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Prognostic factors of long-term allograft survival in 632 CyA-treated recipients of a primary renal transplant

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Abstract A total of 632 cyclosporin (CyA)-treated primary renal allograft recipients with a functioning graft at 6 months were retrospectively evaluated for risk factors correlated with long-term allograft function. Mean follow-up after the 6th month was 68.4 ± 40.6 months. One hundred twenty-one of these patients (19 %) were lost: 29 died (23/29 with a functioning graft), 77 of the remaining 92 (83 %) lost their graft because of chronic allograft dysfunction, 9 due to recurrence of glomerulonephritis, 5 due to renal artery thrombosis, and 1 due to chronic CyA toxicity. At univariate analysis, factors correlated with a better renal (R) and pure renal (PR) allograft survival were: dialysis duration of less than 5 years, fewer than 2 rejections within the 6th post-Tx month, immediate graft function recovery, plasma creatinine below 1.5 mg/dl at the 6th month, age at Tx above 15 years, and receiving a living donor graft. Cox's regression analysis was also performed to obtain relative risks for the same parameters. Long-term dialysis patients had more frequent late recoveries ($P = 0.002$) and reductions in therapy ($P = 0.01$) in order to reduce the side effects of steroids. In young patients receiving an initial oral CyA dose of 17 mg/kg per day, steroids were stopped at the 6th month in order to achieve catch-up growth: only one such patient lost his graft. In contrast, 72 % of the young patients who lost their grafts received an initial oral CyA dosage of 13 mg/kg per day. Thus, young patients did worse not because of steroid withdrawal, but because of inadequate initial CyA dosage. These results suggest that although we cannot exclude alloantigen-independent mechanisms as factors that stimulate progression of chronic allograft dysfunction, it would appear that the initial lesions are induced by events mostly mediated by immunological mechanisms.

Key words Kidney transplantation, prognostic factors · Prognostic factors, kidney transplantation · Long-term kidney transplant survival

Introduction

The introduction of cyclosporin (CyA) has improved short-term renal allograft survival compared to immunosuppression with azathioprine (Aza) and prednisone [3,7,32,36,40,41], but whether CyA also offers an advantage over Aza in the long-term is still controversial. Some investigators have reported a similar graft half-life among patients treated with CyA or Aza [5,10,19,21,31,38]; The loss of advantage in the long-term may be either attributed to the renal toxicity of CyA, which can lead to progressive deterioration of graft function, or to the possibility that alloantigen-independent factors also contribute to the induction of

chronic lesions, which can compromise long-term graft survival [1,8,25,37]. However, Opelz [24] retrospectively reviewed the outcome of thousands of patients recorded in the Collaborative Transplant Study and showed that 5-year graft survival was significantly better in patients given CyA than in those given Aza. Randomized trials have also confirmed the long-term superiority of CyA regimens. In a prospective, controlled trial [28], we showed that 10-year graft survival was 56% among CyA-treated versus 35% among Aza-treated renal transplant recipients, a significant difference. The half-life of grafts functioning after 1 year was 15.4 ± 3.9 years in the CyA group versus 10.6 ± 3.6 years in the Aza group. Similarly, Isoniemi et al. [12] reported that patients assigned to CyA treatment had better graft survival than patients given Aza treatment. Other studies have shown that even for grafts with chronic dysfunction, CyA provides superior renal protection than Aza at 5 years [20] and at 8 years [45]. If such is indeed, the case, the protective effect of CyA could be related to its superior immunosuppressive activity, indicating that immunological factors are those most responsible for late graft dysfunction.

In order to exclude all potentially confounding effects of acute events on long-term outcome, we evaluated the prognostic value of some immunological and some nonimmunological parameters on the long-term outcome of the graft in our CyA-treated primary renal transplant recipients, excluding all failures (death or graft loss) occurring within the first 6 months.

Patients and methods

The subjects of this study were all primary renal transplant recipients treated with CyA since it was first introduced into our Unit in March 1983 and with a functioning kidney at 6 months. The 6th post-transplant month was considered as time zero, and the follow-up was calculated starting from this point. A total of 632 patients were included in the study, 523 of whom received a cadaveric kidney and 109 a kidney from a living related donor.

Therapeutic regimens

Cyclosporin monotherapy (M; n = 127)

CyA was perfused intravenously at a dose of 5 mg/kg over a period of at least 6 h, before transplantation (Tx) and for the first 4 post-Tx days. Then, the drug was given orally in a single morning dose of 15 mg/kg per day, progressively tapered by 2 mg/kg per day to a maintenance dose of 5 mg/kg per day within the 4th post-Tx month.

