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Evaluation of the Architect® tacrolimus assay in kidney, liver, and heart transplant recipients

Christophe Bazin[a], Amélie Guinedor[b], Caroline Barau[c], Claire Gozalo[d], Philippe Grimbert[e], Christophe Duvoux[f], Valérie Furlan[c], Laurent Massias[b], Anne Hulin[a,*]

[a] Laboratory of Pharmacology, AP-HP, CHU H. Mondor, Université Paris XII, Créteil, France
[b] Laboratory of Pharmacology, AP-HP, GH Bichat-Claude Bernard, Université Paris, France
[c] Laboratory of Pharmacology, AP-HP, CHU Bicêtre, Université Paris XI, Bicêtre, France
[d] Laboratory of Pharmacology CHU Reims, Université Reims, France
[e] Department of Nephrology, AP-HP, CHU Henri Mondor, Université Paris XII, Créteil, France
[f] Department of Hepatology, AP-HP, CHU Henri Mondor, Université Paris XII, Créteil, France

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ABSTRACT

The narrow therapeutic range of tacrolimus requires therapeutic drug monitoring to prevent transplant rejection and to minimize nephrotoxicity. The aim of this study was to evaluate the analytical performance of the tacrolimus chemiluminescent microparticle immunoassay (CMIA) in everyday practice comparatively with other methods. CMIA imprecision and accuracy were tested using low, medium, and high concentrations in control samples. The limits of quantification (LOQ) of CMIA and antibody-conjugated magnetic immunoassay (ACMIA) were evaluated using negative whole-blood samples containing 0.4–5.7 ng/ml of tacrolimus from a stock solution. CMIA was compared with ACMIA, enzyme multiplied immunoassay (EMIT), and liquid chromatography–tandem mass spectrometry (LC–MS/MS), using 176 samples from recipients (135 men and 41 women) of heart (n = 19), kidney (n = 107), or liver (n = 50) transplants. CMIA total precision was 5.7%, 3.7% and 3.6% with the low-, medium-, and high-concentration controls, respectively; corresponding values for accuracy were 98%, 104%, and 104%. LOQ was 0.5 (95%CI, 0.22–1.38) with CMIA and 2.5 ng/ml with ACMIA. Linear regression results were as follows: CMIA = 1.2LC–MS/MS + 0.14 (r = 0.98); CMIA = 0.93EMIT + 0.36 (r = 0.975); CMIA = 1.15ACMIA − 0.25 (r = 0.988); and, for tacrolimus concentrations in the 1–15 ng/ml range, of special interest as many transplant recipients are given low-dose tacrolimus, CMIA = 1.05LC–MS/MS + 0.38 (r = 0.94). Two patients had falsely elevated tacrolimus concentrations due to interference in the ACMIA assay; one was a renal transplant recipient who stopped her treatment and had tacrolimus concentrations of 12.5 ng/ml by ACMIA and <0.5 ng/ml by CMIA; the other was an HIV-positive renal transplant recipient whose tacrolimus concentrations by ACMIA were 1.8–43.7-fold those by CMIA. Such interferences with ACMIA, which may be related to endogenous antibodies in the plasma, are likely to negatively impact patient care. In conclusion, the tacrolimus CMIA assay is suitable for routine laboratory use and does not suffer from the interferences seen with ACMIA in some patients.

1. Introduction

Tacrolimus is a potent immunosuppressant drug used to prevent organ transplant rejection. Tacrolimus exhibits substantial toxicity with a narrow therapeutic range and considerable interindividual variability in pharmacokinetic parameters due to genetic polymorphisms, drug–drug interactions, and environmental factors. Therapeutic drug monitoring (TDM) is therefore recommended to prevent rejection and to minimize nephrotoxicity [1–5]. However, many transplant recipients now receive low-dose tacrolimus regimens, and the available immunological tests often perform poorly for monitoring the resulting low blood concentrations [6,7]. The European Consensus Conference on tacrolimus TDM emphasized the intraindividual and interindividual variability in tacrolimus blood levels; selected pharmacokinetic parameters of special interest (area under the concentration-time curve [AUC] and trough concentration [Cmin]); and factors that influence tacrolimus kinetics, including genetic polymorphisms, drug–drug interactions, and

* Corresponding author at: Laboratory of Pharmacology, CHU Henri-Mondor, 51 avenue du Maréchal-de-Lattre-de-Tassigny, 94010 Créteil Cédex, France.
Tel.: +33 1 49 81 27 56; fax: +33 1 49 81 27 57.
E-mail address: anne.hulin@hmn.aphp.fr (A. Hulin).

