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Higher tacrolimus trough levels on days 2–5 post-renal transplant are associated with reduced rates of acute rejection

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Abstract: We analyzed the association between whole-blood trough tacrolimus (TAC) levels in the first days post-kidney transplant and acute cellular rejection (ACR) rates. Four hundred and sixty-four consecutive, deceased-donor kidney transplant recipients were included. All were treated with a combination of TAC, mycophenolate mofetil and prednisolone. Patients were analyzed in four groups based on quartiles of the mean TAC on days 2 and 5 post-transplant: Group 1: median TAC 11 ng/mL (n = 122, range 2–13.5 ng/mL), Group 2: median 17 ng/mL (n = 123, range 14–20 ng/mL), Group 3: median 24 ng/mL (n = 108, range 20.5–27 ng/mL) and Group 4: median 33.5 ng/mL (n = 116, range 27.5–77.5 ng/mL). A graded reduction in the rates of ACR was observed for each incremental days 2–5 TAC. The one-yr ACR rate was 24.03% (95% CI 17.26–32.88), 22.20% (95% CI 15.78–30.70), 13.41% (95% CI 8.15–21.63) and 8.69% (95% CI 4.77–15.55) for Groups 1–4, respectively (p = 0.003). This study suggests that higher early TACs are associated with reduced rates of ACR at one yr.

C.M. O'Seaghdha, R. McQuillan, A.M. Moran, P. Lavin, A. Dorman, P. O'Kelly, D.M. Mohan, P. Little, D.P. Hickey and P.J. Conlon

Department of Nephrology and Transplantation, Beaumont Hospital, Dublin, Ireland

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Corresponding author: Peter Conlon, Department of Nephrology and Transplantation, Beaumont Hospital, Dublin 9, Ireland.
Tel.: +35318093000; fax: +35318376982;
e-mail: peterconlon@beaumont.ie

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Improving long-term graft survival remains the "holy grail" of renal transplantation. Efforts that focus on shortening cold-ischemia time (CIT) or improving HLA-matching yield only modest improvements in outcome. For example, at five yr post-transplant, the difference in graft survival between kidneys with a CIT of < 11 h compared to those of 32–41 h is only 6%, and the difference between zero-mismatch kidneys and six-antigen-mismatched kidneys is only 10% (1). Immunological injury from acute cellular rejection (ACR) and chronic allograft arteriopathy/interstitial fibrosis and tubular atrophy (IFTA), as well as drug nephrotoxicity, are the key mediators of medium to long-term graft loss.

ACR may first manifest clinically several days post-transplant, but the wheels of this process are set in motion as early as in the operating theater. The CD4 T cell, pivotal to both the initiation and co-ordination of the rejection response, recognizes foreign antigens derived from the allograft (2). Whereas previously it was held that this occurred via T cell subsets only in secondary lymphoid organs such as lymph nodes, it is now known that direct interaction between T cells and endothelial cells occurs within the graft and has a critical role in mediating ACR (3). As such, T cells meet transplant antigens and proliferate immediately after engraftment. Alloactivated CD4 T cells subsequently interact with the effector cells of the rejection response: B cells, cytotoxic CD8 T cells and monocyte/macrophages. These cells promote alloantibody production, antigen-specific cell lysis, and delayed type hypersensitivity responses, respectively, and ultimately cause graft destruction (4).

Pharmacological inhibition of this process at its inception should reduce rates of ACR. Indeed, previous studies examining both cyclosporine (5, 6) and sirolimus (7) have shown that drug levels in the immediate post-transplant period are a major determinant of subsequent ACR. It is known that tacrolimus (TAC) < 10 ng/mL is associated with increased rates of ACR by one month post-transplant (8). However, the effect of briefly targeting higher TAC in the immediate post-transplant period has not been explored. We retrospectively analyzed the association between TAC in the first days post-transplant and subsequent ACR rates.

Materials and methods

Our aim was to investigate the effect of higher tacrolimus (Prograf; Fujisawa GmbH, Munich, Germany) concentrations in the first days post-kidney transplant on rates of ACR at one yr. A single-center, retrospective analysis of data from 464 consecutive adult renal transplant recipients was performed at Beaumont Hospital, Dublin, Ireland. Data were collected on patients who received a deceased-donor kidney transplant between 1999 and 2005, and who received a combination of prednisolone, mycophenolate mofetil (MMF) and TAC as immunosuppression. No patients were excluded from the analysis.