Double drug regimen (D; n = 216)

CyA was given at a starting dose of 5 mg/kg per day intravenously, followed by 13 mg/kg per day orally starting on the 5th post-Tx day. CyA was then reduced every 2–4 weeks to a mean maintenance dose of 5 mg/kg per day. Oral methylprednisolone was given in a single morning dose of 16 mg until the end of the 3rd month, at a dose of 12 mg daily until the end of the 6th month, and at a maintenance dose of 8 mg daily thereafter.

Triple drug regimen (T; n = 264)

CyA was administered intravenously at the same starting dose as in the double drug regimen, followed by an oral dose of 10 mg/kg per day starting on the 5th post-Tx day. The dosage was progressively reduced by 2 mg/kg per day every 2–4 weeks to a maintenance dose of 2–3 mg/kg per day; oral methylprednisolone was given at the same dosage as in the double drug regimen, and azathioprine was given at a fixed dose of 1 mg/kg per day.

Pediatric schedule (P; n = 25)

This regimen was used in 20 of 49 patients below 15 years of age and in 5 additional patients with ages ranging from 16 to 21 years. CyA was given intravenously at the same starting dose as in the double drug regimen for the first 3 post-Tx days; starting on the 4th day it was given orally at a dose of 17 mg/kg per day, and it was tapered every 2 weeks by 2 mg/kg per day to a maintenance dose of 10 mg/kg per day. Oral methylprednisolone was given at a single morning dose of 12 mg until the end of the 1st post-Tx month, then progressively tapered by 2 mg/day every month until complete withdrawal by the end of the 6th post-Tx month.

In all patients the CyA dosage was adjusted to keep whole blood trough levels under 800 ng/ml as measured by polyclonal RIA, or 350 ng/ml as measured by a fluorescence polarized immunoassay (FPIA) with a monoclonal antibody.

A core graft biopsy was taken from 172 patients after the 6th post-transplant month either because of a worsening of renal function or because of the onset of proteinuria higher than 1 g/24 h.

Delayed graft function recovery was defined either as the need for dialysis after transplantation or as persistently high plasma creatinine levels for at least 7 days, even with a prompt recovery of diuresis.

Statistical analysis

Living and cadaver kidney recipient groups were compared by means of the Mann-Whitney nonparametric test for continuous variables and the chi-square test for qualitative ones. The variables taken into account in order to evaluate their impact on the long-term outcome of the graft were: sex and age of donor, sex of recipient, age of recipient at transplantation (up to 15 vs 16–45 vs > 45 years), time spent on dialysis (< 60 vs > 60 months), type of dialysis [hemodialysis (HD) vs chronic ambulatory peritoneal dialysis (CAPD)], number of pretransplant blood transfusions (0 vs > 0), number of mismatches for the HLA-A, B, and genomic DR antigens (0 vs 1–2), maximum percentage of historical panel reactive antibodies (PRA; 0 vs any positivity), source of donor kidney (cadaver vs living), time of graft function recovery, therapeutic schedule (M vs D vs T) according to the "intention to treat" principle, number of acute rejections (0–1 vs > 1) within the first 6 months, modification of the originally scheduled therapy (no variation vs any modification of immunosuppression) within the first 6 months, and plasma creatinine at the 6th month (< 1.5 mg/dl or < 133 μmol/l vs > 1.5 mg/dl). HLA-A,B, and DR mismatches were evaluated only in those 200 patients (176 recipients of cadaver kidneys and 24 of living related kidneys) for whom a genomic DR determination was available.

Table 1 Characteristics of patients at transplantation (*MP* methylprednisolone, *PRA* panel reactive antibodies, *CD* cadaveric donors, *LRD* living related donors)

	All patients	CD	*P*	LRD
Number of patients (M/F)	632 (395/237)	523		109
Age (mean ± SD)	34.8 ± 12.5	35.8 ± 12	< 0.001[a]	29.7 ± 11.4
Months on dialysis (mean ± SD)	37.5 ± 37.2	38.8 ± 36.3	< 0.001[a]	31.1 ± 40.9
Mean number of rejection episodes (≤ 6th month)	0.75 ± 0.83	0.73 ± 0.84	NS[a]	0.83 ± 0.78
Number of MP pulses (within the 6th month)	2.51 ± 2.77	2.5 ± 2.8	NS[a]	2.5 ± 2.4
Follow-up after the 6th month (mean ± SD)	68.4 ± 40.6	71.1 ± 41.4	< 0.001[a]	55.2 ± 33.4
Maximum historical PRA (absent vs present)	100/532	90/433	= 0.03[b]	10/99
Mismatches for the HLA locus (176 CD, 24 LRD)				
HLA-A (0 vs ≥ 1)	–	63/113	NS[b]	6/18
HLA-B (0 vs ≥ 1)	–	36/140	NS[b]	6/18
HLA-DR (genomic; 0 vs ≥ 1)	–	20/156	NS[b]	5/19

