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REVIEW

Renal transplantation with expanded criteria donors: Which is the optimal immunosuppression?

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Abstract

The growing gap between demand and supply for kidney transplants has led to renewed interest in the use of expanded criteria donor (ECD) kidneys in an effort to increase the donor pool. Although most studies of ECD kidney transplantation confirm lower allograft survival rates and, generally, worse outcomes than standard criteria donor kidneys, recipients of ECD kidneys generally have improved survival compared with wait-listed dialysis patients, thus encouraging the pursuit of this type of kidney transplantation. The relative benefits of transplantation using kidneys from ECDs are dependent on patient characteristics and the waiting time on dialysis. Because of the increased risk of poor graft function, calcineurin inhibitor (CNI)-induced nephrotoxicity, increased incidence of infections, cardiovascular risk, and malignancies, elderly recipients of an ECD kidney transplant are a special population that requires a tailored immunosuppressive regimen. Recipients of ECD kidneys often are excluded from transplant trials and, therefore, the optimal induction and maintenance immunosuppressive regimen for them is not known. Approaches are largely center specific and based upon expert opinion. Some data suggest that antithymocyte globulin might be the preferred induction agent for elderly recipients of ECD kidneys. Maintenance regimens that spare CNIs have been advocated, especially for older recipients of ECD kidneys. CNI-free regimens are not universally accepted due to occasionally high rejection rates. However, reduced CNI exposure and CNI-free regimens based on mammalian target of rapamycin inhibitors have shown acceptable outcomes in appropriately selected ECD transplant recipients.

Key words: Expanded-criteria donors; Outcomes; Kidney transplantation; Immunosuppression; Survival

Core tip: Kidney donor shortage is chronic, persistent and increasing in most countries worldwide. Therefore, there has been renewed interest in the use of expanded criteria donors (ECD) to increase donor pool. Compared to standard criteria donor kidneys, ECD kidneys are associated with up to a two-fold increased

risk of delayed graft function, acute rejection, and graft loss. The optimal induction and maintenance immunosuppressive regimen for ECD transplant recipients is not known due to shortage of randomized trials. Induction with antithymocyte globulin and maintenance with calcineurin inhibitors-sparing regimens have been advocated, especially for older recipients of ECD kidneys. This review provides insights into topics such as selection of appropriate candidates for kidney transplantation from ECDs, optimal management of ECD transplant recipients and discusses literature data on the immunosuppressive regimens that have been used in this patient population.

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INTRODUCTION

Kidney transplantation has been proven unquestionably the treatment of choice for most patients with end stage renal disease (ESRD) compared with other alternatives for renal replacement therapy. Survival, cardiovascular stability and quality of life have been found superior in allograft recipients compared with similar patients on the wait list[1]. This benefit has been observed among recipients older than 60 years of age as well[2].

There is a large gap between the number of patients waiting for a transplant and the number receiving a transplant. This gap has widened over the last two decades leading to renewed interest in the use of expanded criteria donor (ECD) kidneys in an effort to increase the donor pool. ECD kidneys are used to expand the number of deceased-donor kidney transplants, particularly for elderly recipients.

The Organ Procurement and Transplantation Network (OPTN) instituted a formalized definition of marginal kidneys in 2002 with the advent of ECD[3]. ECD kidneys are those either from a brain-dead donor $\geqslant$ 60 years of age, or a donor 50 to 59 years of age with at least two of the following features: History of hypertension, terminal serum creatinine > 1.5 mg/dL (133 mmol/L), or cerebrovascular cause of death[4]. These criteria for the definition of ECD were based on the presence of variables that increased the risk for graft failure by 70% (relative hazard ratio 1.70) compared with a standard criteria donor (SCD) kidney[5]. Kidney transplants coming from donation after cardiac death (DCD) are not included in this definition. SCD was defined as a donor who does not meet criteria for DCD or ECD[5].

United Network for Organ Sharing (UNOS) allocation policy has required that patients who enter the waiting list for transplantation consent for consideration of ECD kidneys. Patients who agree to be placed on the list waiting for an ECD kidney are also eligible to receive SCD kidneys. Based upon patient age, there may be a survival advantage or disadvantage to waiting longer for a living donor or SCD kidney compared with a shorter wait for an ECD kidney[6]. Several studies have shown that, for younger patients, it is generally worth waiting for a higher-quality kidney. For older patients, a prolonged wait for a SCD kidney is not in their interest[7,8]. In the absence of a living donor, accepting an ECD kidney rather than waiting for a SCD kidney has significantly improved survival in the older ESRD patient. Furthermore, ECD kidneys were associated with higher mortality and higher risk of transplant loss among recipients between 18 to 70 years of age, whereas no significantly increased mortality or increased risk of transplant loss were noted among recipients older than 70 years of age[7]. However, if older patients are fortunate to live in a geographical area where waiting times are relatively short, then it may be in their interest to wait somewhat longer for the higher-quality organ[9].

