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The relative influence of delayed graft function and acute rejection on renal transplant survival

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Abstract Three hundred and eight cadaveric renal transplants were analysed to establish the effects of acute rejection in the first 90 days and delayed graft function (DGF) on graft outcome. There were 120 patients (39 %) with no DGF and no rejection (group 1), 101 patients (33 %) with rejection but no DGF (group 2), 41 patients (13 %) with DGF but no rejection (group 3) and 46 patients (15 %) with both rejection and DGF (group 4). The actuarial 4-year graft survival rates for groups 1,2,3 and 4 were 78.3 %, 65.4 %, 60.1 % and 40.4 %, respectively. The acute rejection rate was 101/221 (46 %) in patients with initial graft function compared with 46/87 (53 %) for those with DGF ($\chi^2 = 1.02$, $P = 0.31$). Cox stepwise logistic regression analysis demonstrated that DGF was a more powerful predictive factor for poor graft survival ($P = 0.001$) than acute rejection occurring in the first 90 days post-transplant ($P = 0.034$). Further efforts at improving graft outcome should concentrate on reducing the incidence of DGF.

Key words Delayed graft function, graft survival, kidney · Graft survival, kidney, delayed graft function · Kidney graft survival, delayed graft function

Introduction

Although it is clear that acute rejection has deleterious effects on renal allograft function and subsequent survival [6, 7, 10, 23], the influence of delayed graft function (DGF) in renal transplantation has been more controversial. Several studies have associated DGF with poorer patient [19] and graft [3–5, 8, 11, 17–19, 21, 22] survival rates; a smaller number of studies have found no such relationship [1, 13, 25, 26]. Many units, including our own, have established non-heart-beating donor programmes, and as these kidneys suffer more warm ischaemia than traditional cadaveric organs and hence have a higher incidence of DGF [27, 28], the influence of this factor on the outcome of renal transplantation assumes even more importance. It has been suggested that there is a relationship between delayed function and acute rejection [28], and the aim of this study was to determine the relative influence of DGF and acute allograft rejection on the outcome of cadaveric renal transplantation.

Patients and methods

A consecutive series of 319 patients receiving cadaveric renal transplants over a 7-year period between 1986 and 1992 were studied. Vascularised transplants that never achieved function (primary non-function, $n = 5$) were included in the analysis but grafts with early vascular thrombosis ($n = 11$, 3.4 %) were excluded, leaving 308 allografts in the study. Patients receiving kidneys from non-heart-beating donors were not studied.

All patients were immunosuppressed with cyclosporin as part of either dual therapy with steroids ($n = 263$) or triple therapy with steroids and azathioprine ($n = 45$). In the dual regimen cyclosporin was started at a dose of 17 mg/kg per day and reduced to a baseline of 5–7 mg/kg per day over a 6-week period. In the triple regimen cyclosporin was started at a dose of 10 mg/kg per day and reduced to a baseline of 4–5 mg/kg per day. Serum cyclosporin levels were measured by HPLC and doses were adjusted to main-

Table 1 Details of patients with initial (IF) and delayed graft function (DGF). Values represent mean (SEM)

	IF (n = 221)	DGF (n = 87)	P value IF vs DGF
Age (years)	41.5 (0.9)	46.0 (1.5)	0.015
Sex (M/F)	143:78	58:29	0.80
DR mismatch	0.71 (0.05)	0.80 (0.08)	0.15
HLA mismatch	2.92 (0.12)	2.79 (0.2)	0.57
Cold ischaemic time (min)	1135 (40)	1234 (82)	0.25
Peak PRA (%)	8.1 (1.4)	13.1 (3.6)	0.13
Current PRA (%)	5.0 (1.1)	8.3 (3)	0.20

Table 2 Relationship between delayed graft function (DGF) and rejection

	No Rejection	Rejection	Total
Initial function	120	101	221
Delayed function	41	46	87
Total	161	147	308

Chi-squared = 1.02, P = 0.31

Table 3 Effects of delayed graft function (DGF) and rejection (REJ) on graft survival rates