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Table 1
Imprecision and bias at low concentrations with Architect® CMIA ($n = 3$).

Theoretical concentration (ng/ml)	0.5	0.75	1	1.5	2	2.5	3	5
Bias (%)	−8	−6.7	+6	−5.3	0	+4.8	+7.7	+13.4
CV (%)	15	11.7	6.6	5.6	7.5	3.9	2.9	2.5

environmental factors [8,9]. The experts recommended the use of assays with quantification limits equal to or less than 1 ng/ml to ensure good precision and accuracy with all current treatment strategies, including low-dose regimens [8,9]; analytical validation studies to evaluate the precision, accuracy, robustness, and functional sensitivity of available tacrolimus assays; and cross-validation of each assay versus the reference method at the relevant laboratory and versus liquid chromatography–tandem mass spectrometry (LC–MS/MS).

Although LC–MS/MS is now available in many large transplant centers, immunoassays are still widely used despite insufficient data on their accuracy, precision, and functional sensitivity. Moreover, cross-validation versus LC–MS/MS is unavailable for many immunoassays.

The aim of this study was to evaluate the analytical performance in everyday practice of the new tacrolimus chemiluminescent microparticle immunoassay (CMIA, Abbott, Rungis, France) on Architect®, using LC–MS/MS as the reference standard. We also compared CMIA with two other immunoassays, antibody-conjugated magnetic immunoassay (ACMIA) on Dimension® RXL (Siemens, Paris-La Défense, France) and enzyme multiplied immunoassay (EMIT) (Siemens) on COBAS Mira®. Such comparisons have not been performed previously [7,10]. In addition, we measured tacrolimus concentrations by ACMIA and CMIA in two patients with falsely elevated tacrolimus concentrations due to interference in the ACMIA. Until the cause of ACMIA interference is identified, an alternative method will be needed, as mistakes in TDM may lead to the use of inappropriate dosages associated with poor patient outcomes [11,12].

2. Patients and methods

2.1. Patients

We studied one blood sample from each of 176 transplant recipients (135 men and 41 women). The transplanted organ was the heart in 19 patients, a kidney in 107, and the liver in 50. Among them, 14 (8%) were recent allogeneic transplant recipients from whom a blood sample was obtained within 21 days after transplantation and 128 (72.7%) were already on low-dose tacrolimus therapy.

The study was approved by our institutional review board, and written informed consent was obtained from each patient before study inclusion, in compliance with French legislation.

2.2. Blood samples

The blood sample was drawn before the morning tacrolimus dose, in an ethylenediaminetetraacetic acid tube. EMIT was carried out daily on fresh samples and the other assays after a short period of freezing at −80 °C.

2.3. Assays

We used the tacrolimus CMIA kit on the Architect® i2000sr system, as recommended by the supplier. This assay requires manual pre-treatment of a whole-blood specimen with methanol/zinc sulfate to precipitate protein and extract the drug. Then, the 30-min immunoassay uses anti-tacrolimus antibody-coated paramagnetic microparticles and an acridinium-tacrolimus tracer [8].

We tested three other methods on the same sample as the CMIA: EMIT, which involves pre-treatment with zinc/methanol, an immunocompetition assay in homogeneous medium, and reading of the enzyme-substrate reaction (on Cobas Mira®, the method used routinely in our laboratory); ACMIA (on Dimension® RXL) in which free and tacrolimus-bound antibody-β-galactosidase conjugates are separated using magnetic particles after erythrocyte lysis by saponin; and LC–MS/MS (the first samples being testing by Dr. Laurent Massias at the Bichat Hospital, Paris, using Quattro [Waters, St Quentin-en-Yvelines, France] and subsequent samples at the Henri Mondor Hospital, Créteil, using Quantum Ultra [ThermoFisher, Courtaboeuf, France].

All four assays used in our study have been validated in accordance with FDA guidelines. Internal quality controls were used for each run and external quality-control assays were performed regularly (Pr Holt, London).

