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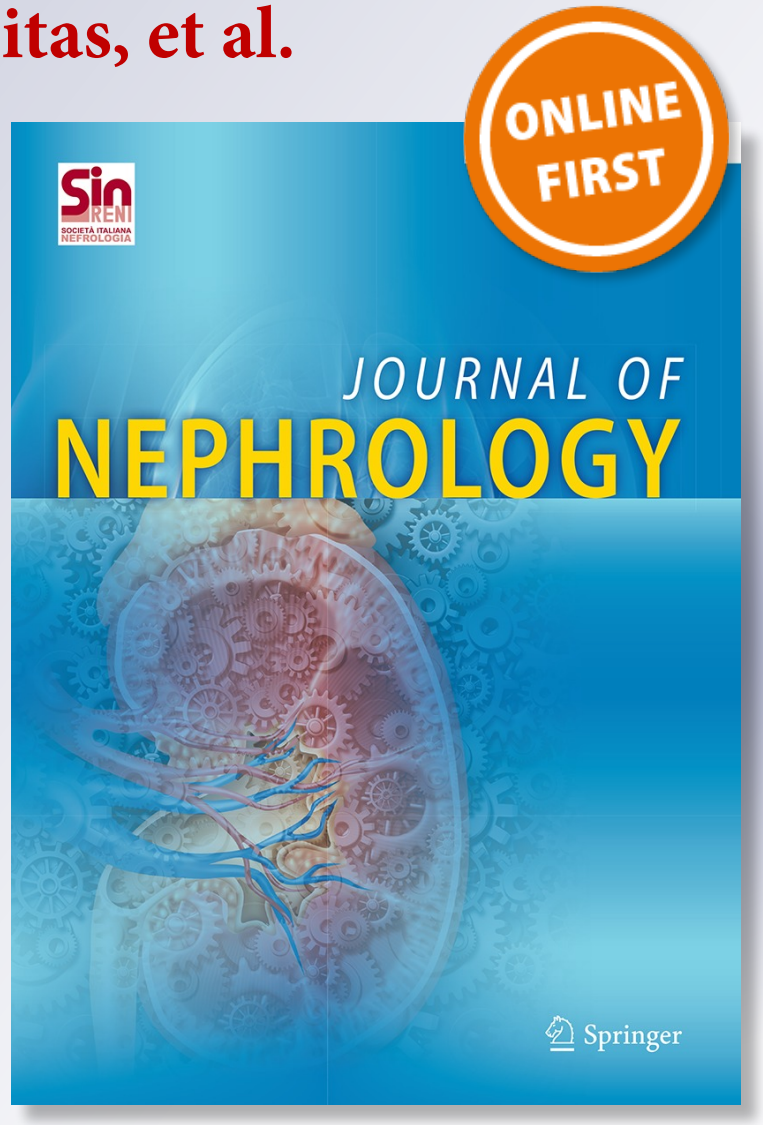

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ORIGINAL ARTICLE

Tacrolimus trough-level variability predicts long-term allograft survival following kidney transplantation

John A. O'Regan[1] · Mark Canney[1] · Dervla M. Connaughton[1] · Patrick O'Kelly[1] · Yvonne Williams[1] · Geraldine Collier[2] · Declan G. deFreitas[1] · Conall M. O'Seaghdha[1] · Peter J. Conlon[1]

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Abstract
Aims The purpose of this study is to investigate tacrolimus trough-level variability from 3 to 12 months following transplantation and its association with allograft survival in renal transplant recipients.
Materials and methods In this observational cohort study, tacrolimus trough-level variability was used as the predictor of all-cause allograft failure (defined as return to dialysis) and patient survival (all-cause mortality).
Results In total, 394 transplants were included in the analysis. Sixty-two transplants failed during the study. Tacrolimus trough-level variability across quartile groups were: Q1 median variability 12.5 %, range 4.76–15.71 % (n = 99), Q2 median variability 18.17 %, range 15.74–21.29 % (n = 96), Q3 median variability 24.63 % range 21.42–28.88 % (n = 100), Q4 median variability 36.91 %, range 28.91–81.9 % (n = 99). Higher tacrolimus trough-level variability was associated with inferior allograft survival in univariate models [hazard ratio per quartile increase (HR), 1.46, 95 % CI 1.16–1.83, p value = 0.001] and multivariate models (HR 1.36, 95 % CI 1.05–1.78, p value = 0.019). Higher tacrolimus trough-level variability was not associated with patient survival; univariate model (HR 1.25, 95 % CI 0.90–1.74, p value = 0.17), multivariate model (HR 1.25, 95 % CI 0.86–1.83, p value = 0.23).
Conclusions Inferior renal allograft survival was observed in recipients with higher variability in tacrolimus trough-levels.

