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Sirolimus Use in Recipients of Expanded Criteria Donor Kidneys

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Abstract

With changing donor characteristics and the growing shortage in organ supply, renal transplant practitioners have sought to optimize the use of expanded criteria donor (ECD) kidneys, which have poorer outcomes than standard criteria donor (SCD) kidneys. The outcomes may represent an acceptable trade-off if ECD transplants offer enhanced overall patient survival by reducing waiting times. ECD kidneys may be more susceptible to toxicity associated with calcineurin inhibitors (CNIs); therefore, a potential strategy to improve outcomes in this growing demographic is the use of CNI-free immunosuppressive protocols. To date, published clinical studies have demonstrated encouraging outcomes using sirolimus-based CNI-free regimens in SCD kidney transplant recipients. We conducted a pilot study to examine outcomes in ECD kidney transplant recipients receiving a CNI-free quadruple drug regimen, consisting of antithymocyte globulin (ATG), sirolimus, mycophenolate mofetil (MMF) and a corticosteroid, compared with outcomes in a retrospective CNI-control group of ECD recipients who had received standard CNI-based immunosuppressive treatment. Patient survival and allograft survival at 1 year were not significantly different between the CNI-free group (n = 13) and the CNI-control group (n = 13) [100% vs 92% and 92% vs 85%, respectively]; nor was the incidence of rejection (26% and 31%) or delayed graft function (38% of patients in both groups). Serum creatinine was significantly lower and the estimated glomerular filtration rate was significantly higher for the CNI-free group at 3–6 months but not at 1 year. Protocol biopsies in the CNI-free patients at 1 year revealed no significant progression of chronic vascular lesions. Banff chronic/sclerosing allograft nephropathy scores were 42% grade I, 25% grades II and III, and 33% grade 0. Thus, a sirolimus-based CNI-free regimen may improve outcomes in ECD kidney transplant recipients and merits further study.

Kidney transplantation is the preferred treatment for patients with end-stage renal disease, since it confers an increase in quality of life and life expectancy compared with maintenance dialysis.[1-4] Un-

Table I. Expanded criteria for kidney donors as listed in United Network for Organ Sharing (UNOS) Policy 3.5.1 (reproduced from UNOS,[13] with permission)

Donor condition	Donor age categories (y)				
	<10	10–39	40–49	50–59	≥60
CVA + HTN + creatinine >132.6 μmol/L				X	X
CVA + HTN				X	X
CVA + creatinine >132.6 μmol/L				X	X
HTN + creatinine >132.6 μmol/L				X	X
CVA					X
HTN					X
Creatinine >132.6 μmol/L					X
None of the above					X

CVA = cerebrovascular accident was cause of death; **HTN** = history of hypertension.

fortunately, there is an increasing disparity between the supply and demand of transplantable kidneys, which has led to longer waiting times and consequently more deaths across the Western world.[5-7] In 2005, there were 2758 Canadians waiting for a kidney transplant, and 66 Canadians died while on the waiting list.[8] Between 1996 and 2000, the mean waiting time for a donor kidney in Canada was 3–8 years for a patient under the age of 40 years.[7] A >2-year waiting time has been shown to be associated with inferior transplant outcomes.[9] The pervasive scarcity of available donor kidneys has led transplant practitioners in Canada and worldwide to maximize the use of organs procured from deceased donors by using kidneys with marginal characteristics, the so-called expanded criteria donor (ECD) kidneys.[5,10-12]

