

BRIEF COMMUNICATION

Lower versus higher starting tacrolimus dosing in kidney transplant recipients

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Abstract

Achieving therapeutic tacrolimus levels is an essential component of balancing immunosuppression in kidney transplantation. At our institution, the starting tacrolimus dose was reduced from .075 mg/kg BD (higher dose [HD]) to .050 mg/kg BD (lower dose [LD]), to better achieve our target level of 6–10 µg/L in the early post-transplant period. Kidney transplant recipients (KTRs) transplanted 1-year before (HD: $n = 64$) and after (LD: $n = 63$) the starting dose reduction were retrospectively compared. Achieved tacrolimus levels were significantly lower in the LD group during the first 14 days posttransplant, but not at day 21 or day 28. A higher proportion of LD KTRs achieved therapeutic levels (day 1–3: 36.1% vs. 18.8%; day 4–7: 50.8% vs. 40.6%, day 8–14: 83.6% vs. 71.7%), while the HD KTRs were more likely to have supratherapeutic levels. Tacrolimus dose was significantly lower on day 5 compared to day 0 in the HD group but similar in the LD group. Rates of delayed graft function, posttransplant diabetes, and treated rejection at 6 months and graft outcomes at 3 years were all similar. Lowering the starting tacrolimus dose increased the proportion of KTRs achieving therapeutic range and minimized dose changes early posttransplant without an impact on clinical outcomes.

KEYWORDS

calcineurin inhibitor: tacrolimus, drug toxicity, immunosuppressant, kidney transplantation: living donor

1 | INTRODUCTION

Tacrolimus, a calcineurin inhibitor, is a standard part of the immunosuppressive regimen for kidney transplant patients (KTRs).^{1,2} Despite this, there have been few studies comparing different starting tacrolimus dosing regimens and their effects on achieving targeted therapeutic levels early posttransplant.³ Case series have demonstrated that high tacrolimus levels may lead to increased adverse effects such as nephrotoxicity and diabetes, while lower dosing may increase the risk of acute rejection.^{3,4}

The Efficacy Limiting Toxicity Elimination (ELITE)-Symphony study established low-dose tacrolimus in combination with mycophenolate, prednisolone, and basiliximab induction, as standard of care for immunosuppression in KTRs with standard immunological risk.⁵ The study demonstrated that the low-dose tacrolimus group had superior kidney function, allograft survival, and acute rejection rates, when compared to regimens with low-dose cyclosporine, low-dose sirolimus, or standard-dose cyclosporine without induction.⁵ A limitation of the ELITE-Symphony, however, is the lack of a “standard-dose tacrolimus” comparator group to determine whether a lower starting dose was

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superior to a higher starting dose. The low-dose tacrolimus group was commenced on a dose of .050 mg/kg BD, with a target trough level of 3–7 $\mu\text{g/L}$, although for the first 4 weeks the mean achieved level was 7–8 $\mu\text{g/L}$.⁵

In comparison, our institution has targeted trough tacrolimus levels of 6–10 $\mu\text{g/L}$ in the first month posttransplant, not dissimilar to levels achieved in the ELITE-Symphony study. This was previously protocolized with a starting tacrolimus dose of .075 mg/kg BD. However, in our experience supratherapeutic levels were common. In response, the starting dose was lowered to the same dose in the ELITE-Symphony of .050 mg/kg BD from November 2016. We retrospectively assessed the change from the previous “higher dose (HD)” starting tacrolimus regimen of .075 mg/kg BD to the “lower dose (LD)” of .050 mg/kg BD, comparing KTRs transplanted 1-year before and after the protocol change. We hypothesized that lowering the starting dose would increase the proportion of KTRs achieving the therapeutic range early posttransplant without increasing the risk of acute rejection. Potential benefits in reducing delayed graft function (DGF) and posttransplant diabetes mellitus (PTDM) were also explored.

