

Title: Evaluating Transplant Donor and Recipient Pharmacogenetics and its Impact on Tacrolimus Pharmacokinetics in Bioequivalence Studies

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Scope of the lecture:

There is strong evidence that pharmacogenetic (PG) polymorphisms in drug metabolizing enzyme and transporter pathways can explain important variability in tacrolimus pharmacokinetics (PK) and exposure in transplant recipients. For instance, CYP3A5 expressers (CYP3A5*1/*1 or CYP3A5*1/*3) require higher than standard doses as compared to non-expressers (CYP3A5*3/*3). Other pathways such as CYP3A4 (*1B and *22) and ABCB1 transporter polymorphisms have been implicated as well. This presentation will review the results of an extensive PK/PG analysis conducted as part of a prospective 6-way cross over bioequivalence study of three formulations in a cohort of 71 transplant recipients.

Learning objectives:

1. There is large unexplained variability in tacrolimus pharmacokinetics.
2. Variability is in part driven by differences in CYP3A4/5 and ABCB1 transporter expression and activity.
3. Pharmacogenetics can explain a clinically important part of this PK variability and preemptive genotyping is recommended.
4. Further studies to indicate that genotype-guided dosing affects long term clinical outcomes are warranted.

Background

Tacrolimus is a narrow therapeutic index immunosuppressant for which the FDA initiated studies to address public concerns related to interchangeability of generic drugs with the brand product. We conducted an FDA supported prospective 6-way cross over bioequivalence study of three tacrolimus formulations in adult renal and liver transplant recipients to compare full pharmacokinetics (PK) of brand and generics during steady-state treatment. Population PK-pharmacogenetic analyses were performed to compare tacrolimus PK profiles across the different formulations together with assessment of covariates to explain observed variability.

Methods

The study included a six period cross-over design with random evaluation of brand and two generic formulations. For each of the six PK evaluations 15 blood samples were collected at pre-dose (before morning dose), 20, 40, 60, 80, 100, 120, 140, 160, 180 minutes and 4, 5, 6, 8, and 12 hours post-dose. Whole blood concentration of tacrolimus and its metabolites, 13-O-desmethyl (DMT) and 15-O-DMT, were determined using a validated liquid chromatography tandem-mass spectrometry (LC-MS/MS) assay. All samples were stored at -80°C until analysis. Population PK parameters were estimated using NONMEM (ver. 7.2). Pharmacogenetic analysis included CYP3A5 (*3 or *1), CYP3A4 (*1B and *22), P450 oxidoreductase (POR*28), and ABCB1 transporter genotype (1236C>T, 2677G>T/A, and 3435C>T). Tacrolimus formulation, patient demographics, clinical chemistry parameters, and polymorphisms in the CYP3A4/5, ABCB1 and P450 oxidoreductase genes were assessed as part of the covariate analysis. Allometrically-scaled body weight was used to account for differences in body size.

Results

A total of 6390 tacrolimus concentration measurements (plus metabolites 13-O-desmethyl (DMT) and 15-O-DMT) from 71 transplant recipients (36 liver and 35 kidney) were available for analysis across the 3 formulations tested. A two-compartment model with first order absorption best described the PK data. Tacrolimus PK exhibited large inter- and intra-patient variability. The estimated oral clearance (CL/F) for individual patients was comparable across formulations. Tacrolimus metabolite profiles were also comparable across the different formulations. In renal transplant recipients, hematocrit and CYP3A5*3 genotype were predictive of tacrolimus clearance. In addition, CYP3A5 expressers had significantly increased CL/F and required higher maintenance doses. There was a trend for lower tacrolimus clearance depending on ABCB1 3435C>T genotype. Donor genotype did not influence tacrolimus PK in renal transplant recipients. In liver transplant recipients, donor CYP3A5 genotype was predictive of tacrolimus clearance.

Conclusions

This study presents a population PK analysis of tacrolimus in adult kidney and liver transplant recipients using very rich PK data for both tacrolimus and its major metabolites. There were no significant differences in tacrolimus PK parameters or metabolite profiles across formulations. Hematocrit and CYP3A5*3 genotype were identified as significant predictors of tacrolimus clearance. In liver transplant recipients, one needs to account for both the donor and recipient genotypes when determining the starting dose.

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