1. Characteristics of Expanded Criteria Donor (ECD) Kidneys

By definition, expanded criteria donors (ECDs) are inferior to 'ideal' or standard criteria donors (SCDs) and provide kidneys with inferior, but satisfactory, outcomes in terms of allograft survival. The clinical characteristics that differentiate SCD and ECD organs are derived from the donor's medical history and cause of death, as well as from the allograft's anatomical, morphological and functional profile.[2,11] For allocation purposes, the United Network for Organ Sharing (UNOS) defines an ECD kidney as a kidney from a deceased donor over the age of 60 years, or from a deceased donor aged 50–59 years with at least two of the following medical criteria: history of hypertension; cerebrovascular accident as a cause of death; or final pre-procurement serum creatinine level >132.6 μmol/L (table I).[13] These grafts have a 70% greater risk of graft failure than a kidney from a donor between the ages of 10 and 39 years whose cause of death was not a cerebrovascular accident and whose creatinine level was <132.6 μmol/L.[13] According to data from US transplant registries (Organ Procurement and Transplantation Network [OPTN] and Scientific Registry of Transplant Recipients [SRTR]), patient survival is 5% lower at 1 year and 8%–12% lower at 3–5 years for ECD kidney recipients compared with SCD kidney recipients, and graft survival is 8% lower at 1 year and 15%–20% lower at 3–5 years for ECD kidneys.[3] For wait-listed patients on dialysis, recipients of ECD kidneys and recipients of SCD kidneys, the adjusted annual death rate is 6.3%, 4.7% and 3.3%, respectively, and the estimated remaining life-years are 15, 20 and 29, respectively.[2]

Thus, in some patients, inferior graft outcome may represent an acceptable trade-off as ECD transplants offer improved overall patient survival by reducing waiting times.[4]

2. ECD Kidney Transplant Outcomes

A recent study compared patient outcomes between ECD recipients and a combined 'standard therapy' group of non-ECD recipients and those still receiving dialysis. Patient survival at 5 years was 76% for the ECD group compared with 75% for the

Table II. Patient outcomes in adult recipients of 101 expanded criteria donor (ECD) and 143 standard criteria donor (SCD) deceased donor kidney transplants at a single centre using a standardized approach[6]

Outcome	ECD (n = 101)	SCD (n = 143)	p-Value
Actual patient survival [no. (%)]	94 (93)	134 (93.7)	1.0
Actual graft survival [no. (%)]	84 (83)	118 (82.5)	1.0
Delayed graft function [no. (%)]	18 (18)	35 (24)	0.27
Follow-up (mo) [mean ± SD]	23.4 ± 14	25.1 ± 14	0.36
Time (days) to sCr <265.2 μmol/L (mean ± SD)	6.3 ± 7.9	7.0 ± 7.3	0.49
Acute rejection [no. (%)]	12 (12)	24 (17)	0.36
Major infection [no. (%)]	18 (18)	31 (22)	0.52
Operative complications [no. (%)]	20 (20)	34 (24)	0.53
Initial length of stay (days) [mean ± SD]	8.1 ± 6.7	7.8 ± 5.6	0.71
Readmissions [no. (%)]	50 (50)	79 (55)	0.43
Viral infections: total [no. (%)]	13 (13)	9 (6.3)	0.11
CMV [no. (%)]	8 (8)	6 (4)	0.27
PVN [no. (%)]	5 (5)	2 (1.4)	0.13
EBV-PTLD [no. (%)]	1 (1.0)	1 (0.7)	1.0

CMV = cytomegalovirus; **EBV-PTLD** = Epstein-Barr virus-post-transplant lymphoproliferative disease; **PVN** = polyomavirus-induced nephropathy; **sCr** = serum creatinine.

combined group.[4] Although excess death accumulated among ECD kidney recipients during the initial higher-risk period, survival in the ECD group equalled that of the combined group at 3.5 years post-transplantation. Long-term relative mortality risk beyond 3 years was 17% lower for recipients of ECD kidneys (relative risk [RR] 0.83; 95% CI 0.77, 0.90; $p < 0.001$). Furthermore, when wait times were >1350 days, the study showed that there was a 27% lower risk of death for ECD recipients than for those receiving standard therapy (RR 0.73; 95% CI 0.64, 0.83; $p < 0.001$). However, when waiting times were <1350 days, an ECD survival benefit was seen only for recipients with diabetes mellitus (RR 0.77; 95% CI 0.64, 0.94; $p = 0.01$). Thus, a thorough understanding of the advantages and disadvantages of ECD kidney transplantation is important in wait-listing practices.[4]