2 | PATIENTS AND METHODS

A retrospective single center cohort study of KTRs at Austin Health transplanted before (HD period: November 2015 to October 2016) and after (LD period: December 2016 to November 2017) the reduction in starting tacrolimus dose from .075 mg/kg BD to .050 mg/kg BD was conducted. The study was approved by the Austin Health Human Research Ethics Committee (Reference Number: LNR/18/Austin/138). Multi-organ transplant recipients were excluded (one in HD and three in LD groups). All kidney only transplant recipients during the study period were included. The standard immunosuppression regimen used in addition to tacrolimus was mycophenolate mofetil 1000 mg BD, glucocorticoids (1000 and 500 mg intravenous methylprednisolone on day 0 and day 1, respectively, 30 mg oral prednisolone from day 2 tapering to 5 mg at week 16 and then maintained on prednisolone thereafter), and basiliximab induction (20 mg intravenously on day 0 and day 4). This was with the exception of one KTR during the LD period where azathioprine replaced mycophenolate due to known hypersensitivity (Table 1). Both tacrolimus and mycophenolate were commenced on day 0 prior to surgery (with the exception of those requiring desensitization for living donor kidney transplantation where mycophenolate 500–1000 mg BD was commenced 14 days prior to transplantation) and continued posttransplant from day 1 twice daily at 8 a.m. and 8 p.m. Anti-thymocyte globulin was not used for induction during the study period. Plasmapheresis sessions were implemented in six KTRs in each of the HD and LD periods for pretransplant donor specific antibodies (DSAs). The two different protocolized starting tacrolimus doses were used during the HD and LD periods, and this was then adjusted by the treating clinicians to aim for the same therapeutic target range of 6–10 $\mu\text{g/L}$ in response to trough levels during the first month. Tacrolimus could be withheld temporarily in response to high tacrolimus levels at the clinician’s discretion. Subsequent target tacrolimus levels were also

identical at 1–3 months (5–8 $\mu\text{g/L}$) and 3–6 (5–7 $\mu\text{g/L}$) months. The use of inhibitors or inducers of CYP3A5 and P-glycoprotein was to be avoided in our protocol. The proton pump inhibitor pantoprazole 40 mg daily was routinely prescribed to all KTRs in both HD and LD groups. Protocol biopsies were performed at 3 and 12 months. Pretransplant screening for DSAs was universally performed but not posttransplant for de novo DSAs. The presence of a DSA is defined by a mean fluorescence intensity of >500.

Data obtained included baseline demographic data, serum tacrolimus levels (measured by Roche Cobas e602 immunoassay) in the first 28 days, and the daily doses of tacrolimus and mycophenolate in the first 3 months posttransplant. Clinical outcomes including rates of treated acute rejection, DGF (excluding living donor transplants) and diabetes mellitus in the first 6 months, infections (cytomegalovirus [CMV] and BK [polyomavirus] infections defined by positive serum polymerase chain reaction, and bacteremia) in the first 12 months, and estimated glomerular filtration rate (eGFR) by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), graft loss, and death in the first 3 years, were compared. DGF was defined as acute graft dysfunction in the first week posttransplant requiring dialysis. For those without DGF, the creatinine-reduction-ratio between day 1 and 2 posttransplant (CRR2) was calculated. Median trough tacrolimus levels (interquartile range [IQR]) and the proportion of KTRs achieving therapeutic (target 6–10 $\mu\text{g/L}$), supratherapeutic (>10 $\mu\text{g/L}$), and subtherapeutic (<6 $\mu\text{g/L}$) levels at certain time intervals (day 1–3, day 4–7, and day 8–14) and time points (day 21 and 28) in the first 28 days posttransplant were compared. For each individual KTR, the mean of measured tacrolimus levels during each of the three intervals of day 1–3, day 4–7, and day 8–14 was used for analysis.

