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A randomized clinical trial of age and genotype-guided tacrolimus dosing after pediatric solid organ transplantation

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Abstract

Background: Tacrolimus pharmacokinetics are influenced by age and *CYP3A5* genotype with *CYP3A5* expressors (*CYP3A5*1/*1 or *1/*3*) being fast metabolizers. However, the benefit of genotype-guided dosing in pediatric solid organ transplantation has been understudied.

Objective: To determine whether age and *CYP3A5* genotype-guided starting dose of tacrolimus result in earlier attainment of therapeutic drug concentrations.

Setting: Single hospital-based transplant center.

Methods: This was a randomized, semi-blinded, 30-day pilot trial. Between 2012 and 2016, pediatric patients listed for solid organ transplant were consented and enrolled into the study. Participants were categorized as expressors, *CYP3A5*1/*1* or *CYP3A5*1/*3*, and nonexpressors, *CYP3A5*3/*3*. Patients were stratified by age (≤ or > 6 years) and randomized (2:1) after transplant to receive genotype-guided (n = 35) or standard (n = 18) starting dose of tacrolimus for 36-48 hours and were followed for 30 days.

Results: Median age at transplant in the randomized cohort was 2.1 (0.75-8.0) years; 24 (45%) were male. Participants in the genotype-guided arm achieved therapeutic concentrations earlier at a median (IQR) of 3.4 (2.5-6.6) days compared to those in the standard dosing arm of 4.7 (3.5-8.6) days ($P = 0.049$), and had fewer out-of-range concentrations [OR (95% CI) = 0.60 (0.44, 0.83), $P = 0.002$] compared to standard dosing, with no difference in frequency of adverse events between the two groups.

Conclusions: *CYP3A5* genotype-guided dosing stratified by age resulted in earlier attainment of therapeutic tacrolimus concentrations and fewer out-of-range concentrations.

KEYWORDS

genetics, immunosuppression, pediatric transplantation, solid organ, tacrolimus, therapeutic drug monitoring, transplantation

Abbreviations: AE, adverse event; AUC, area under the curve; CI, confidence interval; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PK, pharmacokinetic.

1 | INTRODUCTION

Tacrolimus, a calcineurin inhibitor, is a common maintenance immunosuppression drug used after solid organ transplantation. It has a narrow therapeutic index requiring frequent therapeutic drug monitoring to maintain concentrations within the therapeutic range. Subtherapeutic concentrations in the early post-transplant period increase the risk of rejection, while concentrations above the target range contribute to drug-related toxicity.[1-4]

Tacrolimus is almost completely metabolized through the cytochrome P450 enzymes, CYP3A4 and CYP3A5, in the liver and to a lesser extent in enterocytes.[5] ABCB1 also contributes to tacrolimus metabolism to inactive metabolites but to a lesser extent.[6] Single nucleotide polymorphisms (SNPs) in the *CYP3A5* gene significantly influence tacrolimus drug concentrations.[7-10] Compared to nonexpressors (*CYP3A5*3/*3*), *CYP3A5* expressors (*CYP3A5*1/*1*, **1/*3*) require twofold higher doses of tacrolimus to achieve target blood concentrations,[11] and show delayed achievement of target blood concentrations. *CYP3A5*1/*1* genotype of donor has also been associated with higher tacrolimus dose requirements in liver transplant recipients.[12] However, a genome-wide association study at our center[13] and another study by Ghisal et al[14] did not identify association between *CYP3A5* loci and biopsy-proven rejection.

