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Early prediction of renal allograft loss beyond one year

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Abstract. Despite significant improvements in the results of renal transplantation since the introduction of cyclosporin, graft loss beyond the 1st year remains a significant and unresolved problem. In a retrospective analysis, 348 cyclosporin-treated renal transplant recipients with a functioning graft at 12 months were studied. Forty-eight patients in whom graft failure occurred in the 2nd and 3rd years were compared to 300 patients who maintained graft function beyond this time. Both groups were comparable with respect to donor and recipient features. Factors reflecting recipient immunological responsiveness – sensitization, previous transplantation and early rejection episodes – continued to affect graft survival beyond the 1st year. Surprisingly, there was a higher incidence of prior transfusion in the group with graft failure in the 2nd and 3rd years than in those with longer function (65% vs 24%). Serum creatinine levels at 3 and 6 months were also predictive of graft loss amongst patients with a functional graft at 1 year. It remains to be answered whether new immunosuppressive drugs and strategies will overcome these risks for late graft loss.

Key words: Outcome kidney transplantation – Kidney transplantation, outcome – Late graft loss, kidney

Introduction

Substantial improvement has been reported in the results of renal transplantation since the introduction of cyclosporin (CyA). Although 1-year graft survival is the typical measure of outcome in assessing immunosuppressive regimens, reports of the late results of renal transplantation continue to demonstrate an appreciable deterioration in graft survival rate with time. Despite the improved early results with CyA, the incidence of late graft loss has remained comparable to that with azathioprine-based immunosuppression [4, 5, 12, 19, 26].

Consequently, late graft loss remains an unresolved problem. It is unclear whether clinical or laboratory parameters may predict which patients with an apparently successful transplant at 1 year are at greatest risk of subsequent graft loss.

Once established, chronic declines in renal allograft function are unrelenting, showing little response to changes in currently available immunosuppressive therapy [16]. Despite some variability in the rate and course of decline, return to dialysis or the need for retransplantation is inevitable.

It would, therefore, seem that the early identification of patients at risk would provide the best opportunity to evaluate the efficacy of new therapies in reducing or preventing late graft loss.

This report is a single centre, retrospective review of patients who maintained a functioning graft 12 months following transplantation to determine the impact of pre-existing donor/recipient factors and early clinical course in determining ultimate graft survival.

Materials and methods

In the 10-year period from January 1981 to December 1990, 774 renal transplants were performed in 706 patients. The records of patients receiving CyA-based immunosuppression were reviewed. Two groups of patients were identified: in group 1 were those patients in whom graft failure occurred 12–36 months following transplantation, in which rejection was identified as a contributing factor. Fourteen patients with graft losses during this period due to other causes were excluded (Table 1). This group consisted of 48 patients, 39 of whom received cadaver grafts and 9 living related grafts. In group 2 were those patients in whom graft function continued beyond 3 years. No patients were excluded from this group of 300, 219 of whom received cadaver grafts and 81 living related grafts.

Statistical analyses were performed using the chi-square test and Fischer's exact probability test comparing groups of patients, and using Student's t-test for comparing means between groups of patients. A P value less than 0.05 was considered significant.

Results

The two groups were comparable with respect to age and sex of donor and recipient, donor source, cold ischaemia time and recipient diabetes (Table 2).

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Table 1. Non-immunological causes of graft loss 12–36 months following transplantation[a]

Death with functioning graft:	
Cardiovascular complications	7
Malignancy	3
Pancreatitis	1
Pneumonia	1
Unknown	1
Renal artery stenosis:	1
Total	14

[a] These grafts were excluded from analysis

Table 2. Donor and recipient characteristics of cyclosporin-treated renal allografts with function beyond 12 months. P = NS for all parameters

	Group 1	Group 2
Donor	(n = 48)	(n = 300)
Age (years)	24.3 ± 14.1	28.4 ± 16.7
Sex (M:F)	1:1	2:1
Living related	9/48 (19%)	81/300 (27%)
Cadaver	39/48 (18%)	219/300 (73%)
Cold ischaemia time (hours)[a]	14.7 ± 12.4	15.9 ± 9.3
Recipient		
Age (years)	33.5 ± 15.3	36.4 ± 13.6
Sex (M:F)	1:1	2:1
Diabetes	9/48 (19%)	29/300 (10%)