With appropriate donor and recipient profiling, ECD kidneys are associated with intermediate outcomes comparable to SCD kidneys (table II).[6] In this analysis, ECD kidney recipients were selected in part by matching estimated donor renal functional mass to recipient requirement, factoring in recipient age and body mass index and including the use of dual kidneys in some instances. The 2-year patient survival rate was 93%, with a graft survival rate of 83% for both ECD kidney recipients and unmatched SCD kidney recipients. However, despite similar rates of graft and patient survival, renal function was followed longitudinally and was consistently better in SCD kidney recipients (figure 1 and figure 2). The incorporation of the strategy of nephron mass matching into allocation algorithms may be difficult given the ethical tension intrinsic to kidney transplantation.

With an aging population, the proportion of deceased donors aged >50 years has increased from

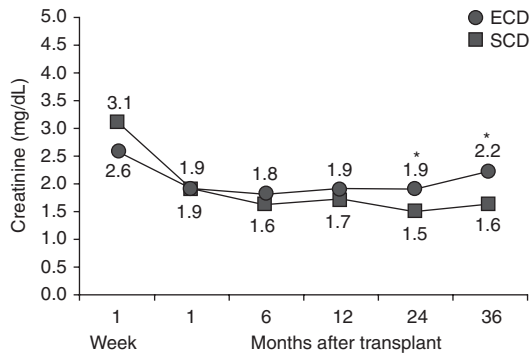

Fig. 1. Renal allograft function up to 36 months post-transplant, as measured by mean serum creatinine levels in expanded criteria donor (ECD) kidney (matched for nephron mass) vs standard criteria donor (SCD) kidney transplant recipients (reproduced from Stratta et al.,[6] with permission). * $p < 0.05$.

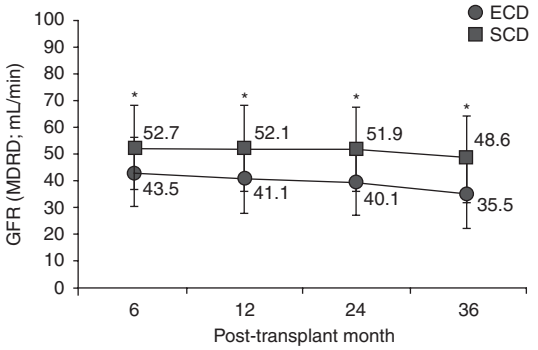

Fig. 2. Renal allograft function up to 36 months post-transplant, by mean calculated glomerular filtration rate (GFR) using the abbreviated modification of diet in renal disease (MDRD) formula, in expanded criteria donor (ECD) kidney (matched for nephron mass) vs standard criteria donor (SCD) kidney transplant recipients (reproduced from Stratta et al.,[6] with permission). * $p < 0.05$.

21% to 31% in the last decade.[6] In addition, cerebrovascular events (versus trauma) are now the leading cause of brain death culminating in deceased organ donation.[14] In the US, the use of ECD kidneys has grown by nearly 40% in the past 10 years, and 20% of deceased donor transplants are now ECD kidneys.[15] In Ontario, Canada, according to the Trillium Gift of Life Network, estimated ECD rates have risen from approximately 8% in 2001 to over 20% in 2005. With changing donor characteristics and the growing crisis in organ supply, it is no longer a question of whether to use ECD kidneys but rather how to optimize outcomes with their use.

