Transpl Int (1998) 11: 46–52

ORIGINAL ARTICLE

M. Ferda Senel
Charles T. Van Buren
Maria Welsh
Barry D. Kahan

Impact of early cyclosporin average blood concentration on early kidney transplant failure

Received: 27 May 1997
Received after revision: 8 August 1997
Accepted: 21 August 1997

M. F. Senel · C. T. Van Buren
M. Welsh · B. D. Kahan (✉)
Division of Immunology and
Organ Transplantation,
Department of Surgery,
The University of Texas Medical School,
6431 Fannin Street, Suite 6.240,
Houston, TX 77030, USA
Fax: + 1 713 500 0785

Abstract This retrospective study served to examine the correlation between the degree of cyclosporin (CyA) exposure, as estimated by a single pharmacokinetic (PK) profile performed at 1 week post-transplant, and the outcome of 290 consecutive renal transplants performed over a 6-year period. For this retrospective analysis patients were stratified into four historical groups based on 12- versus 24-h PK studies and on the use of radioimmunoassay versus fluorescence polarization immunoassay methods for estimates of CyA concentrations. Four PK measures – trough concentration (C_0), average concentration values (C_{av}; i.e., the dosing interval-corrected area under the concentration-time curve), maximum concentration (C_{max}), and time to maximum concentration (t_{max}) – were examined as predictors of patient, graft, and rejection-free survival rates for each of the four groups individually and for all groups combined. Patients with an initial $C_{av} \geq 550$ ng/ml had higher 1-year (88 %) and 6-year (66 %) graft survival rates than patients with $C_{av} < 550$ ng/ml, who had 1- and 6-year graft survival rates of 80 % and 59 %, respectively (P = NS). Statistically significant differences were observed in graft survival rates between patients with $C_{av} < 550$ versus $C_{av} \geq 550$ ng/ml at 30 (88 % vs 96 %; $P < 0.02$), 60 (85 % vs 94 %; $P < 0.007$), 90 (85 % vs 94 %; $P < 0.02$), and 180 (83 % vs 92 %; $P < 0.05$) days. Moreover, patients with $C_{av} < 550$ ng/ml displayed more severe rejection episodes, as judged by Banff classification, than patients who displayed $C_{av} \geq 550$ ng/ml (grades II and III; 71 % vs 50 %; $P = 0.036$). In contrast, the C_0, C_{max}, and t_{max} values did not correlate with patient, graft, or rejection-free survival rates. The pharmacokinetic parameter of C_{av} correlated strongly with early graft survival and may, therefore, be a useful predictor of those renal transplant patients who may require more intensive post-transplant monitoring of CyA concentrations by serial PK studies to improve graft survival.

Key words Cyclosporin, pharmacokinetics, kidney transplantation · Kidney transplantation, cyclosporin, pharmacokinetics

Introduction

The benefits of cyclosporin (CyA) use in renal transplantation [1] to improve graft survival [2] have been partially offset by the agent's narrow therapeutic window [10, 13]. The monitoring of drug concentrations as surrogate markers of immunosuppressive versus toxic effects has been used to compensate for the marked interindividual variations in CyA pharmacokinetics [7] so as to optimize therapeutic effects [14]. Moreover, it