Keywords Transplantation · Tacrolimus · Variability · Kidney

Introduction

Transplantation is the treatment of choice for patients with end-stage kidney disease [1–4]. However, lifelong renal allograft survival is seldom achievable [5, 6]. Causes of long-term allograft failure include immune-mediated injury, polyoma virus nephropathy, recurrent or de novo glomerulonephritis, and other medical or surgical conditions [7, 8]. Immune-mediated injuries associated with long-term allograft outcomes include acute T cell mediated rejection, chronic T cell mediated rejection, acute antibody-mediated rejection, chronic, active antibody-mediated rejection and mixed rejection [9].

Achieving stability in maintenance immunosuppression is key to avoiding both relative under-immunosuppression, which could lead to rejection, and over-immunosuppression [10]. The latter is associated with graft injury from polyoma virus nephropathy as well as recipient illness such as infection [11]. Calcineurin inhibitors such as tacrolimus are used internationally in maintenance immunosuppression regimes [10–13]. Tacrolimus has a narrow therapeutic index and requires trough-level monitoring to maintain therapeutic targets [14]. Many factors can contribute to variability of tacrolimus trough levels: recipient non-adherence, sub-optimal prescribing, specifically tailored strategies to minimise infection risk and pharmacological considerations such as drug absorption, drug metabolism and drug interactions [7,

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15–21]. Recipients with higher variability in levels of tacrolimus are more likely to be at risk of under- or over-immunosuppression. This potentially impacts upon long-term renal allograft outcomes which in turn has been associated with decreased patient survival [22].

We hypothesised that higher variability in tacrolimus trough-levels 3–12 months following renal transplantation may be associated with inferior long-term allograft survival. We additionally sought to investigate whether tacrolimus trough-level variability was associated with patient survival.

Materials and methods

Study sample

The National Kidney Transplant Centre at Beaumont Hospital has performed all adult renal transplants in Ireland since 1987 (previous transplant surgery in Ireland was performed at the Charitable Infirmary, Jervis Street since 1964). We carried out a retrospective analysis of the National Renal Transplant Registry and the Beaumont Hospital Renal Database (Clinical Vision 3.4a Version 1.1.34.1, Clinical Computing, Cincinnati, OH, USA) from Jan 1, 2000 to April 31, 2008. This registry is maintained prospectively by dedicated full-time staff. A total of 1100 adult renal transplants were performed during this study period.

Patient selection and outcomes

Our inclusion criteria considered all adult deceased donor and living donor renal transplant recipients who were immunosuppressed with tacrolimus in the first year post transplant who had a functioning renal allograft after 1 year (defined as not requiring dialysis) and who had follow-up at our centre beyond the initial post transplant year. Patients receiving a second or subsequent renal allograft and patients who were 'nephron-dosed' (i.e. patients transplanted with multiple kidney masses in a single transplantation proceedure) or receiving a transplant from an extended criteria donor were included in the analysis. Renal transplants in paediatric recipients, simultaneous pancreas-kidney transplant recipients, and patients with allograft failure in the first year were excluded from the study. Co-immunosuppression with mycophenolate mofetil 1–2 gms/24 h in twice daily divided doses or azathioprine 1–2 mg/kg/24 h in once daily dose was standard practice over the study period. Oral prednisolone was tapered to 5 mg daily by week four in the general recipient population and complete steroid withdrawal subsequently occurred according to the preference of the treating physician. Follow-up began 12 months after date of transplantation. The outcomes of interest were all-cause allograft loss (censored for death) and patient survival (all-cause mortality).

