PharmGKB

New CPIC Guideline: CYP3A5 and Tacrolimus

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Guidelines regarding the use of pharmacogenetic tests for *CYP3A5* in dosing tacrolimus have been published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium.

Tacrolimus is an immunosuppressive agent administered to transplant recipients to prevent and treat allograft rejection. Clinical use of tacrolimus is complicated by its high inter-patient variability in pharmacokinetics and a narrow therapeutic index. As a result, management of tacrolimus usually includes therapeutic drug monitoring (TDM). Concentrations of tacrolimus are strongly influenced by *CYP3A5* genotype - individuals with the *CYP3A5 *1/*1* or *CYP3A5 *1/*3* genotype (also known as extensive and intermediate metabolizers, respectively) have significantly lower concentrations of tacrolimus as compared to those with the **3/*3* genotype (poor metabolizers). In addition to standard TDM, adjusting the starting dose of tacrolimus based on *CYP3A5* genotype may allow for a more rapid achievement of therapeutic drug concentrations.

In the newly published guidelines, CPIC recommends increasing the starting dose by 1.5 to 2 times the recommended starting dose in CYP3A5 extensive and intermediate metabolizers. This particular CPIC dosing recommendation is unusual in that those with the extensive metabolizer phenotype (typically referred to as the "normal" metabolizer phenotype in other CYP enzymes) require an increase in dose, while those with the poor metabolizer phenotype do not require any change in dose. This is because, in the case of CYP3A5, extensive metabolizers are actually the minority in most worldwide populations (excluding those of African descent), while those with the poor metabolizer phenotype constitute the majority.