RESEARCH ARTICLE

Performance of the Dimension TAC assay and comparison of multiple platforms for the measurement of tacrolimus

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Background: Therapeutic monitoring of tacrolimus is essential for reducing organ rejection and adverse effects. The measurement of tacrolimus in whole blood is taken by many automated platforms. We evaluated the analytical performance of the Dimension TAC assay, which is an upgraded reagent from the previous Dimension TACR assay.

Methods: The evaluations involved determination of precision, linearity, detection capability, and reagent lot-to-lot variability between three lot numbers. Correlation studies were conducted using the Dimension TACR assay, Architect, Elecsys assay, and MassTrak LC-MS/MS.

Results: The total coefficient of variation was below 10%. Acceptable linearity was observed in their respective reportable ranges. The limit of blank, limit of detection, and limit of quantification were 0.29, 0.47, and 0.81 ng/mL, respectively. Correlation analysis indicated that the Dimension TAC assay results were comparable to that of the Dimension TACR assay, Architect, and Elecsys results in liver and heart transplant patients. In kidney transplant patients, the Dimension TAC assay showed the poor correlation with Architect and Elecsys. The results from these assays were slightly higher than that of MassTrak. We found little lot-to-lot reagent variation among the reagents evaluated.

Conclusion: The overall analytical performance of the Dimension TAC assay is acceptable for therapeutic monitoring in clinical practice. Our study that compared different platforms may provide some useful information regarding which test method to use.

KEYWORDS

Dimension TAC assay, immunosuppressive agent, performance evaluation, tacrolimus, transplant

1 | INTRODUCTION

Tacrolimus is an immunosuppressive agent that is used for the prevention and treatment of graft rejection in organ transplant recipients and is used in combination with drugs such as steroids and mycophenolate mofetil.¹⁻⁴ Tacrolimus has a narrow therapeutic index and high inter- and intra-individual pharmacokinetic and pharmacodynamic variability.^{3,5,6} Elevated serum concentrations of tacrolimus may cause clinically significant adverse effects such as nephrotoxicity, neurotoxicity, and hyperglycemia; therefore, therapeutic drug monitoring (TDM)

is important to balance efficacy and safety.⁶ However, the therapeutic range of tacrolimus is set differently based on the transplantation organ, age, and immunosuppression protocol used by the researcher. In addition, blood concentrations of tacrolimus have been reported to vary between laboratories based on the assay platform used.⁷⁻¹¹

Tacrolimus concentration has been measured using various commercial assays that use immunoassay principles, including the fluorescence polarization immunoassay, microparticle enzyme immunoassay, enzyme multiplied immunoassay, radioimmunoassay, enzyme-linked immunosorbent assay, high-performance liquid chromatography-ultraviolet

detection (HPLC-UV), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Because the LC-MS/MS method has low cross-reactivity with the tacrolimus metabolite, this method exhibits higher specificity and selectivity than immunoassays. It also has the advantage of simultaneous measurement with other immunosuppressive drugs such as everolimus and sirolimus and is considered the gold standard analytical method for TDM.^{4,12-15} However, this method has a few limitations such as complex sample processing that requires skilled experts and a high cost for the initial laboratory setup. Therefore, the immunoassay method, which can be automated and is capable of handling multiple specimens, is widely used in laboratories.^{14,16,17}

The TAC assay of the Dimension platform has been widely used in clinical laboratories due to prompt reporting by reduced manual specimen pretreatment.¹⁸ The Dimension TAC assay (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) is based on the affinity chrome-mediated immunoassay (ACMIA) and is an upgraded reagent found in the existing Dimension TACR assay (Siemens Healthineers, USA).¹⁹ In this study, we evaluated the performance of the Dimension TAC assay and identified possible correlations with other assay platforms.

