Transplant International

ORIGINAL ARTICLE

Pharmacokinetics of a once-daily tacrolimus formulation in first nations and caucasian liver transplant recipients

David Peretz[1,*], Ngoc H. On[2,*], Donald Miller[2], Richard Kim[3], Carla Franklin[1], Roman Dascal[1], Cori Knowles[4] & Gerald Y. Minuk[1,2]

1 Section of Hepatology, Department of Medicine, University of Manitoba, Winnipeg, MB, Canada
2 Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, MB, Canada
3 Division of Clinical Pharmacology, University of Western Ontario, London, ON, Canada
4 Astellas Pharma Canada, Markham, ON, Canada

Correspondence
Dr. Gerald Y. Minuk, Morberg Family Chair in Hepatology, University of Manitoba, John Buhler Research Centre, 715 McDermot Ave., Winnipeg, MB R3E 3P4, Canada.
Tel.: (204) 789-3204;
fax: (204) 789-3987;
e-mail: gerald.minuk@umanitoba.ca

*shared co-first authorships.

Significant Statement: Aside from no decrease in tacrolimus Cmin levels, more predictable postconversion Cmin levels and shorter Tmax times, extended-release tacrolimus PK in this Indigenous population was largely similar to those of Caucasians who had undergone previous liver transplantation

SUMMARY

Patient ethnicity may influence the pharmacokinetics (PK) of tacrolimus. Because the Canadian First Nations (FN) constitute a large and increasing segment of the liver transplant population, we undertook to determine whether PK differences exist for a once-daily, extended release formulation of tacrolimus (Advagraf) in FN compared to Caucasian (CAUC) liver transplant recipients. Following achievement of a steady state with Advagraf, blood samples were drawn at 0, 1, 2, 4, 6, 8 and 24 hours for whole blood tacrolimus levels by commercial immunoassay and CYP3A4 and CYP3A5 allele analyses were performed by polymerase chain reactions. Nineteen subjects participated in the study (7 FN and 12 CAUC). The FN cohort had significantly higher AUC (214 ± 48 versus 168 ± 25, $P < 0.05$), Cmax (16.7 ± 4.4 ng/ml versus 11.3 ± 1.7 ng/ml, $P < 0.05$), Cmin (6.1 ± 1.0 ng/ml versus 4.7 ± 0.5 ng/ml, $P < 0.05$) and shorter Tmax (1.6 ± 0.2 hours versus 2.8 ± 0.3 hours, $P < 0.05$) values than CAUCs. CYP3A4 genotypes were C/C in both cohorts, while the CYP3A5 *1/*3 allele was present in 2/5 FN and 0/9 CAUC. The results of this study indicate that once-daily, extended release Advagraf results in higher blood tacrolimus levels and shorter times to Cmax in FN compared to CAUC liver transplant recipients.

Transplant International 2021; 34: 2266–2273

Key words
first nations, Indigenous, pharmacokinetics, tacrolimus, transplantation

Received: 3 May 2021; Revision requested: 20 July 2021; Accepted: 24 July 2021; Published online: 7 October 2021

Introduction

Improvements in the success and long-term survival rates of organ transplant patients are due in part to the availability of therapeutic agents that can effectively suppress immune function and prevent graft vs host disease. The immunosuppressive regimens commonly used for transplant patients include immune modulators (e.g.,

doi:10.1111/tri.13997

azathioprine or mycophenolate mofetil), corticosteroids, and calcineurin inhibitors, either cyclosporine or tacrolimus.

Tacrolimus (FK506) ($C_{44}H_{69}NO_{12}$), which is isolated from the fermentation broth of Streptomyces tsukubaensis [1–3], is a 23-membered macrolide lactone that binds with high affinity to FK binding proteins inside the cell, effectively inhibiting calcineurin and downstream transcriptional activation of cytokines crucial for proliferation of T lymphocytes. It also inhibits insulin release by pancreatic beta cells and increases peripheral insulin resistance in a concentration-dependent manner, resulting in increased rates of post-transplant diabetes mellitus [4].

Tacrolimus can be administered orally with both immediate-release and extended-release formulations available. The oral absorption of tacrolimus is limited and subject to large inter and intra-individual variability [5]. Extended-release formulations of tacrolimus are reported to have a reduced maximum concentration (Cmax) and delayed time to reach maximal concentrations (Tmax) compared with the immediate-release form [6]. Thus, theoretically, by virtue of the lower Cmax concentrations, extended-release tacrolimus may be associated with a lower risk of transplant recipients developing diabetes mellitus.