3. Calcineurin Inhibitor-Related Renal Toxicity

Data on graft outcomes reflect an era dominated by the use of calcineurin inhibitors (CNIs), most notably ciclosporin (cyclosporine) and tacrolimus.[16] In an accompanying article in this supplement, Yilmaz and Sar[17] discuss the role of biopsy for determining the clinical course of CNI-related nephrotoxicity. Despite improvements in acute rejection and better 1-year survival rates with CNI treatment, there has been a lack of effect on long-term graft survival.[18] Histological studies have pointed to CNI-induced nephrotoxicity as one of the key risk factors for the development of chronic allograft nephropathy (CAN) and subsequent graft loss following kidney transplantation.[19] The histological lesions associated with CNI nephrotoxicity include *de novo* or progressive arteriolar hyalinosis, striped fibrosis and tubular microcalcification. The prevalence of CNI-associated lesions increases with time post-transplant. By 10 years, 100% of patients have arteriolar hyalinosis, 88% have striped fibrosis and 79% have tubular microcalcification.[20]

4. The London Health Sciences Centre Pilot Study in ECD Kidney Recipients

CNI-free protocols using sirolimus-based therapy have led to improvements in renal function, though such improvements are not sustained in all studies.[16,21-23] In addition to CNI-related renal toxicity, the increasing use of ECD kidneys as well as increasingly older recipients may also lead to increased long-term graft loss.[24,25] Both donor and recipient age have a detrimental effect on CAN and are the strongest risk factors for graft and patient loss, respectively.[24,26] Given that age and CNI toxicity are both risk factors for CAN and graft loss, and that older kidneys are more susceptible to CNI toxicity,[19] ECD kidneys may be more susceptible to CNI toxicity. Thus, interest has been growing in the use of CNI-free regimens in ECD kidney transplantation.

4.1 Methods

This study was a nonrandomized, open-label, pilot study in 13 recipients of ECD kidneys between February and October 2004, who were compared with contemporaneous controls.[27] A quadruple drug regimen consisting of antithymocyte globulin (ATG) or basiliximab, sirolimus, mycophenolate mofetil (MMF) and a corticosteroid (n = 13) was provided to recipients of ECD kidneys. The definition of ECD kidneys was based on previously reported analyses of donor risk factors[28,29] and predated the UNOS consensus definition. Specifically, recipients were included who received kidneys from deceased donors with any two of the following criteria: age >50 years; history of diabetes; history of hypertension; non-traumatic death; acute tubular necrosis; high inotrope requirement; and cold is-

Table III. Experimental and control group demographics (mean ± SD)

Parameter	Study (n = 13)	Control (n = 13)	p-Value
Recipient			
Age (y)	55.5 ± 3.0	52.4 ± 3.6	NS
Sex (male/female)	8/5	11/2	NS
BMI	25.6 ± 3.0	27.1 ± 1.7	NS
ESRD	PCKD (3), HTN (4), DM (1), GN (4), unknown (1)	PCKD (3), HTN (1), DM (3), GN (4), IgA (2), FSGS (1), ciclosporin (1)	NS
RRT	CAPD (4), IHHD (9)	CAPD (2), IHHD (11)	NS
ABO (A/B/AB/O)	3/2/1/7	3/0/1/9	NS
HLA MM (#)	5 ± 0.96	5 ± 1.1	NS
% PRA	0 ± 4.1	0 ± 29	NS
T-cell crossmatch (+/−)	0/13	0/13	NS
B-cell crossmatch (+/−)	0/13	3/10	NS
CIT (h:min)	14:42 ± 4:53	15:10 ± 4:35	NS
WIT (min:s)	53:55 ± 15:49	52:15 ± 10:00	NS
Donor			
Age (y)	55.5 ± 5.1	55.0 ± 2.5	NS
Cause of death (T/nT)	4/9	3/10	NS
HTN (yes/no)	3/10	4/9	NS
DM (yes/no)	3/10	4/9	NS
sCr at procurement (μmol/L)	104 ± 10.4	75.2 ± 9.1	<0.05
Pressor support (yes/no)	13/0	7/6	<0.05

ABO = ABO blood group; **BMI** = body mass index; **CAPD** = continuous ambulatory peritoneal dialysis; **CIT** = cold ischaemic time; **DM** = diabetes mellitus; **ESRD** = end-stage renal disease; **FSGS** = focal segmental glomerulosclerosis; **GN** = glomerulonephritis; **HLA** = human leukocyte antigen; **HTN** = hypertension; **IHHD** = in-hospital haemodialysis; **MM** = mismatch; **NS** = not significant; **PCKD** = polycystic kidney disease; **PRA** = panel reactive antibodies; **RRT** = renal replacement therapy; **sCr** = serum creatinine; **T/nT** = trauma/non-trauma; **WIT** = warm ischaemic time.