The Eurotransplant Senior Programme (ESP) began in January 1999 with the aim of achieving a more efficient use of kidneys from elderly donors and offering transplantation in elderly patients. It allocates kidneys within a narrow geographic area (Austria, Belgium, Germany, Luxembourg, The Netherlands and Slovenia) from donors aged $\geqslant$ 65 years to recipients $\geqslant$ 65 years regardless of human leukocyte antigen (HLA) system. This allocation scheme was based on the concept of donor to recipient age matching policy, an alternative to the usual HLA-driven allocation procedure[10]. To reduce ischemic damage, kidneys should be transplanted within the Eurotransplant region with the shortest possible cold ischemia time (CIT). Local or regional allocation minimized CIT compared to standard centralized Eurotransplant allocation system. Furthermore, to reduce immunological risk, only non-immunized [*i.e.,* panel-reactive antibody (PRA) < 5%] first transplant recipients were included. The ESP allocation scheme furthermore included the option of transplanting both kidneys to a single recipient in cases in which the donor creatinine clearance was < 70 mL/min. Since initiation of the ESP, availability of elderly donors doubled and waiting time for ESP patients decreased. Local allocation led to shorter CIT and less delayed graft function (DGF) but 5%-10% higher rejection rates were reported. A 5-year analysis of ESP revealed that graft and patient survival were not negatively affected by the ESP allocation when compared with the standard allocation[11].

ECD KIDNEY TRANSPLANTATION OUTCOMES

Inherent to the definition of an ECD kidney is a 70%

Table 1 Expanded criteria donor kidney transplantation: Epidemiological data

Pro	Contra
Annual mortality rate in dialysis patients exceeds 20%[2]	70% increased risk for graft failure *vs* SCD kidneys[12]
Rapidly growing transplant waiting lists and, subsequently, increasingly longer waiting times[1-3]	17% primary graft non-function *vs* SCD kidneys[12]
Survival advantage of ECD kidney transplant recipients over dialysis patients remaining on transplant waiting list[2,4,6,15]	38% of ECD kidneys were discarded *vs* 9% for all other kidneys[12]
	Increased treatment cost and resource use[3,4]
	Mortality in perioperative period greater in ECD kidney recipients[4,13]
	Higher DGF rates, more acute rejection episodes and decreased long-term graft function in ECD *vs* SCD kidneys[12-14]

ECD: Expanded criteria donor; SCD: Standard criteria donor; DGF: Delayed graft function.

increased risk for graft failure compared with a SCD kidney in both older and younger recipients, but to a greater extend in recipients older than 50 years[3,4,12]. Of note, 75% of ECD recipients are more than 55 years old[3,4]. Nonetheless, diminished allograft survival does not suggest lack of therapeutic benefits. Although most studies of ECD kidney transplantation confirm lower allograft survival rates, recipients of ECD kidneys generally have improved survival compared with matched dialysis-treated patients[4,6]. In addition to poorer allograft outcome, grafts from ECD kidneys are associated with increased treatment cost and resource use, primarily resulting from longer length of hospital stay, increased requirement for dialysis after transplantation and a greater number of readmissions[3,4].

Many large retrospective database analysis compared outcomes of ECD with SCD kidney transplants. Overall, mortality in the perioperative period was greater in ECD kidney recipients[4,13]. Kidneys transplanted from ECDs have higher DGF rates, more acute rejection episodes and decreased long-term graft function. Several factors, including prolonged CIT, increased immunogenicity, impaired ability to repair tissue and impaired function with decreased nephron mass may explain these findings[14]. Furthermore, among organs procured from ECDs, 38% were discarded *vs* 9% for all other kidneys[12]. An ECD kidney transplant recipient has a projected average added-life-years of 5.1 years compared with 10 years for a kidney recipient from a SCD[6]. Despite these inferior results, these transplants have definitely survival advantage over dialysis patients remaining on transplant waiting list[4,15]. Therefore, according to a longitudinal study of mortality in a large cohort of ESRD patients, the long-term mortality rate was 48% to 82% lower among transplant recipients (annual death rate, 3.8 per 100 patient-years) than patients on the waiting list, with relatively larger benefits among patients who were 20 to 39 years old, white patients, and younger patients with diabetes[2]. The average increase in life expectancy for recipients of "marginal" kidneys (defined as kidneys procured from old donors with comorbidities such as hypertension or diabetes or with prolonged CIT) compared with the waiting list dialysis cohort that did not undergo transplantation was 5 years[15]. The main pros and cons for ECD kidney transplantation according to epidemiological data are summarized in Table 1.

