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Improvement in late renal allograft survival between 1990 and 2002 in Spain: results from a multicentre case–control study

Francesc Moreso,[1] Angel Alonso,[2] Miguel A Gentil,[3] Miguel González-Molina,[4] Lluis Capdevila,[1] Roberto Marcén,[5] Julio Pascual,[6] and Daniel Serón[1] for the Spanish Late Allograft Dysfunction Study Group*

1 Nephrology Department, Hospital Universitari Vall d'Hebron. Barcelona, Spain
2 Nephrology Department, Hospital Universitario Juan Canalejo, A Coruña, Spain
3 Nephrology Department, Hospital Universitario Virgen del Rocio, Sevilla, Spain
4 Nephrology Department, Hospital Universitario Carlos Haya, Málaga, Spain
5 Nephrology Department, Hospital Ramon y Cajal, Madrid, Spain
6 Nephrology Department, Hospital del Mar, Barcelona, Spain

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Correspondence
Francesc Moreso MD, PhD, Nephrology Department, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119–129, Barcelona, Spain. Tel.: 34 93 274 62 19; fax: 34 93 274 62 19; e-mail: fjmoreso@vhebron.net

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Summary

Epidemiological studies have failed to show an improvement in graft survival beyond 1 year after kidney transplantation possibly because of an increased number of expanded donors and older recipients. Thus, we performed a case–control study matching patients transplanted in different eras by donor and recipient characteristics. We considered renal transplant recipients included in the database of the Spanish Chronic Allograft Dysfunction Study Group in 1990, 1994, 1998 and 2002 ($n = 4842$). We matched patients from these cohorts considering the following variables: donor and recipient age, cause of donor death, hepatitis C virus, panel reactive antibodies and re-transplantation. We identified a total of 896 patients distributed in four cohorts of 224 matched patients. Between 1990 and 2002, the use of cyclosporin decreased (96%, 94%, 80% and 23% respectively, $P = 0.001$), while the use of tacrolimus increased (0%, 1%, 15% and 63% respectively, $P = 0.001$) and the prevalence of acute rejection decreased (46%, 37.9%, 20.6% and 15.8% respectively, $P < 0.001$). One-year serum creatinine was 1.63 ± 0.66, 1.64 ± 0.70, 1.44 ± 0.52 and 1.38 ± 0.75 respectively, $P = 0.001$. Graft survival beyond the first year between 1990 and 2002 significantly improved while patient survival did not. Transplant outcome has improved between 1990 and 2002 when donors and recipients of similar characteristics are compared.

*Participants in the Spanish Late Allograft Dysfunction Study Group: A. Franco, J. Olivares (H.U. Alicante); J.J. Cubero, C. Díaz (H.Infanta Cristina, Badajoz); J. Amenábar, I. Lampreabe (H. Cruces, Barakaldo); L. Guirado, J.M. Díaz, R. Solá (F. Puigvert, Barcelona); J.M. Cruzado, J.M. Grinyó (H. Bellvitge, Barcelona); N. Esforzado, F. Oppenheimer (H.Clínic, Barcelona); J. Lloveras, J.M. Puig (H.del Mar, Barcelona); B. Bayés, R. Lauzurica (H Germans Trias i Pujol, Badalona); C. Cantarell, L. Capdevila (H. Vall d'Hebró, Barcelona); A. Mazuecos, M. Rivero (H. Puerta del Mar, Cádiz); D. del Castillo, R. Pérez Calderón (H. Reina Sofía, Córdoba); C. Asensio, A. Osuna (H. Virgen de las Nieves, Granada); J. Oliver, A. Alonso (H. Juan Canalejo, La Coruña); D. Checa (H. Insular, Las Palmas); J.J. Plaza (F. Jiménez Díaz, Madrid); J. Fernández, D. Sanz (H. Puerta del Hierro, Madrid); A. Andrés (H.12 de Octubre, Madrid); N. Calvo-Romero (H. Clínico San Carlos, Madrid); F. Anaya, M. Rengel (H.Gregorio Marañón, Madrid); C. Jiménez, A. Sanz, F. Escuin (H. La Paz, Madrid); M. Cabello, M. Gonzalez-Molina (H. Carlos Haya, Málaga); A. Alarcón, J. Marco (H. Son Dureta, Mallorca); E. Gómez–Huertas, F. Ortega (H.G. Asturias, Oviedo); P. Errasti (Clínica Universitaria de Navarra, Pamplona); R. Palomar, G Fernández (H. Márques de Valdecilla, Santander); R. Romero, D. Sánchez-Guisande (H.U. Santiago, Santiago de Compostela); M.A. Gentil, P. Pereira (H.Virgen del Rocío, Sevilla); J.M. González-Posada, A. Torres (H.U. La Laguna, Tenerife); F. Crespo, G. Martinez, L. Pallardo, (H. Dr Peset, Valencia); I. Beneyto, J. Sánchez-Plumed (H.G.U La Fe, Valencia); J. Bustamante, A. Mendiluce (H.U de Valladolid, Valladolid); A. Gutiérrez, J.A. Gutiérrez, J. Paul (H. Miguel Servet, Zaragoza).