Data analysis was performed using GraphPad Prism 9.1.2 (GraphPad, San Diego, CA, USA). Continuous variables were presented as median (IQR), and comparisons between two groups were performed using the two-tailed Mann–Whitney *U* test. The Kruskal–Wallis test was used to compare the tacrolimus dose change from day 0 and day 5 in HD and LD groups, and Dunn’s multiple comparison test was performed for intraindividual dose change with HD and LD groups, respectively. Categorical variables were presented as number (percentage of group) and compared using Chi-square tests. A two-sided *p*-value of <.05 was considered significant.

3 | RESULTS

3.1 | Achieved tacrolimus levels in lower (LD) versus higher (HD) dose groups

The study included 127 KTRs consisting of 64 in the HD group and 63 in the LD group. There were no significant differences in baseline recipient, donor, or immunological characteristics between the two groups (Table 1). Compared with the HD group, achieved tacrolimus levels were significantly lower in the LD group during the time intervals of day 1–3 (10.2 [7.6–13.6] vs. 14.0 [10.7–18.8] $\mu\text{g/L}$; *p* < .001), day 4–7 (6.9 [5.6–9.1] vs. 9.1 [6.7–11.6] $\mu\text{g/L}$; *p* < .001), and day 8–14

TABLE 1 Baseline characteristics of kidney transplant recipients in higher (HD) versus lower (LD) dose groups

	Higher dose (HD) (N = 64)	Lower dose (LD) (N = 63)	p-value
Recipients			
Median age (years)	51 (44–60)	55 (45–64)	.27
Female gender (n [%])	23 (36%)	24 (38%)	.80
Body mass index	28.4 (24.6–31.9)	27.9 (25.4–30.9)	.59
Pretransplant diabetes (n [%])	11 (17%)	13 (21%)	.62
Donors			
Donor type (n [%])			
Living	17 (27%)	21 (33%)	.40
Deceased	47 (73%)	42 (67%)	
Deceased donor type (n [%])			
DBD	32 (68%)	26 (62%)	.54
DCD	15 (32%)	16 (38%)	
Median age (years)	55 (44–60)	53 (45–62)	.74
Total ischemic time (h)	9 (6–11)	8 (4–11)	.71
Immunology			
ABO incompatible (n [%])	1 (1.6%)	0 (0%)	.34
Donor specific antibodies (n [%])	17 (27%)	15 (24%)	.72
Peak panel reactive antibody (%)			
≥80%	5 (7.8%)	7 (11.1%)	.53
≥95%	3 (4.7%)	3 (4.8%)	.98
HLA mismatch (n [%])			
0–2	19 (30%)	23 (37%)	.26
3–4	20 (31%)	24 (38%)	
5–6	25 (39%)	16 (25%)	
Zero DR mismatch	16 (25%)	19 (30%)	.52
Repeat transplants	7 (11%)	6 (10%)	.79
Immunosuppression at baseline (n [%])			
Plasmapheresis	6 (9%)	6 (10%)	.98
Basiliximab induction	64 (100%)	64 (100%)	–
Prednisolone	64 (100%)	64 (100%)	–
Tacrolimus	64 (100%)	64 (100%)	–
Mycophenolate/azathioprine	64 (100%)/0 (0%)	62 (98%)/1 (2%)	.31

HD = higher starting dose group (.075 mg/kg BD), LD = lower starting dose group (.050 mg/kg BD). DBD, donation after brain death; DCD, donation after circulatory death; HLA, human leukocyte antigen.

(7.0 [6.4–8.4] vs. 8.2 [6.9–9.4] $\mu\text{g/L}$; $p = .003$) (Figure 1A). However, there was no significant difference at the later time points of day 21 (8.2 [7.4–9.9] vs. 8.8 [7.4–10.1] $\mu\text{g/L}$) or day 28 (8.4 [6.8–9.5] vs. 8.6 [7.6–9.6] $\mu\text{g/L}$).

