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How to cite

MARCÉN, R et al. Evolution of rejection rates and kidney graft survival: a historical analysis. In: Transplantation proceedings, 2009, vol. 41, n° 6, p. 2357–2359. doi: 10.1016/j.transproceed.2009.06.049

This publication URL: https://archive-ouverte.unige.ch/unige:90693
Publication DOI: 10.1016/j.transproceed.2009.06.049

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OUTCOMES

Evolution of Rejection Rates and Kidney Graft Survival: A Historical Analysis

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ABSTRACT

Introduction. New immunosuppressive regimens have dramatically reduced rejection rates but this positive effect has not been followed by an improvement in long-term graft outcomes. The aim of the present work was to investigate the incidence of graft rejection and graft outcomes with various immunosuppressive protocols.

Patients and Methods. Included in our study were 1029 first renal transplantations performed at our unit between November 1979 and December 2007. Basal immunosuppression included azathioprine (AZA) in 198 recipients, cyclosporine (CsA) in 524 recipients, and tacrolimus (TAC) in 307 recipients.

Results. Recipient and donor ages increased progressively from the AZA to the TAC era. Delayed graft function was less frequent among AZA than CsA and TAC recipients (29.8 vs 39.3% vs 42.0%; $P = .014$). The incidence of acute rejection episodes was 68.7% on AZA, 38.2% on CsA, and 11.4% on TAC ($P = .000$). Graft survival rates at 1, 5, and 10 years were 69%, 56%, and 46% on AZA, 82%, 69%, and 54% on CsA, and 88%, 77%, and 60% on TAC, respectively ($P = .001$). However, the differences disappeared when only grafts surviving >12 months were analyzed. On multivariate analysis, the variables associated with worse graft outcomes after 12 months were older recipient age, male gender, longer time on dialysis, lower body weight, and higher serum creatinine level at 6 months.

Conclusions. New immunosuppressants have decreased the incidence of acute rejection. But this was not followed by a significant improvement in graft outcomes after 12 months. The beneficial effects on rejection are possibly affected by the older age of donor and recipient and the worse early graft function.

RENAL transplantation constitutes the best treatment for renal failure. The standardization of transplant recipient selection, improvements in the care of posttransplantation complications, and new immunosuppressants have increased early graft survival,[1] but the long-term results remain unchanged. One of the most important positive effects of the new immunosuppressive drugs has

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0041-1345/09/$–see front matter
doi:10.1016/j.transproceed.2009.06.049

been the dramatic reduction in the incidence of acute rejection episodes and the most intriguing lack of improvement in long-term graft survival.[2] In a previous article, we observed that patients followed up for 10 years did not show improved graft survival following the introduction of cyclosporine (CsA) when compared with azathioprine (AZA) despite a considerable reduction in the acute rejection rate.[3] Since then new immunosuppressants, such as sirolimus, mycophenolate mofetil, and tacrolimus (TAC), have further decreased acute rejection rates. The purpose of the present study was to examine the historical evolution of the incidence of acute rejection episodes and graft outcomes in our population of first renal transplant recipients, according to the therapeutic regimen.

PATIENTS AND METHODS

All 1029 first kidney transplantations performed at our unit from November 1979 to December 2007 were included in the study. There were 645 men and 384 women with mean ages at the time of transplantation to be 44.6 ± 14.9 years. The follow-up was at least 6 months (mean, 94.4 ± 84.2 months). Recipient, donor, and transplant data were systematically collected from the beginning of our transplantation activity. Recipient data included: age, gender, primary renal disease, time on dialysis, and type of dialysis. Donor data included: age, gender, cause of death, as well as warm and cold ischemia times. Transplant data included: HLA matching, anastomosis time, and characteristics of the surgical procedure. Recipients were followed until graft failure, death, or August 31, 2008, whichever occurred first. During the follow-up period, we classified 3 groups of recipients according to their basal immunosuppression. The first was formed by 198 recipients (19.2%) who received AZA and prednisone (AZA group); the second consisted of 524 recipients (50.9%) who received CsA (solution or new formulation) with prednisone alone or combined with other immunosuppressants, such as AZA, mycophenolate mofetil, sodium mycophenolic acid, or everolimus (CsA group), the third consisted of 307 recipients (29.8%) who were treated with TAC in combination with prednisone or, as in the case of CsA, with other immunosuppressants (TAC group).

Data are expressed as mean values ± standard deviations, for continuous variables and percentages (%) for qualitative variables. Comparisons among groups were performed using the analysis of variance test (ANOVA). Graft survival was calculated by the Kaplan-Meier actuarial method, with comparisons between groups performed using the log-rank test. To determine the variables associated with graft survival we used a Cox hazard analysis. A P value of $<.05$ was considered significant.