Age is also an important determinant of tacrolimus clearance. Plasma clearance of tacrolimus in children is higher (2-3 ml/kg/min) compared to adults (1-2 mL/kg/min)[15] due to proportionately larger liver size in children[16] and higher *CYP3A4* activity during the first year of life.[10] Younger pediatric patients therefore need higher doses than adults to achieve similar tacrolimus trough concentrations.[17,18] In our previous study of 37 heart transplant recipients, age and *CYP3A5* genotype together accounted for 35% of the variability in tacrolimus dose requirements ($P = 0.001$) and 52% variability in the concentration/dose ratio ($P < 0.001$).[19] Zhao et al demonstrated that tacrolimus dose should be based on weight, hematocrit, and *CYP3A5* genotype.[9] However, previous studies have not accounted for variability by age and have been limited to kidney transplant recipients, and therefore, it is unclear whether current genotype-guided dosing guidelines for tacrolimus apply to all ages and all organ transplants.[20] We hypothesized that age and genotype-guided starting dose will be associated with earlier and more stable therapeutic drug concentrations compared to standard dosing during 30 days after transplant.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a single-center, randomized, semi-blinded pilot trial comparing *CYP3A5* genotype-guided dosing to standard dosing for tacrolimus. Written informed consent was obtained from parents or legal guardians. Baseline demographics, medical history, and status at listing were collected prior to transplant. The study was reviewed and approved by the Institutional Research Ethics Board and Health Canada (ClinicalTrials.gov ID: NCT01655563).

2.2 | Eligibility Criteria

Inclusion criteria were as follows: (a) age < 18 years old at listing; (b) listing for heart, kidney, and liver transplantation; (c) planned enteral maintenance immunosuppression with tacrolimus post-transplant; and (d) informed consent of legal guardian. Exclusion criteria were as follows: (a) contra-indications to enteral tacrolimus, for example, severe gastrointestinal bleeding; (b) comorbidities that precluded standard dosing, for example, significant renal or hepatic insufficiency; (c) multiple organ transplants or retransplants; and (d) participation in other investigational drug trials within 30 days of study initiation.

2.3 | CYP3A5 genotyping

DNA was extracted from blood after enrollment, and genotyping for *CYP3A5*3* (rs776746) was performed prior to tacrolimus initiation using a TaqMan assay (Applied Biosystems, Foster City, CA) in the institutional-accredited clinical genetic testing laboratory. Participants were categorized as expressors with *CYP3A5*1/*1 (AA)* or *CYP3A5*1/*3 (AG)* and as nonexpressors with *CYP3A5*3/*3 (GG)*.

2.4 | Randomization

Participants were randomized after transplantation by the study coordinator in a 2:1 ratio to genotype-guided dosing vs standard dosing. This ratio was used to ensure that all genotypes were represented in the experimental arm as majority of patients (~70%) were expected to be nonexpressor (*3/*3). Randomization was further stratified by genotype (expressor vs nonexpressor) and by organ type (liver vs nonliver). The completed randomization form was faxed to the research pharmacy. Randomization was stratified by organ type (liver or nonliver) and genotype (expressor or nonexpressor) according to the randomization table provided by the research pharmacist.

2.5 | Study dosing

Both groups received starting dose of tacrolimus for 36-48 hours from a trial supply of commercially available tacrolimus (Prograf ®, manufactured by Astellas). Genotype-guided dosing used a sliding scale algorithm with the lowest dose in older (>6 years) *CYP3A5* nonexpressors and the highest dose in younger (≤6 years) *CYP3A5* expressors (Figure 1). Physicians or nurses caring for the patient, and participants were blinded to genotype and randomization arm but not to the starting dose. Participants were switched from study dosing to clinical dosing after the first 36-48 hours. The participants were followed after tacrolimus initiation for 30 ± 3 days.