[a] Mann-Whitney U-test
[b] Chi-square test

Table 2 Causes of graft failure after the 6th post-transplant month

Total number of failures	121/632 (19.1 %)			
	Death uncensored	Death censored	Causes of death	
Deaths	29/121 (24 %)	23/121 (19 %)	Cardiovascular	9
Chronic graft dysfunction[a]	77/92 (83 %)	77/98 (78 %)	Infectious	8
Recurrence of original glomerulonephritis	9/92 (9.7 %)	9/98 (9.1 %)	Hepatic failure	7
Vascular thrombosis	5/92 (5.4 %)	5/98 (5.1 %)	Neoplastic	4
CyA toxicity	1/92 (1 %)	1/98 (1 %)	Car accident	1

[a] In one case associated with recurrence of original glomerulonephritis

A univariate analysis was first carried out comparing the Kaplan and Meier survival curves by means of the generalized Wilcoxon test [14] in order to evaluate the influence of the aforementioned parameters on both graft and pure graft (death with a functioning kidney censored) survival. Owing to the scant number of patients with this end point, the univariate analysis of the risk factors for death is reported for descriptive purposes only. Cox's regression analysis was then carried out for both graft and pure graft survival. Goodness of fit of Cox's model was assessed by stratified analysis [13].Graft and pure graft half-lives and asymptotic standard errors were calculated according to the formula reported by Cho and Terasaki [6].

Results

The characteristics of patients at transplantation are reported in Table 1; the reported follow-up starts at the 6th post-Tx month. Living related kidney recipients were younger, had spent less time on dialysis, had fewer preformed PRA antibodies, and had been followed for a shorter time than cadaveric kidney recipients. At the 6th post-Tx month, the mean CyA dosage was 303.2 ± 77.6 mg/day in M patients, 317.8 ± 91 mg/day in D patients, 207.4 ± 7 in T patients, and 301.9 ± 128.9 in P patients. T patients received a significantly lower mean CyA dosage at the 6th month (T vs all other regimens: $P < 0.001$), while no statistically significant difference was observed among the other regimens.

Failures observed during the follow-up and causes of death are reported in Table 2. Graft failure due to chronic graft dysfunction was, by large, the major cause of graft loss. Death was the second cause of graft failure: 23 of the 29 deaths observed occurred in patients with a functioning kidney. Cardiovascular disease and infections accounted for most of the deaths in the present series. In nine patients, graft failure was caused by recurrence of glomerulonephritis: four were focal segmental glomeruloscleroses, three were IgA nephritides, and two were membranous nephropathies. Vascular thromboses were associated with either a more generalized atherosclerotic vascular pathology in patients with longstanding hypertensive arteriopathy ($n = 2$) or with complications associated with graft biopsy in hypertensive patients treated with converting enzyme inhibitors ($n = 3$). Only one patient out of ten with a biopsy-proven CyA-associated arteriolopathy lost his graft due to chronic CyA toxicity.

Univariate analysis showed that a dialysis duration of more than 5 years, age at transplantation younger than 15 years, multiple rejection episodes within the 6th post-transplant month, delayed graft function, recovery

Table 3 Univariate analysis

Survival rates (Breslow test)	Graft *P*	Pure graft *P*	Patient *P*
Cadaveric vs living donor	= 0.049	NS	NS
Months on dialysis (< 60 vs > 60)	< 0.001	= 0.006	< 0.001
Age at Tx (< 15 vs 16–45 vs > 45)	= 0.009	< 0.001	NS
Rejection episodes (0–1 vs 2–4)	< 0.001	< 0.001	NS
Graft function recovery (0 vs > 7 days)	= 0.001	= 0.001	NS
Plasma creatinine < 1.5 vs > 1.5 mg/dl at the 6th month	< 0.001	< 0.001	NS

Table 4 Factors associated with dialysis duration

Months on dialysis	< 60	> 60	Student's *t*-test
Age (mean + SD)	33.4 ± 12.8	40.4 ± 9.7	< 0.001 Chi-square test
Therapy modifications (no vs yes)	243/266	43/80	= 0.01
(yes over total)	52 %	65 %	
Graft function recovery (0 vs > 7 days)	453/56	97/26	= 0.002
(late over total →)	11 %	21 %	
Rejection episodes (0–1 vs 2–4)	425/84	97/26	NS
(> 1 over total)	16.5 %	21 %	

