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Effect of the immunosuppressive treatment on long-term renal graft survival

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Abstract

Background. Although new immunosuppressive agents have improved the results of renal transplants (RTs), long-term graft loss remains high. We evaluated the impact of different immunosuppressive regimens on patient and graft survival.

Methods. Data from 3365 patients receiving cadaver RTs in Spain during the years 1990, 1994 and 1998 were retrospectively analysed. All data were entered into a specially designed database. Graft and patient survival rates were estimated by the Cox regression method and results expressed as percentage survival. A maximum-likelihood estimate of the projected graft half-life (median value) was calculated by Weibull regression.

Results. In 1990 graft and patient survival differed significantly from the other treatment years ($P = 0.0006$ and $P = 0.0101$, respectively). The risk of graft loss was significantly higher for cyclosporine (CsA), prednisone (P) and azathioprine (Az) than for CsA + P, which in turn was higher than for CsA + P plus polyclonal antibodies [antilymphocyte globulin (ALG)/antithymocyte globulin (ATG)]. Risk of patient death was also significantly higher for CsA + P + Az than for CsA + P. No significant differences between treatment groups were found in graft and patient survival for 1994 and 1998. The projected median graft life for patients with the most used immunosuppressive regimen for each year was 12.9 years for CsA + P + Az and 15.6 years for CsA + P plus mycophenolate mofetil (MMF).

Conclusions. Triple therapy with Az in 1990 and 1994 and with MMF in 1998 were the most frequently used immunosuppressive regimens in the Spanish kidney transplant population. The best results were seen after induction therapy with polyclonal antibodies.

Keywords: azathioprine; cyclosporine; graft and patient survival; mycophenolate mofetil; polyclonal antibodies

Introduction

At the beginning of the 1990s the most common immunosuppressive regimen was the combination of cyclosporine (CsA), azathioprine (Az) and prednisone (P) [1]. The three drugs were thought to complement each other in the prevention of acute rejection (AR). Later, mycophenolate mofetil (MMF) was introduced and various European [9], tricontinental [3] and US [4] studies of MMF showed that associated with CsA plus P, it significantly reduced the number of AR episodes and increased graft survival, independently of its effect on AR [5]. Another study comparing 3 year graft survival in two groups of patients with a primary renal transplant (RT) receiving MMF or Az associated with CsA plus P showed significantly greater graft survival in the MMF group [6].

After the introduction of tacrolimus (TaC) as a basic immunosuppressive agent, a debate started regarding the importance of one or other of the anticalcineurinic drugs, based on results of CsA monitoring, incidence of AR, renal function obtained and especially on the resultant adverse effects of the different agents and their impact on long-term results after RT. These immunosuppressive agents, however, are nephrotoxic, and the aim has been to find drugs with at least the same immunosuppressive efficacy but without the nephrotoxic effects. Such is the case of sirolimus (SRL), which was initially used in combination with CsA although it is now known that renal function improves after

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stopping the CsA, with no significant increase in risk of AR. Positive results have also been reported with SRL as a basic immunosuppressive treatment combined with MMF in kidney transplant patients [7].

Other questions concern the indications for induction therapy with polyclonal antibodies [antilymphocyte globulin (ALG) and antithymocyte globulin (ATG)] or monoclonal anti-CD3 (OKT3) or anti-interleukin 2 receptor (anti-IL-2R) antibodies: basiliximab and daclizumab. Induction therapy with polyclonal antibodies increased during the 1990s, especially after 1999 with Thymoglobulin. The monoclonal antibody OKT3 was the most frequently used in the 1990s, but today it has almost disappeared from use in induction therapy, being replaced by anti-IL-2R antibodies [8].

This study includes an important number of Spanish patients receiving cadaver kidney transplants under diverse regimens of immunosuppression during the 1990s and analyses the treatments used and their results.