Long-term relative mortality risk was 17% lower for ECD recipients (RR = 0.83; 95%CI: 0.77-0.90; $P < 0.001$) according to a large retrospective cohort study using data from a US national registry of mortality and graft outcomes among kidney transplant candidates and recipients and comparing mortality after ECD kidney transplantation *vs* that in a combined standard-therapy group of non-ECD and those still receiving dialysis[4]. The survival benefit was apparent only at 3.5 years after transplantation due to high early mortality rate in ECD recipients. Subgroups with significant ECD survival benefit included patients older than 40 years, patients of low immunological risk, those with diabetes or hypertension, as well as recipients in organ procurement organizations with long median waiting times (> 3.7 years)[4]. In areas with shorter waiting times, only recipients with diabetes demonstrated an ECD survival benefit[4]. Another study using data from the United States Scientific Registry of Transplant Recipients (SRTR) showed that in wait-listed patients > 70 years of age the risk of death was significantly lower with deceased-donor transplantation *vs* remaining on the waitlist and this benefit extended to those who received an ECD kidney[16]. Schold and Meier-Kriesche[7] found that patients 65 years and older had a slightly longer life expectancy if they accepted an ECD kidney within 2 years of starting dialysis therapy (5.6 years) rather than waiting 4 years to receive either a SCD (5.3 years) or a living donor (5.5 years) kidney. A systematic review of kidney transplantation showed that patients younger than 40 years of age or scheduled for kidney retransplantation should not be listed for an ECD kidney due to poor outcomes[6]. Primary transplant recipients 40 years or older might be listed for an ECD kidney transplant if they have diabetes or are listing in a program with more than 4 years of median waiting time for a SCD kidney[6]. In conclusion, the relative benefits of transplantation using kidneys from ECDs are dependent on patient characteristics and the waiting time on dialysis. Therefore, wait-listed dialysis patients who are older and diabetic and/or hypertensive have poorer survival rates, but typically achieve the greatest relative gains in overall survival and quality of life after transplantation compared with those remaining on dialysis[4,6,15]. The most well established indications for ECD kidney transplantation or, in other words,

Table 2 Subgroups with significant survival benefit after expanded criteria donor kidney transplantation according to epidemiological data[4,6,7,16]

Patients older than 40 yr
Long median waiting time (> 4 yr)
Patients with diabetes or hypertension
Patients of low immunological risk
Dialysis patients with vascular access problems
Dialysis patients whose life expectancy in dialysis is lower than the estimated waiting time for kidney transplantation

subgroups with significant survival benefit after ECD kidney transplantation, according to epidemiological data, are shown in Table 2.

A few single-center observational studies suggested that the patient and graft survival achieved by using ECD kidneys was similar to that obtained with SCDs[6]. However, it is noteworthy that no United States Registry report or European multicenter analysis that included large numbers of patients supported this conclusion. The vast majority of single-center studies and all available multicenter or registry reports showed significantly worse 1- to 15-year patient and graft survival rates after kidney transplantation using ECD kidneys compared with SCD kidneys[6].

Our group demonstrated equivalent graft survival rates in a mean follow-up time of 36.4 mo between recipients from ECD and SCD or living donors > 60 years in the period 2005-2011[17]. Estimated GFR at first year was found statistically different between the ECD and SCD groups (eGFR: 49.9 mL/min per 1.73 m^2 *vs* 64.6 mL/min per 1.73 m^2, $P < 0.001$), but still satisfactory at first year, and at end of follow-up period. Furthermore, comparison of the patients, who received transplants from ECD, even older than 70 years, with those from living donors > 60 years revealed equivalent renal function in short and long term. In conclusion, several studies suggest that in the absence of a living donor, older patients with ESRD should consider accepting an ECD kidney, especially if they have diabetes or face a long wait for a non-ECD kidney[4,7,16,17].

Although graft function, allograft survival, and perhaps, patient survival may be adversely affected by the older donor, the results are still acceptable, including patient and graft outcomes[18]. Furthermore, graft survival from older donors may be mostly related to recipient age. Whereas there is an increase in graft loss and an increased incidence of acute rejection among young recipients who receive kidneys from older donors, the age of the donor has little impact on graft function among older recipients. Therefore, graft survival steadily improves with increasing recipient age, the frequency of acute rejection decreases with every decade of increasing recipient age, and, most importantly, the graft and patient survival are superior when older, deceased donors are transplanted into older recipients[19]. In an analysis of the SRTR database, among recipients > 70 years of age, transplantation of an ECD kidney was not associated with significantly increased mortality, compared with a non-ECD kidney[8]. On the contrary, transplantation of an ECD kidney was associated with increased mortality for recipients < 70 years[8]. However, a single-center, retrospective review of all deceased-donor kidney transplantation demonstrated increased morbidity and mortality in elderly recipients of ECD kidneys[9]. Patients ⩾ 60 years that received ECD kidneys had significantly worse patient survival and graft survival, higher rates of acute rejection, and more complications in the perioperative period than similarly aged recipients receiving SCD kidneys. Further, upon comparing younger (age 40-59 years) ECD recipients with those ⩾ 60 years of age, patient and graft survival rates and perioperative complications were significantly higher in the older age group[9].

THE IMMUNOLOGICAL RISK OF ECD KIDNEY TRANSPLANT RECIPIENTS

Kidneys from older donors are generally more immunogenic than kidneys from young donors. Experimental studies have shown an intense inflammatory response and increased T-cell immune reactivity in recipients of deceased or older donor kidney allografts[20-22]. Subsequently, increased incidence of acute interstitial rejection episodes has been observed among ECD kidney transplant recipients in the early post-transplantation period. The ESP demonstrated acute rejection rate on the order of 30%[11]. It is well established that acute rejection episodes result in functional deterioration. Contrary to interstitial rejection in kidneys from younger donors, kidneys from older donors seem to have an impaired ability to restore tissue[14]. A study by Diet *et al*[23] questioned the increased immunogenicity of ECD transplants. In contrast with previous studies, the incidence of biopsy-proven acute rejection was not higher in recipients of transplants from ECD or donors aged ⩾ 50 years than in recipients of transplants from optimal donors or donors aged < 50 years after adjustment for the immunological risk. These findings underline the fact that the risk of rejection depends on the immunological risk, recipient's age and immunosuppressive regimen rather than the donor status[23].