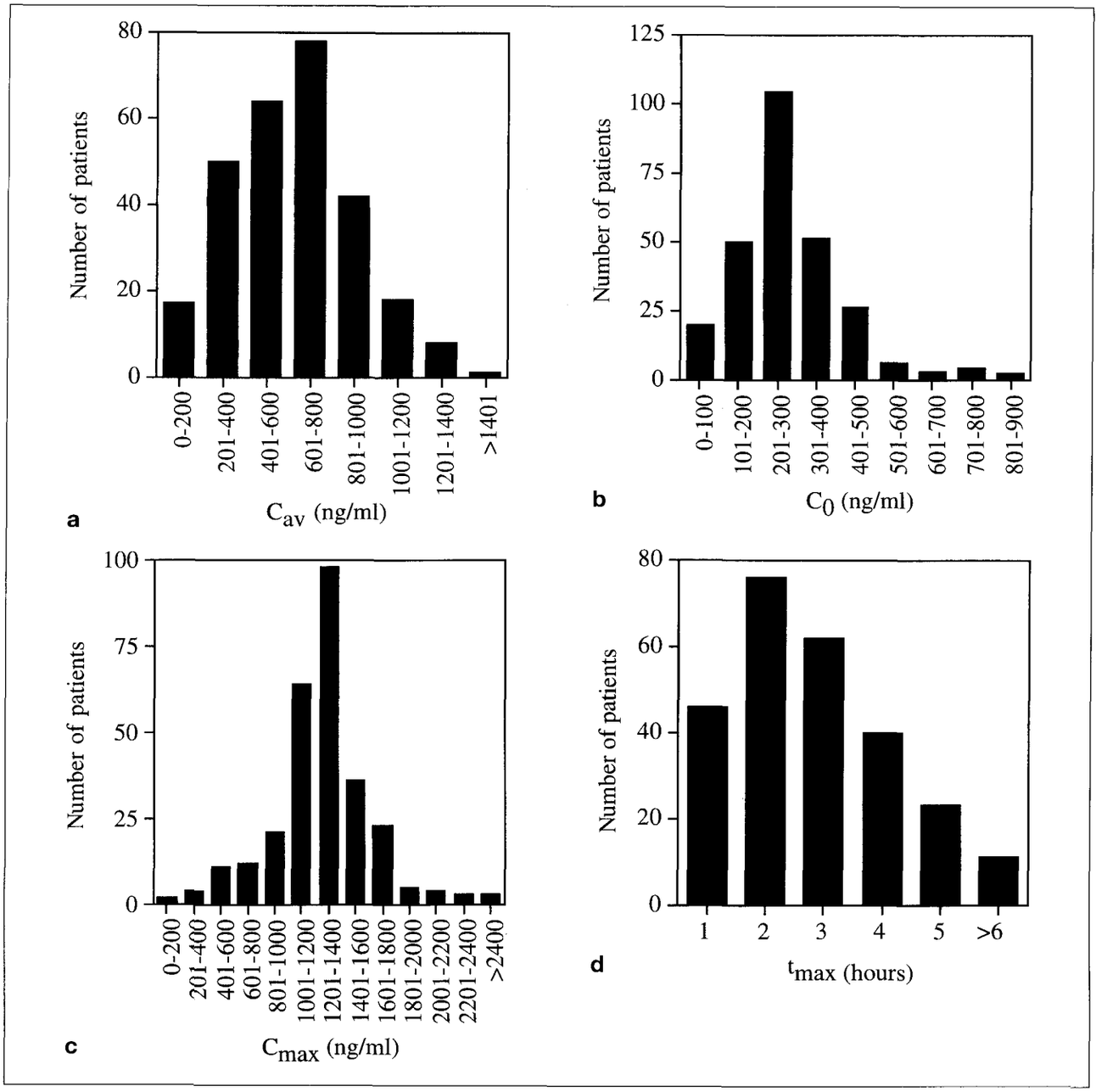

Fig. 1a–d The frequency distribution of: **a** average cyclosporin (CyA) concentration (C_{av}); **b** trough CyA concentrations (C_0); **c** maximum CyA concentrations (C_{max}); and **d** time to maximum CyA concentrations (t_{max}) among all patients

has been shown that CyA average drug concentration (C_{av}), [6] as expressed by the quotient of the area under the concentration-time curve and the dosing interval (AUC; AUC/dosing interval) [9], correlates better than trough concentration (C_0) with clinical events [3, 12].

