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Impact of Once- Versus Twice-Daily Tacrolimus Dosing on Medication Adherence in Stable Renal Transplant Recipients: A Canadian Single-Center Randomized Controlled Trial

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Abstract

Background: Prevalence of immunosuppressant nonadherence in renal transplant recipients is high despite negative clinical outcomes associated with nonadherence. Simplification of dosing has been demonstrated to improve adherence in renal transplant recipients as measured through electronic monitoring and self-report.

Objective: The purpose of this study was to replicate and extend previous findings by measuring adherence with multiple methods in a Canadian sample.

Design: The study design was a randomized controlled medication dosing trial in adult renal transplant patients. The trial length was 4 months.

Setting: This study was conducted within the Solid Organ Transplant (SOT) Clinic at Vancouver General Hospital (VGH; Vancouver, Canada).

Patients: A total of 46 adult renal recipients (at least 1 year post-transplant) were recruited through the SOT clinic. With 8 withdrawals, 38 individuals completed all phases of the study.

Measurements: Medication adherence was measured for a period of 4 months using multiple methods, including electronic monitoring (MEMS [Medication Event Monitoring System]), pharmacy refill data (medication possession ratio [MPR]), and by self-report using the Adherence subscale of the Transplant Effects Questionnaire (TEQ).

Methods: Participants were randomized to twice-daily (n = 19) or once-daily tacrolimus dosing (n = 19) and followed over a 4-month period via monthly clinic study visits. Comparisons between the treatment groups were performed using the Mann-Whitney *U* and chi-square tests, for continuous and categorical variables, respectively.

Results: As outlined in Table 3, the once-daily dosing group showed significantly better MEMS Dose Adherence ($P = .001$), whereas MEMS Timing Adherence showed a tendency toward better adherence for this group, but was not significant ($P = .052$). MEMS Days Adherent ($P = .418$), MPR% ($P = .123$), and self-reported adherence ($P = .284$) did not differ between the once- and twice-daily dosing groups when measured as continuous variables. The MPR% was significantly better for the once-daily dosing group when measured dichotomously but not continuously ($P = .044$). Notably, most of those exposed to once-daily dosing (63.2%) preferred this to the twice-daily regimen.

Limitations: Limitations included small sample size and short follow-up period, precluding the examination of clinical outcome differences.

Conclusions: Results for dose adherence replicate the finding that dose simplification increases adherence to immunosuppressants as measured through electronic monitoring. Such an advantage for the once-daily dosing group was not seen across the 2 other electronic monitoring measurement variables (days and timing adherence). This study extends previous research by examining adherence in once versus twice-daily dosing via prescription refill data in a Canadian sample. Given the gravity of potential health outcomes associated with nonadherence, although results indicate inconsistencies in significance testing across measurement methods, the medium to large effect sizes seen in the data favoring better adherence with once-daily dosing provide an indication of the potential clinical significance of these findings.

Trial registration: This study was registered with ClinicalTrials.gov (NCT01334333) on April 11, 2011.

Abrégé

Contexte: Bien que la non-observance du traitement immunosuppresseur soit associée à de mauvais résultats cliniques, sa prévalence demeure élevée chez les receveurs d'une greffe rénale. Il a été démontré qu'une posologie simplifiée améliorait l'observance thérapeutique mesurée par suivi électronique et auto-évaluation dans cette population.

Objectif: Cette étude visait à reproduire et à élargir les résultats d'études précédentes en mesurant par différentes méthodes l'observance thérapeutique dans un échantillon de patients canadiens.

Type d'étude: Un essai contrôlé à répartition aléatoire d'une durée de quatre mois examinant la posologie médicamenteuse d'adultes greffés rénaux.

Cadre: L'étude s'est tenue au sein de la Solid Organ Transplant Clinic (clinique SOT) du Vancouver General Hospital (VGH; Vancouver, Canada).

Sujets: Quarante-six greffés rénaux adultes ont été recrutés (au moins un an post-transplantation) par l'entremise de la clinique SOT. En raison de huit retraits, l'étude porte sur trente-huit individus ayant complété toutes les phases de l'étude.

Mesures: L'observance thérapeutique a été mesurée sur une période de quatre mois, selon différentes méthodes, notamment le suivi électronique (MEMS), le renouvellement des ordonnances (rapport de possession de médicaments—RPM) et l'auto-évaluation avec la sous-échelle d'observance du *Transplant Effects Questionnaire* (TEQ).

Méthodologie: Les participants ont été répartis aléatoirement pour recevoir du tacrolimus deux fois par jour (n = 19) ou une fois par jour (n = 19) et ont été suivis pendant quatre mois au moyen de visites mensuelles à la clinique. Les comparaisons entre les groupes de traitement ont été effectuées par tests U de Mann-Whitney (variables continues) et tests de chi-deux (variables nominales).