2.4. Analytical validation of the tacrolimus CMIA kit on Architect®

Analytical validation of the tacrolimus CMIA kit was performed using low, medium, and high concentrations (4.3, 8.4 and 16.7 ng/ml, respectively) in control samples, produced by Biorad Laboratories (Marnes-la-coquette, France). Intra-run imprecision was determined using 15 replicates of each control concentration on the first day and inter-run imprecision using 3 replicates per day for 5 days. Using the same samples, bias was evaluated from the difference between the measured concentration and the target concentration. Functional sensitivity was determined by spiking whole-blood aliquots with tacrolimus solution to obtain final tacrolimus concentrations of 0.5, 0.75, 1, 1.5, 2, 2.5, 3, and 5 ng/ml ($n = 3$ per concentration). We also used these spiked samples for ACMIA to determine the functional sensitivity of this assay. The coefficient of variation (CV, %) for each control was plotted versus the concentration, and reciprocal curve fitting was used to calculate the concentration corresponding to a CV of 20% and a bias of 20%. Interference with hematocrit, bilirubin, or total protein for CMIA has been researched.

2.5. Cross-validation

CMIA was compared with the immunological methods (EMIT and ACMIA) and reference method (LC–MS/MS), using Passing–Bablok linear regression and the Bland–Altman representation to determine bias between methods. These comparisons were performed separately in kidney, liver, and heart transplant recipients. Finally, comparison was tested too on samples from two transplant patients who presented falsely concentrations by ACMIA.

2.6. Statistical analysis

Functional sensitivity was assessed using Sigma Plot analysis software (version 6.0, Sytat, San Jose, CA). Correlation and bias statistics were performed using Graph.Pad software (version 5.01, Prism, San Diego, CA).

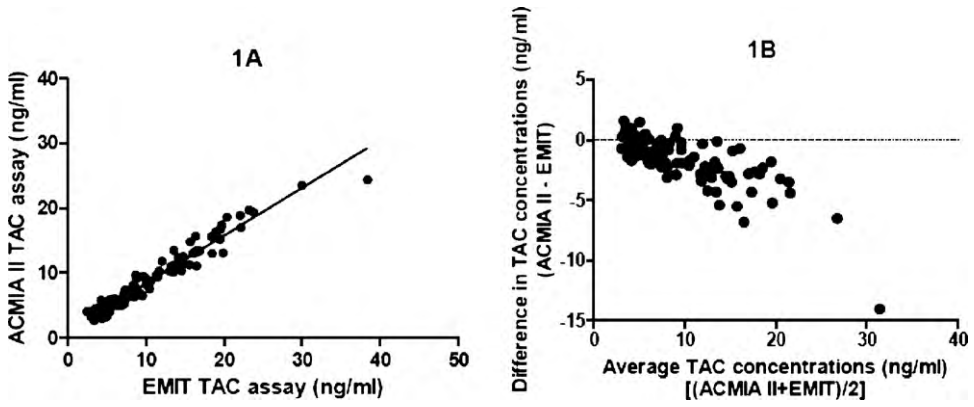

Fig. 1. (A) Passing–Bablok linear regression between ACMIA and EMIT ($n = 103$) (the solid line indicates the regression line), (B) Bland–Altman representation ($n = 103$) (the dashed line indicates no difference between the two methods).

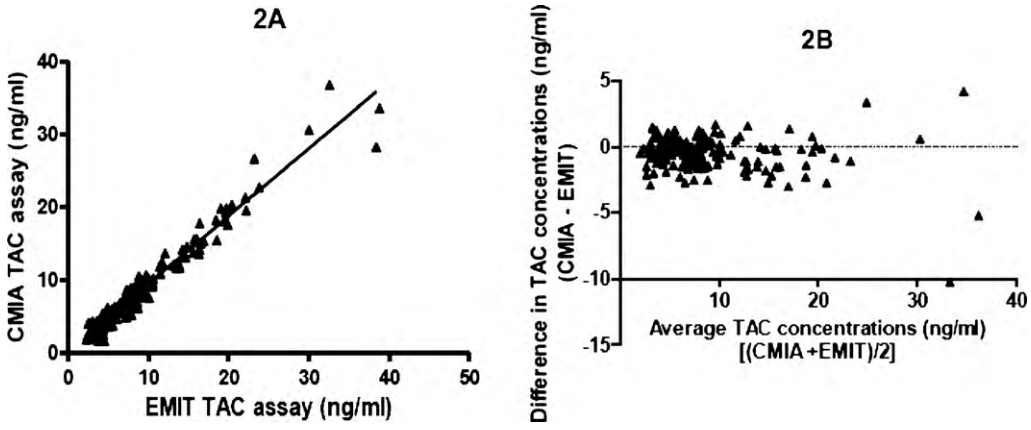

Fig. 2. (A) Passing–Bablok linear regression between CMIA and EMIT ($n = 170$) (the solid line indicates the regression line), (B) Bland–Altman representation ($n = 170$) (the dashed line indicates no difference between the two methods).