2 | MATERIALS AND METHODS

2.1 | Laboratory measurements

Blood tacrolimus concentrations were measured using reagents from the Dimension TAC assay and Dimension TACR assay on a Dimension EXL Integrated Chemistry System (Siemens Healthcare Diagnostics). For comparison, tacrolimus concentrations were also measured using the Architect Tacrolimus assay (Abbott Diagnostics, Lake Forest, IL, USA), which is based on the chemiluminescent microparticle immunoassay, on an Architect i1000SR immunoassay analyzer (Abbott Diagnostics), and the Elecsys Tacrolimus assay reagent (Roche Diagnostics, Mannheim, Germany), which is based on the electrochemiluminescence immunoassay, on a Cobas e 601 immunoassay analyzer (Roche Diagnostics). TAC samples were analyzed using a MassTrak LC-MS/MS Tacrolimus kit (Waters Corporation, Milford, MA, USA) on a Waters Alliance 2795 HPLC unit (Waters Corporation) attached to an MS/MS Quattro Premier XE mass spectrometer (Waters Corporation). The tacrolimus assays were performed in our laboratory according to the manufacturer's instructions. The ethics committee of Asan Medical Center approved this study (approval no. 2015-0821).

2.2 | Precision studies

The evaluation of assay precision was based on the Clinical and Laboratory Standards Institute (CLSI) guideline EP5-A2.²⁰ Quality control (QC) materials corresponding to three assay concentrations (lot no. 33080) were used. Two replicates of each control sample were analyzed twice a day for 20 days, with the two runs separated by at least 2 hours. The mean of each concentration, standard deviation, within-run coefficient of variation (CV), and total CV were calculated.

2.3 | Linearity

We referred to the CLSI guideline EP6-A for linearity measurements.²¹ Patient samples were serially diluted to five concentrations ranging from low to high, based on the measurable range as described by the manufacturer. Each concentration was measured four times. For each concentration, the mean measured value was compared to the expected value.

2.4 | Comparison studies

The evaluations of assay methods were based on the CLSI guideline EP9-A3.²² From October 2015 to January 2016, we obtained samples from heart-lung transplantation (HLT), kidney transplantation (KT), and liver transplantation (LT) patients taking tacrolimus. Whole blood samples were collected from patients with a clinically significant concentration range. Sixty samples were analyzed using different test methods according to the transplanted organ. Deming regression was used to calculate slope, intercept, and correlation coefficient (*R* value).

2.5 | Detection capability

The detection limits were evaluated based on the CLSI guideline EP17-A2.²³ The limit of blank (LoB) was determined by measuring the mean and standard deviation of 20 repeated measurements using a zero-level calibrator as a blank sample. Pooled EDTA whole blood samples were used to determine the limit of detection (LoD). The limit of quantification (LoQ), defined as the minimum concentration with a CV < 20%, was determined by repeated measurements for 20 days with one run. Target concentrations were approximately 1.0, 1.5, 2.0, 2.5, and 3.5 ng/mL. For each concentration, pooled EDTA whole blood samples were aliquoted into 20 samples.

2.6 | Lot-to-lot reagent variation

We referred to the CLSI guideline EP26-A for evaluation of lot-to-lot reagent variation.²⁴ Samples from 42 patients were used to evaluate three reagent lots (lot 1, FB6062; lot 2, GB6160; and lot 3, GC6300). The correlation coefficient (*R* value) was calculated by Deming regression, and percent difference values between lots were calculated using the following formulas

$$\text{Percent difference} = \{(\text{mean1} - \text{mean2}) / \text{mean1} \times 100(\%)\}$$

2.7 | Carryover

High- and low-concentration samples were prepared. After four consecutive measurements of high-concentration samples (H1, H2, H3, and H4), the low-concentration samples (L1, L2, L3, and L4) were measured four times consecutively. The carryover between

TABLE 1 Precision profiles of the tacrolimus assay

Analyte	Level (control material)	Mean concentration	SD	Coefficient of variation (%)	
				Within-run	Total
Tacrolimus (ng/mL)	Low	4.095	0.301	3.4	7.3
	Middle	11.317	0.575	2.6	5.1
	High	18.530	1.051	3.2	5.7

samples (%) was calculated as $\{L1 - (L3 + L4)\} \times 100 / \{(H3 + H2) / 2 - (L3 + L4) / 2\}$,²⁵ and the acceptable limit was set at 5% or less.