All patients were given TAC at 0.15 mg/kg for two doses, starting preoperatively. This was then reduced to 0.1 mg/kg b.i.d., and subsequent doses were based on whole-blood 12-h trough levels. A microparticle enhancement immunoassay (MEIA; Abbott Diagnostics, Dublin, Ireland) was used. Target TAC was 12–14 ng/mL for the first month post-transplant, 10–12 ng/mL for months 2 and 3, and 8–10 ng/mL from three to six months and 6–8 ng/mL thereafter. All patients received MMF at a dose of 500 mg b.i.d. All patients also received 250 mg of intravenous methylprednisolone pre- and post-operatively, 250 mg 12-hourly on day 1 post-operatively and 250 mg once daily on days 2 and 3. Oral prednisolone at 20 mg/day, tapering to 5 mg/day by four wk, was prescribed thereafter. Complete steroid withdrawal occurred according to the preference of the treating physician. Antibody induction with anti-thymocyte globulin (ATG) was reserved for highly sensitized patients and repeat transplants only.

After discharge from hospital, the clinical status of each patient was closely monitored. Each visit included a physician assessment, physical examination and laboratory investigations including full blood count, biochemistry panel, and 12 h TAC.

ACR was described as either biopsy-proven acute ACR or empirically treated ACR. A rejection episode was suspected clinically by an unexplained rise in serum creatinine. Obstruction was ruled out with ultrasound examination. Biopsy-proven ACR was diagnosed from renal biopsy findings scored according to the BANFF criteria (9). Patients in this study were considered to have biopsy-proven ACR if they had BANFF grade 1 (Mild Acute Rejection), 2 (Moderate Acute Rejection) or 3 (Severe Acute Rejection) acute rejection. Empirical ACR was defined as an unexplained rise in serum creatinine of more than 30 mmol/L treated with high dose intravenous methylprednisolone over three to five d without biopsy confirmation. The reported total ACR rate is the sum of both the biopsy-proven ACR rate and the empirical ACR rate.

Baseline, demographic and outcome data were collected throughout the first year post-transplant. Demographic data included donor and recipient age, gender, underlying renal disease and use of pre-transplant dialysis. Baseline transplant information included transplant number, type of transplant, CIT, and number of HLA mismatches and use of induction therapy. Data on complications were also collected, including rates of post-transplant diabetes mellitus (PTDM), TAC nephrotoxicity, and delayed graft function (DGF). DGF was defined as need for dialysis in the first wk post-transplant. PTDM was defined as requirement for oral hypoglycemic agents or insulin for the first time post-transplant.

Patients were divided and analyzed in four groups based on quartiles of the mean TAC on days 2–5 post-transplant: Group 1: TAC 2–13.5 ng/mL (n = 122, median 11), Group 2: TAC 14–20 ng/mL (n = 130, median 17), Group 3: TAC 20.5–28 ng/mL (n = 129, median 24) and Group 4: TAC 28.5–77.5 ng/mL (n = 123, median 33.5).

Demographic and pre-transplant clinical data were assessed using Kruskal–Wallis tests for continuous variables and Pearson chi-square tests for categorical variables. ACR between the groups were analyzed using log-rank tests. Multifactorial analysis using logistic regression was used to determine independent significance from potentially confounding variables. Statistical software used for all of the analysis was STATA (version 8; College Station, TX, USA).

Results

Four hundred and sixty-four patients were included in the study, 277 (59.7%) males and 204

(40.3%) females. The median age of the cohort was 41.8 years (range 4.6–75.5 years).

Patients were analyzed in four groups based on quartiles of the mean TAC on days 2 and 5 post-transplant: Group 1: median TAC 11 ng/mL (n = 122, range 2–13.5 ng/mL), Group 2: median 17 ng/mL (n = 123, range 14–20 ng/mL), Group 3: median 24 ng/mL (n = 108, range 20.5–27 ng/mL) and Group 4: median 33.5 ng/mL (n = 116, range 27.5–77.5 ng/mL).

Our decision to include days 2–5 in the quartile analysis was based on the wide-ranging TAC seen in that time frame, despite all patients receiving the same initial oral dose of 0.15 mg/kg bid. TAC doses were subsequently adjusted in all groups to achieve a target TAC of 12–14 ng/mL by one wk post-transplant. By day 14, differences in TAC decline below significance (p = 0.12) (Fig. 1).

