Transplant International

INVITED COMMENTARY

Intrapatient variability in tacrolimus exposure – a useful tool for clinical practice?

Simon R. Knight[1,2]

1 Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK
2 Centre for Evidence in Transplantation, Royal College of Surgeons of England, London, UK

Correspondence
Simon R. Knight, Oxford Transplant Centre, Churchill Hospital, Old Road, Headington, Oxford OX3 7LE, United Kingdom.
Tel.: +441865227131;
e-mail: simon.knight@nds.ox.ac.uk

Transplant International 2016; 29: 1155–1157

Received: 31 May 2016; Accepted: 3 June 2016

The narrow therapeutic window for calcineurin inhibitors (CNI) remains a challenge in the management of transplant recipients, with underexposure risking acute rejection and overexposure resulting in acute and chronic impairment of graft function. Optimization of CNI exposure by computerized dosing and different monitoring strategies have long been an area of interest in the transplant literature [1,2].

In this issue of Transplant International, Shuker and colleagues report an association between high intrapatient variability (IPV) in tacrolimus exposure and adverse renal transplant outcomes, measured by a composite of graft loss, late biopsy-proven rejection and transplant glomerulopathy, or doubling of serum creatinine [3]. Risk of the composite outcome was 1.4 times higher in patients with high IPV, even after adjustment for confounders. The findings are not necessarily novel; a number of previous studies have demonstrated association between IPV and adverse outcomes in both adult and paediatric recipients, and in different solid organ transplant types [4–7]. This study does, however, represent the largest series to date and includes a number of additional risk factors for poor transplant outcomes in multivariate analysis. The authors also present a method for calculating IPV that can be applied in everyday clinical practice, along with practical examples.

There are some caveats. Whilst this retrospective analysis clearly demonstrates an association between tacrolimus IPV and adverse transplant outcomes, it is not possible to infer causation. There are many events that can occur during the first post-transplant year such as hospital admission, periods of gastrointestinal disturbance, infections and associated antibiotic use and administration of interacting drugs that could both increase tacrolimus IPV but also independently influence the risk of components of the composite endpoint used. The patient population is derived from a single centre over a 10-year period on a similar immunosuppressive regimen, and so whether the magnitude of the effect of tacrolimus IPV on outcomes is the same in other populations remains to be seen.

Despite these limitations, when taken in the context of previous publications from other centres, study of the prospective use of tacrolimus IPV monitoring does appear to be warranted. Routine IPV monitoring has some attraction as it uses existing tacrolimus trough level measurements, making it simple to implement and incurring minimal cost. Two questions, however,

doi:10.1111/tri.12806

remain to be answered: (i) How should the tacrolimus IPV be used to define patients at risk? and (ii) What interventions allow for the reduction of IPV and/or subsequent risk of events?

The study from Shuker *et al.* uses an arbitrary cut-off, defined as the median IPV, of 16.2% to dichotomize between high and low variability. It is not clear exactly what level of IPV represents a significant increase in risk and would warrant further investigation or intervention in a prospective study. Formal validation of IPV as a predictor for adverse outcomes in a prospective cohort may allow the optimal cut-off to be better defined for future use.

Once we have a better understanding of the IPV levels predictive of adverse events, the next step would be to define an intervention to attempt to reduce it and to test the impact of such an intervention in a prospective randomized trial. The difficulty is that the intrapatient variability is likely multifactorial, with drug compliance, oral intake and diet, concomitant medications, gastrointestinal disturbance and even genetic variation contributing. The existing literature plays heavily on noncompliance as a significant contributor to IPV, although the actual evidence for this is limited. One of the few studies that has investigated the relationship between IPV, patient attitude and compliance found that whilst IPV does correlate with patient attitude to their medication and transplant, there was no relationship found between IPV and self-reported compliance [8]. Indirect evidence suggests a possible link, however, with conversion of patients to once-daily tacrolimus formulations improving both compliance and reducing IPV in both kidney and liver transplant recipients [9–11]. These data suggest that where compliance is suspected as a potential contributor, once-daily modified release tacrolimus may benefit some (but not all) patients.

The contribution of other factors to IPV is less certain. Lifestyle and diet may play a role, leading to the suggestion that improved patient education may reduce IPV. Bessa *et al.* explored the role of enhanced education regarding medications delivered by an experienced transplant pharmacist rather than standard nursing care on compliance and IPV in a randomized controlled trial. The intervention had no impact on either the intrapatient variability or self-reported drug adherence, suggesting that enhanced education alone may not have sufficient impact to improve outcomes. Genetic variability in drug metabolism is known to affect interpatient variability in the response to tacrolimus dosing, but may play less of a role in intrapatient variability [12].

It is likely that intrapatient variability in tacrolimus levels is multifactorial, with adherence and other factors playing different roles in different patients. Whilst there is mounting evidence of an association between tacrolimus IPV and adverse transplant outcomes, exactly how the monitoring of IPV can be integrated into clinical practice, and indeed whether this will help to reduce adverse outcomes in those patients with high IPV remains to be seen.

Funding

The author has declared no funding.

Conflict of interest

The author has declared no conflicts of interest.

REFERENCES

1. Knight SR, Morris PJ. The clinical benefits of cyclosporine C2-level monitoring: a systematic review. *Transplantation* 2007; **83**: 1525.
2. Størset E, Åsberg A, Skauby M, *et al.* Improved tacrolimus target concentration achievement using computerized dosing in renal transplant recipients – a prospective, randomized study. *Transplantation* 2015; **99**: 2158.
3. Shuker N, Shuker L, van Rosmalen J, *et al.* A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation. *Transpl Int* 2016; **29**: 1158.
4. Borra LCP, Roodnat JI, Kal JA, Mathot RAA, Weimar W, van Gelder T. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. *Nephrol Dial Transplant* 2010; **25**: 2757.
5. Pollock-Barziv SM, Finkelstein Y, Manlhiot C, *et al.* Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. *Pediatr Transplant* 2010; **14**: 968.
6. 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; **85**: 1404.
7. Whalen HR, Glen JA, Harkins V, *et al.* High intrapatient tacrolimus variability is associated with worse outcomes in renal transplantation using a low-dose tacrolimus immunosuppressive regime. *Transplantation* 2016; Epub ahead of print. PMID 2695072.
8. Tielen M, van Exel J, Laging M, *et al.* Attitudes to medication after kidney transplantation and their association with medication adherence

and graft survival: a 2-year follow-up study. *J Transplant* 2014; **2014**: e675301.
9. Kuypers DRJ, Peeters PC, Sennesael JJ, *et al.* Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. *Transplantation* 2013; **95**: 333.
10. Wu M-J, Cheng C-Y, Chen C-H, *et al.* Lower variability of tacrolimus trough concentration after conversion from prograf to advagraf in stable kidney transplant recipients. *Transplantation* 2011; **92**: 648.
11. Considine A, Tredger JM, Heneghan M, *et al.* Performance of modified-release tacrolimus after conversion in liver transplant patients indicates potentially favorable outcomes in selected cohorts. *Liver Transpl* 2015; **21**: 29.
12. Pashaee N, Bouamar R, Hesselink DA, *et al.* CYP3A5 genotype is not related to the intrapatient variability of tacrolimus clearance. *Ther Drug Monit* 2011; **33**: 369.