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Outcomes of renal transplantation from extended criteria donors in therapy with everolimus, cyclosporine and steroids versus enteric coated micophenolate sodium, cyclosporine and steroids

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Abstract

Introduction: Few studies have tested which is the best immunosuppressive regimen for marginal kidneys. The aim of this study is to compare graft outcomes, renal function and rate of complications between a group of recipients of a kidney graft from marginal donor receiving everolimus, cyclosporine and steroids (group RAD) versus a group receiving cyclosporine, enteric coated micophenolate mofetil (group ECMPS) and steroids.

Methods: In this monocentric retrospective study we compared 38 patients of group RAD and 46 patiens of group ECMPS. We compared graft and patient survival, serum creatinine, eGFR, rate of complications after 2 years of follow up.

Results: We observed similar rate of graft loss and renal function 2 years after transplantation. (graft loss: 79.5% vs 80.1%,p=1.00; serum creatinine 1,82±0,7 Vs 1,66 ±0,5mg/dl,p=0.342; eGFR 51.58±23,32 Vs 59,93 ±22.47ml/min, p =0.188). We also observed no differences in the rate of complications except a higher level of cholesterol in the group receiving everolimus (231.63±42.51 Vs 197.1±34.2mg/dl, p=0.02).

Conclusions: In our experience the outcomes 2 years after transplantation of marginal kidneys receiving an immunosuppressive regimen based on everolimus and cyclosporine resulted similar to a regimen of enteric coated mycopheonolate sodium and cyclosporine.

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Introduction

The terms extended criteria donors refers to transplantable organs that are harvested from cadaveric donors aged >60 years or cadaveric donors aged >50 years with two of the following: history of hypertension, terminal serum creatinine [SCr] level > 1.5 mg/dL or death resulting from a cerebrovascular accident. By definition the outcomes of these organs are inferior to standard criteria donors. Data from the largest registries and from multicenter studies show, except some small exception, decreased short and long term Graft Survival (GS), 1year and 5 year GS ranging respectively from 71 to 86% and from 51 to 63% in ECD Vs 81 - 91% and 68-76% for Standard Criteria Donors (SCD). (reviewed in 1). It has been reported than on average, patient survival is 5% lower at 1 year and 8–12% lower at 3–5 years for ECD kidney recipients [2]. Nonetheless, the long term survival of recipients of a kidney from ECD is still longer than patients who remain on the waiting list or in dialysis. It is yet unknown which is the best immunosuppressive regimen for marginal kidneys. Many authors tested the idea that calcineurin inhibitors (CNI) should be avoided since aged kidneys might be more sensible to the nephrotoxic effect of this class of drug but the results of CNI-free regimens based on the association of mTOR and Micophenolate resulted in higher incidence of acute rejection [9,10]. Different studies have suggested that a CNI minimization regimen based on the association of everolimus (Rad) and low levels of Cyclosporin A (CsA) might be associated with higher eGFR probably because of a reduced exposure to CNI [3]. In this study we compared a immunosuppressive regimen based on Rad, CsA and steroids Vs a standard regimen of EC-MPS, Csa and steroids in recipients of kidney from ECD.

Materials and methods

Patients

In this retrospective single-center study, we selected consecutively from our cohort of transplanted patients those who had received a single renal graft in our institution between 2005 and 2010 from a cadaveric donor aged >60 years. The patients were divided into two groups according to their initial immunosuppressive regimen. In group A were included those who received Rad and CsA microemulsion. For the majority of patients of this group, Rad was started at initial dose of 0,75 mg twice daily, then adjusted to reach a maintenance trough level of 3-8 ng/mL) and Csa was started at a dose of 4 mg/kg in 2 doses then tapered to achieve C2 levels of 350-550 ng/mL after months 3. Some other patients of this group received a dosage of RAD to mantein trough levels between 8 to 12 and Csa between 150 to 300 ng/dl because included in other randomized trial. Patients in group B received EC-MPS (dose of 1440 mg /daily) and CsA (initial dose of 6 mg/kg in 2 doses then tapered to achieve a C2 levels of 500-700 ng/mL). All the patients of both groups received induction therapy with basiliximab 20 mg (Simulect, Novartis Pharma, Basel, Switzerland) on post-transplantation days 0 and 4; methylprednisolone i.v. on days 0-4, followed by oral methylprednisolone in accordance with our institutional protocol.