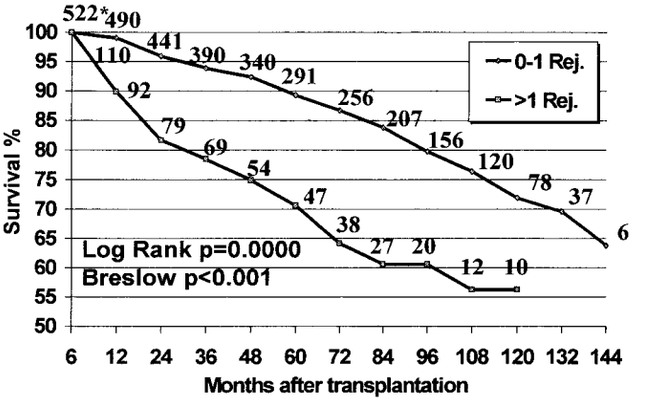

Fig. 1 Graft survival (0–1 rejection vs > 1 rejection). * Patients at risk

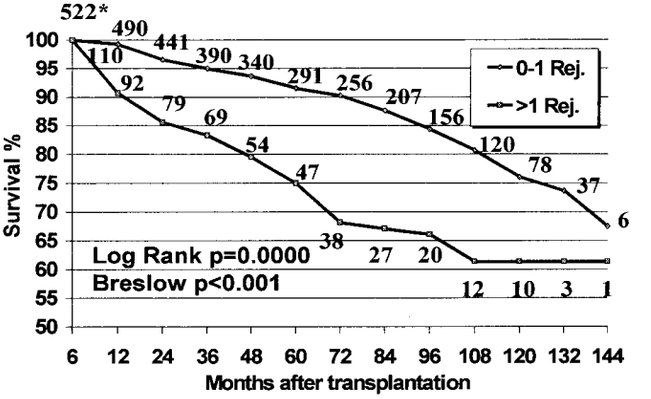

Fig. 2 Pure graft survival (0–1 rejection vs > 1 rejection). * Patients at risk

and plasma creatinine higher than 1.5 mg/dl at the 6th month were significantly associated with lower graft and pure graft survival (Table 3, Figs. 1,2). Of all the parameters taken into account, a dialysis duration of more than 5 years was the only predictor of worse patient survival as well; however, one must bear in mind that the number of deaths observed in the present series was too small to reach statistical relevance and that *P* values are reported for descriptive purposes only.

In order to better elucidate the reasons for worse graft survival in patients with a long dialysis duration, we analyzed these patients further (Table 4). While they did not have more rejections than patients with a shorter dialysis duration, they were older, their graft function recovery was more frequently delayed, and they were more frequently shifted from their original therapeutic schedule. Moreover, in our Unit, a scoring system for allocation of grafts is used that favors small age differences between the donor and the recipient, and indeed, older patients received kidneys from older donors (chi-square: $P = 0.000$).

Age below 15 years at transplantation was a significant negative predictor of graft survival as compared to the other two age groups, and its influence on pure graft survival was even higher, suggesting that associated immunological factors might account for this. Some 41 % (20/49) of these patients had been asked to follow a pediatric schedule in which steroids were withdrawn at the 6th month; only one of these patients lost his graft due to chronic rejection. On the other hand, 13 of the 18 graft failures due to chronic rejection occurred in younger patients receiving a double therapy regimen with lower starting doses of CyA. Finally, patients with prompt recovery of graft function fared significantly better than patients with delayed recovery of graft function, the latter having a significantly higher number of rejection episodes within the 6th post-Tx month ($P = 0.006$).

Living related graft recipients had only a borderline advantage over cadaveric graft recipients in terms of graft survival. This advantage was lost when pure graft survival was taken into account, suggesting that these patients fared better in the long run, probably because

Table 5 Cox's regression analysis

Variable	Graft survival			Pure graft survival		
	RR	*P*	95% CI	RR	*P*	95% CI
Age at Tx (< 15 vs < 45)	2.81	< 0.01	1.487–5.307	4.23	< 0.01	2.108–8.515
Age at Tx (16–45 vs > 45)	0.92	0.057	0.670–1.083	0.99	NS	0.571–1.746
Rejection episodes (0–1 vs 2–4)	2.06	< 0.01	1.347–3.155	1.96	< 0.01	1.226–3.151
Months on dialysis (< 60 vs > 60)	2.10	< 0.01	1.402–3.164	1.96	< 0.01	1.226–3.146
Recovery of graft function (0 vs > 7 days)	1.57	= 0.055	–	1.66	< 0.05	1.024–2.713
Plasma creatinine < 1.5 vs > 1.5 mg/dl (at the 6th month)	1.72	< 0.01	1.163–2.550	1.93	< 0.01	1.224–3.039

of a reduced incidence of deaths rather than of a reduced incidence of rejections.