Résultats: Comme indiqué dans le tableau 3, lorsque l'observance est mesurée par MEMS, le groupe ayant reçu une dose quotidienne unique a montré une observance nettement supérieure au niveau de la dose ($P = 0.001$), de même qu'une tendance vers une meilleure observance du traitement au niveau du moment, quoique cette dernière ne soit pas significative ($P = 0.052$). Le nombre de jours d'observance mesuré par MEMS ($P = 0.418$), le pourcentage RPM ($P = 0.123$) et l'observance auto-déclarée ($P = 0.284$) n'ont pas différé entre les groupes lorsque mesurés comme variables continues. Le pourcentage RPM était significativement plus élevé pour le groupe traité une fois par jour, lorsque mesuré de façon dichotomique, mais non continue ($P = 0.044$). La majorité des patients traités par une dose unique quotidienne (63.2%) ont préféré ce schéma posologique à une prise deux fois par jour.

Limites: La petite taille de l'échantillon et la courte période de suivi empêchent l'examen des différences observées dans les résultats cliniques.

Conclusion: Les résultats sur l'observance de la dose reproduisent la conclusion selon laquelle un dosage simplifié augmenterait l'observance du traitement immunosuppresseur, lorsque mesurée par MEMS. Un tel avantage pour le groupe recevant une dose quotidienne unique n'a pas été observé pour les deux autres variables de mesure par MEMS (observance en jours et du moment de la prise du médicament). La présente étude élargit les recherches antérieures en examinant l'observance de la posologie (une ou deux fois par jour) avec les données de renouvellement des ordonnances dans un échantillon canadien. Compte tenu de la gravité des effets potentiels de la non-observance thérapeutique sur la santé, et bien que les résultats indiquent des incohérences entre les méthodes de mesure dans la vérification des hypothèses, l'ampleur moyenne à grande de l'effet observé dans les données favorisant une meilleure observance à une dose unique quotidienne souligne l'importance clinique potentielle de ces résultats.

Keywords

Advagraf, electronic monitoring, medication adherence, Prograf, renal transplantation, tacrolimus

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What was known before

Simplification of dosing regimen has been demonstrated to improve immunosuppressant adherence in renal transplant recipients as measured through electronic monitoring and self-report.[1-3]

What this adds

The purpose of this study was to replicate these findings using a randomized controlled trial using multiple adherence measures within a Canadian sample. Although results replicate the finding that dose simplification results in better adherence

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to immunosuppressants as measured through one specific electronic monitoring assessment and one measurement of pharmacy refill data, the advantage is not supported when other adherence measurement methods are used. Nonetheless, this study extends previous findings by showing an effect via analysis of prescription refill data within a Canadian sample and by calling attention to the potential differences between adherence measurement methods (even differing electronic measurement methods).

Introduction

A critical aspect of real-world functioning following renal transplantation involves how adherent individuals are to their medication regimens. Nonadherence to immunosuppressant medications post-transplant is related to increased morbidity and mortality and has been shown to significantly increase rate of graft rejection.[4,5] Regardless, extant research has reported variable and relatively high rates of nonadherence following organ transplant, with rates of up to 86% reported in older renal transplant recipients.[6,7]

Previous research suggests that medication dosing regimens may be an important factor influencing medication adherence implementation. For instance, research with individuals receiving antihypertensive medications using electronic monitoring has shown that adherence improved (from 59.0% to 83.6%) when thrice-daily dosing was compared with once-daily dosing.[8] Research examining once-daily in comparison to twice-daily tacrolimus dosing in renal transplant recipients has indicated that switching from a twice-daily dose is safe and does not lead to significant changes in blood glucose, potassium, or magnesium in this group.[9,10] In addition, in a 2-year study in renal transplant recipients, approximately 35% of participants indicated a preference for once-daily dosing.[10] More recent research indicates improved adherence as measured via electronic monitoring in one randomized controlled trial in this group.[1] Nonetheless, other studies using self-report measures of adherence indicate mixed results. Two observational studies (1 cross-sectional and 1 prospective) indicate improved adherence for once-daily tacrolimus.[2,3] By contrast, a randomized trial (using self-report adherence diaries) found no difference in adherence between once- and twice-daily dosing in renal transplant recipients.[11]

In this study, we wished to further clarify the relationships between tacrolimus dosing schedule and implementation adherence (ie, the extent to which the patient's dosing behavior corresponds with the prescribed regimen)[12] among renal transplant recipients in western Canada. Specifically, we aimed to determine whether previous findings of improved adherence for once- versus twice-daily dosing of tacrolimus could be replicated in a randomized controlled trial using multiple adherence implementation measures. Toward these ends, we examined not only electronic monitoring and self-report measures of adherence but also pharmacy prescription refill records. To our knowledge, this is the first randomized controlled trial to assess adherence in these dosing regimens via multiple adherence measurement methods and within a Canadian sample. Based on previous literature focusing on electronic monitoring and self-report adherence measurements, we hypothesized that once-daily dosing would be associated with increased adherence as measured by electronic monitoring. Although literature is mixed with respect to self-reported adherence, and nonexistent for pharmacy refill data, we also hypothesized that once-daily dosing would be associated with improved adherence as assessed via these methods.