The baseline demographic characteristics of patients included in the study are summarized in Table 1. Significant differences were detected between the four groups for both recipient and donor age with increasing donor and recipient ages in the higher quartile groups. There were no significant baseline differences seen between the groups in terms of other demographic and pre-transplant clinical variables. Antibody induction was used equally between all four groups.

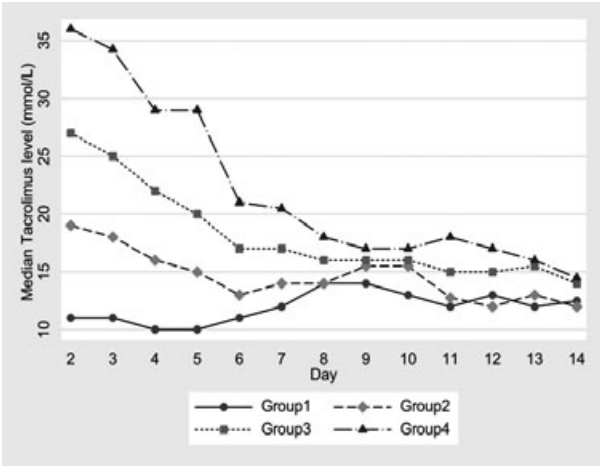

Fig. 1. Rates of decline in TAC during first two wk post-transplant.

Complications occurring during hospitalization and outpatient follow-up are presented in Table 2. Of note, observed rates of DFG did vary significantly. The Group 1 rate was 9.4% as compared with 18.69%, 30.55% and 25.86% in Groups 2, 3 and 4 (p = 0.003). Logistic regression analysis demonstrates TAC group, donor age and CIT to be independent factors influencing rates of DGF (Table 3). Similarly, the rate of decline in serum creatinine during the first post-transplant week was attenuated in the higher TAC groups, but this difference was undetectable by day 7 (Fig. 2). PTDM occurred more frequently in Group 4 when compared to other groups, although this finding did not reach statistical significance. There was no observed difference in rates of biopsy-proven TAC nephrotoxicity between the groups. Three-yr follow-up data were available for 341 patients and five-yr data for 121, and is shown in Tables 3 and 4. There were no detectable difference in patient or graft survival at three or five yr post-transplant, and median serum creatinine concentrations were similar in all four groups at both time-points.

Over the course of one yr following transplant, there were 79 cases (16.84%) of ACR seen, 57 (72.2%) of which were of biopsy-proven. When examined by quartile, a graded reduction in the rates of ACR was seen for each incremental days 2–5 TAC in the total ACR group. A similar reduction was seen for Groups 1–3 in the biopsy proven group, but no discernable differences were

Table 1. Baseline demographics

	Group 1	Group 2	Group 3	Group 4	p-Value
Median TAC (ng/mL)[a]	11 (2–13.5)	17 (14–20)	23.5 (20.5–27)	32.5 (27.5–77.5)	–
Patients (n)	117	123	108	116	–
Gender, M/F (%)	44/56	45/55	35/65	39/61	0.362
Age (median)	37.4	38.8	45.6	53.8	<0.001
Donor age (median)	32.5	36	43	42	<0.001
CIT (median)[b]	19	18.5	19	19	0.694
HLA mismatch	3	3	3	3	0.669
Transplant no. (% 1st/% 2nd or greater)	82.0/18.0	77.2/22.8	82.4/17.6	77.6/22.4	0.643
PRA % 0–10/11–49/50–100	85.3/4.3/10.4	79.7/11.4/8.9	84.1/8.4/7.5	75.6/12.2/12.2	0.313
Antibody induction (%)	17 (14.52)	18 (14.63)	18 (16.67)	20 (17.24)	0.937

[a]Median tacrolimus trough, range in parentheses.
[b]Cold ischemia time.

Table 2. Patient outcomes at one yr post-transplant

	Group 1	Group 2	Group 3	Group 4	p-Value
Graft survival (95% CI)	94.87 (88.94–97.66)	95.12 (89.46–97.78)	97.2 (91.56–99.09)	95.69 (89.95–98.18)	0.6107
Patient survival (95% CI)	96.88 (90.62–98.98)	100	97.73 (91.22–99.43)	97.78 (91.41–99.44)	0.90
DGF (n; %)	11 (9.4)	23 (18.69)	33 (30.55)	30 (25.86)	0.003
PTDM (n; %)	8 (6.83)	8 (6.5)	8 (7.4)	14 (12.06)	0.326
Creatinine (median) (μmol/L)	124	116.5	130.5	114	0.2066
TAC nephrotoxicity (%)	20 (17.09)	22 (17.88)	21 (19.44)	17 (14.65)	0.911

