Kidney Medicine

Serum Creatinine and Tacrolimus Assessment With VAMS Finger-Prick Microsampling: A Diagnostic Test Study

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Rationale & Objective: Kidney transplant recipients require frequent venipunctures. Microsampling methods that use a finger-prick draw of capillary blood, like volumetric absorptive microsamplers (VAMS), have the potential to reduce the pain, inconvenience, and volume of blood loss associated with venipuncture. This study aimed to provide diagnostic accuracy using VAMS for measurement of tacrolimus and creatinine compared to gold standard venous blood in adult kidney transplant recipients.

Study Design: Diagnostic test study. Prospective blood samples for measurement of tacrolimus and creatinine were collected using Mitra VAMS and venipuncture immediately before and 2 hours after tacrolimus dosing.

Setting & Participants: A convenience sample of 40 adult kidney transplant participants in the outpatient setting.

Tests Compared: Method comparison was assessed by Passing-Bablok regression and Bland-Altman analysis. The predictive performance of VAMS measurement compared to venipuncture was also assessed through estimation of the median prediction error and median absolute percentage prediction error.

Results: A total of 74 tacrolimus samples and 70 creatinine samples were analyzed from 40 participants. Passing-Bablok regression showed a systematic difference between VAMS and venipuncture when measuring tacrolimus and creatinine with a slope of 1.08 (95% CI, 1.03-1.13) and a slope of 0.65 (95% CI, 0.6-0.7), respectively. These values were then corrected for the systematic difference. When used for Bland-Altman analysis, corrected values of tacrolimus and creatinine showed a bias of -0.1 µg/L and 0.04 mg/dL, respectively. Tacrolimus (corrected) and creatinine (corrected) microsampling values when compared to corresponding venipuncture values met median prediction error and median absolute percentage prediction error predefined acceptability limits of <15%.

Limitations: This study was conducted in a controlled environment using a trained nurse to collect VAMS samples.

Conclusions: In this study, VAMS was used to reliably measured tacrolimus and creatinine. This represents a clear opportunity for more frequent and less invasive sampling for patients.

Visual Abstract included

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Managing kidney transplant patients requires close monitoring of tacrolimus and creatinine concentrations to ensure therapeutic effectiveness of the principal immunosuppressant and maintenance of the patient's kidney function. Transplant recipients require adequate tacrolimus exposure to ensure they retain their graft.[1] Close monitoring of immunosuppressant therapy is key in maintaining the balance between limiting drug toxicity and preventing allograft rejection in an individual patient.[2] Therapeutic drug monitoring, which involves individualization of drug dosage by maintaining drug concentrations within a predefined target range, is recognized as a key intervention for immunosuppressants such as tacrolimus, and therapeutic drug monitoring requires frequent venipunctures. Kidney transplant patients undergo repeated venipunctures during long-term management of their allograft.[3] Venipuncture is also required for frequent assessment of kidney function, drug related side effect surveillance, measurement of routine cardiovascular risk markers (eg, cholesterol and triglycerides) and screening for viruses (eg, BK virus). Venipuncture sampling involves significant time, travel, and pain imposts on patients.[4]

Microsampling methods that use a finger-prick draw of capillary blood such as volumetric absorptive microsamples (VAMS) have the potential to reduce the burden and the volume of blood loss compared with that experienced by venipuncture.[5-7] VAMS devices wick a known quantity of blood (10, 20, or 30 µL) onto an absorbent polymeric tip attached to a plastic holder.[6,8,9] Microsampling techniques may also offer the potential for self-sampling, thereby potentially reducing intrusion of the clinical environment into patients' activities of daily living.[10]

In their recent consensus report, the Immunosuppressive Drug Scientific Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicity grouped the benefits of microsampling into patient acceptability and augmented frequency of sampling.[11] The report recommended cross-validating microsampling strategies with established sampling procedures to determine feasibility in

PLAIN-LANGUAGE SUMMARY

This study aimed to validate microsampling using a volumetric absorptive microsampler (VAMS) instead of venous blood samples for measurement of tacrolimus and creatinine. The measurement of these 2 agents via finger-prick would allow for less invasive monitoring of kidney function and tacrolimus concentrations in kidney transplant patients. In our study, a nurse took samples from 40 adult kidney transplant patients at 2 different times (before dose and 2 hours after tacrolimus) using both VAMS and a venous blood sample. We found that VAMS devices were a reliable way to measure these agents. Using microsampling could have significant patient benefits, and this study paves the way for future studies including patients perfoming their own blood testing using VAMS at home.