At Cox's regression analysis, recipient gender was no longer significant. The relative risks (RR) of the remaining covariates for graft and pure graft survival are reported in Table 5.

Considering only patients with a functioning kidney at 1 year, graft half-life was 19.99 years (SE 22.47), while pure graft half-life was 24.77 years (SE 30.99).

Of the 172 patients who had a graft biopsy taken after the 6th month, 15 developed CyA toxicity; only one lost his kidney in the long term due to a CyA-related arteriolopathy. In nine patients, graft biopsy showed a late acute rejection, and in three a recurrence of their original glomerulonephritis. Most patients who had a graft biopsy showed either clear signs of chronic rejection (76/172, 44%) or aspecific findings, such as focal interstitial fibrosis, mesangial sclerosis, and focal segmental sclerosis (69/172, 40%).

Discussion

This retrospective analysis was based on a selected series of primary renal transplant recipients with grafts functioning at 6 months. Some 20% of failures were the result of patient death, most of which occurred in patients with a functioning graft. There is no general consensus on whether death in transplant recipients should or should not be considered a cause of graft failure [18] since death may not be caused by direct immunological events but rather may be related to side effects of immunosuppression. Inclusion or exclusion of death with a functioning kidney in the survival analysis may lead to different results. Indeed, a significant increase in graft half-life was observed by Matas et al. [16] when death with a functioning graft was censored, especially in high-risk patients such as diabetics and patients aged over 50, indicating that, in such cases, death may be considered an important nonimmunological cause of graft loss. We therefore evaluated both graft survival and pure graft survival, in which death with a functioning graft was censored. In the present selected series, the graft half-life was about 20 years and the pure graft half-life about 25 years, much better than that reported by multicenter analyses [10,24,38] but similar to that found in a previous prospective trial in primary renal transplant recipients performed in our Unit [28] and to that of a retrospective analysis by the Leuven Collaborative Group for Transplantation [45].

In many of the patients whose grafts failed and from whom a biopsy was taken, chronic rejection was diagnosed. However, although the Banff classification [35] attempts to define the histological features of chronic rejection, it is often difficult to discriminate lesions caused by immunological attack from those induced by either reduced nephron mass or ischemia. Indeed, in 40% of our biopsies, histology was not clear. Because of this lack of clarity in the histological criteria that define chronic rejection, we decided, in this series, to analyze the factors that were correlated with the long-term survival of the graft, independently of histological parameters.

At multivariate analysis, the occurrence of more than one acute rejection within the first 6 post-transplant months was a strong predictor of late graft failure, in terms of both graft and pure graft survival. These data confirm the important role [15,17,44] of early immunological events on the induction of lesions eventually leading to a late poor outcome of the graft. Another independent factor associated with late graft failure was a plasma creatinine higher than 1.5 mg/dl at the 6th post-transplant month. These data are in agreement with findings from a previous study in our CyA-treated patients with stable renal function at 1 year [20]. Since the criterion for patient selection in this series was the presence of a graft functioning at 6 months and not stable function, the present data further confirm the important role of a low plasma creatinine value in the early post-transplant period as a positive predictor of long-term survival.

As pointed out by previous studies [27,31] and confirmed in this series, young recipient age was the most significant parameter correlated with long-term graft failure. We discontinued steroids in some of our children in order to obtain catch-up growth [9] and one

might question whether this therapeutic strategy may have altered the long-term results. In fact, although we had a high frequency of late acute rejections in these young patients, the withdrawal of steroids did not account for a worse outcome in younger patients. In fact, only one of the children who stopped methylprednisolone lost his graft. In contrast, 72 % of the children who lost their grafts were maintained on steroids but received an initial oral CyA dosage of 13 mg/kg per day, while only one child who started with 17 mg/kg per day experienced graft failure. Due to the reported inadequate CyA absorption in children [46], it is possible that an inappropriate initial CyA dosage might have had more of an impact on long-term graft survival than late steroid withdrawal. The unfavorable impact of young age on pure graft survival RR (4.23) compared to uncensored graft survival RR (2.81) confirms the notion that factors related to therapeutic manipulation strongly influence long-term results. Moreover, the fact that recipient age above 45 years was not a negative prognostic factor with respect to pure graft survival confirms the belief that older age per se is not a cause of immunological graft failure [27]. Given our scoring system, which allocates kidneys from older donors to older recipients, this reduces the role of age-induced reduction of nephron mass and/or the presence of unsuspected vascular disease in the graft of the donor in the progression of chronic graft dysfunction. It has been reported that male recipients of female donor organs have a worse outcome in the long run [1,10,11,23,37]. This may be attributed to a mass discrepancy with an insufficient number of nephrons for the male recipient. However, in this series, in which early graft losses were excluded, the gender of the donor was not related to graft outcome, since male recipients of female donor organs were not at a higher risk of losing their graft. At odds with some authors [10,29,47] but in agreement with others [27,30], donor age did not correlate with long-term graft survival in our series.

