Commentary to BJCP 2021 00034

A new method to calculate intra-patient variability in tacrolimus concentrations.

Author:

Teun van Gelder, Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, The Netherlands

Address: Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Email: T.van_Gelder1@lumc.nl

In this issue of the journal Yin et al publish their study on a new method to calculate intra-patient variability (IPV) in tacrolimus concentrations in kidney transplant patients[1]. IPV reflects the fluctuations in tacrolimus concentrations over time, in patients on maintenance treatment treated with a stable dose. Clinicians taking care of transplanted patients will recognize the situation where despite a stable dose the pre-dose concentrations collected in an individual patient at every out-patient clinic show quite a bit of variability and in fact sometimes are below and sometimes above the target range. Such fluctuations typically occur without clear cause.

Several groups have shown that a high IPV is associated with poor long term outcome, including late acute rejections, deterioration of renal function and graft loss[2 3]. The explanation is assumed to be that patients with a higher IPV more often have tacrolimus concentrations outside the target range, and as a result they can either develop alloreactivity (if concentrations are below target) or tacrolimus related (nephro)toxicity if exposure is above target. Evidence for the first mechanism comes from studies that show development of de novo Donor Specific Antibodies (dnDSA) in patients with high IPV[4]. Evidence for the latter was found by demonstrating progression to moderate or severe fibrosis and tubular atrophy in paired protocol biopsies from patients with high IPV, obtained at 3 months and 2 years after kidney transplantation[5].

Instead of using IPV to quantify variability Yin et al have used a “variability score” as a new method. Previously this variability score was used to analyze the impact of changes in HbA1c on overall survival in elderly patients with diabetes[6]. The tacrolimus variability score (TVS) that they have used counts the number of clinically significant changes in tacrolimus pre-dose concentrations (defined as changes in exposure of more than 2 ng/mL) divided by the number of measurements. All tacrolimus concentrations collected between month 1 and month 12 after transplantation were included. The large population of 1343 kidney transplant patients was divided into two groups, with either a high TVS (>0.30) or low TVS (<0.30). The threshold was based on a ROC analysis, and divided the population into two groups of almost equal size (655 patients in the low TVS group, and 688 in the high TVS group). In a multivariate analysis TVS was an independent predictor for graft failure. The prognostic value of the TVS was better compared with IPV (based on calculation of the coefficient of variation (CV). TVS was only tested as a dichotomous parameter (below or above TVS = 0.30) and data on the performance of TVS as a continuous parameter are not provided.

Although both IPV and TVS are associated with long term outcome after kidney transplantation, and both methods focus on changes in drug concentrations over time, but not necessarily quantify the

time a patient is either below or above the target range. If tacrolimus pre-dose concentrations fluctuate between 5 and 7.5 ng/mL IPV and TVS will be high, but it is questionable if this will result in induction of allo-reactivity or nephrotoxicity. But if these concentrations go below 3 ng/mL, or above 10 ng/mL (arbitrarily chosen values) such changes in exposure may be more detrimental. Possibly an even better correlation with outcome would be found if "time below target" would be calculated.

Nevertheless, despite these limitations IPV and TVS do provide a warning signal that a patient is at risk. Recently Kuypers et al stressed the role of medication non-adherence as a cause for fluctuating tacrolimus concentrations, especially if associated with missed clinic appointments or other indications of nonadherence to follow-up[7]. Taber et al found that a high IPV was especially detrimental if caused by medication non-adherence[8]. Assuming non-adherence is the driving factor for IPV, IPV was also listed as a modifiable risk factor, and various interventions including switching from twice daily to simplified once daily drug regimens have been proposed[9]. However, the evidence that such interventions do result in a lower IPV, and that based on these interventions the prognosis improves, is weak at best[10]. There are many retrospective association studies, but very few prospective clinical trials investigating the effects of interventions on variability and/or clinical outcome.

The paper from Yin is the first to test TVS as a risk factor for long term outcome after kidney transplantation, and it would be good if this method would also be tested in independent data sets. In this analysis tacrolimus pre-dose concentrations obtained within the first post-transplant year were included, but samples collected within the first month were excluded. Especially in the first few weeks after surgery many samples are drawn for therapeutic drug monitoring, and post-operative changes in gastrointestinal motility, infectious complications and changes in corticosteroid dosing may affect the pharmacokinetics of tacrolimus and result in more variability. Given the short intervals between measurements in the immediate post-operative weeks a temporary drop, of only a few days, below target may have less impact than a similar drop in long term follow up, when intervals between samples may be as long as 3 -4 months.