Introduction

During the last two decades, the introduction of new immunosuppressants has been associated with a decline in the prevalence of acute rejection from approximately 50% in the early 1990s to less than 15% at present and with an improvement in 1-year graft survival [1–3]. However, studies evaluating graft outcome beyond the first year have failed to show a significant improvement in graft survival [4]. The reason for the discrepancy between early and late results is not fully understood.

The demographic modification of donor and recipient characteristics may contribute to explain the lack of improvement in graft survival after the first year. Donor age has steadily increased as well as the proportion of donors with associated risk factors for early graft failure: stroke, previous history of hypertension and/or elevated serum creatinine before organ recovering [5]. The recipient characteristics at the time of transplant have also evolved in a time-dependent manner as recipient age, the proportion of re-transplants and degree of sensitisation has increased. All these factors are associated with decreased death censored graft survival and may contribute to counterbalance the beneficial effect of reducing acute rejection in the last two decades [6]. Another major risk factor for graft failure is hepatitis C virus (HCV) infection and the proportion of HCV positive recipients during the study period has significantly decreased in Spain [7,8].

Thus, the aim was to compare the evolution of graft survival between 1990 and 2002 in renal transplants controlling for major donor and recipient characteristics. For this purpose, we compared four matched cohorts of patients transplanted in 1990, 1994, 1998 and 2002.

Patients and methods

Study design

To describe time-dependent modifications between 1990 and 2002, patients receiving a renal allograft in Spain in 1990, 1994, 1998 and 2002 were considered. Only adult transplant centres were invited to participate and only adult patients (≥18 years) receiving a single kidney transplant functioning at the end of the first year were considered. Patients receiving multi-organic or double transplants were excluded. Last follow-up was on 31st December 2005.

Clinical variables

The following variables were evaluated in each patient at the time of surgery: source of the organ (living or deceased donor), donation before or after cardiac death, cause of donor death (trauma, stroke or others), age and gender of the donor and the recipient, height and weight of the recipient, presence of hepatitis B surface antigen and HCV antibodies in the donor and the recipient, aetiology of end-stage renal disease, time on dialysis, last panel reactive antibodies (PRA), number of human leucocyte antigen (HLA) mismatches, and cold ischaemia and re-anastomosis times.

After surgery, the presence of delayed graft function and acute rejection were recorded. Immunosuppressive treatment at 1-year was described on an intention-to-treat basis and classified into five major groups: (i) cyclosporin (CsA)-based not associated with mycophenolate mofetil (MMF), (ii) CsA-based associated with MMF, (iii) tacrolimus-based treatment (iv) sirolimus-based immunosuppressive regimen and (v) other treatments. At 3 months and 1 year, serum creatinine and 24 h proteinuria were recorded.