Previous studies have documented significant ethnic differences in the pharmacokinetic (PK) properties of tacrolimus that could result in over- or under-immunosuppression and altered glucose homeostasis [7–9]. These differences may relate to differences in intestinal CYP3A (CYP3A4 and CYP3A5) expression or P-glycoprotein activity as no differences are observed when tacrolimus is administrated intravenously [10]. Indeed, intestinal CYP3A5 expression, based on the presence of the CYP3A5*1 allele of the transplant recipient, has been shown to be an important predictor of tacrolimus dose after liver transplant [11].

Nonadherence to immunosuppressive treatment is another factor that contributes to over- or under-immunosuppression and potentially, adverse outcomes for various transplant populations [12]. Extended-release tacrolimus formulations limit the risk of nonadherence by virtue of being administrated once rather than twice daily [7].

There are an estimated 1.2 million Indigenous peoples (largely First Nations, FN) living in Canada. As with other North American Indigenous populations, a high prevalence of viral hepatitis, nonalcoholic steatohepatitis, and autoimmune chronic liver disease has resulted in FN peoples representing an important and increasing percentage of the liver transplant population [13]. In addition to being disproportionally represented in the liver transplant population, FN peoples also have significantly higher rates of diabetes mellitus and nonadherence with prescribed medications [14,15]. These findings underscore the importance of documenting tacrolimus PK in this patient population.

The present study was designed to document and compare the relative PK profiles of a once-daily, extended-release tacrolimus formulation as well as CYP3A5*3 and CYP3A4*22 genotype frequencies in FN and Caucasian (Cauc) liver transplant recipients.

Materials and methods

Patients

Study patients were derived from the Post-Liver Transplant Clinic at the Health Sciences Centre in Winnipeg, Manitoba. Approximately 175 patients were being followed in the clinic with 10-15% being of FN ethnicity. Patient ethnicity was based on self-identification.

The following study criteria were employed: Subjects had to be between the ages of 18 and 70 years, a minimum of 12 months removed from the transplant procedure, no acute rejection episodes within the previous 3 months, no evidence of pretransplant liver disease recurrence and stable immediate-release tacrolimus dosage during the previous 3 months. Patients were excluded if they were smokers, unable to abstain from caffeine or alcohol during the study period, were receiving macrolide drugs or azole anti-fungal agents, known to have absorption problems, unable to take oral medications, had undergone gastric sleeves or restrictive procedures, and pregnant or unable or unwilling to provide informed consent.

Pre-study variables

Liver biochemistry and renal function were derived from the patients' last clinic visit (within 2-4 weeks of the study). Liver status was assessed by the results of liver enzyme (ALT, AST, AP and GGT) and function tests (total bilirubin, albumin, and INR values) while plasma creatinine levels and the estimated glomerular filtration rate (eGFR) were derived from the Modification of Diet in Renal Disease (MDRD) equation with six variables served to reflect renal function. Patients were defined as having renal dysfunction if the eGFR was below 60 ml/min.

Study design

This was a prospective, single-center, open-label study conducted at the Health Sciences Centre and University

of Manitoba, Winnipeg, Manitoba, Canada. Sequential patients seen in the Liver Transplant Follow-up Clinic between May and September 2018 who fulfilled the study's enrollment criteria were invited to participate.

Following informed written consent, FN and Cauc subjects who had been receiving immediate-release tacrolimus capsules (Prograf®) for maintenance immunosuppression were converted to a once-daily, extended-release formulation (Advagraf®). Conversion was done on an equal dose basis (i.e., 1 mg/d of immediate-release = 1 mg/d of extended-release tacrolimus). PK determinations were performed a minimum of seven days postconversion.

Following establishment of venous access, a baseline blood sample was obtained. Patients then received their extended-release tacrolimus (between 8:00 and 9:00 a.m.) with 200 mL of water (T = 0). Further blood sampling was obtained at times 0, 1, 2, 4, 6, 8, and 24 hours. In the initial 14 patients (5 FN and 9 Cauc), the T = 24-hour sample included an additional 30 ml of blood for CYP3A allele testing. Following the 8-hour sample, patients were discharged with instructions to return the next day for the final 24-hour sample. Concomitant drugs were not altered during the PK study.

The study was approved and monitored by the Research Ethics Board committee at the University of Manitoba and carried out according to the declaration of Helsinki and its amendments following the principles of good clinical practice. All study subjects provided signed informed consent and were free to withdraw from the study at any time.

