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Perspective

Effects of Genetic Polymorphisms

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DESCRIPTION

Efflux pumps and members of the cytochrome P-450 (CYP) isoenzyme system located in the liver and gastrointestinal tract affect the bioavailability and metabolism of cyclosporine and tacrolimus. The frequency and severity of these medications' side effects are proportional to their overall exposure, which is determined by the time of treatment and drug concentration in the blood. Variable expression of functional *CYP3A4, CYP3A5,* and P-glycoprotein (PGP) efflux pumps, which may be the result of single-nucleotide polymorphisms found on the genes encoding for *CYP3A4, CYP3A5,* and PGP, could be one factor contributing to the inconsistent pharmacokinetics of calcineurin inhibitors. The most prevalent polymorphisms of *CYP3A5* are *CYP3A5*3* and *CYP3A5*6*. Given the range of polymorphisms known to impact *CYP3A4, CYP3A5,* and the multidrug resistance-1 (*MDR1)* gene, using genetic markers to alter initial doses of cyclosporine or tacrolimus may be tricky (the gene that codes for PGP). Carriers of *CYP3A5*1* have consistently higher tacrolimus clearance rates than *CYP3A5*3* homozygotes, according to studies. The effects of *CYP3A5* alleles on cyclosporine metabolism, as well as the *MDR1 C3435T* polymorphism on tacrolimus metabolism, are still debated.

Pharmacogenetics investigates the link between single-gene polymorphisms and their effects on pharmaceutical pharmacokinetics and pharmacodynamics. Pharmacogenomics examines genetic composition and its impact on medication activity *in vivo* using more complicated models of genetic diversity. Analyzing the interactions of proteins and medications in people with genetic polymorphisms could give clinicians another tool for making logical therapeutic decisions on a patient-by-patient basis. Pharmacogenomic analysis may be particularly effective in therapy regimens involving drugs with a limited therapeutic range, a high cost, or severe side effects when taken incorrectly.

Because of their extremely variable pharmacokinetics, narrow therapeutic range, expense, and importance to the transplant recipient's long-term survival, pharmacogenetics may be warranted in predicting later therapy with calcineurin inhibitors. This article examines the medical literature on single-nucleotide polymorphism (SNP) genotypes of major metabolic enzymes and transport proteins, as well as their effects on calcineurin inhibitor pharmacokinetics.

Calcineurin inhibitors

The calcineurin inhibitors are cyclosporine and tacrolimus. The Food and Drug Administration has approved the use of two cyclosporine formulations, Sandimmune and Neoral, both manufactured by Novartis Pharmaceuticals. Sandimmune, also known as cyclosporine, is a capsule that releases medication quickly. Neoral, also known as cyclosporine (modified), is a microemulsionformer that reduces intraindividual absorption variability. Sandimmune and Neoral are not bioequivalent and should not be used interchangeably unless dose changes are made. Generic versions, on the other hand, are bioequivalent to both Sandimmune and Neoral. Prograf is a brand of Tacrolimus that is offered as an immediate-release capsule (Astellas Pharma US). cyclosporine injectable drugs, cyclosporine oral solutions, cyclosporine eye drops, a topical tacrolimus ointment, and a tacrolimus injectable product are among the other formulations.

Calcineurin inhibitors weaken the immune system by inhibiting T cells from producing interleukin-2 (IL-2). The intracellular immunophilins cyclophilin and FKBP-12 are binded by cyclosporine and tacrolimus, which are chemically separate compounds. Both molecules bind to calcineurin and block its phosphatase activity, which is essential for the transport of nuclear factors from activated T cells to the chromosomes, where cytokine production takes place. The growth of the inflammatory response *via* B cells and T cells is inhibited when IL-2 production is reduced. The immune system's overall function is substantially harmed by the reduced inflammatory response.

Despite the fact that cyclosporine and tacrolimus are both highly lipophilic compounds, their absorption kinetics is very different. Cyclosporine absorption is heavily reliant on gastrointestinal function and bile secretion. As a result, Sandimmune absorption kinetics is very variable both between individuals and within

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individuals. Peak blood concentrations are reached in 2-6 hours. Neoral provides patients with rapid and consistent absorption, with peak blood concentrations reached in 1.5-2 hours. Sandimmune and Neoral have elimination half-lives of 19 and 8.4 hours, respectively. Tacrolimus is reliably absorbed and excreted, with a half-life of 8.7 hours. Product labelling notes pharmacokinetic variability of 20-30 percent among patients.

Efflux pumps and members of the cytochrome P-450 (CYP) isoenzyme system located in the liver and gastro-intestinal tract affect the bioavailability and metabolism of cyclosporine and tacrolimus. P-glycoprotein (PGP), which is encoded by the multidrug resistance-1 *(MDR1*), also known as the *ABCB1* gene, is the major efflux pump involved in transporting cyclosporine and tacrolimus. PGP is a transmembrane transporter that carries a variety of endogenous chemicals from the cytoplasm to the cell's outside. PGP reduces the oral bioavailability of medicines in the intestines by discharging them from the inside of enterocytes into the gut lumen. CYP enzymes, specifically *CYP3A4* and *CYP3A5*, are responsible for the metabolism and systemic clearance of tacrolimus and cyclosporine once they reach the bloodstream. The *CYP3A4* and *CYP3A5* enzymes are substrates for several therapeutically valuable medications. They are found in large amounts in intestinal cells and, together with PGP, may limit the oral bioavailability of several medicines. *CYP3A4* and *CYP3A5* are also abundant in the liver and are responsible for much of the first-pass clearance of tacrolimus and cyclosporine from the hepatic portal vein as well as systemic clearance.

CONCLUSION

For renal transplant recipients receiving tacrolimus as an immunosuppressant, practitioners can expect *CYP3A5*1* carriers to have a tacrolimus clearance 25-45% greater than that of *CYP3A5*3* homozygotes, with proportional dosing needs to maintain adequate immunosuppression. Since inadequate immunosuppression is linked to graft rejection, evaluation of *CYP3A5* polymorphisms may be helpful in determining an appropriate starting dosage, rapidly achieving adequate immunosuppression, and ultimately improving the outcome of renal transplantation.