RESULTS

The characteristics of recipients, donors, and graft function for each immunosuppressive regimen are shown in Table 1. There was a progressive increase in recipient and donor ages and decreases in HLA compatibility and in length of time on dialysis among recipients on TAC. Delayed graft function incidence was lower in the AZA than the other 2 groups. Acute rejection incidence decreased from 70% in the AZA group to 38.2% in the CsA group and 11.4% in the TAC group ($P = .000$). Graft losses due to acute rejection were more common in the AZA than in the other 2 groups: 12.1% on AZA; 5.5% on CsA; and 1.4% on TAC ($P = .000$). Graft survival rates at 1, 5, and 10 years were 69%, 56%, and 46% in the AZA group; 82%, 69%, and 54% in the CsA group and 88%, 77%, and 60% in the TAC group, respectively ($P = .014$). However, the differences disappeared when we analyzed only grafts surviving more than 12 months. Graft survival rates at 5 versus 10 years were 84% versus 67% in the AZA group; 84% versus 66% in the CsA group; and 88% versus 70% in the TAC group, respectively ($P = .484$). However, treatment with TAC seemed to improve graft survival among recipients younger than 50 years graft survival rates at 5 and 10 years were 57% and 48% on AZA; 72% and 55% on CsA; and 82% and 72% on TAC, respectively ($P = .000$). These differences were less prominent when we analyzed grafts surviving more than 1 year ($P = .058$). Moreover, there were no differences in graft survival after 1 year between treatment with TAC versus the new formulation of CsA, namely, at 5 years the outcomes were 88% vs 87% ($P = .661$). Upon Cox analysis the variables associated with graft survival were female recipient (hazard rate [HR] = 0.81; 95% confidence

Table 1. Characteristics of Patients and Immunosuppression

	AZA	CsA	TAC	*P*
No.	198	524	307	
Age of recipient (y)	36.4 ± 11.5	43.7 ± 14.8†	50.7 ± 15.0†§	.000
Gender (male/female)	127/71	323/201	196/111	.743
Time on dialysis (mo)	34.6 ± 25.0	33.6 ± 33.9	27.4 ± 28.3†§	.007
Age of donor (y)	29.0 ± 14.7	37.7 ± 12.3†	47.5 ± 16.6†§	.000
HLA mismatches	2.5 ± 1.2	3.5 ± 1.3†	4.3 ± 1.1†§	.000
Delayed graft function (no/yes)	139/59	317/207	178/129	.014
Early acute rejection (no/yes)	62/136	324/200	272/35	.000
Serum creatinine at 6 mo (mg/dL)	1.4 ± 0.5	1.7 ± 0.8†	1.6 ± 0.7*	.000
Serum creatinine at 60 mo (mg/dL)	1.4 ± .7	1.7 ± 0.7†	1.7 ± 0.7†	.001
Graft loss by acute rejection	24	29†	4‡§	.000
Graft loss by technical vascular complications	11	35	15	.555

*$P < .05$ vs AZA.
†$P < .01$ vs AZA.
‡$P < .001$ vs AZA.
§$P < .01$ vs CsA.

interval [CI] 0.83–0.69; $P = .046$), donor age in years (HR = 1.01; 95% CI 1.00–1.02; $P = .001$), time on dialysis (HR = 1.03; 95% CI 1.00–1.07; $P = .033$), delayed graft function (HR = 1.26; 95% CI 1.05–1.50; $P = .014$), occurrence of an acute rejection episode (HR = 1.23; 95% CI 1.02–1.44; $P = .032$), and TAC immunosuppression (HR = 0.66; 95% CI 0.50–0.86; $P = .002$). When only grafts functioning more then 12 months were analyzed, the significant variables included in the model were age at transplantation (HR = 1.01; 95% CI 1.01–1.02; $P = .002$), female gender (HR = 0.66; 95% CI 0.41–0.87; $P = .002$), time on dialysis (HR = 1.04; 95% CI 1.00–1.08; $P = .041$), body weight at transplantation (HR = 0.98; 95% CI 0.97–0.99; $P = .003$), and serum creatinine level at 6 months (HR = 1.65; 95% CI 1.38–1.98; $P = .000$).

DISCUSSION

Our results reconfirmed that the new protocols of immunosuppression have improved short-term graft survival, but the differences disappeared when we analyzed grafts surviving beyond the first year. The effects of new immunosuppressants on graft survival are controversial. When analyzing 1-year graft survival rates and half-lives for kidney grafts, Hariharam et al[4] concluded that from 1988 to 1996 there was a substantial improvement in short-term and long-term survival of kidney grafts. In a previous work, we observed that immunosuppression with CsA resulted in better short-time patient and graft survival that was not maintained in the long-term, despite a dramatic reduction in the incidence of acute rejection episodes.[3] These findings were confirmed in other studies in which decreased acute rejection rates did not tend to increase long-term graft success.[2] An acute rejection episode has been considered one of the strongest negative prognostic factors; consequently a reduction in its rate should improve graft survival.[5] It has been hypothesized that the explanation for the discrepancies between a reduced rejection rate and the lack of an improved outcome could be due to the persistence of rejection episodes with the most functional impact or to the differences in donor and recipient characteristics that can affect graft survival.[2] We have observed progressive increases in recipient and donor ages and in the incidence of delayed graft function, and decreases in the incidence of acute rejection episodes and in the percentage of graft losses therefrom and worse graft function among patients on CsA or TAC. The multivariate analysis suggested that the negative impact of donor and recipient ages, increased incidence of delayed function, and higher serum creatinine values could be markers of the quality of the donor and of the nephrotoxicity of anticalcineurin drugs that may offset the beneficial effects of the reduced incidence of acute rejection episodes. Nevertheless, the new immunosuppressive regimens can improve graft outcomes when they are administered to selected populations. Immunosuppression with TAC has increased graft survival after the first year, obtaining differences almost at statistical significance for recipients younger than 50 years of age in whom we avoided some detrimental factors.

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