Methods

Population and Setting

Participants were recruited from the Solid Organ Transplant (SOT) Clinic at Vancouver General Hospital (VGH) in Vancouver, BC, Canada. To be eligible, participants met the following inclusion criteria: (1) capable of giving informed consent; (2) no visual, hearing, or other sensory/motor impairments that may interfere with the testing procedures; (3) fluent in the English language; (4) minimum of Grade 6 education (due to reading requirements of questionnaires); (5) absence of psychosis; (6) absence of acute illness (eg, metastatic cancer), neurological disease, and other major organ failure (eg, end-stage liver disease); and (7) minimum 1 year post-transplant with a successful kidney graft and stable kidney functioning (estimated glomerular filtration rate [eGFR] above 25 mL/min per 1.73 m^2). Participants were excluded from the study if they did not meet all of the above requirements.

Design and Procedure

A flowchart describing participant recruitment and participation is presented in Figure 1. Potential participants were contacted using a recruitment letter that was followed up by a telephone call to determine their interest and schedule participation. Approximately 31% of those meeting inclusion criteria for the study showed interest in and were scheduled to complete the study. A total of 46 individuals were enrolled in the study, of which 38 completed all required study visits. Barriers to enrollment included difficulty obtaining transportation to study visits, requirement for additional clinic visits over standard care, preference for non-English language, and required randomization of medication formulation. Reasons for withdrawal from the study are also summarized in Figure 1.

At the initial study visit (coordinated with participants' regular clinic visit), trained research assistants randomly assigned each of the 46 participants to receive either the once-daily Advagraf (tacrolimus extended release; n = 24) or twice-daily Prograf (tacrolimus; n = 22) tacrolimus formulation using a random number generator. At this time,