At the same time, ECD kidney transplant recipients are mostly of advanced age. It is well established that the immune response is significantly affected by the ageing process. Although there is heterogeneity among individual patients, in general terms, both innate and adaptive immunity decrease with increased age, resulting in a decreased likelihood of immunologic rejection and increased risk of infection[24]. For patients 18 years of age, the rejection rate was 28% compared to only 14% for those aged 70 years[25]. This finding

Table 3 Expanded criteria donor kidney transplantation: Maximizing benefit

Modifying allocation rules for ECD kidneys in an effort to match the appropriate kidney to the appropriate recipient
Minimizing risk factors for DGF: Lowering CIT, pulsatile perfusion preservation
Preimplantation renal biopsy for ECD kidney recipients
Simultaneous dual ECD kidney transplantation
Restricting the use of ECD kidneys to patients of low immunological risk
Applying individualized immunosuppressive regimens

ECD: Expanded criteria donor; DGF: Delayed graft function; CIT: Cold ischemia time.

is consistent with the previous experimental data showing that ageing is associated with a reduced cellular immunity and $CD4^+$ T-cell response and a reduced ability to reject the skin allograft[26]. However, immune senescence is likely to be affected by the accumulation of memory T cells observed in aged recipients who often have an alloimmune response to transplantation[27]. This paradox may be explained by recent data showing that aged mice are able to reject a skin allograft at a similar rate to that observed for young transplant recipients, independently of donor age, but display an interleukin (IL)-17-mediated response mediated by memory $CD4^+$ cells rather than a classical interferon (IFN)-response[28]. Thus, ageing seems to cause more qualitative rather than quantitative changes in the alloimmune response.

Independent of the real rejection rates in the elderly transplant recipients the risk of transplant loss from rejection is increased in older recipients compared with younger patients. Importantly, these differences in rejection and infection were independent of baseline immunosuppression. It is possible that elderly patients received less overall immunosuppression than younger recipients because of their decreased rate of rejection, yet the older patients still had an increased risk of infectious death, which emphasizes the vulnerability of the older transplant candidate[29]. Despite the potential decrease in acute rejection rate, there is an increased risk of chronic allograft nephropathy among older recipients, which is enhanced if the allograft is from an older donor, as it is the case in ECD kidney transplant recipients[30].

OPTIMAL IMMUNOSUPPRESSION IN ECD KIDNEY TRANSPLANT RECIPIENTS

General principles

The goal of any immunosuppression protocol should be to achieve an adequate immunosuppression level that offers a minimal risk of infection without increasing the risk of rejection. This is particularly important among older patients because patient death is the most common cause of graft loss and infection is a leading cause of death. As already mentioned, the majority of ECD transplant recipients are of advanced age. Although the relative incidence of acute rejection among older adults is unclear, increased immunosuppression to suppress rejection may increase vulnerability to infection[31]. In addition, the pharmacokinetics and effects of drugs are altered in older adults[29]. Therefore, initial calcineurin inhibitor (CNI) doses should be reduced because, at any given dose, higher than normal blood levels result from a decline in cytochrome P450 activity. Moreover, rapid corticosteroid tapering is recommended since corticosteroids have many untoward effects in older adults. On the other hand, ECD transplants are complicated by increased rates of DGF and acute rejection, especially in the early post-transplantation period, and adequate level of immunosuppression is desired under these circumstances. Therefore, optimal management is a challenge in ECD kidney transplant recipients.

In any case, older patients and recipients of ECD kidneys often are excluded from transplant trials and, therefore, the optimal induction and maintenance regimen for them is not known. Approaches are largely center specific and based upon expert opinion.

Management for an ECD kidney is based on potential nephron-protecting strategies, including CIT minimization, pulsatile perfusion preservation, immunosuppression focused on nephrotoxicity minimization, and adequate infection prophylaxis[29,30]. Routine donor preimplantation renal biopsy may be useful to evaluate the integrity of renal anatomy in ECD kidneys and select the viable grafts. Furthermore, the successful use of ECD kidneys can be enhanced by restricting the use of these kidneys to unsensitized patients receiving a first graft, and minimizing, if feasible, other risk factors for acute tubular necrosis, such as hemodynamic stability and total ischemic time[32]. In addition, limited evidence also suggests that transplanting two ECD kidneys, rather than one, in one recipient might help improve outcomes[33]. Lastly, we should always underline the importance of appropriately matching organs with recipients, particularly for ECD organs. Modifying allocation rules for ECD kidneys should be considered in an effort to match the appropriate kidney to the appropriate recipient[5-7]. In general, the life expectancy of the recipient should approach the expected survival of the allograft. The main strategies to maximize benefit in ECD kidney transplantation are summarized in Table 3.