Living related renal transplants are usually considered to have a better outcome than cadaveric renal transplants although, in a recent analysis, Terasaki et al. [39] found only a marginal benefit of parental transplants when compared to cadaveric grafts. In our series, most of the living donors were parents; only a few were not. At univariate analysis, we found that receiving a graft from a living donor gave an advantage over receiving a cadaveric transplant. This advantage was lost, however, when pure graft survival was taken into account, suggesting that these patients probably did better in the long run because of less frequent deaths rather than because of fewer rejections. Moreover, at multivariate analysis, this factor was not an independent covariate. Reasons for this are most likely the small number of living donor transplants and the fact that several living donor kidney recipients were young patients.

In most studies, delayed graft function has also been found to have a negative impact on graft survival [22,26]. In the present series, we confirmed the negative predictive value of delayed graft function on late pure graft survival, although the significance for graft survival was only of borderline statistical value. Patients with delayed graft function also had significantly more rejections within the first 6 months, and this may have reduced the relative impact of delayed graft function per se on graft outcome. Early injury secondary to prolonged ischemia and reperfusion may be a factor in the progression of chronic allograft dysfunction independent of immune mechanisms. However, in a recent multivariate analysis in primary cadaveric renal transplants with a plasma creatinine below or equal to 2.0 mg/dl at 1 year, actuarial graft survival was significantly worse in patients with both delayed graft function and rejection than in those with delayed graft function but no rejection [42]. It is well known that ischemia may increase the expression of histocompatibility antigens on the endothelial surface [34], thus favoring the onset of rejection, but one should also bear in mind that delayed graft function may either mask an ongoing rejection, so delaying its treatment [2], or be the consequence rather than the cause of rejection. Accordingly, recipients with high levels of preformed cytotoxic antibodies have been reported to have a higher incidence of early nonfunction [4,33].

Another independent predictor of poor allograft survival in the long run was a dialysis duration of more than 5 years. To the best of our knowledge, this is the first time that a relationship between prolonged dialysis and poor long-term graft survival has been found. Further analysis of patients with more than 5 years of dialysis showed that they were significantly older, that they had received kidneys from older donors, that they more frequently had delayed graft function, and that they were more frequently shifted from their originally scheduled treatment. It is, therefore, possible that some or all of these factors played a role in both delayed recovery and long-term survival. Some of these data are apparently in disagreement with the favorable outcome of older patients, as reported above. However, one should take into account that many older patients with a long dialysis become frail, and this often leads the clinician to reduce immunosuppressive drugs, particularly in patients who have dialysis- or age-related complications such as bone disease, hypertension, cardiovascular disease, diabetes, etc. These data advise caution against excessive reductions in therapy, even in older patients, unless there are serious reasons for doing this.

In conclusion, in this series, most of the factors correlated with a poor long-term graft outcome were related to immunological events occurring within the 6th posttransplant month. The negative impact of young age at transplantation also seems to be correlated with inadequate initial immunosuppression. The unfavorable ef-

fect of a long time spent on dialysis is influenced, at least in part, by reductions in immunosuppressive therapy. It has been suggested that early stages of chronic rejection are alloantigen-dependent and reversible, whereas the later changes (presumably alloantigen-independent) are progressive and irreversible [43]. The negative roles of rejection, therapy modification, and delayed graft function associated with rejection suggest that, although alloantigen-independent mechanisms cannot be ruled out as adjunctive factors in the progression of graft dysfunction, the initial lesions are most likely induced by events mediated in large part by immunological mechanisms. Moreover, the superior graft half-life of our CyA-treated patients as compared to Aza-treated ones [28] suggests that these immunological mechanisms may be persistently operative.