An initial analysis of the pharmacokinetic studies of 160 consecutive renal transplant recipients documented that patients with C_{av} values < 350 ng/ml on their first postoperative AUC profile displayed significantly poorer 1-year graft survival rates than those with C_{av} values ≥ 350 ng/ml, and patients with C_{av} ≥ 550 ng/ml had the lowest incidence of acute rejection episodes [11]. Because of the cumbersome nature and cost of pharma-

cokinetic measurements, these observations have not been re-examined in de novo renal transplant recipients. The present study analyzed the impact of the C_{av} value on patient, graft, and rejection-free survival rates, and on the severity of acute rejection episodes among 290 consecutive renal transplant patients stratified on the basis of a C_{av} value < 550 or ≥ 550 ng/ml on a single 1-week CyA PK profile. The single C_{av} value correlated strongly with early graft survival and with the severity of acute rejection episodes.

Patients and methods

Patients

The study cohort consisted of all 290 consecutive patients who received cadaveric (CAD; $n = 240$) or living-related (LRD; $n = 50$) renal transplants between December 1988 and September 1994. Excluded from the study were 20 patients who received antithymocyte globulin (ATGAM; Upjohn) or OKT3 (Orthoclone; Ortho) as induction therapy due to acute tubular necrosis. The study protocol was approved by the Institutional Committee for the Protection of Human Subjects. Patient ages ranged from 18 to 72 years (mean ± SD = 41.7 ± 12.4 years). The study included 117 female and 173 male patients. The mean follow-up time was 30.7 ± 25.2 months.

Immunosuppressive regimen

Immunosuppression was routinely initiated with intraoperative intravenous (i.v.) administration of 500 mg of methylprednisolone (Solumedrol; Upjohn), which was subsequently tapered to 120 mg/day at day 1, to 30 mg/day prednisone (Pred) at 1 week, to 20 mg/day at 1 month, and to 10 mg/day at 1 year post-transplant. Cyclosporin (CyA; Sandimmune; Novartis, Basel, Switzerland) was initiated 4 h after revascularization at a dose of 3 mg/kg per day by continuous i.v. infusion. The CyA dose was then adjusted to achieve steady-state whole blood concentrations of 400 ng/ml [11].

Pharmacokinetic study design

For each patient a pharmacokinetic profile was obtained only once, i.e., during the 1st post-transplant week. Every patient was treated according to one of three consecutive protocols:

(1) daily doses of oral (p.o.) CyA (14 mg/kg) 6 h after the discontinuation of i.v. CyA, with a 24-h kinetic study performed with blood samples obtained 30 min before and 2, 4, 6, 8, 10, 12, 14, and 24 h after drug administration;
(2) two daily 7 mg/kg CyA doses p.o. 6 h after the discontinuation of i.v. CyA, with a 12-h kinetic study performed with blood samples obtained at 0, 2, 4, 6, 8, 10, and 12 h after drug administration; or
(3) administration of 7 mg/kg CyA p.o. during the i.v. infusion, with a 12-h kinetic study performed with blood samples obtained 30 min before and 2, 4, 6, 8, 10, and 12 h after drug administration.

CyA levels were measured by the monoclonal whole blood radioimmunoassay (RIA; Inc Star, Stillwater, Minn., for the first 100 transplant recipients) or by the selective monoclonal antibody-based fluorescence polarization immunoassay (FPIA; TDx, Abbott Laboratories, Abbott Park, Ill., for the latter 190 recipients). AUC values were calculated by the trapezoidal rule and C_{av} values were calculated on the basis of the dosing interval (in hours).

