Satisfactory performance of the Abbott ARCHITECT i2000 tacrolimus Immunoassay against the LC-MS/MS tacrolimus assay demonstrated in kidney transplant patients from the Northern Territory, Australia

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Research article

Keywords: Renal transplantation, Calcineurin inhibitors - tacrolimus, Northern Territory, Turnaround time, Liquid Chromatography (LC) with Mass Spectrometry (MS), Chemiluminescent Micro particle Immunoassay, Drug monitoring, Clinical Pharmacology

Posted Date: June 21st, 2019

DOI: https://doi.org/10.21203/rs.2.10537/v1

Abstract

Background Tacrolimus, a post-transplant immunosuppressive drug with a narrow therapeutic window requires close monitoring of levels to avoid under-immunosuppression or toxicity. Top End Renal Services in the Northern Territory (NT) refer to South Australia (SA) for drug levels as there was no local service. We aimed to evaluate the Abbott ARCHITECTi2000 immunoassay against the liquid chemistry tandem mass spectroscopy (LC-MS/MS) used in SA for measuring tacrolimus levels to provide on-site service in NT. Methods 465 specimens were collected over 5 months and analyzed over several reagent lots. We used Passing-Bablok regression plots and Bland–Altman plots to assess the agreement between tacrolimus levels on both platforms. Results The Passing-Bablok regression plot demonstrated a slope of 1.172 (CI 1.136 to 1.207) with an intercept of 0.262 (CI 0.040 to 0.472). In Deming analysis, the slope was 1.095 (CI 1.074 to 1.116) with an intercept of 0.773 (CI 0.592 to 0.955), correlation coefficient (r) was 0.9782. Bland-Altman plot demonstrated positive bias for Abbott ARCHITECT results. The mean absolute bias was 1.494 ug/L and the mean percentage bias was 18.78%. Within run imprecision, Co-efficient of Variation (%) was 5.1, 2.7, 4.3, 3.4 and 3.5 at tacrolimus concentration levels of 4.2, 6.5, 9.5, 17.2 and 24.4 µg/L. Results turnaround time improved by 80%. Conclusion The results demonstrate that Abbott ARCHITECT i2000 is an acceptable method to monitor levels of tacrolimus. The positive bias could be justifiable if the drug levels are initially based and then monitored on results from the same platform.

Background

Kidney transplantation operation for Northern Territory (NT) patients is performed at Central and Northern Adelaide Renal Transplantation Services (CNARTS) at the Royal Adelaide Hospital in South Australia, approximately 3000km away. Patients are transferred back to Darwin after about 4 weeks post-transplantation for ongoing follow up by the local renal unit at the Royal Darwin Hospital (RDH) in the Top End of the NT. The Top End Renal Transplant services follows up around 200 patients either with a renal transplant or on immunosuppression for immunological kidney disease. Approximately 60% of this cohort has tacrolimus as one of their immunosuppressive drugs.

Poor transplant survival outcomes in Indigenous population of NT have been attributed to increased risk of infections and rejection (1-4). Hence, these patients need very close monitoring of immunosuppression. The second generation calcineurin inhibitor, tacrolimus, has become one of the main immunosuppressant since its discovery in the early 1990’s. Therapeutic drug monitoring of tacrolimus is recommended to prevent toxicity or rejection, which leads to a greater improvement in the transplant outcomes.

Tacrolimus narrow therapeutic index, wide inter- and intra-individual pharmacokinetic variability, and susceptibility to cytochrome P450 related drug interactions requires close monitoring of blood levels (5). The most common adverse effects of tacrolimus are nephrotoxicity and neurotoxicity and are dependent on the levels (6,7).

Tacrolimus is available either as immediate release or extended release preparations in 500mcg, 1mg & 5mg capsules. The Symphony study, which assessed a regimen based on Daclizumab induction, 2 g Mycophenolate mofetil, low-dose tacrolimus and steroids, has had a major influence on dosing and managing levels of tacrolimus based on trough concentration monitoring (8).

RDH has not provided a therapeutic drug monitoring service for tacrolimus and blood samples were routinely sent to South Australia for analysis by liquid chemistry tandem mass spectroscopy (LC-MS/MS). A recent audit of the time taken between collection of blood samples and receipt of results indicated the potential for delaying clinical decision making, especially where acute indications for monitoring existed (9). Mass spectrometric methods were initially proposed for establishing a service at RDH, however, the Abbott ARCHITECT method was investigated due to the existence of the platform at RDH for other services and the ease of use of automated immunoassay platforms.

Abbott ARCHITECT is a widely employed assay for tacrolimus in Australia with an analytical measurement range of 2.0 to 30.0 µg/L. The recommended therapeutic range for tacrolimus trough concentration monitoring in solid organ transplantation claimed by Abbott ARCHITECT is 5.0 – 20.0 ug/L (10). In South Australia, an overall range of 5.0-15.0 ug/L is recommended for renal transplant patients, based on clinical consensus guidelines (11). However, the target can vary depending on the use of induction therapy or co-administration of mTOR inhibitors (Sirolimus or Everolimus) and variable patient immunosuppression requirements (11).