[a] Cadaver grafts

Table 3. HLA compatibility. P = NS for all parameters

	Group 1	Group 2
Cadaver (n = 258)		
Mismatches		
6 (A + B + DR)	7/39 (18%)	31/219 (14%)
≥ 4 (A + B + DR)	26/39 (67%)	174/219 (79%)
O-A	6/39 (15%)	27/219 (12%)
O-B	3/39 (8%)	22/219 (10%)
O-DR	7/39 (18%)	3/219 (14%)
Living related (n = 90)		
HLA-identical	2/9 (22%)	38/81 (47%)
Haploidentical	7/9 (78%)	43/81 (53%)

Table 4. Differences in sensitization, pre-transplant transfusions and previous transplants between groups 1 and 2

	Group 1	Group 2	P-value
Pretransplant PRA > 40			
Total	7/48 (15%)	10/300 (13%)	NS
First cadaver	4/33 (12%)	21/194 (11%)	NS
Historical PRA > 40			
Total	22/48 (46%)	52/300 (17%)	< 0.001
First cadaver	15/33 (45%)	30/194 (15%)	< 0.001
Pre-transplant transfusion	31/48 (65%)	72/300 (24%)	< 0.01
Previous transplant	9/48 (19%)	34/300 (11%)	NS

Table 5. Comparison of rejection episodes in the first 90 days

	Group 1	Group 2	P-value
No rejection	19/48 (39%)	185/300 (62%)	< 0.01
≥ 2 Rejection episodes	13/48 (27%)	39/300 (13%)	< 0.05

Compatibility

HLA compatibility between donors and recipients is shown in Table 3. In cadaver grafts there was no difference between the two groups with respect to either overall match or zero mismatches at any particular locus. In the patients receiving living related transplants, 22% (2/9) of those in group 1 received an HLA-identical kidney. This compared to 47% (38/81) of those in group 2, although this difference failed to reach statistical significance.

Sensitization (Table 4)

Similar proportions of patients in each group had elevated panel reactive antibodies (PRA) in serum samples obtained closest to transplantation. However, in group 1, there was a significantly greater incidence of highly sensitized patients based on historical serum samples than in group 2 ($P < 0.001$).

Transfusions (Table 4)

Only 24% (72/300) of the patients in group 2 had had a transfusion prior to transplantation, compared to 65% (31/48) of those in group 1 ($P < 0.01$).

Regrafts (Table 4)

In group 1, 19% of the patients were regrafts, compared to only 11% in group 2; however, this difference did not reach statistical significance.

Rejection episodes (Table 5)

A significantly greater proportion of the patients in group 2 did not have a rejection episode in the first 3 months (62% vs 39%, $P < 0.01$). In addition, this group had less than half the incidence of multiple rejection episodes – 13% versus 27% for group 1 ($P < 0.05$) – during the first 90 days.

Early graft function (Table 6)

The two groups were comparable with respect to delayed graft function, defined as the absence of a fall in serum creatinine on the 1st post-operative day. However, the mean serum creatinine was significantly higher ($P < 0.01$) at 90

Table 6. Comparison of early graft function

	Group 1	Group 2	*P*-value
Delayed function[a]	36% (12/33)	31% (60/194)	NS
Mean serum creatinine (μm/l)			
90 days	225 ± 136	159 ± 63	< 0.01
180 days	251 ± 130	160 ± 67	< 0.01
Serum creatinine > 200 μm/l			
90 days	21/48 (44%)	49/300 (16%)	< 0.001
180 days	24/48 (50%)	52/300 (17%)	< 0.001

[a] First cadaver transplants

and 180 days in patients in group 1. The 90-day serum creatinine was > 200 μm/l in 44% of the patients in group 1, compared to only 16% of those in group 2 ($P < 0.001$). This difference was also apparent for the 180-day serum creatinine (50% vs 17%, $P < 0.001$). Thus, a greater proportion of patients whose grafts failed in years 2 and 3 had impaired renal function at 3 and 6 months post-transplantation.