Although CNIs are excellent drugs, nephrotoxicity is a major concern, especially in older recipients of ECD kidneys. These kidneys may be more vulnerable to the adverse effects of immunosuppressive medications such as CNIs. Therefore, various strategies of CNI withdrawal, minimization as well as avoidance or CNI addition after induction have been utilized by a number of investigators. Of note, in kidneys with

Table 4 Modifying and individualizing the immunosuppressive regimen in expanded criteria donor kidney transplantation: Main strategies

Induction with ATG
Reduce overall immunosuppression burden, especially in elderly recipients of ECD kidney transplants
Reduced CNI exposure regimens (target CNI blood levels 25%-50% lower)
Delayed CNI introduction regimens
CNI-free regimens based on MMF and steroids with ATG induction
CNI-free Belatacept-based regimens
Reduced CNI exposure and CNI-free mTOR-inhibitors-based regimens

ATG: Antithymocyte globulin; ECD: Expanded criteria donor; CNI: Calcineurin inhibitor; mTOR: Mammalian target of rapamycin; MMF: Mycophenolate mofetil.

assumed reduced nephron mass such as ECD kidneys, the immunological risk should be kept as low as possible by accurate pretransplant risk assessment and risk-adjusted immunosuppression during the post-transplant period to avoid further damage[6].

Although the optimal immunosuppressive regimen for ECD kidney transplant recipient has not been determined as yet, several maneuvers and modifications have been proposed in an effort to improve outcomes in this high-risk patient population. These are briefly presented in Table 4 and further discussed later in this review.

Induction immunosuppression

There are limited data concerning the benefits and adverse effects associated with different induction regimens in ECD kidney transplant recipients. A retrospective analysis of United Network of Organ Sharing (UNOS) data from 2003 to 2008 among high-risk older (> 60 years) recipients who received high-risk kidneys showed that, in the entire cohort, older recipients who received rabbit antithymocyte globulin (rATG) had the lowest cumulative rate of acute rejection within the first year after transplantation compared with those who received interleukin-2 (IL-2) receptor antagonists or alemtuzumab[34]. Despite the high rejection rates, IL-2 receptor antagonists were associated with transplant loss in only high-risk recipients who received high-risk donor organs. These data suggest that ATG might be the preferred induction agent for high-risk elderly recipients of a high-risk donor organ, such as an ECD kidney. No significant difference in death-censored graft survival was noted on multivariate analysis in patients who received anti-IL-2 receptor antibody or rATG. However, there was an increased risk of death among recipients of anti-IL-2 receptor antibody compared with rATG. Patients induced with alemtuzumab had an increased risk of death-censored graft loss and death compared with rATG. In the abovementioned study, a high-risk recipient was defined as one having a peak panel reactive antibody > 20% or a prior kidney transplantation or of black race. High-risk donor kidneys included ECD kidneys, kidneys following cardiac death or kidneys having a CIT > 24 h[34].

It is in the current practice of our group to use in ECD transplant recipients induction with rATG to ameliorate preservation injury and moreover minimize the state of DGF due to acute tubular necrosis[17].

Maintenance immunosuppression

The optimal combination of medications for maintenance immunosuppression among ECD kidney transplant recipients is unknown. Regimens that spare CNIs have been advocated, especially for older recipients of ECD kidneys[29]. However, such regimens, as well as those associated with the withdrawal of CNIs, have been associated with an increased incidence of acute rejection[35]. Guidelines suggest that tacrolimus and mycophenolate should be used as first-line maintenance immunosuppressive agents following transplantation, but there are no separate recommendations for older recipients[36]. In the abovementioned retrospective analysis of UNOS data from 2003 to 2008, tacrolimus use was associated with a decreased risk of rejection for high-risk elderly patients who had a high-risk donor, but there was no decrease in risk of rejection with low-risk donor-recipient combinations[34]. Although there was no association between tacrolimus use and death-censored transplant loss, tacrolimus was associated with a decreased risk of death (RR range, 0.77-0.85 depending on risk group). Interestingly, mycophenolic acid use was associated with a significant decrease in transplant failure and death in both high- and low-risk patient groups. For example, in a recipient with low immunologic risk who received a high-risk donor transplant, such as from an ECD, mycophenolic acid use was associated with a 28% decrease in transplant failure (RR = 0.72; 95%CI: 0.59-0.89) and a 16% lower likelihood of death (RR = 0.84; 95%CI: 0.72-0.98)[30]. Steroid use had no significant effect on either patient or transplant survival. Although there are no randomized comparisons, the recent data from Gill *et al*[34] suggest that tacrolimus and mycophenolic acid might be the preferred immunosuppressive agents in patients older than 60 years with respect to patient and transplant survival.

Several suggestions have been made on the optimal combination of immunosuppressants to preserve renal function following kidney transplantation from ECD kidneys. However, randomized trials, necessary to better define the optimal induction and maintenance regimen for ECD kidney transplant recipients, are largely lacking.

