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INVITED COMMENTARY

Tacrolimus only for breakfast …*

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*Commentary on 'Renal function, efficacy and safety postconversion from twice- to once-daily tacrolimus in stable liver recipients: an open-label multicenter study', by Joanna San'ko-Resmer, *et al.* [Transpl Int 2012; 25: 283].

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In this issue of Transplant International Sanko-Resmer and colleagues [1] assessed renal function, safety and efficacy in stable adult liver transplant recipients converted from the conventional Tacrolimus twice-daily formulation (Prograf™) to the novel once-daily formulation (Advagraf™) in a multi-centre, open-label, single-sequence, crossover phase III study. After a 6-week run-in period 98 patients were converted to Advagraf™ on a 1:1 (mg for mg) total daily dose basis and followed for 12 weeks. Although Tacrolimus doses remained stable, mean Tacrolimus whole-blood trough levels significantly decreased around 15% (7.5 ng/ml vs. 6.5 ng/ml; $P < 0.0001$) after conversion and 25.5% of patients needed a dose adjustment, with similar numbers of patients requiring an increase and a decrease of Tacrolimus dose. Renal function, the primary endpoint, was stable, no rejection occurred and only a low incidence of treatment-related adverse events was reported. Interestingly, a lower within-patient variability of Tacrolimus trough levels was found after conversion.

It is well known that therapeutic regimens after solid organ transplantation are complex and non-adherence is considered a major cause of rejection and graft loss. Tacrolimus has a narrow therapeutic window and high within-patient variability in Tacrolimus levels was associated with inferior outcomes after kidney transplantation [2]. To improve adherence and consistency of exposure a patient-friendly once-daily (morning) oral formulation of

Tacrolimus might be useful, but evidence for the safe conversion of liver transplant recipients was sparse, and benefits and risks not well documented. This large phase III study filled this gap and provided further evidence that.

1 The conversion of stable liver transplant recipients to Advagraf™is safe. The results of this large multicentre trial extend previous observations from *de novo and maintenance* liver and kidney transplant recipients that the once-daily Tacrolimus formulation has similar efficacy and safety compared to the conventional twice-daily formulation [3–9]. Taken together, current evidence suggests therapeutic equivalence of the two Tacrolimus formulations. This is in contrast to most generic formulations, which demonstrate only bioequivalence in healthy volunteers.

2 After 1:1 conversion to Advagraf™ blood levels decreased by approximately 15%, similar to renal allograft recipients [8,9]. Interestingly, the change in trough level may depend on the CYP3A5 genotype, as renal allograft recipients with the CYP3A5*3/*3 allele (non-expressors) had a more profound decrease in tacrolimus levels, whereas CYP3A5*1 expressors did not experience a significant change after conversion [8,9]. This observation highlights the importance of a thorough pharmacological assessment of any novel Tacrolimus formulation (including generic formulations) in the target population.

3 Close initial monitoring is mandatory after conversion to Advagraf™. A substantial number of patients required dose adjustments, and it is of particular importance to closely monitor patients with drug levels at the lower therapeutic range, given the fact that levels may further decrease. This lesson from the current trial should also be standard practice after conversion to any other Tacrolimus formulation.

4 Despite slightly lower exposure, no rejections occurred, so eventually lower exposure might be sufficient for effective rejection prophylaxis. Unfortunately, we do not have good evidence from clinical trials for the lowest effective drug exposure in maintenance patients, and many transplant physicians continue forever with the same target ranges beyond the initial 6 month period. To really explore the benefits and risks of lower Tacrolimus exposure, further rigorous prospective randomized studies are needed, which specifically address different target ranges.

5 The lower within-patient variability, which already was observed in previous studies [4,10] merits further investigation. A more consistent exposure seems desirable, and a once-daily formulation may simplify the drug regime since the total number of capsules is reduced and patients are not bound to a strict evening intake time. However, it is unclear whether or not this will lead to better clinical outcomes and investigations on the impact of a once-daily formulation on patient adherence and outcomes are desperately needed.

In summary, the introduction of a new once-daily Tacrolimus formulation is certainly not a breakthrough in the immunosuppressive treatment for transplanted patients, but the new formulation offers a safe and proven treatment alternative for physicians and patients and may be a small step towards an individualized immunosuppressive regimen.

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