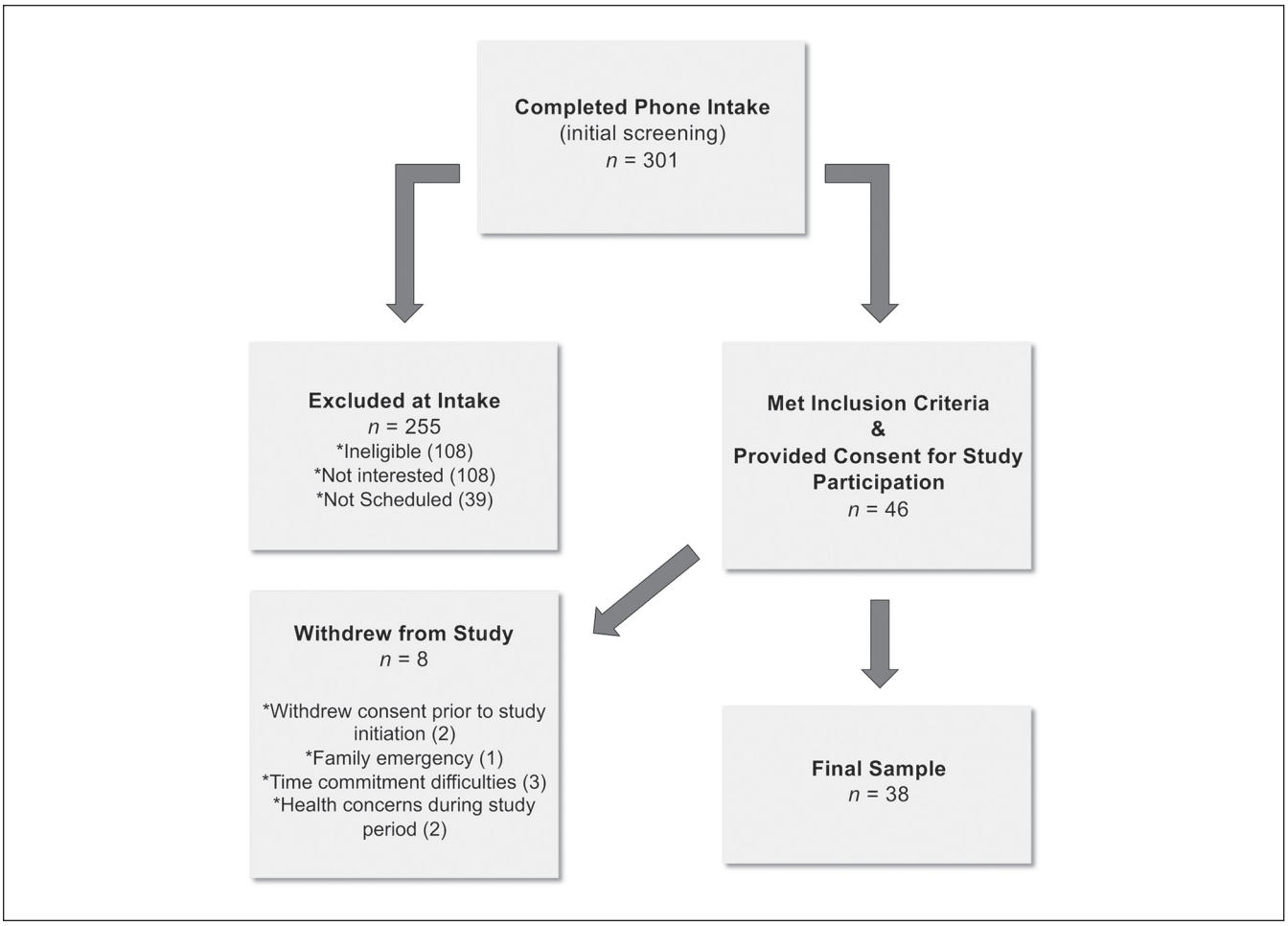

Figure 1. Participant recruitment flowchart.
Note. Regarding inclusion/exclusion criteria at intake, participants who indicated less than 3 of 4 preferences as "English" for speaking, reading, writing, and thinking on an acculturation questionnaire were considered ineligible due to language requirements for neurocognitive testing necessary for the larger study, of which these participants were a part; in addition, those reporting any of the abovementioned physical or mental health exclusions were ineligible. Not interested = participants who declined study participation due to lack of interest; Not scheduled = participants who expressed interest in the study, but who had scheduling conflicts and did not participate.

participants also received medication counseling and instructions for use of the MEMS (Medication Event Monitoring System) caps and completed study questionnaires. Participants at the SOT Clinic routinely receive medications from the SOT Clinic pharmacy, which facilitated an immediate change in tacrolimus formulation. All participants received a 1-month supply of their assigned study medication and returned once per month for study appointments to refill medications and complete study questionnaires. A total of 5 study visits over a 4-month duration were completed.

All participants signed letters of informed consent and received Can$20.00 per study visit to offset time and travel expenses. Ethics boards at the University of British Columbia, Simon Fraser University, and Vancouver Coastal Health Authority approved the protocol for this study. This study is registered with ClinicalTrials.gov (NCT01334333).

Data Collection

Demographic information was collected from all participants during the initial study visit. This included age, sex, current employment status, living situation (ie, alone or with others), ethnicity, and level of education. In addition, *Health* and *Medical History* questionnaires created by our laboratory were completed with participants and validated against available medical records to provide relevant medical and transplant-related history (eg, number of renal transplants, type of transplant, time since transplant, eGFR and hemoglobin levels, and chronic kidney disease [CKD] G category).[13,14]

Medication adherence was measured using multiple methods. Electronic monitoring through the MEMS 6 caps was undertaken for the span of the 4-month study period. During the initial study visit, participants were taught how to properly open and close bottles using these caps. They were

instructed to take their daily (once or twice depending on formulation) tacrolimus dose from the MEMS cap–equipped bottles and to only open the cap when taking their prescribed medication dose. Three measurements were computed using the MEMS PowerView software: (1) percentage of doses each participant retrieved from the MEMS cap–equipped bottle (ie, number of doses retrieved, divided by the number of doses assigned during the study period, multiplied by 100; MEMS Dose Adherent), (2) percentage of days during the study period on which the correct number of doses were taken (ie, 1 dose/day for those in the once-daily group and 2 doses/day for those in the twice-daily group; MEMS Days Adherent), and (3) percentage of doses taken within a near-optimal interdose interval (calculated as the interval between bottle openings – 12 ± 3 hours or within a 9-15 hour range for twice-daily, and 24 ± 6 hours or within an 18-30 hour range for once-daily dosing[15]; MEMS Timing Adherent). As much of the extant adherence literature has examined adherence dichotomously, we also computed adherence/nonadherence dichotomous variables for MEMS Dose, MEMS Days, and MEMS Timing Adherent measures; on these dichotomous measures, as patients may take fewer or more doses than prescribed, participants who retrieved between 90% and 110% of doses (MEMS Dose Adherent Dichotomous) and/or had at least 80% accurate dosing (MEMS Days Adherent Dichotomous and MEMS Timing Adherent Dichotomous) were categorized as adherent. In all instances, similar cut-points have been used in the transplant adherence literature.[16]

Pharmacy refill data were also collected through the SOT pharmacy databases and records. Data available for the study period were used to calculate a medication possession ratio (MPR), reflecting the amount of prescribed medication an individual obtained within a specified period compared with that which they should have obtained during that period. Medication possession ratios were multiplied by 100 to provide a continuous percentage measure of adherence (MPR%). A dichotomous MPR% variable (MPR% Dichotomous) was then also computed, for which MPRs between 90% and 110% were considered adherent and those above or below this level as nonadherent, consistent with criteria previously used for pill count data.[16]