Reduced steroid exposure regimens

The goal of immunosuppression in elderly should consist of a reduction of the risk of CNI nephrotoxicity along with a limited use of steroids because of the increased risk of infections, fractures, myopathy, and other steroid-related side effects. Aull *et al*[37] showed that an early corticosteroid withdrawal regimen of

rATG induction, tacrolimus, and mycophenolate mofetil is associated with excellent patient and kidney graft survival in a population consisted of 55% deceased donor kidney transplants, 46% of whom were ECD. However, the success of steroid-sparing strategies has not been proved in ECD kidney transplantation to date because all trials available were mainly developed with SCD kidney transplantation[6]. Segoloni *et al*[38] described a series of 88 patients receiving kidneys from marginal donors whose immunosuppressive protocol consisted of monoclonal anti-IL-2 receptor antibodies, mycophenolate mofetil (MMF), and steroids. When serum creatinine levels were less than 2.6 mg/mL, tacrolimus was started and MMF was subsequently withdrawn when the tacrolimus through level increased above 15 ng/mL. Steroid was tapered to 5 mg at day 45 and then progressively reduced. The acute rejection rate was 13.6%. At 3 years and 4 years after transplant, 80% and 100% of patients, respectively, were off steroids with a 4-year patient and graft survival of 98% and 79%, respectively. Incidence of infections and malignancy were also acceptable.

Reduced CNI exposure and CNI-free regimens

Recipients of ECD kidneys are at increased risk for graft dysfunction/loss, and may benefit from immunosuppression that avoids CNI nephrotoxicity. CNI-induced vasoconstriction and subsequent hypoxia could be more detrimental in elderly organs. On a molecular level calcineurin inhibitors accelerate pathways already activated during physiological ageing[29-31].

CNIs are the mainstay of immunosuppression in renal transplantation. Their use has decreased acute rejection rates and improved short-term patient and graft survivals. However, they are associated with chronic graft dysfunction as well as increased risks of cardiovascular disorders and of malignancies[36]. ECD kidneys may be particularly susceptible to CNI-mediated vasoconstriction that may prolong ischemic injury in the early post-transplant phase. In the long term, chronic CNI nephrotoxicity is a major concern[23,25]. Furthermore, CNIs may be associated with worse short- and long-term graft function, particularly in ECD kidneys, with frequent preimplantation structural damage.

Reduced CNI exposure regimens have been examined in a number of clinical studies with the aim of minimizing nephrotoxicity. Two possible strategies have been proposed for CNI toxicity minimization: To delay CNI introduction until a certain level of renal graft function is achieved, and more radical, complete CNI-free strategies[6]. Another maneuver in the context of reduced CNI exposure regimens could be to target towards lower CNI levels in ECD as compared with SCD kidney transplant recipients. This strategy has not been evaluated so far and, therefore, no recommendation can be made. However, it is in the practice of our group to target about 25%-50% lower CNI levels long term in this patient population with satisfactory preliminary results regarding patient and graft survival as well as renal function in short- and long-term[17].

Delayed CNI introduction has been analyzed in several nonrandomized studies, including induction therapy with anti-IL 2 receptor antibodies or ATG[38-43]. Reported acute rejection rates were low at 6% to 23%, DGF rates were 31% to 54%, and patient and graft survival were within the reported ranges for SCD kidney transplantation. In a long-term study including 101 ECD kidney recipients, Stratta *et al*[44] used ATG or alemtuzumab with MMF and steroids, and, only when serum creatinine level was less than 4 mg/dL, a moderate tacrolimus dose was introduced. With 4-year patient and graft actuarial survival rates of 93% and 74%, this trial constitutes potentially the best long-term experience to date on delayed CNI introduction.

Regarding CNI-free initial immunosuppression, several European studies analyzed experiences based on MMF and steroids with ATG induction, showing acute rejection rates of 24% to 26%, a DGF rate of 30%, and 5-year actuarial graft survival rates of 65% to 70%[45-48]. For example, Arbogast *et al*[45] investigated a therapeutic regimen consisting of a CNI-free, MMF-based immunosuppressive induction/maintenance protocol in conjunction with a short course (4-10 d) of rATG in 89 patients of mean age 63.8 years who received an organ from an elderly cadaver donor (mean age 66.8 years). Cumulative 5-year patient and graft survival was excellent with 88% and 70%, respectively, but only a historical control group under CNI therapy was available for comparison. The same group subsequently investigated a regimen of strictly monitored MMF [target mycophenolic acid (MPA) trough levels between 2-6 mg/mL] and steroids combined with a polyclonal-monoclonal induction regimen consisting of a low dose, single shot of rATG and the IL-2-receptor-antibody basiliximab[46]. Thirty elderly recipients (67.8 ± 3.8 years) of renal transplants from deceased donors (69.4 ± 13.3 years) were recruited consecutively for this 5-year prospective, open, single center, pilot trial. One-year patient and renal allograft survivals were 87% and 83%, respectively; death-censored 1-year graft survival was 97%. Mostly steroid-sensitive rejection episodes were observed in 46% of patients, with only 3 patients requiring antibody therapy[46]. However, CNI-free regimens have been occasionally complicated by unacceptably high acute rejection rates. Therefore, in a study of basiliximab induction and MMF and steroid maintenance therapy, a large subgroup of patients experienced acute rejection rate of 45% and was subsequently converted to CNI therapy[49].

