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Time-dependent variability in tacrolimus trough blood levels is a risk factor for late kidney transplant failure

Ruth Sapir-Pichhadze[1,2], Yao Wang[2], Olusegun Famure[2], Yanhong Li[2] and S. Joseph Kim[1,2,3,4]

[1]Division of Nephrology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Division of Nephrology and the Kidney Transplant Program, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada; [3]Division of Nephrology and the Renal Transplant Program, St Michael's Hospital, Toronto, Ontario, Canada and [4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Wide variations in tacrolimus levels have been identified as a risk factor for inferior kidney allograft survival but past studies have not properly accounted for the dynamic nature of drug exposure over time. Here we evaluated whether time-varying exposure to tacrolimus increases the risk of long-term adverse outcomes in a retrospective cohort study in adult kidney transplant recipients on tacrolimus-based immunosuppression. Time-dependent Cox proportional hazards models were used to examine the association between the standard deviation of tacrolimus levels (TacSD) starting at 1-year post-transplant and the composite end point of late allograft rejection, transplant glomerulopathy, or total graft loss (including death). Among 356 patients, there was a significant 27% increase in the adjusted hazard of the composite end point for every 1-unit increase in TacSD (hazard ratio 1.27 (95% confidence interval 1.03, 1.56)). There was also a graded increase in the relative hazard for the composite end point by TacSD threshold (hazard ratios 1.33, 1.50, 1.84, and 2.56 for TacSD 1.5, 2, 2.5, and 3, respectively). The results were similar for total graft loss and the composite end point excluding death. Thus, increased time-dependent TacSD may be an independent risk factor for adverse kidney transplant outcomes. TacSD may serve as a monitoring tool to identify high-risk patients. Whether interventions to decrease TacSD will improve outcomes requires further study.

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Correspondence: *S. Joseph Kim, Division of Nephrology and the Kidney Transplant Program, Toronto General Hospital, University Health Network, 585 University Avenue, 11C-1183, Toronto, Ontario, Canada M5G 2N2. E-mail: joseph.kim@uhn.ca*

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Late kidney transplant failure carries grave implications for survival in kidney transplant recipients.[1,2] Over the past decade, long-term kidney allograft survival remained relatively stagnant.[3–5] This was observed despite significant improvements in short-term (i.e., 1-year) outcomes.[6–10] Improvements seen in short-term outcomes can be at least partially attributed to advances in maintenance immunosuppressive therapy. One of the major advances in transplant therapeutics was the introduction of tacrolimus-based maintenance immunosuppressive regimens in the early 1990s.[9–11]

Tacrolimus is a potent immunosuppressant with a narrow therapeutic window.[12] Patients on tacrolimus are at risk for adverse events related to both excessive and insufficient immunosuppression. Excessive immunosuppression may compromise graft survival from drug-related toxicity or BK virus nephropathy and increase the risk of mortality from cardiovascular, infectious (e.g., cytomegalovirus), and malignant causes.[13] In contrast, insufficient immunosuppression may result in immune-mediated allograft injury, leading to acute allograft rejection or transplant glomerulopathy.[14] The resulting impairment in kidney function[15–17] and allograft failure[18] may increase the risk of mortality. To avoid both excessive and insufficient exposure to immunosuppression, tacrolimus trough blood levels are continuously monitored in kidney transplant recipients.

In an effort to study drug non-adherence, prior studies used summary measures of drug fluctuations over a specified period of time and related these measures to graft and patient outcomes.[19–24] These studies have typically shown that wide variations in trough tacrolimus blood levels are associated with acute rejection[19,21] and allograft failure.[24] However, prior studies did not properly account for the time-varying nature of tacrolimus trough blood levels.[25]

Apart from non-adherence, intra-patient fluctuations in tacrolimus levels may also result from drug prescription patterns, variability in drug absorption/metabolism,[26–28] and drug–drug interactions.[29–33] Although some studies considered the effects of mycophenolate mofetil (MMF) co-administration on tacrolimus clearance and long-term

graft failure,[19,24] none have assessed whether risk factors for non-adherence (such as recipient age and sex) or abnormal tacrolimus absorption or metabolism (e.g., in diabetic patients) could modify this relationship.

To examine the impact of time-dependent exposure to tacrolimus on long-term kidney allograft outcomes, we conducted a cohort study using our center's database. As fluctuations in tacrolimus levels over time can result in both excessive and insufficient immunosuppression, the main composite end point in the study included the long-term kidney allograft outcomes of late acute rejection, transplant glomerulopathy, graft failure, or death with function. We also corroborated the relationship between fluctuations in tacrolimus trough blood levels and long-term kidney allograft outcomes with a secondary composite end point that excluded death (i.e., late acute rejection, transplant glomerulopathy, and graft failure).