Measurements and definitions

Pre-dose measurements of whole-blood tacrolimus concentrations were measured in the renal biochemistry laboratory at our institution with locally available MEIA Technology (micro-particle enhancement immunoassay provided by Abbot Diagnostics, Dublin, Ireland).

Allograft failure was defined as return to dialysis.

Predictor

All patients included in the study were prescribed oral tacrolimus in twice daily divided doses (Prograf®, Fujisawa Pharmaceutical Company, Munich, Germany; then Astellas Pharma Europe Ltd, Staines, UK). To allow for stabilisation of drug dosing a lead in time of 3 months from date of transplantation was observed. Inclusion of all tacrolimus trough levels from 3 to 12 months after transplantation led to the calculation of tacrolimus trough-level variability. Variability for individual transplant recipients was calculated using the co-efficient of variation formula:

$$\left[\sum(\mathrm{tac}_{\mathrm{mean}} - \mathrm{tac}_{\mathrm{x}}) \div \mathrm{n}\right] \div \mathrm{tac}_{\mathrm{mean}}$$

where '$\mathrm{tac}_{\mathrm{x}}$' represents consecutive tacrolimus trough-levels from three to 12 months post transplant, '$\mathrm{tac}_{\mathrm{mean}}$' is their mean and 'n' is the number of trough samples taken in that patient. This tacrolimus trough-level variability result was then expressed as a percentage and used as the predictor of the study's outcomes.

Covariate assessment

Demographic patient data and baseline transplantation data were collected prospectively in the transplant database. Demographic data included donor age, donor sex, recipient age, recipient sex, cause of end-stage kidney disease and time spent on maintenance dialysis pre-transplantation. Baseline transplantation data included date of transplant, type of transplant (deceased donor, living donor, expanded criteria donor, 'nephron dosing' i.e. patients transplanted with multiple kidney masses in a single transplantation procedure), number of re-transplants, level of panel reactive antibodies, human leukocyte antigen (HLA) type and major donor allele mismatches, serological cytomegalovirus (CMV) status of donor and recipient, cold ischaemic times, and post-operative complications including delayed graft function which was defined as "requiring dialysis in the week following transplantation". Panel reactive antibodies as a variable was divided categorically into the

following groups; <10, 10–49 and >50 %. Acute rejection was defined as pathological evidence of acute rejection on transplant biopsy. Pathological evidence of acute rejection was reported by a single renal pathologist according to the current Banff criteria at time of biopsy. Immunosuppression boosts included intravenous corticosteroids ± anti-thymocyte globulin for acute cellular rejection where appropriate. Serum creatinine at 1 year follow-up was obtained from the laboratory archive.

Statistical methods

Patients were divided into four groups based on quartiles of trough-level tacrolimus variability. Categorical variables were expressed as percentages and compared with Pearson's Chi-squared tests. Continuous variables were expressed as medians with interquartile ranges and compared using the Wilcoxon rank-sum test. Kaplan–Meier estimates were performed for all-cause allograft loss (censored for death) and all-cause recipient mortality. Cox Proportional Hazards models were performed using the primary endpoints with adjustments for potential confounding variables (which were selected based on their accepted impact on allograft outcomes). These covariates included recipient age and gender, donor age and gender, cold ischaemic time, delayed graft function, panel reactive antibodies, HLA mismatches, donor positive/recipient negative CMV mismatch, acute rejection and time spent on maintenance dialysis. All data were analysed using STATA Version 10.0 (College Station, Texas). A p value of less than 0.05 was considered to indicate statistical significance.

Results

Study patients

Three hundred and ninety-four renal transplants in 390 patients were identified. All renal transplants were included in the analysis and their baseline characteristics across quartile groups are provided in Table 1. Median follow-up was 6.94 years ranging from 1.09 to 12.44 years. Sixty-two allografts failed over the study period.

Tacrolimus trough-level variability across the groups was as follows, Q1: median variability 12.5 %, range 4.76–15.71 % (n = 99), Q2 median variability 18.17 %, range 15.74–21.29 % (n = 96), Q3 median variability 24.63 % range 21.42–28.88 % (n = 100), Q4 median variability 36.91 %, range 28.91–81.9 % (n = 99). There were a smaller proportion of males in the highest tacrolimus trough-level variability quartile (Q4: 49 % versus Q1: 69 %, Q2: 72 %, Q3 64 %; p value = 0.006). Otherwise, there were no significant differences across quartile groups for baseline demographic and transplant data.

