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Opinion Article

# Impact of *CYP3A5* Polymorphisms on Tacrolimus Dosing in Renal Transplant Patients

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## DESCRIPTION

Tacrolimus is a calcineurin inhibitor extensively used as an immunosuppressant in renal transplantation to prevent allograft rejection. Due to its narrow therapeutic index and significant interindividual variability in pharmacokinetics, dosing requires careful monitoring to balance efficacy and toxicity. Among the known contributors to this variability, genetic polymorphisms in cytochrome P450 3A5 (*CYP3A5*) have emerged as key determinants of tacrolimus metabolism and clearance.

*CYP3A5* is responsible for the hepatic and intestinal metabolism of tacrolimus. The most clinically relevant polymorphism is *CYP3A5*3* (rs776746), a splice variant that results in non-functional protein due to a premature stop codon. Individuals homozygous for the *3 allele (*3/*3) are classified as non-expressers, whereas those carrying at least one *1 allele (*1/*3 or *1/*1) express functional enzyme and metabolize tacrolimus more rapidly.

This genotype significantly affects tacrolimus pharmacokinetics. Expressers require 1.5 to 2 times higher doses of tacrolimus to reach target trough concentrations compared to non-expressers. Without genotype-guided adjustment, expressers are at higher risk for sub therapeutic exposure and acute rejection, while non-expressers may be prone to toxicity, including nephrotoxicity, neurotoxicityand infections.

Multiple clinical studies across diverse populations have confirmed the impact of *CYP3A5* on tacrolimus dosing. A landmark study from Spain involving 320 renal transplant recipients showed that *CYP3A5* expressers needed a median dose of 0.20 mg/kg/day versus 0.12 mg/kg/day for non-expressers to maintain therapeutic levels. Incorporating genotyping into the pre-transplant evaluation significantly reduced the time to achieve target concentration and minimized the need for frequent dose modifications.

In light of these findings, international clinical guidelines, including those from CPIC and the Dutch Pharmacogenetics Working Group, now recommend *CYP3A5* genotyping for all renal transplant patients prior to initiating tacrolimus. Dosing strategies based on genotype have been shown to improve early post-transplant outcomes and reduce hospital stays.

At Valencia Institute of Medical Sciences, *CYP3A5* genotyping has been integrated into the electronic health record system, allowing automatic dosage recommendations based on genotype. This protocol has shortened the median time to reach therapeutic levels from 5.2 days to 2.7 days and reduced adverse drug reactions by 18% in the first month post-transplant.

Ethnic variability in *CYP3A5* allele frequency further underscores the importance of personalized dosing. The *1 allele is common in individuals of African descent (50–60%) but rare in Europeans (10–15%). In mixed populations such as Latin America and Southeast Asia, intermediate frequencies necessitate universal pre-transplant screening to ensure accurate dosing.

The Pharmacoproteomic dimension adds further refinement. Quantification of *CYP3A5* protein levels in donor and recipient liver biopsies has been explored as an adjunct tool to explain outlier pharmacokinetics not fully accounted for by genotype alone. This approach, though still experimental, holds promise in cases of atypical drug response.

The cost-effectiveness of preemptive genotyping has been evaluated in European health systems. A model simulation study in Spain showed that incorporating *CYP3A5* testing reduced total healthcare costs by decreasing acute rejection episodes, intensive care admissionsand prolonged hospitalization, making it a financially sustainable strategy for public health institutions.

*CYP3A5* polymorphisms play a pivotal role in tacrolimus dosingand genotype-guided strategies can significantly enhance the precision of immunosuppressive therapy in renal transplantation. As pharmacogenomics becomes more integrated into clinical workflows, testing for *CYP3A5* should be considered a standard of care in transplant pharmacotherapy to ensure both graft survival and patient safety.

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