Subjects and methods

Data were retrospectively analysed from 3365 patients with cadaver RTs in Spain during the years 1990, 1994 and 1998. According to data from the Spanish National Transplant Organization, a total of 4869 patients received a kidney transplant in Spain during these years. Thus, the following were excluded from the study: 255 patients younger than 18 years of age, 374 patients from hospitals who refused to participate in the study, 671 patients who lost their graft during the first post-transplant year (the analysis was started from the end of the first post-transplant year as the main aim of this study was to study CAN), and 204 patients for whom sufficient follow-up data were not available. Some immunosuppressive treatment groups were not included in survival analyses because too few cases were available. Thus, the resulting total numbers of patients included in the final analysis according to year and group of immunosuppression were 725 in 1990, 995 in 1994 and 1356 in 1998.

We analysed the immunosuppressive regimens used during the above-mentioned years together with their results. Variables studied included AR rate, suppression of P or Az, addition of MMF, change of anticalcineurin agent, time after modification of immunosuppressive therapy, patient and graft survival, risk of graft loss or patient death and estimated graft half-life.

Because no further follow-up data were available, analyses of graft and patient survival were restricted to 6.5 years for subjects transplanted in 1994 and 2.5 years for patients transplanted in 1998.

Clinical AR was defined as confirmed or suspected AR in patients who received anti-rejection therapy.

Statistical analyses

All the data were entered into a specially designed database. The results are expressed as the mean ± standard deviation (SD) unless otherwise indicated and a $P < 0.05$ was considered as statistically significant. Continuous variables were compared using Kruskall–Wallis tests and categorical variables were compared by using the chi-square test.

Graft and patient survival rates were estimated by simple and multiple Cox proportional hazards regression and results expressed as percentage survival. Additional analysis of graft survival was done after censoring data on patients who died with a functioning graft.

Maximum-likelihood estimates of the projected graft half-life (median value), before and after censoring for deaths with a functioning graft, was calculated by means of Weibull regression.

Results

Immunosuppressive treatment

The changes made in the immunosuppressive treatments for years 1990, 1994 and 1998, were as follows: in patients transplanted in 1990, Az was discontinued 3.2 ± 3.2 years and P 6.0 ± 3.0 years post-transplant. MMF was added after 8.2 ± 1.4 years and CsA replaced by TaC after 8.9 ± 1.0 years. These times of modification in treatment did not differ significantly between groups.

For patients transplanted in 1994, Az was stopped 2.0 ± 1.9 years, P 4.1 ± 1.7 years and MMF added 4.0 ± 1.3 years post-transplant. CsA was changed to TaC after 4.8 ± 1.3 years. The percentage of subjects discontinuing Az was significantly higher for those receiving CsA + P + Az ($P < 0.0001$), while the time to addition of MMF was significantly lower for those receiving CsA + P and polyclonal antibodies ($P = 0.0005$). No other significant differences between treatment groups were observed.

For patients transplanted in 1998, Az was stopped 1.4 ± 1.1 years, and P 2.0 ± 0.8 years while MMF was added 0.6 ± 0.5 years post-transplant. CsA was changed to TaC after 0.9 ± 0.7 years. The percentage of patients discontinuing P and changing from CsA to TaC was significantly higher for those treated with CsA + P + MMF ($P < 0.0001$) than for the other treatment groups. The proportion of patients incorporating MMF was significantly higher among subjects receiving CsA + P ($P < 0.0001$). No other significant differences were observed.

Acute rejection

The incidence of AR was similar in 1990 and 1994 (37.2 and 38.4%, respectively, P = NS) and significantly lower in 1998 (24.1%, $P < 0.001$).

Cytotoxic antibodies

In 1990, 1994 and 1998 the percentage of patients with levels of cytotoxic antibodies above 15% were 11, 7.3 and 10.7%, respectively. In 1990 there were no differences between the groups of immunosuppression, but in 1994 and 1998 those patients receiving induction therapy with OKT3 had significantly higher levels

of cytotoxic antibodies ($P = 0.02$ and $P = 0.0001$, respectively).