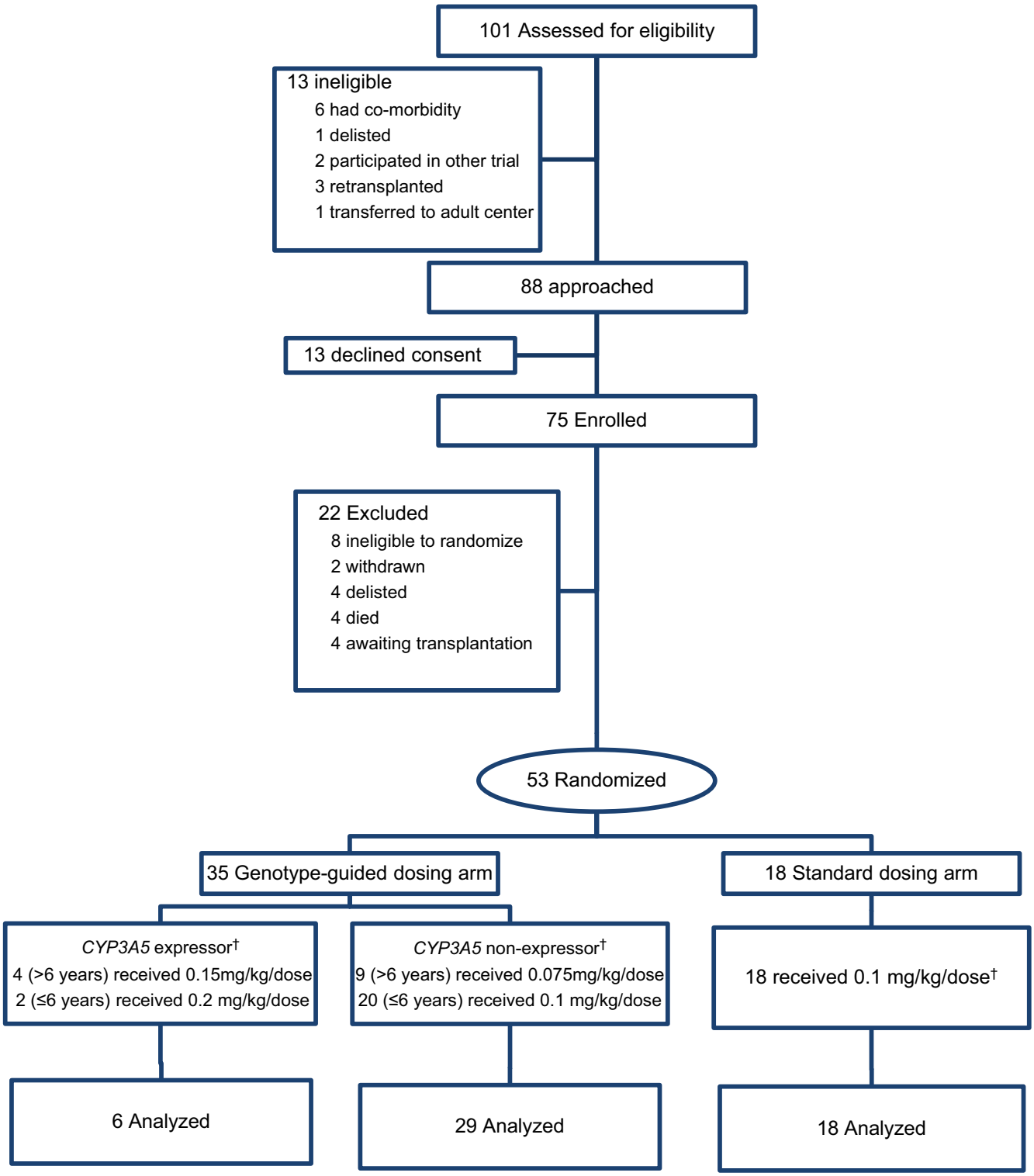

FIGURE 1 Enrollment and randomization consort diagram
†Capped at maximum 5 mg per dose.

2.6 | Tacrolimus concentrations

The first steady-state trough concentration of tacrolimus (C0) in whole blood was measured at 36-48 hours (usually after 3-4 doses) after study drug initiation. Target therapeutic trough concentrations for the first 12 weeks post-transplant were 10-12 μg/L (heart and kidney) and 12-15 μg/L (liver). Tacrolimus trough concentrations were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS-MS) (Applied Biosystems and MDS Sciex) in the institutional-accredited therapeutic drug monitoring laboratory. Coefficient of variation of

this method of tacrolimus assay is 4-6%, and lower limit of detection is <1 μg/L. Tacrolimus dose and frequency, and tacrolimus 12 hours post-dose trough concentrations were captured throughout hospital stay and on subsequent clinical outpatient visits.