Tacrolimus pharmacokinetics

Whole-blood tacrolimus concentrations were plotted over a 24-hour period, and the resulting area under the curves (AUCs) for extended-release tacrolimus were determined using the linear trapezoidal method. From these individual plasma drug vs time curves, the Cmax, Cmin, and Tmax values were also obtained. Pharmacokinetic parameters were analyzed using WinNonlin noncompartmental modeling software. Oral clearance (CL/F) was determined for each patient using the following equation:

$$\mathrm{CL}/F = \mathrm{Dose}/\mathrm{AUC}$$

The volume of distribution was determined using the following equation:

$$\mathrm{VzF} = \mathrm{Dose}/(\mathrm{Lambda}\,Z{*}\mathrm{AUC}).$$

where Lambda Z is the elimination rate constant estimated by linear regression of the time versus log concentration curves.

Tacrolimus determinations

Tacrolimus levels were measured in whole blood by UPLC/MSMS in the Department of Clinical Chemistry at the Health Sciences Centre, Winnipeg, Manitoba. The assay's limit of quantitation is 1.0 μg/l, and therapeutic trough levels in this patient population are 5–10 μg/l.

CYP3A5*3 and CYP3A4*22 genotype determinations

DNA was extracted from blood samples drawn at T = 24 hrs and Taqman based genotype testing was carried out as previously described [16,17]. Specifically, the single nucleotide variant at rs776746 was targeted for the CYP3A5 genotype and rs35599367 for the CYP3A4*22 genotype.

Statistics

All data were expressed as mean ± standard error of the mean (SEM). Potential differences in PK values between the FN and Cauc patient groups receiving extended-release tacrolimus including C_0, C_{max}, C_{min}, $AUC_{0\text{-}24}$, T_{max}, CL, and Vd were assessed by either T-test (for parametric data) or Mann–Whitney U test (for nonparametric data) using GraphPad Prism, version 6 software (San Diego, CA, USA). Statistical significance was defined a priori as $P < 0.05$.

Results

The demographic, clinical, and biochemical findings of the study population are provided in Table 1. There were no significant differences between the FN and Cauc cohorts.

Following conversion from immediate- to extended-release tacrolimus, Cmin levels did not significantly decrease and were less variable (-0.1%, 95% CI: -12.3 to 12.1 vs -11.8%, 95% CI: -21.8 to -1.6) in FN compared with Cauc patients (Fig. 1). Only 1/7 FN had 20% or more reductions in Cmin levels compared with 5/12 Cauc patients (Fig. 1b).

Individual blood tacrolimus levels measured over the 24-h period following oral dosing of extended-release tacrolimus are shown in Table 2 and Fig. 2, and the collective PK analysis of the study is provided in Table 3.

Transplant International 2021; 34: 2266–2273

Table 1. Study population.

	FN ($N = 7$)	Caucasian ($N = 12$)	P Value
Age (years)	47.0 ± 11.8	58.8 ± 14.3	0.09
Sex			
Male	4	7	
Female	3	4	
Weight (kg)	99.4 ± 25.2	92.6 ± 12.0	0.68
Height (cm)	171.6 ± 18.1	166.0 ± 7.1	0.54
Biochemistry			
ALT (0–30 U/l)	48.3 ± 45.0	33.8 ± 36.1	0.51
AST (10–32 U/l)	47.1 ± 32.1	49.6 ± 73.3	0.92
ALP (30–120 U/l)	113.0 ± 24.1	146.9 ± 115.6	0.36
GGT (5–38 U/l)	73.1 ± 45.0	144.1 ± 336.6	0.50
Alb (35–50 G/l)	36.1 ± 5.8	38.9 ± 6.9	0.40
T-bili (3–18 μmol/l)	20.6 ± 24.1	11.0 ± 5.5	0.38
INR (0.9–1.1)	1.18 ± 0.21	1.07 ± 0.25	0.35
Creatinine (44–106 μmol/l)	171.6 ± 176.6	115.4 ± 37.6	0.47
Pretransplant CLD			
HCV	4	2	
Immune-mediated	0	6	
Alcohol	2	1	
NASH	0	1	
Other	2	1	
Post-transplant (years)	13.1 ± 10.7	13.4 ± 7.1	0.95

Alb, albumin; ALT, alanine aminotransferase; ALT, alkaline phosphatase; AST, aspartate aminotransferase; CLD, chronic liver disease; FN, First Nations; GGT, gamma-glutamyl transferase; HCV, hepatitis C virus; INR, International Ratio of Prothrombin Times; NASH, nonalcoholic steatohepatitis; T-bili, total bilirubin.

Oral clearance and Vd were similar in FN and Cauc patients. Following normalization for dose, AUC, Cmax, and Cmin values were also similar in the two cohorts. However, the time to Tmax was significantly reduced in FN compared with Cauc patients (1.7 ± 0.5 vs 2.8 ± 1.2 hrs, $P < 0.05$) (Table 3, Fig. 3).