According to the end of cycle report (Cycle: 67, 29 January - 18 June 2018) of Royal College of Pathologist Quality Assurance Program/ Australia (RCPAQAP), 26 laboratories out of all 47 laboratories employed Abbott ARCHITECT (i1000,i2000,i4000) as their tacrolimus testing platform (13). In the report, only eight LC-MS/MS laboratories performed tacrolimus testing. However, there may be under representation of LC-MS/MS laboratories in the RCPAQAP, as many laboratories participate in overseas proficiency testing programs like the LGC Standards Proficiency Testing program (formerly the United Kingdom National External Quality Assessment Service, UK NEQAS), where 148 out of 304 laboratories employ LC-MS.

Methods

Specimen collection

The specimens were from transplant inpatients and outpatient renal transplant clinics in The Top End Renal Service (TERS). The TERS includes RDH, Katherine Hospital, Gove Hospital and numerous remote health clinics in NT. The usual timing for specimen collection was between 7am and 8am in the morning mostly on Mondays or Tuesdays for outpatients and around 7am for inpatients.

Aliquots of EDTA whole Blood specimens with requests for tacrolimus were referred for analysis by LC-MS/MS platform in the Department of Clinical Pharmacology, The Queen Elizabeth Hospital, SA. The rest

of each specimen was analysed locally on the Abbott ARCHITECT i2000 platform in the Territory Pathology laboratory at RDH.

Four hundred and sixty-five specimens were collected between 18th January and 12th June 2018 at an average of about 20 specimens per week. EDTA specimens were stored refrigerated at 2-8°C prior to testing for up to 7 days.

Abbott ARCHITECT i2000 assay

The Abbott ARCHITECT tacrolimus assay is a competitive immunoassay method with Chemiluminescent Micro particle Immuno Assay (CMIA) technology. According to the manufacturer's instructions, blood specimens were pre-treated by rapidly vortex mixing of 200 µL of EDTA whole blood with 200 µL of precipitation reagent, followed by centrifugation to obtain clear supernatant for analysis. Tacrolimus in the specimen competes with tacrolimus acridinium-labelled conjugate for the available binding sites on the anti-tacrolimus antibody coated paramagnetic microparticles. The resulting chemiluminescent signal is indirectly related to the amount of tacrolimus in the specimen.

The analytical measurement range on Abbott ARCHITECT tacrolimus immunoassay is 2 ug/L to 30 ug/L. A minimum reportable value of 2 ug/L (ng/mL) is based on the claimed functional sensitivity of the Abbott ARCHITECT method. Specimens with a tacrolimus concentration of > 30.0 µg/L were diluted 1:2 with zero calibrator provided by Abbott ARCHITECT. Six calibrators were available: 0, 3, 6, 12, 20 and 30 µg/L.

According to ARCHITECT, "Internal reference standards for ARCHITECT tacrolimus are manufactured using tacrolimus powder (purity ≥ 98.0% as anhydrous base). ARCHITECT Tacrolimus calibrators are manufactured gravimetrically and tested against internal reference standards at each concentration level".

As all pre-treated specimens should be tested within 30 minutes, the assay was performed each day in batches depending on the number of specimens received and spread across several reagent lots. The reagent lot numbers during the period were 78003M800, 79001M800, 80007M800, 80008M800, 84006M800, and 85002M800.

Liquid chemistry tandem mass spectroscopy (LC-MS/MS)

LC-MS/MS analysis was performed essentially according to the method of Koal et al, 2004 (12), using an AB Sciex API3200 tandem mass spectrometer coupled to a Shimadzu Prominence Ultra Performance Liquid Chromatography (UPLC) system. Whole blood samples (50 L) were precipitated with 100 L of an ice-cold methanol solution containing zinc sulphate and ascomycin (internal standard, Sigma-Aldrich). Samples were centrifuged at 15, 000 g. The supernatant was transferred to auto sampler vials for injection (25 L) onto the UPLC system. Calibration and internal quality control samples were included with

each analytical run using registered in vitro diagnostic kits comprising Chromsystems 6-level blood calibrators (Astral Scientific) and UTAK quality control samples (PM Separations). The analytical measurement range was 2.3 to 44 g/L and samples with tacrolimus concentrations > 44 g/L were diluted 1:2 with the Chromsystems blank calibrator. External quality assurance was provided through participation in an international immunosuppressant proficiency testing program (LGC Standards Proficiency Testing, Lancashire, UK). Between-run precision for the UTAK quality control samples ranged from 4.8% to 10.9% for the lowest control (mean concentration 2.7 g/L).

Methods of analysis

Initially results of 40 specimens were analysed and then extended to the results of 465 specimens collected over 5 months to compare the Abbott ARCHITECT i2000 assay against the LC-MS/MS assay.

Precision of the Abbott ARCHITECT method was assessed through repeated analysis of four levels of Bio-Rad QC material and one pooled whole blood specimen Table 1. Each specimen was analysed for at least 10 times and it was performed under single calibration with calibrator reagent lot number of 78003M800. For long-term precision Standard deviations (SD) and Coefficient of Variations (CV) of Bio-Rad Liquichek™ whole blood immunosuppressant quality control materials were evaluated on laboratory information system (LIS), LabTrak (Table 2). The assayed QC comes in four levels; selected period was from 13th of March until 20th of May 2018 with the QC lot number of 26260. During this period, reagent lot numbers used were 80008M800 and 84006M800 and three calibrations happened during the period.