3.2 | Likelihood to achieve targeted therapeutic range and dose changes early posttransplant

During the time intervals of day 1–3, day 4–7, and day 8–14, LD KTRs were more likely to achieve therapeutic tacrolimus levels of 6–10 $\mu\text{g/L}$

and less likely to have supratherapeutic levels compared with the HD group (Figure 1B). For instance, 79.7% of HD KTRs (vs. 54.1% of LD group) had supratherapeutic levels at day 1–3. In contrast, 36.5% of LD KTRs had subtherapeutic levels at day 4–7 compared with 18.8% in the HD group. However, at day 8–14 the proportion of LD group with subtherapeutic levels decreased to 12.7% (vs. 8.3% in HD group), with no difference by day 21 (Figure 1B). The intraindividual twice daily tacrolimus dose significantly decreased from day 0 to day 5 in the HD group (6.0 [5.0–6.6] vs. 4.5 [4.0–5.6] mg; $p < .0001$) but not in the LD group (4.0 [3.5–4.5] vs. 4.0 [3.3–4.5] mg; $p = .90$) (Figure 2), suggesting that the lower starting dose required fewer dose changes to achieve

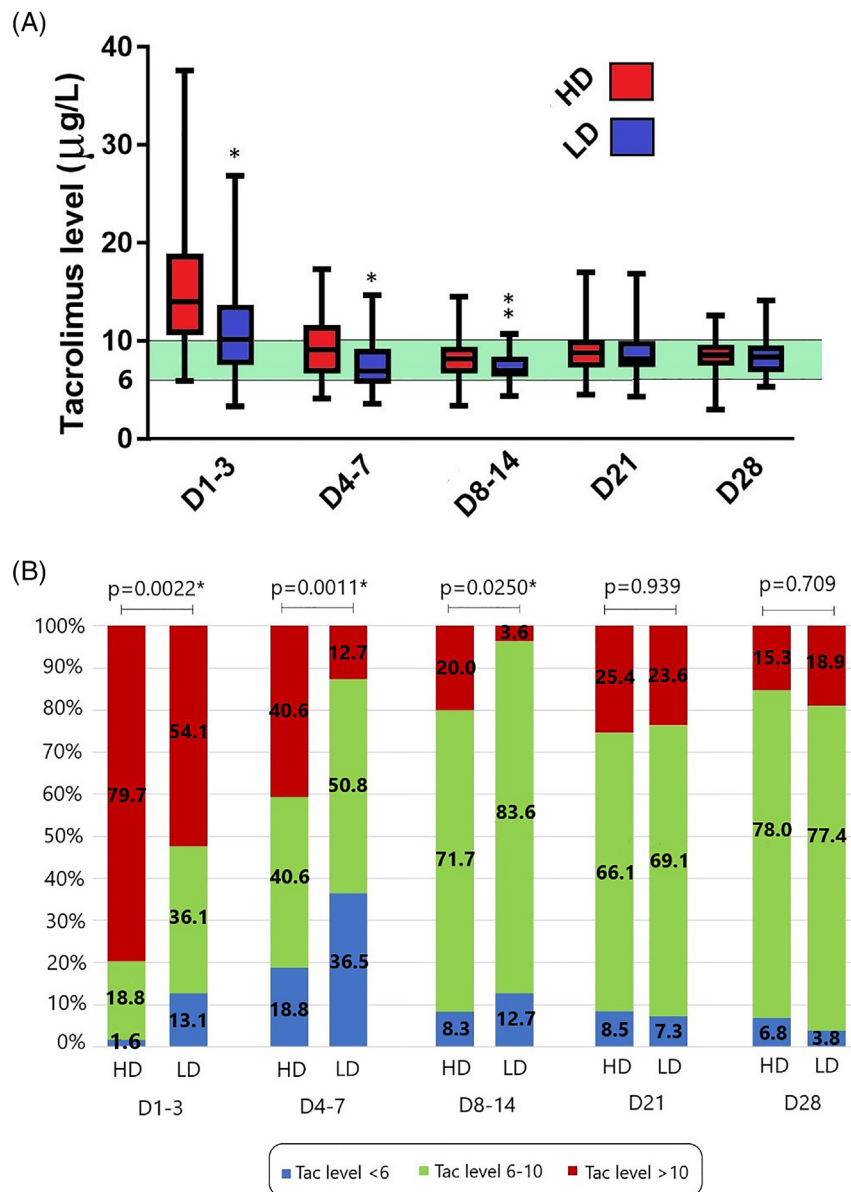


FIGURE 1 Achieved tacrolimus levels ($\mu\text{g/L}$) and the proportion achieving the targeted therapeutic range ($6\text{--}10\ \mu\text{g/L}$) in HD versus LD groups. (A) Box plots: midline = median, box = 25th–75th percentile, error bars = minimum–maximum. * $p < .001$, ** $p = .003$. The green shaded area demonstrates the targeted range of trough tacrolimus levels of $6\text{--}10\ \mu\text{g/L}$ in the early posttransplant period. (B) The numbers demonstrate the percentage of individual patients in each group with tacrolimus levels ($\mu\text{g/L}$) being in the intended therapeutic range (tacrolimus level $6\text{--}10$), suprathreshold (tacrolimus level > 10), or subtherapeutic (tacrolimus level < 6). HD = higher starting dose regimen ($.075\ \text{mg/kg BD}$), LD = lower starting dose regimen ($.05\ \text{mg/kg BD}$). Incomplete data due to KTRs being transferred back to their parent hospitals excluded from analysis (day 8–14: $n = 4$ for HD, $n = 8$ for LD; day 21: $n = 5$ for HD, $n = 9$ for LD; day 28: $n = 5$ for HD, $n = 10$ for LD). For the time intervals of day 1–3, day 4–7, and day 8–14, the mean of measured tacrolimus levels from each individual KTR during each interval was used for analysis. HD, higher dose; LD, lower dose; KTR, kidney transplant recipient