References

1. Brenner BM, Cohen RA, Milford EL (1992) In renal transplantation, one size may not fit all. J Am Soc Nephrol 3: 162–169
2. Cacciarelli T, Sumrani N, Delaney V, Hong JH, DiBenedetto A, Sommer BG (1993) The influence of delayed renal allograft function on long-term outcome in the cyclosporine era. Clin Nephrol 39: 335–339
3. Calne RY, White DJG, Evans DB, Thiru S, Henderson RG, Hamilton DV, Rolles K, McMaster P, Duffy TJ, McDougall BR, Williams R (1981) Cyclosporin A in cadaveric organ transplantation. BMJ 282: 934–936
4. Canafax DM, Torres A, Fryd D, Heil JE, Strand MH, Ascher NL, Payne WD, Sutherland DER, Simmons RL, Najarian JS (1986) The effects of delayed function on recipients of cadaver renal allografts. Transplantation 41: 177–181
5. Cecka JM (1994) Outcome statistics of renal transplants with an emphasis on long term survival. Clin Transplant 8: 324–327
6. Cho YW, Terasaki PI (1988) Long-term survival. In: Clinical transplants. Terasaki P (ed) UCLA Tissue Typing Laboratory, Los Angeles, pp 277–282
7. European Multicentre Trial Group (1983) Cyclosporin in cadaveric renal tranpslantation: one year follow-up of a multicentre trial. Lancet II:986–989
8. Feehally J, Harris KPG, Bennett SE, Walls J (1986) Is chronic renal transplant rejection a non-immunological phenomenon ? Lancet I:486–488
9. Ghio L, Tarantino A, Edefonti A, Mocciaro A, Giani M, Guerra L, Berardinelli L, Vegeto A (1992) Advantages of cyclosporine as sole immunosuppressive agent in children with transplanted kidneys. Transplantation 54: 834–838
10. Gjertson DW (1992) Survival trends in long-term first cadaver-donor kidney transplants. In: Clinical transplants 1991. Terasaki P, Cecka JM (eds) UCLA Tissue Typing Laboratory, Los Angeles, pp 225–235
11. Hostetter TH (1994) Chronic transplant rejection. Kidney Int 46: 266–279
12. Isoniemi HM, Ahonen J, Tikkanen MJ, Willebrand EO von, Krogerus L, Eklund BH, Höckerstedt KV, Salmela KE, Häyry PJ (1993) Long-term consequences of different immunosuppressive regimens for renal allografts. Transplantation 55: 494–499
13. Kalbfleisch JD, Prentice RL (1980) The statistical analysis of failure time data. John Wiley & Sons, New York, pp119–142
14. Kaplan EL, Meier P (1958) Non parametric estimation for incomplete observations. J Am Stat Assoc 53: 457–481
15. Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, Persson NH (1993) The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporine regimens. Transplantation 56: 307–315
16. Matas AJ, Gillingham KJ, Sutherland DER (1993) Half-life and risk factors for kidney transplant outcome: importance of death with function. Transplantation 55: 757–761
17. Matas AJ, Gillingham KJ, Payne WD, Najarian JS (1994) The impact of an acute rejection episode on long-term renal allograft survival ($t_{1/2}$). Transplantation 57: 857–859
18. Mickey MR (1989) Kidney transplant mortality relationships. In: Terasaki PI (ed) Clinical transplants 1988. UCLA Tissue Typing Laboratory, Los Angeles, pp 263–276
19. Mihatsch MJ, Thiel G, Ryffel B (1988) Histopathology of cyclosporine nephrotoxicity. Tranplant Proc 20 [Suppl 3]: 759–771
20. Montagnino G, Colturi C, Tarantino A, Masa A, Banfi G, Aroldi A, Viganò E, Cesana B, Ponticelli C (1991) The impact of azathioprine and cyclosporine on long-term function in kidney transplantation. Transplantation 51: 772–776
21. Myers BD, Ross J, Newton L, Luetscher J, Pelroth M (1984) Cyclosporine-associated chronic nephropathy. N Engl J Med 311: 699–705
22. Naimark D, Cole E (1994) Determinants of long-term renal allograft survival. Transplant Rev 8: 93–113
23. Neugarten J, Silbiger S (1994) The impact of gender on renal transplantation. Transplantation 58: 1145–1152
24. Opelz G (1994) Effect of the maintenance immunosuppressive drug regimen on kidney transplant outcome. Transplantation 55: 443–446
25. Paul LC, Fellstrom B (1992) Chronic vascular rejection of the heart and the kidney – have rational treatment options emerged ? Transplantation 53: 1169–1179
26. Peeters J, Roels L, Vanrenterghem Y, for the Leuven Collaborative Group for Transplantation (1995) Chronic renal allograft failure: clinical overview. Kidney Int 48 [Suppl 52]:S-97–S-101
27. Pirsh JD, D'Alessandro AM, Sollinger HW, Hoffmann RM, Roecker E, Voss BJ, Lorentzen D, Knechtle SJ, Reed A, Kalayoglu M, Belzer FO (1992) The effect of donor age, recipient age and HLA match on immunologic graft survival in cadaver renal transplant ecipients. Transplantation 53: 55–59
28. Ponticelli C, Civati G, Tarantino A, Quarto di Palo F, Corbetta G, Minetti L, Vegeto A, Belli L (1996) Randomized study with cyclosporine in kidney transplantation: 10 year follow-up. J Am Soc Nephrol 7: 792–797
29. Rao KV, Kasiske BL, Odlund MD, Ney AL, Andersen RC (1990) Influence of cadaveric donor age on posttransplant renal function and graft outcome. Transplantation 49: 91–95
30. Roels L, Waer M (1994) The aging donor kidney: survey of complications and long-term results. J Nephrol 7: 19–26
31. Schweitzer EJ, Matas AJ, Gillingham KJ, Payne WD, Gores PF, Dunn DL, Sutherland DE, Najarian JS (1991) Causes of renal allograft loss. Ann Surg 214: 679–688