Donor and recipient age

The ages of the donors in 1990, 1994 and 1998 were 32.5 ± 14.6, 40.7 ± 15.8 and 43.7 ± 16.9 years and that of the recipients were 42.9 ± 12.2, 44.8 ± 12.7 and 47.1 ± 13.1 years, respectively. In 1990, the only difference between treatment groups was in the age of the recipient, being significantly higher for the group receiving CsA + Az + P ($P = 0.0015$). However, in 1994 the treatment groups differed significantly in donor and recipient age in the groups receiving CsA + Az + P ($P = 0.0048$) and CsA + Az + P + ALG/ATG ($P = 0.021$). There were also significant differences in age of both donor and recipient in 1998 for the groups receiving OKT3 ($P = 0.005$) and CsA + Az + P ($P < 0.0001$).

Graft and patient survival

Figures 1–3 show graft survival. Immunosuppressive therapy had the greatest impact on graft and patient survival in 1990 ($P = 0.0006$ and $P = 0.01$, respectively).

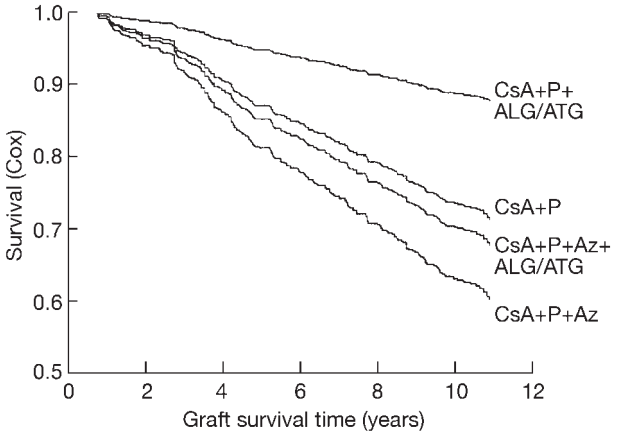

Fig. 1. Graft survival for patients transplanted in 1990.

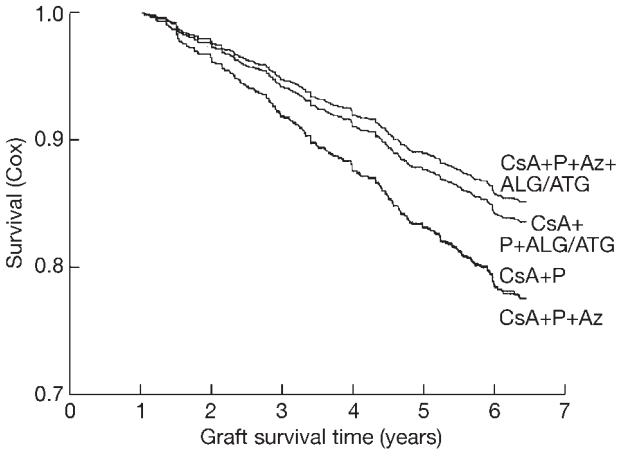

Fig. 2. Graft survival for patients transplanted in 1994.

