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ORIGINAL ARTICLE

An mTOR-inhibitor-based protocol and calcineurin inhibitor (CNI)-free treatment in kidney transplant recipients from donors after cardiac death: good renal function, but high incidence of conversion to CNI

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Summary

Donor after cardiac death (DCD) grafts have excellent survival despite the high incidence of delayed graft function (DGF). We assessed the feasibility of a mammalian target of rapamycin inhibitor (mTOR-I) protocol in uncontrolled DCD kidney transplantation and compared it with brain-dead donor (DBD) transplantation under calcineurin inhibitor (CNI) treatment.

This retrospective study (2002–2011) included 109 Maastricht category II DCD patients and 218 standard-criteria DBD as controls. Immunosuppression consisted of polyclonal antibody induction, mycophenolate mofetil, prednisone, and mTOR-I (starting on day 6) in the DCD group and tacrolimus in the DBD group. DGF occurred in 72.5% of the DCD group vs. 26.1% of the DBD group ($P = 0.001$). Patient survival at 1 year was 99.1% vs. 95.9% ($P = 0.112$), and graft survival was 89% vs. 92.2% ($P = 0.253$). Patient survival at 5 years was 85.3% vs. 90.1% ($P = 0.340$) and graft survival was 85.5% vs. 78.8% ($P = 0.166$). During the first year, 46.8% ($n = 51$) of DCD patients were converted to CNI therapy. Serum creatinine at 1 year was 1.5(1.26–2) mg/dl vs. 1.4(1.16–1.8) mg/dl ($P = 0.078$). At 1 year, the acute rejection rate was 7.3% vs. 12.5% ($P = 0.766$). mTOR-I-based therapy was not associated with inferior graft function or higher rejection rates than standard CNI therapy. DCD kidney transplantation with an mTOR-I-based protocol is feasible but is associated with a high conversion rate to CNI-based therapy.

Introduction

Kidney transplantation improves the quality of life and increases the life expectancy of patients with end-stage kidney disease [1]. Several strategies have been adapted to expand the donor pool and decrease waiting lists, such as transplantation of kidneys from donors after cardiac death (DCD).

Donors after cardiac death transplants have been associated with a survival advantage compared with remaining on hemodialysis, despite the relatively high incidence of primary nonfunction (PNF) and delayed graft function (DGF) compared with transplantation from brain-dead donors (DBD) [2]. Consequently, calcineurin inhibitor (CNI)-based therapy has been used in these transplant

recipients to avoid rejection, with good results in terms of renal and patient survival. Despite the good results and the low risk of rejection with CNI therapy, CNI in DCD transplants can cause more acute nephrotoxicity involving acute renal vasoconstriction and perpetuating DGF [3].

Some authors have proposed minimization of CNI therapy in DCD transplants to avoid DGF, with satisfactory survival and functioning grafts [4–7]. Other authors have also proposed a CNI-free treatment and an mTOR-I-based therapy in DCD transplants to avoid DGF, with good graft and patient survival [8].

The aim of this study was to assess the feasibility and safety of an mTOR-I protocol in uncontrolled DCD kidney transplantation and to compare the clinical outcome of an mTOR-inhibitor-based protocol and calcineurin inhibitor-free treatment in DCD renal transplantation with calcineurin inhibitor therapy in standard-criteria donor kidney transplantation from DBD.

Methods

Clinical and histological data

A retrospective analysis was conducted in 109 consecutive uncontrolled DCD renal transplants (category Maastricht II type) under CNI-free treatment compared with 218 DBD performed in Hospital Clinic, Barcelona, from December 2002 to December 2011.