Participants also completed the *Adherence* subscale of the *Transplant Effects Questionnaire* (*TEQ*) at the end of the study period (TEQ Adherence) to provide a measure of self-reported adherence.[17] This scale has 5 items related to medication adherence behaviors, which are endorsed on a Likert scale ranging from strongly agree to strongly disagree (eg, "Sometimes I think I do not need my anti-rejection medicines"), for a score range of 5 to 25, with higher scores indicating greater adherence. Test-retest reliability of responses to the Adherence subscale after a 1-month interval has been found to be high ($r = .77$).[17] Responses to this subscale also significantly correlate with the Short Form Health Survey (SF-36; a measure of quality of life related to health),[18] in renal transplant recipients.[19]

Health literacy was examined using the Health Literacy Questionnaire (HLQ),[20] which assesses both intrinsic and extrinsic facets and the social and cognitive skills associated with health literacy. The HLQ is a 44-item questionnaire that provides a multidimensional profile of health literacy. In the first section (23 items), items are responded to via a 4-point Likert scale ranging from 1 (*strongly disagree*) to 4 (*strongly agree*). In the second section (21 items), items are responded to using a 5-point Likert scale ranging from 1 (*cannot do*) to 5 (*very easy*). To reduce the probability of Type I error and the number of variables, a total HLQ score (sum of scores for items 1-44) was computed. The total possible score ranged from 44 to 197, with higher scores indicating higher self-reported health literacy.

Data Analysis

A review of the transplant adherence literature[21] indicates that the distribution of adherence data is often highly skewed, and that the implications of this are often not appropriately considered in data analysis. With this in mind, the Kolmogorov-Smirnov test was used to determine whether our continuous adherence measurement variables were normally distributed. Results indicated nonnormal distributions for MEMS Dose Adherent ($P < .001$), MEMS Days Adherent ($P < .001$), MPR% ($P < .001$), and TEQ Adherence ($P = .008$). As a result, we used the Mann-Whitney U (nonparametric) test to determine whether differences existed between the once- and twice-daily prescribed tacrolimus groups for these continuous measures. An independent-samples t test was used to examine MEMS Timing Adherent between groups. The chi-square test $(\chi)^2$ was used to compare categorical variables between groups.

Results

Sample Characteristics

Table 1 shows the sample characteristics. The study sample included significantly more men (n = 22) than women (n = 16) across treatment groups ($t[37] = 17.51$, $P < .001$); however, sex distributions were equivalent in both groups. All participants were in G categories 1 to 3 of CKD based on eGFR levels. In total, 22 participants were assigned to the twice-daily tacrolimus dosing group and 24 to the once-daily dosing group. After accounting for participant withdrawals, data from 19 participants were available for each of the once- and twice-daily study groups (comparison of demographic and clinical variables between those who withdrew and those who completed the study was not possible as most of the participants who withdrew did so prior to the collection of this medical and demographic information).

Table 1. Baseline Demographic and Health Characteristics by Tacrolimus Dosing Group.

	Participants (N = 38)	
	Once-daily (n = 19)	Twice-daily (n = 19)
Variable	N (%)/mean ± SD	N (%)/mean ± SD
Age	52.26 ± 13.28 (range: 29-77)	52.95 ± 11.60 (range: 24-66)
Sex: male	11 (57.9)	11 (57.9)
Ethnicity		
White	7 (36.8)	11 (57.9)
Asian	8 (42.1)	2 (10.5)
Other	4 (21.1)	6 (31.6)
Education	14.32 ± 2.31	14.32 ± 2.28
English as a second language: yes	8 (42.1)	5 (26.3)
Living situation: Alone	3 (15.8)	5 (26.3)
Transplant > 1	2 (10.5)	1 (5.3)
Type of transplant: cadaveric	8 (42.1)	11 (57.9)
Time since transplant	7.25 ± 5.61	8.00 ± 6.61
Time on dialysis pre-transplant	2.88 ± 2.25	2.62 ± 2.56
Tacrolimus level (μg/L)	6.28 ± 1.52	6.01 ± 1.57
Hemoglobin level (g/L)	126.17 ± 18.63	135.05 ± 18.04
Estimated glomerular filtration rate level (mL/min/1.73 m^2)	66.67 ± 20.10	57.00 ± 16.54
Creatinine level (μmol/L)	103.67 ± 47.59	113.37 ± 34.50
KDIGO CKD G category		
G1	3 (16.7)	—
G2	10 (55.6)	8 (42.1)
G3	4 (22.3)	11 (57.9)
G4	1 (5.6)	—
Health Literacy Questionnaire total score	155.92 (16.81)	154.00 (14.29)

Note. KDIGO = The Kidney Disease: Improving Global Outcomes; CKD = chronic kidney disease.