Data evaluation

Data were collected from the medical records of each patient and from the database of the transplant unit of our institution. The analysis after 2 years of follow up included: patient and graft survival, recipient serum creatinine and eGFR (by means of creatinine clearance), 24 hours proteinuria, cholesterol levels, blood pressure, rate of acute rejection, delayed graft function, CMV infection and limphocele.

Statistical analysis

The continuous variables are expressed as mean values and standard deviation, or median values and quartiles when they were not normally distributed according to the Shapiro-Wilk test; the comparisons were made using t test and Wilcoxon's rank-sum test when appropriate. The non-continuous variables were compared using the $\chi 2$ test or Fisher's exact test as appropriate. Death-uncensored graft survival is expressed using Kaplan-Meier curves; the differences between the survival curves were assessed by means of the log-rank test. All the tests were performed using SPSS software.

Results

85 patients were selected for this analysis, of whom 46 in the EC-MPS group and 39 in the RAD group. Basal characteristic of the donors and recipients are expressed in table 1. 2 years graft survival was 79.5 % in group RAD and 80.4% in group ECMPS (p=1.00); the Kaplan-Meier curves for the analysis of death uncensored graft loss resulted similar (p value of log rank: 0,879). (See Figure 1). 5 patients (12.8%) receiving Everolimus died (3 for infections,1 for cardiovascular complication, 1 for unknown reason), while 9 (19.5%) patients died in group B (3 for infections, 4 for cardiovascular complications, 1 for trauma and 1 for unknown reason) p: 0,40. 3 patients in the RAD group returned to dialysis during the observational time (2 renal vein thrombosis and 1 cortical necrosis). No patients of the ECMPS group returned to dialysis during the follow up.

2 patients of the Rad group were switched from everolimus to EC-MPS and 1 patient of the other group was switched from EC-MPS to Rad. Renal function was similar between the 2 groups: SCr was 1.82±0.7 and 1.66±0.5 mg/dl (p=0.342) and eGFR was 51.58 ± 23.32 Vs 59.93± 22.47ml/min (p=0.188). We also have found no difference in proteinuria: 337.63±201.38 Vs 293.87±290.89mg/24 hours respectively for the Evl and EC-MPS study.

In table 2 are shown the results of the other parameters that we have evaluated. In particular we observed higher levels of cholesterol in the group receiving Rad (respectively 231.63±42.51 Vs 197.1±34.2 mg/dL; p=0,02) and similar value of blood pressure, rate of acute rejection, CMV infection, DGF, lymphocele.

Table 1: Characteristic of the patients and results 2 years after transplantation

	Group RAD	Group ECMPS	p.
Age at transplantation (years)	58 (38-72)	61 (42-77)	0.035
Male sex	31(79.4%)	37 (80.4%)	0.913
Mean follow up (days)	730 (0-730)	730 (7-730)	0.630
Death	5 (12.8%)	9 (19.5%)	0.403
Return to Dialysis	3 (7.8%)	-	
Serum creatinine (mg/dl)	1.82±0.7	1.66±0.5	0.342
eGFR (ml/min)	51.58 ± 23.32	59.93± 22.47	0.188
Proteinuria (mg/24h)	337.63±201.38	293.87±290.89	0.534
Trough cyclosporin level (ng/ml)	102,04 ± 49.6	127,03±49.0	0.069
Peak cyclosporin level (ng/ml)	550.12±249.1	639.14±252.3	0.199
Everolimus (ng/ml)	7.53 ±3.47	-	
Serum cholesterol (mg/dl)	231.63±42.51	197.1±34.2	0.02
Systolic blood pressure (mm/Hg)	135 (120-170)	130 (110-160)	0.464
Diastolic blood pressure (mm/Hg)	80 (60-100)	80 (60-90)	0.380
Number of antihypertensive drugs	2 (0-4)	2 (0-4)	0.213
CMV infection	8 (20.5%)	9 (19.5%)	0.829
Acute rejection	9 (23.0%)	5 (10.8%)	0.052
DGF	6	12	0.229
Lymphocele	6 (15.3%)	4 (8.6%)	0.524
Use of statin	14 (35.8%)	11 (23.9%)	0.100