Discussion

CyA-based immunosuppression has dramatically improved early graft survival rates in the past decade. Many centres now report 1-year graft survival rates of 80% or better. However, the rate of subsequent graft loss 1–3 years following renal transplantation is similar to that seen with earlier azathioprine-based immunosuppression [5]. While able to reduce early rejection episodes and improve early graft survival rates, CyA has been unable to slow the rate of later attrition, most of which is due to chronic rejection. Are there unique risk factors contributing to this later immunological loss? To determine this, we compared patients who lost their transplants during the 2nd and 3rd years with those who retained them during this same period.

It is recognised that grafts from HLA-identical, living related donors have both superior early survival and longer half-lives in comparison to transplants from haploidentical or cadaver donors [2, 25]. For cadaver kidney transplantation some controversy persists with respect to the impact of HLA matching on graft survival in CyA-treated patients. In our analysis of cadaver transplants, the degree of HLA matching, which was uniformly poor in both groups, was not predictive of graft failure beyond the 1st year.

The large multicentre data bases of Terasaki and Opelz [11, 23] both demonstrate a significant effect of HLA matching on graft outcome. Opelz [23] concluded that the beneficial effect of matching for HLA-A + B + DR extends throughout the entire post-transplant period. Data from the UCLA registry [11] and from the Eurotransplant centres [27] suggest that HLA-DR matching is associated with improved short-term results, while HLA-A and/or B antigen matching confers significant longer term benefit. Studies from the UK Transplant Service [4, 10] have examined the impact of beneficial HLA matching – defined as no DR incompatibilities with at most one AB mismatch – at various time intervals following transplantation. These suggested that the major impact of beneficial HLA matching is in the early post-transplant period but that it dwindles and is negligible beyond 6–12 months. The influence of centre effect – one of the major determinants in the outcome of kidney transplants – may, however, obscure any effect of HLA matching. In other studies [3, 12, 18] examining the effect of HLA matching from single centres, there was little or no improvement in graft survival by matching.

In Canada there is no national organ-sharing scheme, and within our own centre cadaver kidneys are allocated on the basis of a number of criteria in addition to HLA match. A high degree of HLA mismatching is, therefore, common in our program. With only a small number of well-matched recipients, it is not surprising that we were unable to demonstrate any beneficial effect of HLA matching on graft survival beyond the 1st year.

Although the results may not match those of non-sensitized patients, previous studies have demonstrated that patients can be successfully transplanted despite high PRA levels [20, 28]. These sensitized patients are at an increased risk of immunologically mediated graft loss in the early post-transplant period. This is due either to the effects of antibodies undetected by standard pre-transplant cross-matching or to a state of augmented cellular immune responsiveness, of which humoral sensitization is an index. Better results have been reported in patients with historically high PRA levels who undergo spontaneous loss of antibody activity prior to transplantation [6]. From our analysis, however, these patients are significantly more prevalent amongst those with graft failure in the 2nd and 3rd post-transplant years. It is likely that this remote sensitization reflects heightened immune responsiveness even though the reactivity was transient. It has been our practice to taper immunosuppression during the 1st year in all patients with an apparently successful transplant. This may be to the detriment of those patients with a history of sensitization who possibly require additional maintenance immunosuppression beyond the early post-transplant period to preserve long-term graft function.

Inappropriate reduction of immunosuppression could also possibly account for earlier losses in other patients. Whilst neither was of statistical significance, there was a greater prevalence of diabetics and females in the group with graft failure in the 2nd and 3rd years than in the group maintaining function beyond this time. We were unable to account for this observation but speculate that it may relate to attempts to reduce steroid and/or cyclosporin dosages, hoping to improve blood sugar control in diabetics and minimize cosmetic side effects in females.

Prior to the introduction of CyA, many transplant centres reported superior graft survival in patients who had received pre-transplant blood transfusions [21, 24]. A number of studies of CyA-treated patients, however, have failed to demonstrate any early graft survival advantage for transfused patients [15, 16, 22]. In our own analysis of patients with graft function at 1 year, those who received transfusions were at a higher risk of graft loss in years 2

and 3. Whilst this may well be a fortuitous finding, the possibility of a delayed adverse effect should be considered. It is also questionable whether any marginal graft survival benefits gained by a policy of pre-transplant transfusion do, in fact, outweigh the risk of transfusion-induced sensitization. As a consequence of this, as well as the potential risk of transfusion-transmitted diseases, our centre presently does not perform planned pre-transplant transfusions unless clinically indicated.

