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Tacrolimus Once-Daily Formulation in the Prophylaxis of Transplant Rejection in Renal or Liver Allograft Recipients

A Viewpoint by Helio Tedesco Silva Jr

Division of Nephrology, Hospital do Rim e Hipertensão, Universidade Federal de São Paulo, São Paulo, Brazil

Calcineurin inhibitors, such as ciclosporin (cyclosporine) and tacrolimus, are still the basis of immunosuppression after solid organ transplantation. Between 1995 and 2004, the use of tacrolimus after kidney and liver transplantation increased from <10% to 72% of patients and from ≈40% to 89% of patients.[1] These findings are perhaps associated with the more favourable efficacy/safety profile of tacrolimus over ciclosporin.

Tacrolimus once-daily (OD) formulation [Advagraf®][1] was developed to produce bioequivalent exposure (area under the concentration-time curve [AUC]) to tacrolimus and a similar correlation between trough concentration and AUC as compared with standard tacrolimus administered twice daily. Indeed, both in kidney and in liver transplant recipients these pharmacokinetic characteristics were confirmed at steady state with somewhat less intrapatient variability favouring tacrolimus OD. Therefore, transplant physicians will be adjusting tacrolimus OD doses using the same target trough concentration ranges that are used for standard tacrolimus.

Moreover, using the same therapeutic drug monitoring strategy as for standard tacrolimus, tacrolimus OD had to show a comparable efficacy and safety profile. In one phase III clinical trial comparing tacrolimus OD and standard tacrolimus with ciclosporin,[2] the efficacy, safety and tolerability of tacrolimus OD and standard tacrolimus were very similar, although no study-specified comparison was done between tacrolimus OD and standard tacrolimus. Interestingly, (unlike standard tacrolimus) tacrolimus OD did not show a statistically significant reduction in the incidence of biopsy confirmed acute rejection compared with ciclosporin. Whether this finding is due to the open-label design of the trial, where the experimental group is always observed more carefully, or suggests reduced effectiveness is not known. Similarly, small differences were also observed in the safety profile. Nevertheless, a double-blind study comparing tacrolimus OD and standard tacrolimus has finished 1-year follow up and the results will be available soon to elucidate this issue.[3]

One open question is whether the difference in the tacrolimus time-concentration curves produced by tacrolimus OD and standard tacrolimus will result in significant clinical and measurable differences in transplant outcomes. The absence of the evening peak after the administration of tacrolimus OD may be associated with less toxicity, as has been demonstrated for aminoglycosides.[4] Improved compliance and perhaps less long-term nephrotoxicity, which will eventually result in preservation of native or allograft renal function and prolongation of allograft survival, are features to be closely monitored in patients receiving tacrolimus OD. ▲

References

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1 The use of trade names is for product identification purposes only and does not imply endorsement.