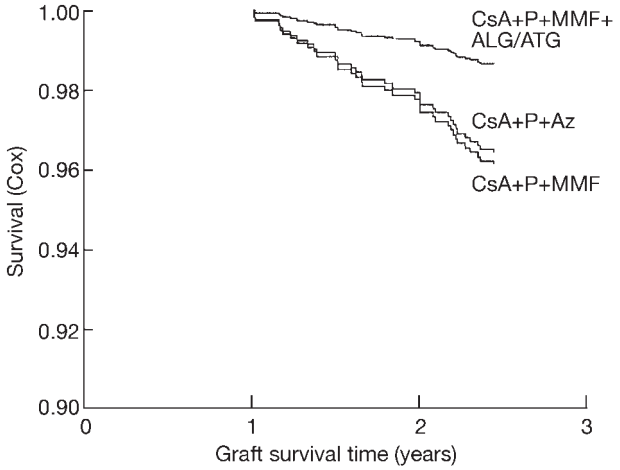

Fig. 3. Graft survival for patients transplanted in 1998

The relative risk of graft loss and patient death was higher for those treated with triple therapy with Az (RR 1.49, 95% CI 1.07–2.07, $P = 0.01$ and RR 1.89, 95% CI 1.17–3.07, $P = 0.01$, respectively) and lower for those treated with CsA + P + ALG/ATG (RR 0.39, 95% CI 0.18–0.82, $P = 0.01$ and RR 0.66, 95% CI 0.26–1.63, $P = 0.3$, respectively). In 1994 and 1998, no significant differences between treatment groups were found in graft or patient survival.

The estimated graft half-life in patients treated with CsA + P + ALG/ATG was 36.0, 15.3 and 21.1 years for 1990, 1994 and 1998, respectively, and for the group that also received Az it was 16.8, 15.7, 8.6 years, respectively. In patients receiving the most frequently used immunosuppressive treatment at the time (CsA + P + Az in 1990 and 1994 and CsA + P + MMF in 1998) the estimated graft half-life was 12.9, 12.9 and 15.6 years, respectively. After taking into account the cause of death and donor age as well as the immunosuppressive treatment, the estimated graft half-life increased when the donor was younger than 60 years of age and death was due to cranioencephalic trauma, especially in those groups receiving polyclonal antibody therapy and no Az (46.9, 18.1 and 23.9 years, respectively).

Calculation of the overall estimated graft half-life for 1990, 1994 and 1998, without separating the groups according to immunosuppression regimen, showed significant differences in both non-censored deaths (14.7, 13.68 and 18.71 years, $P = 0.0031$) and censored deaths with a functioning graft (15.43, 13.51 and 17.72 years, $P = 0.0071$).

Discussion

During 1990, 1994 and 1998 the main immunosuppressive agent of choice in Spain was CsA. Its introduction in the 1980s led to a reduction in the number of episodes of AR and short-term improvement after RT. However, despite this, the rate of AR at the beginning of the 1990s was still as high as 40–60% [9].

The most common immunosuppressive regimen in 1990 and 1994 in Spain was the combination of CsA + Az + P. Data from the Collaborative Transplant Study (CTS) show that during these years this was the most universally accepted regimen, although it did not provide the best results in terms of graft survival, even after adjusting for the fact that this group included patients with the highest immunological risk [1]. Our study confirms that patients treated with triple therapy with Az had the lowest rates of graft survival and the highest rates of patient mortality. This lends support to those transplant groups that decided to suppress Az in most cases, although this withdrawal was rather late.

In 1998 there was a significant increase in estimated graft half-life and a significant reduction in episodes of AR. Severe, recurrent and late AR is the greatest risk factor for CAN, and thus for graft loss [8]. In this year, 45.4% of patients received an immunosuppressive regimen consisting of CsA + P + MMF. A retrospective study [5] showed that MMF reduces the relative risk of chronic renal failure by 27%, independently of its effect on AR, and data from the Spanish Cooperative Study Group of CAN showed a protective effect of MMF on renal function in established CAN [10]. These data support the concept that MMF can modify the course of CAN.

The patients in our study having the best-estimated graft half-life were those treated with induction therapy with polyclonal antibodies. Published data show that this induction therapy increased during the 1990s, although this increase was not significant [9]. The number of Spanish patients who received this therapy was small, especially in 1990 (22.8%) and 1998 (17.6%), although there was an increase in 1994 (34%). At these times results of immunosuppressive regimens with polyclonal antibody induction were already significantly better than those obtained in other groups of immunosuppression. Our results confirm these data and, more particularly, patients with the greatest estimated graft half-life were those treated with polyclonal antibody induction that received their organs from donors younger than 60 years of age dying of cerebral trauma.