Definition of variables

The total number of HLA mismatches was calculated as the addition of the number of mismatches in the A, B and DR loci. Delayed graft function was defined as haemodialysis requirements during the first week after surgery once accelerated or hyperacute rejection, vascular complications and urinary tract obstruction were ruled out. The diagnosis of acute rejection was defined at each centre based on clinical and/or histological data.

The ethical committee of the Hospital Universitari de Bellvitge approved this study. Medical records review was performed according to Spanish law with reference to clinical data confidentiality protection. A blinded code was assigned to each participating hospital to take into consideration the centre effect.

Statistics

To generate four homogeneous cohorts with regard to pretransplant variables, each patient of the 1990 cohort was matched with patients of the 1994, 1998 and 2002 cohorts considering six pretransplant variables: donor age categorised as <40, 41–50, 51–60 or >61 years; cause of donor death categorised as trauma or stroke; recipient age categorised as well as donor age; HCV serology categorised as positive or negative; number of transplant categorised as first transplantation or re-transplantation; and degree of sensitisation categorised as PRA <10%, 11–50% or >51%. Patients with a missing value in any of these six variables were excluded from the analysis.

Descriptive results are expressed as the mean ± standard deviation for continuous variables. Frequency and Contingency Tables were employed to describe categorical

and ordinal variables. Comparison between years of transplant was done by means of chi-square test for categorical data, Kruskal–Wallis test for ordinal or not normally distributed continuous data and ANOVA for continuous normally distributed data.

Kaplan–Meier analysis was used to estimate overall graft survival, death censored graft survival and patient survival. Log rank test was employed to compare differences between groups.

Univariate Cox regression analysis was employed to analyse variables associated with death-censored graft survival. The following variables were considered: donor age (older/younger than 60 years), cause of donor death (trauma/stroke), patient age (older/younger than 60 years), re-transplant, PRA (lower/higher than 25%), HCV serology, delayed graft function, acute rejection, serum creatinine and proteinuria at 3 months, difference in serum creatinine and proteinuria between 3 months and 1 year, diabetes mellitus (none/before transplantation/new-onset diabetes at 3 months) and mean arterial pressure at 3 months. All variables associated with death-censored graft failure with a *P*-value <0.10 in the univariate analysis were included in a multivariate backward Cox regression analysis.

Results

Missing values for each of the matching variables were distributed as follows: donor age ($n = 159$, 3.3%), cause of donor death ($n = 622$, 12.8%), patient age ($n = 35$, 0.7%), HCV serology ($n = 400$, 8.3%), number of transplant ($n = 2$, 0.04%) and degree of sensitisation ($n = 965$, 19.9%). In 1999, of 4842 patients (41.3%), at least one of these variables was not available and accordingly they were not considered for the study. Finally, four cohorts of 224 patients accomplishing the inclusion criteria were selected. In all cohorts, the proportion of trauma as the cause of donor death was 71.9%, the proportion of positive HCV recipients was 6.7% and the proportion of re-transplants was 5.4%. According to the study design, donor age, recipient age and PRA were not different among groups (Table 1). The donor and recipient gender was well balanced among these four cohorts. The number of HLA mismatches was higher in patients transplanted in 1998 and 2002. Despite cold ischaemia and re-anastomosis times were progressively shortened, the prevalence of delayed graft function was not significantly reduced. All demographic data form donors and recipients are summarised in Table 1.

The maintenance immunosuppression in 1990 and 1994 mainly consisted in CsA and steroids; in 1998, the majority of patients received CsA, MMF and steroids and in 2002, the most common regimen was based on tacrolimus (Fig. 1). Steroids were withdrawn at 1 year in 3.6%, 0.4%, 3.1% and 6.8% of patients in the 1990, 1994, 1998 and 2002 cohorts respectively ($P < 0.001$).