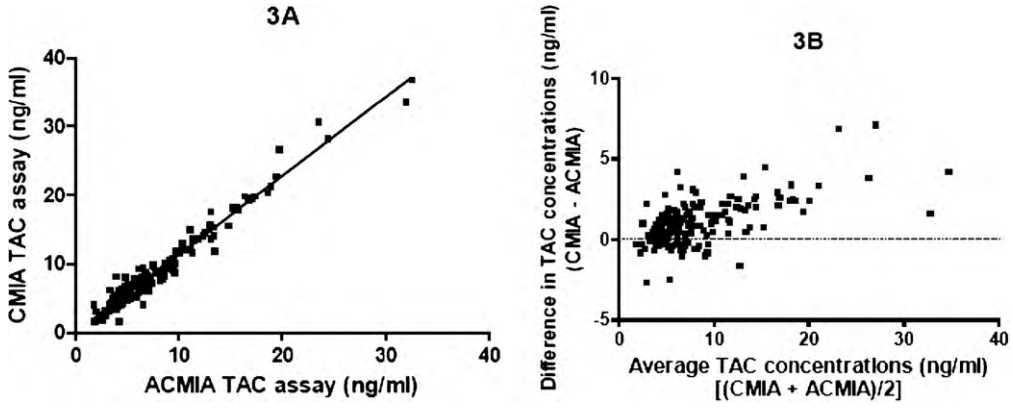

Fig. 3. (A) Passing–Bablok linear regression between CMIA and ACMIA ($n = 103$) (the solid line indicates the regression line), (B) Bland–Altman representation ($n = 103$) (the dashed line indicates no difference between the two methods).

Table 2
Imprecision and bias at low concentrations with Dimension® RXL ACMIA ($n = 3$).

Theoretical concentration (ng/ml)	0.5	0.75	1	1.5	2	2.5	3	5
Bias (%)	+248	+84	+59	ND	+4.5	ND	+3	ND
CV (%)	44.5	14.0	15.2	ND	12.0	ND	6.0	ND

ND: not determined.