A greater number of tacrolimus trough-levels were drawn in patients with higher variability during routine post transplant follow-up (Q1: median 6, Q2: median 8, Q3: median 10, Q4: median 10, p value = 0.001).

Allograft survival

Renal allograft survival functions at 3 and 5 years respectively were as follows: Q1: 100, 97 %, Q2: 97, 93 %, Q3: 94, 84 %, Q4: 92, 87 %. Kaplan–Meier analysis of allograft failure probability across quartile groups demonstrated inferior allograft survival in higher tacrolimus trough-level variability quartiles (Fig. 1). Results for univariate analysis using a Cox proportional hazards model showed a 46 % increase in the hazard for allograft loss per quartile increase in tacrolimus trough-level variability (HR 1.46, 95 % CI 1.16–1.83, p value = 0.001) (Table 2). When comparing quartiles to Q1 (lowest variability quartile) as a referent quartile in univariate analysis, the hazard ratios were as follows: Q2: HR 1.98 (95 % CI 0.77–5.03, p = 0.15), Q3: HR 4.06 (95 % CI 1.73–9.54, p = 0.01), Q4: HR 3.40 (95 % CI 1.43–8.05, p = 0.005). When this model was adjusted for confounding co-variates (recipient age, recipient sex, donor age, donor sex, cold ischaemic time, delayed graft function, panel reactive antibodies, HLA mismatches, CMV mismatch (donor positive/recipient negative), acute rejection, time spent on maintenance dialysis) this attenuated the association to a 36 % increase per quartile but remained highly statistically significant (HR 1.36, 95 % CI 1.05–1.78, p value = 0.019) (Table 2). When comparing quartiles to Q1 (lowest variability quartile) as a referent quartile in mulitvariate analysis, the hazard ratios were as follows: Q2: HR 2.02 (95 % CI 0.68–5.97, p = 0.20), Q3: HR 4.76 (95 % CI 1.73–13.06, p = 0.002), Q4: HR 2.92 (95 % CI 1.04–8.21, p = 0.042).

Patient survival

Patient survival at 3 and 5 years respectively were as follows: Q1: 98, 97 %, Q2: 97, 95 %, Q3: 98, 90 %, Q4: 97, 94 %. There was no difference observed in patient survival across quartile groups (Fig. 2). Univariate analysis using a Cox proportional hazards model did not demonstrate a statistically significant association between tacrolimus trough-level variability and patient survival (HR 1.25, 95 % CI 0.90–1.74, p value = 0.17) (Table 2). Multivariate analysis did not affect this result. (HR 1.25, 95 % CI 0.86–1.83, p value = 0.23) (Table 2).

Table 1 Baseline characteristics of study participants by quartile of tacrolimus trough-level variability

Median tacrolimus trough-level variability (%)	Q1 12.5 N = 99 [IQR]	Q2 18.2 N = 96 [IQR]	Q3 24.6 N = 100 [IQR]	Q4 36.9 N = 99 [IQR]	p value
Age (year)	44 [34–55]	41 [29–58]	46 [33—55]	41 [29–57]	0.51
Male sex (%)	69	72	64	49	0.006
Donor age (year)	41 [24–50]	42 [29–51]	43 [30–52]	37 [24–47]	0.42
Donor male sex (%)	55	58	56	54	0.93
Cause of end-stage renal disease (%)					0.21
Diabetes mellitus (%)	8	3	7	3	
Polycystic kidney disease (%)	13	10	15	16	
Glomeronephritis (%)	23	33	27	21	
Interstitial nephritis (%)	2	1	3	2	
Miscellaneous (%)	45	41	40	45	
Unknown (%)	8	11	8	12	
Months on maintenance dialysis	23 [16–36]	23 [12–35]	26 [14–22]	22 [13–41]	0.73
Second or subsequent renal transplants (%)	25	23	27	25	0.93
Living donor transplants (%)	4	3	1	3	0.61
Cold-ischaemic time (h)	18 [16–20]	18 [16–22]	16 [14–20]	19 [16–21]	0.1
Delayed graft function (%)[a]	14	9	18	12	0.34
Number of HLA mismatches	3 [2–4]	3 [2–4]	3 [2–4]	3 [3–4]	0.115
Panel reactive antibodies at baseline (%)					0.34
<10	67	75	66	70	
10–49	20	11	14	11	
50–100	13	14	20	19	
Acute rejection (%)[b]	8	17	19	15	0.15
Creatinine 1 year post transplant (umol/L)[c]	120 [103–141]	125 [109–141]	131 [113–160]	125 [104–144]	0.07
Median number of tacrolimus levels[d]	6 [4–9]	8 [6–12]	10 [7–15]	10 [7–17]	0.001

