Ten-Year Follow-up of Pharmacokinetics-Guided Very Early Cyclosporine Minimization Synchronized With Everolimus Initiation in De Novo Kidney Transplantation

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ABSTRACT

Background. Minimization of calcineurin inhibitor (CNI) from the 1st week after kidney transplantation (KT) may reduce the risk of CNI nephrotoxicity.

Methods. Ten de novo KT recipients who received full exposure cyclosporine (CsA) and prednisolone as initial therapy were enrolled. Initial CsA minimization was 50% and started at day 7 after KT. This was synchronized with everolimus (EVL) initiation. Target trough level of EVL was 3–8 ng/mL. Pharmacokinetics studies of CsA and EVL were studied at week 4. The CsA dosage was further reduced to keep a lowest value of serum creatinine and a target EVL level. Primary outcomes were estimated glomerular filtration rate (eGFR) at baseline and last follow-up.

Results. Patients' mean age at last follow-up was 60.6 ± 11.7 years. Follow-up duration was 121.6 ± 12.8 months. Pharmacokinetics study found that Cmax of CsA ranged from 309 to 1,896 ng/mL, mean area under the receiver operating characteristic curve (AUC) of CsA was 3,449 ± 1,402 ng·h/mL, C0 of EVL was 5.2 ± 1.5 ng/mL, Cmax of EVL was 15.4 ± 4.6 ng/mL, and AUC of EVL was 99.7 ± 26.1 ng·h/mL. Achieved nadir serum creatinine was 1.03 ± 0.33 mg/dL. Achieved best eGFR (Modification of Diet in Renal Disease formula) was 99.7 ± 26 mL/min. eGFR at 12 months was 82 ± 25 mL/min. Last serum creatinine was 1.32 ± 0.45 mg/dL. Last eGFR was 57.2 ± 13.55 mL/min. Actuarial death-censored 10-year graft survival was 100%. Actuarial 10-year patient survival was 80%.

Conclusions. Our intervention can lead to an average of 75% CsA minimization and a very good eGFR at 10 years.

CHRONIC allograft nephropathy (CAN) is an important cause of late allograft loss for long-term kidney transplant recipients. This is characterized by progressive renal allograft dysfunction characterized by interstitial fibrosis, tubular atrophy, vascular changes, and glomerulosclerosis. It is known that calcineurin inhibitor (CNI) nephrotoxicity can lead to CAN. Pathologic changes of CNI nephrotoxicity have been shown to be universal by 10 years and exacerbate CAN [1]. Strategies to reduce CNI nephrotoxicity may benefit the prevention and treatment of CAN. Minimization of CNI from the early period after transplantation is one strategy to reduce nephrotoxicity of CNI. However, the long-term effect is not known.

Everolimus is a potent immunosuppressive agent. It is one of the mammalian target of rapamycin (mTOR) inhibitors that are different from the primary drug, sirolimus. Previous study has shown that CsA and everolimus have synergistic immunosuppressive activities. In addition, CsA can increase the bioavailability of everolimus and it is possible to reduce the dose of both drugs when they are

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combined [2]. Previous studies have shown good renal function and 1-year graft survival in renal transplant recipients who were randomized to receive low-dose (1.5 mg/d) or high-dose (3 mg/d) of everolimus combined with reduced-dose CsA. [3]. However, the optimum reduction of CsA to combine with everolimus is not clearly known. We therefore report the 10-year outcomes of a pharmacokinetics-guided very early minimization of CsA in conjunction with everolimus initiation in de novo kidney transplant recipients. Minimization of CsA started at the period from 1 to 2 weeks after transplantation.

METHODS

Ten de novo kidney transplant recipients were enrolled. All had panel reactive antibodies PRA <50% and cold ischemia time <24 hours. Initial immunosuppression included standard-exposure CsA microemulsion (target trough level, 250–350 ng/mL) and prednisolone. The CsA dosage was reduced initially by 50% on day 7 or when best serum creatinine was achieved. Everolimus was initiated on the day of CsA reduction. The dose of everolimus was adjusted to achieve the target level of 3–8 ng/mL. After achieving the target everolimus level, the dose of CsA was further adjusted to maintain a trough level of 100–200 ng/mL and stable serum creatinine. The adjustment was aimed to achieve a lowest value of serum creatinine for each individual patient and not higher than before everolimus initiation.