2.8 | Statistical analyses

EP Evaluator Release 8 software (David G. Rhoads Associates, Kennett Square, PA), SPSS for Windows (ver. 18.0; SPSS Inc., Chicago, IL, USA), and Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA) were used for the statistical analyses.

3 | RESULTS

3.1 | Precision studies

For each concentration, the mean, standard deviation, within-run CV, and total CV are summarized in Table 1. The total CV of low-, medium-, and high-concentration QC materials was 7.3%, 5.1%, and 5.7%, respectively. The CV of low-concentration material was higher than that of high-concentration material.

3.2 | Evaluation of linearity

The linear range, the range at which the coefficient of determination (R^2) is slightly greater than 0.99, was 1.6–31.7 ng/mL (Figure 1).

3.3 | Comparison studies

Comparisons between the Dimension TAC assay, Dimension TACR assay, Architect Tacrolimus assay, Elecsys Tacrolimus assay, and MassTrak LC-MS/MS Tacrolimus kit are shown in Table 2 and Figures 2 and 3. In the all samples, the R value was greater than .90 in the comparison between the Dimension TAC assay and Dimension TACR assay,

Elecsys assay. In the HLT group, the R values were all .90 or greater. In the KT group, the R value was less than .90, except for the Dimension TACR assay. In the LT group, the R value was greater than .90 only in the comparison between the Dimension TACR assay and Elecsys assay. In all organ transplant patients, the tacrolimus concentration was lowest when measured with the MassTrak LC-MS/MS Tacrolimus kit method.

3.4 | Detection capability

The mean results for LoB and LoD were 0.119 and 0.837 ng/mL, respectively. The LoB was 0.287 ng/mL, and the LoD was 0.469 ng/mL. The LoD was smaller than the lower limit of the measurement range suggested by the manufacturer. The LoQ was 0.808 ng/mL.

3.5 | Lot-to-lot reagent variation

The R value between three lots was greater than .975. The percent difference was 6.6% between lots 1 and 2, 9.6% between lots 1 and 3, and 9.9% between lots 2 and 3 (Figure 4).

3.6 | Carryover

The carryover between samples was 0.41%.

4 | DISCUSSION

The total CV% for low- and high-concentration QC materials was 7.3 and 5.7%, respectively, for the Dimension TAC assay, better than the existing Dimension TACR assay, with CV% of 8.1% and 5.9%, respectively, for low- and high-concentration QC materials.²⁶ Previously, another study reported a total CV% of 5.9–7.5% for the Dimension

FIGURE 1 Linearity of the Dimension TAC assay as estimated by the Dimension EXL Integrated Chemistry System analyzer. First-order models (A) and percent recovery (B) between assigned and measured values, including the difference between the linear and nonlinear fit at each concentration

TABLE 2 Comparative evaluation of various tacrolimus assays

Specimen	Candidate method	Comparative method	N	Slope (95% CI)	Intercept (95% CI)	Correlation coefficient	Syx
All	Dimension TAC	Dimension TACR	180	0.791 (0.768-0.814)	1.387 (1.158-1.616)	.9809	0.821
		Architect	180	0.932 (0.849-1.015)	0.544 (-0.280-1.368)	.8313	2.905
		Elecsys	180	0.969 (0.908-1.029)	0.797 (0.197-1.397)	.9121	2.152
		MassTrak	180	0.734 (0.666-0.802)	0.373 (-0.305-1.051)	.8165	2.432
HLT	Dimension TAC	Dimension TACR	60	0.916 (0.870-0.963)	0.648 (0.220-1.075)	.9818	0.561
		Architect	60	1.147 (1.078-1.216)	-0.841 (-1.486 to -0.195)	.9757	0.805
		Elecsys	60	1.056 (0.994-1.118)	0.259 (-0.312-0.831)	.9754	0.750
		MassTrak	60	0.797 (0.726-0.869)	-0.125 (-0.787-0.536)	.9431	0.868
KT	Dimension TAC	Dimension TACR	60	0.828 (0.792-0.864)	0.648 (0.887-1.494)	.9818	0.586
		Architect	60	0.919 (0.681-1.157)	0.350 (-1.622-2.321)	.5577	3.789
		Elecsys	60	0.947 (0.779-1.115)	0.994 (-0.408-2.395)	.7746	2.711
		MassTrak	60	0.745 (0.567-0.923)	0.277 (-1.205-1.759)	.6347	2.867
LT	Dimension TAC	Dimension TACR	60	0.759 (0.726-0.793)	1.278 (0.878-1.678)	.9860	0.943
		Architect	60	0.875 (0.766-0.985)	0.844 (-0.451-2.138)	.8942	3.031
		Elecsys	60	0.961 (0.875-1.047)	0.613 (-0.414-1.639)	.9421	2.422
		MassTrak	60	0.718 (0.812-0.825)	0.494 (-0.778-1.767)	.8490	3.003