Data presented as median with interquartile range for continuous variables and percentages for categorical data. Presented with p value for trends across quartiles; Wilcoxon rank-sum for continuous variables and Pearson's Chi-squared tests for categorical variables

HLA Human Leukocyte Antigen (major antigens alleles A, B, DR)

[a] Delayed graft function defined as the recipient requiring dialysis in the first week following transplantation

[b] Acute rejection is defined as pathological evidence of rejection on transplant biopsy

[c] Creatinine measured in micromoles per litre. Conversion factor from umol/L to mg/dL divide by 88.4

[d] Median number of tacrolimus trough levels included in the calculation of tacrolimus trough level variability

Discussion

This study investigated the relationship between tacrolimus trough-level variability from 3 to 12 months after kidney transplantation and allograft survival and the principle results are twofold. Firstly, our data demonstrates a significant association between higher tacrolimus trough-level variability and inferior allograft survival in renal transplant recipients. Secondly, tacrolimus trough-level variability was not associated with all-cause mortality in renal transplant recipients.

This is the largest study to examine the question of variability in tacrolimus levels and transplant outcomes and has the longest duration of follow-up. Our findings are consistent with other studies that have investigated tacrolimus variability and renal allograft outcomes. A previous study from the Netherlands observed that high within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcomes following kidney transplantation when dichotomous groups (low variability and high variability determined from outpatient tacrolimus trough-levels) were compared for the composite endpoint of allograft loss, chronic allograft nephropathy and doubling of serum creatinine concentrations [23]. More recently, a Canadian study observed that increased time dependent standard deviation of tacrolimus levels after the first year post transplant was associated with adverse allograft outcomes [24].

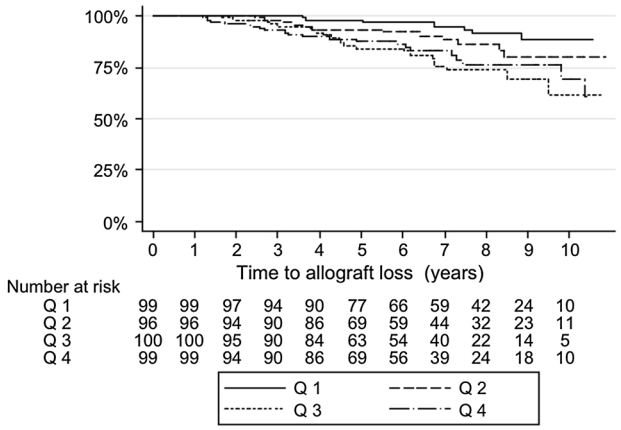

Fig. 1 Kaplan–Meier estimate of renal allograft survival (censored for death) per quartile of tacrolimus trough-level variability

We have considered potential mechanisms which could explain or confound our findings. The first significant mechanism leading to tacrolimus trough level variability is non-adherence and this may provide an explanation for the association we found between higher tacrolimus trough-level variability and inferior allograft outcomes [7, 16–19, 25, 26]. Direct measurements of adherence are not feasible in routine clinical practice. Challenges for the transplant recipient while attempting to maintain optimal tacrolimus adherence may include the following: multiple prescribers, forgetfulness, suboptimal understanding of the significance of maintenance immunosuppression or alternative health beliefs, sub-optimally stocked pharmacies, financial considerations and/or social vulnerability. In the period where tacrolimus trough-level variability was measured in this study (3–12 months), we expected that tacrolimus dose adjustment had decreased to a minimum when compared to the immediate post transplant period. We also expected better adherence, in general, due to increased patient contact with more frequent outpatient visits.

