Transpl Int (1994) 7: 284–287

ORIGINAL ARTICLE

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Long-term renal allograft function

Received: 6 May 1993
Received after revision: 27 August 1993
Accepted: 30 September 1993

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Abstract Long-term function of transplanted kidneys was measured as ^{51}Cr EDTA clearance (GFR). All kidneys transplanted in 1985 with preserved function after 6 months were again studied after 12, 24, 36, and 60 months. Grafts lost due to the patient's death were excluded. There was no significant GFR difference at 6 months between grafts with continued function (median 42 ml/min, range 15–79 ml/min; n = 69) and those that failed later (median 39 ml/min, range 20–87 ml/min; n = 18). Median GFR of surviving grafts remained stable, but individual variations included reductions by 5–49 ml in 29 patients and increases by 5–33 ml in 22 patients. Nine of the failing grafts showed a continuous but rarely linear decline, while eight had initially increased GFR. The long-term GFR changes were not statistically correlated with the dosage of cyclosporin at 6 months or with later dose reductions. In conclusion, renal transplant function may deteriorate in the long-term but can also improve.

Key words Kidney transplantation, long-term function · Long-term function, kidneys · ^{51}Cr EDTA clearance, long-term

Introduction

Late loss of kidney function after transplantation is often referred to as chronic rejection, even in the absence of histopathologic evidence. Schematically, the process is considered to proceed at a set pace that is linear over time. The purpose of this study on transplanted kidneys with preserved function 6 months post-transplantation was to monitor their continued function until the 5-year follow-up or definite failure, using ^{51}Cr EDTA clearance as a measure of glomerular filtration rate (GFR), and to evaluate circumstances for late failures, with respect to histopathologic findings in biopsy specimens and the immunosuppressive regimen.

Patients and methods

Patients

Patients who received renal transplants in 1985 and had preserved graft function after 6 months underwent clearance examinations 6, 12, 24, 36, and 60 months post-transplantation. Results from patients who died with a well functioning graft (n = 9) were excluded from the analysis. The median age of the other 87 consecutive patients was 40 years (range 10–70 years). Sixteen (18%) had diabetic nephropathy. Sixty-five (75%) received first transplants, 17 (20%) second, and 5 third or fourth transplants. The median age of the donors was 44 years (range 13–74 years). Twenty-seven patients (31%) received kidneys from living related donors.

Immunosuppressive regimen

According to running protocols, cyclosporin A (CyA) and prednisolone were given alone to 31 patients and supplemented with azathioprine for 47 patients, 0.9 (range 0.3–1.8) mg/kg body weight (BW). The median dose of prednisolone was 11 mg by 6 months, 9 mg by 1 year, 7 mg by 3 years, and 6.5 mg by 5 years post-transplantation.

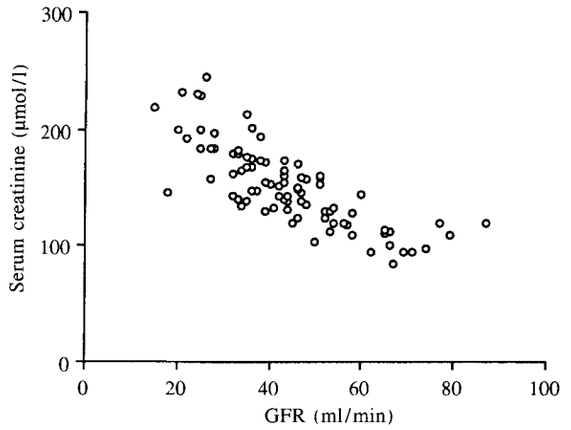

Fig. 1 Correlation between serum creatinine and clearance of ^{51}Cr EDTA in 85 individual patients 6 months post-transplantation. Logarithmic regression $r^2 = 0.66$