For baseline group characteristics and statistical comparisons between the study groups, see Table 1; no statistically significant differences were seen for demographic and baseline illness variables examined between the study groups. In addition, no significant group differences were seen in scores on a health literacy measure nor on a self-reported adherence measure administered at the initial study visit (time of randomization). For post-assessment comparisons of health variables between groups, see Table 2. A significant difference between groups was only seen for tacrolimus serum level. Interestingly, although tacrolimus serum levels did not differ at the outset of the study, those taken at the conclusion of the study were significantly higher in the twice-daily dosing group ($P = .002$), though both groups were within target range.

Once- Versus Twice-Daily Tacrolimus Effects on Measured Adherence

Table 3 shows group comparisons. With respect to continuous measures, level of medication adherence significantly differed between once- and twice-daily tacrolimus groups as measured by the MEMS Dose Adherent variable ($P = .001$). The once-daily tacrolimus group had a higher mean percentage of adherence as determined via the number of doses taken during the monitoring period (mean = 102.17%, SD = 3.99 vs mean = 95.94, SD = 9.03). Although MEMS Days Adherent did not significantly differ between groups, MEMS Timing Adherent showed a tendency toward better adherence in the once-daily group (once-daily: 95.07%, twice-daily: 89.10%; $P = .052$) that was not statistically significant. In consideration of dichotomous measures, adherence as measured by MPR% (MPR between 90% and 110% considered adherent) significantly differed between the once- and twice-daily tacrolimus groups ($P = .044$). In the once-daily group, 15 participants were considered adherent (78.95%), whereas in the twice-daily group 9 participants were adherent (47.37%). See Table 4 for correlational analyses across groups; in these analyses, higher percent dose adherence (large effect size), timing adherence (medium to large effect size), and on-target MPR% (medium effect size) were also each significantly associated with once-daily dosing, providing additional support for the aforementioned group differences. No significant group differences were found for self-reported medication adherence. All other effect sizes are estimated to be small, with some approaching a medium effect size (ie, r or $V = 0.3$).[22] With the exception of correlations between MEMS Days Adherent and MEMS Timing Adherent with MPR% continuous variables, the 3 categories

Table 2. Post-Assessment Health Characteristics by Tacrolimus Dosing Group.

	Participants (N = 38)		
	Once-daily (n = 19)	Twice-daily (n = 19)	χ^2/t
Variable	N (%)/mean ± SD	N (%)/mean ± SD	*P* value
Tacrolimus (μg/L)	4.83 ± 1.44	6.20 ± 1.08	.002*
Hemoglobin (g/L)	124.11 ± 17.59	132.53 ± 18.90	.164
Estimated glomerular filtration rate (mL/min/1.73 m^2)	63.94 ± 21.39	57.68 ± 19.52	.358
Creatinine (μmol/L)	107.63 ± 45.55	113.42± 34.05	.660
KDIGO CKD G category			.334
G1	2 (11.1)	1 (5.3)	
G2	8 (44.4)	5 (26.3)	
G3	8 (44.4)	13 (68.4)	

Note. Tacrolimus level was that obtained closest to the end of study participation. All other values were collected at the first visit post–study completion; *t* test results for continuous variables and Pearson chi-square test results for categorical variables; CKD = chronic kidney disease; KDIGO = The Kidney Disease: Improving Global Outcomes.
*$P < .01$.

Table 3. Medication Adherence Measurements by Tacrolimus Dosing Group.

	Once-daily (n = 19)	Twice-daily (n = 19)	χ^2/U	*r*/*d*/*V*
Measure	N (%)/mean ± SD	N (%)/mean ± SD	*P* value	Effect size
MEMS Dose Adherent	102.17 ± 3.99	95.94 ± 9.03	.001**	0.528
MEMS Dose Adherent (Dich)	19 (100)	16 (84.2)	.071	0.293
MEMS Days Adherent	93.76 ± 3.53	89.09 ± 11.08	.418	0.135
MEMS Days Adherent (Dich)	19 (100)	16 (84.2)	.071	0.293
MEMS Timing Adherent	95.07 ± 5.63	89.10 ± 11.48	.052	0.660
MEMS Timing Adherent (Dich)	19 (100)	16 (84.2)	.071	0.293
MPR%	109.52 ± 13.35	106.73 ± 27.12	.123	0.253
MPR% (Dich)	15 (78.9)	9 (47.4)	.044*	0.327
TEQ Adherence	20.33 ± 3.73	21.58 ± 3.52	.284	0.180

Note. N's represent the number of participants considered adherent using each variable and %'s represent the percent of each group considered adherent by each measure. For MEMS Dose Adherent and MPR%, values greater than 100% were possible. Effect sizes are presented as Pearson's *r* for Mann-Whitney *U* tests (continuous data), Cohen's *d* for the *t* test, and as Cramer's *V* for chi-square tests (dichotomous data). For Pearson's *r* and Cramer's *V*: 0.1 = small, 0.3 = medium, 0.5 = large; for Cohen's *d*: 0.2 = small, 0.5 = medium, 0.8 = large. MEMS = Medication Event Monitoring System; MPR = medication possession ratio; TEQ = Transplant Effects Questionnaire; dich = dichotomous.
*$P < .05$. **$P < .01$.