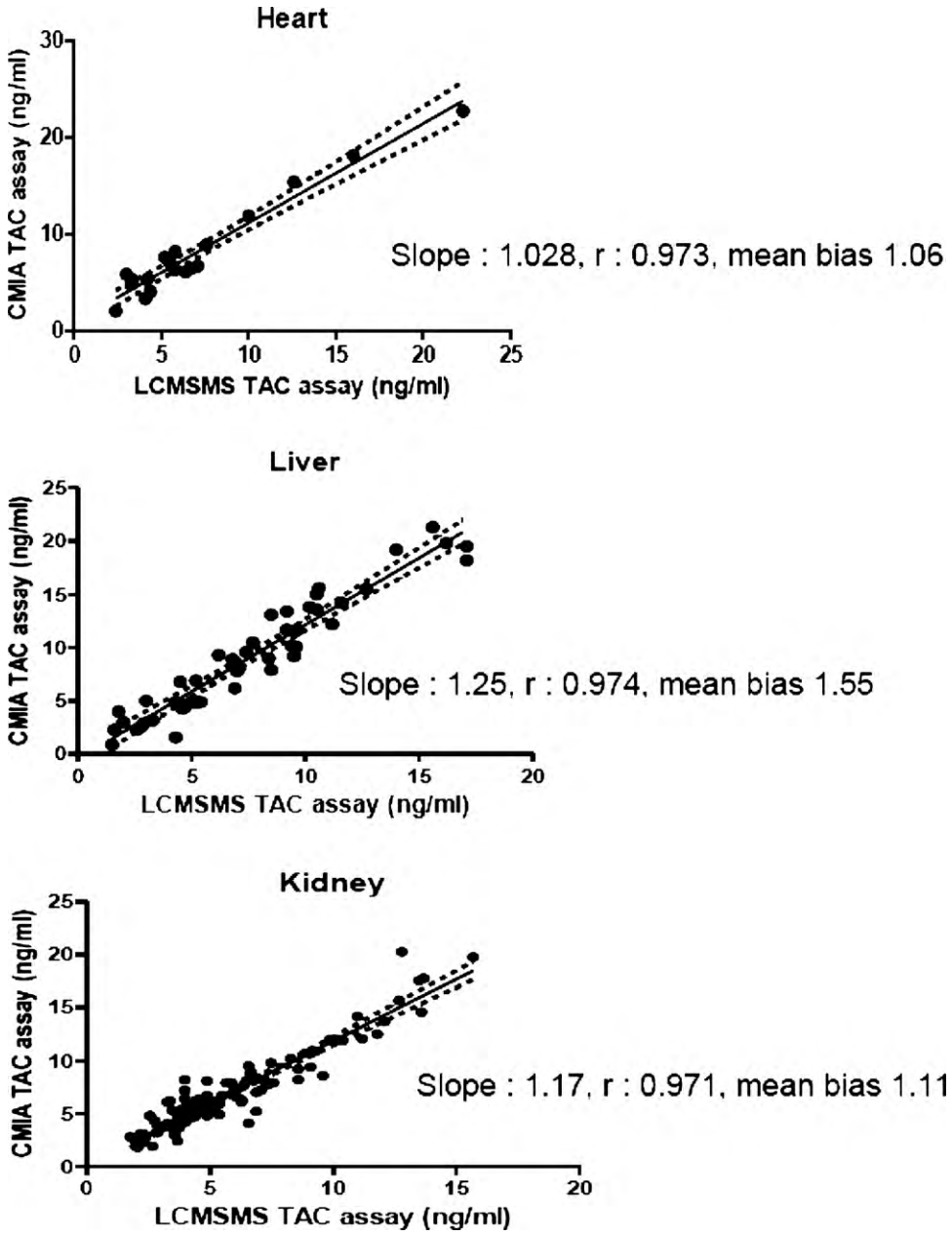

Fig. 4. Linear regression in 19 heart, 50 liver, and 107 kidney transplant patients. The regression parameters are reported.

3. Results

3.1. Analytical validation

Total imprecision of the assay was good, with CVs of 5.7, 3.7, and 3.6 for the low-, medium-, and high-concentration controls, respectively. Biases were −2%, +4%, and +4% for the low-, medium-, and high-concentration controls, respectively. Tables 1 and 2 show the imprecision and bias obtained with the spiked samples used for the functional sensitivity assessment of CMIA and ACMIA, respectively. Functional sensitivity was 0.5 [95%CI, 0.22–1.38] ng/ml with CMIA and 2.5 ng/ml with ACMIA. We previously found that functional sensitivity was 3 ng/ml with the first-generation reagent Dimension® RXL. We found no interference with hematocrit, bilirubin, or total protein for CMIA (data not shown).

3.2. Clinical cross-validation

3.2.1. Comparisons of immunological methods

Fig. 1 shows the linear regression and Bland–Altman representation comparing ACMIA and EMIT. Mean slope [range] was 0.777 [0.74–0.81] with a regression coefficient of 0.975 and a mean bias of −1.66 ng/ml. Because only 4.5% of samples had tacrolimus concentrations greater than 20 ng/ml, and because the concentrations in these samples showed considerably greater scatter than those in the other samples, we compared ACMIA and EMIT in the subset of samples having tacrolimus concentrations less than 20 ng/ml. The regression slope was unchanged but mean bias increased to −1.45 ng/ml.

Fig. 2 shows the linear regression comparing CMIA and EMIT. Mean [range] slope was 0.927 [0.90–0.96], the regression coefficient was 0.975, and mean bias was −0.47 ng/ml. Omitting samples

Table 3
Correlations linking patient tacrolimus concentrations by ACMIA, CMIA, and EMIT to those by LC–MS/MS.

Method	*n*	Slope	Intercept	r_2	Average bias (ng/ml)
ACMIA	103	0.982	0.05	0.96	−0.12
CMIA	176	1.131	0.028	0.962	0.92
EMIT	170	1.177	0.04	0.925	1.50

with tacrolimus concentrations greater than 20 ng/ml changed neither the regression slope nor the mean bias.

