Population Pharmacokinetics of Tacrolimus in Pediatric Renal Transplant Recipients on Two Different Formulations - Twice-daily Prograf® and Once-daily Advagraf®

SoJeong Yi¹, Hyeong-Seok Lim², Seonghae Yoon¹, Seol Ju Moon¹, Sang-il Min³, Jongwon Ha³, In-Jin Jang¹*

¹Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital; ²Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, Seoul, South Korea; ³Department of Surgery, Seoul National University College of Medicine and Hospital, Seoul, South Korea

Objectives: To evaluate the population pharmacokinetics of tacrolimus for both once-daily (Advagraf®) and twice-daily (Prograf®) formulations in pediatric renal transplant recipients

Methods: Thirty-eight children (age 7.0-16.3 years) in stable status after renal transplant took Prograf twice-daily until day 7 after study participation and from day 8 to 14 the tacrolimus regimen was converted to Advagraf once-daily on a 1:1 ratio for their total daily dose. From day 15 to 28, the dose of Advagraf was titrated based on the trough concentration. Concentration-time profiles were obtained for 24 h after dosing at day 7, 14, and 28. Population pharmacokinetic parameters were estimated using NONMEM (ver. 7.3) and the influence of covariates on pharmacokinetics were examined for CYP3A5 genotype, demographics and clinical laboratory results. The adequacy of model was evaluated using standard goodness-of-fit diagnostics and visual predictive checks.

Results: Tacrolimus pharmacokinetics was best described by a two-compartment model with mixed first- and zero-order absorption kinetics for both formulations. The relative bioavailability of Advagraf to Prograf was 0.705, and the pharmacokinetic parameters of Advagraf including absorption rate constant, apparent clearance and apparent volume of distribution were significantly different from those of Prograf. The apparent clearance in CYP3A5 non-expressers (with *3/*3 genotype) were 24.6% and 29.1% lower for Prograf and Advagraf, respectively, than those of CYP3A5 expressers (with *1/*1 or *1/*3 genotype). Due to circadian variation in twice-daily regimen, the rate constant on evening dose was smaller than that on morning dose (0.687 vs. 2.08 h⁻¹).

Conclusions: The conversion to once-daily Advagraf from twice-daily Prograf requires 30% higher daily dose and once-daily regimen can reduce the circadian variation of absorption. Dose-adjustment according to CYP3A5 genotype will be needed on both formulations.