* p value < 0.05

the therapeutic levels in LD group. The daily tacrolimus dose was significantly higher at day 0, 2, and 5 in HD versus LD group although the magnitude of the differences was reduced from day 0 to day 5. However, this was no longer different at 1–3 months posttransplant (Table 2). Similarly, daily mycophenolate doses at 3 months were not significantly different between the two groups.

3.3 | Clinical outcomes

During the 6-month posttransplant follow-up, there were no significant differences between the HD and LD groups in the rates of DGF, CRR2, or PTDM (Table 3). Furthermore, infection rates at 12 months, as measured by bacteremia and viremia for CMV and BK, were not different (Table 3). Treated rejection rates at 6 months were not different, with the majority diagnosed at a median of 8–10 days posttransplant in the context of DGF. At 3 years, there was one death

(at 10 and 30 months) in each group, two graft losses in each group (at 4–11 months), with similar graft function between the two groups (Table 3). The proportion of KTRs with eGFR decline $\geq 30\%$ from 1 to 3 years posttransplant, a surrogate outcome for long-term death and graft failure,⁶ was also similar in HD versus LD group (Table 3).

4 | DISCUSSION

This study demonstrates the reduction in protocolized starting “HD” of tacrolimus $.075\ \text{mg/kg BD}$ to “LD” $.050\ \text{mg/kg BD}$, achieved a higher proportion of tacrolimus levels in the therapeutic range of $6\text{--}10\ \mu\text{g/L}$ in the first 14 days posttransplant, with a lower frequency of suprathreshold levels. This reflected the significant dose reduction from day 0 to day 5 in HD group, which was not required in the LD group. Although this protocol change led to more LD KTRs having subtherapeutic levels at day 4–7, the difference was modest by day

