Transplant International

INVITED COMMENTARY

Routine adherence monitoring after renal transplantation

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Transplant International 2019; 32: 600–602

Received: 26 February 2019; Accepted: 26 February 2019

Successful renal transplantation requires lifelong immunosuppression, usually with a combination of drugs, to prevent rejection and immunologically mediated damage to the graft. To achieve maximum effect, these immunosuppressive agents must be taken regularly as prescribed. This is particularly true of critical-dose drugs such as tacrolimus, with a narrow therapeutic window between efficacy and toxicity. There is good evidence that poor adherence to immunosuppression is deleterious to graft outcomes, with one systematic review suggesting a sevenfold increase in the risk of graft loss in poorly adherent patients [1].

Assessment of medication adherence is challenging. Non-adherence can take a number of forms, including missed doses, complete discontinuation, mistimed dosing or incorrect dosing. It may affect one or all drugs in the regimen and depend on a number of factors such as side effect profile, dose frequency, route of administration and lifestyle factors (peer pressure, work and social commitments). In everyday clinical practice adherence is rarely formally assessed, with clinicians relying on identifying patients from at-risk groups (younger age, male sex, lower education status [2]) or using surrogate markers for adherence (low or variable tacrolimus levels, early acute rejection episodes, poor clinic attendance).

Formal assessment of adherence is usually reserved for the clinical trial setting, with use of self-reporting questionnaires, smartphone monitoring, prescription refills or electronic pill-counting. Whilst these methods might give a better estimate of true medication compliance, they are often expensive, subject to manipulation and the measurement itself may have an effect on adherence [3].

In the current edition of Transplant International, Gustavsen and colleagues [4] evaluate a number of possible methods for the assessment of adherence in a real-world renal transplant population for use in a national transplant registry. Patients were recruited to two cohorts – a prospective cohort randomised to more or less intensive adherence assessment, and a cross-sectional cohort to control for the potential effect of assessment itself on adherence. Adherence was assessed by a combination of the self-reported Basel Assessment of Adherence to Immunosuppressive medication Scale (BAASIS), tacrolimus trough intrapatient variability (IPV) and an adherence score from the treating clinician. Interestingly, the adherence tools appeared to capture different patient populations, and whilst more

doi:10.1111/tri.13422

intensive assessment captured more nonadherence events, it did not appear to affect adherence behaviour overall. Poor adherence, as measured by the tools used here, did not significantly increase the risk of biopsy-proven acute rejection, but was associated with an increased risk of *de novo* donor-specific antibody development.

The focus in this study was to identify tools that can be used in routine clinical practice for registry purposes. As such the validated BAASIS questionnaire is a simple to administer, fast self-reporting tool consisting of just four questions regarding missed doses and administration timing over the past 4 weeks. Return rates in the current study were good (82% at 1 year), although there may be an element of selection bias in those patients prepared to take part.

Measurement of tacrolimus IPV is also straightforward, requiring three or more trough tacrolimus measurements over a time-period that can be used to calculate a co-efficient of variation. High IPV has shown association with poor clinical outcomes [5,6], and is associated with other non-adherence attitudes and behaviours [7,8]. However, it only captures adherence to tacrolimus, and adherence to other immunosuppressants may differ depending on dose frequency and side effect profile. Once patients are more than 1-year post-transplant, the frequency of trough measurements decreases meaning that IPV is assessed over a longer period and may miss shorter-term fluctuations in levels. Despite this limitation, 88% patients in the current cohort had sufficient data for IPV calculation at 1 year.

The benefit of the addition of clinician adherence assessment is less clear. As already described, clinicians assess adherence based upon demographic risk, clinical events and drug levels. The latter has quite a large influence, and so there is likely to be considerable overlap with those non-adherent patients identified through high tacrolimus IPV. This is supported by the higher Cohen's kappa value reported for the association between clinician's score and IPV, although agreement was still only fair. At 1-year post-transplant, patient-clinician interaction is likely to be limited making assessment challenging. Indeed, rates of clinician-scored non-adherence at 1 year (7%) were lower than those assessed by the BAASIS questionnaire (32%) and tacrolimus IPV (13%).

One of the major drawbacks of the study from Gustavsen and colleagues is the lack of a gold-standard assessment for true non-adherence, making it difficult to identify the optimal tool or combination of tools for monitoring. Pill-counting was attempted in one arm of the study, but return rates were poor (43%) and further analysis was not possible. This highlights the difficulties of pill-counting in a real-world patient group, suggesting that it is not a suitable tool for adherence assessment outside the clinical trial setting.

Overall, the study from Gustavsen and colleagues suggests that routine adherence assessment for registry purposes is possible using any of these three tools, and that a combination of tools may be required for a complete picture. Ultimately, the usefulness of these assessments will depend on response rates, but incorporation of these measures in a national registry has the potential to provide a very useful dataset to assess factors influencing adherence in the long-term post-transplantation. These tools may also prove useful in adherence assessment in clinical trials where the primary purpose of the study is not to influence adherence and formal assessment (e.g. pill counting) is not feasible.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflict of interest.

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