the clinical setting.[11-13] Several studies have examined the feasibility of single drug immunosuppressant monitoring using dried blood spot or VAMS techniques in comparison to blood sampling based on venipuncture.[13-24] However, fewer studies have investigated tacrolimus and creatinine measurement simultaneously using VAMS compared to venipuncture-collected venous blood (VB) samples.[21]

This study aimed to perform a clinical bridging study to compare the measurement of tacrolimus and creatinine on VAMS collected by finger-prick compared to standard VB samples collected using venipuncture in adult kidney transplant patients.

METHODS

Study Design

A prospective, sequential, purposive sampling validation study, known as the MERIT study, was undertaken at the Royal Brisbane and Women's Hospital Kidney Transplant Outpatient Unit (Brisbane, Australia). Ethics approval for this study was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/18/QRBW/179) and the University of Queensland Human Research Ethics Committee (UQ 2018001180).

Eligibility Criteria

Kidney and kidney-pancreas transplant patients attending the Royal Brisbane and Women's Hospital Kidney Transplant Outpatient Unit for posttransplant follow-up care were invited to participate in the study. Patients were eligible for inclusion if they were 18 years of age or older and prescribed tacrolimus and had been stable on their current dose for greater than 7 days. Exclusion criteria included current pregnancy, lactation or current diagnosis with hepatitis B, hepatitis C, or HIV.

Sample Collection

All samples for tacrolimus and creatinine measurement were taken by a trained research nurse. Liquid VB samples (venipuncture samples) and VAMS (finger-prick capillary blood microsamples, Neoteryx Mitra) were collected immediately before (pre-dose) and 2 hours after patients took their usual dose of tacrolimus. Patients were observed orally ingesting their regular dose of tacrolimus. Details of blood collection are provided in Item S1.

Analytical Methods and Whole Blood to Plasma Adjustment

Tacrolimus and creatinine concentrations were measured using validated ultra-performance liquid chromatography with mass spectrometric detection. The assays for VAMS samples once collected and dried share a common pathway of sample preparation. Further information on the assay methodology, limit of quantification of each drug, and quality control results are presented in Item S2. Tacrolimus and creatinine concentrations were measured in whole blood in the VAMS samples and whole blood for tacrolimus and serum for creatinine in venous samples.

Statistical Analysis

This study followed recommendations outlined in the Immunosuppressive Drug Scientific Committee of the International Association of Therapeutic Drug Monitoring and Clinical Toxicity for sample analysis.[11] Forty patients were planned to be recruited into this study. There was limited data to inform a power calculation; however, this number was considered adequate to compare different blood sampling techniques based on data from previous studies.[25,26] Baseline characteristics of the study cohort were described using simple statistics in Microsoft Excel.

To examine the correlation between tacrolimus and creatinine concentrations measured by VAMS and venipuncture, a Passing-Bablok regression analysis was performed using R studio. This technique was chosen as it makes no assumptions about the distribution of data and is more resistant to outliers when compared to other regression tests.[11,27,28] If significant correlation was not demonstrated initially then a correction factor was employed. Using the corrected value the data were then reanalyzed and applied in subsequent Bland-Altman analysis and predictive performance testing.

Bland-Altman analysis was used to calculate bias, and the percentage difference plots were generated to visualize the data using Graphpad Prism. The criteria for clinical acceptance using an incurred sample reanalysis test was set before analysis, for a bias of 80%-120% around the percentage difference of matched VB and matched VB and VAMS samples for at least 67% of samples in accordance with earlier studies and US Food and Drug Administration guidelines.[11]

The predictive performance of microsampling (VAMS) compared to venipuncture was tested by using the method

Table 1. A Summary of the Demographic and Clinical Characteristics of Study Participants

Characteristic	Values
Number of participants	40
Male	65% (26)
Age (y)	53 [27-77]
First graft	92% (36)
Time since transplant (y)	5 [1-18]
Hematocrit	0.41 [0.27-0.48]
Tacrolimus total daily dose (mg)	4 [0.5-15]
Tacrolimus (μg/L)	8.74 [2.66-31.49]
Serum Creatinine (μmol/L)	134 [61-438]