Patient group	Actuarial graft survival (%)			
	1 year	2 years	3 years	4 years
No DGF/No (n = 120)	97.5	91.8	89.8	78.3
No DGF/REJ (n = 101)	82.7	73.5	69.3	65.4
DGF/No REJ (n = 41)	73.1	63.2	60.1	60.1
DGF/REJ (n = 46)	54.8	42.3	40.4	40.4

tain levels in the range 100–300 ng/ml. Azathioprine was given at a dose of 1.5 mg/kg per day and adjusted according to white blood cell counts. The steroid protocol in all patients was prednisolone, 100 mg/day, reduced to 40 mg over the 1st week and then more gradually reduced to 10 mg on alternate days by 6 months post-transplant.

For the purposes of this study, early acute rejection was defined as cellular rejection occurring in the first 90 days post-transplant. Rejection was diagnosed using clinical and biochemical parameters including the response to anti-rejection therapy, but needle core biopsies were performed in all cases. In general, first rejection episodes were treated with high-dose pulses of intravenous steroids (0.5 g methylprednisolone daily for 3 days). Second and third rejections were treated either with a second course of steroids or with anti-T-cell preparations (OKT3 or ATG), according to the severity of the histological findings. DGF was defined as the need for dialysis in the first 7 days post-transplant with the specific exclusion of a single early post-operative dialysis performed for hyperkalaemia. Kidneys with delayed function were carefully monitored for rejection by performing needle core biopsies at weekly intervals until function was established.

For statistical analysis, discrete variables were compared using the chi-squared test with Yates' correction, and continuous variables were compared using the Mann-Whitney or Students' t-tests where appropriate. A multivariate analysis of factors affecting graft survival was carried out using Cox logistic regression analysis with a forward stepwise selection. The parameters entered into the model were: recipient age, sex, race, diabetes, transplant number, donor source, blood transfusion, donor age, peak and historical panel reactive antibody status, HLA matching, ischaemic times and, finally, acute rejection and delayed graft function. Kaplan-Meier survival curves were constructed and differences were compared using the log-rank statistic.

Results

Initial graft function occurred in 221 patients (72 %); the remaining 87 patients (28 %) had DGF. The details of patients in these two groups are shown in Table 1. One hundred and sixty-one patients (52 %) did not have any acute rejection in the first 90 post-operative days. Ninety-five patients (31 %) had a single early rejection episode, 40 (13 %) had two rejections and 12 patients (4 %) had three rejections documented in the first 90 days. The rate of biopsy proven acute cellular rejection was not significantly higher in patients with DGF (53 %) than in those with initial graft function (46 %; χ^2 = 1.02, P = 0.31; Table 2). Multivariate logistic regression analysis indicated that both acute rejection and DGF exerted a significant and independent effect on renal transplant survival. The regression coefficients (+ standard error) for acute rejection (1.013 + 0.478; P = 0.034) and DGF (1.537 + 0.432; P = 0.001) demonstrated that DGF was the more powerful influence. The influence of DR matching yielded a P value of 0.09; none of the other factors in the multiple regression model were found to be significantly related to subsequent graft survival.

There were 120 patients (39 %) with no DGF and no rejection (group 1), 101 patients (33 %) with rejection but no DGF (group 2), 41 patients (13 %) with DGF but no rejection (group 3) and 46 patients (15 %) with both rejection and DGF (group 4). Non-thrombotic primary non-function occurred in only two kidneys in group 3 and three kidneys in group 4. The effects of the various combinations of rejection and DGF on graft survival are shown in Fig. 1 and Table 3. Allografts with initial function and no early rejection had the best survival figures, but it is clear that the worst graft survival was noted in patients with DGF, whether or not this was associated with acute rejection. The actuarial 4-year graft survival rates for groups 1, 2, 3 and 4 were 78.3 %, 65.4 %, 60.1 % and 40.4 %, respectively. Although the