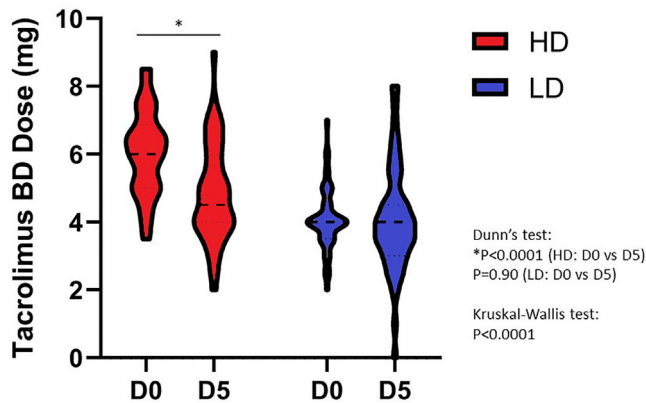


FIGURE 2 Tacrolimus dose from day 0 to day 5 in HD versus LD groups. Tacrolimus dose expressed as twice daily dose (mg BD). Density plots (midline long dashed line = median; dotted lines = 25th and 75th percentiles). HD day 0: 6.0 (5.0–6.6) mg versus HD day 5: 4.5 (4.0–5.6) mg ($p < .0001$), LD day 0: 4.0 (3.5–4.5) mg versus LD day 5: 4.0 (3.3–4.5) mg ($p = .90$) (Dunn's multiple comparison test); Kruskal–Wallis test ($<.0001$). HD, higher dose; LD, lower dose

8–14 and no longer significant by day 21. Overall, tacrolimus levels in the first 14 days posttransplant were lower in the LD group. The difference in the tacrolimus levels between the two groups did not impact on short-term clinical outcomes, including treated acute rejection, infection, DGF, or PTDM, or medium-term outcomes of graft function, graft failure, or death at 3 years. Both groups had similar baseline immunological profile and immunosuppression regimen (other than starting tacrolimus dose), with comparable tacrolimus dosing at 1–3 months and mycophenolate dosing at 3 months. Our treated acute rejection rate of 25%–26% at 6 months was higher than the 11.3% in the tacrolimus arm of the ELITE-Symphony study, which excluded borderline rejection.⁵ This could be related to our lower threshold to biopsy for DGF and 3-month protocol biopsies. After excluding border-

line rejection in our study, the rejection rate of 15%–21% was comparable with the binational ANZDATA registry (18.5%–21.6% in 2017).⁷

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for KTRs noted that the initial dosing of tacrolimus posttransplant is under-researched, with few trials directly comparing different doses or target levels.³ An updated 2019 Immunosuppressive Drugs Scientific Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicity consensus paper commented that there were limited studies investigating the effect of tacrolimus exposure on the risk of acute rejection or toxicity.^{8,9} The KDIGO guideline outlined two different approaches to initial tacrolimus dosing, namely standard and low dosing, with different trough tacrolimus level targets in the early posttransplant period.³ Standard dosing reflects the recommendation by the manufacturer Astellas Pharma, with a starting dose of .075–.150 mg/kg BD to achieve a target level of 10 $\mu\text{g/L}$ (range of 5–15 $\mu\text{g/L}$). This is in contrast to the low dosing defined by the ELITE-Symphony study, with a starting dose of .050 mg/kg BD and a target level of 5 $\mu\text{g/L}$ (range of 3–7 $\mu\text{g/L}$).⁵ However, the mean achieved tacrolimus levels of 7–8 $\mu\text{g/L}$ was higher than the originally intended range in the first 4 weeks posttransplant. The low-dose tacrolimus group demonstrated superior outcomes when compared to the other three nontacrolimus groups. There was, however, no standard-dose tacrolimus comparator group, and studies directly comparing the outcomes of standard versus low dosing tacrolimus dosing early posttransplant are lacking. A unique aspect of our study, albeit its retrospective and nonrandomized nature, is the two comparator groups of tacrolimus dosing, demonstrating no differences in clinical outcomes. Our LD group had the same starting dose of .050 mg/kg BD, with our targeted and achieved levels similar to the achieved levels in the ELITE-Symphony study. Similarly, the starting dose and levels achieved in the first 7 days from our HD group were similar to those recommended for standard dosing.

