

# THE MOST DIFFERENT GENERICS OF TACROLIMUS ARE BIOEQUIVALENT TO EACH OTHER AND BRAND IN KIDNEY AND LIVER TRANSPLANT PATIENTS: A RANDOMIZED, CONTROLLED TRIAL.

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## Background

Although the United States Food and Drug Administration's (FDA) generic drug approval process has a long-term successful track record, it is discussed whether approval of generics of narrow therapeutic index immunosuppressants, such as tacrolimus, based on two-way cross-over studies in healthy volunteers and comparison of the pharmacokinetics of test/ reference products using average bioequivalence metrics is valid and safe in transplant patients. Among others, concerns regarding bioequivalence of generics with each other and bioequivalence in high-risk patients such as CYP3A5 expressors were raised.

## Methods

To address such concerns, we carried out an appropriately powered, prospective, fully replicated, partially blinded, randomized, 3-treatment, 6-period crossover bioequivalence study including kidney (n=35) and liver transplant (n=36) patients comparing the most disparate tacrolimus generics (test, Generic HI, Generic LO) on the United States market with the innovator's tacrolimus (reference) and with each other. Patients were genotyped for CYP3A5 and ABCB1 polymorphisms. Bioequivalence of tacrolimus and its major metabolite were assessed.

## Results

FDA average bioequivalence (ABE) and scaled average bioequivalence (SCABE) acceptance criteria were met for all product comparisons for AUC,  $C_{max}$ , and  $C_{min}$  (trough blood concentration) in both kidney and liver transplant subjects. Intra-individual variability was similar for all products. European Medicines Agency (EMA) acceptance criteria for narrow therapeutic index drugs were also met with the only exception of Brand *versus* Generic LO, where the upper limit of the 90%-confidence intervals was 111.3% (kidney) and 112.12 (liver). These were only slightly above the upper EMA acceptance criterion for AUC of 111.11%. SCABE was also observed for the major tacrolimus metabolite 13-O-desmethyl tacrolimus. Kidney transplant function or other safety parameters were not affected by the 6 switches of formulations within 42 days and, as assessed by daily dried blood spot collection, trough blood concentrations stayed stable.

## Conclusions

Using an innovative bioequivalence study design, our results provide evidence that tacrolimus generic substitution including switching among generics in transplant recipients is safe and that aforementioned concerns seem unfounded. (Funded by the United States National Institutes of Health and the Food and Drug Administration: Office of Generic Drugs (U01 FD004573); ClinicalTrials.gov number, NCT01889758)