RESULTS

A total of 517 patients who underwent kidney transplantation over the study period and initiated on tacrolimus-based maintenance immunosuppression were identified in the Comprehensive Renal Transplant Research Information System database. After implementing our exclusion criteria, the final study cohort consisted of 356 patients (see Supplementary Material I online). Recipient, donor, and transplant characteristics measured at baseline (i.e. 1-year post-transplant) are presented in Table 1.

The median follow-up was 3.72 years (95% confidence interval (95% CI): 2.35, 5.08) beyond the first year post-transplant. A total of 62 events were documented during 1385.4 person-years at risk; 16 patients had late acute rejection; 6 developed transplant glomerulopathy; 10 lost their graft; and 20 patients died. Biopsy confirmed acute rejection events were primarily acute cellular (90.8%) and mixed (cellular and antibody-mediated) rejection (9.2%). Allograft failure was primarily a consequence of acute rejection or transplant glomerulopathy (76.2%). One of the patients, whose grafts failed from rejection, demonstrated features of BK nephropathy in a preceding biopsy. Less common causes of allograft failure included isolated interstitial fibrosis and tubular atrophy (14.3%), primary disease recurrence (4.7%), and recurrent urinary tract infections (4.7%).

Median tacrolimus dose was 4 mg/day during the first 4 years of follow-up and decreased to 3 mg/day beyond 5 years of follow-up. These doses corresponded with median trough tacrolimus blood levels of approximately 7.0 ng/ml in the first 4 years of follow-up and 6.5 ng/ml beyond 5 years of follow-up (Supplementary Material II online). A median of 15 trough tacrolimus blood level measurements was used to calculate each TacSD (standard deviation of tacrolimus levels) measurement (Supplementary Material III online).

Extended Kaplan–Meier analyses showed a cumulative incidence of 24.8% by 5-year post-transplant for the composite end point in patients with TacSD >2 compared with 16.3% in patients with TacSD $\leqslant 2$ (Figure 1b). The difference between the two curves did not reach statistical significance (log rank $P=0.21$). Similar analysis for a secondary end point excluding death showed a 5-year cumulative incidence of 16.1% vs. 9.3% (log rank $P=0.34$) in patients with TacSD >2 vs. TacSD $\leqslant 2$ (Figure 1e). For both composite and secondary composite end points, the differences between the curves were further accentuated when the threshold of TacSD was increased to >2.5 or >3 (Figure 1c, d, f, and g, respectively).

Table 1 | Recipient, donor, and transplant characteristics at baseline (1-year post-transplant)

Baseline characteristics	Number of patients ($n=356$)	Summary measure[a]
Mean recipient age in years (s.d.)	356	52.1 (12.5)
Recipient sex (%)		
Male	200	56.2
Female	156	43.8
Recipient race (%)		
Caucasian	233	65.5
Non-Caucasian	123	34.5
Mean recipient BMI (s.d.)	355	26.3 (6.5)
Cause of ESRD (%)		
Diabetes	68	19.1
Non-diabetes	288	80.9
Median number of years on dialysis before transplant (IQR)	355	3.5 (1.3, 6.4)
D+/R− CMV status (%)		
Yes	48	13.48
No	308	86.52
Rejection in first year (%)		
Yes	34	9.5
No	322	90.5
Number of hospitalizations in the first year		
0	221	62.0
1	81	22.8
2	29	8.2
$\geqslant 3$	25	7.0
Mean recipient CKD-EPI eGFR (s.d.)	329	58.0 (19.0)
Delayed graft function		
Yes	80	22.5
No	276	77.5
Median peak panel-reactive antibodies (IQR)	345	4 (0, 24)
Mean donor age in years (s.d.)	355	46.5 (14.4)
Expanded criteria donors (%)		
Yes	74	20.8
No	282	79.2
Mean donor BMI (s.d.)	350	26.62 (5.29)
Median number of HLA mismatches (IQR)	313	4 (3, 5)
Donor type (%)		
Deceased	199	55.9
Living	157	44.1
Transplant era (%)		
2000–2005	121	34.0
2006–2007	145	40.7
2008–2010	90	25.3

Abbreviations: BMI, body mass index; CKD-EPI, chronic kidney disease epidemiology collaboration; CMV, cytomegalovirus; ESRD, eGFR, estimated glomerular filtration rate; end-stage renal disease; HLA, human leukocyte antigen; IQR, interquartile range.

For non-normally distributed variables, the summary measure is the median and IQR. The summary measure for binary or categorical variables is the proportion.

[a]The summary measure for normally distributed continuous variables is the mean and s.d.