A full pharmacokinetics study of CsA and everolimus exposure was done at steady state. The latter is defined by the time with stable serum creatinine and no further dose adjustment of everolimus and CsA being required. Ten samples of blood at time 0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 9, and 12 hours before and after the exposure of CsA and everolimus were drawn to measure the area under the receiver operating characteristic curve (AUC) of both drugs. Everolimus and CsA level were measured by means of fluorescent polarization immunoassay. After the result of pharmacokinetics study, the dose of CsA was further decreased according to the obtained Cmax of CsA. At this time, the target C2 and trough levels of CsA were 500–600 and 50–100 ng/mL, respectively. The important goal was to keep serum creatinine at the lowest level of each individual. Dose of corticosteroid was used according to the local protocol. That started with 1,000 mg pulse intravenous methylprednisolone in the operating room. Corticosteroid was then gradually tapered to the dose of 20 mg/d prednisolone at day 30, 10 mg/d at day 180, and 5 mg/d at 1 year. There was no steroid avoidance in this cohort. Serum creatinine was measured three times weekly during the hospitalization period, then every week until the 3rd month, every month until the 6th month, every 2 months until the 12th month, then every 3 months or when clinically indicated. Renal allograft biopsy was done when acute allograft dysfunction and/or significant proteinuria occurred. Acute allograft dysfunction was defined by an elevation of serum creatinine by >25% of the previous value. Significant proteinuria was defined by a proteinuria >1 g/d or spot urine protein/creatinine ratio >1. Primary outcomes were estimated glomerular filtration rate (eGFR) at several time points, including at baseline, 1 year, and last follow-up. Secondary outcomes were 1- and 10-year graft and patient survivals. eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) formula. Actuarial graft and patient survivals were determined by means of Kaplan-Meier survival analysis.

RESULTS

Ten patients were enrolled. Eight received living related kidney transplants and 2 received deceased-donor kidney transplants. Causes of end-stage renal disease were diabetes mellitus ($n = 4$), chronic glomerulonephritis ($n = 3$), hypertension ($n = 2$), and autosomal dominant polycystic kidney disease ($n = 1$). Mean age at enrollment was 50.2 ± 11.3 years. Mean age at last follow-up was 60.6 ± 11.7 years. Mean HLA mismatch was 2.4 ± 1.07. Mean follow-up duration was 121.6 ± 12.8 months. Nine patients did not receive induction therapy. One patient (with PRA 40%) received anti–interleukin-2 induction therapy. Mean initial dose of CsA before initiation of everolimus was 282 ± 81 mg/d. Mean CsA trough level before initiation of everolimus was 247 ± 89 ng/mL. At the time of the pharmacokinetics study, mean dose of CsA was 135 ± 46 mg/d.

Results of the pharmacokinetics study found that there was a wide variation of AUC of CsA (3,449.9 ± 1,402.1 ng·h/mL; range, 1,334–6,386). Mean trough CsA level was 100.3 ± 42.7 ng/mL (range, 50–176). Mean Tmax of CsA was 1.45 ± 0.36 hours (range, 1–2). Mean Cmax of CsA was 958.7 ± 447.3 ng/mL (range, 309–1,896 ng/mL). Mean trough level of everolimus was 5.2 ± 1.51 ng/mL (range, 3.06–7.56). Mean T max of everolimus was 1.5 ± 0.31 hours (range, 1–2). Mean Cmax of everolimus was 15.25 ± 4.64 ng/mL (range, 9.61–23.92). Mean AUC of everolimus was 99.7 ± 26.1 ng·h/mL (range, 67.7–155.7). The summary of the pharmacokinetics study is presented in Table 1. Linear regression analysis found that trough level of everolimus was significantly correlated with AUC ($r = 0.72$; $P = .02$).

CsA dosage was further reduced according to the method described above. The result of the pharmacokinetics study

Table 1. Results of Pharmacokinetics Studies

Variable	Cyclosporine	Everolimus
C0		
Mean	100.3 ± 42.7 ng/mL	5.2 ± 1.51 ng/mL
Range	50–176	3.06–7.56
C max		
Mean	958.7 ± 447.3 ng/mL	15.25 ± 4.64 ng/mL
Range	309–1,896	9.61–23.92
T max		
Mean	1.45 ± 0.36 h	1.5 ± 0.31 h
Range	1–2	1–2
AUC		
Mean	3,449.9 ± 1,402.1 ng.h/mL	99.7 ± 26.1 ng.h/mL
Range	1,334–6,386	67.7–155.7
Dose at intervention 1		
Mean	282 ± 31 mg/d	0
Range	225–325	0
Dose at intervention 2		
Mean	135 ± 45 mg/d	0.58 ± 0.12 mg bid
Range	50–200	0.5–1.0

Note. Intervention 1: initiation of everolimus; intervention 2: pharmacokinetics study.
Abbreviation: AUC, area under the receiver operating characteristic curve.