Results presented as percentage (number) or median [range].

described by Sheiner and Beal.[29] Concentrations measured by microsampling VAMS (C_{VAMS}) were compared with concentrations measured through initial VB collection via venipuncture (C_{VB}) for bias and imprecision. Bias was assessed by calculating the median percentage error (Item S3: equation 1). Imprecision was estimated by calculating the root median square prediction deviation error (Item S3: equation 2) and median absolute percentage prediction error (Item S3: equation 3). In accordance with the criteria established by the Food and Drug Administration, acceptable values for median percentage prediction error and median absolute percentage prediction error were set at <15%.[11,29-31] Equations involved in the calculation of bias and imprecision are outlined in Item S3.

RESULTS

Patient Demographics

A summary of the demographic and clinical characteristics of the 40 study participants is provided in Table 1. A total of 74 tacrolimus samples were analyzed from 37 participants (3 participants were not taking tacrolimus). The average tacrolimus concentration was 9.4 μg/L with range of 2.7-35.8 μg/L. A total of 70 creatinine concentrations were analyzed from 40 patients with 10 participants not having a 2-hour creatinine venous measurement because of sample labeling error. The average creatinine was 1.69 mg/dL with a range of 0.69-4.84 mg/dL.

Passing-Bablok Regression Analysis

Results for the Passing-Bablok regression analysis examining the correlation between tacrolimus and creatinine concentrations measured via VAMS and venipuncture are shown in Table 2 and Fig 1. A systematically significant difference of 8% was found using a Passing-Bablok regression fit of tacrolimus concentration measured via VAMS versus venipuncture 1.08 (95% confidence interval [CI], 1.03-1.13) (Fig 1A). This difference was used to derive the following conversion formula:

VAMS tacro (tacrolimus VB concentration) = (C_{VAMS} + 0.59) / 1.08 based on VAMS measurement. This conversion formula was used to recalculate all tacrolimus VAMS values, and these corrected values were used in the subsequent Bland-Altman analysis and predictive performance testing.

Passing-Bablok regression fit for creatinine showed a significant difference of 35% undermeasurement in VAMS with correlation values of 0.65 (95% CI, 0.57-0.74) (Fig 1B). This difference was used to derive the following conversion formula of VAMS creat = (C_{VAMS} - 25.53) / 0.65). This conversion formula was used to recalculate all creatinine VAMS values, and these corrected values were used in the subsequent Bland-Altman analysis and predictive performance testing. No significant systematic or constant difference between VB and VAMS samples was observed using the corrected values for both tacrolimus and creatinine.

Bland-Altman Analysis

Results from the Bland-Altman analysis are shown in Table 2 with the percentage difference vs average plots displayed in Fig 2. The VAMS Bland-Altman difference ratios plot of corrected tacrolimus measurements showed a percentage difference vs average of -1.6% with 95% limits of agreement of -21.7 to 18.4% (Fig 2A). The VAMS Bland-Altman difference ratios plot of creatinine measurements showed a percentage difference vs average of 1.42% with a 95% limit of agreement of -34.1 to 36.9% (Fig 2B).

Incurred Sample Reanalysis

Assessment by applying an incurred sample reanalysis test whereby 67% of samples are required to be within 20% of VB samples was conducted. Both VAMS samples passed the incurred sample reanalysis criteria. If a lower 10% variation of tacrolimus concentrations was applied, 68% of Tacro VAMS samples met a 10% incurred sample reanalysis.

Predictive Performance

Results of the predictive performance of microsampling methods compared to venipuncture are summarized in Table 2. Median percentage error associated with VAMS measurement of tacrolimus and creatinine compared to venipuncture was 0 μg/L and 0.01 mg/dL respectively. Square root mean errors were for tacrolimus were low at 0.6%, representing a good correlation or a small imprecision between the 2 methods. Creatinine was higher with a root median square prediction deviation error of 14.1%, but this is still within the predefined acceptable levels.

Median absolute percentage prediction error associated with VAMS measurement of tacrolimus and creatinine compared to venipuncture was 6.5% and 13%, respectively. These median absolute percentage prediction error values were less than 15% thereby meeting the acceptance criteria.