In my view an important advantage of TVS, compared to the calculation of IPV based on the coefficient of variation, is that IPV is less affected by outliers. Such outliers have a strong impact on IPV, as it is based on the standard deviation of all collected tacrolimus concentrations. Another factor to take into account is the mean tacrolimus concentration. If the mean tacrolimus concentration is 6.5 ng/mL a patient with high IPV/TVS will occasionally be exposed to tacrolimus concentrations that go as low as 4 ng/mL. However, if the mean tacrolimus concentration is 4.5 ng/mL the fluctuations may bring the exposure to values below 3 ng/mL for prolonged periods of time, with risk of immune activation and development of dnDSA. In large datasets it may be possible to analyze the impact of IPV or TVS by dividing the population into subgroups (tertiles or quartiles) with different mean tacrolimus concentrations.

With the coefficient of variation, intra-patient variability and the new tacrolimus variability score it is possible to identify patients at risk of poor outcome. The association has been confirmed by many transplant centers, and it is time to study the effects of interventions on variability and clinical outcome.

Conflicts of interest:

In the last 3 years TvG has received lecture fees and study grants from Chiesi and Astellas, in addition to consulting fees from Roche Diagnostics, Vitaeris, CSL Behring, Astellas, Aurinia Pharma and Novartis. In all cases money has been transferred to hospital accounts, and none has been paid to his personal bank accounts. TvG does not have employment or stock ownership at any of these companies, and neither does he have patents or patent applications

References:

[1] Yin S, Wang X, Huang Z, Fan Y, Song T, Lin T. Tacrolimus Variability Score outperforms coefficient of variation in predicting clinical outcomes of living kidney transplantation. British Journal of Clinical Pharmacology xxxxxxxxxx
[2] Sapir-Pichhadze R, Wang Y, Famure O, Li Y, Kim SJ. Time-dependent variability in tacrolimus trough blood levels is a risk factor for late kidney transplant failure. Kidney Int. 2014 Jun;85(6):1404-11. doi: 10.1038/ki.2013.465. Epub 2013 Dec 11. PMID: 24336032
[3] Shuker N, Shuker L, van Rosmalen J, Roodnat JI, Borra LC, Weimar W, Hesselink DA, van Gelder T. A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. Transpl Int. 2016 Nov;29(11):1158-1167. doi: 10.1111/tri.12798. Epub 2016 Jun 28.
PMID: 27188932
[4] Del Bello A, Congy-Jolivet N, Danjoux M, Muscari F, Lavayssière L, Esposito L, Hebral AL, Bellière J, Kamar N. High tacrolimus intra-patient variability is associated with graft rejection, and de novo donor-specific antibodies occurrence after liver transplantation. World J Gastroenterol. 2018 Apr 28;24(16):1795-1802. doi: 10.3748/wjg.v24.i16.1795. PMID: 29713132
[5] Vanhove T, Vermeulen T, Annaert P, Lerut E, Kuypers DRJ. High Intrapatient Variability of Tacrolimus Concentrations Predicts Accelerated Progression of Chronic Histologic Lesions in Renal Recipients. Am J Transplant. 2016 Oct;16(10):2954-2963. doi: 10.1111/ajt.13803. Epub 2016 Apr 21. PMID: 27013142
[6] Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA(1c), HbA(1c) variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diabetes Endocrinol. 2018 Jun;6(6):476-486. doi: 10.1016/S2213-8587(18)30048-2. Epub 2018 Apr 16. PMID: 29674135
[7] Kuypers DRJ. Intrapatient Variability of Tacrolimus Exposure in Solid Organ Transplantation: A Novel Marker for Clinical Outcome. Clin Pharmacol Ther. 2020 Feb;107(2):347-358. doi: 10.1002/cpt.1618. Epub 2019 Sep 23. PMID: 31449663
[8] Taber DJ, Hirsch J, Keys A, Su Z, McGillicuddy JW. Etiologies and Outcomes Associated with Tacrolimus Levels out of Typical Range that Lead to High Variability in Kidney Transplant Recipients. Ther Drug Monit. 2021 Feb 8. doi: 10.1097/FTD.0000000000000863. Online ahead of print. PMID: 33560095
[9] Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, Duvoux C, Jardine AG, Kamar N, Krämer BK, Metselaar HJ, Nevens F, Pirenne J, Rodríguez-Perálvarez ML, Samuel D, Schneeberger S, Serón D, Trunečka P, Tisone G, van Gelder T. Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. Transplantation. 2017 Apr;101(4S Suppl 2):S1-S56. doi: 10.1097/TP.0000000000001651. PMID: 28328734
[10] Stifft F, Stolk LM, Undre N, van Hooff JP, Christiaans MH. Lower variability in 24-hour exposure during once-daily compared to twice-daily tacrolimus formulation in kidney transplantation. Transplantation. 2014 Apr 15;97(7):775-80. doi: 10.1097/01.TP.0000437561.31212.0e. PMID: 24686426