CMIA and ACMIA are compared in Fig. 3 ($n = 103$). Mean slope [range] of the linear regression was 1.15 [1.11–1.18], the regression coefficient was 0.988, and mean bias was 1.21 ng/ml. When samples with tacrolimus concentrations greater than 20 ng/ml were omitted, the regression slope increased to 1.2 and mean bias decreased to 1.08 ng/ml.

3.2.2. Comparison with the LC–MS/MS method (reference standard)

We had previously compared the two LC–MS/MS methods (Quattro Waters and Quantum Ultra) used in our study. Mean slope was 1.029 and the regression coefficient was 0.987. Table 3 reports the regression parameters for the three immunological methods versus LC–MS/MS. For tacrolimus concentrations in the 1–15 ng/ml range (the range seen in clinical practice with current low-dose regimens), regression between CMIA and LC–MS/MS was linear: CMIA = 1.053 LC–MS/MS + 0.377, $r = 0.948$, with a mean bias of 0.7 ng/ml ($n = 161$).

3.2.3. Organ effect

Fig. 4 shows linear regressions between CMIA and LC–MS/MS in the heart, liver, and kidney transplant patients.

3.3. Specific cases

We studied 2 patients in greater detail. One was a renal transplant patient from the Reims University Hospital who had a tacrolimus concentration determined by ACMIA of 12.5 ng/ml 2 months after stopping her treatment. The same sample had tacrolimus concentrations <2.5 ng/ml by EMIT and <0.5 ng/ml by LC–MS/MS. The CMIA showed a concentration <0.5 ng/ml. The other patient was an HIV-infected renal transplant patient monitored by ACMIA in a non-hospital laboratory. ACMIA showed a large increase in tacrolimus concentrations. By EMIT on the same sample, concentrations were within the therapeutic range. By CMIA, concentrations were also therapeutic (Fig. 5).

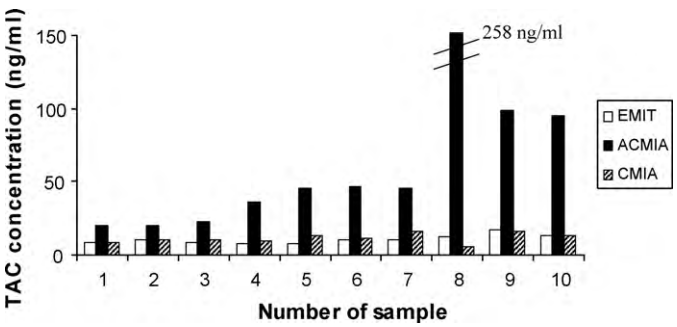

Fig. 5. Tacrolimus concentrations obtained using immunoassays in 10 samples from an HIV-infected renal transplant recipient with falsely elevated tacrolimus levels by ACMIA.

4. Discussion

From an analytical viewpoint, the manual pre-treatment step required by CMIA on Architect® did not appear as a disadvantage in our study. Furthermore, pre-treatment is also required for LC–MS/MS and EMIT. CMIA has an LOQ of less than 1 ng/ml, which complies with recommendations issued at the European Consensus Conference [9] and is better than the quantification limits of ACMIA and EMIT. The results of two studies comparing CMIA on Architect® to other assays (ACMIA and the Abbott microparticle enzyme immunoassay MEIA) [7,10] are largely consistent with those of our study. Precision and accuracy of CMIA were satisfactory, with bias ranging from −2% to +4% and total CV values of less than 6%. We found no interference with hematocrit, bilirubin, or total protein (data not shown).

From a clinical viewpoint, we found good correlations between immunological methods, although slopes and biases were not identical. Immunoassays are affected by cross-reactions with various tacrolimus metabolites including M-I (13-O-demethyl), M-II (31-O-demethyl), M-III (15-O-demethyl), and M-V (15,31, di-O-demethyl). Cross-reactions depend on the type of antibody used and, consequently, vary across immunoassays [13,14]. Therefore, tacrolimus monitoring should be performed using the same conditions at all time points. The optimal sampling time is just before the next dose (trough concentration) and the analytical technique must remain the same over time.