2.7 | Tacrolimus pharmacokinetics

Steady-state tacrolimus pharmacokinetic (PK) profile was performed (generally between 5 and 12 days post-tacrolimus initiation). Whole blood samples were drawn from an indwelling peripheral or central venous catheter and were collected in EDTA tubes at C1, C2, C4, C6, C8, C10, and C12. For three young infants (≤6 months), an abbreviated PK profile was collected at C1, C2.5, C6, and C9. A 12-hour area under the curve (AUC) was calculated via trapezoidal rule.

2.8 | Clinical and laboratory data

Weight, blood pressure, concomitant medications, and creatinine levels were captured from medical records at baseline and study follow-up. At our center, heart transplant recipients receive rabbit antithymocyte globulin, kidney recipients receive either basiliximab or rabbit antithymocyte globulin, and liver recipients receive steroids as standard induction. Maintenance immunosuppression included prednisolone in all kidney and liver transplants and sensitized heart transplants, and mycophenolate mofetil in all heart, kidney transplants, and a subset of liver transplant patients requiring neural/renal sparing protocols. The rejection was assessed on clinically indicated or surveillance biopsies. Hypertension was defined as systemic hypertension requiring the administration of antihypertensive agents. Hyperglycemia was defined as glucose level higher than upper limit of normal reference range [<1 month (2.7-5.5 mmol/L), 1 month- < 6 months (3.2-6.0 mmol/L), and 6 months-<19 years (3.9-6.0 mmol/L)], and neurotoxicity included any neurological adverse events including seizures and posterior reversible encephalopathy syndrome. Estimated glomerular filtration rate (eGFR) was calculated using the revised Schwartz bedside formula[21]: eGFR (mL/min/1.73 m^2) = 36.52 × height (cm)/serum creatinine (umol/L) and eGFR < 90 mL/min/1.73 m^2 was classified as any kidney injury.

2.9 | Adverse events (AEs) monitoring and reporting

All AEs were routinely assessed and recorded by the Qualified Investigator or MD delegate and reported to the Institutional Research Ethics Board. AEs were classified by intensity, severity, relationship to investigational agent, expectedness of the event, treatment or action taken, and clinical outcome. All serious, unexpected adverse drug reactions to the study medication were reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. A copy of any serious, unexpected adverse drug reaction reports was sent to the Data and Safety Monitoring Committee. All AEs were managed according to the standard clinical management practices and followed over a 30-day follow-up period.

2.10 | Study outcomes

The primary goal was to compare the efficacy of genotype-guided tacrolimus dosing during 30-day follow-up after transplant. The primary outcome (efficacy) was time to achieve therapeutic tacrolimus trough concentrations and to maintain stable therapeutic trough concentrations, which is defined as two consecutive concentrations at least 48 hours apart in the therapeutic range without any changes in tacrolimus dose. Additional efficacy outcomes included tacrolimus concentration/dose ratio, frequency of out-of-range concentrations (defined as concentrations greater than ±1 μg/L outside target therapeutic range for organ type), frequency of dose adjustments, and tacrolimus AUC. The secondary outcome (safety) was frequency of AEs between the two dosing arms during follow-up.