The optimal target range of tacrolimus levels early post-kidney transplantation remains controversial in the literature. A recent

TABLE 2 Tacrolimus and mycophenolate daily doses early posttransplant in higher (HD) versus lower (LD) dose groups

	Higher dose (N = 64)	Lower dose (N = 63)	p-value
Tacrolimus daily dose (mg)			
Day 0	12.0 (10.0–13.3)	8.0 (7.0–9.0)	<.0001
Day 2	10.0 (8.0–12.0)	8.0 (6.0–8.0)	.0003
Day 5	9.0 (8.0–11.3)	8.0 (6.5–9.0)	.0019
Month 1	7.0 (5.0–10.0)	6.0 (5.0–10.0)	.93
Month 2	5.0 (3.9–7.0)	5.3 (4.0–8.0)	.30
Month 3	4.0 (3.0–6.0)	4.0 (3.0–7.0)	.34
Mycophenolate daily dose (mg) ^a			
Month 3	2000 (1500–2000)	1750 (1500–2000)	.06
0–1250 mg (n [%])	7 (11%)	14 (23%)	.13
1500–1750 mg	15 (23%)	17 (27%)	
2000 mg	42 (66%)	31 (50%)	

^aLD: n = 1 on azathioprine instead of mycophenolate from day 0.

TABLE 3 Clinical outcomes in higher (HD) versus lower (LD) dose groups

	Higher dose (N = 64)	Lower dose (N = 63)	p-value
Delayed graft function ^a (n [%])	22 (47%)	20 (48%)	.94
CRR2 ^b	.39 (.24–.54)	.42 (.26–.58)	.36
Treated rejection at 6 months ^c			
Time of diagnosis posttransplant (days)	8 (7–10)	10 (7–71)	.32
Total (n [%])	15 (25%)	14 (26%)	.90
Borderline TCMR excluded	9 (15%)	11 (21%)	.45
Rejection types (n [%])			
Borderline	6 (10%)	3 (6%)	.15
TCMR	1 (2%)	7 (13%)	
- 1A	1 (2%)	1 (2%)	
- 1B	0 (0%)	4 (8%)	
- 2A	0 (0%)	2 (4%)	
AbMR	6 (10%)	3 (6%)	
Mixed	2 (3%)	1 (2%)	
- 1A	2 (3%)	0 (0%)	
- 1B	0 (0%)	1 (2%)	
No rejection	49 (75%)	39 (74%)	
Infection at 12 months (n [%]) ^d			
CMV viremia	11 (19%)	16 (30%)	.18
BK viremia	6 (11%)	11 (21%)	.14
Bacteremia	7 (12%)	6 (11%)	.88
Diabetes at 6 months (n [%]) ^e			
Excluding pretransplant diabetes ^e	12 (20%)	8 (15%)	.42
Total ^e	23 (39%)	21 (38%)	.93
eGFR (mL/min/1.73 m ²)			
3 months	55 (46–66)	54 (45–62)	.48
1 year	54 (46–69)	55 (46–63)	.31
3 years	58 (45–73)	54 (43–65)	.14
≥30% decline between 1 and 3 years (n [%]) ^f	7 (11%)	7 (11%)	.98
Death at 3 years (n [%])	1 (2%)	1 (2%)	.99
Graft failure (death censored) at 3 years (n [%])	2 (3%)	2 (3%)	.99

AbMR, antibody mediated rejection; CMV, cytomegalovirus; CRR2, creatinine-reduction-ratio between day 1 and 2 posttransplant; eGFR, estimated glomerular filtration rate; KTR, kidney transplant recipient; TCMR, T cell mediated rejection.

^aLiving donors excluded: *n* = 17 for HD, *n* = 21 for LD.

^bCRR2 = creatinine-reduction-ratio between day 1 and 2 posttransplant; KTRs with delayed graft function were excluded (*n* = 22 for HD, *n* = 20 for LD).

