Usefulness of Delayed Introduction of Tacrolimus in Kidney Transplants Using Type-III Donors After Circulatory Death

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ABSTRACT

Introduction. Our study compares 2 immunosuppressive strategies to reduce tacrolimus nephrotoxicity and its risk of acute tubular necrosis: delayed introduction of tacrolimus plus thymoglobulin vs initial tacrolimus plus basiliximab on the results of kidney transplant (KT) using type-III donation after circulatory death (III-DCD).

Material and methods. We analyzed all the transplants performed using type-III DCD in our hospital (42 cases). They were distributed in a first stage with delayed tacrolimus (3°-4° day) + thymoglobulin and a second one with initial tacrolimus + basiliximab, with a follow-up of 6 months. The rate of delayed graft function, the evolution of renal function, and the incidence of rejection were compared.

Results. 28 patients received thymoglobulin with delayed tacrolimus, and 13 patients received basiliximab and tacrolimus from day 0 (1 excluded). There were no significant differences in delayed graft function (27% group 1 and 23% group 2) or in rejection (10.7% and 15.4%), respectively. Serum creatinine at day 3, 7, 14, 30, and 180 showed no statistically significant differences. The levels of tacrolimus measured at 10, 30, 90, and 180 days after transplantation were similar, except for the first month: 10.10 ± 2.3 in group 1 and 12 ± 1.7 ng/mL in group 2 ($P = .007$).

Conclusions. Delayed introduction of tacrolimus does not seem to suppose a benefit in KT using type-III DCD; therefore, the use of thymoglobulin, with its higher profile of adverse effects, seems unjustified in patients with normal immunological risk.

KIDNEY transplants (KT) using donation after circulatory death (DCD) have had a considerable growth in the last years, accounting for 24% of all transplants performed in Spain during 2017 [1]. These kidneys are exposed to an increased risk of delayed graft function (DGF), greater need for dialysis, difficulty in the diagnosis of acute rejection, longer hospital stays, and a worse graft function. In addition, calcineurin inhibitors (CNI) have a nephrotoxic effect due to vasoconstriction, increasing the risk of acute tubular necrosis [2–8]. Certain strategies try to compensate this negative effect, such as the delayed introduction of tacrolimus (TAC) (day 3 to 7 posttransplant) or low doses from the beginning (day 0) [5–9]. To avoid acute rejection due to insufficient immunosuppression, induction therapy with thymoglobulin or with interleukin-2 receptor inhibitors is usually included [2–8]. Nevertheless, the use of thymoglobulin brings an increased risk of complications that must be carefully compared with the benefits of avoiding TAC in the initial phase [9,10]. We have analyzed our experience with respect to type of induction and moment of TAC introduction and its relation with graft evolution.

MATERIAL AND METHODS

All kidney transplants performed using type-III DCD in our hospital (42) were retrospectively analyzed, with a follow-up of 6

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0041-1345/18
https://doi.org/10.1016/j.transproceed.2018.10.022

months. The transplants were classified according to the initial immunosuppression in 2 groups: a first group (28 transplants), from 2014 until July 2016, with thymoglobulin (cumulative dose of 5–7 mg/kg) + delayed TAC (3°-4° day) and a second group (13 transplants), from August 2016 to 2017, with basiliximab (20 mg on day 0 and 4) + initial TAC. In both groups, low doses of tacrolimus (0.05 mg/kg/12 h) were used. One patient was excluded because he did not receive induction therapy.

Demographic data of the population, evolution of renal function, and TAC levels, as well as incidence of DGF, risk of rejection, and graft survival, were analyzed. We also studied the days of hospitalization and readmissions, as well as the adverse effects derived from the immunosuppression used.