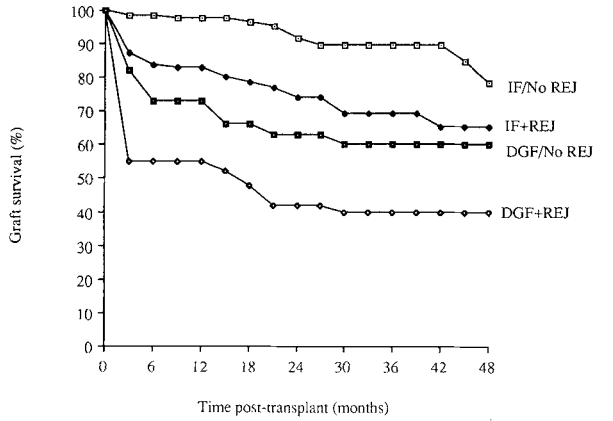

Fig. 1 Influence of delayed graft function (DGF) and acute rejection (REJ) on renal allograft survival (*IF* initial function)

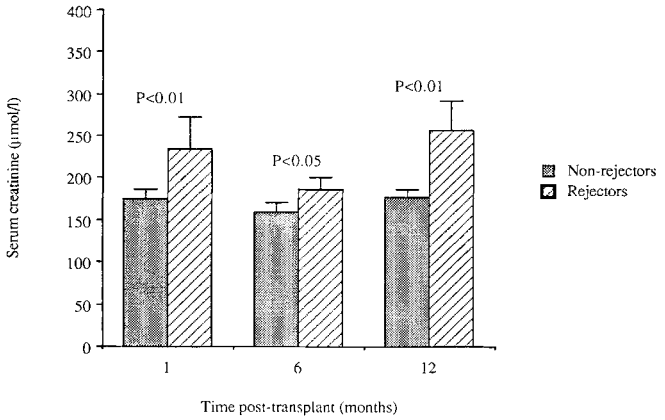

Fig. 2 Effects of acute rejection on renal function. Values represent mean + SEM

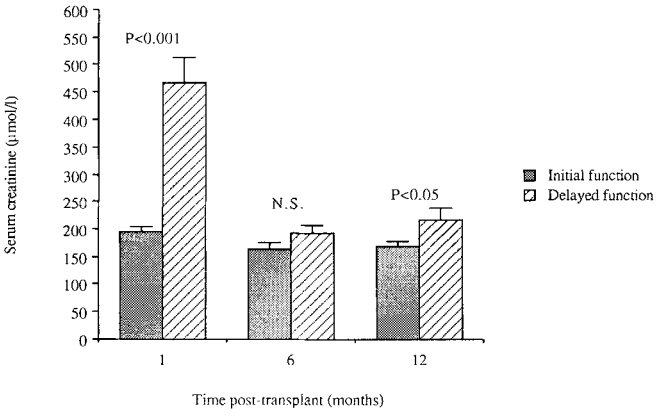

Fig. 3 Effect of delayed graft function on renal function. Values represent mean + SEM

differences in graft survival between these groups became apparent in the first 3 months after transplantation, DGF was associated with both early and long-term decreases in graft survival (Fig. 1).

One hundred and twenty-eight of the 263 patients (49 %) receiving dual therapy suffered 180 rejection episodes in comparison to 31 rejections in 19 of the 45 patients (42 %) on triple therapy. In the comparison of dual and triple therapy there were no statistically significant differences in the incidence ($\chi^2 = 0.41$, $P = 0.52$) or severity ($\chi^2 = 2.82$, $df = 2$, $P = 0.244$) of rejection. The histopathological gradings of severity in the 211 biopsies showing rejection were mild ($n = 39$), moderate ($n = 127$) and severe ($n = 45$).

The effect of acute rejection on subsequent renal function is shown in Fig. 2. Non-rejectors had a relatively stable creatinine in the 1st year; however, in patients with rejection, serum creatinine was high initially, recovered a little by 6 months and then significantly deteriorated by 12 months. A similar pattern was seen in patients with DGF (Fig. 3) who had a 12-month creatinine approximately 60 μmol/l higher than patients with initial function.

Discussion

It is clear that events occurring in the first few months post-transplant predict subsequent graft function and survival [9, 10, 15, 16]. In this study the graft survival curves relating to different combinations of rejection and DGF (Fig. 1) are relatively parallel after the 1st year, demonstrating that long-term survival is programmed early in the course of a transplant.