^cIncomplete data due to KTRs being transferred back to their parent hospitals, excluded from analysis: treated rejection: *n* = 5 for HD, *n* = 10 for LD.

^dIncomplete data due to KTRs being transferred back to their parent hospitals, excluded from analysis: infection: *n* = 7 for HD, *n* = 10 for LD.

^eIncomplete data due to KTRs being transferred back to their parent hospitals, excluded from analysis: diabetes: *n* = 5 for HD, *n* = 8 for LD.

^fDeath and graft failure included.

randomized trial suggested that maintaining tacrolimus levels over 7 µg/L was associated with a lower risk of acute rejection compared with achieved target levels of 3–7 µg/L. However, the immunosuppressive regimen differed being steroid-free, with the use of daily extended release tacrolimus, and the study examined the posttransplant period of 4–12 months.¹⁰ The lower target range was also substantially below ours at 6–10 µg/L in the first month. In contrast, a pooled analy-

sis of three clinical trials could not identify an association between trough tacrolimus levels early posttransplant (from day 3 to month 6) and acute rejection.¹¹ On the other hand, the association between higher tacrolimus concentrations and subsequent side effects has been demonstrated in other studies.^{12,13}

There were several limitations in our study. First, due to the retrospective nonrandomized nature of the study, unaccounted

confounders impacting on tacrolimus levels and clinical outcomes in the HD and LD groups across the two eras might exist. Clinicians were not blinded to the changes in starting tacrolimus dosing, with the potential to unintentionally influence their decision on the frequency and degree of dose titration. Second, the sample size was relatively modest and therefore possibly insufficient to detect a small difference in clinical outcomes. Third, all KTRs received basiliximab induction regardless of their baseline immunological risk during the study period, and this could limit the generalizability of our findings in centers where anti-thymocyte globulin use is more prevalent, in contrast to only 5.2% in Australia in 2017.⁷ Fourth, our study population were primarily Caucasians with a high prevalence of CYP3A5*3 genotype,¹⁴ which is associated with an LD requirement. Our study findings may therefore not be applicable to a different ethnic background. Fifth, posttransplant monitoring for de novo DSA is not standard of care or reimbursed in Australia, and therefore the impact of starting tacrolimus dosing on the risk of developing de novo DSA, subsequent chronic antibody mediated rejection and resultant graft failure could not be determined in this study. Nevertheless, 3-month protocol surveillance biopsies did not identify an increase in rejection in the LD group. Graft outcomes at 3 years were also no different between the two groups. In addition, the proportion of KTRs with $\geq 30\%$ eGFR decline between 1 and 3 years, a recognized surrogate outcome for death-censored graft failure with a c-statistic of .75, was also similar, supporting the hypothesis that a reduced tacrolimus starting dose would unlikely impact on long-term graft outcome.

In conclusion, this study demonstrates that the change to the lower starting tacrolimus dose from .075 mg/kg BD to .05 mg/kg BD resulted in a higher proportion of KTRs achieving the target therapeutic range of 6–10 $\mu\text{g/L}$ in the early posttransplant period. This reduced the frequency of suprathreshold levels and the magnitude of tacrolimus dose changes while transiently increased the risk of subtherapeutic levels, with no differences in clinical outcomes observed. Optimizing the starting dose of tacrolimus and targeted trough levels in the early posttransplant period remains an area of further research to strike the balance of adequate immunosuppression and minimization of adverse effects.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose in relation to this present study.

AUTHOR CONTRIBUTIONS

Justin C. M. Chua and Peter F. Mount participated in the study design. Justin C. M. Chua and Darren Lee collected data. Justin C. M. Chua,

Darren Lee, and Peter F. Mount analyzed the data. Justin C. M. Chua drafted the manuscript. Darren Lee and Peter F. Mount revised the manuscript. Justin C. M. Chua, Darren Lee, and Peter F. Mount approved the manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study is available from the corresponding author upon reasonable request.

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