Elevated serum creatinine at 1 and 2 years has been shown to be associated with a higher likelihood of subsequent graft loss [1, 9, 17]. In our patients even earlier elevations of serum creatinine – at 3 and 6 months – were more prevalent in patients with subsequent allograft failure in years 2 and 3. Patients with functional grafts at 1 year who had a serum creatinine greater than 200 μm/l at 3 and 6 months were significantly more prevalent amongst the earlier failures. Such an elevation in serum creatinine reflects a significant reduction in functional renal mass and, hence, minimal reserve in the event of subsequent injury or insult, immunological or otherwise. Acute rejection in the early post-transplant period is a major factor contributing to loss of functional renal tissue in the transplant recipient. Despite apparently successful anti-rejection therapy, patients in our study who developed multiple rejection episodes during the first 90 days remained at risk of subsequent graft loss. Other studies have reported similar outcomes in this group of patients [1, 9]. It is possible that acute rejection in the early period following transplantation may represent the beginning of a continuous immunological process in patients who go on to develop chronic rejection. Alternatively, non-immunological mechanisms may be responsible. Progressive deterioration in the function of the remaining viable parenchyma after treatment of an acute rejection may occur due to hyperfiltration injury similar to that described in native kidneys [7, 13].

In allografts as with the native kidney, proteinuria is a clinical correlate of declining renal function [8, 14]. We were unable to analyse this within our study. However, Kasiske et al. [14] found that it occurs relatively late in the course of chronic rejection and was not an early marker of subsequent graft loss. In their study, also looking at patients with functional grafts at 1 year, there was no discernable difference in proteinuria between those with stable function and those with deteriorating function until 52 weeks.

In conclusion, it would seem that in CyA-treated patients, underlying immunological factors, or rather recipient immunological responsiveness, continues to exert a major influence on long-term renal allograft survival, despite successful early outcome with a functional allograft at 12 months. Sensitization, pre-transplant transfusions, as well as early rejection episodes, adversely influence graft survival beyond the 1st year.

In addition, renal function based on serum creatinine at 3 and 6 months is predictive of long-term graft survival in cyclosporin-treated recipients with a functional kidney at 1 year. Those patients with an elevated serum creatinine greater than 200 μm/l at 90 and 180 days are at significant risk of subsequent graft failure.