chaemic time >24 hours. To compare outcomes in this ECD recipient group, a retrospective CNI-control group was established by randomly selecting 13 kidney transplant recipients of donors matching the above expanded donor criteria who had received a CNI-based immunosuppressive treatment regimen between October 2002 and January 2004 at the London Health Sciences Centre. Donor and recipient characteristics were well matched in both study groups, with the exception of a higher inotrope requirement and higher serum creatinine at the time of procurement for donors in the CNI-free group (table III). The CNI-free group initially received basiliximab for induction (n = 2) but this drug was subsequently replaced by ATG (n = 11) following the randomized trial by Brennan et al.[30] demonstrating reduced acute rejection in high-risk recipients treated with thymoglobulin compared with those treated with basiliximab. The CNI-control group (ciclosporin [n = 2] or tacrolimus [n = 11]) had received basiliximab (n = 1) or ATG (n = 7) for induction. Renal allograft survival, function, rejection and complications were compared at 1, 2, 3, 4, 5, 6 and 12 months. The CNI-free group underwent protocol biopsy at 3 and 12 months. Implantation biopsies were not routinely performed in either group.

4.2 Results

Patient survival and allograft survival at 1 year were not significantly different between the CNI-free group and the CNI-control group (100% vs 92% and 92% vs 85%, respectively; p = NS). Delayed graft function, defined as the need for dialysis beyond the first postoperative day, was common, occurring in 38% of patients in both groups. The incidence of biopsy-proven acute cellular rejection was 4/13 (31%) in the control group and 3/13 (23%)

in the study group (p = NS). All rejection episodes responded to corticosteroid pulse therapy. One rejection in the study group was the result of noncompliance, and another was a subclinical rejection on protocol biopsy. Two CNI-free patients were converted from sirolimus to tacrolimus because of drug toxicity (one pleural effusion, one oesophagitis). Two CNI-free patients experienced wound complications, including one wound dehiscence, compared with none of the CNI-control group. Serum cholesterol levels were not significantly different between the study and control groups; however, four study participants were initiated on lipid-lowering treatment compared with two controls. No study participants developed post-transplant diabetes, whereas one control participant developed this complication.

At all timepoints before 1 year, serum creatinine was significantly lower and estimated GFR (eGFR by modification of diet in renal disease [MDRD] equation) was significantly higher for the CNI-free group. However, at 1 year these differences no longer reached statistical significance: eGFR was 52.3 ± 27.6 mL/min for the CNI-free group and 38.4 ± 17.8 mL/min for the CNI-control group (p = 0.11) [figure 3], and serum creatinine was 127 µmol/L for the CNI-free group and 146 µmol/L for the CNI-control group (p = 0.12) [figure 4]). Follow-up

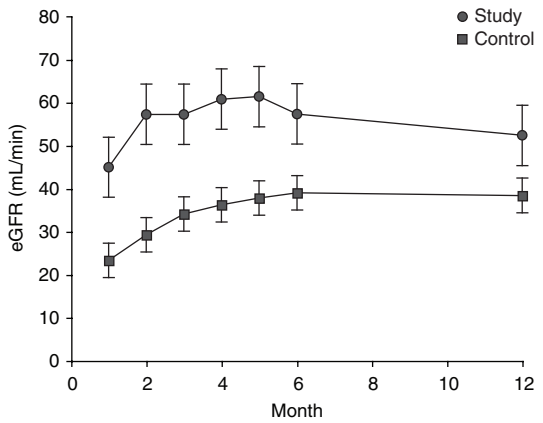

Fig. 3. Estimated glomerular filtration rate (eGFR) for calcineurin inhibitor (CNI)-free vs CNI-control recipients of expanded criteria donor kidney transplants. Significant differences between CNI-free and control group at all timepoints (p = 0.04) but not at month 12 (p = 0.11).

