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Conversion From Calcineurin Inhibitors to Sirolimus in Kidney Transplant Recipients: A Retrospective Cohort Study

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ABSTRACT

Background. Replacing a calcineurin inhibitor (CNI) with sirolimus (SRL) may preserve kidney graft function. However, at the present time, only short follow-up after conversion is available. The aim of this study was to assess whether conversion from a CNI-based to an SRL-based maintenance regimen was safe and effective.

Materials and methods. We performed a retrospective cohort study among kidney graft patients whose CNI was withdrawn to be replaced by SRL. Two-tailed paired *t* tests were used to compare glomerular filtration rates (GFRs) and proteinuria levels before and up to 2 years after conversion. We used linear regression to determine the factors associated with changes in renal function after conversion.

Results. The 193 study subjects had a mean GFR at conversion of 41 ± 16 mL/min/1.73 m^2 a median proteinuria level of 0 g/L (interquartile range = 0–0.15). After conversion, the GFR was stable: at 1 year, the change was −0.34 mL/min/1.73 m^2 (95% confidence interval [CI] = −2.71, 2.03) and at 2 years, −0.96 mL/min/1.73 m^2 (95% CI = 4.26, 2.34). There was a small but significant increase in dipstick proteinuria at 1 year of +0.5 g/L, (95% CI = 0.20, 0.75). On multivariate analysis, proteinuria ≥ 1 g/L at the time of conversion was the only predictor of deteriorating GFR at 1 year (β: −7.91 mL/min/1.73 m^2; 95% CI = −14.10, −1.70). SRL had to be discontinued in 31% of patients.

Conclusion. Conversion from CNI to SRL resulted in stable graft function at 2 years and in a slight increase in proteinuria. Despite the relatively high reconversion rate, this strategy offers a reasonable alternative to CNIs for most patients.

CHRONIC ALLOGRAFT NEPHROPATHY (CAN) is one of the major causes of late renal transplant loss. The dramatic impact of modern immunosuppression on short-term allograft survival has not translated into improved long-term success.[1] Many factors, including calcineurin inhibitor (CNI) nephrotoxicity,[2] have been suggested to lead to CAN. A meta-analysis of randomized controlled trial in which CNIs were withdrawn from a sirolimus (SRL)-containing regimen showed a significant increase in glomerular filtration rate (GFR).[3] However, the observation that SRL potentiates CNI nephrotoxicity[4] may explain the improvement in GFR associated with CNI withdrawal. Hence, a better strategy in terms of nephroprotection may be conversion from CNIs to SRL in a regimen that also contains mycophenolate mofetil (MMF) or azathioprine, and steroids. Although available evidence indicates that better graft function in the short term is obtained after conversion from CNIs to SRL, there is little information exists as to whether this early benefit is sustained after 6 to 12 months.[5] Hence, this lack of experience and the possible SRL-induced side effects may deter clinicians from replacing CNIs with SRL.

The aim of this study was to assess whether conversion from a CNI-based to an SRL-based maintenance regimen was safe and effective to preserve graft function as well as to examine proteinuria and side effects up to 2 years after

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0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.08.049

conversion. We also sought to identify clinical factors associated with changes in kidney graft function after conversion.

PATIENTS AND METHODS

Patients

We performed a retrospective cohort study among patients who received a kidney graft in the two University of Montreal centers that offer adult renal transplantation. We included all patients who were converted from a CNI-based to a SRL-based regimen. All patients initially received a CNI, in combination with an antiproliferative agent (MMF or azathioprine) and corticosteroids (CS) in most cases; or with CS alone. SRL trough levels were targeted to 10 to 15 ng/mL in patients deemed to be at high immunologic risk and to 8 to 12 ng/mL in the other subjects. Follow-up was censored on July 1, 2007, or at patient death, whichever happened first.