Our data not only confirm that DGF is associated with poorer long-term graft survival but also suggest that DGF is a more important risk factor than acute rejection. This finding may have important implications for national organ sharing programmes. It is clearly established from large multicentre studies that tissue matching at the HLA-B and -DR loci improves renal allograft survival [2, 20, 24]. In order to achieve good matching, kidneys must be transported between centres and this inevitably increases the cold ischaemic time and hence the incidence of DGF [11]. Although better HLA matching is likely to mean less early rejection [23], this is only secured at the expense of a higher incidence of DGF; our data suggest that this is not necessarily a good trade-off.

The reasons why DGF is such an important marker of poor long-term graft survival are not known at the present time. Patients with DGF are certainly more difficult to manage in the early post-transplant period than patients with good initial function. All patients in the present study were immunosuppressed with cyclosporin, and although the doses used were usually re-

duced in patients with DGF, it is likely that the nephrotoxic effects of cyclosporin were more marked in kidneys that had already sustained a degree of ischaemic damage sufficient enough to result in DGF.

Graft survival was progressively lower in patients with acute rejection, DGF and a combination of the two, and this suggests that poor graft survival results from a summation of nephrotoxic insults. The majority of late graft losses now occur as a result of the chronic rejection process leading to a progressive loss of functional nephrons. It is predictable that allografts with a lower number of functional nephrons after the important early weeks post-transplant are likely to have a shorter lifespan. The relationship between DGF and chronic rejection is not clear, but ischaemia is a prominent mechanism in both processes and there is some evidence of a relationship between the two [27].

Some workers have found higher rejection rates in DGF kidneys and have attributed poorer survival to this feature [1, 10–12, 19, 29]. The proposed underlying mechanism is thought to be an upregulation of adhesion molecules and HLA antigen expression as a consequence of pronounced ischaemia [28]. However, this issue is also controversial with other groups disputing such a relationship [3, 16]; our own findings are in agreement with the latter. Transplant biopsy rates tend to be higher in patients with DGF and this may lead to confusion as protocol biopsies have been noted to show a higher incidence of histological rejection than clinical rejection [14]. It is possible that in some studies rejection is being over-diagnosed in the DGF group. The opposing view has also been presented with the suggestion that undiagnosed rejection is being left untreated in patients with DGF [29]. We do not believe that this criticism can be levelled at the present study as all patients with DGF were biopsied on a weekly basis until recovery of function. The issue of rejection rates in DGF is crucial. In this study, where DGF was not associated with a higher incidence of rejection, DGF per se has been shown to be a predictor of allograft survival. Contrary to this finding, a recent large multivariate analysis of primary cadaveric renal transplants demonstrated that DGF was associated with a high incidence of rejection and, in this situation, DGF per se was not associated with decreased graft survival when adjusting for rejection [29]. The biopsy policy in the latter study was virtually identical to our own and the differences described may come down to the histological interpretation of the lymphocytic infiltrate in kidney transplants with DGF.

In our unit we have noticed an increase in the rate of DGF in cadaveric kidneys over the last 4 years (unpublished data) and have attributed this to increasing donor age and cold ischaemic times. Recipient age was also higher in the DGF group in this study and this may be a relevant factor. In response to falling transplant numbers, we have also recently started a non-heart-beating donor programme and the incidence of DGF in these kidneys has been 100 % with a mean post-transplant dialysis time of 3 weeks [27]. In view of the findings presented here there is some concern that although we have successfully reversed the fall in transplant numbers by introducing non-heart-beating donation, this will eventually lead to poorer long-term graft survival figures.

This study has demonstrated that rejection and DGF are both associated with poorer long-term renal allograft survival, with the worst results in patients with a combination of the two. Multivariate analysis suggests that DGF exerts the single most important deleterious influence on graft survival. Modern immunosuppressive drugs have dramatically improved the results of renal transplantation and further efforts at improving graft outcome should address the problems created by DGF. Although the positive effects of good HLA matching are undeniable, this may be counteracted by increased ischaemic times and it may be that regional rather than national organ sharing would be more beneficial.

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