CYP3A genotyping of the initial patient data set (5 FN and 9 Cauc patients) are provided in Table 4. There were no known clinically relevant CYP3A4 alleles detected in any of the patients. With regard to CYP3A5, there were two patients, both FN, with the *1 / *3 allele mutation, which is associated with the CYP3A5 expresser phenotype.

Discussion

The present study compared tacrolimus PK profiles in FN and Cauc liver transplant recipients following stable conversion to a single daily dose, extended-release tacrolimus formulation. Oral clearance, Vd, AUC, Cmax, and Cmin values were similar in both cohorts and within previously reported ranges for transplant recipients [18,19]. The only differences observed were no significant decrease in tacrolimus Cmin levels, and less variable Cmin levels following conversion in FN patients. FN patients also exhibited a shorter time period to achieve Tmax compared with Cauc patients.

Conversion from immediate- to extended-release tacrolimus is typically performed on a 1:1 mg equivalent basis [20]. However, significant reductions in Cmin values have been reported in kidney transplant patients using this formula, albeit not to the extent that dose adjustments were required [20–23]. Fewer studies have examined changes in Cmin following conversion to extended-release tacrolimus in liver transplant patients [24,25]. In one study reported by Comuzzi *et al*, no differences in Cmin values were reported in liver transplant patients [24]. In contrast, in a conversion study involving 28 adult liver transplant patients, Merli *et al* reported reductions in Cmin requiring dose adjustment in approximately 40% of patients while 25% had increases in Cmin requiring dose adjustment [25]. Our findings in FN patients were more in keeping with the Comuzzi report while those in Caucs were comparable to Merli *et al*. Unfortunately, ethnic-specific results of Cmin variability were not provided in either of the above two reports.

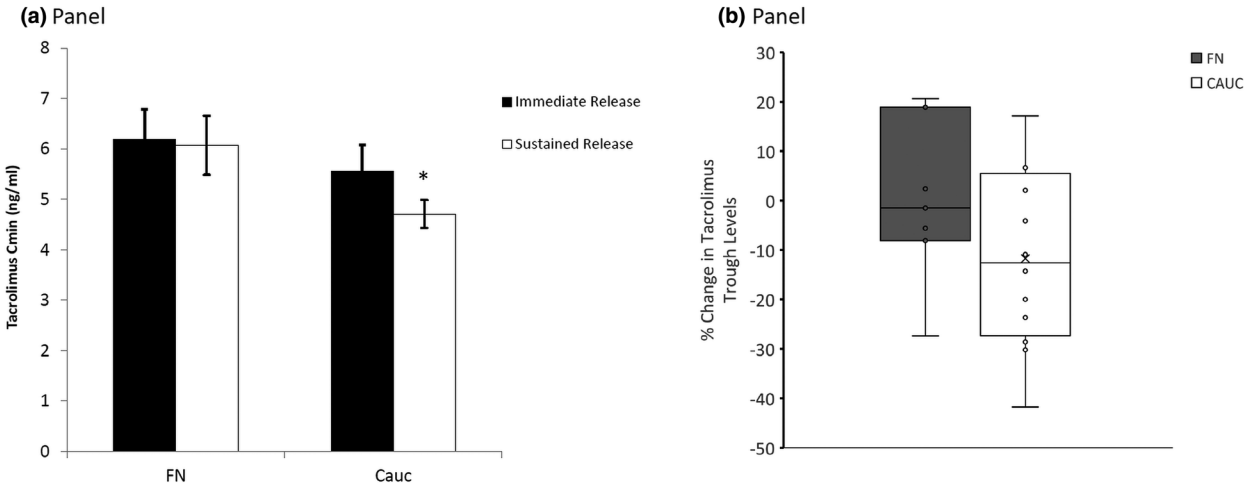

Figure 1 Comparison of trough values in FN and Cauc liver transplant patients on twice-daily immediate-release tacrolimus and following conversion to a once-daily extended-release formulation (Panel a). Values represent the mean + SD; * $P < 0.05$ compared with immediate-release tacrolimus in same group. Changes in trough values following conversion from twice-daily immediate-release to a once-daily extended-release tacrolimus (Panel b). Box and whisker plots represent the median change (line in the box), first and third quartile ranges (outer edges of box) and the minimum and maximum values.

Table 2. Plasma tacrolimus levels in First Nations and Caucasian liver transplant patients taking extended-release Advagraf.