In DCD type II, death is declared based on the demonstration of unequivocal and irreversible absence of circulation and spontaneous breathing for at least 5 min and after the application of advanced cardiopulmonary resuscitation maneuvers for an adequate time (recommended by international resuscitation guidelines) [9]. After declaration of death, donors are immediately heparinized (3 mg/Kg body weight; i.v.) and undergo external chest compressions (LUCAS™, Jolife AB 2005, Lund, Sweden) and mechanical ventilation. A rapid femoral cannulation is performed, and normothermic regional perfusion (NRP) is started in the abdomen (Maquet™, Getinge Group, Extracorporeal Life Support, Maquet Holding B.V. & Co. KG, Rastatt – Germany). Hematocrit, serum creatinine and transaminase levels, gaseous, acid–base and ionic compositions, and temperature are monitored throughout NRP.

We included a randomized control group (matched 2:1) of DBD selected on the basis of year of transplantation, recipient/donor age, panel reactive antibodies (PRA), and previous number of transplants.

The parameters analyzed included recipient/donor age, gender, body mass index, time on dialysis, number of previous transplants, cold ischemia time, immunosuppressive therapy, and side effects. Kidney graft function was evaluated by recording serum creatinine, donor-estimated glomerular filtration rate (eGFR ml/min/1.73 m^2), and 24-h proteinuria at 3 months, 1 year, and 5 years.

Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation, with subsequent recovery of renal function. PNF was defined as the absence of graft function during surgery due to thrombosis. Graft failure was defined as an irreversible loss of graft function with the need to resume dialysis.

Indication biopsies were taken if graft function deteriorated. Acute rejection (AR) was determined according to the diagnostic criteria proposed at the 2007 Banff Conference [10].

The study was approved by the hospital ethics committee, and all patients gave informed consent.

Immunosuppression and anti-infective prophylaxis

All recipients of a DCD renal transplant received polyclonal (rabbit antithymocyte globulin) antibodies (7 daily doses of 1.25 mg/kg, adjusted according to lymphocyte count) as induction. Preoperatively, they were treated with a 2000 mg loading dose of mycophenolate mofetil followed by 1000 mg every 12 h. Prednisone was administered at a dose of 500 mg, 125 mg, and 0.5 mg/Kg on the day of surgery, postoperative day 1, and postoperative day 2, respectively, and was then tapered to a dose of 20 mg at discharge. On postoperative days 6, 7, and 8, an mTOR-I (rapamycin or everolimus) was given at a dose of 6 mg/Kg followed by 3 mg on postoperative day 9 to reach levels of 8–12 ng/ml.

Three months after allografting, maintenance immunosuppression included an mTOR-I (trough level 5–10 ng/ml), mycophenolate mofetil (1000–2000 mg/day), and prednisone (5 mg/day). Later adjustments of maintenance immunosuppressants were made during the follow-up period and were based on clinical events or biopsy data. Patients in the DCD group who developed AR were converted from mTOR-I to CNI (protocol below). All patients received cytomegalovirus (CMV) prophylaxis (valganciclovir) for 3 months postoperatively, regardless of CMV serostatus. Oral PcP prophylaxis (trimethoprim/sulfamethoxazole 400/80 mg/day) was administered 6 months postoperatively.

Transplant recipients from brain-dead donors received induction according to the protocol of the center: The use of polyclonal antibodies (rabbit antithymocyte globulin; thymoglobulin) was based on the same schema. Prednisone was administered with the same schema, and tacrolimus was initiated at 0.1 mg/Kg/12 h trough level 8–10 ng/ml, as well as mycophenolate mofetil (2000 mg/day) or mycophenolate sodium (1440 mg/day). Three months after transplantation, maintenance immunosuppression included tacrolimus (trough level 5–10 ng/ml),

mycophenolate mofetil (1000–2000 mg/day) or mycophenolate sodium (1080–1440 mg/day), and prednisone (5 mg/day). Later adjustments of maintenance immunosuppressants were made during follow-up and were based on biopsy data or clinical events. CMV prophylaxis with the same scheme was initiated.