2.11 | Statistical analysis

Continuous variables were summarized as median (interquartile range), and categorical variables were reported as frequencies and proportions. Medians were compared using Wilcoxon rank-sum test, and proportions were compared with Fisher's exact test. Time to first therapeutic concentration and time to stable trough concentrations were described using Kaplan-Meier survival. The log-rank test was used to assess across stratum differences. To account for repeated measurements within subjects, tacrolimus out-of-therapeutic range and dose adjustments were analyzed with repeated measures logistic regression models. Tacrolimus blood concentration and tacrolimus concentration/dose ratios were analyzed with mixed-effect models. AEs were analyzed using Poisson models adjusting for follow-up duration, genotype, and organ type. The occurrence of any kidney injury was assessed using a repeated measures generalized linear model adjusted for eGFR at tacrolimus initiation, time since tacrolimus initiation, genotype, and organ type. All models were adjusted for genotype and organ type. All statistical analyses were carried out using intention-to-treat method and performed using SAS v9.4 (SAS statistical software, Cary, NC).

2.12 | Study power

The enrollment target was 75 patients with the goal of randomizing 60 patients in a 2:1 ratio. Assuming a median time to first therapeutic concentration of 5 days, using a log-rank test, a sample size of 60 provides 80% power at alpha of 0.05 to detect a 2.5-day difference between the two dosing arms in the time to achieve first therapeutic concentration.

3 | RESULTS

During the trial recruitment and follow-up period (2012-2016), 88 eligible participants listed for solid organ transplant were approached, 75 were consented and enrolled, 22 were excluded (8 ineligible to randomize, 2 withdrawn, 4 delisted, 4 died, and 4 awaiting

TABLE 1 Characteristics of 53 trial participants by randomization arm

Variable	Genotype-guided dosing (n = 35)	Standard dosing (n = 18)	*P*-value
Age at transplant (median, IQR)	2.8 (0.7-13.5)	1.3 (0.8-5.9)	0.30
Males (%)	19 (54%)	5 (28%)	0.085
Race/ethnicity			0.74
White/Caucasian	26 (74%)	12 (67%)	
Asian	7 (20%)	4 (22%)	
Black	0 (0%)	1 (6%)	
Mixed[a]	2 (6%)	1 (6%)	
Organ type			0.35
Heart	8 (23%)	7 (39%)	
Kidney	11 (31%)	3 (17%)	
Liver	16 (46%)	8 (44%)	
Donor type			0.52
Deceased, unrelated	10 (29%)	7 (39%)	
Living, related	19 (54%)	10 (56%)	
Living, unrelated	6 (17%)	1 (6%)	
CYP3A5 Genotype			0.42
*1/*1 (expressor)	1 (3%)	2 (11%)	
*1/*3(expressor)	5 (14%)	3 (17%)	
*3/*3 (nonexpressor)	29 (83%)	13 (72%)	

Note. [a]Participant with more than one ethnicity.

transplantation) resulting in 53 randomized after transplantation (35 to genotype-guided dosing and 18 to standard dosing; Figure 1). A total of 7 patients (4 from genotype-guided dosing arm and 3 from standard dosing arm) began but did not complete 36-48 hours of study dosing and were analyzed in their original assigned groups in an intention-to-treat model. All participants completed study follow-up; 33 had PK testing. A total of 17% of participants in the genotype-guided dosing arm and 28% in the standard dosing arm were *CYP3A5* expressors. Median (IQR) age at transplant was 2.1 (0.75-8.0) years, and 45% participants were male. Characteristics of participants by randomization arm are described in Table 1.

3.1 | Efficacy

Figure 2a shows the time to achieve first tacrolimus blood concentration in the therapeutic range. Participants in the genotype-guided dosing arm achieved therapeutic range earlier than those in the standard clinical dosing arm ($P = 0.049$). The median (IQR) time to achieve first therapeutic concentration was 3.4 (2.5-6.6) days in the genotype-guided arm and 4.7 (3.5-8.6) days in the standard arm. 69% participants in the genotype-guided arm achieved stable therapeutic concentrations while only 44% in the standard arm achieved stable therapeutic concentrations within 30 days ($P = 0.089$). The median time to achieve stable therapeutic concentrations was 18 (14-27) days in those in the genotype-guided arm; however, in the standard dosing arm, median time could not be generated because <50% participants achieved stable therapeutic concentration during study follow-up. Figure 2B shows the difference in time to stable concentrations by dosing arm; the difference did not reach statistical significance ($P = 0.13$).