During this time the monoclonal antibody available was OKT3, which was used in percentages as low as 5.6, 9.8 and 4.7% of patients in the three study years, respectively. The effect of TaC on graft and patient survival could not be evaluated due to the small number of patients treated with this calcineurin inhibitor.

All the patients received steroids. At this time, CTS data showed greater graft survival in patients in whom P was discontinued, with no greater long-term deterioration in renal function compared with patients who continued P, but provided adequate doses of CsA were given [1]. However, P was suppressed in very few patients (11.3–15%), although this was similar to CTS data (10%). The tendency was for withdrawal to take place progressively earlier (mean 6, 4 and 2 years for 1990, 1994 and 1998, respectively), although this was still late. It should be recalled that if suppression of P is not done early enough there is no benefit regarding most of the side effects. Once these side effects start they do not usually disappear. Early withdrawal of steroids during these years only took place in 10% of patients. It was successful in 79% when suppression was made at least 6 months after transplant in patients without AR and with good renal function [11], i.e. in selected cases.

The worst results in terms of both patient and graft survival were seen in the groups having Az in their regimen of immunosuppression, more especially the combination of CsA + Az + P, in fact the most common regimen in 1990 and 1994.

There was also a progressive, although moderate tendency during these years for CsA to be replaced by TaC, from 8.9% of patients in 1990 to 16% in 1998, whereas TaC was replaced by CsA in just 0.1% of patients. CsA was only withdrawn after 1998, in 16% of patients, and although the reason was not analysed in this study, it was probably in patients with worsening kidney function due to CsA toxicity [12].

In conclusion, this study shows the evolution of immunosuppressive therapy in Spanish kidney transplant patients during the 1990s and its effect on graft and patient survival. There was a remarkable improvement in the estimated graft half-life and a reduction in AR episodes in 1998. There was a positive influence of induction therapy with polyclonal antibodies and a negative influence if patients received triple therapy with Az.

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Conflict of interest statement. None declared.

References

1. Opelz G. Effect of the maintenance immunosuppressive drug regimen on kidney transplant outcome. *Transplantation* 1994; 58: 443–446
2. European Mycophenolate Mofetil Cooperative Study Group. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; 345: 1321–1324
3. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; 61: 1029–1037
4. US Renal Transplant Mycophenolate Mofetil Study Group. Mycophenolate mofetil in cadaveric renal transplantation. *Am J Kidney Dis* 1999; 34: 296–303
5. Ojo AO, Meier-Kriesche HU, Hanson JA *et al.* Mycophenolate mofetil reduces late renal allograft loss independent of acute rejection. *Transplantation* 2000; 69: 2405–2409
6. Matthew TH for the Tricontinental Mycophenolate Mofetil Renal Transplant Study Group. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation—results at three years. *Transplantation* 1998; 65: 1450–1454

7. Flechner S, Goldfarb D, Modlin CH *et al*. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. *Transplantation* 2002; 74: 1070–1076
8. Pascual M, Theruvath T, Kawai T *et al*. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med* 2002; 346: 580–590
9. Helderman JH, Bennett WM, Cibrik DM *et al*. Immunosuppression: practice and trends. *Am J Transplant* 2003; 3: 41–52
10. Gonzalez Molina M, Seron D, Garcia del Moral R *et al*. Treatment of chronic allograft nephropathy with mycophenolate mofetil after kidney transplantation. A Spanish multicenter study. *Transplant Proc* 2002; 34: 333–336
11. Hricik DE, Whalen CC, Lautman J *et al*. Withdrawal of steroids after renal transplantation – clinical predictors of outcome. *Transplantation* 1992; 53: 41–45
12. Ducloux D, Fournier V, Bresson-Vautrin *et al*. Mycophenolate mofetil in renal transplant recipients with cyclosporine-associated nephrotoxicity. *Transplantation* 1998; 65: 1504–1056