Sex	Race	Transplant Year	DNA ICF	Dose (mg/kg)	Hour 0	Hour 1	Hour 2	Hour 4	Hour 6	Hour 8	Hour 24
M	Caucasian	2011	Yes	0.020	4.4	5.3	12.2	10.6	9.9	8	4.6
M	First Nation	2001	Yes	0.021	3.9	7.1	6.8	5.7	5.5	5.4	4.1
M	Caucasian	2009	No	0.016	4.2	4.5	8.1	7.1	5.9	5.3	4
M	Caucasian	1995	Yes	0.018	5	5.8	6.5	6.6	5.5	5.2	4.4
M	Caucasian	2007	Yes	0.046	6.4	9.5	10.3	10.7	10.3	10.4	6
M	First Nation	2003	Yes	0.036	5.8	8.4	13.6	12.1	10.7	9.3	6.3
F	First Nation	1987	Yes	0.056	9.4	16.2	14.9	14.8	12.5	11.8	8.7
F	Caucasian	2000	Yes	0.020	5.1	6.7	9.4	7.9	6.8	6.9	4.9
F	Caucasian	2001	Yes	0.059	4.9	13.8	14.5	14.9	10.7	8.1	4.5
M	Caucasian	2013	Yes	0.063	6.2	6.5	7	19.3	12.8	12.8	6.7
F	First Nation	2010	Yes	0.083	4.6	19.5	27.8	12.4	9.3	7.8	4.5
M	Caucasian	2009	Yes	0.045	3	6.4	14.9	7.5	5.6	4.7	2.9
F	Caucasian	2012	Yes	0.030	6	9.2	9.1	9.4	8.5	7.6	4.9
F	Caucasian	2002	Yes	0.027	5	7.8	10.3	8.2	7.2	6.6	4.7
F	First Nation	2016	Yes	0.044	6.4	9.4	23.4	16.7	14.4	12.3	6.4
M	Caucasian	2002	Yes	0.021	5.5	7.4	12.6	11.4	8.2	7.7	4.8
M	First Nation	2015	Yes	0.049	6.5	13.3	17.8	11.3	9.7	8.6	5.7
M	First Nation	2017	Yes	0.027	5.3	8.5	8.5	7.1	7	6.8	5.1

Regarding the impact of ethnicity on tacrolimus PK, Mancinelli *et al* reported that African-Americans (AA) required higher tacrolimus dosages than Asians or Caucasians [10]. Moreover, bioavailability was significantly reduced (9.9% versus 19%) and Cmax levels lower in AA compared with Caucasians. In a study by Jacobson *et al*, 144 AA adult renal transplant recipients had consistently lower Cmin levels when compared to 551 non-AAs, despite receiving 60% higher daily doses [8]. In addition, median tacrolimus concentrations one-week post-transplant were lower in AAs, despite similar initial doses. Studies by Grover *et al* examined twice-daily tacrolimus PK in 24 Native American renal transplant patients [26]. These studies found reduced oral clearance in Native Americans, which corresponded to a lower dose required for immunosuppression when compared to other ethnic populations [27]. However in the present study, oral clearance of extended-release tacrolimus was similar in FN and Cauc liver transplant patients. The latter finding, together with similar Vd,