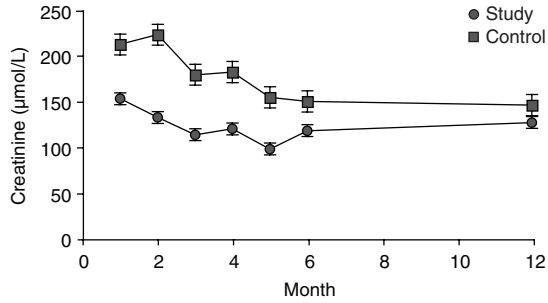

Fig. 4. Serum creatinine in calcineurin inhibitor (CNI)-free vs CNI-control recipients of expanded criteria donor kidney transplants. Significant differences at 1–6 months but not at 12 months (p = 0.12).

continues for both groups. Progression of chronic histological changes in the CNI-free group, as indicated by the Banff chronic/sclerosing allograft nephropathy score, is illustrated in figure 5. No significant progression of chronic vascular lesions was noted at 1 year; however, tubular atrophy and interstitial fibrosis did progress in some individuals, suggesting that these processes are independent of calcineurin inhibition, perhaps reflecting progression of donor disease and/or immunological and nonimmunological stresses such as rejection and ischaemia-reperfusion injury. The frequencies of Banff CAN scores in the CNI-free group were as follows: 42% grade I, 25% grades II and III, and 33% grade 0. Since there were no protocol biopsies

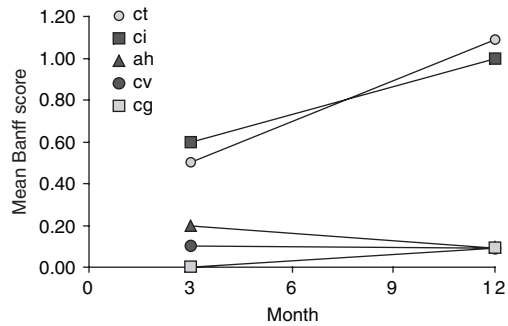

Fig. 5. Chronic histological changes assessed by protocol biopsy in recipients of expanded criteria donor kidneys receiving calcineurin inhibitor (CNI)-free immunosuppression. Progression of chronic changes, indicated by the Banff CAN score. No significant progression of chronic vascular lesions was noted at 1 year. **ah** = arteriolar hyalinosis; **cg** = chronic glomerulopathy; **ci** = interstitial fibrosis; **ct** = tubular atrophy; **cv** = fibrointimal thickening.

in the CNI-control group, comparisons may be made with 2-year biopsy data from a previous study of SCD kidney recipients treated with basiliximab, ciclosporin, MMF and steroids showing Banff CAN scores of 42% grade I, 38% grades II and III, and 21% grade 0.[21]

4.3 Discussion

Although this trial was not randomized, the contemporaneous controls were randomly chosen from a pool of ECD recipients treated with more conventional CNI-based immunosuppression. As a result, the control group was comparable to the study group with respect to important donor and recipient characteristics. Moreover, 1-year graft survival (85%) in our CNI-control ECD group was similar to that reported for ECD kidney recipients (81%).[15] Notably, the 92% 1-year graft survival in our CNI-free group of ECD recipients compares favourably with the 91% 1-year graft survival in recipients of SCD kidneys reported by SRTR.[15] Despite the encouraging results at 1–6 months, the difference in renal function at 1 year was no longer statistically significant, although the 14-mL/min difference in eGFR, if it is representative of clinical practice, may be clinically important. This value approaches the 15-mL/min improvement in GFR observed at 2 years in a meta-analysis of CNI-free therapy.[23] The lack of statistical significance observed in this study probably relates to a lack of statistical power in this small sample size or to a lack of durable benefit of this drug regimen. Planned analyses after 2 years of follow-up will examine the durability of the effect of CNI avoidance on renal function and graft survival.

