83.9% vs. 59.8%, p=0.002). Patients with declining renal function were converted at a later median time point after transplantation (6.0 yrs (IQR 4.1-11.5 yrs) vs. 3.6 yrs (IQR 1.0-7.2 yrs) p<0.001) and a higher proportion was on cyclosporine-based therapy (92.9% vs. 80.7%, p=0.05) and treated with >2 types of antihypertensive drugs (53.6% vs. 36.1%, p=0.04). The median time of complete CNI withdrawal after transplantation was 4.8 yrs (IQR 1.8-7.8 yrs) and the median follow-up time after CNI withdrawal was 3.4 yrs (IQR 2.9-5.1 yrs).

Of the 56 patients converted because of deteriorating renal function, 25 (44.6%) had undergone a renal biopsy within 1 year before switch. One biopsy could not be evaluated due to insufficient amount of cortex. Chronic structural changes compatible with mild to moderate CAN-IF/TA were demonstrated in 24/24 biopsies in combination with arteriolar hyalinosis (20/24) and chronic transplant glomerulopathy (1/24). Five biopsies also identified recurrent disease: IgA nephropathy (4/24) and diabetic nephropathy (1/24).

Renal function

The effects of complete CNI withdrawal with MMF on renal function were evaluated by sequential eGFR measurements, ranging from 2 years before until at least 3 years after conversion to MMF. The CNI withdrawal was performed stepwise in four weeks. Figure 1 shows renal function at different time points and trends in renal function over time for both groups. The eGFR significantly increased immediately after conversion in both groups (group 1: 4.9±2.4 mL/min/1.73 m^2, p=0.04; group 2: 5.4±1.8 mL/min/1.73 m^2, p=0.004). Group 1 had a stable renal function before and after conversion (slope before : 0.11±0.09 mL/min/1.73 m^2/month; after: 0.04±0.06 mL/min/1.73 m^2/month, p=0.52). Group 2 demonstrated a progressive gradual loss of eGFR towards conversion (-0.34±0.07 mL/min/1.73 m^2/month), that stabilized after conversion (0.01±0.05 mL/min/1.73 m^2/month) with a significant difference between the slopes (p<0.001).

Proteinuria did not differ significantly at the time of conversion, at the first visit after CNI withdrawal and at the last visit within both groups (group 1: 0.19 g/24 h (IQR 0.13-0.33 g/24 h) vs. 0.23 g/24 h (IQR 0.16-0.37 g/24 h) vs. 0.21 g/24 h (IQR 0.16-0.33 g/24 h), respectively, p=0.12; group 2: 0.37 g/24 h (IQR 0.15-1.28 g/24 h) vs. 0.42 g/24 h (IQR 0.24-0.69 g/24 h) vs. 0.31 g/24 h (IQR 0.18-0.60 g/24 h), respectively, p=0.54).

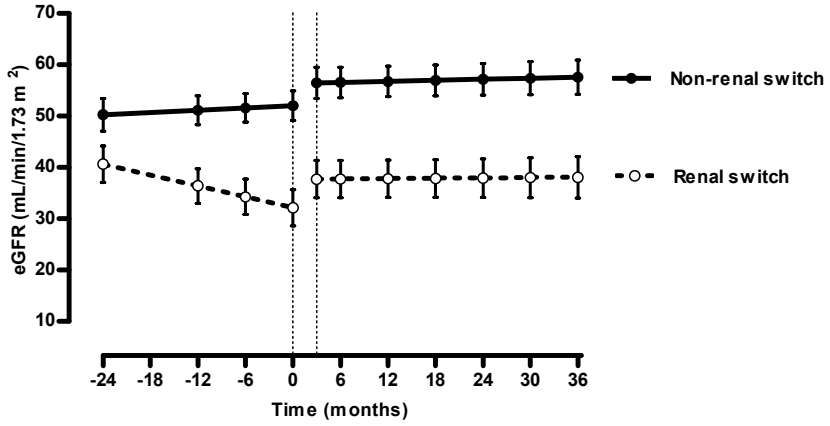

Figure 1. Renal follow-up before and after conversion to mycophenolate mofetil-based regimen
Linear mixed model showing the trends in eGFR-slopes before and after late CNI elimination.
Plotted are the model-predicted means and 95% confidence intervals. Solid lines: patients switched for nonrenal reasons (group 1); dotted lines: patients switched because of deteriorating renal function (group 2).