RESULTS

Demographic data of both populations were comparable, as shown in Table 1. The evolution of creatinine at days 3, 7, 14, 30, and 180 (excluding those who required dialysis in the first days) was 4.05 ± 2.5, 2.27 ± 1.7, 2.09 ± 1.3, 1.49 ± 0.7, and 1.45 ± 0.49 mg/dL for group 1 and 3.15 ± 1.5, 2.08 ± 1.3, 2.07 ± 1.3, 1.73 ± 1.2, and 1.6 ± 0.8 mg/dL for group 2 (pNS). Proteinuria at 6 months was 462.75 ± 417.11 in group 1 and 350.83 ± 190.27 mg/24 hours in group 2 (pNS). Tacrolimus levels measured at 10, 30, 90, and 180 days after transplantation were 10.81 ± 3.3, 10.10 ± 2.3, 9.6 ± 3.5, and 7.8 ± 2.06 ng/mL for group 1 and 10.36 ± 2, 12 ± 1.7, 9.4 ± 2.2, and 8.1 ± 2.28 ng/mL for group 2, showing similar levels, except for the first month (P=.007) (Table 1).

Three patients in group 1 (10.7%) and 2 in group 2 (15.4%) experienced rejection, without statistically significant differences (pNS). There were also no significant differences for DGF: 27% in group 1 and 23% in group 2 (pNS). The duration of the first admission was 25.68 ± 24.67 for group 1 and 19.85 ± 13.79 days for group 2, with a total hospitalization duration over 6 months of 31.61 ± 30.89 in group 1 and 22.23 ± 15.43 days in group 2 (pNS).

The rates of moderate-severe infection were 38.5% in group 1 and 15.4% in group 2, with specific rates for CMV 3.8% and 7.7%, respectively. Regarding cytopenias, there were no statistical differences, either; the minimum leukocyte numbers in the first month were 3214.29/μL ± 1380.48 and 4230.77/μL ± 1819.52 (Table 2).

Graft and patient survival rates were similar. The causes of graft loss were vascular problems or patient's death. In group 1, one graft loss was due to venous thrombosis and hemorrhagic infarction, and other presented arterial thrombosis. There were 3 deaths in group 1 (cardiorespiratory arrest, lung adenocarcinoma [recurrence], unknown cause) and 1 death in group 2 (acute lung edema, heart failure).

Table 1. Demographic Data of Study Population

	Thymoglobulin	Basiliximab	Outcome (P)
Donors			
Age	54.5 ± 11.31	56.67 ± 14.74	.648
Sex	F 67.9%, M 32.1%	F 69.2%, M 30.8%	1
High blood pressure	28.6%	7.7%	.272
Diabetes	10.7%	7.7	1
Cold ischemia time	13.39 ± 8.07	11.33 ± 8.7	.609
Creatinine	0.72 ± 0.56	0.61 ± 0.19	.074
Recipients			
Age	54.86 ± 12.36	57.25 ± 12.53	.793
Sex	F 71.4%, M 28.6%	F 69.2%, M 30.8%	1
High blood pressure	85.7%	84.6%	1
Diabetes	32.1%	23.1%	.822
Ischemic heart disease	46.4%	15.4%	.116
1st transplant	89.3%	69.2%	.253
Waiting list time	207.14 ± 208.92	95.75 ± 125.67	.085
Panel reactive antibody	9.65 ± 24.94	0	.367

Abbreviations: F, female; M, male.

DISCUSSION

Kidneys from donors after circulatory death suffer a more intense ischemic damage due to the period of absence of blood flow before cold perfusion, and this effect is responsible for a considerably higher rate of DGF after transplant [4,5,11]. This is especially relevant in type-II DCD where circulatory cessation can be extremely long and as many as 70% or more cases develop DGF. Nevertheless, the cases of type-III DCD are not comparable. In these cases of "controlled" DCD, the period of circulatory cessation is considerably shorter. The Spanish legislation requires a 5-minute period of cardiac arrest; after that, the diagnosis of death can be made. In cases of super-rapid retrieval of the organs, an additional 3–4 minute period until cold perfusion must be considered (and almost no additional period in those cases using extracorporeal membrane oxygenation) [1]. For this reason, the risk of DGF in type-III is not comparable to that in type-II DCD, and, in fact, it is probably not very different to that observed with donors after brain death (up to 30%-40%). For this reason, the justification of "especial" immunosuppressive protocols that imply higher risks are probably not justified. This is why we analyzed and present our experience.