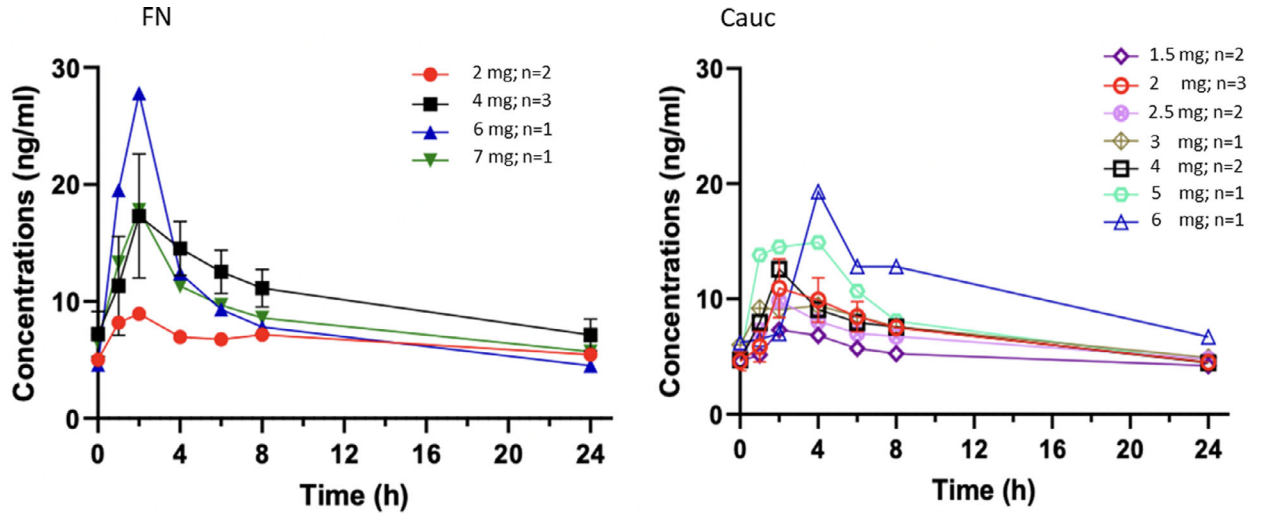

Figure 2 Whole-blood tacrolimus concentration versus time following various doses of oral once-daily extended-release tacrolimus in FN (Panel a) and Cauc (Panel b) liver transplant patients. Those doses with more than one subject represent the mean values and where indicated standard deviation of the mean.

Table 3. Pharmacokinetic analysis of extended-release tacrolimus in First Nations and Caucasian liver transplant recipients.

		$AUC_{0\text{-}24hr}$† (ng*hr/ml)	Cmin† (ng/ml)	Cmax† (ng/ml)	Vd (L/Kg)	CL/F (l/hr)	Tmax (hrs)
First Nation (FN)	Mean ± SD	59 ± 23	1.77 ± 0.91	4.23 ± 1.19	439 ± 175	11.9 ± 7.4	1.7 ± 0.5*
	95% CI	[42–76]	[1.1–2.4]	[3.4–5.1]	[309–569]	[13.5–27]	[1.3–2.1]
Caucasian (Cauc)	Mean ± SD	63 ± 20	1.84 ± 0.69	4.15 ± 1.20	378 ± 130	11.4 ± 6.2	2.8 ± 0.5
	95% CI	[52–74]	[1.5–2.2]	[3.5–4.8]	[304–452]	[13.9–21]	[2.2–3.4]

*$P < 0.05$ compared with Cauc based on CI.

†Values were normalized to dose (mg).

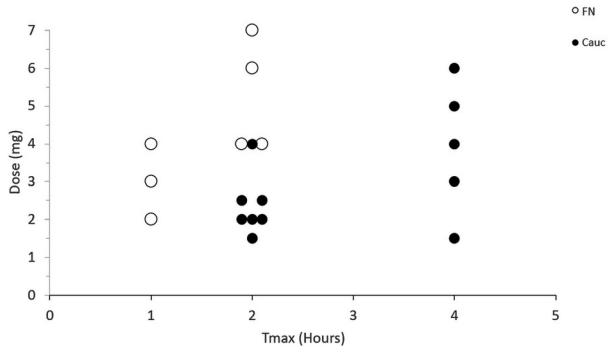

Figure 3 Individual distribution of Tmax values for single-dose extended-release tacrolimus in FN and Cauc liver transplant patients.

AUCs, Cmax, and Cmin levels suggest dose adjustments are not required. They also suggest the risk of tacrolimus-related post-transplant diabetes mellitus, which is concentration dependent, is unlikely to be increased in FN patients.

Although not statistically significant, the FN patients in this study were approximately 10 years younger than Caucs. This difference may be relevant in that PK determinations can be age related [28]. However, the impact of age on PK tends to occur at an older age (beyond 65 years) whereas the mean ages of FN and Cauc patients in the present study were 47 ± 11.8 and 58.8 ± 14.3 years respectively [29]. Moreover, previous studies suggest it is not the chronologic age of subjects that influence PK determinations but rather the size and status of the individual's liver and kidneys [30]. In liver transplant recipients, donor livers are rigorously assessed for proper size and function and in the present study, creatinine values in FN and Cauc subjects were similar at the time the PK studies were performed.

In terms of the CYP3A genotypes, clinically relevant genetic variations within the CYP3A4 allele are uncommon. Regarding CYP3A5, the majority of the population, both in Caucasian and Asians lack functioning

Table 4. Genetic mutations in the CYP3 allele from First Nations and Caucasian liver transplant recipients.