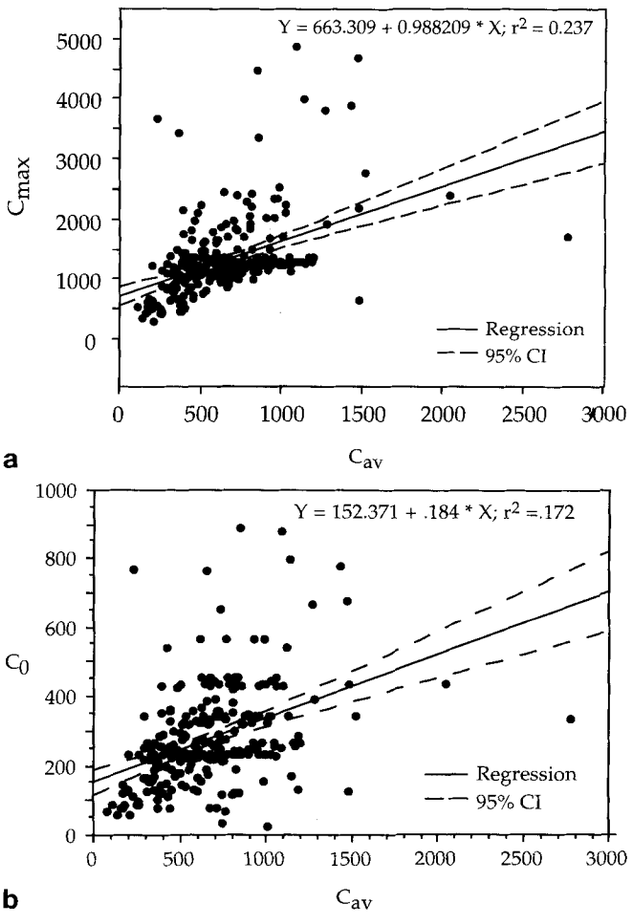

Fig. 2 The correlation of average CyA concentration (C_{av}) values with: **a** the maximum cyclosporin (CyA) concentration (C_{max}) or **b** the trough CyA concentration (C_0)

Patients were assigned to one of the four study cohorts according to the type of kinetic study and the type of assay used to measure CyA blood concentrations. Patients in group 1 underwent 24-h kinetic studies with blood concentration estimated by RIA; those in group 2, 24-h kinetic studies with FPIA analysis; those in group 3, 12-h kinetic studies with FPIA analysis; and those in group 4, 12-hour kinetic studies, for which i.v. and p.o. CyA was administered simultaneously, with FPIA analysis. Groups 1, 2, 3, and 4 included 100, 89, 44, and 57 patients, respectively.

Diagnosis of acute rejection

Renal allograft rejection episodes were only diagnosed by a positive biopsy, which was performed when serum creatinine values either failed to fall after transplantation or when they inexplicably increased by more than 30%. All slides were examined by a pa-

Table 1 Demographic characteristics of patients with $C_{av} < 550$ versus ≥ 550 ng/ml

Demographic factor	Patient group	$C_{av} < 550$ ng/ml		$C_{av} \geq 550$ ng/ml		P[a]
Number enrolled[b]						
	All	127		163		NS
	1	54		46		NS
	2	46		43		NS
	3	18		26		NS
	4	9		48		NS
Age[b]						
	All	41.7 ± 12.5		41.8 ± 13		NS
	1	41.8 ± 12.7		41.5 ± 13		NS
	2	41.6 ± 13		42.7 ± 13.2		NS
	3	41.9 ± 12.5		40.7 ± 12.6		NS
	4	40.9 ± 12.4		41.9 ± 11.7		NS
Gender[a]						
		Female (%)	Male (%)	Female (%)	Male (%)	
	All	50 (40)	77 (60)	67 (41)	96 (59)	NS
	1	18 (34)	36 (66)	15 (33)	31 (67)	NS
	2	20 (43)	26 (57)	14 (32)	29 (68)	NS
	3	8 (44)	10 (56)	14 (54)	12 (46)	NS
	4	4 (44)	5 (56)	24 (50)	24 (50)	NS
Donor source[a]						
		Living-related (%)	Cadaveric (%)	Living-related (%)	Cadaveric (%)	
	All	20 (16)	107 (84)	30 (18)	133 (82)	NS
	1	10 (18)	44 (82)	16 (35)	30 (65)	NS
	2	4 (9)	42 (91)	5 (12)	38 (88)	NS
	3	4 (22)	14 (78)	3 (12)	23 (88)	NS
	4	2 (22)	7 (78)	6 (9)	42 (91)	NS
HLA Match[b]						
	All	2.0 ± 1.9		2.1 ± 1.9		NS
	1	2.0 ± 1.8		2.4 ± 1.9		NS
	2	1.9 ± 1.8		2.1 ± 1.9		NS
	3	1.8 ± 1.8		2.0 ± 2.0		NS
	4	2.4 ± 2.0		2.2 ± 1.9		NS
Diabetes mellitus[a]						
		Yes (%)	No (%)	Yes (%)	No (%)	
	All	26	101	46	117	NS
	1	9 (17)	45 (83)	16 (35)	30 (65)	0.04
	2	11 (24)	35 (76)	10 (23)	33 (77)	NS
	3	4 (22)	14 (78)	7 (27)	19 (73)	NS
	4	2 (22)	7 (67)	13 (27)	35 (73)	NS