Acute rejection and graft loss

One patient in each group experienced an acute rejection episode. In group 1, acute interstitial rejection occurred in a stable male recipient of a 1-2-1 HLA-antigen mismatched kidney with a previous acute rejection episode and an MPA-AUC of 79 µg·h/mL at day 10

after CNI discontinuation. After successful treatment with steroids and antithymocyte globulin the CNI was reintroduced. In group 2, a female recipient of a 1-1-0 HLA-antigen mismatched kidney experienced graft loss (2.5 yrs after conversion) after reduction of immunosuppression with acute vascular and interstitial rejection in the context of severe abdominal tuberculosis. Three other patients in group 2 returned to dialysis: two due to CAN-IF/TA with progressive renal failure after 1.2 and 3.1 yrs after conversion to MMF and one after ICU-admission for pneumocystis jiroveci pneumonia complicated by irreversible acute tubular necrosis at 6.2 yrs after CNI withdrawal.

Four biopsies (4.8%) were performed (range 3.0-3.7 yrs after CNI withdrawal), because of a deterioration of renal function or increase in proteinuria in group 1. Three biopsies showed mild to moderate CAN-IF/TA, two biopsies signs of chronic transplant glomerulopathy and one recurrent IgA nephropathy. The MPA-AUCs were <60 µg·h/mL in all patients at the time of the biopsy.

MMF dosing and change of immunosuppressive regimen

The mean daily MMF dose was comparable at the time of conversion in both groups (group 1: 1786±481 mg; group 2: 1750±504 mg, p=0.60). The mean daily dose of MMF was higher in group 1 at 3 months after conversion (2228±666 mg vs. 1737±456 mg, p<0.001) and 3 years after conversion (1862±868 mg vs. 1427±729 mg, p=0.005). The MPA exposure was measured in 68 patients in group 1 (81.9%) and 41 patients in group 2 (73.2%) during and/or after conversion. AUC monitoring of MPA was infrequently performed (median 2.0 times during and/or after withdrawal). The mean MPA-AUC was between 60-90 µg·h/mL in 56.0% of cases in both groups, >90 µg·h/mL in 9.2% and <60 µg·h/mL in 34.9% of cases.

The immunosuppressive regimen was changed after the initial conversion in eleven patients in group 1 (13.3%) and nine patients in group 2 (16.1%). In group 1, the maintenance regimen was converted to triple therapy, consisting of a combination of prednisone, MMF, with either a CNI or an mTOR inhibitor in two and one patients, respectively. MMF was substituted for a CNI in three patients in group 1 and five patients in group 2, or for an mTOR inhibitor in four patients in group 1 and one patient in group 2, or for azathioprine in one patient in group 1 and three patients in group 2. There were various reasons for switching the immunosuppressive treatment; in group 1: diarrhea (2/11), leucopenia (1/11), acute rejection (1/11), transplant glomerulopathy (2/11), infection (1/11), malignancy (3/11) and pregnancy wish (1/11); in group 2: diarrhea (4/9), leucopenia (1/9) and infection (4/9).

DISCUSSION

The results of this retrospective evaluation of late complete CNI withdrawal in daily clinical practice showed an immediate and significant improvement in renal function after elective withdrawal in patients with stable renal function and those with progressive loss of function. More importantly, in the latter patient group, the slope of renal function over time improved significantly and stabilized after CNI withdrawal. Late CNI withdrawal and conversion to MMF in this observational cohort was safe, and not accompanied by excess acute rejection. The largest retrospective study on CNI reduction in transplant recipients with chronic allograft nephropathy had a median follow-up time of 651 days, but in only a minority of the patients (15%) the CNI was completely stopped [19]. In the Creeping Creatinine Study, elimination of the CNI in the presence of MMF resulted in improved renal function at 6 months in patients with biopsy-confirmed CAN and there was no risk of acute rejection [16]. A smaller trial randomized only 39 patients with biopsy-proven CAN and had to be stopped prematurely after 32 weeks. The reason was significantly better graft function after complete CNI withdrawal without the occurrence of acute rejection [17]. The present observational study confirms these previous data and the successful implementation of late CNI elimination in daily practice with only a low risk of acute rejection, while extending the observed beneficial effect on renal function to the intermediate- to long-term.

The immediate improvement in graft function is most likely explained by intrarenal hemodynamic changes [20]. CNIs cause renal vasoconstriction, especially of the afferent arterioles, followed by a decrease in GFR, renal plasma flow and increased renal vascular resistance [20]. Prolonged CNI use and intermittent daily vasoconstriction may lead to chronic tubulointerstitial lesions as well as impaired regional perfusion in case of progressive vascular hyalinosis. The stabilization of renal function for at least 3 years after CNI withdrawal also suggests an impact on chronic CNI-related nephrotoxic effects. Normalization of nitric oxide synthesis and reduced expression of transforming growth factor-β may also contribute to these changes [21].