Statistical analysis

Data are expressed as means ± standard deviation or range as appropriate. Comparisons were carried out using the Student *t*-test, Mann–Whitney *U*-test, chi-square test, or Wilcoxon *Z*-test, as appropriate. Kaplan–Meier curves were used to assess patient and graft survival. Results are reported on an intention-to-treat basis. The significance level was established as $P < 0.05$. Statistical analyses were conducted with the SPSS statistical package, version 17.0 (SPSS System, Chicago, IL, USA, 2008).

Results

Patient characteristics

Donor and recipient characteristics are summarized in Table 1. A total of 89% of the donors were male in the DCD group compared with only 55% in the DBD group ($P < 0.001$). Cold ischemia time was longer in the DBD group than in the DCD group (17 ± 5 h vs. 14 ± 3 h; $P < 0.001$).

The PNF rate was 7.3% ($n = 8$) in the DCD vs. 1.8% ($n = 4$) in the DBD group ($P = 0.024$), and DGF occurred in 66% of patients in the DCD group compared with 26.1% in the DBD group ($P = 0.001$). The median (range) length of DGF was 18 (1–55) days in the DCD group vs. 9 (1–35) days in the DBD group ($P < 0.001$). The median length of follow-up was 54 (12–108) months.

Table 1. Characteristic population.

	DCD $n = 109$	DBD $n = 218$	*P*-value
Recipient age	49 ± 11 (24–70)	49 ± 12 (23–71)	0.693
Recipient gender (male)	55%	57.3%	0.706
Recipient BMI (Kg/m^2)	26.22 ± 11	25.51 ± 5	0.357
Time on dialysis (months)	45 ± 34	48 ± 36	0.72
P.R.A (<25%)	90	88.5	0.838
Number RT:			0.885
1	91.70%	92.2%	
2	8.30%	7.8%	
Donor age	45 ± 13 (15–65)	47 ± 14 (12–71)	0.078
Donor gender (male)	89%	55%	<0.001
Donor BMI (Kg/m^2)	26.4 ± 10	26.62 ± 8	0.245
Recipient with donor specific antibody	4.5%	6.8%	0.728
Cold Ischemia (h)	14 ± 3	17 ± 5	<0.001

DBD, brain-dead donors; DCD, donor after cardiac death; BMI, body mass index; P.R.A, panel.

Graft and patient survival

One-year patient survival in the DCD group was 99.1% vs. 95.9% in the DBD group ($P = 0.112$). In the DCD group, one patient died from an infectious disease at 22 days after transplantation. In the DBD group, five patients died from cardiovascular events and four patients from infectious diseases at a mean time of 148 (2–355) days.

Graft survival at 1 year was 89% in the DCD group vs. 92.2% in the DBD group ($P = 0.253$). Death-censored graft survival and PNF censored at 1 year were 96.3% in the DCD group vs. 93.6% in the DBD group ($P = 0.995$). In the DCD group, there were three graft losses due to chronic graft nephropathy and one due to loss of medical monitoring. In the DBD group, nine patients lost their grafts due to chronic allograft nephropathy, two patients due to AR, and three patients due to loss of medical monitoring.

Patient survival at 5 years was 85.3% in the DCD group vs. 90.1% in the DBD group ($P = 0.340$). In the DCD group, four patients died from cardiovascular events, three from infectious disease, one from a tumor, and two from unknown cause. In the DBD group, six patients died from cardiovascular events, four from infectious diseases, four from tumoral disease, and two from unknown cause.

Graft survival censored for death and PNF at 5 years was 85.5% in the DCD group vs. 78.8% in DBD group ($P = 0.166$).