Differences in individual recipients' tacrolimus pharmacokinetics can contribute to variability. First-pass metabolism of tacrolimus occurs in the intestinal wall by P-glycoprotein but the majority of oxidation occurs in the liver by cytochrome P450 enzymes (CYP). Genetic polymorphisms of the CYP3A subfamily are known to significantly affect the metabolism of tacrolimus [27]. For example, patients expressing certain CYP3A5 enzymes (CYP3A5*1/*1 or *1/*3) are "fast" or "intermediate" metabolisers and require higher daily doses of tacrolimus to maintain therapeutic levels. Approximately 80 % of Caucasians are homozygous for the CYP3A5*3 allele i.e. non-expressers of the enzyme [28]. To date, conflicting evidence exists as to whether CYP3A5 genetic variations contribute to tacrolimus variability [29, 30]. However, given that CYP3A5 expressers can metabolise tacrolimus more rapidly, this mechanism could be particularly

Table 2 Cox proportional hazards models demonstrating an increased probability of allograft loss per quartile increase in tacrolimus trough-level variability

	Hazard Ratio	Standard error	95 % Confidence interval	p value
All-cause allograft failure				
Univariate model				
Tacrolimus trough-level variability	1.46	0.171	1.16–1.83	0.001
Multivariate model				
Tacrolimus trough-level variability	1.36	0.18	1.05–1.78	0.019
Patient survival				
Univariate model				
Tacrolimus trough-level variability	1.25	0.21	0.90–1.74	0.17
Multivariate model				
Tacrolimus trough-level variability	1.25	0.24	0.86–1.83	0.23

Also presented are Cox proportional hazards models of tacrolimus trough-level variability demonstrating a non-statistically significant association with patient survival

Covariate adjustment for outcomes include: recipient age, recipient sex, donor age, donor sex, cold ischaemic time, delayed graft function, HLA mismatches, panel reactive antibodies[a], CMV donor positive/recipient negative mismatch, acute allograft rejection[b], time on maintenance dialysis pre-transplantation

HLA Human Leukocyte Antigen (major antigens alleles A, B, DR), *CMV* cytomegalovirus

[a] Panel reactive antibodies were divided into <10, 10–49 and 50–100 % groups

[b] Acute rejection is defined as pathological evidence of rejection on transplant biopsy

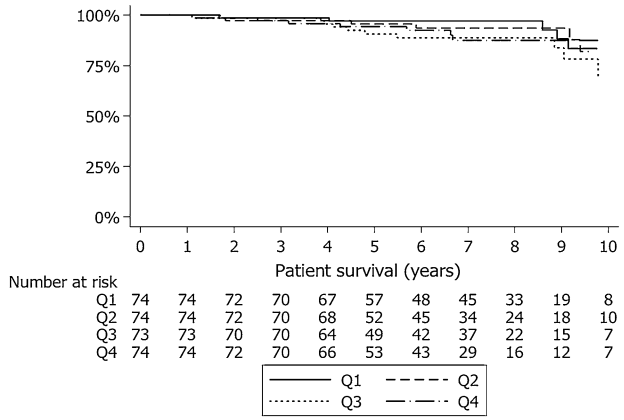

Fig. 2 Kaplan–Meier estimate of patient survival per quartile of tacrolimus trough-level variability

relevant in the setting of non-adherence. Short-term co-prescribing of medications which can alter normal tacrolimus metabolism could have confounded our observation by causing temporary fluctuations in recipients' trough-levels. In particular, inhibitors of cytochrome P450 3A4 (macrolide antibiotics, calcium channel blockers, proton-pump inhibitors, anti-fungals, amiodarone etc.) or inducers of cytochrome P450 3A4 (rifampacin, dapsone, phenytoin etc.) are frequently prescribed during clinical practice.