Six months' worth of Turnaround time (TAT) data for samples sent for analysis to QEH from July 2017 till December 2017 was compared to three months' data for samples analysed locally at RDH from April 2018 to June 2018 (Table 3). TAT was analysed in Microsoft Excel. 539 episodes were recorded from July 2017 until December 2017 for QEH LC-MS/MS results. Time from collection of specimens until authorisation time of results was taken into main consideration. As greater than 7 days is considered as outlier for QEH, 28 specimens were removed from analysis and 511 episodes were taken into consideration for QEH TAT. 271 episodes were recorded from April until June 2018 for Abbott ARCHITECT method locally. Greater than 2 days was considered as outliers. 27 episodes were removed leaving 236 results for analysis for RDH (table 3).

Analyse-it software (Analyse-it Software Limited, Leeds, England) was used to generate Passing-Bablok regression plots (Figures 1 and 2) and Bland–Altman plots (Figures 3 and 4). These plots assessed the agreement between tacrolimus results on Abbott ARCHITECT i2000 and LC-MS/MS platforms. The Passing-Bablok plot illustrates the comparability of two platforms.

Bias was analysed in detail by Bland–Altman plots (Figure 3 and 4). In figure 3 absolute differences of the two methods were plotted against the averages of the two measurements whereas figure 4 illustrates percentage differences. In both plots mean difference is shown by a solid horizontal line whilst the interrupted horizontal lines define the limits of agreement, which covers 95% of values.

Further EP Evaluator® Software was employed to perform Deming regression. The regression analysis data is presented in Table 4, intercept, slope, and 95% CIs are presented. 95% CIs of intercept values that include 0 indicate the absence of systematic differences, whilst 95% CIs of the slope coefficient that include 1 indicate that there are no proportional differences.

Results

Tacrolimus concentrations ranged from 2.3 µg/L to 43.0 µg/L for Abbott ARCHITECT (2.3 µg/L to 39.0 µg/L on LC-MS/MS). There was a good spread of results up to 21.9 µg/L on Abbott ARCHITECT (the corresponding LC-MS/MS result being 19.4 µg/L). Beyond that concentration only three highly elevated results in the range of 40.0 µg/L were seen (Abbott ARCHITECT 43.3, 41.2, 37.6 µg/L and corresponding LC-MS/MS results being 39.4, 38.7, 38.7 µg/L respectively. These specimens required dilution to obtain the results as the analytical range is up to 30.0 µg/L.

The Passing-Bablok regression plot for all 465 results is demonstrated in figure 1. The analysis demonstrated a very good correlation with a correlation coefficient (R) of 0.9782. Slope and intercept of both regression analyses indicate a positive bias of results on Abbott ARCHITECT i2000 Tacrolimus results compared to that of LC-MS/MS. Bias was further evaluated with Bland-Altman bias plot. Absolute and percentage bias was analysed separately. Figure 3 illustrates absolute differences between methods. The mean bias was 1.494 with a 95% of Limit of agreement of -0.496 to 3.484. Figure 4 shows Bland-Altman plot for percentage differences in two methods. The percentage mean difference between two methods was 18.78 % with a 95% confidence interval of -2.60% to 40.17%.

Further evaluation of bias was performed after excluding three results in the range of 40 µg/L, the results spanned from 2.0 µg/L to 20.0 µg/L for evaluation. The absolute mean bias was 1.492 µg/L with a 95% of Limit of agreement -0.476 to 3.460. The percentage mean difference between the two methods is 18.88 % with a 95% confidence interval of -2.43% to 40.19%. Re-evaluation of Bland-Altman bias analysis emphasised the bias results obtained before.

The same bias evaluation was carried out for the specimens having results in the range from 2.0 to 12.0 µg/L on Abbott ARCHITECT (LC-MS/MS 2.3 to 11.4 µg/L) which demonstrated very similar results. The mean bias being 1.306 µg/L with a 95% of Limit of agreement -0.307 to 2.919 and the percentage mean difference of 19.18 % with a 95% confidence interval of -2.40% to 40.75%. The within run imprecision CV of the Abbott ARCHITECT assay was 5.1, 4.3, 3.4, 3.5, and 2.7% at concentrations of 4.2, 9.5, 17.2, 24.4 and 6.5 µg/L respectively (Table 1), whilst longer term CV ranged from 2.7 to 3.4% for four levels of Bio-Rad QCs (Table 2).

90th percentile Turnaround Time from collection of specimens to release of results improved from 6.05 days down to 1.24 days by local Abbott ARCHITECT assay compared to LC-MS/MS based in SA.

Discussion

Even though mass spectrometric methods are favoured for analysis of whole blood tacrolimus, capital cost, need of expertise and laboratory infrastructure limit small scale laboratories' accessibility to MS platforms. The availability of user-friendly automated immunoassay methods that allow random-access testing with fast turnaround times are an attractive alternative option.