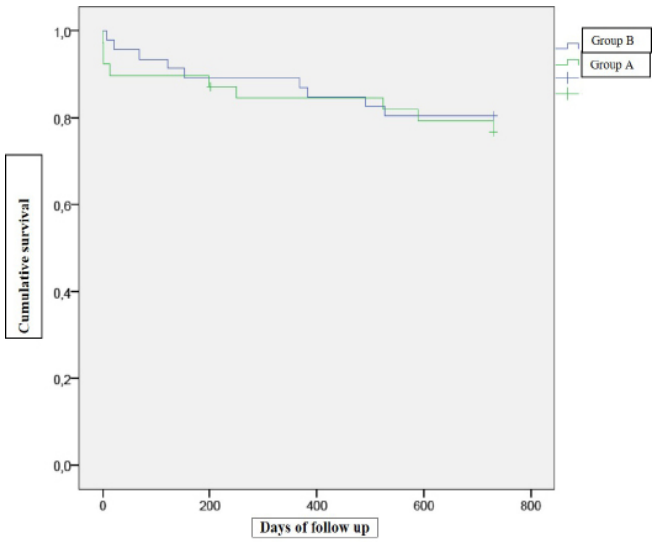

Figure 1: Kaplan Meier Curves for death uncensored graft survival

Discussion

In our retrospective study we found no differences in the rate of graft loss, renal function and rate of adverse event in a cohort of transplanted patients from ECD who received a regimen of Rad and CsA versus those who received CsA and ECMPS.

One of the potential advantage of the use of mTor inhibitors is the possibility of a strong minimization of CNI exposure. Several studies have tested different associations of blood levels of Rad and CsA with discordant results. In brief, the majority of studies that compared different levels of Csa and Rad showed better renal function and graft survival for those patients who maintained low levels of cyclosporine provided that Rad dosage was maintained [3,4]. Other studies comparing Rad and CsA Vs EC-MPS and CsA have demonstrated non-inferiority in terms of renal function and graft loss (5,6,7) when RAD was used with lower levels of CsA except for a small study published by our group in which the authors showed a better renal function using particularly low levels of cyclosporine [8] in association with higher level of Rad. However, it's extremely difficult to compare the outcomes of these studies, because the maintenance levels of CsA were different and the target level of CsA were expressed by protocol sometimes as trough level, and others as peak levels. Older studies that compared standard levels of CsA plus Rad versus standard CsA and ECMPS showed a worst renal function in the recipients receiving Rad suggesting a negative effect when full dosage of both drug are given together. In our retrospective analysis we were not able to identify any advantage in terms of better renal function for patients receiving Rad. These findings probably might be in relation with the fact that the Csa levels that we recorded were higher than the values of the arm with better renal function of the Everest study [3] (Csa C2 between 150-300 ng / dl and Rad between 8-12 ng / dl). Several reasons might have influenced the suboptimal levels of Csa that we observed: firstly, we included in our analysis patients who have been transplanted between 2002 and 2010, and in the first part of this period the experience with Rad was initial and the interaction between Csa and Mtor was not fully explored. Secondly, being our study retrospective, the maintenance levels of the immunosuppressive drugs was not defined with the precision of a prospective trial. Finally, physicians could have been reluctant to use higher dosages of Rad in elderly recipients of kidneys from marginal donors who may be more sensible to the adverse effect of this drug.

Adverse event (ADE) of mTOR inhibitors are a frequent cause of drug discontinuation. The most frequently ADE reported included proteinuria, hypercholesterolemia, lymphocele, delayed graft function, delay in wound healing and anemia [11]. In our experience, in consideration that the rate of complications that we observed in the 2 groups were similar, the use of Rad is safe in recipients of marginal donors except for a higher risk of developing hypercholesterolemia.

Although our study has several limitations, being low-powered, retrospective and monocentric, it show that Rad is safe even in kidney transplantation from marginal donors. The possible role of this drug in marginal kidney remains unclear but our data suggests similar safety to standard regimen of ECMPS. The potential benefits of a strong minimization of calcineurin inhibitors in this type of donors should be tested in a randomized prospective trial.

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