Renal function and proteinuria

There were significant differences at 3 months in creatinine and eGFR: 1.7 (1.3–2.1) mg/dl in the DCD group vs. 1.5 (1.2–1.9) mg/dl in the DBD group ($P = 0.005$), eGFR 50 ± 12 vs. 56 ± 9 ml/min/1.73 m² ($P = 0.032$); however, no differences were observed at 1 year: 1.5 (1.26–2) mg/dl in the DCD group vs. 1.4 (1.16–1.8) mg/dl in the DBD group (P 0.078), eGFR 56 ± 10 vs. 58 ± 14 ml/min/1.73 m² (P 0.425) or at 5 years: 1.37 (1.1–1.71) mg/dl in the DCD group vs. 1.35 (1.08–1.99) mg/dl in the DBD group (P 0.8), eGFR 57 ± 17 vs. 58 ± 14 ml/min/1.73 m² ($P = 0.870$). At 1 year, differences were observed in proteinuria: 259 (176–612) mg/24 h in the DCD group vs. 225 (122–392) mg/24 h in the DBD group ($P = 0.011$). There were no differences in proteinuria at 5 years: 227 (147–734) mg/24 h in the DCD group vs. 239 (112–623) mg/24 h in the DBD group ($P = 0.123$).

Acute rejection episodes

At 1 year, biopsy-proven and treated AR episodes occurred in 7.3% of patients in the DCD group vs. 12.5% in the DBD group ($P = 0.766$) (Fig. 1). Acute T-cell-mediated rejection ≥ Banff IA occurred in three patients (2.8%) in the DCD group and in 22 patients (10.6%) in the DBD group ($P = 0.025$). All responded to methylprednisolone bolus treatment, whereas one patient in the DBD group lost his graft at a mean post-transplant time of 11 months. Moreover, acute antibody-mediated rejection occurred in five DCD patients (4.6%) and four patients (1.9%) in the DBD group (P 0.142). These patients were treated with rituximab, plasma exchange, and intravenous immunoglobulins and responded to treatment, whereas one patient in the DBD group lost his graft at 8 months.

At 5 years, biopsy-proven and treated AR episodes occurred in 3.7% of patients in the DCD group vs. 6.4% in the DBD group ($P = 0.638$).

Immunosuppressive therapy and mTOR-I therapy complications

During the first year, 46.8% ($n = 51$) of DCD patients were converted to a CNI treatment at a mean time of 2.9 months (8–348 days). The reasons for treatment conversion were surgical problems in 14 patients (mainly wound-healing problems, fistulas, lymphoceles, hernias, and lymphorrhea).

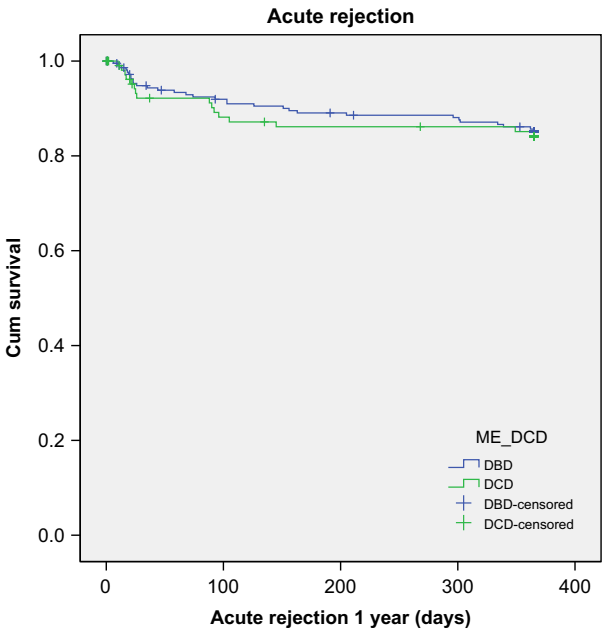

Figure 1 Acute rejection rate at 1 year in kidney transplants from donors after cardiac death (DCD) and donors after brain death (DBD). *P*-value 0.766.

Other causes were an acute rejection episode ($n = 8$), anemia or leucopenia ($n = 8$), edemas ($n = 6$), diarrhea ($n = 3$), proteinuria ($n = 3$), suspected pneumonitis ($n = 2$), dyslipidemia ($n = 2$), and at the physician's discretion without any further reason ($n = 5$). All of them continued with CNI, mycophenolic acid, and prednisone. Within the DCD group, differences were found between the patients who stayed on the original CNI-free protocol and those who were converted to a CNI due to a complication in creatinine at 1 and 5 years (Table 2). At 1 year, 8 (15.6%) of the DCD patients who persisted on the CNI-free protocol showed more than 0.5 g of proteinuria vs. 4.5% in DCD patients receiving CNI therapy.