In recent years, the role of chronic CNI nephrotoxicity in late renal graft failure has been questioned [22]. A retrospective study from the Mayo clinic identified glomerular disease and cellular and antibody-mediated immunologic injury as important causes of death-censored graft loss, while CNI-related toxicity only rarely attributed [23]. A recent prospective study following patients after for cause biopsies, indicated antibody-mediated or mixed rejection as the major cause of late graft failure, whereas CNIs did not play a role [24]. In the DeKAF study, patients with late allograft dysfunction with evidence of antibody-mediated injury had an increased risk of graft loss [25]. Patients only showing signs of CNI toxicity were less likely to experience graft failure [25]. Our results suggest that CNI use may have been the underlying cause of progressive deterioration of renal

function in this cohort of patients, and that CNI-related nephrotoxicity should not be neglected as a potentially important determinant of late and progressive graft dysfunction.

Most randomized studies on CNI withdrawal have shown an improvement in renal function, but mainly early after transplantation there is an increased risk of acute rejection [8, 10-11, 26-28]. The CAESAR trial found no difference in renal function at 12 months, despite a 50% increase in acute rejection after CNI withdrawal at 4 to 6 months after transplantation [8]. Abramowicz et al. compared CNI withdrawal or continuation of triple-drug therapy in stable renal transplant recipients 12 to 30 months after transplantation [10-11]. A significant improvement in renal function was documented after CNI withdrawal, but also a higher incidence of (chronic) rejection was noted at 5 years [11]. It appears that CNI elimination is associated with an increased acute rejection rate, especially early after transplantation and in case of inadequate dosing of MMF or steroids [8, 11, 28]. In a concentration-controlled randomized study, late CNI withdrawal resulted in significant improvement in renal function as compared to MMF withdrawal, especially in patients with an eGFR<50 mL/min/1.73 m^2, but ≥30 mL/min/1.73 m^2, up to 3 years [13]. These findings suggested that AUC monitoring of MPA, while preventing underdosing of MMF, reduced the occurrence of acute rejection after CNI withdrawal.

The beneficial effect of conversion to MMF on renal function, in patients with deteriorating renal function in this study, are in contrast with the CONVERT and ASCERTAIN studies evaluating late CNI withdrawal, but with conversion to an mTOR inhibitor [14-15]. Both studies failed to show better renal function in the intention-to-treat analysis. Only patients with an eGFR>40 mL/min in the CONVERT trial or GFR>50 mL/min in the ASCERTAIN study, who continued mTOR inhibitor treatment during 2 years, had a moderate but significant benefit in renal function with a low risk of acute rejection. These data may indicate that patients should be converted to an mTOR inhibitor well before they developed irreversible (structural) changes and a gradual decline in renal function. The lack of benefit, in patients with an eGFR<40 mL/min or <50 mL/min in the CONVERT and ASCERTAIN studies, respectively, may also relate to the relatively high rates of mTOR inhibitor discontinuation and reintroduction of CNI-based therapy. A randomized study comparing CNI withdrawal with adequate exposure of either MMF or an mTOR inhibitor would be needed to draw more definite conclusions on possible distinct effects in patients with impaired or deteriorating renal allograft function.

The main obvious limitation of our study is the observational character, but it does allow evaluation of a perceived beneficial strategy in daily clinical practice and provides long-term data on the course of renal function after complete CNI withdrawal. Although the study has no data on donor specific antibodies or (repeat) protocol biopsies, the observed results suggest a beneficial effect of CNI elimination on the course of renal function. Another limitation may be that the large majority of patients used cyclosporine,

whereas tacrolimus is currently the most frequently prescribed CNI after renal transplantation. Cyclosporine and tacrolimus, however, share comparable vasoconstrictive and nephrotoxic properties. Further, CNI withdrawal with therapeutic drug monitoring of MPA was only optional, therefore from the current study no conclusions can be drawn on the benefit of concentration-controlled dosing of MMF.

In summary, in our clinical experience, late CNI withdrawal with adequate MMF dosing was safe in the large majority of patients with a low risk of acute rejection. The immediate improvement in renal function after withdrawal was sustained on the intermediate- to long-term, with a significant deviation and stabilization of the eGFR slope over time, in those converted because of progressive loss of renal function. Within the multifactorial pathogenesis and progression of chronic renal allograft dysfunction, the impact of prolonged CNI exposure should not be disregarded.

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