Table 3. Patient outcomes at three yr post-transplant (n = 341)

	Group 1	Group 2	Group 3	Group 4	p-Value
Graft survival (95% CI)	91.45 (84.70–95.31)	90.64 (83.70–94.72)	93.29 (86.43–96.75)	91.14 (84.14–95.14)	0.60
Patient survival (95% CI)	94.62 (87.53–97.73)	95.75 (89.08–98.39)	96.59 (89.80–98.89)	94.36 (86.97–97.62)	0.90
Creatinine (median) (μmol/L)	128.5	112	133	113	0.49

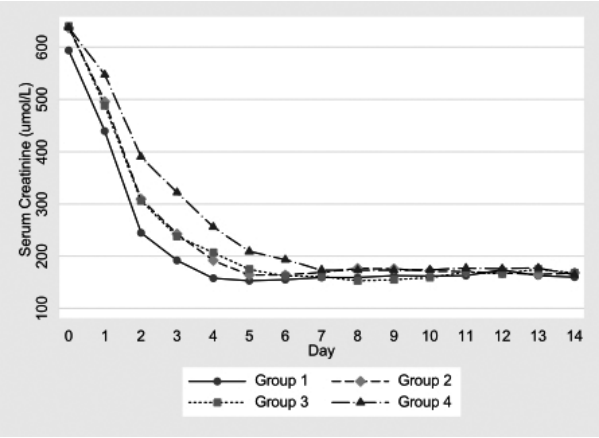

Fig. 2. Rates of decline in serum creatinine in Groups 1–4.

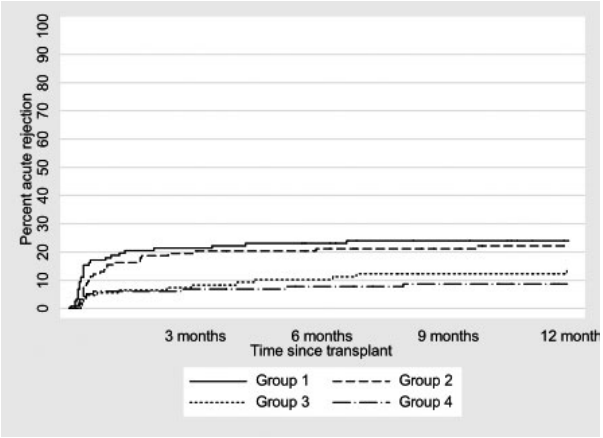

Fig. 3. Total ACR episodes for Groups 1–4.

detected between Groups 3 and 4. ACR rates at one, three, six and 12 months for both groups are presented in Table 4 and also in Figs. 3 and 4. A log-rank test to determine equity of outcome shows a significant difference for rates of total ($p = 0.003$) and biopsy proven ACR ($p = 0.006$) for the four groups.

Results of Cox proportional hazards models of variables associated with ACR are presented in Tables 5 and 6. Logistic regression analysis demonstrates both TAC and DGF are independent of other factors in determining outcome for both total ACR (Table 7) and biopsy-proven ACR (Table 8), whereas recipient age is marginally for significant for biopsy-proven ACR. A correlation between recipient age and TAC was also observed ($R = 0.2934$) (Fig. 5).

Discussion

ACR is a major factor in determining long-term graft outcome and its occurrence is heavily weighted towards the immediate post-transplant period (10). The critical influence of maintaining

Table 4. Patient outcomes at five yr post-transplant (n = 121)

	Group 1	Group 2	Group 3	Group 4	p-Value
Graft survival (95% CI)	82.27 (71.92–89.09)	82.85 (72.78–89.46)	88.64 (79.18–93.96)	85.25 (75.45–91.35)	0.6107
Patient survival (95% CI)	91.66 (80.60–96.55)	91.25 (80.40–96.23)	92.22 (80.86–96.96)	92.99 (85.02–96.80)	0.9055
Creatinine (median) (umol/l)	120	135	134	100	0.484

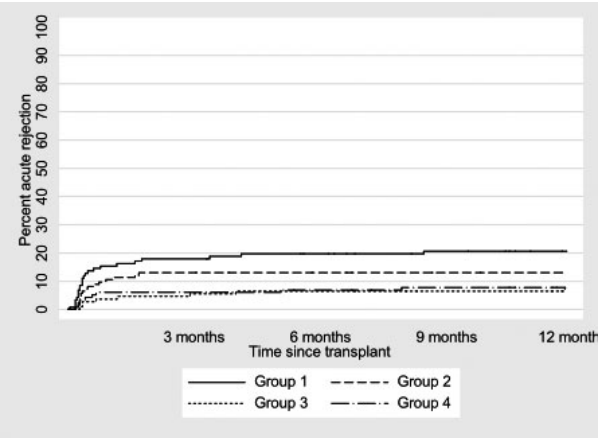

Fig. 4. Biopsy-proven ACR episodes for Groups 1–4.