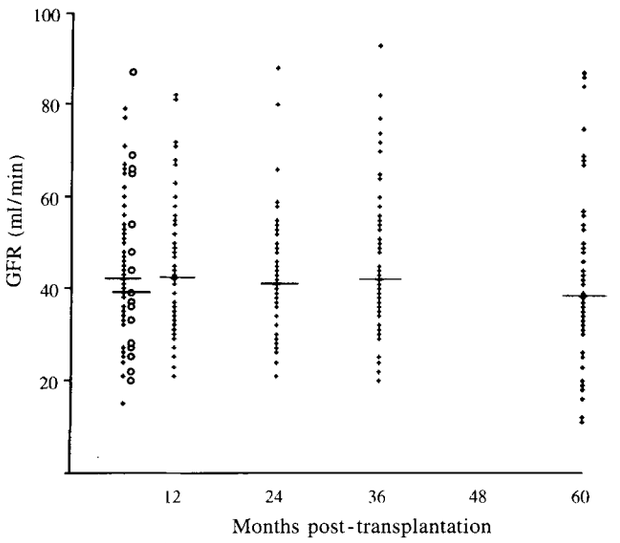

Fig. 2 Individual ^{51}Cr EDTA clearance values 6 months until 5 years post-transplantation for functioning grafts (♦, $n = 69$) and at 6 months for grafts that failed during follow-up (○, $n = 18$. Median values are indicated by *horizontal bars*. There are no significant differences between any groups

The initial CyA dose was based on the patients' BW, but continued dosage was according to trough concentration in plasma or blood and graft function. Nine patients, five with HLA-identical living donors, were treated with azathioprine and prednisolone only.

Methods

The 87 patients underwent 388 of 394 scheduled clearance investigations. ^{51}Cr EDTA was given as a single bolus injection [4] and the plasma slope was used to calculate GFR, except with expected values below 20 ml/min, when the filtrated isotope was recovered in the urine [8]. GFR was expressed as ml/min per 1.73 m^2 body surface area. Serum creatinine was measured using a modified Jaffé method. CyA trough concentration level was measured in plasma or blood with three different techniques in different eras. There is no accurate conversion factor relating the various methods. Therefore, only the 5-year follow-up analyses obtained by a monoclonal antibody radioimmunoassay on whole blood samples (Cyclo-Trac, Incstar, Stillwater, Minn., USA) are reported.

Statistics

Unless otherwise stated, values given represent the median, with the range indicated within parentheses. Differences between groups of patients were calculated with the Mann-Whitney U-test and paired data were evaluated using the Wilcoxon signed rank test.

Results

The investigation 6 months post-transplantation showed a wide range of serum creatinine and GFR values (Fig. 1). There was a good correlation between the two measures of renal function ($r^2 = 0.66$ for log creatinine to GFR), but in the individual case, serum creatinine could not accurately predict GFR.

Until the 5-year follow-up, 18 patients had lost graft function, 2 due to death with failing grafts. The causes of graft failure – as established by histopathologic investigation of biopsies obtained from the still functioning graft in 14 cases and from tissue from removed transplants in 3 – were recurrence of original disease ($n = 6$), chronic vascular rejection ($n = 4$), de novo glomerulopathy or transplant glomerulopathy ($n = 5$), acute cellular rejection ($n = 1$), and widespread fibrosis ($n = 1$). One case was not investigated.

Figure 2 shows that for the cohort of patients who retained graft function after 5 years ($n = 69$), median GFR remained unchanged: 42 (15–79), 42 (21–82), 41 (21–88), 42 (20–93), and 38 (11–87) ml/min at 6, 12, 24, 36, and 60 months post-transplantation, respectively ($P = 0.23$ for 6 months vs 5 years). In the individual case, the outcome until 5 years post-transplantation varied between a fall by 49 ml/min in GFR and an increase by 33 ml/min. This variation is illustrated in Fig. 3. GFR increased by 5 ml/min or more in 22 patients. Constant GFR was observed in about one-third of the patients. Changes in either direction were rarely gradual. Thus, improvement or deterioration was often observed early or at the end of the observation period, followed or preceded by stable values. Comparing functioning grafts from living related and cadaveric donors, the change in GFR did not differ ($P = 0.43$, Fig. 3).