Even being a popular method there are concerns regarding analytical performance of immunoassay platforms. Cross-reactivity with active and inactive drug metabolites can compromise analytical specificity of immunoassays, which can lead to an unpredictable overestimation of the true drug concentrations (14,15). Tacrolimus is metabolised by cytochrome P450 isoenzymes 3A4 and 3A5 (CYP3A4/5) system. According to Abbott ARCHITECT package insert "Nine different metabolites of tacrolimus have been identified; several of the metabolites have been found and tested in whole blood "(10). Drugs and other variables like pharmacogenetic variability in CYP3A4/5, age, disease conditions and time since the transplant affect the expression of the enzyme. Metabolites could cross react with antibodies in immunoassay platforms causing specificity issues (15).

Nevertheless, Christians U et al 1991 stated, compared to cyclosporine metabolites which could reach higher trough values than the parent compound, tacrolimus (FK506) metabolite fraction in blood was relatively small (16,17). However, A K Gonschior et al (1996) pointed out that tacrolimus metabolites could add up to 44.8% of the tacrolimus blood concentration (range 16-152%) in kidney transplant recipients whereas in liver transplant recipients it is up to 42% (range 0-145%) (18). This study further analysed metabolite patterns in kidney graft recipients during the early and late postoperative periods. Tacrolimus and dimethyl hydroxy tacrolimus concentrations are higher during the postoperative period. This study demonstrated tacrolimus metabolite concentrations and the metabolite patterns depend on the type of graft, time after transplantation and liver function (18).

Of the four metabolites tested, Abbott ARCHITECT package insert reports the greatest cross reactivity of 94% for 31-O-Demethyltacrolimus when spiked with 10 µg/L solutions and the least cross reactivity of 8% for 13-O-Demethyltacrolimus (10). For some patients these metabolites could potentially cause significant interference in the ARCHITECT assay (19).

In addition to cross-reactivity, relative differences between assays may, in part, also be due to differences in assay calibration (20). Different immunoassay platforms and different LC-MS/MS assays lack standardization in terms of methodology, leading to large inter-laboratory imprecision and inaccuracy (23, 24). Levine et al (20) compared the performance of 17 laboratories measuring tacrolimus by ARCHITECT to 9 laboratories using LC-MS technology. Although both method groups showed similar accuracies compared to a reference method, inter-laboratory precision was poorer for the LC-MS group (CVs 11.4 – 18.7%) compared to ARCHITECT (CVs 3.9 – 9.5%), due to the heterogeneity in LC-MS sample preparation, calibrator source and instrument platform.

Annesley TM et al (21) demonstrated how harmonisation of platform and employing the same reagent kit, results of 40 proficiency specimens in seven laboratories improved significantly. The study

demonstrated 4.4% was the largest mean bias obtained compared to reference measurements which is a validated LC-MS/MS method used by Analytical Services International (21).

Interestingly, a more recent comparison of inter-laboratory precision for LC-MS/MS and various immunoassay methods, suggests that LC-MS/MS performs similar to CMIA for the measurement of tacrolimus (22), probably reflecting the increased use of registered in vitro diagnostic calibrator kits by LC-MS laboratories. The availability of higher order reference materials (e.g. European Reference Material DA110a) will significantly aid in inter-laboratory harmonisation.

According to ARCHITECT, “Internal reference standards for ARCHITECT tacrolimus are manufactured using tacrolimus powder (purity ≥ 98.0% as anhydrous basis). ARCHITECT Tacrolimus calibrators are manufactured gravimetrically and tested against internal reference standards at each concentration level” mentioned in the “standardisation” section in calibrator information insert (23). Even though the method is traceable to an internal standard, information about traceability to ERM-DA110a was not provided in method insert. Likewise, the Chromsystems calibrators used in the LC-MS/MS analysis are traceable to certified reference materials and traceability to ERM-DA110a is not particularly mentioned.

Literature on longer-term data are limited on the performance of Abbott ARCHITECT chemiluminescent micro particle immunoassay (CMIA) method over several calibrations against LC-MS/MS as in this study. In our study, a mean positive bias percentage of 19%, with absolute mean positive bias of 1.5 µg/L was observed in Abbott ARCHITECT results compared to LC-MS/MS results. The percentage and absolute bias remained about the same over different concentration brackets of 2 -12, 2-20 and 2-40 µg/L.

De, B. K., et al in 2009 determined a mean bias of 0.36 µg/L (ng/ml) in Abbott ARCHITECT i2000 compared to LC-MS/MS in the analytical measurement range of 2-30 µg/L (24). Similar information is provided in the Abbott ARCHITECT tacrolimus package insert, reporting a mean bias of 0.51 µg/L (ng/ml) and 95% confidence intervals of 0.31 µg/L (ng/ml) to 0.71 µg/L (ng/ml) compared to LC-MS/MS for concentrations in the range of 2 to 20 µg/L (ng/ml) (10). In contrast, data from our study showed a relatively higher positive bias. As discussed above, this could be due to differential calibration of both Abbott ARCHITECT and LC-MS/MS (21), or may be due to a large proportion of indigenous patients, who may have different exposures to tacrolimus metabolites compared to other ethnic groups.