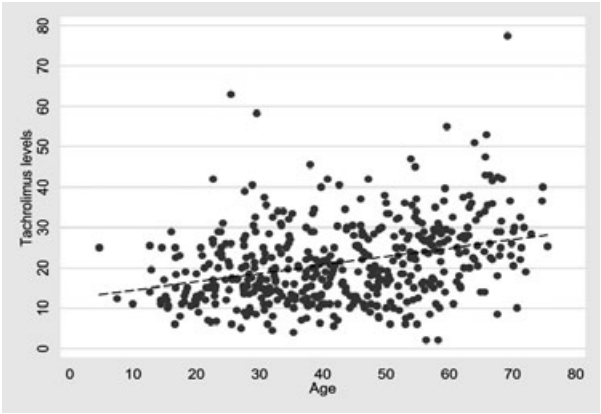

Fig. 5. Correlation between recipient age and TAC.

adequate early levels of immunosuppressive medications has been previously emphasized. Perico et al. (6) found that cyclosporine levels on day 2 post-transplant were highly predictive of ACR episodes. Similarly, El-Sabrout et al. describe a significant reduction in ACR rates without an increase in toxicity after a loading dose of sirolimus (7). Staatz et al. identified a strong relationship between median TAC in the first post-transplant month and ACR (8). Interestingly, their data were also further analyzed by stratification into three groups based on median TAC, and those with the highest (10–15 ng/mL) values experienced no episodes of ACR.

We found that both total and biopsy-proven ACR were reduced in a linear, graded fashion at all time points and for all TAC increments, bar between Groups 3 and 4 of the biopsy-proven cohort. Our results suggest that targeting TAC similar to those seen in Group 3 (about 24 ng/mL) immediately post-transplant can yield extremely low ACR rates in the long term. As there was no difference observed in biopsy-proven ACR rates between Groups 3 and 4, we propose that a target TAC similar to that seen in Group 3 (median

Table 5. Multi-factorial logistic regression for DGF

	Odds ratio	SE	*p*-Value	95% CI	
Group	1.503026	0.2407273	0.011	1.098086	2.057294
Age	1.020217	0.0138215	0.140	0.9934836	1.047669
Donor age	1.038571	0.0151646	0.010	1.00927	1.068723
Sex	1.238572	0.4534026	0.559	0.6043979	2.538164
CIT	1.087171	0.0364442	0.013	1.018037	1.160999
PRA	1.344308	0.3499168	0.256	0.8071143	2.239042
HLA	1.06607	0.1361743	0.616	0.8299608	1.369348

Table 6. Rates of total and biopsy-proven acute ACR

	Group 1	Group 2	Group 3	Group 4
Total ACR (%)				
1 month (95% CI)	18.80 (12.81–27.14)	15.45 (10.14–23–14)	5.56 (2.53–11.95)	6.03 (2.92–12.24)
3 months	21.37 (14.98–29.96)	20.33 (14.22–28.58)	8.33 (4.43–15.40)	6.90 (3.51–13.57)
6 months	23.11 (16.48–31.87)	21.20 (14.96–29.55)	10.26 (5.82–17.77)	7.77 (4.12–14.41)
12 months	24.03 (17.26–32.88)	22.20 (15.78–30.70)	13.41 (8.15–21.63)	8.69 (4.77–15.55)
Biopsy-proven ACR (%)				
1 month	15.38 (9.99–23.30)	10.57 (6.28–17.5)	3.70 (1.41–9.57)	6.03 (2.92–12.24)
3 months	17.95 (12.09–26.19)	13.01 (8.18–20.35)	5.56 (2.53–11.95)	6.03 (2.92–12.24)
6 months	19.69 (13.55–28.12)	13.01 (8.18–20.35)	6.52 (3.16–13.19)	6.91 (3.52–13.35)
12 months	20.63 (14.33–29.19)	13.01 (8.18–20.35)	7.69 (3.91–14.83)	7.83 (4.15–14.50)