Overall, 60% participants had at least one out-of-range tacrolimus concentration in the genotype-guided arm and 71% in the standard dosing arm during study follow-up. The odds of out-of-range concentrations over 30-day follow-up were significantly lower in the genotype-guided dosing arm than the standard dosing arm [OR (95% CI) = 0.60 (0.44, 0.83), $P = 0.002$].

There was no significant difference in tacrolimus AUC between the genotype-guided dosing arm (n = 25) and the standard dosing arm (n = 8) (141 ± 54 vs. 134 ± 67, respectively, $P = 0.82$). When tacrolimus blood concentrations were indexed to dose received, the tacrolimus concentration/dose ratio tended to be higher in the genotype-guided arm 145 (118, 172) compared to standard dosing arm 100 (62, 138) μg/L per mg/d, although did not reach statistical significance ($P = 0.059$). There was no significant difference in requirement for dose adjustment between the genotype-guided and the standard dosing arm (OR [95% CI] = 1.20 [0.87, 1.66]).

3.2 | Safety

A total 192 AEs were reported during 30-day follow-up (Table 2). 11% were possibly tacrolimus-related with no difference by dosing

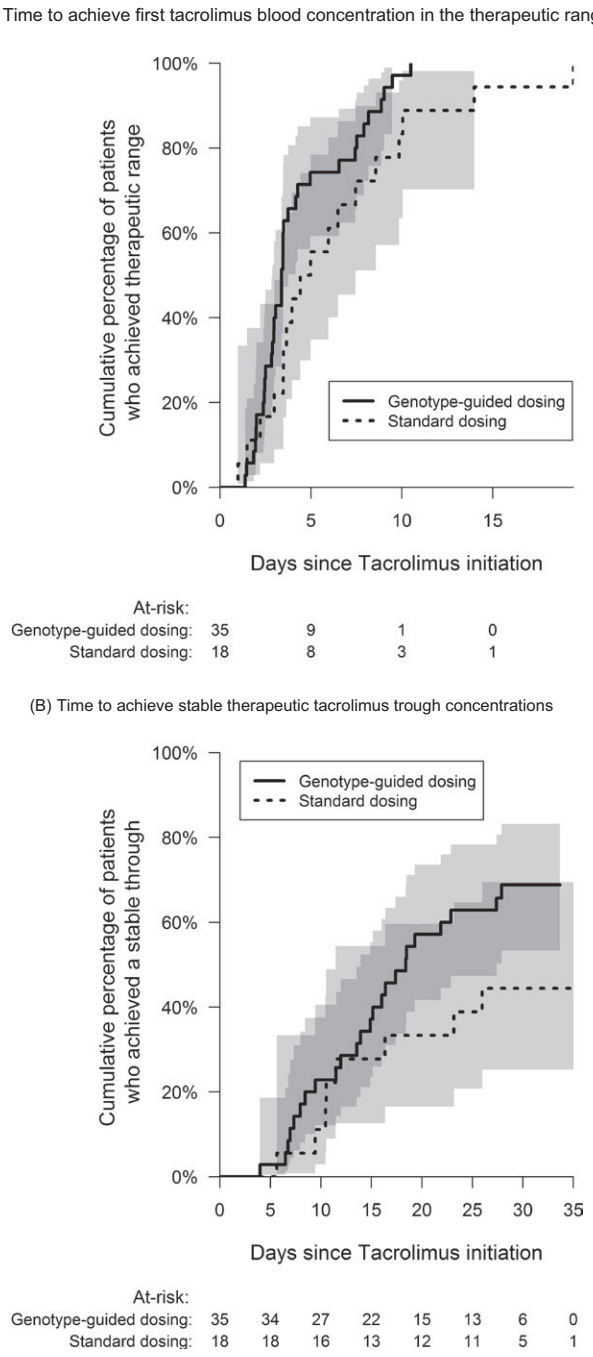

FIGURE 2 (A) Time to achieve first tacrolimus blood concentration in the therapeutic range was lower with genotype-guided dosing (solid line, n = 35) compared to standard dosing (dash line, n = 18) (P = 0.049). (B) Time to achieve stable therapeutic tacrolimus blood concentrations (two consecutive concentrations at least 48 hours apart in the therapeutic range without change in tacrolimus dose) was not significantly different between dosing arms. Solid line, genotype-guided dosing arm (n = 35); dash line, standard dosing arm (n = 18) (P = 0.13)