Our study, although retrospective, not randomized, and with a short number of cases, suggests that the use of TAC since the initial phase of transplant seems not to be an obstacle for the recovery of graft function and the delayed introduction, with the almost obligated use of thymoglobulin to prevent rejection and the risks that this drug imply, are probably not justifiable. Another strategy that we have not tested is the delayed introduction of TAC using basiliximab induction but probably, according to our results, this do not add any advantage with respect to the recovery of renal

Table 2. Evolution of Renal Function, Tacrolimus Levels, Risk of DGF, Rejection, Hospitalization, and Adverse Effects

	Thymoglobulin	Basiliximab	Outcome (*P*)
Evolution of creatinine (mg/dL)			
Day 3	4.05 ± 2.48	3.15 ± 1.47	.542
Day 7	2.27 ± 1.71	2.08 ± 1.26	.769
Day 14	2.09 ± 1.26	2.07 ± 1.27	.976
Day 30	1.49 ± 0.72	1.73 ± 1.2	.649
Day 180	1.43 ± 0.49	1.57 ± 0.77	.643
Day Cr <2 mg/dL	42.96 ± 104.23	12.58 ± 14.77	.466
Levels of tacrolimus (ng/mL)			
FK introduction day	3.3 ± 1.9	0	
1° Level	12.06 ± 7.48	10.04 ± 5.71	.465
Day 7	11.63 ± 5.02	10.81 ± 3.48	.511
Day 10	10.81 ± 3.3	10.36 ± 2	.435
Day 30	10.10 ± 2.3	12 ± 1.7	.007
Day 90	9.6 ± 3.5	9.4 ± 2.2	.604
Day 180	7.8 ± 2.06	8.1 ± 2.28	.631
Primary objectives and hospital stay			
DGF	26.9% (7/26)	23.1% (3/13)	.795
Rejection	11.5% (3/26)	15.4% (2/13)	.735
Proteinuria 6 mo	462.75 ± 417.11	350.83 ± 190.27	.804
Days 1° admission	25.68 ± 24.67	19.85 ± 13.79	.803
Total days	31.61 ± 30.89	22.23 ± 15.43	.546
Readmissions 6 mo	0.29 ± 659	0.39 ± 0.768	.918
Adverse effects			
Infection	38.5%	15.4%	.270
CMV	3.8%	7.7%	.670
Anemia	8.24 ± 0.98	8.45 ± 0.9	.452
Leukopenia	3214.29 ± 1380.48	4230.77 ± 1819.52	.105
Thrombocytopenia	93,071.43 ± 42,866.66	105,538.46 ± 35,053.81	.627

Abbreviations: CMV, cytomegalovirus; Cr, creatinine; DGF, delayed graft function; FK, tacrolimus.

function and possibly might increase the risk of graft rejection.

Another conclusion of our study is that the rate of DGF was considerably low (in both arms) and very similar to that in our transplants with brain death donors. This might be explained by the frequent use in our center of normothermic extracorporeal perfusion and preservation of organs using machine perfusion [1]. This fact supports the idea of the adequacy of "conventional" immunosuppressive protocols instead of "exceptional" protocols such those used in type-II DCD.

In our study, we observed a tendency to more infections and leukopenia in group 1, which can be attributed to the use of thymoglobulin [9]. The rate of CMV infection were similar in both groups, but it must be considered that patients receiving thymoglobulin received universal prophylaxis with valganciclovir (for 1 month), whereas in group two only D+/R- cases received prophylaxis.

In conclusion, the delayed introduction of tacrolimus does not seem to suppose a benefit in KT using type-III DCD with respect to renal function recovery; therefore, the use of thymoglobulin, with its higher profile of adverse effects, seems unjustified in patients with normal immunological risk.

ACKNOWLEDGMENTS

This study was carried out in collaboration with the group of IDIVAL-Hospital Universitario Marqués de Valdecilla and RED-INREN RD16/0009/0027. Instituto de Salud Carlos III. Ministerio de economía y competitividad.

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