

**COMMENTARY**

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

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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.<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4</sup> 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.<sup>5</sup>

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.<sup>6</sup> 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.

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 alloreactivity 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.<sup>7</sup> Taber et al. found that a high IPV was especially detrimental if caused by medication non-adherence.<sup>8</sup> 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.<sup>9</sup> However, the evidence that such interventions do result in a lower IPV, and that

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based on these interventions the prognosis improves, is weak at best.<sup>10</sup> 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 with the calculation of IPV based on the coefficient of variation, is that TVS 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.

## COMPETING INTERESTS

In the last 3 years, T.v.G. 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. T.v.G. does not have employment or stock ownership at any of these companies, and neither does he have patents or patent applications.

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