DISCUSSION

In this study we found VAMS to be a reliable approach for measuring blood concentrations of tacrolimus and

Table 2. Method Comparison and Predictive Performance Between Venous Blood (VB) and Microsamples (VAMS) for Each Agent

Comparison	Passing-Bablock regression		Bland-Altman absolute difference		Bland-Altman ratio % difference vs average	Incurred sample reanalysis		Median Percentage Error	Root Median Square Prediction Error	Median Absolute Prediction Error
	Slope (95% CI)	Intercept (95% CI)	Bias** (95% LOA)	Bias SD**	Bias (95% LOA)	Bias SD	N(%)	MPE**	RMSE**	MAPE (%)
VB Tacro vs VAMS Tacro	1.1 (1-1.1)	-0.6 (-1- -0.3)	-0.1 (-2-1.7)	1	-1.6 (-21.7-18.4)	10.2	71 (96%)	0	0.6	6.5
VB Creat vs VAMS Creat	1 (0.9-1.2)	-2.9 (-19.5-13.8)	3.4 (-50-57)	27	1.42 (-34.1-36.9)	18.1	53 (76%)	1	14.1	13

CI, confidence interval; LOA, limit of agreement; RMSE = root median square prediction deviation error; SD= standard deviation.
Description of sample comparison:
VAMS Tacro = tacrolimus blood concentration estimate based on VAMS collection and use of a correction formula*.
VB Tacro = tacrolimus blood concentration measurement based on venopucture sampling
VAMS Creatinine = creatinine plasma concentration estimate based on VAMS collection and use of a correction formula*.
VB Creatinine = creatinine plasma concentration measurment based on venepucture sampling
*Correction formulas: VAMS Tacro = (C_{VAMS} + 0.59) / 1.08.
VAMS Creat = (C_{VAMS} - 25.53) / 0.65.
**Expressed in µg/L for tacrolimus, µmol/L for creatinine.

creatinine concentrations in adult kidney transplant recipients. The predictive performance of microsampling approaches met the predefined acceptance criteria for tacrolimus and creatinine. The demonstrated difference in concentrations between venipuncture samples and microsampling met pre-established acceptance criteria and is suitable for use in clinical practice, with magnitude of the difference unlikely to result in routine changes to patient management.

Koop et al[32] analyzed creatinine and tacrolimus from a single dried blood spot in 21 pediatric patients. They found that dried blood spot microsampling was a reliable method of analyzing both tacrolimus and creatinine from a single sample; the creatinine values were found to be higher than plasma values yet were considered acceptable for interpretation purposes.[32] Koop et al[32] had 6% of samples that were unusable due to technique error, and 2 patients withdrew from the study as they found the finger-pricking required for the dried blood spot technique more painful than a venous sample. This contrasted to our study in which we previously reported that 85% (n=33) of adult participants preferred finger-prick sampling.[33] A study by Kindem et al[22] of VAMS tacrolimus samples in 39 pediatric patients taken at 3 different time points found that VAMS were accurate for assessment of tacrolimus concentrations. Undre et al[34] analyzed tacrolimus in 82 adult kidney and liver transplant patients and found that VAMS provided a consistently higher result (22.5%) than venous concentrations. VAMS devices were used to obtain vancomycin and creatinine concentrations in 60 adult patients by Andriguetti et al,[35] and they found that VAMS creatinine required a small correction formula (2%) but did provide acceptable results. Marshall and colleagues[21] assessed 131 samples collected via venipuncture and VAMS device to analyze tacrolimus and creatine at a single time point. They found tacrolimus was undermeasured by 7% and creatinine was undermeasured by 9%; however, both could be reliably assessed from VAMS devices.

In another study analyzing tacrolimus collected on VAMS in 82 liver and kidney transplant patients, Undre et al[34] found that VAMS gave a 22.5% higher tacrolimus result. Veenhof et al[31] found a significant systematic difference of 12% lower tacrolimus concentrations in VAMS and corrected for this difference.