Even though our study demonstrated a positive bias of Abbott ARCHITECT results against LC-MS/MS results, within run and between run imprecisions were quite satisfactory. Within run CVs of 2.7, 3.5, 3.4, 4.3 and 5.1% were seen at concentration levels of 6.5, 24.4, 17.2, 9.5, and 4.2 µg/L respectively. Between-run CVs of the platform over two months across two reagent lots and three calibrations were 2.7, 3.2, 3.4, and 3.2% for 4 levels of Bio-Rad QC of 3.7, 9.4, 17.9 and 25.3 µg/L respectively. Similar inter-laboratory CVs were reported in the RCPAQAP End-of-Cycle Report of Special Therapeutic Drugs and Antibiotics Program for tacrolimus (13) over an analytical range of 4 to 25 µg/L, with overall group CVs for the Abbott ARCHITECT platform of 6.4% (n=26 Labs out of all 47 labs) compared to 10% for the LC-MS/MS platform (n=8 labs) mid-2018.

TAT improved significantly by introducing Abbott ARCHITECT platform locally. Laboratory TAT for the LC-MS/MS platform is same-day for samples received on weekdays, the major contributors to longer TAT for RDH samples were related to inter-state transport and delivery times.

Conclusion

In conclusion, Abbott ARCHITECT is a quite precise assay with a positive bias against LC-MS/MS platform. The bias is most likely due to a combination of cross-reactivity of metabolites in the Abbott ARCHITECT platform and lack of standardisation of both immunoassay and LC-MS/MS platforms. The improvement in TAT for the locally available assay may improve the time taken for clinical decisions and enhance patient outcomes. However, clinicians will need to be mindful of the potential for discordant clinical decisions between the two methods at the limits of the target range, particularly as newly transplanted patients return to NT from SA where early dosage adjustment is based on tacrolimus levels measured by LC-MS.

The Declarations:

Ethical consideration

The study was approved by the Human Research Ethics Committee (HREC) of the NT Department of Health and Menzies School of Health Research (HREC Reference number: 2018-3178). There was waiver of consent, so individual consent was not obtained.

Competing interests: The authors state that there are no conflicts of interest to disclose.

Sources of funding: Study is not funded by any institution.

Author’s Contribution: Primary authors are Geetha Rathnayake and Manohar Mogulla and all other authors contributed equally.

Consent for publication: Personal or clinical details or images of participants are not included in this analysis.

Availability of data and material: All the data about biochemistry results are available from Territory pathology.

Acknowledgements

We would like to acknowledge the laboratory staff at the RDH and QEH. We also acknowledge the staff in the renal units and the all the patients within the TERS

List Of Abbreviations

LC-MS/MS: Liquid Chromatography (LC) with Mass Spectrometry (MS)

NT: Northern Territory

SA: South Australia

TERS: Top End Renal Services

TEHS: Top End Health Services

RDH: Royal Darwin Hospital

CI: Confidence Intervals

CV: Coefficient of Variation

KRT: kidney Replacement Therapy

EDTA: Ethylenediaminetetraacetic acid

QEH: Queen Elizabeth Hospital

TAT: Turnaround time

LOA: Limits of Agreement

QC: Quality Control

CMIA: Chemiluminescent Microparticle Immunoassay

HREC: Human Research Ethics Committee

SD: Standard Deviation

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Tables

Table 1: Within run precision performance of the ARCHITECT platform using four levels of Bio-Rad QCs and a pooled whole blood patient specimen (n= number of replicates)

Sample	n	Mean Concentration µg/L	SD	CV (%)
Bio-Rad QC L1	11	4.2	0.21	5.1
Bio-Rad QC L2	10	9.5	0.40	4.3
Bio-Rad QC L3	11	17.2	0.59	3.4
Bio-Rad QC L4	10	24.4	0.85	3.5
Pooled patient whole Blood	10	6.5	0.18	2.7

Table 2: Between-run precision performance of the Abbott ARCHITEC tacrolimus method using four levels of Bio-Rad QCs for two months across three calibrations and two lots of reagents (n= number of replicates)

Sample	n	Mean concentration (µg/L)	SD	CV (%)
Bio-Rad QC L1	64	3.7	0.1	2.7
Bio-Rad QC L2	62	9.4	0.3	3.2
Bio-Rad QC L3	59	17.9	0.6	3.4
Bio-Rad QC L4	59	25.3	0.8	3.2

Table 3: Turnaround time data for results, from collection time to release of results for Abbott ARCHITECT local assay and for specimens referred to SA

	Period months	n	TAT (Collection to authorisation)	
			50% percentile	90% percentile
QEH LCMS/MS results	6	511	2.34 days	6.05 days
local Abbott ARCHITECT results	3	236	0.32 days	1.24 days

Table 4: Table 4 Regression analysis data for Deming and Passing-Bablok for 465 paired results. CI- 95% Confidence Intervals are shown in parentheses. n= number of specimens

	n	Slope (CI)	Intercept (CI)
Passing-Bablok	465	1.172 (1.136 to 1.207)	0.262 (0.040 to 0.479)
Deming	465	1.095 (1.074 to 1.116)	0.773 (0.592 to 0.955)

