

## Different Preparations of Tacrolimus and Medication Errors

To the Editor:

We would like to alert the transplant community to potential medication errors with a new once-daily preparation of Tacrolimus (Advagraf™, Astellas, Tokyo, Japan).

Advagraf™ has been licensed in Europe in adult kidney and liver allograft recipients in 2007. The FDA has recently considered Advagraf™ approvable in kidney and liver transplantation and the drug is already available in Canada. Several studies have established its safety and noninferiority compared to twice-daily Tacrolimus (Prograf™, Astellas) (1,2). It is expected, though unproven, that a once-daily preparation will help with compliance and improve outcomes. Our unit is currently in the process of listing the drug on the hospital formulary and we were concerned about the potential for errors if a once-daily and a twice-daily preparation are available concurrently.

It has now come to our attention that Astellas has indeed reported such medication errors with Advagraf™ in a letter to the Royal Pharmaceutical Society (3). According to this report, Astellas has now received reports of pharmacists dispensing the once-daily instead of the twice-daily preparation (3). Another incident is also reported whereby a general practitioner incorrectly prescribed Advagraf™ for a patient maintained on Prograf (3).

To our knowledge, this issue has not yet been raised within the transplant community. A PubMed query for 'Advagraf', 'once-daily Tacrolimus', 'modified-release Tacrolimus' and 'error' yielded no results on April 25, 2008. Studies on Advagraf™ have not reported any incidents but this is not surprising as the setting of a clinical trial is certainly less vulnerable to such medication errors. A recent review article does not address the issue either (4).

It is currently difficult to gauge the risk. The very recent report from Astellas (3), however, suggests that this is no theoretical concern. Transplant surgeons and physicians, general practitioners, nurses, pharmacists and auxiliary staff are all involved in the prescription and dispensing of immunosuppressive medication. Practitioners who are not routinely involved in the care of transplant patients may be particularly vulnerable to errors. Patients themselves may or may not be aware of the issue or could be too unwell to spot the error. This may be particularly true during admissions in hospitals without transplant expertise. The

fact that Advagraf™ and Prograf™ are available in identical strength tablets is of particular concern.

The issue is further compounded by the fact that US patent protection for Tacrolimus has just expired. LifeCycle Pharma (Horsholm, Denmark) has just completed a phase II study of their generic, LCP Tacro™, in renal transplant recipients (ClinicalTrials.gov identifier NCT00496483). The appearance of generic preparations of Tacrolimus may thus leave further room for medication errors.

We suggest a high degree of vigilance when Advagraf™ and Prograf™ or even further preparations of Tacrolimus are available concurrently. The European Medicines Agency has already considered such errors and suggested different capsule appearances (5). We believe that additional precautions, such as warnings or package inserts for both preparations should be contemplated. We emphasize the need to educate all health-care professionals who are involved in the concurrent prescription and dispensing of Advagraf™ and Prograf™.

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