No differences were observed between the DCD and DBD patients in infections and surgical complications requiring rehospitalizations during the first year. Infections occurred in 29.4% of the DCD patients during the first year and surgical problems in 11.8% (mainly wound-healing problems, fistulas, lymphoceles, hernias and lymphorrhea) requiring hospitalization, while infections occurred in 28.4% of the DBD group and surgical problems in 6.9% ($P = 0.477$). No significant differences were observed in the incidence of CMV infections during the first year (DCD 9.2% vs. DBD 6.4%; P 0.375).

Effect of DGF on outcomes within the groups

In the DCD group (excluding patients with PNF), differences in 1-year graft survival were not found between patients with DGF ($n = 29$) and those without DGF ($n = 72$): 95.8% vs. 100%, P 0.525 (Table 3). In the DBD group (also excluding patients with PNF), patients with DGF ($n = 57$) do not presented worse graft survival at 1 year 96.8% vs. 98.2%, (P 0.135). One-year patient survival in the DCD group was 100% for those without DGF vs. 98.6% in the DGF group; ($P = 0.713$). In the DBD group, 1-year patient survival was 98.1% vs. 91.2%; ($P = 0.033$).

Table 2. Renal function in DCD group: comparison between patients who remain in CNI-free protocol and patients converted to a CNI for a complication.

	DCD CNI-free $n = 58$	DCD CNI-conversion = 51	*P*-value
Creatinine 1 year (mg/dl)	1.4 (1.19–1.75)	1.7 (1.34–2.16)	0.037
Creatinine 5 years follow-up (mg/dl)	1.29 (1.06–1.51)	1.54 (1.1–1.85)	0.013
Proteinuria 1 year (mg/dl)	273 (178–818)	256 (176–602)	0.916
Proteinuria 5 years follow-up (mg/dl)	390 (195–1400)	179 (118–719)	0.178

DCD, donor after cardiac death; CNI, calcineurin inhibitor.

Table 3. Effect of DGF on outcomes between groups.

	DCD (109)			DBD (218)		
	No DGF [n 29]	DGF [72]	*P*-	No DGF [n 157]	DGF [n 57]	*P*-
1-year graft survival (%)	29 (100)	68 (94.4)	0.358	149 (94.9)	51 (89.5)	0.494
1-year death-censored graft survival (%)	29 (100)	69 (95.8)	0.525	152 (96.8)	56 (98.2)	0.135
1-year patient survival (%)	29 (100)	71 (98.6)	0.713	154 (98.1)	52 (91.2)	0.033
1-year AR (%)	5 (17.2)	11 (15.3)	0.461	21 (13.4)	10 (17.5)	0.53
1-year creatinine	1.6 (1.33–1.90)	1.5 (1.21–2.0)	0.873	1.4 (1.15–1.80)	1.54 (1.20–1.89)	0.108
1-year proteinuria	374 (176–795)	240 (178–591)	0.319	227 (118–380)	224 (139–443)	0.491

Eight patients in DCD group presented PNF and have been excluded. Four patients presented PNF in DBD group and have been excluded from the analysis. DBD, brain-dead donors; DCD, donor after cardiac death; DGF, delayed graft function; y, year; AR, acute rejection.

Discussion

Transplantation from DCD donors is one of the strategies that increases the number of donor organs at reasonable cost [11]. DCD transplants have been related to a higher incidence of DGF, PNF, and, in some reports, to a higher incidence of AR [12–14]. In most centers, these results were obtained with CNI-based immunosuppressive regimens, but with minimization of CNI exposure [4–7, 15].

Following the positive experiences already reported with CNI treatment [5], in our study, we aimed to explore an mTOR-I-based protocol as an alternative to CNI protocols.