The proportion of patients suffering from acute rejection episodes progressively decreased from 46% in 1990 to 37.9% in 1994, 20.6% in 1998 and 15.8% in 2002 ($P < 0.001$). Furthermore, the proportion of patients suffering from more than 1 acute rejection episode was also significantly reduced (5.8% in 1990, 5.8% in 1994, 2.6% in 1998 and 0.9% in 2002; $P < 0.001$).

Serum creatinine at 1 year was lower in 1998 and 2002, whereas proteinuria at 1 year was not different among cohorts. Mean, systolic and diastolic blood pressure at 1 year were also lower in 1998 and 2002 cohorts as well as total serum cholesterol (Table 2). Use of statins, number of anti-hypertensive drugs and use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBII) progressively increased during the study period. Furthermore, new-onset diabetes mellitus requiring antidiabetic treatment was similar between groups (Table 3).

Table 1. Demographic characteristics of the four cohorts of patients.

Variable	1990	1994	1998	2002	*P*
Donor age (years)	31.7 ± 14.3	32.7 ± 14.4	32.7 ± 14.2	32.5 ± 14.3	ns
Donor gender (m/f)	160/64	145/79	165/59	153/71	ns
Patient age (years)	39.4 ± 11.4	39.8 ± 11.3	39.5 ± 11.0	39.6 ± 11.2	ns
Patient gender (m/f)	150/74	152/72	155/79	145/79	ns
PRA (%)	0.6 ± 4.8	1.0 ± 7.2	0.9 ± 6.6	0.8 ± 5.6	ns
HLA A mm (0/1/2)	29/119/75	42/108/70	30/109/83	24/127/71	ns
HLA B mm (0/1/2)	36/135/53	34/128/55	18/121/83	13/99/109	<0.001
HLA DR mm (0/1/2)	88/122/5	90/115/9	61/139/22	55/133/31	<0.001
CIT (h)	20.7 ± 6.4	19.6 ± 5.8	18.3 ± 5.7	18.4 ± 4.9	<0.001
RT (min)	48 ± 16	53 ± 16	50 ± 20	40 ± 25	<0.001
DGF (%)	25.1	27.2	21.8	22.4	ns

PRA, panel reactive antibodies; mm, mismatches; CIT, cold ischaemia time; RT, re-anastomosis time; DGF, delayed graft function; HLA, human leucocyte antigen.

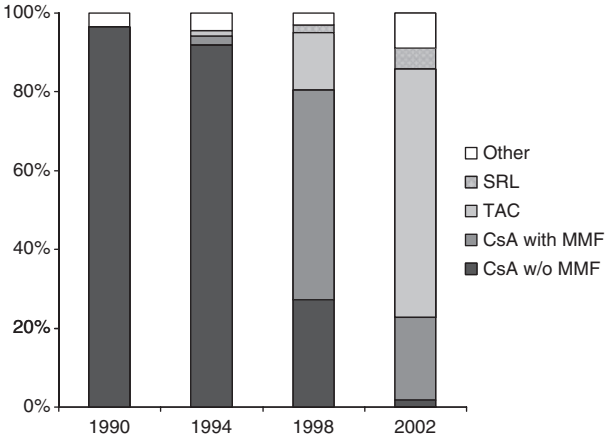

Figure 1 Immunosuppressive treatment in the four cohorts. CsA, cyclosporin; MMF, mycophenolate mofetil; TAC, tacrolimus; SRL, sirolimus.

Death censored graft survival significantly improved from 1990 to 2002, whereas there was no significant difference in patient survival (Fig. 2a and b). Univariate and multivariate Cox regression analysis showed that independent predictors for death-censored graft survival adjusting for year of transplant were donor age, HCV infection, acute rejection, serum creatinine and proteinuria as shown in Table 4.

Finally, as the prevalence of acute rejection steadily decreased between 1990 and 2002, we further analysed the association between acute rejection and late graft failure by means of a univariate Cox regression analysis in the 1990, 1994 and 1998 cohorts. In this analysis, the 2002 cohort was not considered as the low prevalence of acute rejection and low number of events did not allow estimating relative risk with sufficient precision. Relative risk and 95% confidence intervals for death-censored graft failure associated with acute rejection were 1.93 (1.22–3.07), 2.18 (1.21–3.91) and 6.66 (2.62–16.9) in the 1990, 1994 and 1998 cohorts respectively.