Figures

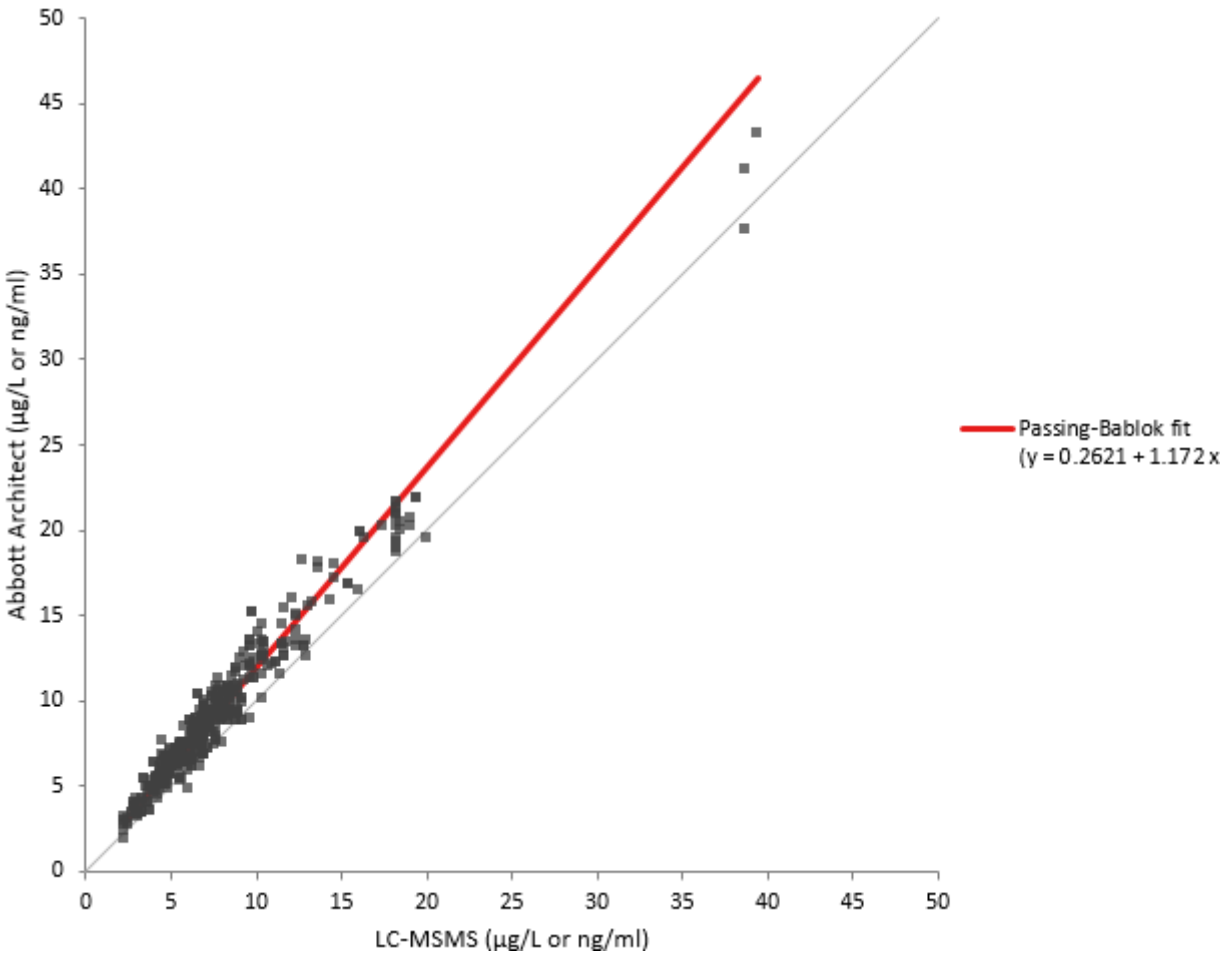

Figure 1

Passing-Bablok regression plot for the Abbott ARCHITECT i2000 vs LC-MS/MS correlation data for 465-paired results. The red line represents the line of regression and the ash line indicates the line of identity (Line of equality).