This demonstrates there is variability of tacrolimus results in the current literature. Our result was a modest 8% higher tacrolimus concentration in VAMS samples. Our findings, which over- rather than underpredicted, are similar, though not as marked, as some others. The variation in our findings may not be clinically relevant when adjusting doses of tacrolimus, noting the pharmaceutical industry manufactures the drug in 0.5-mg dosage increments for a typical dose of 5 mg for each administration. A dosage adjustment of trough concentrations on the order of 8% difference would be 0.4-0.56 µg/L based on the an assumed trough concentration between 5-7 µg/L. Tacrolimus concentrations on Bland-Altman analysis using

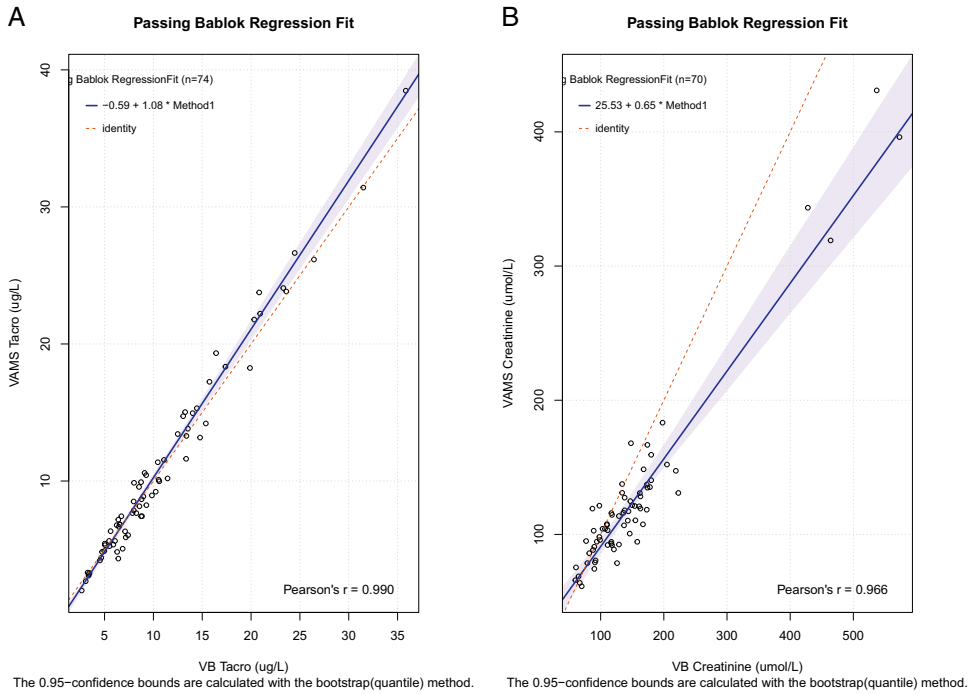

Figure 1. Passing-Bablock regression fit between venous blood (VB) and microsamples (VAMS) for tacrolimus (A) and creatinine (B).
Description of sample comparison:
VAMS Tacro = tacrolimus blood concentration estimate based on VAMS collection
VB Tacro = tacrolimus blood concentration measurement based on venepucture sampling
VAMS Creatinine = creatinine plasma concentration estimate based on VAMS collection
VB Creatinine = creatinine plasma concentration measurment based on venepucture sampling
Creat, creatinine; Tacro, tacrolimus; VAMS, volumetric absorptive microsamples; VB, venous blood sample.

VAMS showed a consistent result across the concentration range.

The creatinine results in this study were significantly under the venous measurements. This is different to the results of Koop et al[32] who found that creatinine from dried blood spots measured higher than venous levels, but they only had a small number of samples. Marshall et al[21] found that there was a 9% underestimation of creatinine on VAMS. Both of these are different to our results of 35% underestimation. Variations could be due to laboratory or patient factors; however, providing there is consistency in the laboratory used, these differences can be adjusted and the results of our adjusted values met all the acceptance criteria.

Earlier studies in the literature report a microsample attrition rate as high as 30% because of poor sample quality.[20,32] Attrition was thought to be because of error by the collector and could be a risk if patients were collecting their own sample. We did not address this point in our study, with a trained nurse collecting samples, and note that no samples were lost because of poor collection technique. Labeling error meant that not all creatinine venous samples were obtained; however, all VAMS samples provided a creatinine result. However, if there was not a venous sample to pair with, these results were not included in the analysis. This is similar to a recent studies by Marshall et al[21] and Kindem et al[22] who reported high sample success with nurse collection of VAMS.