Discussion

In patients with similar donor and recipient characteristics, we observed that between 1990 and 2002, the incidence of acute rejection decreased to one-third, 1-year serum creatinine decreased from 1.63 to 1.38 mg/dl and death censored graft survival significantly improved after the first year. On the other hand, patient survival remained stable despite a better control of classical cardiovascular risk factors such as hypertension and dyslipaemia in the most recently transplanted cohorts.

During the last two decades, the introduction of new immunosuppressants, especially MMF and tacrolimus, has been associated with an important reduction in the incidence of acute rejection [1,2]. As acute rejection results in a functional and structural damage of the graft, it has been assumed that decreasing its incidence should be associated with an improvement in late graft outcome. However, this assumption has not been confirmed in epidemiological studies. For example, in a study evaluating renal transplants performed between 1995 and 2000, it was not possible to demonstrate a significant improvement in graft survival after the first year, despite a significant reduction in the incidence of acute rejection rate [4]. The authors observed that during the study period, the proportion of rejection episodes with a partial recovery of renal function increased. Despite the authors corrected for different confounding variables, it was not clear whether the changing pattern of acute rejection could be the reason for the lack of improvement of late allograft survival. Other factors, especially the modification of the donor and recipient characteristics, could also explain the changing pattern of rejection episodes. Older donor age may explain the major proportion of rejection episodes with incomplete recovery of renal function as the probability for recovery after interstitial acute rejection is significantly decreased in recipients of old donors, probably because of the impaired repair capacity of senescent tissue [9]. Thus, the analysis of the impact of acute rejection episodes occurring in different eras on graft outcome has the limitation to require many adjustments for the changing characteristics of the populations being compared. For this reason, we matched patients according to main donor and recipient confounding factors. The main advantage of this approach is that it allows comparing the effect of the introduction of new treatments at different time periods in patients with similar donor and recipient

Table 2. Clinical and biochemical data at 1 year in the four cohorts of patients.

Variable	1990	1994	1998	2002	*P*
Creatinine (mg/dl)	1.63 ± 0.76	1.64 ± 0.70	1.44 ± 0.52	1.38 ± 0.45	<0.001
Cholesterol (mg/dl)	232 ± 48	231± 43	219 ± 44	200 ± 36	<0.001
Proteinuria (g/day)	0.24 ± 0.68	0.31 ± 0.95	0.28 ± 0.72	0.26 ± 0.73	ns
SBP (mmHg)	139 ± 18	137 ± 16	134 ± 18	131 ± 16	<0.001
DBP (mmHg)	84 ± 10	83 ± 10	80 ± 11	77 ± 11	<0.001
MAP (mmHg)	102 ± 11	101 ± 11	98 ± 12	95 ± 11	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Table 3. Percentage of patients receiving different treatments at 1-year in the four cohorts.

Variable	1990	1994	1998	2002	*P*
Statins (%)	5.0	19.7	35.9	33.9	<0.001
ACEI (%)	6.3	12.1	24.2	32.0	<0.001
≥2 drugs for HT	47.7	39.0	51.2	55.6	0.043
Treatment NODAT (%)	7.7	5.8	10.3	10.4	ns

ACEI, angiotensin converting enzyme inhibitors; HT, arterial hypertension; NODAT, new-onset diabetes mellitus after transplantation.