We considered measurement bias as a potential confounder for the association we observed. Because we used trough-level samples collected during routine clinical practice in the calculation of our predictor, it is impossible to guarantee that non-trough samples, taken in error, were not included. Furthermore, we considered a potential confounding influence from the number of trough samples used in the calculation of variability; we expected less variability with a greater number of trough-levels. However recipients with higher variability were subjected to increased trough-level monitoring during the 3–12 month period post transplantation. This probably reflects an increased clinical requirement to monitor patients who had greater variability, particularly if trough-levels fell outside therapeutic ranges.

One final confounding element that we could not correct for is intercurrent illness in the 3–12 months where tacrolimus variability was calculated. Our study design was unable to capture all inpatient and outpatient illness and treatments which could have led to higher tacrolimus variability and possibly inferior allograft outcomes. Any increased tacrolimus trough-level monitoring during a period of illness was included in the calculation of an individual recipient's variability.

The implications of our findings translate to important clinical considerations during routine management of transplant recipients. More focus is needed on strategies to improve long-term renal allograft survival. Tacrolimus trough-level variability is readily calculable and could potentially be used as a clinical tool at the bedside or in outpatient settings to identify recipients with highly variable tacrolimus trough-levels so that at-risk groups who are vulnerable to under-immunosuppression may be identified. Health care professionals should strive to encourage better adherence when interacting routinely with transplant recipients and these patients should be informed of potential risk associated with higher trough-level variability. Additional surveillance or services to maintain optimal immunosuppression adherence may be considered. Physicians managing transplant patients should also anticipate the effect of altering tacrolimus dosing and of co-prescribing on tacrolimus variability.

Once daily preparations of tacrolimus such as Advagraf® (Astellas Pharma Europe Ltd, Staines, UK) may reduce non-adherence by halving the required frequency of calcineurin dose administration [27], however the omission of a 'once-daily' dose due to non-adherent behaviour can lead to more prolonged periods of under-immunosuppression.

The implication that higher trough-level variability is associated with inferior allograft survival suggests potential avenues for future research. A prospective trial could provide a more accurate understanding of the relationship between tacrolimus trough-level variability and allograft survival by including some of the following elements; protocol tacrolimus trough-level measurements, pharmacogenetic information, short-term prescriptions for intercurrent illness information, records of inpatient and outpatient illness and their treatments, more specific allograft outcomes. In the future, a prospective trial comparing a novel therapy with current standard therapy could provide insights into renal allograft outcomes with regimes that are not associated with immunosuppression variability.

We present a large adult cohort (394 transplants in 390 recipients) with the longest median follow-up (6.9 years) examining tacrolimus trough-level variability as a predictor of renal allograft survival. This study has several limitations. Firstly, the donor and recipient population is predominately Caucasian and so the observation may lack external validity with non-Caucasian populations. Secondly, our predictor was calculated using samples collected during routine clinical practice rather than protocol measurement. Non-trough samples may have been included. Thirdly, we could not correct for the effects of intercurrent illness and subsequent treatment of this illness on tacrolimus variability. Fourthly, a composite endpoint of all-cause allograft failure was used. A more specific outcome such as chronic, active antibody mediated rejection is more desirable than all-cause allograft failure as potential explanations for our association include under-immunosuppression leading to unwanted immune responses. Retrospectively, however, such data was unavailable due to the routine use of previous pathological diagnoses such a "chronic allograft nephropathy" which

have since been dismissed. Lastly, as in all observational studies, cause and effect cannot be concluded. Despite this study's limitations, our data is consistent with previous observations demonstrating a significant association between higher tacrolimus variability and higher rates of renal allograft loss.

Conclusions

In conclusion, we observed a statistically significant association between higher tacrolimus trough-level variability and inferior allograft survival. Tacrolimus trough-level variability was not significantly associated with patient survival. These results highlight the importance of tacrolimus variability as a therapeutic consideration in the post transplant setting. Health care providers should maximise efforts to avoid higher tacrolimus variability in the first year post transplant.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval This study was a retrospective observational study using data from a prospectively gathered National Registry of Renal Transplant Recipients.

Informed consent Particularly, patients or their personal medical record charts were not contacted as all data was retrieved from the transplant database as is, so informed consent was not sought.

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