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References

1. Abele R, Novick AC, Braun WE, Steinmuller D, Buszta C, Greenstreet R, Hinton J (1982) Long-term results of renal transplantation in patients with a functioning graft for 2 years. Transplantation 34: 264–267
2. Albrechtsen D, Flatmark A, Brynger H, Frodin L, Gabel H, Groth CG, Lundgren G, Maurer W (1988) Impact of blood transfusions and HLA matching on national kidney transplant programs: the first Swedish-Norwegian study of cyclosporine. Transplant Proc 20: 257–260
3. Alexander JW, Vaughan WK, Pfaff WW (1987) Local use of kidneys with poor HLA matches is a good as shared use with good matches in the cyclosporine era: an analysis at one and two years. Transplant Proc 19: 672–674
4. Bradley BA, Gillis WR, Gore SM (1989) A preliminary analysis of late renal allograft failure. In: Terasaki PI (ed) Clinical transplants. UCLA Tissue Typing Laboratory, Los Angeles, pp 175–183
5. Calne R, Wood AM (1985) Cyclosporine in cadaveric renal transplantation: three year follow up of a European multicentre trial. Lancet II: 549
6. Falk JA, Cardella CJ, Halloran P, Robinette M, Arbus G, Bear R (1985) Transplantation can be performed with positive (non-current) crossmatch. Transplant Proc 17: 1530–1532
7. Feehally J, Bennett SE, Harris KPG, Walls J (1986) Is chronic renal transplantation rejection a non-immunological phenomenon? Lancet II: 486–488
8. First MR, Vaidya PN, Maryniak RK, Weiss MA, Munda R, Fidler JP, Penn I, Alexander JW (1984) Proteinuria following transplantation: correlation with histopathology and outcome. Transplantation 38: 607–612
9. Foster MC, Rowe PSA, Dennis MJS, Morgan AG, Burden RP, Blamey RW (1990) Characteristics of cadaveric allograft recipients developing chronic rejection. Ann R Coll Surg Engl 72: 23–27
10. Gilks WR, Gore SM, Bradley BA (1990) Renal transplant rejection transient immunodominance of HLA mismatches. Transplantation 50: 141–146
11. Gjertson DW (1989) Short and long-term effects of HLA matching. In: Terasaki PI (ed) Clinical transplants. UCLA Tissue Typing Laboratory, Los Angeles, pp 353–360
12. Gordon RD, Starzl TE, Hakala RJ, Schroter GPJ, Rosenthal JT, Weil R, Iwatsuki S, Carpenter BJ (1987) Long-term results of cyclosporine-steroid therapy in 131 non-matched cadaveric renal transplants. Clin Transplant 1: 44–48
13. Hostetter TH, Rennke HG, Brenner BM (1982) Compensatory renal haemodynamic injury – a final common pathway of residual nephron destruction. Am J Kidney Dis 1: 310–314
14. Kasiske BL, Heim-Duthay KL, Tortorice KL, Rao KV (1991) The variable nature of chronic declines in renal allograft function. Transplantation 51: 330–334
15. Kerman RH, Buren CT van, Lewis RM, Kahan BD (1988) Successful transplantation of 100 untransfused cyclosporine-treated primary recipients of cadaveric renal allografts. Transplantation 45: 37–40
16. Knight RJ, Kerman RH, Welsh M, Golden D, Schoenberg L, Buren CT van, Lewis RM, Kahan B (1991) Chronic rejection in primary allograft recipients under cyclosporine-prednisone immunosuppressive therapy. Transplantation 51: 355–359
17. Lewis RM, Janney RP, Gidden DL, Kerr NB, Buren CT van, Kerman RH (1989) Stability of renal allograft function associated with long-term cyclosporine immunosuppressive therapy – five year follow up. Transplantation 47: 266–272
18. Matas AJ, Frey DJ, Gillingham HJ, Noreen HJ, Reinsmoen NL, Payne WD, Dunn DL, Sutherland DER, Najarian JS (1990) The impact of HLA matching on graft survival and on sensitization

after a failed transplant – evidence that failure of poorly matched renal transplant does not result in increased sensitization. Transplantation 50: 599–607
19. Montagnino G, Colturi C, Tarantino A, Masa A, Benfi G, Aroldi A, Vigano E, Cesana B, Ponticelli C (1991) The impact of azathioprine and cyclosporine on long-term function in kidney transplantation. Transplantation 51: 772–776
20. Norman DG, Barry JM, Wetzsteon PJ (1985) Successful cadaver kidney transplantation in patients highly sensitized by blood transfusions. Transplantation 39: 253–255
21. Opelz G (1985) Current relevance of the transfusion effect in renal transplantation. Transplant Proc 17: 1015–1022
22. Opelz G for the Collaborative Transplant Study Group (1987) Improved kidney graft survival in non-transfused recipients. Transplant Proc 20: 149–152
23. Opelz G (1991) HLA matching should be utilized for improving kidney transplant success rates. Transplant Proc 23: 46–50
24. Sanfilippo F, Vaughn WK, Lefor WM, Specs EK (1986) Multivariate analysis of risk factors in cadaveric donor kidney transplantation. Transplantation 42: 28–34
25. Takiff H, Mickey MR, Cicciarelli J, Terasaki PI (1987) Factors important in ten-year kidney graft survival. Transplant Proc 19: 666–668
26. Terasaki PI, Mickey MR, Cecka M, Cicciarelli J, Cook D, Iwaki Y, Toyotoma A, Wang L (1987) Overview. In: Terasaki PI (ed) Clinical transplants. UCLA Tissue Typing Laboratory, Los Angeles, pp 467–490
27. Thorogood FJ, Persijn GG, Schreuder GM, Amaro JD, Zantvoort FA, Houwellingen JC, Rood JJ van (1990) The effect of HLA matching on kidney graft survival in separate post transplantation intervals. Transplantation 50: 146–150
28. Turka LA, Goguen JE, Gagne JE, Milford EL (1989) Pre-sensitization and the renal allograft recipient. Transplantation 47: 234–240