* $P \leq 0.05$ was considered significant
[a] Chi-square test
[b] Student's t-test

thologist who was unaware of the CyA C_{av} values. The severity of the rejection episodes was graded as mild for the presence of tubulitis (grade I), moderate for vasculitis (grade II), or severe for interstitial hemorrhage (grade III). Graft loss was defined as return to dialysis or death.

Statistical analysis

The parameters of patient, graft, and rejection-free survival rates, as well as severity of rejection episodes, were analyzed for the entire study cohort and compared between patients with C_{av} values < 550 ng/ml versus values ≥ 550 ng/ml. In addition, the study sought to correlate adverse outcomes with other concentration measures, such as trough concentration (C_0), which was stratified as 0–150, 151–250, or > 250 ng/ml, maximum CyA concentration (C_{max}), which was stratified as < 800, 800–1200, or > 1200 ng/ml, and time to maximum concentration (t_{max}), which was stratified as < 2, 2–4, or > 4 h. The patient, graft, and rejection-free survival parameters were analyzed by the log-rank test. To compare demographic characteristics among low versus high C_{av} groups, Fisher's exact test, the chi-square test, Student's t-test, and the analysis of variance (ANOVA) were used. The chi-square test was used to compare C_{av} with the severity of rejection episodes. The Pearson

Table 2 Pharmacokinetic parameters (C_{av}, C_{max}, t_{max}, and C_0) of the patient groups

Patient group	C_{av}	P*[a,b]	C_{max}	P*[a,b]	t_{max}	P*[a,b]	C_0	P*[a,b]
Group 1	612 ± 352	NS	1559 ± 795	0.001	3.7 ± 2.3	NS	278 ± 146	NS
Group 2	635 ± 344	NS	1219 ± 628	NS	3.8 ± 2.9	NS	282 ± 124	NS
Group 3	682 ± 288	NS	1059 ± 269	0.03	2.9 ± 2.0	NS	267 ± 168	NS
Group 4	788.2 ± 217	0.03	1192 ± 331	NS	3.0 ± 1.8	NS	300 ± 128	NS
All	665 ± 322	–	1303 ± 633	–	3.5 ± 2.4	–	275 ± 134	–

* $P \leq 0.05$ was considered significant
[a] Compared to all
[b] Student's t-test

Table 3 Six-year actuarial patient and graft survival rates and rates of rejection-free intervals for patients with $C_{av} < 550$ versus ≥ 550 ng/ml

	$C_{av} < 550$ ng/ml	$C_{av} \geq 550$ ng/ml	P*
Patients	127	163	–
Patient survival (%)	88 %	90 %	NS[a]
Graft survival (%)	59 %	66 %	NS[a]
Rejection-free (%)	41 %	54 %	NS[a]
Acute rejection:			
Mild (%)	29 %	50 %	0.036[b]
Moderate/severe (%)	71 %	50 %	0.036[b]