32. Sheil AGR, Hall BM, Tiller DJ (1983) Australian trial of cyclosporine (CyA) in cadaveric donor renal transplantation. Transplant Proc 15 [Suppl 1]: 269–273
33. Shoskes D, Churchill B, McLorie G, Khoury A (1990) The impact of ischemic and immunologic factors on early graft function in pediatric renal transplantation. Transplantation 50: 877–880
34. Shoskes DA, Parfrey NA, Halloran PF (1990) Increased major histocompatibility complex antigen expression in unilateral ischemic acute tubular necrosis in the mouse. Transplantation 49: 201–207
35. Solez K, Axelsen RA, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, Crocker BP, Droz D, Dunnill MS, Halloran PF, Häyry P, Jennette JC, Keown PA, Marcussen N, Mihatsch MJ, Morozumi K, Myers BD, Nast CC, Olsen S, Racusen LC, Ramos LL, Rosen S, Sachs DH, Salomon DR, Sanfilippo F, Verani R, Willebrand E von, Yamaguchi Y (1993) International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. Kidney Int 44: 411–422
36. Starzl TE,Weil R III, Iwatsuki S, Klintmalm G, Schröter GP, Koep LJ, Iwaky I, Terasaki PI, Porter KA (1980) The use of cyclosporin A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 151: 17–26
37. Terasaki PI, Koyama H, Cecka JM, Gjertson DW (1994) The hyperfiltration hypothesis in human renal transplantation. Transplantation 57: 1470–1480
38. Terasaki PI, Yuge J, Cecka JM, Gjertson DW, Takemoto S, Cho Y (1994) Thirty-year trends in clinical kidney transplantation. In: Clinical transplants 1993. Terasaki P, Cecka JM (eds), UCLA Tissue Typing Laboratory, Los Angeles, pp 553–562
39. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S (1995) High survival rates of kidney transplants from spousal and living unrelated donors. N Engl J Med 333: 333–336
40. The Canadian Multicentre Transplant Study Group (1983) A randomized clinical trial of cyclosporin in cadaveric renal transplantation. N Engl J Med 309: 809–815
41. Thiel G, Harder F, Lörtscher R, Brünischolz M, Landmann J, Brunner F, Follath F, Wenk M, Mihatsch M (1983) Cyclosporin A used alone or in combination with low-dose steroids in cadaveric renal transplantation. Klin Wochenschr 61: 991–1000
42. Troppmann C, Gillingham KJ, Gruessner RWG, Dunn DL, Payne WD, Najarian JS, Matas AJ (1996) Delayed graft function in the absence of rejection has no long-term impact. A study of cadaver kidney recipients with good graft function at 1 year after transplantation Transplantation 61: 1331–1337
43. Tullius SG, Hancock WW, Heemann UW, Azuma H, Tilney NL (1994) Reversibility of chronic renal allograft rejection: critical effect of time after transplantation suggests both host immune dependent and independent phases of progressive injury. Transplantation 58: 93–99
44. Vanrenterghem Y (1995) Acute rejection and renal allograft outcome. Nephrol Dial Transplant 10 [Suppl]:29–31
45. Vanrenterghem Y, Peeters J (1994) Impact of cyclosporine on chronic rejection and graft vasculopathy. Transplant Proc 26: 2560–2563
46. Whithington PF, Emond JC, Whithington SH, Broelsch CE, Backer AL (1990) Small-bowel length and the dose of cyclosporine in children after liver transplantation. N Engl J Med 322: 733–738
47. Yuge J, Cecka JM (1992) Sex and age effects in renal transplantation. In: Clinical transplants 1991. Terasaki P, Cecka JM (eds), UCLA Tissue Typing Laboratory, Los Angeles, pp 257–267