CI, confidence intervals; HLT, heart-lung transplantation; KT, kidney transplantation; LT, liver transplantation, Syx, standard error of estimate.

FIGURE 2 Scatter plots and Bland-Altman bias plots of tacrolimus concentration among multiple platforms. Method comparisons were investigated for all samples. Data points represent patient samples analyzed via Dimension TAC assay vs Dimension TACR assay (A) vs Architect Tacrolimus assay (B) vs Elecsys Tacrolimus assay (C) and vs MassTrak LC-MS/MS Tacrolimus kit (D). In the scatter plots, the solid line is the Deming regression and upper and lower 95% confidence limits, and dotted line is 1:1 line. In the bias plots, the solid lines represent average bias

TAC assay, consistent with our results.²⁷ International Association of Therapeutic Drug Monitoring and Clinical Toxicology recommends the imprecision goals of <9% for ACMA tacrolimus assay.²⁸ Therefore, the Dimension TAC assay has acceptable precision for clinical use.

The linearity of the assay was excellent, with a slope of 1.000 and an intercept of 0.658 at a clinically significant concentration range.

The LoD and LoQ were lower than 0.7 and 1.0 ng/mL, respectively, which are the values provided by the manufacturer. In this study, the LoQ was 0.808 ng/mL, lower than the value (1.0 ng/mL) suggested by the European Consensus Conference on tacrolimus optimization.²⁹ These results show that the assay performed sufficiently in measuring low-concentration tacrolimus. In addition, Dimension TAC assay

FIGURE 3 Scatter plots and Bland-Altman bias plots of tacrolimus (TAC) concentration among multiple platforms. Method comparisons were investigated separately for specimens derived from heart-lung transplantation (HLT), kidney transplantation (KT), and liver transplantation (LT) patients. Data points represent patient samples analyzed via Dimension TAC assay vs Dimension TACR assay (A, HLT; B, KT; C, LT) vs Architect Tacrolimus assay (D, HLT; E, KT; F, LT) vs Elecsys Tacrolimus assay (G, HLT; H, KT; I, LT) and vs MassTrak LC-MS/MS Tacrolimus kit (J, HLT; K, KT; L, LT). In the scatter plots, the dotted lines are the Deming regression and upper and lower 95% confidence limits, and dashed line is 1:1 line. In the bias plots, the solid lines represent average bias

FIGURE 4 Scatter and Bland-Altman bias plots of tacrolimus (TAC) concentration among three reagent lots. Lot 1 vs lot 2 (A), lot 1 vs lot 2 (B), and lot 2 vs lot 3 (C). In the scatter plots, the dotted lines are the Deming regression and upper and lower 95% confidence limits, and dashed line is 1:1 line. In the bias plots, the solid lines represent average bias