Belatacept, a selective costimulation blocker, may preserve renal function and improve long-term

outcomes *vs* CNIs. BENEFIT-EXT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXTended criteria donors) is a 3-year, Phase Ⅲ study that assessed a more (MI) or less intensive (LI) regimen of belatacept *vs* cyclosporine in adult ECD kidney transplant recipients[50]. The co-primary endpoints at 12 mo were composite patient/graft survival and a composite renal impairment endpoint. Patient/graft survival with belatacept was similar to cyclosporine (86% MI, 89% LI, 85% cyclosporine) at 12 mo. Fewer belatacept patients reached the composite renal impairment endpoint *vs* cyclosporine. The mean measured glomerular filtration rate was 4-7 mL/min higher on belatacept *vs* cyclosporine, and the overall cardiovascular/metabolic profile was better on belatacept *vs* cyclosporine. The incidence of acute rejection was similar across groups. Overall rates of infection and malignancy were similar between groups; however, more cases of posttransplant lymphoproliferative disorder (PTLD) occurred in the central nervous system on belatacept[50]. More recently the 3-year results of this trial have become available and the abovementioned promising findings of this CNI-free regimen have been confirmed[51].

Reduced CNI exposure, mTOR-inhibitors-based regimens

Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) appear to permit a CNI-sparing regimen among stable kidney recipients. However, the promising initial results in SCD kidney transplantation using CNI-free sirolimus and MMF-based immunosuppression after basiliximab induction have not been confirmed in larger scale randomized controlled trials, which showed increased acute rejection rates and complications, worse graft function but equivalent graft survival[52].

Some small nonrandomized studies assessed the potential of combined sirolimus and MMF in patients after ECD kidney transplantation[53-61]. Therefore, CNI-free sirolimus-based therapy compared with MMF-based treatment in kidney transplantation with advanced-age donors was associated with an acceptable outcome, but increased proteinuria in sirolimus-treated patients was noted in the intention-to-treat analysis[58]. CNI-free immunosuppression regimen, consisting of ATG induction, sirolimus, MMF and steroids, have been applied in recipients of dual kidney transplantation from elderly donors[54]. Excellent results have been demonstrated with a lower DGF rate and a better renal function as compared with earlier dual kidney transplant recipients treated with CNI-based regimen. However, in another study, the investigators were not able to find an advantage in acute rejection and graft function with their CNI-free approach for dual kidney transplantation using ECDs compared with the results of a conventional cyclosporine A and MMF strategy[59]. A study analyzed the results obtained with the use of a CNI-free immunosuppressive protocol (ATG induction, plus sirolimus, MMF, and low doses of steroids) in terms of graft and patient survival as well as posttransplant clinical complications over 2 years in recipients of ECD kidneys[55]. Under this immunosuppressive protocol, 78.04% of the patients completed the follow-up. A protocol biopsy was performed in 17 patients (53.1%) within 2 years posttransplant of which 82.31% were diagnosed as chronic allograph nephropathy grade I. The incidence of clinical complications was low and not significantly different from that reported with other immunosuppressive schemes. Death-censored graft survival was 95.12%. Another study introduced the idea of a CNI-free regimen in 13 recipients of ECD kidneys treated with induction therapy and maintained on sirolimus, MMF and prednisone and demonstrated excellent 2-year patient and graft survival and good renal allograft function although longer follow-up in larger randomized controlled trials are necessary to establish these findings[60]. Similarly, low-dose sirolimus-based triple immunosuppression with ATG induction offered 100% patent and graft survival in 27 ECD kidney transplant recipients with the achievement of stable renal function over a mean follow-up of 20.2 mo[61]. However, mild progression of histological damage and increased risk of bacterial infection detected in this study are a major concern.

In a large report on the potential for CNI-free immunosuppression, the United States registry has shown that the adjusted hazard ratio for overall graft loss for patients on sirolimus and MMF therapy at discharge doubles that observed with tacrolimus and MMF[62]. Only 33% of the kidney transplantation procedures included in this report used kidneys from donors older than 50 years, and no specific analyses are available for ECDs. One may conclude that the potential for CNI-free sirolimus and MMF-based therapy in ECD kidney transplant recipients has not been adequately established to date. Consequently, extrapolation of the best results obtained with anti-IL-2 receptors, MMF, steroids, and moderate exposure to tacrolimus might constitute an advisable strategy[52].

It is well established that first attempts to minimize CNI nephrotoxicity by reducing the dose or withdrawing CNI from the immunosuppressive regimen have been limited by high acute rejection rates[63]. More recently, an early abrupt conversion from cyclosporine to everolimus has shown a significant increase in renal function with an acceptable acute rejection rate at 6 mo after transplantation[64]. Furthermore, a clinical trial in patients with no immunological risk, who received conventional immunosuppression for 6 mo, showed that patients converted from cyclosporine to everolimus displayed lower acute rejection rates and improved renal function *vs* those who remained on treatment with MMF or cyclosporine[65]. In a retrospective registry-based study from Portugal,

everolimus appears to be an effective, safe alternative to CNI for maintenance therapy in selected kidney transplant recipients[66]. The potentially protective role of everolimus on renal allograft dysfunction offers an attractive option in recipients of ECD kidneys.