5. Calcineurin Inhibitor-Free Regimens in ECD Kidney Recipients

Several studies have examined the effects of CNI-free immunosuppressive regimens with encouraging results, and some reports have included ECD kidneys in their populations.[22,31,32] However, few studies to date have evaluated this treatment regimen in an unmixed cohort of ECD-like kidney transplant recipients. A recent study by Furian et al. involving dual kidney transplantation evaluated a CNI-free protocol, consisting of ATG, MMF, sirolimus and corticosteroids, in 30 patients and compared results with a retrospective control group of 25 patients treated with a CNI-based regimen.[33] Patient survival and graft survival were 100% and 96% at 1 year in the CNI-free group compared with 100% and 87% in the CNI group (p = NS). Renal function was significantly better in the CNI-free group compared with the CNI group at 1, 3 and 6 months, but not at 1 year. In contrast, recent results from Cruzado et al.[34] suggest that CNI-free immunosuppression with the same regimen offered no advantage in 42 recipients of dual kidney transplants, compared with 36 CNI controls and, if anything, led to a numerically higher risk of uninephrectomy and a trend towards decreased graft survival with no improvement in kidney function.

Re et al.[35] have recently reported the effects of using a CNI-free protocol (ATG, sirolimus, MMF and corticosteroids) in 41 ECD recipients. They found a 2-year patient survival of 87%, a 2-year graft survival of 83% (or death censored graft survival of 95%), a 1-year acute rejection rate of 17%, and similar 1- and 2-year serum creatinine levels (132.6 ± 63.6 and 130.8 ± 22.9 μmol/L, respectively). The Banff score in 2-year protocol biopsies (of 53% of patients) revealed a diagnosis of grade I in 82% of biopsies and grade II in 8%. Another smaller 1-year study by Pisani et al.[36] evaluated a similar protocol in 18 ECD kidney recipients. The study showed that 17 of 18 patients had good recovery with a mean creatinine level of 159.1 ± 70.7 μmol/L after 1 month. However, switching to a CNI from sirolimus was required in five patients because of sirolimus-related adverse effects.

Reported studies, including our experience, have been inconsistent in their use of pulsatile perfusion. In a recent study by Matsuoka and colleagues[37] more than 4600 ECD kidney transplants reported to UNOS were analysed, including over 900 that utilized pulsatile perfusion during the retrieval process. Despite the perfused group having worse characteristics for graft demise, the 3-year graft survival was similar to nonperfused kidneys, and the delayed graft function rate was significantly lower. Unfortu-

nately, no powered randomized controlled trial has been published. Whether pulsatile perfusion could improve long-term function and outcome in combination with CNI-free regimens remains to be tested.

6. Conclusion

The data presented herein suggest that a maintenance immunosuppressive regimen with polyclonal antibody induction, sirolimus, MMF and a corticosteroid may provide excellent prophylaxis against rejection in recipients of ECD kidney transplants while avoiding the potential nephrotoxicity of CNIs. Enthusiasm for this approach needs to be tempered by the discouraging preliminary results of a number of studies using this regimen in combination with interleukin (IL)-2-receptor antibody induction, which prompted the following advisory to healthcare professionals issued in August 2006 by Health Canada and Wyeth (manufacturer of Rapamune [sirolimus]): "Based on information from recent clinical trials, the use of Rapamune, mycophenolate mofetil (MMF), and corticosteroids, in combination with IL-2 receptor antibody (IL2R Ab) induction, is not recommended in the de novo organ transplant setting."

We believe that a large, adequately powered, multicentre study utilizing ATG induction is warranted to confirm or refute the benefits and demonstrate the safety of this CNI-free regimen in ECD kidney recipients. Tailoring immune suppression to the needs of the recipient based on ECD characteristics is one potential strategy to try to maximize the benefits from this growing demographic and ultimately improve the quality of life and survival of patients who would otherwise remain on a growing waiting list.

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