Table 7. Multifactorial logistic regression for total ACR

Variable	Odds ratio	SE	p-Value	95% CI	
Group	0.587	0.093	0.001	0.429	0.803
Age	0.981	0.011	0.128	0.958	1.005
Donor age	1.006	0.013	0.595	0.981	1.032
Sex	1.398	0.461	0.309	0.732	2.667
CIT	1.003	0.033	0.926	0.941	1.068
PRA	0.975	0.252	0.922	0.587	1.617
HLA	0.975	0.113	0.828	0.776	1.224
DGF	3.650	1.536	0.002	1.599	8.329

Table 8. Multifactorial logistic regression for biopsy proven ACR

Variable	Odds ratio	SE	p-Value	95% CI	
Group	0.536	0.111	0.003	0.356	0.805
Age	0.969	0.014	0.046	0.941	0.999
Donor age	0.995	0.015	0.751	0.965	1.025
Sex	0.928	0.366	0.850	0.427	2.014
CIT	0.999	0.038	0.990	0.926	1.078
PRA	1.237	0.365	0.470	0.693	2.208
HLA	1.046	0.151	0.754	0.788	1.388
DGF	8.186	4.208	<0.001	2.988	22.423

23.5 ng/mL) would achieve the optimal balance between efficacy and toxicity.

To avoid toxicity, the TAC dose was promptly adjusted to achieve a target range of 12–14 ng/mL before the end of the first post-transplant week. Despite this, a tendency towards increased toxicity was observed and warrants discussion. We noted a significant increase in rates of DGF in Groups 1–4, increasing from 9.4% to 30.55%. However, as most centers report rates of DGF in the range of 20–40% (11), it is perhaps the surprisingly low incidence of DGF in Group 1 that is most noteworthy. This finding should also be viewed in the context of an unacceptably high ACR rate of 24.03% by one yr post-transplant. Although we found TAC to be independently associated with DGF by multivariate analysis, increasing CIT and donor age were also factors. Despite a slower fall to nadir creatinine with higher TAC, differences were undetectable by the end of the first wk post-transplant (Fig. 2).

There was a trend towards increased PTDM in patients with median initial TAC of 33.5 ng/mL (Group 4), although this did not reach statistical significance ($p = 0.32$). The potential for TAC to induce this complication is well known, although it is unclear if this is a dose-related phenomenon. Two recent studies were unable to demonstrate an association between TAC trough levels and the development of PTDM at any time point out to five yr post-transplant (12, 13). However, in an earlier study of 76 patients, Rodrigo et al. found that TAC of >24 early post-transplant was an independent risk factor for the development of PTDM (14). Although PTDM was defined as requirement for oral hypoglycemic agents or insulin for the first time post-transplant in our study, the authors acknowledge that the overall sensitivity for the diagnosis of PTDM would be increased through the use of American Diabetes Association or WHO definitions of DM. Future prospective studies in this area should employ these stricter criteria for the diagnosis of PTDM.

That an initial dose of 0.15 mg/kg should yield such a wide range of early TAC is testament to the variability in TAC handling in humans. To implement the findings of this study into clinical practice, knowledge of an individual's response to the drug before they are transplanted would be useful. This question is being addressed by an Australian study that is soon to be reported (15).

Perhaps the most striking observation is the effect of age. Age and first TAC trough appear to correlate in our group (Fig. 5). While the multifactorial analysis does show an inverse correlation between age and biopsy-proven ACR, the effect is marginal. Although it was previously proposed that elderly patients were less immunologically active (16), most studies now show that there is no relevant effect of recipient age on immunological reactivity (17–19), although increasing deceased-donor age may be a factor (20). Conversely, increasing recipient age does appear to affect TAC pharmacokinetics in both children and adults, with higher TAC seen in older patients despite equivalent dosing (21–23). We propose that the incremental TAC seen is largely due to age-related changes in its handling and that this accounts for the observed reduction in ACR rates. This suggests that younger patients would benefit from a higher initial TAC dose, targeting TAC similar to those observed in Group 3 (median TAC 24 ng/mL).

This study demonstrates a clear association between TAC in the first wk post-transplant and reduced long-term ACR rates. Aggressively managing TAC dosing in this critical period of antigen presentation and immunological activation may result in reduced rates of long-term allograft damage.

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