* $P \leq 0.05$ was considered significant
[a] Log-rank test
[b] Chi-square test

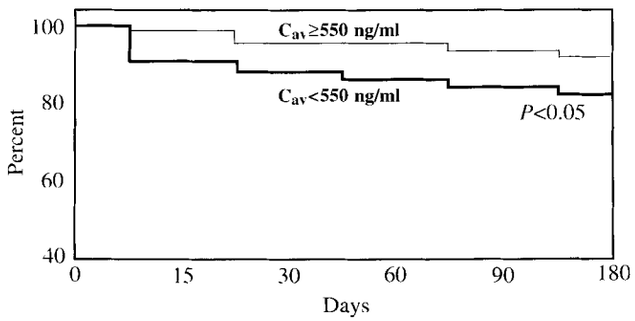

Fig. 3 Post-transplant 180-day graft survival rates for patients with average CyA concentration (C_{av}) values < or ≥ 550 ng/ml

correlation coefficient was used to examine the relationships between the pharmacokinetic parameters. SAS (SAS Institute, Cary, N.C.) and Excel (Microsoft, Santa Rosa, Calif., version 7.0) applications were used for statistical calculations on an IBM-compatible personal computer with a Pentium processor. A P value ≤ 0.05 was considered significant.

Results

Six-year analysis

This retrospective analysis examined the correlation between C_0, C_{max}, t_{max}, or low (< 550 ng/ml) versus high (≥ 550 ng/ml) C_{av} values and patient, graft, and rejection-free survival rates, as well as severity of rejection episodes. The overall mean C_{av}, C_0, C_{max}, and t_{max} values were 664.63 ± 322.17 ng/ml, 275.44 ± 134.35 ng/ml, 1303.24 ± 632.95 ng/ml, and 3.5 ± 2.4 h, respectively (Fig. 1A–D). The pharmacokinetic parameters of C_0, C_{max}, and t_{max} did not correlate with patient, graft, and rejection-free survival rates, or with severity of rejection episode (data not shown). Neither the C_{max} ($r^2 = 0.237$) nor the C_0 ($r^2 = 0.17$) values correlated with C_{av} values (Fig. 2A–B). The t_{max} values were similar in all groups.

The demographic characteristics of age, gender, donor source (CAD versus LRD), HLA match, and presence of diabetes mellitus were not significantly different between patients with C_{av} values < 550 ng/ml and those with $C_{av} \geq 550$ ng/ml (Table 1). However, in group 1 the incidence of diabetes mellitus was higher among patients with $C_{av} \geq 550$ ng/ml than among those with $C_{av} < 550$ ng/ml. An analysis of the individual groups showed that the mean C_{av} was higher for group 4, and the mean C_{max} was higher for group 1 than the mean C_{av} and C_{max} values for all groups combined (Table 2). The higher C_{av} value in group 4 may have resulted from the concomitant administration of i.v. and p.o. CyA.

The 6-year mean patient and graft actuarial survival rates and the rejection-free survival rates were 89 %, 63 %, and 49 %, respectively, for all patients combined.

Table 4 Actuarial graft survival rates of all patient groups combined

Days/years	All groups combined		P*
	C_{av} < 550 ng/ml	C_{av} ≥ 550 ng/ml	
30	88 %	96 %	< 0.02
60	85 %	94 %	< 0.007
90	85 %	94 %	< 0.02
180	83 %	92 %	< 0.05
360	80 %	88 %	NS
6-year	59 %	66 %	NS

* $P \leq 0.05$ was considered significant (log-rank test)

Table 5 Ratio of mild versus moderate or severe rejections among patients with C_{av} < 550 versus ≥ 550 ng/ml

Days/years	C_{av} < 550		C_{av} ≥ 550		I
	Mild	Moderate/Severe	Mild	Moderate/Severe	
30	17 %	83 %	36 %	64 %	NS
60	17 %	83 %	39 %	61 %	< 0.05
90	20 %	80 %	41 %	59 %	0.04
180	22 %	78 %	46 %	54 %	0.02
360	24 %	76 %	46 %	54 %	0.03
6 years	29 %	71 %	50 %	50 %	0.036

* $P \leq 0.05$ was considered significant (chi-square test)

Patients with C_{av} ≥ 550 ng/ml experienced 6-year patient, graft, and rejection-free survival rates of 90 %, 66 %, and 54 %, respectively, compared with 88 %, 59 %, and 41 % for patients with C_{av} < 550 ng/ml (Table 3). The 6-year patient and rejection-free survival rates were similar in all four groups. In contrast, in group 1 the patients with C_{av} ≥ 550 ng/ml had longer 6-year actuarial graft survival rates (73 %) than patients with C_{av} < 550 ng/ml (55 %; P < 0.03).