Sample #	Race	CYP3A4 genotype (rs35599367)	CYP3A5 genotype (rs776746)
	First Nations	C/C	*3/*3
	Caucasian	C/C	*3/*3
	Caucasian	C/C	*3/*3
	Caucasian	C/C	*3/*3
	First Nations	C/C	*1/*3 (expressor)
	First Nations	C/C	*3/*3
	Caucasian	C/C	*3/*3
	Caucasian	C/C	*3/*3
	Caucasian	C/C	*3/*3
	First Nations	C/C	*1/*3 (expressor)
	First Nations	C/C	*3/*3
	Caucasian	C/C	*3/*3
	Caucasian	C/C	*3/*3
	Caucasian	C/C	*3/*3
			*1/*3 is a CYP3A5 expressing genotype
			*3/*3 is a CYP3A5 nonexpressing genotype

CYP3A5 and approximately 20% carry at least once copy of the functional CYP3A5*1 allele [31–33]. Although 2 of 7 FN patients in this study were CYP3A5 expressers, the limited number of subjects precluded any definitive conclusions. Furthermore, CYP3A5 genotype testing was not carried out on the donor and tacrolimus PK is affected by both recipient CYP3A5 and donor liver genotype.

There are a number of limitations to this study that warrant emphasis. First, the number of subjects was small. Second, as mentioned above, CYP3A5 genotype testing of donors was not performed. Third, although thought to share a common ancestry, the extent of genetic overlap between Canadian FNs and other North American Indigenous populations is unclear [34]. Thus, the applicability of these findings to other Indigenous populations remains to be determined.

In conclusion, the results of this study suggest Canadian FN transplant recipients do not require dose adjustments when transitioning from immediate- to extended-release tacrolimus formulations and are not at increased risk of developing post-transplant diabetes mellitus or other concentration-dependent tacrolimus-induced adverse effects.

Authorship contributions

Peretz, Knowles, Minuk, and Miller contributed to research and design; Franklin conducted experiments; Miller contributed new reagents or analytic tools; Peretz, On, Miller, Kim, Franklin, Dascal, and Minuk performed data and analysis; Miller, Minuk, Peretz, and On wrote or contributed to the writing of the manuscript.

Funding

No funders.

Conflict of interest

Ms Knowles was an employee of Astellas Pharmaceuticals during the study period.

Acknowledgements

The authors would like to thank Ms R. Vizniak for her prompt and accurate typing of the manuscript.

REFERENCES

1. Vicari-Christensen M, Repper S, Basile S, Young D. Tacrolimus: review of pharmacokinetics, pharmacodynamics, and pharmacogenetics to facilitate practitioners' understanding and offer strategies for educating patients and promoting adherence. *Prog Transpl* 2009; **19**: 277.
2. Tanaka HKA, Marusawa H. Physicochemical properties of FK506, a novel immunosuppressant isolated from Strepomyces tsukubaensis. *Transplant Proc* 1987; **14**: 11.
3. Plosker GL, Foster RH. Tacrolimus: a further update of its pharmacology and therapeutic use in the management of organ transplantation. *Drugs* 2000; **59**: 323.
4. Ozbay LA, Smidt K, Mortensen DM, Carstens J, Jorgensen KA, Rungby J. Cyclosporin and tacrolimus impair insulin secretion and transcriptional regulation in INS-1E beta-cells. *Br J Pharmacol* 2011; **162**: 136.
5. Hooks MA. Tacrolimus, a new immunosuppressant–a review of the literature. *Ann Pharmacother* 1994; **28**: 501.
6. Astagraf XL prescribing information 12/2015. www.astellas.us/docs/astagraftXL.pdf.
7. Merli MD, Menna S, Giusto M, *et al*. Conversion From twice-daily to once-daily tacrolimus. administration in liver transplant patient. *Transpl Proc* 2010; **42**: 1322.
8. Jacobson PA, Oetting WS, Brearley AM, *et al*. Novel polymorphisms associated with tacrolimus trough