The VAMS device offers advantages in sample preparation and is simple to use for sample collection.[36]

Changing blood collection practice to microsampling has patient benefits. These include convenience of sampling in the local community or at home, ease of transport of samples, and small volume blood loss. In response to the COVID-19 pandemic, Ansari et al[37] investigated patient self-sampling with capillary sampling of 15 analytes; 70% of patients indicated they would recommend self-sampling, and 87% found self-sampling easy to conduct. We previously showed microsampling added quality to a patient's life through decreased pain and health burden compared to repeated venipuncture.[33] In our cohort, 95% of patients reported being interested in trialing finger-prick based sampling at home, and 72% said they would be willing to provide more blood samples if collection was via a finger-prick.[33]

Microsampling may also enable more frequent monitoring of patient immunosuppressant concentrations. This may be particularly important in a subgroup of transplant patients whose concentrations fluctuate, which correlates with a greater risk of allograft rejection.[38,39] Microsampling

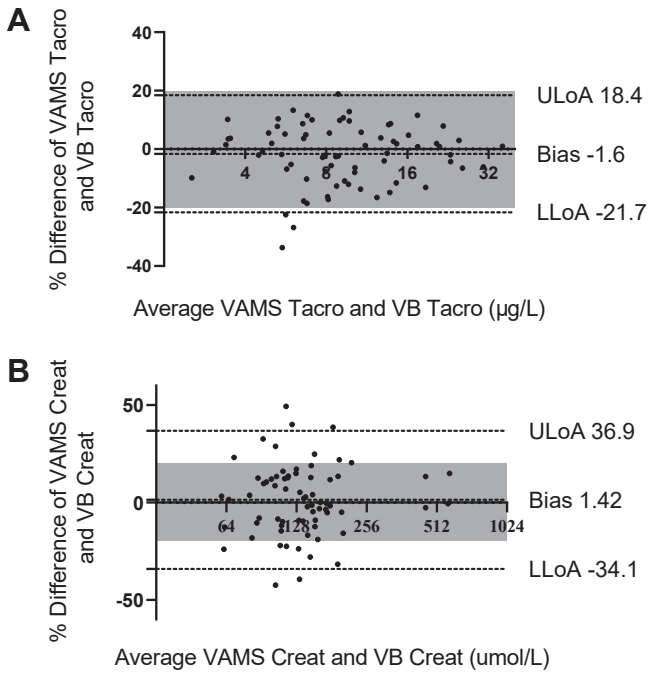

Figure 2. Bland-Altman analysis of venous blood (VB) and microsamples (VAMS) for tacrolimus (A) and creatinine (B).

could also be utilized as part of a limited sampling strategy to estimate area-under-the-concentration-time curve, which is likely to provide a better estimate of drug exposure than trough measurement.

This study is unique in that it compared measurement of tacrolimus and creatinine VAMS vs samples acquired via venipuncture at 2 separate time points. Limitations of this study include that the samples were collected in a controlled environment by a research nurse and not by the patients themselves. This may have influenced the sample quality as evidenced by no sample loss because of poor collection or overfilling of VAMS, which has been reported in other studies.[40] Planned future studies include pharmacokinetic profiling using VAMS as well as studies whereby patients are taught and then self-collect with VAMS in real world outpatient settings with paired VB samples. A limitation of this study is that cost benefit analysis of microsampling was not undertaken. Although the microsampling device may incur a cost, the benefits in terms of reduced travel/lost work time and less trained phlebotomist time should offset the cost of the device. Patient acceptability and willingness to provide more samples via microsampling are benefits for microsampling.[33]

In conclusion, use of microsampling for tacrolimus and creatinine for concentration and kidney function monitoring could prove to be a transformative innovation for the care and long-term follow-up of kidney transplant patients. Our study demonstrates accurate results can be generated through the microsampling approach with VAMS. The future of patients providing samples at home and allowing transplant services to remotely monitor their kidney function and drug concentrations is within reach. Home sampling allows for more patient samples and the ability to personalize immunosuppressant treatment in transplant patients, potentially leading to better patient outcomes. VAMS may be the tool that realizes that goal.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Sample collection procedure