Table 4. Correlations Between Tacrolimus Formulation and Adherence Measures Examined.

	1	2	3	4	5	6	7	8	9	10
1. Tacrolimus Formulation	—									
2. MEMS Days Adherent	.280	—								
3. MEMS Days Adherent (Dich)	.293	.848**	—							
4. MEMS Dose Adherent	.417**	.851**	.853**	—						
5. MEMS Dose Adherent (Dich)	.293	.848**	1.000**	.853**	—					
6. MEMS Timing Adherent	.321*	.952**	.794**	.831**	.794**	—				
7. MEMS Timing Adherent (Dich)	.293	.848**	1.000**	.853**	1.000**	.794**	—			
8. MPR%	.067	.361*	.231	.313	.231	.371*	.231	—		
9. MPR% (Dich)	.327*	.083	.181	.234	.181	–.010	.181	–.359*	—	
10. TEQ Adherence	–.174	–.074	–.279	–.173	–.279	–.047	–.279	–.042	.181	—

Note. MEMS = Medication Event Monitoring System; MPR = medication possession ratio; TEQ = Transplant Effects Questionnaire; dich = dichotomous.
*Correlation is significant at the .05 level (2-tailed). **Correlation is significant at the .01 level (2-tailed).

of adherence measures (electronic, pharmacy, and self-report) did not correlate with one another. As expected, significant associations were demonstrated between variables of the same adherence category (ie, MEMS adherence variables correlated with one another as did MPR% variables).

Patient Preferences for Once- Versus Twice-Daily Dosing

Following completion of the study, participants were given the choice of continuing with or switching to the once-daily medication formulation. Pharmacy records indicated that 18 of 19 (94.74%) participants randomized to the twice-daily regimen chose to continue with that dosing, 12 of 19 (63.16%) who had been assigned to the once-daily regimen chose to continue with that dosing, whereas 7 (36.84%) chose to revert to twice-daily dosing. Notably, a relatively high percentage of those exposed to once-daily dosing in this study appeared to prefer this to their previous twice-daily regimen. Qualitatively, participants completed preference questionnaires following completion of the study, with many of those uninterested in the once-daily dosing, noting that they preferred twice-daily dosing due to maintaining their original routine, need to take other medications twice daily, and/or worries that changing dosing may impact health.

Discussion

Our findings provide some replication of previous research demonstrating that dose simplification is related to improved medication adherence in renal transplant participants, with significant differences seen between study groups specifically with respect to dose adherence and pharmacy refill data. By contrast, other measures of adherence examined did not indicate statistically significant group differences in our small sample. Importantly, our results extend previous research by comparing adherence between once- and twice-daily tacrolimus dosing groups using multiple methods (electronic monitoring, pharmacy refill data, and self-report) in a Canadian sample, and demonstrate that dose simplification is related to improved adherence as assessed through both measures of electronic monitoring (%Dose Adherence) and analysis of pharmacy refill data. Although other group differences in adherence were not supported in this study, it is notable that our sample was small, and as such our study likely lacked statistical power to detect smaller statistical differences between groups. Our results also suggest satisfaction with the simplified regimen for most of the patients who were randomized to once-daily dosing as demonstrated by the large percentage of patients who preferred to continue with this regimen following study completion.[10] Preference for maintenance of twice-daily dosing was driven by interest in maintaining routine, requirements of other medications to be taken twice daily, and worries that changing dosing may impact health. Interestingly, although tacrolimus serum levels did not differ at the outset of the study, at the conclusion of the study, levels were significantly higher in the twice-daily dosing group. Similar differences in tacrolimus levels have been reported in previous studies examining once- versus twice-daily dosing and have been unrelated to outcomes such as acute rejection.[1]

Recent research in other illness groups has proposed that there is no gold standard measure of medication adherence, and as such the use of multiple methods may provide the most thorough understanding of adherence difficulties.[23] However, as seen here and in previous work, the use of multiple methods may also introduce inconsistencies.[23] Discrepancies were observed even across electronically measured variables of adherence, with only MEMS Dose Adherent significantly differing between dosing groups (demonstrating a large effect), whereas MEMS Timing Adherent showed a tendency that was not statistically significant. Adherence may, thus, depend on the chosen measurement methods, and given the disparities between the different adherence measures examined, it appears prudent to better determine how each of these measures relates to specific health outcomes for renal transplant recipients.