arm. 4% were serious AEs; none were tacrolimus-related. There was no significant difference in the incidence of AEs between the study arms except for hematological AEs in which incidence was lower in genotype-guided dosing arm (0.41 [0.17, 0.99]). The most frequent early post-transplant complications included any kidney injury (66%), hypertension (49%), graft rejection (9%), hyperglycemia (6%), and seizures (4%) (Table 2).

4 | DISCUSSION

In this randomized pilot clinical trial comparing age and genotype-guided to standard tacrolimus starting dose in pediatric solid organ transplant recipients, we provide evidence that *CYP3A5* genotype-guided dosing was safe and resulted in earlier attainment of target therapeutic concentrations with significantly fewer out-of-range concentrations than with standard dosing. In addition, 69% participants in the genotype-guided arm were able to maintain stable concentrations compared to only 44% in the standard arm during study follow-up, although this difference did not reach significance likely due to overall low proportion of participants (60%) meeting this end-point. While further studies are needed to include adjustments not only to starting dose but also to subsequent dose titrations to improve maintenance of stable therapeutic concentrations, the findings underscore the importance of stratifying genotype-guided dosing by age in a pediatric population. This is also the first trial that encompasses the three largest solid organ groups undergoing transplantation.

The findings in our study were consistent with findings by Thervet et al[22] that patients in genotype-guided dosing arm achieved first therapeutic target concentrations earlier than standard dosing arm. However, another randomized trial in adult kidney transplant recipients did not find any difference in proportion of patients achieving first steady-state therapeutic concentrations with *CYP3A5* genotype-guided dosing.[23] Similar to other studies,[22,23] this study showed no difference in the occurrence of AEs between the two arms during study follow-up although the definition of hypertension was different from current Hypertension Canada's 2017 guideline.[24] While the trial was not designed to study differences in clinical outcomes, prior studies in adults have reported high (15%-30%) intrapatient variability in tacrolimus trough concentrations[1,25] with individuals with higher variability demonstrating higher risk of rejection and poor graft outcomes.[1-3] In another retrospective study, patients with subtherapeutic or supratherapeutic concentrations showed higher incidence of delayed graft function and longer hospital stay compared to those with therapeutic concentrations.[26] The ability to reduce the frequency of out-of-target concentrations through more precise individualized dosing therefore has a strong potential to improve clinical outcomes. The ability to reduce hospital length of stay and costs of frequent therapeutic drug monitoring in addition to reducing costs associated with complications could also result in substantial cost savings to the healthcare system.[27]

Other factors can influence tacrolimus concentrations including organ type, liver function, hemoglobin levels, concomitant medications, feeding status, as well as donor genotype in liver transplants that can alter tacrolimus bioavailability or alter clearance through