Figure 2 further shows that the group of 18 patients who were to lose their grafts during follow-up could not be distinguished by their GFR at the 6-month evaluation (median 39, range 20–87 ml/min; $P = 0.28$). As demonstrated in Fig. 4, the individual time-course was not linear in most cases and included initial increases in GFR in 8 of the 18 patients.

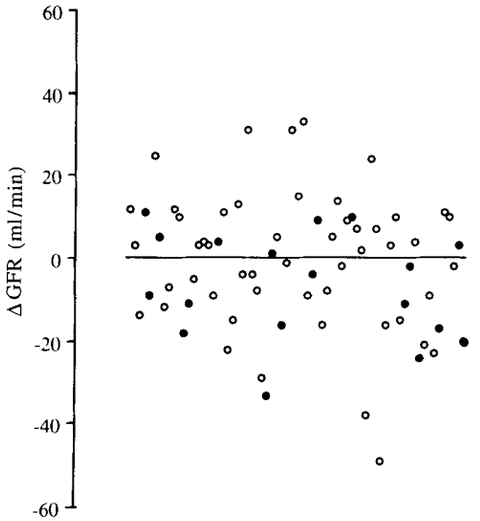

Fig. 3 Net change in ^{51}Cr EDTA clearance (ml/min per 1.73 m^2 body surface area) from 6 months to 5 years post-transplantation in 69 patients with preserved function. (○ Grafts from cadaveric donors, ● grafts from living related donors)

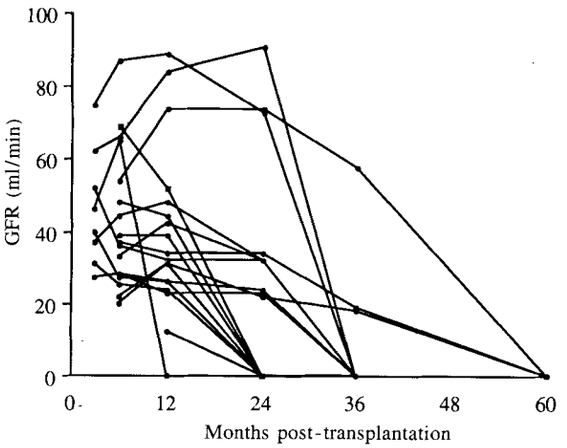

Fig. 4 Individual development of ^{51}Cr EDTA clearance in 18 patients with graft failure 6 months to 5 years post-transplantation. Failed grafts set to GFR 0

Serum creatinine values gave similar results: there was no difference at 6 months between grafts to be lost versus grafts to function (median 155 vs 146 μmol/l, respectively; $P = 0.22$) and no further change for grafts functioning at 5 years post-transplantation (median 153 μmol/l). The GFR increase of 5 ml/min or more in the 22 patients caused a fall in serum creatinine from a median of 150 to 128 μmol/l.

For patients taking CyA, the immunosuppressive treatment at 6 months post-transplantation was not predictive of the further course. Doses of CyA were 3.4 (1.4–7.6) mg/kg BW for patients with graft loss versus 3.7 (1.2–7.9) mg/kg BW for those with retained function ($P = 0.44$), and doses of prednisolone were 11.5 (7.5–25) mg vs 11.0 (5.0–20) mg; ($P = 0.98$). The proportion of patients taking azathioprine was not different – 8/15 versus 39/63 – and the doses taken were 0.9 (0.6–1.1) versus 0.9 (0.3–1.8) mg/kg BW ($P = 0.68$). Within the limits given, there was no apparent relationship between the prescribed dose of CyA at 6 months and the long-term GFR. During follow-up, CyA was stopped completely in only one patient who subsequently lost his graft. In the patients with preserved function, the prescribed dose of CyA was tapered to 2.4 (1.2–4.4) mg/kg BW. This dose corresponded to a whole blood trough level of 61 (15–200) μg/l ($n = 63$, including four patients with a concentration below the detection limit 30 μg/l calculated as 15 μg/l). The correlation between the prescribed dose and the recorded trough level was statistically significant ($P = 0.005$) but far from accurate ($r^2 = 0.13$). There was no statistically significant correlation between the individual changes in CyA dose 6 months to 5 years post-transplantation and the change in GFR that occurred during that period.