concentrations: results from a multicenter kidney transplant consortium. *Transplantation* 2011; **91**: 300.
9. Chadban S. New-onset diabetes after transplantation–should it be a factor in choosing an immunosuppressant regimen for kidney transplant recipients. *Nephrol Dial Transplant* 2008; **23**: 1816.
10. Mancinelli LM, Frassetto L, Floren LC, *et al*. The pharmacokinetics and metabolic disposition of tacrolimus: a comparison across ethnic groups. *Clin Pharmacol Ther* 2001; **69**: 24.
11. Chen L, Prasad GVR. CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment. *Pharmgenomics Pers Med.* 2018; **7**: 23.
12. Carcas-Sansuan AJ, Almeida-Paulo HL, Almeida-Paulo GN, *et al*. Conversion from Prograf to Advagraf in adolescents with stable liver transplants: Comparative Pharmacokinetics and 1-year follow-up. *Liver Transpl* 2013; **19**: 1151.
13. Zhang M, Uhanova J, Minuk GY. Liver transplant outcomes in a Canadian First Nations population. *Can J Gastroenterol* 2011; **25**: 307.
14. Turin TC, Saad N, Jun M, *et al*. Lifetime risk of diabetes among First Nations and Non-First Nations people. *CMAJ* 2016; **188**: 1147.
15. Minuk GY, O'Brien M, Hawkins K, *et al*. Treatment of chronic hepatitis C in a Canadian Aboriginal population: Results from the PRAIRIE study. *Can J Gastroenterol* 2013; **27**: 707.
16. Guililat M, Keller D, Linton B, *et al*. Drug interactions and pharmacogenetic factors contribute to variation in apixaban concentration in atrial fibrillation patients in routine care. *J Thromb Thrombolysis* 2020; **49**: 294.
17. Woolsey SJ, Mansell SE, Kim RB, Tirona RG, Beaton MD. CYP3A Activity and expression in nonalcoholic fatty liver disease. *Drug Metab Dispos* 2015; **43**: 1484.
18. Florman S, Alloway R, Lalayoglu M, *et al*. Conversion of stable liver transplant recipients from a twice-daily Prograf-based regimen to a once-daily modified release tacrolimus-based regimen. *Transplant Proc* 2005; **37**: 1211.
19. Woillard J-B, de Winter BCM, Kamar N, Marquet P, Rostaing L, Rousseau A. Population pharmacokinetic model and Bayesian estimator for two tacrolimus formulations—twice daily Prograf and once daily Advagraf. *Br J Clin Pharmacol* 2011; **71**: 391.
20. Barraclough KA, Isbel NM, Johnson DW, Campbell SB, Staatz CE. Once-versus twice-daily tacrolimus. Are the formulations truly equivalent? *Drugs* 2011; **71**: 1561.
21. Gallego-Valcarce E, Ortega-Cerrato A, Llamas-Fuentes F, *et al*. Conversion to tacrolimus extended-release formulation: short-term clinical results. *Transplant Proc* 2009; **41**: 2326.
22. de Jonge H, Kuypers DR, Verbeke K, *et al*. Reduced Co concentrations and increased dose requirements in renal allograft recipients converted to the novel once-daily tacrolimus formulation. *Transplantation* 2020; **90**: 523.
23. Iaria G, Sforza D, Angelico R, *et al*. Switch from twice-daily tacrolimus (prograf) to once-daily prolonged-release tacrolimus (advagraf) in kidney transplantation. *Transplant Proc* 2011; **43**: 1028.
24. Comuzzi C, Lorenzin D, Rossetto A, *et al*. Safety of conversion from twice-daily tacrolimus (Prograf) to once-daily prolonged-release tacrolimus (Advagraf) in stable liver transplant recipients. *Transplant Proc* 2010; **42**: 1320.
25. Merli M, Di Menna S, Giusto M, *et al*. conversion from twice-daily to once-daily tacrolimus administration in liver transplant patient. *Transplant Proc* 2010; **42**: 1322.
26. Grover A, Frassetto LA, Benet LZ, Chakkera HA. Pharmacokinetic differences corroborate observed low tacrolimus dosage in Native American renal transplant patients. *Drug Metab Dispos* 2011; **39**: 2017.
27. Uber PA, Mehra MR, Scott RL, Prasad AK, Park MH. Ethnic disparities in the pharmacologic characteristics of tacrolimus in heart transplantation. *Transplant Proc* 2001; **33**: 1581.
28. Crooks J, O'Malley K, Stevenson IH. Pharmacokinetics in the Elderly. *Clin Pharmacokinet* 1976; **1**: 280.
29. Aymanns C, Keller F, Maus S, Harmann B, Czock D. Review on Pharmacokinetics and Pharmacodynamics and the Aging Kidney. *CJASN* 2010; **5**: 314.
30. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; **57**: 6.
31. Shiraga T, Matsuda H, Nagase K, *et al*. Metabolism of FK506, a potent immunosuppressive agent, by cytochrome P450 3A enzymes in rat, dog and human liver microsomes. *Biochem Pharmacol* 1994; **47**: 727.
32. Dai Y, Hebert MF, Isoherranen N, *et al*. Effect of CYP3A5 polymorphism on tacrolimus metabolic clearance in vitro. *Drug Metab Dispos* 2006; **34**: 836.
33. Felipe CR, Garcia C, Moreira S, Olsen N, Silva HT, Pestana OM. Choosing the right dose of new immunossuppressive drugs for new populations: importance of pharmacokinetic studies. *Transplant Proc* 2001; **33**: 1095.
34. Achilli A, Perego UA, Lancioni H, *et al*. Reconciling migration models to the Americas with the variation of North American native mitogenomes. *PNAS* 2013; **110**: 14308.