We report one of the largest series of patients receiving a kidney allograft from a DCD who were treated *de novo* with an mTOR-I-based CNI-free regimen. Neither AR nor detrimental effects of mTOR inhibition on long-term outcomes proved to be a problem in grafts extremely susceptible to DGF. In our series of uncontrolled DCD renal transplant recipients receiving an mTOR-I-based regimen, the incidence of DGF was high but was similar to that of reports from other groups using a CNI-based regimen [2]. However, our DCD group also showed good renal and patient outcomes with low AR rates at the one follow-up compared with DBD kidney transplantation. These results demonstrate that an mTOR-I-based treatment is feasible and may represent an alternative to CNI-based therapy in DCD kidney transplantations. However, the initial CNI-free treatment was associated with a high incidence of conversions to CNI-based therapy.

In our series, 1-year patient and graft survival were similar in DCD and DBD patients. Renal function at 1 year did not differ between the two cohorts despite a worse GFR in DCD patients at 3 months than in DBD patients. These latter findings are consistent with reports in the literature [16].

In our serie, the DCD group with DGF was not associated with worse 1-year graft survival. In other series, DGF in DCD recipients does not seem to be related to worse long-term graft function, AR, or patient survival. However, DGF in DBD transplant recipients does predict worse long-term graft function, AR, and worse patient survival [17–20].

mTOR-I-based therapy was not associated with a higher incidence of AR in our series; however, in other studies of DBD patients, CNI-free mTOR-inhibitor-based immunosuppression was associated with a higher incidence of AR [21]. This could be due to the use of lymphocyte-depleting antibodies in our series in contrast to other CNI-free protocols using anti-CD-25-antibodies. Polyclonal antibodies are directed against several T and B lymphocyte epitopes, which seems to have positive effects regarding immunological regulation, regulatory T lymphocytes, reducing ischemia–reperfusion injury, improving early graft function, and decreasing DGF [22]. Recent reports indicate that mTOR-I-based therapy seems to promote a novel immunoregulatory pathway inducing the upregulation of ILT3(high)ILT4(high) dendritic cells. This effect was associated with an increase in the number of Tregs and expansion of the CD8(+)CD28(−) T-cell population inhibiting the donor-specific alloreactive effector immune responses [23, 24].

One of the problems we observed in our protocol was the high rate of conversion to CNI therapy. This has been observed in various studies of *de novo* use of CNI-free mTOR-I-based treatment strategies and in very early conversion studies [25]. In our series, the mean time to conversion was 2.9 months. Various factors may be responsible for this finding, the most important being wound complications. *De novo* mTOR-I therapy has been recognized as a risk factor for wound-healing problems [26], but was not strongly related to AR in our series, and patients remaining on CNI-free therapy had better graft survival at the final follow-up.

Our study has several limitations. First, the design was retrospective. Moreover, there was no direct DCD control group receiving CNI-based treatment *de novo*. Therefore, the results could only be compared with those in a contemporary group of patients with the same characteristics who

received an allograft from a DBD with CNI-based treatment. Nevertheless, outcome was similar or better in the DCD patients than in the group of standard donor recipients receiving standard therapy.

In conclusion, our findings show that DCD kidney transplantation with an mTOR-I-based protocol is feasible and safe using lymphocyte-depleting antibody induction; however, this protocol is associated with a high conversion rate to CNI-based treatment. Nevertheless, CNI-free *de novo* treatment in DCD transplantation was not associated with inferior graft function or with a higher AR rate compared with DBD kidney transplant recipients receiving standard treatment. DGF was not associated with worse long-term graft function or worse survival in DCD patients.

Authorship

AS-E: Collected, analyzed data, and wrote the paper. FD: Study design, data analysis, wrote and reviewed manuscript. IR, NE, MJR, FC, J-VT: Data collection and manuscript review. LP: Manuscript review. ÁR: Data collection and manuscript review. JMC: Manuscript review. FO: Design of the study and manuscript review.

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