Measurements

GFR, as estimated using the abbreviated MDRD equation,[6] was calculated before as well as 1 and 2 years after conversion to SRL. Patients who lost their graft and survived were imputed to show a GFR of 5 mL/min/1.73 m^2. Patients who died with a functioning graft were imputed based upon their last estimated GFR. As an indirect comparison group, we measured the annual decline in GFR among our whole cohort of kidney transplant recipients who still had functioning grafts after the first posttransplant year (n = 639). Proteinuria was measured in grams per liter using a urinary dipstick. Clinical factors identified as potential determinants of a change in graft function and included in regression analyses were: recipient age, gender, center, motive for conversion (biopsy proven or empirical nephroprotection versus all other motives), baseline CNI (tacrolimus versus cyclosporine [CsA]), time elapsed between transplant and conversion, rejection before conversion, graft function at conversion, and proteinuria at conversion. Detailed clinical data collected by chart review and electronic database by trained research nurses were validated by a local investigator.

Statistical Analyses

We performed two-tailed paired t tests to compare GFR values and proteinuria content before conversion and 1 and 2 years there after. The annual decline for the whole transplant cohort was determined using SAS proc mixed to account for repeated measures. We used multiple linear regression to determine factors associated with the magnitude of the change in renal function at 1 year after conversion.

RESULTS

The baseline patient characteristics, immunosuppressive regimens, and motives for conversion for 193 patients are listed in Table 1. During the follow-up, patient and graft survivals were 91% and 83%, respectively. The median time from transplant to conversion was 3.5 years (interquartile range [IQR] = 0.94–8.05). At conversion, the mean GFR was 41 ± 16 mL/min/1.73 m^2. At 1 and 2 years, the GFR was stable: −0.34 mL/min/1.73 m^2 (95% confidence interval [CI] = −2.71, +2.0 mL/min/1.73 m^2) at 1 year and −0.96 mL/min/1.73 m^2 (95% CI = −4.26, 2.34 mL/min/1.73 m^2) at 2 years. This figure compared favorably with the decline observed after the first posttransplant year among our whole cohort of kidney transplant recipients: −1 mL/min/1.73 m^2/y (95% CI = −1.2, −1.0 mL/min/1.73 m^2/y). On both univariate and multivariate analyses, only proteinuria ≥ 1 g/L at the time of conversion was predictive of a poorer GFR at 1 year (β: −7.91 mL/min/1.73 m^2; 95% CI: −14.10, −1.70). At conversion, the median level of proteinuria was 0 g/L (IQR = 0–0.15) with only 2% of patients showing proteinuria ≥ 5 g/L. There was a small but significant increase in dipstick proteinuria at 1 year (+0.5 g/L; 95% CI = 0.20, 0.75). Six percent of patients displayed dipstick proteinuria ≥ 5 g/L at 1 year.

Table 1. Patient Baseline Characteristics (n = 193)

Age in years (SD)	45 (13)
Male gender (%)	111 (58)
Transplant period (%)	
1978–1996	48 (25)
1997–2000	48 (25)
2001–2003	48 (25)
2004–2006	49 (25)
Median time to conversion in years (IQR)	3.5 (0.94–8.05)
CNI used before conversion (%)	
Cyclosporine	79 (41)
Tacrolimus	110 (57)
History of rejection before conversion (%)	41 (21)
Adjunctive agent used with sirolimus (%)	
Mycophenolate mofetil	110 (70)
Azathioprine	12 (6)
None or not determined	45 (23)
Motives invoked for conversion (%)	
Empirical nephroprotection	46 (24)
Biopsy-proven CNI toxicity	76 (39)
Cancer	30 (16)
Nonrenal CNI-related side effects	31 (16)
Others (BK virus, diabetes, hemolytic uremic syndrome)	10 (5)

SD, standard deviation; IQR, interquartile range; CNI, calcineurin inhibitor.

SRL had to be discontinued in 31% of patients. The most frequent reasons for switching back to CNIs were related to the digestive tract (14%), skin (14%), anticipated or actual wound-healing concerns (14%), rejection (12%), pulmonary pathologies (8%), edema (8%), or proteinuria (7%). Detailed information regarding side effects encountered with SRL is provided in Table 2.