Trials of everolimus combined with reduced-exposure CNI have yielded good renal function whilst maintaining efficacy. The combination of everolimus with reduced-exposure CNI may offer advantages both for young as well as for older transplant recipients who receive an ECD graft. Everolimus, by allowing reduction in CNI exposure, has the potential to improve outcomes and minimize CNI-associated toxicities. Given the vulnerability of older patients (and older grafts) to CNI-induced nephrotoxicity, minimization of CNI dose is highly desirable in "old-for-old" patients[67]. There is good rationale for using reduced-exposure CNI regimen from the outset in ECD transplant recipients and, in case of low immunological risk, CNI withdrawal is a feasible option. CNI-free regimens are particularly desirable in recipients with advanced baseline histopathological lesions and/or GFR < 50 mL/min[67].

We have always to take into account when interpreting study results that initial studies are generally characterized by suboptimal use of everolimus and sirolimus (high trough levels, high loading dose). On the contrary, today CNI-free schemes appear to perform much better than those applied 10 years ago.

As already mentioned, it is in the practice of our group to target about 25%-50% lower CNI levels long term in an attempt to diminish the nephrotoxicity effect in ECD transplant recipients. Furthermore, it is in our practice as well, when considered safe, to switch to a CNI-sparing regimen using an mTOR inhibitor[17].

CONCLUDING REMARKS

The data presented so far regarding reduced CNI exposure or even CNI-free regimens may justify the use of such immunosuppressive regimens, at least in ECD transplant recipients of low immunological risk. However, a recent study from Switzerland showed that in ECD kidneys recipients of low immunological risk, defined as the absence of pretransplant donor-specific HLA antibodies, 1-, 3- and 5-year graft survival was significantly better when recipients were treated with Tacrolimus than when they were treated without Tacrolimus and comparable to SCD kidneys during the first six years. Furthermore, ECD kidneys recipients treated with Tacrolimus had a higher median estimated creatinine clearance than those treated without Tacrolimus. Graft function from one to three years was better preserved in ECD recipients treated with Tacrolimus compared with those treated without Tacrolimus. According to this study, in recipients with low immunological risk Tacrolimus-based immunosuppression seems to improve graft survival and to preserve graft function in kidney transplants with reduced baseline nephron mass, such as ECD kidneys, which are highly vulnerable to additional hits[68].

It is unclear whether the choice of maintenance immunosuppression modulates the negative effect of advanced donor age on outcome after renal transplantation. A study from Austria evaluated patient and graft survival based on donor age and immunosuppressive therapy in 1829 patients who received their first transplant between 1990 and 2003[69]. This study concluded that in median follow-up time of 7 years, use of CNIs 90 d after kidney transplantation is associated with improved patient survival even after adjustment for confounders, but its beneficial association with actual and functional graft survival is lost or at least reduced if kidneys from donors older than 50 years are used[69].

Apart from being more susceptible to CNI-induced nephrotoxicity, kidneys from ECDs may elicit a strong inflammatory response, predisposing recipients to an increased risk of cancer after transplantation. This association between different donor types and the risk of cancer was assessed in a study using the Australian and New Zealand Dialysis and Transplant Registry[70]. Compared to recipients of living donor kidneys, recipients of ECD kidneys were at an increased risk of cancer, particularly for genitourinary cancer and post-transplant lymphoproliferative disease, over a median follow-up period of 4.4 years. Therefore, this study demonstrated that recipients of ECDs have an overall increased risk of cancer by at least 1.5 times compared to recipients of SCD and living-donor kidneys independent of age, sex, and time on dialysis[70]. With increasing utility of ECD kidneys worldwide, it is conceivable that the use of these organs is contributing to the escalating burden of cancer in transplanted patients. However, the impact of cancer on the overall and cause-specific survivals in the context of receiving ECD compared to SCS kidneys and the trade-off between death on the waiting list and the increased risk of cancer after receiving ECD kidneys remains to be determined. Strategies to ensure adequate cancer surveillance in these recipients should be considered, particularly in those with other risk factors for cancer development, such as older recipients, Epstein-Barr Virus naive recipients, or the use of T cell depleting antibody as induction or as treatment for acute rejection.

ECD kidneys and elderly recipients usually are excluded from randomized clinical trials assessing the efficacy and safety of new immunosuppressive drugs and combinations. Consequently, results for pharmacological regimens in the lower risk transplant recipients may not be valid in this higher risk population. Specific well-designed controlled trials of immunosuppressive strategies are urgently needed in ECD kidney transplantation. Therefore, recommendations regarding optimal immunosuppressive regimen in this patient population should be made with caution. However, reducing the overall immunosuppression burden appears

to be a prudent approach in this high-risk kidney transplant recipients. Reduced CNI exposure regimens or even CNI-free regimens, in selected cases, may improve survival of ECD kidney transplants. In the context of such regimens, m-TOR inhibitor everolimus appears to offer advantages in ECD kidney recipients both in terms of improving outcomes and preserving renal function as well as in terms of minimizing CNI-associated adverse events, such as cardiovascular morbidity/mortality and malignancies, particularly prevalent in this patient population. Finally, we should always bear in mind that, apart from applying individualized immunosuppressive regimen, appropriate selection of ECD kidney transplant recipients and close peri- and post-operative follow-up are of prime importance in order to maximize the benefits associated with the increasingly widespread use of ECD kidney allografts.

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