Although the incidence of acute rejection episodes was similar in patients with C_{av} < and ≥ 550 ng/ml, the incidence of episodes diagnosed as moderate (grade II) or severe (grade III) was significantly greater among patients with C_{av} < 550 ng/ml than among those with C_{av} ≥ 550 ng/ml (71 % vs 50 %; P = 0.036; Table 3).

Early phase analysis

After analyzing overall 6-year results, we analyzed the outcomes for the 1st year alone by dividing the year into periods of 30, 60, 90, 180, and 360 days. Although patient and rejection-free survival rates were similar for patients with C_{av} < 550 and ≥ 550 ng/ml across all time periods, graft survival rates at 30, 60, 90, and 180 days were significantly higher among patients with C_{av} ≥ 550 ng/ml (Table 4; Fig. 3).

The mean C_0, C_{max}, and t_{max} values for all patients at all time periods did not correlate with patient, graft, or rejection-free survival rates. When the analyses were performed for each group individually, patients with C_{av} ≥ 550 ng/ml in group 1 had significantly higher 60-, 90-, and 360-day graft survival rates, and those in group 2 had significantly higher 180-day graft survival rates, than patients with C_{av} < 550 ng/ml (data not shown).

The proportion of grade II or III acute rejection episodes during each of the four time periods (60-, 90-, 180-, or 360-day) was higher among the patients with C_{av} < 550 ng/ml than those with C_{av} ≥ 550 ng/ml (Table 5).

Discussion

The large intra- and interindividual variability in drug pharmacokinetics obfuscates the therapeutic window of CyA [10]. Although trough levels are currently used to monitor CyA treatment, they provide an incomplete index of drug exposure and, thereby, of clinical immunosuppression. In contrast, pharmacokinetic monitoring of the AUC profile [4, 16] based on several timed whole blood samples yields a valuable estimate of exposure. Dose-interval-corrected C_{av} values correlate better with the occurrence of acute rejection episodes than do trough levels [8]. The potential benefits of AUC monitoring include a reduced number of routine clinical visits, fewer dosing changes, and better monitoring of patient compliance, as well as avoidance of errors due to spurious single trough level values and variability of sampling time with respect to dose administration. A recent study in which a high-performance liquid chromatography (HPLC) method was used to measure drug concentrations showed that the percent coefficient of variation of the AUC was lower than that of trough lev-

els. Therefore, AUC values are more reproducible than those of trough levels [16]. Failure to observe a correlation between AUC values and acute rejection episodes or nephrotoxicity in a study using a polyclonal RIA on serum samples [15] may be attributed to the nonspecific nature of the assay. Another study, in which the HPLC method was used to analyze 104 pharmacokinetic studies from 45 patients, showed a strong correlation between the pharmacokinetic parameters of C_{max} and AUC and the incidence of acute rejection episodes [9].

The present study retrospectively analyzed four cohorts of patients with similar demographic characteristics. It documented that post-transplant C_{av} values ≥ 550 ng/ml were associated with higher 30-, 60-, 90-, and 180-day graft survival rates, a time frame of events likely to be related to the pharmacokinetic findings. However, overall 6-year graft or patient survival rates did not correlate with C_{av} values. Because all pharmacokinetic studies were performed within 1 week after transplantation, it is more reasonable to correlate the C_{av} values with early graft survivals, and thus the combined analysis suggests that early post-transplant C_{av} predicted early, but not late, graft survival.

The present study failed to show any correlation between other pharmacokinetic parameters, such as C_0, t_{max}, or C_{max}, and patient, graft, or rejection-free survival rates. Furthermore, the C_0 ($r^2 = 0.18$) and C_{max} ($r^2 = 0.24$) values did not correlate well with C_{av} values.