Item S2: Assay development for tacrolimus and creatinine

Item S3: Equations used for predictive performance calculations

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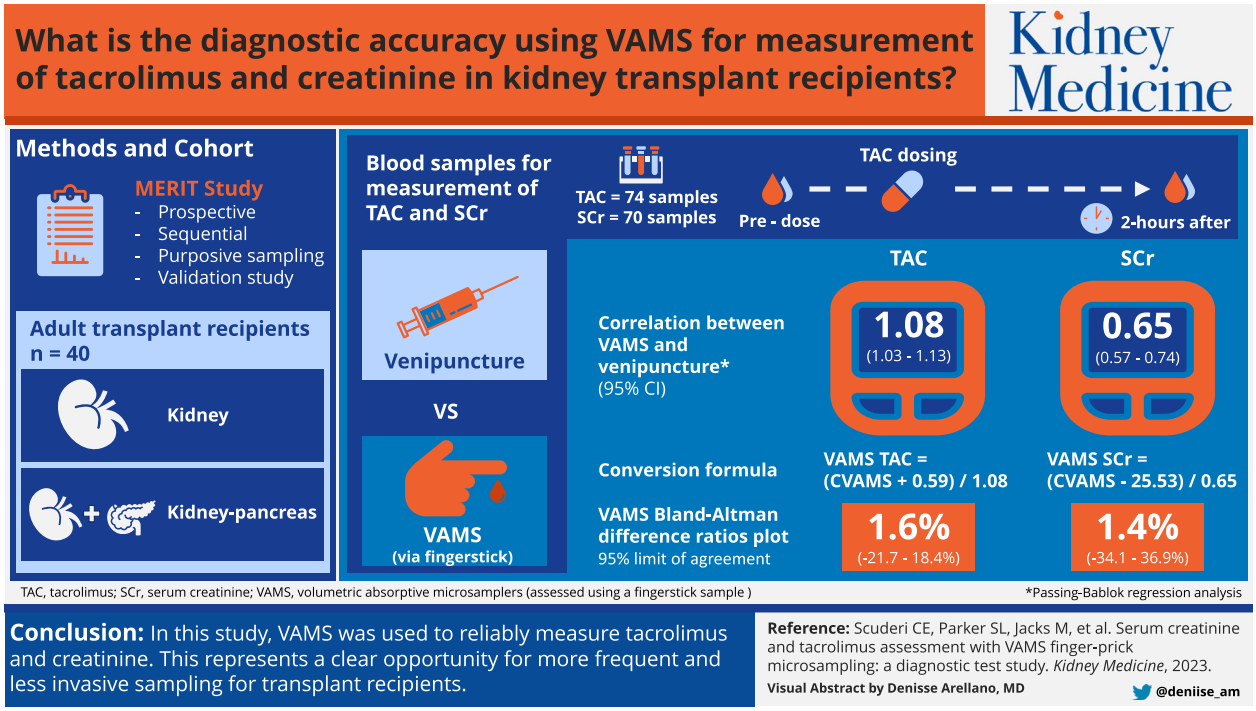
What is the diagnostic accuracy using VAMS for measurement of tacrolimus and creatinine in kidney transplant recipients?
Kidney Medicine
Methods and Cohort
MERIT Study
- Prospective
- Sequential
- Purposive sampling
- Validation study
Adult transplant recipients
n = 40
Kidney
Kidney-pancreas
Blood samples for measurement of TAC and SCr
TAC = 74 samples
SCr = 70 samples
Venipuncture
VS
VAMS
(via fingerstick)
TAC dosing
Pre - dose
2-hours after
TAC
SCr
Correlation between VAMS and venipuncture*
(95% CI)
1.08
(1.03 - 1.13)
0.65
(0.57 - 0.74)
Conversion formula
VAMS TAC = (CVAMS + 0.59) / 1.08
VAMS SCr = (CVAMS - 25.53) / 0.65
VAMS Bland-Altman difference ratios plot
95% limit of agreement
1.6%
(-21.7 - 18.4%)
1.4%
(-34.1 - 36.9%)
TAC, tacrolimus; SCr, serum creatinine; VAMS, volumetric absorptive microsamplers (assessed using a fingerstick sample)
*Passing-Bablok regression analysis
Conclusion: In this study, VAMS was used to reliably measure tacrolimus and creatinine. This represents a clear opportunity for more frequent and less invasive sampling for transplant recipients.
Reference: Scuderi CE, Parker SL, Jacks M, et al. Serum creatinine and tacrolimus assessment with VAMS finger-prick microsampling: a diagnostic test study. Kidney Medicine, 2023.
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