Discussion

A stable renal function during long-term follow-up has previously been reported for groups of renal transplant patients treated with CyA [1, 7, 9, 10, 16]. This is true provided that cases with definite failure are excluded and those functioning are presented as a group. The present study demonstrates that the stable values for functioning grafts reflect a wide range of decreasing and increasing function in individual patients. In one previous report with adequate measurements of kidney function (DTPA clearance) [16], mean values did not vary with time, but in individual patients there were changes and in both directions, as in the present series.

Improved or decreased GFR may be overlooked if only serum creatinine is measured because this is an insensitive marker of renal function, especially in the normal or near-normal range. Serum creatinine is also influenced to a significant extent by factors other than renal function, such as diet [17] and body composition [2], which may change much in the long run. The formula clearance only partly compensates for these limitations [2] and the endogenous creatinine clearance adds others [16].

To evaluate change of long-term graft function, linear regression of the inverse of creatinine has been used [1, 9, 10]. This calculation assumes a renal disease or damage with linear progression over time in each case, which does not apply to the general renal transplant population, as made evident by our investigation.

The function of a renal transplant depends on a number of factors. It may be impaired by acute and chronic rejection, recurrence of original disease, toxicity of various drugs, and hemodynamic disturbance [13]. These harmful effects may be more or less counteracted in each case by

reparative forces: CyA nephrotoxicity may be reversible, and rejection and recurrent renal disease can sometimes be reversed by treatment. A compensatory improvement in function by hemodynamic mechanisms or growth can probably occur as in other single kidneys and in kidneys otherwise damaged or diseased [3, 6, 12]. Adult kidneys transplanted into children have been demonstrated to grow after the 1st post-transplant year [5].

In contrast to what has been reported for patients treated with azathioprine and prednisolone, GFR at 6 months post-transplantation was of no prognostic value with regard to future function. This discrepancy has previously been observed [14] and is probably related to the better immunosuppressive effect and/or to the nephrotoxic effect of CyA.

The fact that no correlations were obtained between doses of immunosuppressive agents and graft function does not, of course, mean that there is no such influence. The range of doses prescribed may be too narrow and drug effects may be complicated by interacting factors. Furthermore, the effects of changes in the immunosuppressive regimen are difficult to evaluate in retrospect and also in prospective studies [7, 11, 18] since dosages must be interferred with as transplant function is challenged. This includes reduction of CyA dosage as a useful and necessary instrument [1, 14, 19]. The lower doses of CyA given to patients with impaired graft function, as reported by Salomon et al. [15] may, thus, be the effect rather than the cause of failure. The doses used by our patients are lower than in most published series. The extent to which immunosuppression may be reduced is difficult to assess in the long run since moderate reductions in immunosuppressive therapy are unlikely to cause immediate effects in this phase. In the present series, only 5 of 17 late graft losses were due to chronic vascular rejection. One acute rejection occurred in an overtly noncompliant patient and one graft rapidly became severely fibrotic. Whether the various types of glomerulopathy that caused the other graft losses could have been prevented by a higher dosage of CyA remains uncertain. Our results suggest that individually prescribed combinations of low-dose cyclosporin and prednisolone, with optional azathioprine, are reasonably safe with regard to the risk of rejection within 5 years and may allow the various mechanisms that may increase GFR to prevail.

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