We found satisfactory correlations between each immunological method, including CMIA, and the LC–MS/MS reference method. In a multisite study [10], Passing Bablock slopes between CMIA and LC–MS/MS differed significantly between the laboratories in the US (0.81) and those in Austria (1.24). In another study comparing CMIA and LC–MS/MS on patient samples, mean slope was 1.07 and bias was +0.36 ng/ml [11]. We found a slope of 1.13 overall and 1.05 for concentrations in the 1–15 ng/ml range; corresponding bias values were +0.9 ng/ml and +0.7 ng/ml, respectively. These data indicate good performance of the CMIA for low concentrations. In our study, only 16 (9.09%) samples had tacrolimus concentrations greater than 15 ng/ml, but these considerably diminished the relationship between CMIA and LC–MS/MS values. At least two reasons may explain this fact: one is the heterogeneity of our patient population (kidney, liver, and heart transplants; recently transplanted patients and long-term stable transplant patients) and the other is absence of an international tacrolimus standard or tacrolimus reference assay recognized by the Joint Committee for Traceability in Laboratory Medicine. The regression data are important to clinicians, most notably when a change in the technique used for a given patient occurs (e.g., monitoring in a non-hospital laboratory instead of a hospital laboratory).

When we performed separate evaluations of the patient subgroups defined by the nature of the transplanted organ, we found slopes greater than 1 and positive bias. These findings probably reflect cross-reactions with metabolites. In vitro, the active metabolite M-II (31-O-demethyltacrolimus) and inactive metabolite M-III (15-O-demethyltacrolimus) show 94% and 45% cross-reaction, respectively, with the CMIA [10–12]. The active metabolite M-II can represent approximately 15% of the tacrolimus concentration determined in pre-dose specimens from renal transplant recipients [13]. The percentage of each metabolite may differ according to the transplanted organ and time since transplantation. Such differences may explain the differences in CMIA versus LS–MS/MS regression parameters obtained in our laboratory in heart, liver, and kidney transplant patients. However, the small number of patients in each group led to substantial variability. Another important possibility is that bias resulted from a matrix effect unique to patient specimens with LS–MS/MS. LS–MS/MS

methods can show bias due to internal standard stability, ion suppression effects, or the calibrator matrix [10].

Tests of samples from two patients with unexpectedly high tacrolimus concentrations by ACMIA showed interference in the ACMIA between antibodies in the patient samples and the antigen-antibody reaction. Such interference is not seen with methods that use methanol-based manual pre-treatment, which appears to eliminate patient antibodies by precipitation [15–21]. The ACMIA uses saponin-based pre-treatment, which causes cell lysis but does not eliminate antibodies [19–22]. A recent study identified an endogenous antibody present in the patient plasma that recognized an epitope on the antibody-enzyme conjugate used in the ACMIA, resulting in falsely elevated tacrolimus values [20]. Similar interferences have been reported in transplant patients for other analytical parameters such as parathyroid hormone [23]. The interfering antibodies may be heterophile antibodies, anti-galactosidase antibodies, antibodies associated with the treatments used by transplant patients (Ig, polyclonal, or monoclonal antibodies) or, more probably, HLA-specific antibodies associated with hyperimmunization. The possibility that interferences may affect tacrolimus assay results is of crucial importance, as tacrolimus dosage adjustments based on false assay results may lead to severe patient outcomes. For instance, decreasing the tacrolimus dosage when the assay shows a falsely elevated plasma concentration may lead to acute rejection in allogeneic transplant recipients. Our HIV-infected patient stopped his treatment when the ACMIA showed a tacrolimus concentration of 40 ng/ml. He was rapidly admitted, tested using the EMIT, and restarted on tacrolimus, which prevented acute rejection. Our other patient with falsely elevated tacrolimus concentrations had no clinical consequences, as her tacrolimus treatment has been stopped 2 months earlier. She was retested because the physicians were surprised to find a noticeable tacrolimus concentration despite discontinuation of the drug.

Our data indicate that the manual pre-treatment step required by the CMIA is an advantage, as it eliminates potentially interfering antibodies, and does not induce substantial interoperator variability. The same applies to the CMIA for sirolimus [24]. Laboratories should take care when selecting assay methods and inform clinicians of differences across methods, particularly when monitoring tests for a transplant patient are shifted from the hospital to a non-hospital laboratory.

In conclusion, the Architect® CMIA is robust, very precise, and sensitive (LOQ, 0.5 ng/ml). Therefore, it should prove valuable for monitoring patients on the new low-dose strategies [6]. CMIA performs comparably to the reference LC–MS/MS method, most notably in the 1–15 ng/ml range. It is not susceptible to interference by antibodies in hyperimmunized patients. Thus the Architect® CMIA is suitable for tacrolimus TDM in everyday practice.

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