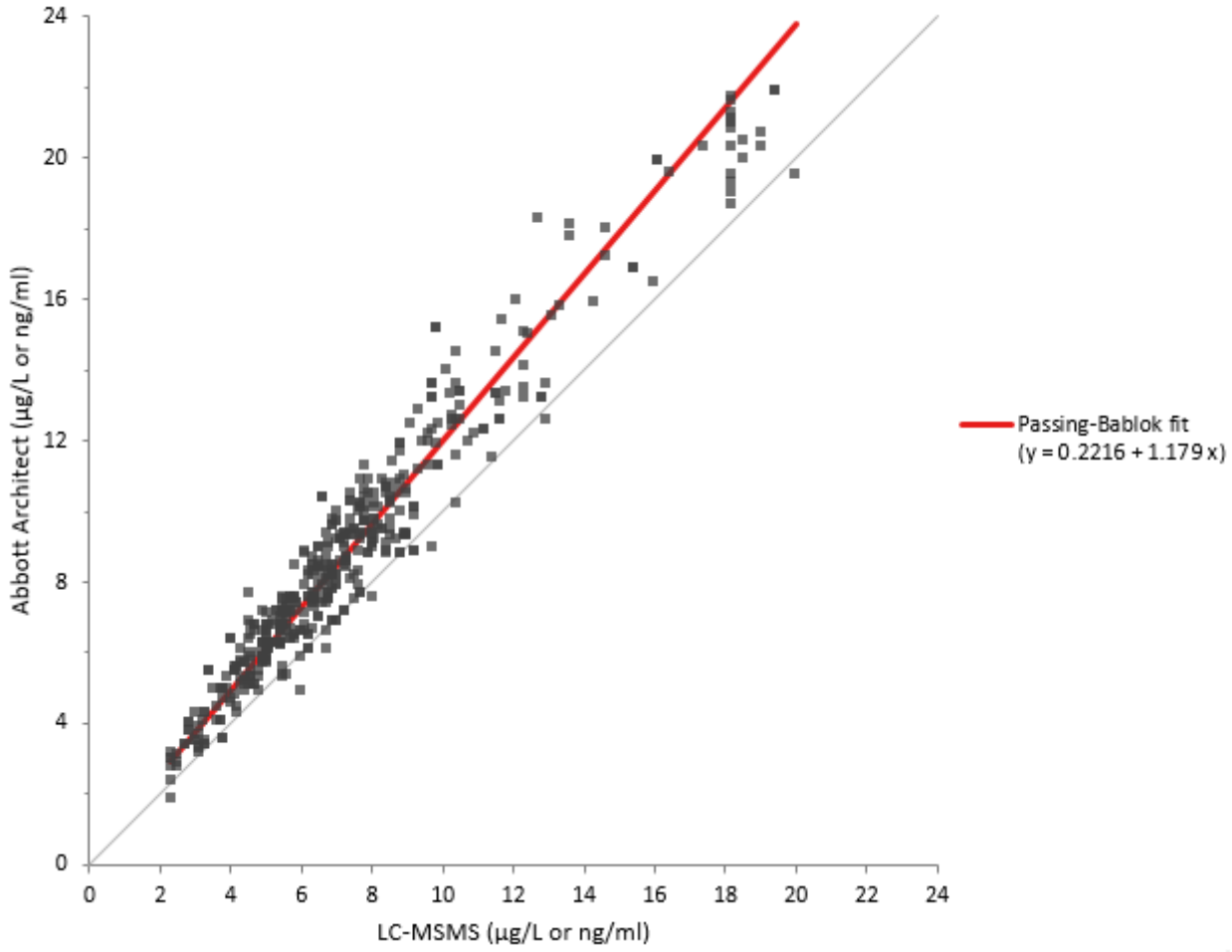

Figure 2

Passing-Bablok regression plot for the Abbott ARCHITECT i2000 vs LC-MS/MS. The results spread up to 24.0 µg/L. n=462, 3 paired results around 40.0 µg/L were excluded. The red line represents the line of regression and the ash line indicates the line of identity (Line of equality).