DISCUSSION

Preservation of kidney graft function has become the focus of much research interest in recent years, since it is associated not only with graft survival[7] but also with cardiovascular mortality.[8] Withdrawing CsA at 4 to 6 months after transplantation from a regimen containing daclizumab, MMF, and CS was associated with a greater rate of acute rejection episodes than continuing low-dose CsA.[9] Using low-dose SRL from the baseline in combination with daclizumab, MMF, and CS resulted in reduced graft survival and a greater rate of acute rejection episodes than prescription of low-dose tacrolimus combined with the

Table 2. Treatment Failure and Side Effects Associated With Conversion to SRL

Sirolimus failure (%) (n = 193)	59 (31)
Duration of treatment with sirolimus in days (interquartile range)	
Failure group	159 (68–657)
Ongoing treatment group	970 (475–1581)
Motives invoked for discontinuing sirolimus (%) (n = 59)	
Proteinuria	4 (7)
Acute rejection	7 (12)
Edema	5 (8)
Skin lesions (acne, folliculitis, rash)	8 (14)
Digestive tract (diarrhea, colitis, mouth ulcers)	8 (14)
Pulmonary symptoms (BOOP, cough, effusions)	5 (8)
Anticipated or actual wound healing concerns	8 (14)
Deteriorating renal function or return to dialysis	4 (7)
Other	10 (17)
Most frequent side effects reported (%) (n = 193)	
Proteinuria	10 (5)
Edema	59 (31)
Skin lesions (acne, folliculitis, rash)	24 (12)
Digestive tract (diarrhea, colitis, mouth ulcers)	23 (12)
Cytopenia	12 (6)
Pulmonary symptoms (BOOP, cough, effusions)	5 (3)
Dyslipidemia	8 (4)

same agents.[10] Conversion from a regimen based on CNI to one based on SRL after the first months following transplantation represents an interesting therapeutic alternative. Although a systematic review of the literature[5] had indicated that such an approach yields improved graft function at 6 and 12 months, little data exist as to whether the benefit is sustained.

We studied the evolution of graft function among a large cohort of subjects whose CNIs were withdrawn and replaced with SRL. In the majority of cases, the conversion was performed to avoid CNI-associated nephrotoxicity, whether a biopsy was performed or not. Our results showed a small decrease in graft function at 1 and 2 years after transplantation, which was less than that observed among our whole cohort of kidney transplant recipients after the first posttransplant year, suggesting that conversion may be beneficial to preserve renal function; the effect was maintained at 2 years. Our results differ from the findings reported in a recent systematic literature review,[5] which noted a 5 to 6 mL/min increase in GFR following conversion. Two reasons may explain this discrepancy. First, we imputed a GFR of 5 mL/min to patients who survived but lost their grafts, which yielded a more conservative, accurate estimate of graft function than to simply exclude subjects whose grafts were lost. Without this imputation strategy, the change in GFR was +1.8 mL/min/1.73 m^2 at 1 year and +2.7 mL/min/1.73 m^2 at 2 years, which is closer to the values reported by others. Second, our group of patients may have shown poorer function, since 25% of them already displayed a GFR below 30 mL/min at conversion and may have been less likely to benefit from therapeutic intervention.

We observed a small increase in proteinuria after conversion to SRL. The increase was generally not significant clinically. However, 6% of patients did develop nephrotic-range proteinuria at 1 year after conversion, a finding that has been reported by others.[5] Both we and others have reported that proteinuria at baseline was associated with a poorer response to conversion in terms of GFR.[11] Regarding safety, the most frequent reasons invoked for discontinuation were digestive, cutaneous, and wound-related in our cohort. We observed a 31% rate of discontinuation of SRL, which was similar to the pooled average of rates reported in clinical trials of SRL conversion (28%), but slightly higher than those in most other observational studies (17%).[5]

In conclusion, we observed that conversion from CNIs to SRL resulted in stable graft function at 1 and 2 years and in a slight increase in proteinuria. Despite a relatively high reconversion rate, SRL offers a reasonable therapeutic alternative to CNIs for most patients.

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