Although differences in adherence seen between groups did not readily translate to differences in clinical blood levels examined (ie, hemoglobin, creatinine, tacrolimus, eGFR) in this study, there was only a 4-month follow-up period, and thus potential long-term clinical impacts of poorer adherence could not be captured. It is likely that a longer-term follow-up study may reveal differences in clinical outcomes (eg, lab values, graft rejection, loss) associated with lower adherence in a twice-daily tacrolimus group and would allow further exploration of the relationship of various dosing errors (dosing, days, timing) with outcome. Clinically, although the precise levels of nonadherence required to lead to poor outcomes have not yet been determined,[24] even small deviations from a prescribed regimen have the potential to negatively impact the intended effect of treatment.[25,26]

Previous literature reporting significant differences in adherence between once- and twice-daily dosing of tacrolimus has not generally reported data that readily lend to calculation of effect sizes.[1-3] Nonetheless, examination of one study reporting no significant differences between dosing regimens indicated a trivial effect size for adherence (Cohen's $d = 0.157$; calculated from data provided in original publication).[11] By contrast, effect sizes for relationships tested in this study were small to medium, with the exception of MEMS Dose Adherent (large effect). Clinically, however, when evaluating the practical significance of effect sizes, the gravity of the outcome in question as well as the quality of the measurement should be considered.[27] In the case of nonadherence, from a practical perspective, associated complications of morbidity and potential mortality[4,25] imply that medium (MPR% and MEMS timing adherence data) and large (MEMS dose Adherence data) effect sizes observed in this study are highly significant. This study relied on well-

validated measures of adherence, further adding to the clinical importance of our findings.

Our results did not reveal significant differences in adherence between treatment groups when self-report adherence ratings were considered. Previous research indicates mixed results with respect to differences in self-reported adherence among those with once- versus twice-daily prescriptions.[2,3,11] Examination of effect sizes from previous research examining self-reported adherence (and those seen in this study) indicates that the magnitude of these differences is likely to be small and thus more difficult to detect in smaller samples. Previous research has found the prevalence of nonadherence as measured through self-report to be lower than that detected through electronic monitoring,[28] possibly reflecting a lower sensitivity in detecting nonadherence, which may also explain the mixed results of studies using these measures.[2,3,11] Our review of previous studies examining self-reported adherence between once- and twice-daily tacrolimus dosing highlights the need going forward for researchers to include effect size data in their analyses to aid in interpretation.

Limitations of our study include a small sample size and a short follow-up period that precluded the examination of clinical outcome differences (ie, rejections, graft losses, death) between the 2 treatment groups. Our present findings of generally small to medium effects of adherence differences between treatment groups highlight the importance of sample size considerations for future study planning, as acquisition of larger samples allows for better detection of small to medium effects. Although our sample size was adequate to reveal moderate to large associations between dosing type and adherence (ie, dose adherence, timing adherence, and dichotomized pharmacy data), we had limited power to detect the significance of smaller effects seen for other measured variables. Nonetheless, examination of results for the other adherence measures suggests that, with the exception of self-report data, group differences seen with small to medium effect sizes for other adherence measures also consistently favored once-daily dosing, supporting the reliability of the conclusions drawn herein. Future research with larger samples may be able to better determine whether inconsistencies between adherence measures used here replicate and further clarify the utility of different adherence measures in predicting important health-related outcomes.

In relation to our sample, it is also notable that although our final sample included approximately 50% of those contacted who met the inclusion criteria and were interested in participating in the study, many potentially eligible individuals were not interested in participating due to the length of the study and number of clinic visits involved, distance required to travel to the clinic, conflicts with other activities including work schedules, and worries about changing tacrolimus dosing schedule. As a result of this study's exclusionary criteria and self-selection into the study, our sample may not be completely representative of the population of renal transplant patients in Canada. It is possible that those who self-selected into the study differ in respect of some illness and demographic variables compared with their transplanted peers.

Conclusions

Our results provide support for replication of an advantage to once- versus twice-daily tacrolimus dosing among renal transplant recipients from a large urban transplant center in western Canada. To our knowledge, this is also the first study to extend previous findings using indices from pharmacy refill data in addition to electronically measured and self-reported adherence. By showing an association between tacrolimus dosing and adherence with some measures of adherence, but not others, this study calls attention to the differences observed between various measures of medication adherence used frequently in the literature. Importantly, this suggests that these measures may not necessarily be used interchangeably, and that more research is needed to better determine the predictive utility of different measures of adherence for specific health outcomes among renal transplant recipients going forward.

With respect to future research, our results serve as a call to researchers to report effect sizes of analyses and to remain mindful of power and sample size considerations in the assessment of adherence. From a clinical standpoint, this study confirms the previously reported relationship between dose simplification and improved adherence in a Canadian sample of renal transplant recipients. This study also highlights important issues in the measurement of adherence that warrant consideration by prescribing practitioners and those monitoring adherence in this group. Future research would also benefit from the inclusion of patient-research partners in the study design to ensure feasibility, tolerability, and practicality from the patients' perspective on aspects such as number of visits, spacing between visits, and length of follow-up.

Ethics Approval and Consent to Participate

The study protocol was approved by the research ethics boards at the University of British Columbia, Simon Fraser University, and Vancouver Coastal Health Authority.

Consent for Publication

Consent for publication has been provided by all authors.

Availability of Data and Materials

The data and materials are not available for this study.

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