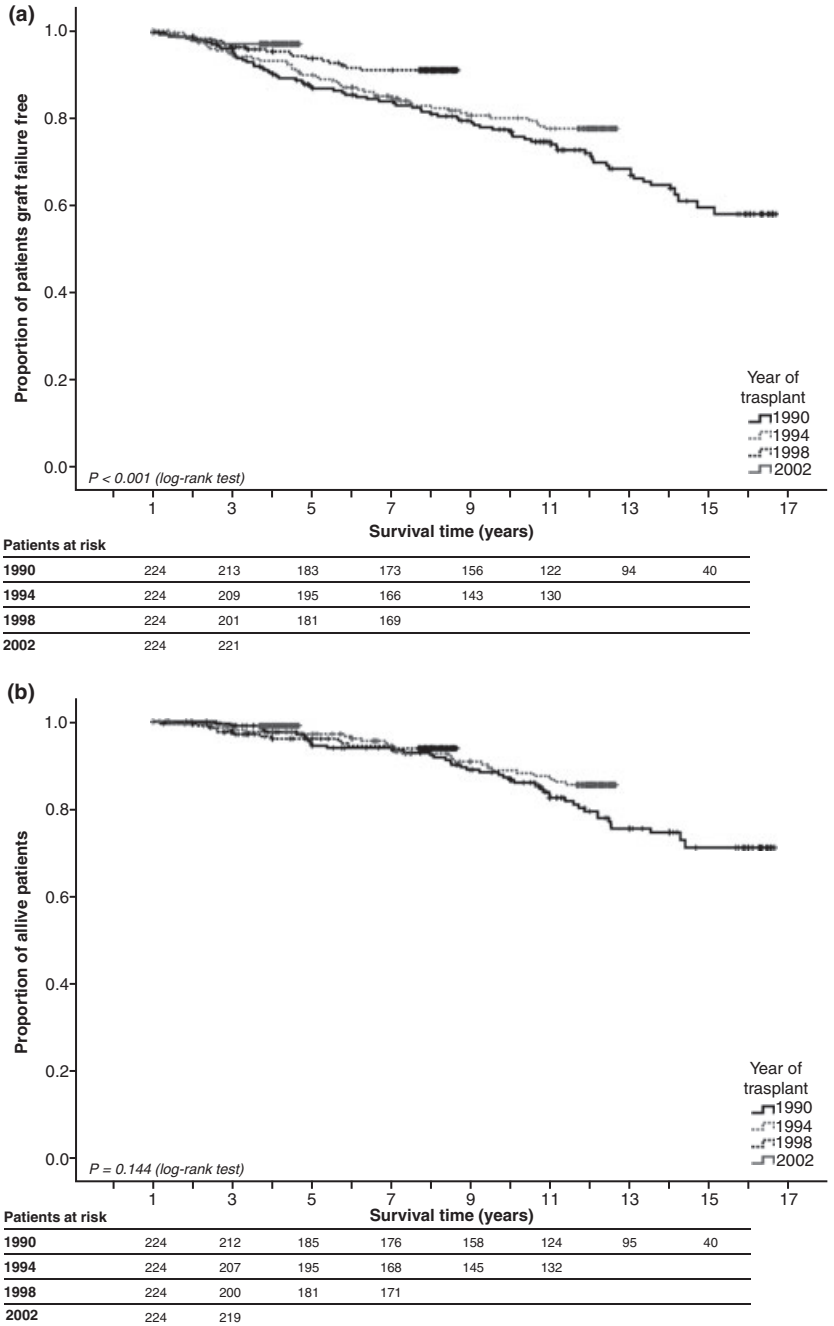

Figure 2 Death-censored graft survival (a) and patient survival (b) in the four cohorts of patients.

Table 4. Multivariate Cox regression analysis for death-censored graft survival.

Variable	Beta	Standard error	*P*-value	Relative risk	95% confidence interval	
Virus hepatitis C positive	0.790	0.309	0.010	2.203	1.203	4.035
Donor age >60 years	0.650	0.283	0.021	1.916	1.101	3.334
Acute rejection	0.680	0.179	<0.001	1.974	1.391	2.801
Serum creatinine at 3 months (mg/dl)	0.811	0.113	<0.001	2.250	1.804	2.806
Difference in serum creatinine between 3 months and 1 year (mg/dl)	0.949	0.104	<0.001	2.582	2.106	3.167
Proteinuria at 3 months (g/day)	0.326	0.108	0.003	1.385	1.121	1.712
Difference in proteinuria between 3 months and 1 year (g/day)	0.456	0.092	<0.001	1.578	1.317	1.892