showed better detection capability than the existing Dimension TAC assay.²⁶

In all transplant recipient samples, the tacrolimus concentration measured using the MassTrak LC-MS/MS Tacrolimus kit was lower than that measured using the Dimension TAC assay. In the range of 1.0–15.0 ng/mL, the mean bias between the two methods was 1.39 ng/mL. This finding is consistent with previous studies that showed higher levels in the immunoassay due to cross-reactivity between the antibody and tacrolimus metabolites. In our study, the immunoassay methods always yielded a slightly higher tacrolimus concentration compared to MassTrak (mean bias 1.18–2.65 ng/mL) in all transplant groups. In a study that compared MassTrak to the Architect immunoassay, the mean bias was 0.81 ng/mL; however, in this study, the mean bias was higher than that of the Architect immunoassay.^{30,31} Previous studies have reported positive biases of 28.2%, 33.1%, and 16.6%, respectively, in the enzyme multiplied immunoassay technique (EMIT), cloned enzyme donor immunoassay, and ACMA compared to the LC-MS/MS method.^{32–34} Other laboratories set the different method or instrument setup that may have caused the differences in results, although the

same LC-MS/MS kit was used. Differences include the use of mass detectors other than the one used in our study and use of electrospray ionization source and mode.^{30,35} In the HLT and LT patients, there was excellent correlation among the immunoassay methods (R value of .8942–.9860). In the KT group, the regression line slopes of the Dimension TAC assay and the Architect and Elecsys assay were 0.919 and 0.947, respectively, thus the measured tacrolimus results were not significantly different. However, the R values were .5577 and .7746, respectively, indicating poor correlation. Because tacrolimus metabolism depends on individual factors. Tacrolimus is metabolized mainly by the cytochrome P450 3A4 system in the liver, tacrolimus metabolites could be accumulated in patients with liver dysfunction, resulting in an increase in tacrolimus level in the blood.^{10,36} The factors including drug can influence liver injuries after kidney transplantation.³⁷ In addition, in kidney transplant patients, a false-positive result can occur in the ACMA due to interference with endogenous antibodies, heterophilic antibodies, and rheumatoid factor.^{38–40} In the KT group, the regression line slopes of the LC-MS/MS method and the Architect and Elecsys assay were 0.796 and 0.757, respectively, and the R values were .8037 and .6998, respectively (data not shown). These values were also not significantly different from those of the Dimension TAC assay. The results were also similar to those of new assay when we compared Dimension TAC assay with other assays. The poor correlation among the different immunoassay methods in the KT patients could be due to the various assay platforms. However, a limitation in this study is that the interference effects of several endogenous compounds and metabolites were not analyzed. So, further research is needed.

The differences in mean values among the three reagent lots tested were less than 10%. According to a 3-year survey of the immunosuppressive drug by the College of American Pathologists, the mean tacrolimus concentration increased stepwise every year due to changes in the immunoassay reagent.⁴¹ In addition, based on a previous report of lot-to-lot reagent comparability for α -fetoprotein, ferritin, and CA19-9, the percent differences ranged widely from 0.1% to 18.6%.⁴² In many laboratories, the typical tolerance limit was $\leq 10\%$ between reagent lots. Because tacrolimus is a drug used for maintenance of immunosuppression after transplantation, it is necessary to not only continuously monitor tacrolimus concentration but also to obtain consistent results.^{41,43,44} Dimension TAC assay showed lot-to-lot consistency when applying the tolerance limit commonly used; this is advantageous because consistency of results can be obtained for a substantial period of time.

The bioavailability and pharmacogenetics of tacrolimus between transplant patients are highly variable; therefore, precise and accurate results are important. It is also important to maintain tacrolimus blood levels because it has a narrow therapeutic range, and efficacy and toxicity are associated with trough levels. However, standardization of tacrolimus assay platforms has not yet been established, resulting in interlaboratory variability in results.²⁹ The results should be consistent in one clinical laboratory to avoid the inappropriate clinical interpretation of each patient results. The Dimension TAC assay showed better precision, linearity, detection capability, and minimal lot-to-lot reagent variability than existing Dimension TAC assay. These performances

can be attributed to ensure consistent results. And, this assay was comparable with other tacrolimus assays, similar to existing assay. New assay reagent is based on the ACMA method, and advantages include ease of testing, convenience, and faster reporting times due to a fully automated process from pretreatment to analysis. Although there have been many studies on tacrolimus TDM, our study compared different platforms based on the type of transplanted organ; therefore, this study may provide some useful information regarding which test method to use. We believe the Dimension TAC assay may be suitable for TDM of transplant patients.

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