TABLE 2 Adverse events assessed during trial follow-up up to 30 d

	Genotype-guided dosing (n = 35)	Standard dosing (n = 18)	Incidence rate ratio [95% CI] (unless otherwise specified)
Any adverse event	121	71	0.89 [0.66,1.19]
Severity of adverse event			
Mild	106 (88%)	61 (86%)	0.92 [0.67, 1.26]
Moderate	12 (10%)	6 (8%)	1.29 [0.48, 3.48]
Severe	3 (2%)	4 (6%)	0.49 [0.11, 2.25]
Possibly drug-related adverse event	15 (12%)	7 (10%)	1.29 [0.52, 3.20]
Serious adverse event	5 (4%)	2 (3%)	1.70 [0.32, 8.93]
Possibly drug-related serious adverse event	0 (0%)	0 (0%)	
Adverse events by system			
Cardiovascular	19 (16%)	16 (23%)	0.68 [0.35, 1.34]
Dermatologic	3 (2%)	2 (3%)	0.75 [0.12, 4.59]
Gastrointestinal	21 (17%)	4 (6%)	2.53 [0.86, 7.43]
Hematologic	9 (7%)	12 (17%)	0.41 [0.17, 0.99]
Infectious disease	18 (15%)	5 (7%)	1.88 [0.69, 5.10]
Immunologic	8 (7%)	8 (11%)	0.47 [0.18, 1.26]
Metabolic	7 (6%)	1 (1%)	3.06 [0.38, 24.91]
Genitourinary	14 (12%)	8 (11%)	1.20 [0.50, 2.88]
Neurologic	7 (6%)	4 (6%)	1.01 [0.29, 3.51]
Respiratory	13 (11%)	10 (14%)	0.69 [0.30, 1.58]
Others	2 (2%)	1 (1%)	1.13 [0.10, 13.05]
Common tacrolimus-related adverse events			
Biopsy-proven rejection	3 (9%)	2 (11%)	0.63 [0.11, 3.75]
Hypertension	15 (43%)	11 (66%)	0.75 [0.34, 1.65]
Hyperglycemia	2 (6%)	1 (6%)	0.86 [0.08, 9.44]
Seizures	1 (3%)	1 (6%)	0.63 [0.04, 10.46]
Any kidney injury[a]	26 (49%)	9 (50%)	1.75 [0.75, 4.09][b]

[a]eGFR< 90 ml/min/1.73 m^2.

[b]Multivariate odds ratio from repeated measure generalized linear model.

the effect on *CYP3A5* activity.[12,28-30] However, the current trial was not designed or powered to study the confounding influence of donor genotype and other factors such as organ type and biochemical factors.

Although the trial planned to randomize 60 of the 75 patients enrolled, only 53 were randomized due to a higher than expected attrition post enrollment related to delisting before transplant or ineligibility for randomization post-transplant. Nonetheless, this trial suggests that genotype-guided dosing of tacrolimus is superior to standard dosing. In addition, it lays the groundwork for a larger trial that would allow validation of effect of genotype-guided dosing on clinical outcomes, inclusion of other factors in the algorithm for individualized dosing, and individualization not only of the starting dose but also of subsequent dose titrations in the early post-transplant period. Efforts are underway to develop individualized tacrolimus dosing algorithms that incorporate clinical and genetic factors using a precision medicine approach applied to a multicenter pan-Canadian study.[31] Children are exposed to tacrolimus throughout their post-transplant life. Minimizing fluctuations in tacrolimus concentrations has the potential to increase graft longevity, minimize post-transplant complications, and potentially reduce healthcare costs, an important imperative in the era of precision medicine.

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AUTHORS' CONTRIBUTIONS

Seema Mital involved in the conception or design of the work. Sandar Min, Nadya Nalli, and Tanya Papaz collected the data. Myriam Lafreniere-Roula, Cedric Manlhiot, Nadya Nalli, Sandar Min, and Seema Mital analyzed and interpreted the data. Sandar Min and Seema Mital drafted the article. Sandar Min, Seema Mital, Nadya Nalli, Hartmut Grasemann, Steven M Schwartz, Binita M Kamath, Vicky Ng, Rulan S Parekh, and Cedric Manlhiot critically revised the article. Sandar Min, Tanya Papaz, Myriam Lafreniere-Roula, Nadya Nalli, Hartmut Grasemann, Steven M. Schwartz, Binita M. Kamath, Vicky Ng, Rulan S. Parekh, Cedric Manlhiot, and Seema Mital finally approved the version to be published.

CONFLICT OF INTEREST

There is no conflict of interest.

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