Although the present investigation did not document a correlation between the C_{av} value and rejection-free survival rate, it did demonstrate a strong correlation between C_{av} and the severity of the rejection episode and early graft survival. These findings support previous reports that showed improved outcomes after kidney transplantation in patients with greater CyA exposure, confirming the benefit of a high level of CyA exposure in the post-transplant period for early graft survival. Serial measurement of C_{av} values after transplantation should assist in determining which patients show consistently high exposure to CyA and, thus, those who may enjoy a high overall survival rate. Implementation of such a protocol may be accelerated by the use of the new microemulsion formulation of CyA, which is more consistently absorbed than the previous formulation. This formulation may permit the use of abbreviated kinetic profiles that reduce the number of blood samplings and drug assays, thereby reducing the cost of AUC monitoring [5].

Acknowledgements This work was supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK 38016–10).

References

1. Calne RY, White DJ, Thiru S, Evans DB, McMaster P, Dunn DC, Craddock GN, Pentlow BD, Rolles K (1978) Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet II: 1323
2. Canadian Multicenter Transplant Study Group (1983) A randomized clinical trial of cyclosporine in cadaveric renal transplantation. N Engl J Med 309: 809–815
3. Frey FJ, Horber FF, Frey M (1988) Trough levels and concentration time curves of cyclosporine in patients undergoing renal transplantation. Clin Pharmacol Ther 43: 55–62
4. Grevel J, Kahan BD (1990) Area under the curve monitoring of cyclosporine therapy: the early post-transplant period. Ther Drug Monit 13: 89–95
5. Grevel J, Kahan BD (1991) Abbreviated kinetic profiles in area under the curve monitoring of cyclosporine therapy. Clin Chem 37: 1905–1908
6. Kahan BD (1988) Optimization of cyclosporine therapy. Transplant Proc 25: 5–9
7. Kahan BD, Welsh M, Knight R, Katz S, Lewis R, Grevel J, Van Buren CT (1992) Pharmacokinetic strategies for cyclosporine therapy in organ transplantation. J Autoimmun 5: 333–341
8. Kahan BD, Welsh M, Rutzky L, Lewis R, Knight R, Katz S, Napoli K, Grevel J, Van Buren CT (1992) The ability of pretransplant test-dose pharmacokinetic profiles to reduce early adverse events after renal transplantation. Transplantation 53: 345–351
9. Kasiske BL, Heim-Duthoy K, Rao KV, Awni WM (1988) The relation between cyclosporine pharmacokinetic parameters and subsequent acute rejection in renal transplant recipients. Transplantation 46: 716–722
10. Lindholm A (1991) Therapeutic monitoring of cyclosporine: an update. Eur J Clin Pharmacol 41: 273–283
11. Lindholm A, Kahan BD (1993) Influence of cyclosporine pharmacokinetics, trough concentrations, and AUC monitoring on outcome after kidney transplantation. Clin Pharmacol Ther 54: 205–218
12. Moyer TP, Post GR, Sterioff S, Anderson CF (1988) Cyclosporine nephrotoxicity is minimized by adjusting dosage on the basis of drug concentration in blood. Mayo Clin Proc 63: 241–247
13. Napoli KL, Kahan BD (1991) Considerations for monitoring cyclosporine in transplant recipients. Clin Lab Med 11: 671–691
14. Ptachcinski RJ, Venkataramanan R, Rosenthal JT, Burckart GJ, Taylor RJ, Hakala T (1985) Cyclosporine kinetics in renal transplantation. Clin Pharmacol Ther 38: 296–300
15. Sommer BG, Sing DE, Henry ML, Ferguson RM, Orozs CG (1988) Serum cyclosporine kinetic profile. Failure to correlate with nephrotoxicity or rejection episodes following sequential immunotherapy for renal transplantation. Transplantation 45: 86–90
16. Takahara S, Kokado Y, Kameoka H, Moutabarrik A, Jiang H, Ishibashi M, Okuyama A, Nishi Y, Chiba N, Sonoda T (1994) Clinical evaluation of trough levels and area under the curve in cyclosporine- and FK506-treated kidney transplant recipients. Transplant Proc 26: 2802–2806