Population Pharmacokinetics and Inter-Occasional Variability of Mycophenolic Acid in Lung Transplant Recipients with Cystic Fibrosis

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Purpose
Mycophenolic acid (MPA) is an immunosuppressant and the major active metabolite of the prodrug mycophenolate mofetil (MMF) that is widely used for the prophylaxis of acute allograft rejection in solid organ transplantation. The objective of this work was to develop a population pharmacokinetic (PK) model for MPA in adult lung transplant recipients and compare the PK parameters in patients with (CF) or without (NCF) cystic fibrosis.

Methods
Ten lung transplant patients (5 CF and 5 NCF) were enrolled in this pilot, open-label, pharmacokinetic study. Three separate 12-hr PK visits were conducted for each patient with at least a 2-week break between each visit. Patients were admitted to the clinical research unit after an overnight fast, and had serial blood samples drawn at various times in accordance with the morning MMF dose. Demographic (age, weight, gender) and clinical (serum creatinine, albumin, creatinine clearance) data were collected, and a population PK model was developed using nonlinear mixed effects modeling (NONMEM). The contribution of physiological and pathological factors, and the inter-occasional variability were assessed.

Results
For both CF and NCF patients, MPA serum concentration-time profiles were best described by a two-compartment PK model with first-order absorption. Significant inter-occasional variability in oral clearance (CL/F) was observed in CF patients. The estimated MPA parameters (± SE) for NCF patients were: CL/F = 8.97 ± 1.37 L/hr, V1/F = 40.1 ± 14.7 L, Q/F = 23.8 ± 5.6 L/hr, V2/F = 2190 ± 3670 L, and Ka = 2.19 ± 1.15 hr⁻¹. CF patients had a slower absorption rate (Ka = 0.70 ± 0.23 hr⁻¹) and a greater CL/F (11.7 ± 2.2 L/hr). Relative oral bioavailability of CF patients against NCF patients was 0.81.

Conclusion
Lung transplant recipients with CF had about 20% lower relative oral bioavailability and significant inter-occasional variability in CL/F. The population PK model developed in this study can be used to optimize MPA dosing in adult lung transplant recipients.