characteristics. However, our approach has also some limitations. It implies a reduction in the available number of studied patients and consequently, a reduction in the statistical power. Moreover, in the present study, the matching procedure implied the selection of low immunological risk young recipients receiving kidneys from relatively young donors. Thus, we selected a population of transplants that better represents the standard recipient of 1990 than that of 2002. Nevertheless, our data suggest that the introduction of new immunosuppressive drugs between 1990 and 2002 implied a real improvement in graft survival beyond the first year. This improvement may be just the consequence of decreasing the incidence of acute rejection and better preserving renal function at 1 year. The introduction of MMF in the 1998 and 2002 cohorts may have also contributed to the improvement in late graft outcome independently of reduction in acute rejection rate. In this sense, it has been described that the attrition rate after the first year was lower in patients receiving MMF than in azathioprine treated patients [10]. Additionally, prevention of nephrotoxicity might have also contributed to this improvement but, unfortunately, our data do not allow to properly address this point. Nearly all patients received an anti-calcineurinic regimen and consequently, in the present study, there are no data suggesting that during this period, policies aimed to prevent nephrotoxicity such as conversion to less nephrotoxic immunosuppressive regimens have been actively employed [11]. Despite CsA and tacrolimus levels at different time point were not available, our data do not suggest that prevention of nephrotoxicity might significantly contribute to explain the improvement in late allograft survival.

Our data do not allow exploring the strength of the association between the use of new immunosuppressants, decreased incidence of acute rejection and amelioration of graft survival after the first year in different subsets of patients, such as transplants performed with old donors and/or old recipients.

During the study period, cold ischaemia time was shortened from 21 to 18 h, but the reduction in the prevalence of delayed graft function did not reach statistical significance. However, this reduction of cold ischaemia time may have also contributed to a superior long-term outcome. In this sense, it has been described of a 20% risk reduction in late graft failure for every 5 h reduction of cold ischaemia time in renal transplants with donors younger than 50 years [12].

As expected, multivariate Cox regression analysis confirmed that acute rejection is an independent predictor of death-censored graft failure. We attempted to quantify the strength of this association in the four studied cohorts analysing separately the relative risk for each cohort. In the 1998 cohort, the relative risk for graft failure associated with acute rejection was three times higher than in the 1990 and 1994 cohorts. Unfortunately, in the 2002 cohort, there were few graft failures to analyse this point properly. A possible explanation for this observation is that new immunosuppressive treatments have allowed preventing mild, but not severe, rejection episodes. Unfortunately, in our database, there are no data on renal function before and after acute rejection to address this point properly.

Patient survival did not improve in these cohorts of patients despite significant efforts to control classic cardiovascular risk factors better. A more active attitude towards hypertension control is reflected by an increased use of ACEI/ARBII leading to a better blood pressure control in the more recent cohorts [13]. One-year total serum cholesterol was also significantly reduced in 2002 because of more frequent use of statins during the first year [14]. Furthermore, renal function, a major risk factor for cardiovascular events and patient survival, was significantly ameliorated [15]. However, the lack of improvement in patient survival in the present study could be explained by the selection of young recipients receiving kidneys from young donors, a population with very low mortality. For example, in the 2002 cohort, only two patients died during follow-up.

In summary, our data show that renal allograft survival has improved between 1990 and 2002 after the first year when donors and recipients of similar characteristics were compared. Consequently, the lack of improvement in graft survival after the first year in epidemiological studies evaluating the evolution of late graft failure during the last two decades is mainly the consequence of the modification of donor and recipient characteristics that counterbalance the beneficial effect of new immunosuppressants.

Authorship

FM and DS: participated in the research design, performance of the research, data analysis and writing of the paper. AA, MAG, MG-M, LC, RM and JP: participated in the research design and performance of the research.

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