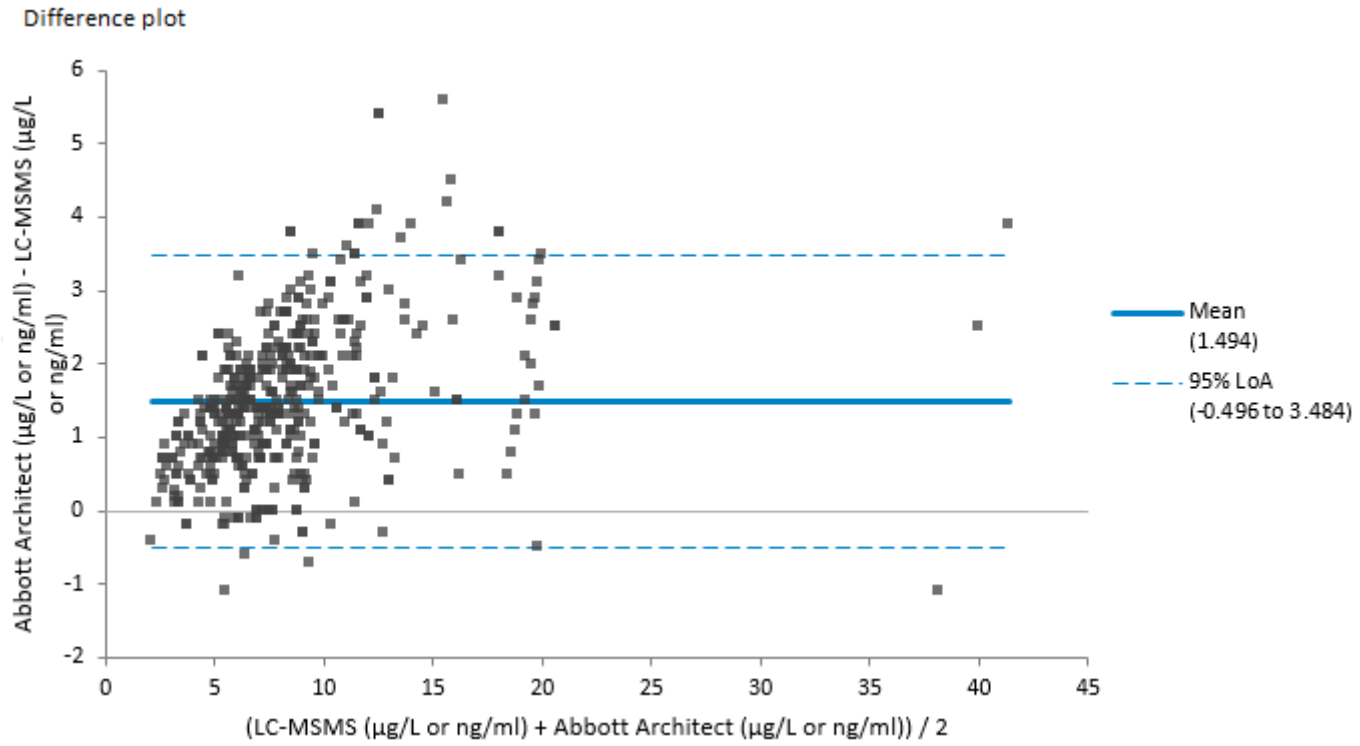

Figure 3

Bland-Altman bias plot for absolute differences for Abbott ARCHITECT i2000 tacrolimus results vs LC-MS/MS results. Mean= mean bias, 95% LOA=95% of Limit of agreement

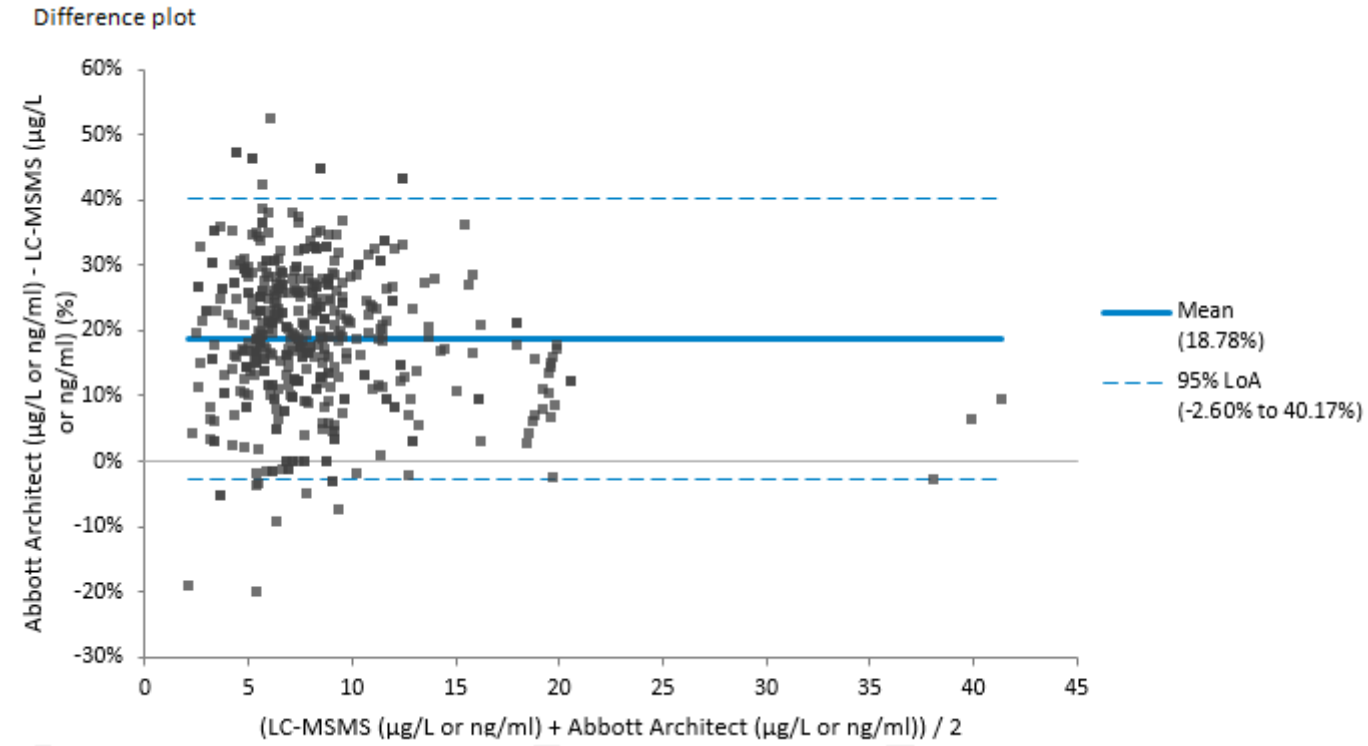

Figure 4

Bland-Altman bias plot for percentage difference for Abbott ARCHITECT i2000 tacrolimus results vs LC-MS/MS results. Mean= mean bias, 95% LOA=95% of Limit of agreement.